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Effectiveness of Japanese encephalitis SA 14-14-2 live attenuated vaccine among Indian children: Retrospective 1:4 matched case-control study

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ABSTRACT

Objectives: We estimate the effectiveness of Japanese encephalitis (JE) SA 14-14-2 live-attenuated vaccination single dose campaign among children aged 1–15 years in India during 2006–07.
Methods: Acute encephalitis syndrome (AES) cases hospitalized following vaccination campaigns during the years 2006–08 were investigated retrospectively. The laboratory-confirmed JE cases were detected from the surveillance laboratories based on anti-JE IgM antibody by ELISA or viral RNA detection by RT-PCR in sera or cerebrospinal fluid. Consent was sought from parents or guardians. Four community controls were chosen randomly per case during house-to-house survey employing individual matching on age, gender and residence during the risk period. Vaccination history was enquired from the child's guardian and verified from vaccination card at home or records at health centre. Conditional logistic regression was conducted on matched case-control sets.
Results: We studied 149 cases and matched 596 controls. Vaccination effectiveness was 43.8% (95% CI, 1.9–67.8) based on vaccination card or record. However, effectiveness was 72.2% (95% CI, 56.2–82.4) based on parental history or card/record. Vaccination effectiveness in Assam state was higher than in Uttar Pradesh state.
Conclusions: We concluded that the single subcutaneous dose of SA 14-14-2 JE vaccine provided moderate effectiveness in Indian children.

Introduction

Background/rationale

Japanese encephalitis (JE), caused by a mosquito-borne flavivirus, is an acute central nervous system infection. An estimated 68,000 cases are reported globally each year, mostly among children [1]. JE is reported commonly in Southern and Eastern Asia including China, Nepal and India. There is no treatment for JE. Vector-control measures are not operationally feasible, are costly and of limited value [2]. It causes significant illness with mortality in almost one-third and similar number of recovered patients experience disability [3]. However, the vaccines offer an opportunity to control the problem. The success in controlling JE by vaccination has been shown by countries in Asia like Japan, Taiwan and Republic of Korea [4]. The concerns about cost, supply, side effects, and effectiveness have made it difficult for low and middle income countries to achieve disease control. In India, mouse brain derived inactivated JE vaccine was used earlier, but capacity was insufficient to meet

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the national need [4].The SA 14-14-2 live attenuated JE vaccine has been used in China for more than 20 years with an effectiveness of 80% for a single dose and 97.5% for a two-dose regimen with a 1-year interval among children less than 15 years of age [5]. Also, a single dose resulted in 99.3% effectiveness in preventing JE in Nepal [6] administered only weeks before exposure to infection and 98.5% after 12–15 months [7]. The protective effectiveness was 96% after 5 years [8]. Also, sustained antibody response was detectable after 5 years [9].

The Government of India introduced the SA 14-14-2 JE vaccine as an epidemic response, following large outbreaks of acute encephalitis syndrome (AES) in 2005 attributed mostly to JE in Uttar Pradesh (UP) and other states [10]. A single-dose vaccine was offered to the children aged 1–15 years during mass vaccination campaigns held a few weeks before the start of JE transmission season in the year 2006. However, data on safety, immunogenicity and effectiveness were not available due to lack of population-level studies in Indian children. Also, a different dosage regimen was followed in India than in China and South East Asian countries.Therefore, a community-based 1:4 individually-matched case-control study was conducted among children aged 1–15 years and resident in JE high-risk districts in Uttar Pradesh (UP) and Assam states in India.

Objectives

The study was aimed at determining the effectiveness of a single dose of SA 14-14-2 JE vaccine administered during mass vaccination campaigns in the years 2006 and 2007.

Material and methods

Study design

A community-based 1:4 individually-matched case-control study was conducted in highly endemic JE districts in UP and Assam following mass vaccination campaigns among children aged 1–15 years in the years 2006 and 2007. The national vector bone disease control programme (NVBDCP) conducted nationwide syndromic surveillance by establishment of sentinel hospitals and laboratories for diagnostic testing [3,11].

Setting

Participants

Cases. The clinical case definition of acute encephalitis syndrome (AES) as applied by the NVBDCP was employed. The definition of AES case was as an individual with 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 [3]. Children living in the selected 13 districts of eastern UP [Gorakhpur, Kushinagar, Deoria, Siddharthanagar, Maharajganj, Sant Kabir Nagar, Basti, Balrampur, Bahraich, Shravasti, Gonda, Ambedkar Nagar, Mau] and four districts of eastern Assam [Dibrugarh, Shivasagar, Golaghat, Jorhat], experiencing vaccination campaigns in 2006 or 2007, were eligible for participation in the study. Cases were identified through the AES surveillance registers maintained at Baba Raghav Das (BRD) Medical College in Gorakhpur (UP) and Assam Medical College in Dibrugarh (Assam). The states of UP and Assam have differences in seasonality of disease, climate, rainfall and other aspects. The AES cases were sampled with cerebrospinal fluid (CSF) and/or sera as per clinical indications and surveillance guidelines. The JE confirmed case was defined as a patient with the presence of JE virus-specific IgM antibody in a single CSF or serum as detected by IgM capture ELISA or detection of JE virus genome in CSF by reverse transcriptase polymerase chain reaction (RT-PCR) [11,12]. IgM antibodies against JE virus in CSF and serum were detected using the indigenously developed 96-well plate IgM ELISA assay kit supplied by the National Institute of Virology (NIV), Pune India [13]. Because the NIV kit had not been certified by the World Health Organization (WHO) at the time of the study, confirmatory testing of CSF was proposed with a commercial kit (XCyton Diagnostics Ltd, Bangalore, India) used in the WHO surveillance studies [14]. Also, for sera detected positive for IgM by the NIV kit, confirmatory testing with a commercial kit (XCyton) was proposed [15]. The NIV kit was validated later by the WHO [16]. JE virus genome detection in CSF was carried out by real time PCR at NIV Pune in IgM negative cases sampled early in the phase of illness [10,17–18].

The laboratory confirmed cases met the following additional eligibility criteria: age 1 year–<16 years at the time of the vaccination campaigns, onset of symptoms at least two months after the vaccination, continuous residence in the district during the risk period, and no known serious underlying medical or immunocompromised conditions. The disease outcome of confirmed JE cases was recorded as alive or dead at discharge from hospital and, if alive, health condition as recovered with sequelae or without sequelae. Case records of JE patients were retrieved from hospitals, traced at residence address and verified for age, case definition, inclusion/exclusion criteria, disease outcome, etcetera as required in the pre-specified study protocol.

Controls. Controls were chosen randomly from neighbourhood of the cases according to the matching variables including age at disease onset, gender, residence and no encephalitis-like illness during the risk period. Four controls were matched individually for each case. Siblings of cases and more than one control per household were not included because of potential over-matching. For age matching, age categories of cases and matching criteria for controls were: age 1–2 years (within 3 months, but not <1 year), 3–4 years (within 6 months), 5–15 years (within 1 year but not >15 years). Controls were also without underlying medical or immunocompromising conditions.

Ethical aspects. Study protocol, survey instruments and consent/assent forms in English and local languages were reviewed and approved by the ethical committees at the selected hospitals and the research ethics committee at the National Institute of Virology (Pune, India) and the PATH (Seattle, USA). All parents or guardians provided written informed consent. Assent was additionally sought from study participants aged 7–17 years.

Variables

Vaccination ascertainment

JE SA 14-14-2 vaccine is a live attenuated vaccine containing the SA 14-14-2 virus strain. It was procured by the Government of India as five-dose vials in the form of lyophilized powder requiring reconstitution with supplied sterile saline as diluent. The vaccine was stored and transported between 2–8 °C. Single 0.5 ml dose was administered separately as subcutaneous injection using 25 G needle of length 1.5 cm on lateral surface of thigh or arm. JE vaccination history was elicited from the child's guardian by verbal enquiry followed by examination of vaccination cards at home and records at health centres for confirmation. Vaccination history was ascertained only at the end of the interview and was verified by a separate study personnel blinded to the vaccination status at household and status of the participant as case or control. JE vaccination history was categorized as confirmed (written record like vaccination card, counterfoil, or record at health facility or school register), probable (credible parent or guardian verbal report but

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