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A cohort event monitoring to determine the adverse events following administration of mouse brain derived, inactivated Japanese Encephalitis vaccine in an endemic district in Sri Lanka

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ABSTRACT

Introduction of human immunization reduced Japanese Encephalitis (JE) cases dramatically in Sri Lanka. However, the increased reporting of adverse events following immunization (AEFI) affected vaccine acceptance by the community. Against this background, we describe the incidence of overall AEFI and incidence and profile of AEFI, thought to be causally related to the mouse-brain derived JE vaccine.

A follow-up of 9798 vaccine recipients was performed for a period of two weeks post-vaccination. Parents self-recorded observed signs and symptoms. The self-records were collected by trained supervisors. All monitored children who manifested symptom/s were investigated in details by medical officers experienced in AEFI investigations within two weeks after ending the follow-up period. Using the results of the investigation, the causality assessment was performed.

The estimated cumulative incidence rate of overall AEFI was 8.6 children per 100 immunizations. The same for observed AEFI consistent with causal association to the inactivated JE vaccine was 4.3 children (95% CI—3.9–4.7%) per 100 immunizations. The most frequent AEFI was fever (81%). The frequency of high fever (>102 °F) was 26%. Other major AEFI were body ache (22%) vomiting (21%), urticaria (19%), pruritus (5%), and headache (5%). Though 83% of children with AEFI thought to be causally related to the vaccine sought medical care, only 6.6% required hospitalizations.

The incidence rate of AEFI in the cohort event monitoring was several-fold higher than that reported through the national AEFI surveillance system. The incidence rate of allergic manifestations among Sri-Lankan children approached what was reported for non-endemic settings and was higher than in other JE endemic populations elsewhere. Contrary to the belief of medical practitioners and the general public, incidence of seizures was low and vaccine related other neurological manifestations were absent.

1. Introduction

Japanese Encephalitis (JE) is the most frequent cause of viral encephalitis in Asia [1]. Since the first outbreak in 1971, there have been no JE outbreaks in Sri Lanka till 1985 [2]. Following three consecutive, major outbreaks in 1985–1987, an immunization campaign with the mouse-brain derived (MBD) JE vaccine was launched in 1988. The MBD JE immunization schedule consisted of a primary series of two doses offered at an interval of 1–4 weeks followed by two booster doses offered one and four years after the primary series, respectively. As a result, JE cases declined from 812 (incidence rate of 4.7/100,000) in 1987 [3] to 26 sporadic cases (incidence rate of 0.1/100,000) in 2006 [4]. Sri Lanka conducted annual immunization campaigns with the MBDJE vaccine (Beijing-1-strain) in 18 of the 26 districts until transitioning to the island-wide, routine immunization with the live attenuated JE vaccine (LAJEV) SA 14-14-2 in 2009 [5].

In spite of the high immunization coverage and the steady decrease in the disease burden, the reported morbidity due to adverse events following immunization (AEFI) started to impact the JE immunization campaign. Through the routine, passive AEFI surveillance system, the programme managers initially observed a gradual increase in the JE vaccine specific AEFI rate from 5.1/100,000 (1998) to14.6/100,000 immunizations (2002) [6]. In subsequent 4 years, the JE vaccine specific AEFI rate was

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30.8/100,000, 57.6/100,000,192.6/100,000 and 92.5/100,000 immunizations, respectively [5].

The gradual increase in JE vaccine specific AEFI rates till 2002 may be partly explained by the improved reporting of AEFI as a result of continuous strengthening of the AEFI surveillance system. However, the same could not be attributed to the increase in AEFI rates in subsequent 3 years. The abrupt increase in JE vaccine specific AEFI rates during 2003–2005, in particular in 2005, coincided with high numbers of systemic allergic manifestations and to a lesser extent with seizures. The reporting rate of allergic manifestations increased from 23.8/100,000 immunizations in 2003 to 125.6/100,000, and 57.4/100,000 immunizations in 2005 and 2006, respectively. This is in contrast to the reporting rates of allergic reactions of 0.29 and 0.56/100,000 immunizations observed in 1998 and 2002. While the proportion of allergic manifestations among all JE specific AEFI remained 5.8% and 5.5%, respectively, in 1998 and 2002, the same was higher in the range of 62% (2006)–76% (2003) in subsequent years, indicating the contribution of allergic manifestations to the abrupt increase in MBD JE specific AEFI rates after 2002. To a lesser extent, seizures which accounted for a reporting rate of 0.7/100,000 immunizations in 2003 had increased to 13.2/100,000 and 6.9/100,000 immunizations in 2005 and 2006 [5].

Higher numbers of allergic manifestations and seizures among vaccinees than seen in previous years were initially observed by the paediatricians. This led to their expression of safety concerns regarding the MBD JE vaccine. Subsequently, it resulted in intensified surveillance on these AEFIs. The resultant publicity had a negative impact on acceptance of the vaccine by parents due to fear of ill-effects following immunization [7,8]. In the study area, Anuradhapura district, the immunization coverage of the first JE dose declined to 93.2% in 2005 as compared to the median coverage of 98.4% in 1997–2004. Even further declines were seen for the second dose to 87.4% as compared to the median coverage of 98.2% during the same 7 year period of reference [9]. The reluctance of health workers to provide the second dose to those who manifested with allergic reactions and seizures following the first dose and the reluctance of some parents to vaccinate their children with the second dose as a result of the adverse publicity regarding allergic reactions attributed to the dramatic decline in the second dose.

In this context, quantification of the burden of AEFI attributable to the MBD JE vaccine was essential to conclude if there was really a safety issue. Second, describing the profile of individual AEFI was required to substantiate or alleviate perceived ill-effects of this vaccine by parents, medical practitioners and health workers. Third, irrespective of the safety issues of MBDJE vaccine, due to cost considerations, there was a need for evaluating a safe and cost-effective alternative JE vaccine. All these were deemed necessary for determining the strategic direction of the national JE immunization campaign. In view of above, (a) we designed a study to determine the incidence of overall AEFI, incidence and profile of AEFI thought to be causally related to the MBD JE vaccine in a cohort of vaccinees in 2006 (b) conducted a study on safety and efficacy of the alternative LAJEV SA-14-14-2 in 2007 and (c) conducted post-marketing surveillance of AEFI due to LAJEV from 2009 to 2012. After completing the strategic decision making process based on this series of studies, we describe the first study on safety of the MBDJE vaccine conducted in the JE endemic, Anuradhapura district in Sri Lanka during the annual JE immunization campaign conducted in July–August 2006.

2. Materials and methods

In annual JE immunization campaigns, children aged 1–10 years were targeted for either the primary series or booster doses of the MBD JE vaccine (Beijing-1 strain). The primary series consisted of two doses offered at an interval of 1–4 weeks on completion of the first year of life. The first booster dose (3rd dose) was due one year after the primary series and the second booster (4th dose) was recommended four years after the primary series. Accordingly, our study population comprised (1) children aged one year who received their primary doses, (2) children aged two years who received their first booster dose, (3) children aged five years who received their second booster dose and additionally, (4) any child who did not belong to these age groups but was under 10 years and received any of the due MBDJE vaccine doses from the public sector immunization clinics in the Anuradhapura district in 2006. The total target population for the immunization campaign was 55,055. Children resident in other districts who received JE vaccines from Anuradhapura district and private sector immunizations were excluded. These children received no other concomitant vaccines.

Since all children immunized in the entire district could not be followed up, we selected a study sample. The required sample size was determined based on the population proportion of AEFI due to MBDJE Vaccine with a specified relative precision [10] on the assumption that the observed prevalence was equal to incidence given that the duration of majority of AEFI was of a very short duration (prevalence = incidence × duration) [11]. Due to the limitations of estimates derived from the national AEFI surveillance system, we selected more valid, research-based estimate of systemic AEFI due to MBDJE vaccine (4.4%) reported in USA and Thailand [12] as the population proportion. The required sample size when compensated for the possible loss to follow-up was 10,200.

The required study sample was selected from 4 of the 19 Medical Officer of Health (MOH) areas in the district that performed the highest number of JE immunizations in 2005. The number of participants to enrol from each of four selected MOH areas was determined proportionate to the number of JE immunizations performed in each MOH area in 2005. Subsequently, 3465 from Anuradhapura NPE, 2940 from the Anuradhapura NPC, 2415 from Medawachchiya and 1680 were from Thalawa MOH areas were enrolled for the study. All children who were administered MBD JE vaccine in public sector immunization clinics in selected MOH areas whose parent/s consented for participating in the study were prospectively and consecutively enrolled for follow-up until the required sample size was achieved. Given that the campaigns were held in two rounds of one-week duration, two-weeks apart, we had to enrol our study sample in both rounds. The short duration of a round enabled us to enrol early and late vaccinees while enrolment in both rounds facilitated including recipients of first and second doses in addition to the recipients of booster doses. Parents/guardians were explained about the study, voluntary nature of participation and non-influence of their decision on up-take of subsequent vaccines in the event of not giving consent for participation. Parents of participating children signed a consent form. The majority (99.8%) consented based on the explanation that their participation contributed to a national cause and due to non-availability of any invasive procedures in the follow-up.

In the first stage, enrolled participants were followed-up for a period of two weeks post-vaccination to collect information on AEFI due to the MBD JE vaccine. In line with the national and global standard case definition, an AEFI was defined as any untoward medical occurrence subsequent to JE immunization during the follow-up period that did not necessarily have a causal relationship with the JE vaccine [13]. In this context, any unfavourable or unintended sign, symptom or abnormal laboratory finding was considered as an AEFI.

For soliciting AEFI, a pre-tested, self-administered questionnaire with a self-recorded diary to record basic information on occurrence of any symptom and sign during the follow-up period of two weeks was handed over to parents/guardians of participants. The