Active safety monitoring of measles-mumps-rubella vaccine in the National Immunisation Programme of Sri Lanka

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(Index words: Adverse events following immunisation, MMR vaccine, causality, cohort event monitoring)

Abstract

Objectives This study was designed to report incidence and characteristics of selected adverse events following immunisation which have consistent causal association (AEFIc) with Measles-Mumps-Rubella (MMR) vaccination given at the age of one year in the National Immunisation Programme of Sri Lanka.

Methods The data presented here were obtained from a cohort event monitoring study. It was carried out in the Jaffna Regional Directorate of Health Services area from November 2012 to December 2014. A representative sample of 3002 infants who received MMR immunisation were actively followed up for adverse events (AE) using over the phone interviews, self-reporting, and home or hospital visits up to 45 days. All AEs were reviewed by two investigators independently in two step-wise processes to detect the AEFIc. Seven AEFIc were detected using standard case definitions and onset time limit criteria. They were subjected to further analysis to describe the incidence rates and characteristics.

Results Of the 2398 (80%) infants who completed follow up of 45 days, 1321 infants experienced 2621 AEFI. Of them 209 were classified as AEFIc. Incidence of AEFIc was 87/ 1000 immunisation. They were mainly non-serious and resolved completely. There were no fatal or life threatening AEFIs. Incidence per 1000 immunisations; allergic reactions 0.83, injection site reactions 4.58, fever≥100.4° F or lasting more than ≥ 3 days 9.59, macular papular rash 2.92, parotitis 2.92 and generalised convulsions 1.25.

Conclusion The MMR vaccine used in NIP of Sri Lanka had low incidence of AEFIc and were mainly non-serious in nature.

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Introduction

Measles-mumps-rubella (MMR) vaccine prevents three important diseases and its inclusion in the National Immunisation Programmes (NIP) of many countries is a cost effective public health intervention [1-3]. The combined MMR vaccine was first licensed in United States of America in 1970s. The single component vaccines had been licensed even before [4-7].

Currently a range of MMR vaccine preparations are available in the market. Immunogenicity and safety of these different preparations depend on the virus strains used in manufacture and the manufacturing process [8-11]. Edmonston strain and non Edmonston derived strains are used for measles component. Jeryl Lynn mumps vaccine strain is used more than other strains such as Urabe, Hoshino, Leningrad-3, L-Zagreb in many countries. RA 27/3 rubella vaccine strain is used in most vaccines while others used include Matsuba, Takahashi, and TO-336 [12]. Studies have documented the immunogenicity and safety of most of these giving the option to individual countries to select a preparation which it could afford [1, 4, 9, 10, 13-17].

The NIP of Sri Lanka uses the MMR vaccine manufactured by the Serum Institute of India which is a World Health Organisation (WHO) prequalified preparation [18, 19]. This contains Edmonston-Zagreb Measles virus, Wister RA 27/3 rubella virus and Leningrad-Zagreb Mumps virus. Short term (4-8 weeks) and long term (5-6 years) immunogenicity of this preparation has been documented to be similar to other MMR preparations [10, 20, 21].

Despite some safety concerns reported from Brazil, the preparation is believed to be safe, as subsequent studies have reported that the rate of serious adverse events following this extensively used preparation is low [22-27]. This observation was supported by the World Health Organization and individual authors [11, 28, 29].

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However, the above are not without methodological limitations inherent to safety monitoring such as under reporting, different surveillance methods and retrospective study design resulting in difficulty in carrying out valid comparison [25-27].

In addition, a systematic review published in 2003 has remarked about the inadequacy of reporting safety outcomes in MMR vaccine studies in general [4]. This justifies the need for continuous post marketing safety surveillance of vaccines as long as the preparation is in the market.

Perception about safety concerns hampers the acceptance of the vaccine by parents and the consequences could be detrimental to children and overall public health of the country. Drop in vaccination rate after the fraudulent paper which appeared in the *Lancet* and the subsequent measles epidemics in UK is evidence of such negative consequence [30]. This justifies the need for authentic data regarding safety concerns about vaccines.

In most countries, spontaneous reporting scheme (SRS) is in-built into the NIP and provides post marketing safety surveillance data for all vaccines. Though considered as the most feasible and sustainable method, major limitations of SRS include under-reporting and lack of accurate denominator data [31]. These limitations restrict the use of data from SRS in estimating the incidence rates.

A large (N = 453,119) clinical trial from Egypt reported that incidence of fever (2.51%), injection site pain (2.37%), rash (0.17%) and parotitis (0.04%) following the same MMR vaccine preparation which is currently used in Sri Lanka, when given at the age of 18-24 months [25].

Frequency of adverse events following immunisation (AEFI) not only depends on the vaccine preparation, but also age of recipients, immunisation related errors, and surveillance method. To the best of our knowledge, no studies have reported the safety of MMR vaccine in Sri Lanka.

In order to fill this gap, in this paper, we report the incidence rate of important AEFI and their characteristics following MMR vaccination at the age of one year. Study was carried out after the vaccine was introduced for the first time in our NIP in October 2011.

Methods

The data presented here were obtained from a large cohort event monitoring (CEM) study carried out in the Jaffna Regional Directorate of Health Services area, Sri Lanka from November 2012 to December 2014 to monitor safety of MMR and live Japanese encephalitis vaccine (LJEV) [32]. Cohort event monitoring is a prospective observational study design used by many researchers to monitor safety of medicines or vaccines in public health programmes [33-36]. Two cohorts were recruited for this study: Infants who received 1st dose of MMR vaccine at the age of 1 year, and infants who received the LJEV at the age of 9 months. Estimated sample size for each cohort was 3000 as the WHO recommends that a cohort of 3000 gives 95% probability of identifying a minimum of one adverse event (AE) occurring at the rate of 1:1000 [37]. Since the recruitment of both cohorts took place mostly during the same time period and from the same immunisation clinics, some infants being recruited into both cohorts was unavoidable.

The findings on safety of LJEV have been published previously and gives a detailed account of selecting and recruiting the cohort, follow up, detecting AEs, identifying AEFIs, causality assessment, data collection tools and definitions [32]. In brief, infants who were brought to selected immunisation clinics for their first dose of MMR vaccine at the age of one year were recruited and actively followed up using over the phone interviews with parents on days 1, 3, 14, 30 and 45 to monitor for any AEs. In case of significant AEs, additional data were collected by home visits, hospital visits and additional follow up interviews. Self-reporting by parents was encouraged. All the AE identified in infants who completed follow up were analysed in a two-step process to estimate the incidence of adverse event following immunisation which have consistent causal association with MMR (AEFIc). Methods relevant to subsequent analysis of these AEFIc following MMR vaccine to determine the incidence rate of important AEFIc are outlined here.

Based on literature review and investigators' personal experience in vaccine pharmacovigilance, 6 AEFIc were selected for further analysis [9, 12, 14]. Case definition and time limit for onset of each AEFIc were determined. Brighton collaboration case definitions, WHO documents on vaccine pharmacovigilance, and published articles were perused in this process (Table 1) [38-50]. Using the case definition and onset time limit criteria, two investigators independently went through the data and identified the cases which were within the selected six AEFIc under review. Differences between investigators were resolved by discussion and consensus. Incidence rates and characteristics of cases in these selected six AEFIc are presented in this study. This study was approved by the Ethics Review Committee of Faculty of Medicine, University of Colombo (EC/12-089).

Results

Of the 3002 infants recruited into the MMR cohort, 2398 (80%) completed follow up until 45 days: 471 of them were in both LJEV and MMR cohorts. Mean age was 1 year and 10 days, 51% were males.

Figure 1 gives the number of AE, AEFI, and AEFIc. There were no fatal or life threatening AEFIs during

follow up. Of the total 2621 AEFI reported in 1321 infants, 209 were classified as AEFIc giving an incidence of AEFIc 87/1000 immunisation. In this 209 AEFIc, 53 were assessed as one of the 6 AEFIc under review. Incidence rates of these AEFIc are given in Table 2. For completeness of data, details of other AEFIc (n=156) are also shown in the same table.

Two infants presented with generalised urticaria (allergic reactions) without systemic involvement on day 2 of immunisation. One infant was hospitalized and the other was treated at an outpatient clinic. Both recovered completely within three days. Other than these two cases, there were no immediate allergic reactions or life threatening anaphylactic reactions in the cohort.

Table 1. Case definition and time limit used in this study for the selected 6 AEFIc following MMR vaccine

AEFIc	*Time limit of onset from the day of vaccination*	*Case definition; key clinical characteristics*
Allergic reactions	Up to 3 days	One/ more of the following clinical features of allergy: 1. Generalized urticaria /hives 2. Respiratory involvement 3. Cardio vascular compromise
Injection site reactions	Up to 7 days	1. Any description of morphological or physiological change at or near the injection site OR 2. Induration/swelling/nodule/abscess/cellulitis at or near the injection site.
Fever	Up to 21 days	1. ≥ 100.4 °F (axillary temperature, measured with mercury thermometers) AND lasting for ≥ 3 days; Not associated with any infection.
Macular papular rashes	Up to 21 days	Rash consisting of both macules (a flat area of < 0.5 cm in diameter of skin or mucosa with altered colour or texture) and papules (a discrete, solid, levated body of < 0.5 in diameter).
Parotitis	Up to 21 days	Parotid region swelling with or without fever.
Generalised convulsive seizures	Up to 21 days	History of unconsciousness AND generalized, tonic, clonic, tonic-clonic, or atonic motor manifestations.

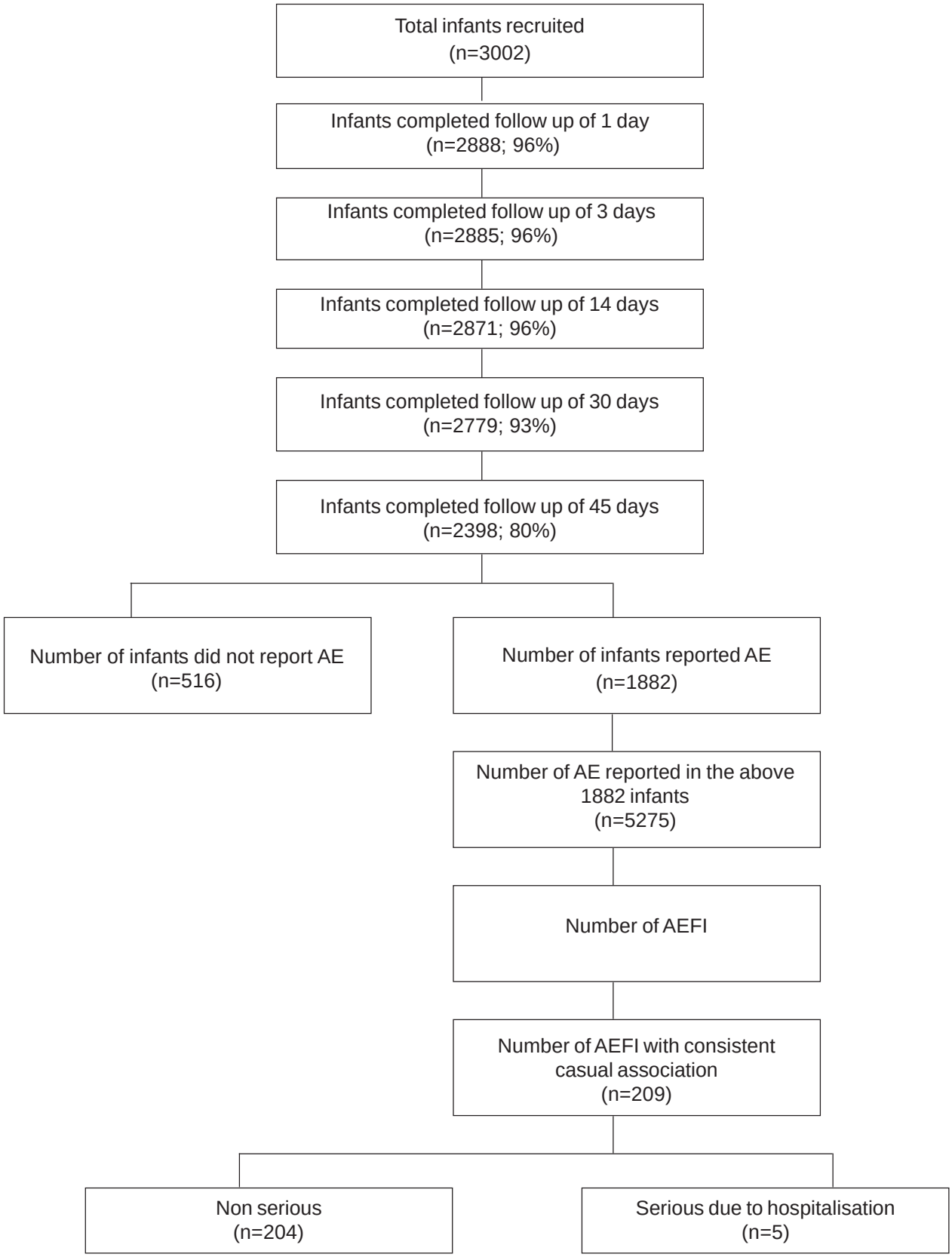
Source: References 35 - 45

Table 2. Incidence rate of AEFIc following MMR vaccine during the cohort event monitoring

A*EFIc*	*Number (n=209)*	*Incidence of AEFIc per 1000 immunisations* (Confidence interval)*
Selected AEFIc		
Allergic reactions	2	0.83 (0.1-3.0)
Injection site reactions	11	4.58 (2.3-8.2)
Fever ≥ 100.4 °F lasting for ≥ 3 days duration	23	9.59 (5.7-13.5)
Macular papular rashes	7	2.92 (1.2-6.0)
Parotitis or parotid region swelling	7	2.92 (1.2-6.0)
Generalised convulsive seizure	3	1.25 (0.3-3.7)
Other AEFIc		
Irritability	118	49.2 (40.3-58.1)
Fever ≥ 100.4°F ≥ 2 days	32	13.34 (8.7-18.0)
Injection site reactions	1	0.41 (0-1.5)
Parotitis	1	0.41 (0-1.5)
Persistent crying ≤ 3 hours	4	1.67 (0.5-4.3)

*the number of infants who completed 45 days were taken as denominator n=2398

Figure 1. **Schematic representation of the AEFI reported during cohort event monitoring following MMR immunisation**



Common injection site reactions were erythema, swelling, induration and pain around the injection site. All were small, less than 2cm in diameter and were reported within 3 days. None required any medical attention and all recovered within 2-3 days.

Fever ≥100.4°F or fever lasting for ≥ 3 days duration was reported in 23 infants and 4 (17%) of them were hospitalised. Mean duration of fever was 3.7 days.

Macular papular rashes were reported in 7 infants and 3 of them required medical attention. Severity varied from mild transient exanthema to measles like rashes. All recovered, average duration was 4 days.

Seven infants presented with clinical evidence of parotitis comprising of unilateral parotid enlargement and fever. Mean time of onset was 14.6 days and complete recovery occurred in 4.6 days; three infants required medical attention.

Three infants had seizures. In all three, the seizures were preceded by fever and were generalized in nature prompting a clinical diagnosis of febrile seizures. Seizures had occurred on day 6, 10 and 13 following the MMR vaccination. One infant had a past history of febrile seizures. Two infants were hospitalised and one was managed in an outpatient clinic. All three infants had only one episode of seizures and recovered completely.

Five children who experienced AEFIc were hospitalised: 2 with febrile convulsion, 2 for fever and 1 with an allergic reaction. Mean duration of hospital stay was 2.4 days and all had recovered completely on discharge.

Discussion

This study has provided evidence that the MMR vaccine which contain Edmonston-Zagreb Measles virus, Wister RA 27/3 rubella virus and Leningrad-Zagreb Mumps virus, used in the NIP in Sri Lanka is relatively safe with no reports of any fatal or life threatening AEFI up to 45 days. The adopted CEM provides reliable information on safety profile of the vaccine and show no evidence of any potentially serious AEFI. Loss to follow up is linearly correlated with the duration in any prospective longitudinal study and we too observed the same limitation. Despite our efforts to minimize loss to follow up, at the end of 45 days we still observed 20% loss to follow up.

In this study, we successfully followed up 2871 (96%) infants until 14 days. After that the dropout rates were 7% at 30 days and 20% at 45 days (figure 1). Whenever an infant could not be contacted for follow up interviews, we communicated with the public health team of the relevant Medical Officer of Health (MOH) area to verify any serious events or deaths in their area in the given period. Since most of the serious and fatal events occur within 14 days, where we had only 4% infants lost for follow up and as serious events or deaths are generally known to MOH of an area, we strongly believe that the possibility of missing a serious event or death in our cohort due to loss to follow up is remote [51]. In this paper, we have reported that the incidence of AEFIc with MMR vaccine is 87/1000 immunisations which is lower than the incidence of 130.6/1000 immunisations reported for LJEV using the same CEM study design from the same area [32].

In this paper, in addition to overall incidence of AEFIc occurring with MMR vaccine, we have also documented the incidence rate of six key individual AEFIc and their characteristics. To the best of our knowledge, this is the first time such detailed safety data are reported for a MMR vaccine preparation in Sri Lanka.

The incidence of allergic reactions was 0.8/1000 immunisation in our study and they were confined to generalized urticaria only. Data on incidence of non-serious allergic reactions was lacking in most published literature on safety of MMR vaccine [12, 52]. However, we feel that this finding is important as health care professionals can use this data to reinforce the public trust regarding this vaccine.

Injection site reactions were estimated to be 4.58/1000 immunisation (0.46%) in our study which is considerably lower than the rates reported from India (4.3%) and Egypt (5.25%) with the same MMR vaccine preparation [21, 25]. Even the WHO has reported a much higher rate of 17-30% [12]. However, even for LJEV, we have reported a similarly low incidence of injection site reaction [32]. This could be explained by differences in injection techniques, skill of the vaccinators, age of study participants, reporting methods and definitions used for detecting injection site reactions. In addition, we have used stringent case definitions for injection site reactions while most other studies have not reported the case definitions which they used [21, 25].

Parotitis is another AEFI worth mentioning when it comes to reporting safety data of MMR vaccines. Since this is also a feature of mumps, parents could become anxious when a vaccinated infant develops swelling or pain in the area of parotid glands. This could hamper the trust parents have in immunisation programmes. Incidence of parotitis in our study was 2.9/1000 immunisation (12 month old infants) compared to 0.4/1000 immunisation (16-24 months old infants) and 25/1000 immunisation (5-7 year old children) reported from Egypt for the same MMR vaccine preparation [25]. Incidence of 10.42/1000 immunisation (12 months old infants) and 21.3/1000 immunisation (4-6 year old children) were reported from Iran for a different MMR vaccine preparation [53]. Differences in age of study participants, primary / booster vaccination, definitions used for detecting parotitis, and follow up method could have contributed for this difference.

Incidence of febrile convulsion, a serious and worrisome AEFIc, was 1.25/1000 in our study which is higher than the incidence reported by the WHO (1 in

2000-3000 immunisation) and lower than in the Iran study (57/1000) [12, 53]. Differences in vaccine strains and study design could have accounted for this difference.

Advantages of CEM in vaccine pharmacovigilance include completeness of data and clear description of adverse events: Our study has endorsed these advantages. We have observed that the incidence of overall and most of the individual AEFIc tend to be lower in our study for both LJEV and MMR vaccine presented in this paper [32]. The low incidence reported in our study is reliable because we used strict definitions and strict guideline in applying those definitions. We have calculated the incidences using AEFI with consistent causal association to MMR immunisation whereas this information was not clear in the studies we have used for comparison [21, 25, 53].

Varying case definition used in identifying an AEFI prevented meaningful comparison of data from earlier studies. This prompted the development of standard case definitions for vaccine pharmacovigilance, which we have used in our study [38].

Even though the data does not confirm that the vaccine has caused the adverse event, it documents the strength of association between the vaccine and the AEFI. When the causality is assessed objectively and independently using standard validated set of criteria, it decreases the disagreement between assessors and improves the likelihood of a relationship [54]. Hence, it is highly recommended that researchers use a validated causality assessment method in pharmacovigilance studies. If all researchers use a single causality assessment method when studying the same products, it will allow comparison and compilation in the form of meta-analysis and systematic reviews. In case of vaccine pharmacovigilance, the WHO has already published a causality assessment method which we have used in our study [39]. Causality assessment will be also very valuable to address the safety of vaccines in NIPs and to develop corrective actions to sustain the immunisation programme.

Conclusion

We conclude that the newly introduced MMR vaccine preparation in the NIP in Sri Lanka is safe, as the incidence of overall and individual AEFIc were low with few serious AEFIs and all recovered completely. Our study supports the use of CEM in vaccine pharmacovigilance.

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Conflicts of interest

There are no conflicts of interest.

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