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Investigation of an outbreak of hypersensitivity-type reactions during the 2004 national measles-mumps-rubella vaccination campaign in Brazil

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ABSTRACT

Introduction: During Brazil's national measles, mumps, and rubella (MMR) vaccination campaign in August 2004, an unexpectedly high rate of hypersensitivity-type adverse events (HAEs) was reported.

Materials and methods: We reviewed information about children with suspected HAEs reported by clinicians to Brazil's national passive surveillance system for adverse events following immunization (AEFI), compared attack rate of HAE by manufacturer of MMR vaccine used in the campaign, and conducted a case–control study to determine possible risk factors for HAEs.

Results: During the 2004 national campaign, the rate of HAEs following MMR vaccination was one log higher for manufacturer A (15.2/100,000 doses administered) compared to the other two manufacturers (1.2 and 0.6/100,000 doses; $p < 0.0001$); a similar pattern was observed retrospectively in analysis of the 2000–2003 AEFI surveillance (0.95 vs. 0.07 per 100,000 doses administered; $p < 0.0001$). In the case–control study, among the 49 case-patients with HAEs identified, reported symptoms included conjunctival injection (60%), urticaria (55%), fever (54%), and facial edema (53%); no deaths occurred. The median time interval between vaccination and symptom onset was 42 min (range: 5 min–24 h). We did not identify any differences in the proportion of case-patients and control children with a history of known allergy to food (including egg, egg-containing products or gelatin), drugs, or environmental antigens.

Discussion: Our study highlights the importance of a well-functioning routine AEFI surveillance system linked with mass vaccination campaigns. Such a system in Brazil permitted timely detection of HAEs and validation of a safety signal associated with one vaccine manufacturer. Unlike earlier publications, this outbreak linked to a single manufacturer of MMR showed no association with a prior allergic history to eggs or other foods, including gelatin; subsequent studies implicate the dextran stabilizer in MMR from manufacturer A as the likely cause of HAEs.

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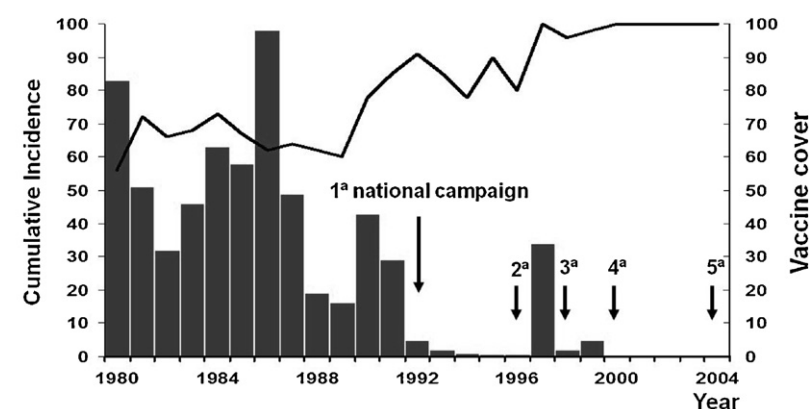
1. Introduction

Prior to inclusion of measles vaccination in Brazil's routine childhood National Immunization Program (NIP) in 1992, large periodic epidemics swept the country [1]. As routine vaccination coverage was suboptimal, complementary “mop-up” national measles vaccination campaigns targeting one-to-four year old children were conducted during 1992, 1996, 1998, 2000 and 2004 (Fig. 1). By 2000, endemic circulation of measles virus had been eliminated in Brazil [2]. Intermittent measles outbreaks continued, however, due to importation [3,4].

Abbreviations: 95% CI, 95% confidence interval; AEFI, adverse events following immunizations; HAEs, hypersensitivity-type adverse events; MMR, measles mumps and rubella vaccine; OR, odds ratio; NIP, National Immunization Program; SD, standard deviation.

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Source: Brazilian Ministry of Health

Fig. 1. Measles cumulative incidence (1/100,000) and vaccine cover (%), Brazil, 1980–2004.

Live attenuated measles vaccine, frequently administered in combination with mumps and rubella (MMR) vaccines, is both very effective and generally safe. The most common expected MMR-related systemic adverse reactions include headache and acute fever in 4–9% of recipients, depending on the strain of vaccine virus [5]. Serious post-MMR vaccination adverse events occur rarely; both immediate hypersensitivity-type adverse events (HAEs) and immune thrombocytopenic purpura occur at or are reported approximately once per 40,000 doses administered [6,7]. HAEs may include a wide array of symptoms, including cutaneous erythema, laryngeal edema, or more seriously anaphylaxis (~3.5/million doses) [8]. Previously published reports of HAE-type reactions following measles-containing vaccination have focused mainly on the link to children's pre-existing allergies to egg protein, gelatin, or antibiotics (e.g. neomycin) used in vaccine production [9–11].

The World Health Organization recommends that the safety of mass immunization campaigns be monitored via surveillance of adverse events following immunizations (AEFI) combined with rapid investigations of signals as needed [12]. During the 2004 national MMR vaccination campaign in Brazil, the routine AEFI surveillance system detected a major increase in HAEs. We present these results and a follow-up case-control study conducted in two Brazilian states to determine possible risk factors in young children with HAE(s) among MMR vaccines.

2. Methods

2.1. Background

The 2004 National MMR Vaccination Campaign was launched in all 27 states of Brazil (estimated 2004 population = 179 million) on August 16, with a completion date of August 21, the day of national mobilization against measles (D-day). Three brands of MMR (A, B, and C) were distributed to 13, 11, and 3 states, respectively; each state used only one brand during the campaign. On D-day, NIP authorities received an unexpectedly large number of HAE reports via either the AEFI surveillance system or direct phone call, from seven states, most of them using only MMR brand A (MMR.A) vaccine. The campaign in the 13 states using MMR.A vaccine was immediately suspended and an investigation launched.

2.2. Passive AEFI surveillance

We reviewed data from the Brazilian NIP and AEFI surveillance system (established in 1998 as a passive surveillance system) [13]. We retrospectively analyzed data from suspected cases of HAEs reported to the AEFI surveillance system by clinicians from 2000 to 2004. The rate of HAE (per 100,000 doses) in Brazil was

calculated for each brand of MMR vaccine, using estimated total doses administered as the denominator, and suspected cases reported to the surveillance system as the numerator.

2.3. Case-control study

We launched a case-control study in Santa Catarina and Paraná states in southern Brazil on September 21 and October 20, 2004, respectively. These two states were chosen (out of the seven that had reported HAE cases during the campaign) because of the substantial number of reported HAE cases, their historical excellence in surveillance activities, and the support available at health facilities for the field investigation.

Case-patients were defined as one-to-four year old children with suspected HAEs following vaccination with MMR.A during the 2004 national campaign and reported to the national AEFI surveillance system by clinicians. Post-vaccination HAEs were defined as the acute onset of exanthema, urticaria or facial or peripheral edema within 24 h after MMR vaccination during the August 2004 national campaign. For each case, one or more asymptomatic children from the same age-group vaccinated during the same campaign and residing in nearest-neighbor households were enrolled as controls.

Parents of both case-patient children with HAEs and their controls were interviewed, from two weeks to two months after the HAE, using a standardized questionnaire to collect: basic demographic data, medical history of children (including prior vaccination[s]; history of known allergy to foods [including gelatin, eggs] and antibiotics); history of recurrent respiratory problems (including asthma), and specifics about symptoms observed after receiving MMR vaccination; as well as the type (if any) of medical care received following vaccination.

Differences in the proportion of case-patient and controls groups exposed were analyzed (in the univariate analysis using a Chi-square, or Fisher exact test as appropriate); continuous variables (e.g. age distributions) were evaluated using a student T-test. The odds ratio was used as the measure of association in the univariate analysis, and an unconditional logistic regression model was used to evaluate the independent effect of variables on outcome. Software used included EpiInfo versions 6.04d and 3.2.2 for univariate and multivariate analyses, respectively.

3. Results

3.1. Passive AEFI surveillance

During the D-day of National Campaign, a total of 467 HAEs in MMR vaccines one to four years of age were reported from seven

Table 1

Rates of acute hypersensitivity-type reactions (per 100,000 doses of MMR vaccine administered^a) by manufacturer, on Day 1 of the National MMR Vaccination Campaign, Brazil – August 2004.

Manufacturer	Doses administered ^a	Number	Rate
A	2,500,000	382	15.3
B	5,000,000	58	1.2
C	4,200,000	27	0.6
Total	11,700,000	467	4.0

^a Approximated values.

of 27 states; subsequent active searches identified suspected cases of HAE in additional states. Based on the approximately 11,700,000 doses of MMR vaccine administered on D-Day of the national campaign, the estimated rate of hypersensitivity-type reactions was 4.0 per 100,000 doses. Rates of HAEs stratified by the three manufacturers providing vaccine during campaign are presented in Table 1.

Among the 218 children with information about clinical characteristics of suspected HAEs occurring within 24 h of MMR vaccination, symptoms included erythematous-type rash in 166 (76%), urticaria in 18%, and facial edema in 1%. Eleven children (5%) had suspected anaphylactic reactions (e.g. hypotension, shock, laryngeal edema or dyspnea); no deaths occurred.

A review of historical immunization data at NIP showed ~57 million doses of MMR vaccine were administered from 2000 to 2003. During which, 754 AEFI reports were received (rate=1.3 per 100,000 doses), 67% were hypersensitivity-type (rate=0.8 per 100,000 doses). The rate of reported HAE following MMR vaccine produced by manufacturer A (MMR.A) was significantly higher than those observed for other manufacturers (0.95 vs. 0.07 reactions per 100,000 doses administered; $p < 0.0001$).

Within 24 h after suspension of the campaign, the Ministry of Health announced a national recall of MMR.A vaccine. Public health announcements were disseminated about the reported risk associated with vaccination and the importance of persons with allergic-type reactions seeking immediate medical attention. Testing of a sample of implicated and non-implicated lots of MMR vaccine to compare the viral strains and the presence of trace ingredients were conducted at the reference laboratory in Brazil. No contaminants were identified.

3.2. Case-control study

We enrolled 49 case-patient children and 185 controls to study potential risk factors. Among case-patients, the estimated time interval between vaccine administration and HAE onset was a mean of 42 min (range: 5 min–24 h); 75% of parents reported symptom onset within 2 h of MMR vaccine administration. Although sex, race, and family income were similar in case-patient and controls ($p > 0.05$), case-patient children were significantly younger than controls: a mean age (± 1 standard deviation [1 SD]) of 30 months ± 15 months vs. 36 months ± 14 months, respectively ($p = 0.006$) (Table 2). The most frequently reported symptoms included: conjunctival injection (60%), urticaria (55%), fever (54%), facial edema (53%) and exanthema (41%) (Table 3). No HAE-related deaths or anaphylaxis were reported from the 13 cities in Paraná and Santa Catarina states which reported suspected post-vaccination HAEs during the August 2004 campaign.

Among the 49 case-patients, 94% sought medical care, and three were hospitalized. Interviewed parents of 79% who sought medical attention for HAEs in this study reported their child(ren) received at least one type of medication including: antihistamine in 71%, antipyretic in 35%, and a corticosteroid in 15%.

Administration of a previous MMR before the 2004 campaign was reported by parents in 98% of case-patient children compared

Table 2

General characteristics of case-patients and controls, Paraná and Santa Catarina States, Brazil – 2004.

	Cases N = 49	Controls N = 185	p value
Age (months), mean [$\pm$ SD]	30 [± 15]	36 [± 14]	0.006
Female (%)	59	52	0.36
White race (%)	87	83	0.44
Income, ^a monthly (%)			
<500 R ^a	25	29	0.60
>500 R	75	71	
Household members, mean	4.2	4.7	0.14

^a Monthly family income, in Brazilian Reais.

to 94% of controls ($p > 0.05$). The interval between first and second MMR doses was a mean of 16 ± 14 months in case-patients vs. 22 ± 13 in controls ($p = 0.01$). We did not identify any differences in the proportion of case-patients and control children with a history of known allergy to food (including egg, egg-containing products or gelatin), drugs, or environmental antigens (Table 4). A family history of allergies (e.g. in parents, grandparents, brothers or sisters) was also not more common in either case-patient or control groups (Table 4). A prior history of asthma also was not associated with HAE ($p > 0.05$), but the proportion of children with a history of recurrent, acute upper respiratory tract infection was higher among case-patients (45%) than in controls (25%): odds ratio (OR) = 2.46; 95% confidence interval (95%CI) = 1.21–5.01; ($p = 0.006$) (Table 4). In an unconditional logistic regression model, the interval between previous MMR dose and the implicated MMR.A brand of vaccine was significantly shorter in case-patient children compared to controls after adjusting for age (Table 5).

4. Discussion

The national surveillance system for AEFI in Brazil was successful in the timely identification of a higher than expected rate of HAE among young children during the National MMR Vaccination Campaign of 2004. Analysis of HAE patients by the MMR vaccine brand received and doses distributed data revealed brand A had a rate of HAE almost 15-fold higher than other brands used in the campaign. A retrospective review of AEFI surveillance system reports from 2000 to 2003 confirmed significantly higher rates of HAE in children who had received MMR.A brand compared to other MMR vaccine brands. Based on this information, the 2004 National Campaign was interrupted in the 13 states using MMR.A vaccine to allow for the recall of ~five million doses of implicated MMR.A vaccine. The campaign continued uneventfully subsequently using another brand of MMR not known to have a high rate of HAEs.

Table 3

Frequency of reported symptoms in case-patient children with hypersensitivity-type adverse reactions (HAEs) following administration of MMR.A brand of vaccine, Paraná and Santa Catarina States, Brazil – 2004.

Symptom	Percent of total (N = 49)
Conjunctival injection	60
Urticaria	55
Fever	54
Facial edema	53
Exanthem	41
Vomiting	35
Pallor	35
Labial cyanosis	24
Palpitations	23
Hoarseness	23
Cough	18
Dyspnea	12

Table 4
Univariate analysis showing frequency of selected allergy-related history with unmatched odds ratios (OR) and 95% confidence intervals (95%CI), 49 case-patients and 185 controls enrolled from Paraná and Santa Catarina States, Brazil – 2004.

	Percent exposed		OR	95% CI	p-Value
	Case-patients	Controls			
Allergy to					
Food ^a	6	8	0.74	0.16–2.92	0.64
Drugs ^b	14	9	1.76	0.61–4.98	0.23
Environmental allergens	6	4	1.48	0.29–6.54	0.57
History of					
Asthma	14	11	1.3	0.46–3.54	0.57
Family Allergy	26	29	0.85	0.38–1.87	0.65
Recurrent upper respiratory tract infection	45	25	2.46	1.21–5.01	0.006

^a Type of allergy to food reported included cow's milk, beans, chocolate and seafood. No reported allergies to gelatin or eggs.
^b Drugs most commonly cited were antibiotics, including amoxacillin (1 case: 4 controls), sulfa-containing (2 controls), erythromycin (1 control), penicillin (1 case: 2 controls). Vaccine was cited by one control but the type was not determined.

A 2008 report from Italy, where an increase in allergic reactions after MMR.A was also detected, found elevated IgG levels to dextran in case patients but not controls [14].

Dextran has been long used as a volume expander in clinical medicine and hypersensitivity reaction rates of ~0.6% have been well documented [15]. While such a rate may seem to be low enough to be tolerated in clinical medicine, the risk benefit equation may change in the setting of millions of doses of preventive vaccines being administered to otherwise healthy children. For example, approximately 700 children with suspected HAEs were reported in the first days of the 2004 MMR campaign in Brazil. Among MMR vaccines used in the 2004 campaign, manufacturer A uniquely contains dextran [per package insert: Dextran 70 (Sigma–Aldrich, St. Louis, MO), though no data on concentration is provided]; it has since been withdrawn by the national drug regulatory authorities [16]. As part of this investigation, a complementary immunologic study of 19 case patients who reported reactions within 2 h after MMR.A vaccination and 31 controls confirmed higher rates of IgG to Dextran 70 in cases vs. controls [17].

The most likely mechanism of dextran hypersensitivity is IgG and immune complex-mediated Type III reaction with complement activation and anaphylotoxin release [18]. IgE-mediated mechanism has been ruled out in most studies [19,20]. The fact that our cases were also of moderate severity, no child reported was known to have experienced a confirmed anaphylactic shock or a fatal outcome despite the large number of HAE cases, supports that this outbreak was probably not IgE-mediated. The onset of post-vaccination HAEs in this report (median of 42 min) was fairly rapid, and antihistamines and corticosteroids were widely used by clinicians to treat our patients.

Our multivariate results showed case-patients had a shorter interval between their dose of MMR during the 2004 campaign and prior MMR doses compared to controls, after adjusting for age. The closer in time exposures to the specific allergen can trigger reactions more often (e.g. in hymenoptera venom allergy). To

test this hypothesis, we attempted to identify the lot number(s) and manufacturers of any MMR vaccine administered prior to this 2004 campaign for those children enrolled in our case–control study; unfortunately, lot and brand information was not routinely recorded on their vaccination cards.

Historically, HAEs in children following MMR vaccination was thought most commonly to be due to pre-existing allergies to gelatin, or to trace amounts of egg proteins or antibiotics used during vaccine production [10–12,21]. IgE antibody to gelatin and milk were demonstrated in eleven percent of 36 patients with hypersensitivity type reactions [21]. This may have occurred due to cross-reactions between proteins contained in the milk or gelatin [22]. It is possible that prior exposure to gelatin from previous vaccinations could sensitize children to other potential antigens known to be included in the implicated MMR.A vaccine (e.g. casein), which may explain at least in part HAEs observed following administration to MMR.A brand of vaccine. However, our case–control study showed case-patients with suspected HAEs following vaccination with MMR.A were not more likely to have an allergic history (to gelatin, eggs, egg-containing products or other foods and drugs); overall only 26% of case-patient relatives reported any known history of allergy.

This investigation had some limitations. Although cases of hypersensitivity after MMR.A vaccine occurred in seven states, we only included suspected cases reported in two states (Paraná and Santa Catarina) in our case–control study for logistical reasons. Furthermore, we investigated only cases reported to the AEFI surveillance system; we did not conduct active surveillance for other cases that might not have been reported. The description of signs and symptoms was based on the recollections of parents or adults who observed children during the episodes, and were not verified by health professionals. Finally, the last interviews were conducted two months after the vaccination campaign began.

Our investigation reinforces the value of conducting surveillance for AEFIs in conjunction with mass vaccination campaigns

Table 5
Results of an unconditional logistic regression with interval between first and second doses of MMR, adjusted for age (two different models), case–control study, Paraná and Santa Catarina States, Brazil – 2004.

Variables	OR	95% IC	p-Value
First model			
MMR interval < 6 months (dichotomous) <u>3.43</u>	1.47–8.02	0.004	0.56
Age < 36 months (dichotomous)	1.28	0.57–2.86	
Second model			
MMR interval < 6 months (dichotomous) <u>4.73</u>	1.27–17.68	0.02	0.94
Age > 23 months (3/0)	0.94	0.21–4.24	
Age < 35 months (2/0)	1.35	0.48–3.78	0.57
Age < 47 months (1/0)	1.24	0.42–3.62	0.70
Age < 59 months (0/0)	1.0	Referent	–

in either developed [23,24] or less developed settings [25,26]. The results also highlight the importance of tracking of vaccine lot numbers and manufacturers when multiple brands are used simultaneously. Though the intrinsic adverse reaction rate of a vaccine remains unchanged, a mass campaign magnifies the number of persons vaccinated and if the reaction is acute, the resultant clustering of adverse events in time and place can facilitate the detection of otherwise rare reactions. Even though MMR.A has been licensed for use since 1990, its higher risk for HAE relative to other MMRs only came into public health focus as a result of the 2004 mass campaign. As more vaccines are being developed targeting diseases of poverty in less developed countries [27] combining good AEFI surveillance with mass campaigns may be an efficient mechanism for unmasking rarer risks of these vaccines during post-licensure safety monitoring.

In conclusion, high vaccination coverage levels with MMR vaccines remains essential for measles elimination. In Brazil, our results demonstrate the importance of having a functional AEFI surveillance system. The willingness of a population to accept mass campaigns in children is strongly influenced by their confidence in vaccine safety. Most AEFIs are mild, but since more serious reactions such as anaphylaxis, shock, respiratory compromise or death are possible, it remains essential to promptly investigate AEFIs to clarify reasons for their occurrence, to maintain public confidence, and to assist manufacturers in identifying previously unknown problems with their vaccines.

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