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Risk factors and familial clustering for fever 7–10 days after the first dose of measles vaccines

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ABSTRACT

Background: Seven to ten days after a first dose of a measles-containing vaccine (MCV; i.e., MMR or MMRV), children have elevated fever risk which can be associated with febrile seizures. This study investigated individual and familial factors associated with fever 7–10 days after MCV.
Methods: Retrospective cohort study among children who were <36 months of age at receipt of MCV in six sites of the Vaccine Safety Datalink from 1/1/2000 to 12/31/2012. We evaluated medically-attended clinic or emergency department visits with a code for fever 7–10 days after any MCV ("MCV- associated"). We evaluated factors associated with MCV-associated fever using χ^2 and multivariable logistic regression analyses.
Results: Among 946,806 children vaccinated with MCV, we identified 7480 (0.8%) MCV-associated fever visits. Compared with children without fever after MCV, children with MCV-associated fever were more likely to have received MMRV than MMR (OR 1.3 95% CI 1.2, 1.5), have had medically attended fever both following previous vaccines (OR 1.3 95% CI 1.1, 1.6) and at any other previous time (OR 1.7 95% CI 1.6, 1.8), have had at least 1 prior seizure (OR 2.2 95% CI 1.7, 2.7), and have had >3 medical visits within the 6 months before MCV (OR 1.7 95% CI 1.6, 1.8). In families with multiple MCV-immunized children, after adjusting for healthcare seeking behavior care for fever, those whose siblings had MCV-associated fever were more likely to also have MCV-associated fever (OR 3.5 95% CI 2.5, 4.8).
Discussion: Children who received MMRV vaccine or who had prior medically-attended fevers and seizures during the first year of life had increased risk of fever after a first dose of measles vaccine. After adjusting for familial propensity to seek care, MCV-associated fever still clustered within families, suggesting a possible genetic basis for susceptibility to developing fever due to measles vaccines.

1. Background

Fever is a common non-specific response to various stimuli such as infection and immunization and some have suggested fever has a beneficial role in response to infection [1]. In the context of immunization, however, fever is considered an adverse event that can lead to increased medical visits. Following immunization with measles-mumps-rubella (MMR) vaccines at both 12 and 18 months of age, a significantly increased risk of emergency room visits during the 1–2 weeks following vaccination occurs, with the majority of diagnoses being fever, febrile seizures (FS) and viral exanthema [2]. Vaccine-associated adverse reactions such as fever and FS may have a negative impact on the public's perception of vaccine safety and may lead to parental lack of confidence, concern, and reluctance to vaccinate [3,4].

Both measles-containing vaccines (MCV), MMR and measles-mumps-rubella-varicella (MMRV), are associated with fever, with

Abbreviations: ACIP, Advisory Committee on Immunization Practices; CDC, Centers for Disease Control and Prevention; CI, Confidence Interval; ICD-9, The International Classification of Diseases, 9th Revision; MCV, Measles-containing vaccines; MMR, Measles-Mumps-Rubella vaccine; MMRV, Measles-Mumps-Rubella-Varicella vaccine; VSD, Vaccine Safety Datalink.

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5–15% of vaccine recipients experiencing fever [5]. Following a first dose of MCV, risk of fever increases 7–10 days after vaccination in 1–2 year old children [6–12], with MMRV being associated with approximately twice as many fever visits than are same-day, separately administered MMR and varicella vaccines [9,11,12]. An important consequence of fever due to MCV is an increased risk of FS [9,13–21] during the same 7–10 days post-vaccination as fever [9,11,12,18,22].

Clinical features affecting risk for fever following MCV are not well understood. Recent studies found that the risk of fever and seizures after MCV was greater when the vaccine was administered late in the second year (≥15 months of age) versus when administered early in the second year (<15 months) [11,22]. Differential risk for post-vaccination adverse events by age further raises the possibility that in addition to properties inherent to the vaccine, host factors could influence susceptibility to post-vaccine adverse events.

The aims of this study were to identify risk factors associated with developing fever following MCV vaccination, and determine whether some families are more susceptible to fever due to MCV.

2. Methods

2.1. Study population

The Vaccine Safety Datalink (VSD) is a collaboration between the Centers for Disease Control and Prevention and eight integrated healthcare organizations (sites) [23]. This retrospective cohort study included members between ages 10 and 36 months at a first dose of any MCV (i.e. MMR or MMRV) from January 1st, 2000 through December 31st, 2012 in 6 VSD sites. All children were required to be members for at least the month following vaccination to ensure capture of fever after MCV.

We identified fever visits using ICD9 code 780.6* [9,24]. We defined fever due to a MCV as any clinic or emergency department visit with a fever code 7–10 days after a first dose of any MCV (henceforth known as "MCV-associated fever"). We previously showed that MCV-associated fever rate is much higher than the background rate of fever in this age group [9,12]. This current study analyzed all fevers during post-vaccination days 7–10 as if they were due to MCV.

Participating VSD sites were Group Health Cooperative (Washington State), Kaiser Permanente (Colorado, Northern California, Northwest [Oregon/Washington], Southern California), and Marshfield Clinic (Wisconsin). Institutional Review Boards of all participating sites approved this study.

2.2. Statistical analyses

We used Pearson's χ^2 tests and multivariable conditional logistic regression to evaluate factors associated with MCV-associated fever. We used conditional logistic regression to assess histories of medically attended fever and MCV-associated fever among siblings as predictive factors for MCV-associated fever in the child. The conditional logistic regression analyses adjusted for ethnicity/race, and stratified on VSD site and calendar year because fever rates differed by VSD site and calendar year, and some sites exclusively used MMR or MMRV over time. We therefore only compared odds of fever within the same site over the same time period in the same stratum, which improved our estimates' accuracy. Because ethnicity/race adjustment excluded one VSD site due to missing data (Marshfield), we also conducted sensitivity analyses including all children unadjusted for ethnicity/race.

To assess familial clustering of MCV-associated fever, we used a family sub-cohort limited to individuals with 1) at least one sibling with whom they shared the same mother and 2) the sibling received MCV between ages 10 and 36 months. We identified this sub-cohort using the mother's study ID variable in VSD data ("MomId"). We performed a permutation test (unadjusted for covariates) within this family sub-cohort to assess whether sibling pairs were more likely to be concordant for MCV-associated fever than unrelated, random pairs of children [25].

We further refined the family sub-cohort to include only children with previously vaccinated siblings (henceforth named "older" siblings). We performed logistic regression within this refined sub-cohort to assess whether MCV-associated fever in the older sibling predicted MCV-associated fever in the child (Fig. 1A). The outcome was MCV-associated fever in the child and the independent variable was prior MCV-associated fever in the older sibling. We further adjusted this model by including older sibling fever unrelated to MCV (i.e., 15–60 days after MCV) to account for differences between families in healthcare seeking behavior for fever (Fig. 1B).

We also investigated for a specific risk of MCV-associated fevers within families distinct from a general susceptibility to fever and/or seeking care for fever. The outcome was MCV-associated fever in the child and the independent variable was prior MCV-associated fever in the older sibling, adjusting for the number of fever visits prior to vaccination for the child and the number of fever visits 15–60 days after MCV for the older sibling. We hypothesized that adjusting for the child's individual fever susceptibility would minimally change the odds ratio (OR) estimate related to MCV-associated fever because it adjusted for family susceptibility to fever rather than being specifically associated with MCV-associated fever.

To compare and enhance our ability to interpret the models above, we assessed how well older sibling fever unrelated to MCV predicted fever unrelated to MCV in the child. The outcome was fever unrelated to MCV in the child and the independent variable was fevers unrelated to MCV in older siblings, adjusting for the number of fever visits prior to vaccination in the child. We hypothesized that adjusting for additional fevers unrelated to MCV would alter the OR estimate of fever unrelated to MCV in the child because it measured the same fever risk in both the older sibling and in the child (Fig. 1C).

3. Results

The study population consisted of 946,806 individuals who received a first dose of any measles-containing vaccine from 2000 to 2012, 7480 (0.8%) of whom had a medically attended MCV-associated fever. Most children (98%) were ≤24 months of age at vaccination.

Several factors were significantly more common among those with MCV-associated fever (Table 1). Among the 72.3% of children with available ethnicity/race data, MCV-associated fever was significantly less common among Black ($P < 0.0001$) and Other ($P = 0.004$) races. Multivariable stratified logistic regression analysis demonstrated that MCV-associated fever was associated with MMRV instead of MMR vaccine [OR 1.3 95% Confidence Interval (CI) 1.2, 1.5], fever following previous vaccines (OR 1.3 95% CI 1.1, 1.6), any prior fever (OR 1.7 95% CI 1.6, 1.8), prior seizures (OR 2.2 95% CI 1.7, 2.7), and >3 medical visits within 6 months before vaccination (OR 1.7 95% CI 1.6, 1.8). Children with MCV-associated fever were less likely to have missed vaccine-associated well-child visits by age 7 months (OR 0.9 95% CI 0.8, 1.0), and to be black race (OR 0.7 95% CI 0.6, 0.8; Table 2). Estimates from sensitivity analyses unadjusted for ethnicity/race were qualitatively similar.