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Parental risk factors for fever in their children 7–10 days after the first dose of measles-containing vaccines

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ABSTRACT

We evaluated whether parental clinical conditions were associated with fever after a first dose of measles-containing vaccine (MCV) in the child in a cohort study including 244,125 children born in Kaiser Permanente Northern California between 2009 and 2016 who received MCV between ages 1 and 2 years. Each child was linked with his/her mother and father when possible. Parental clinical conditions present before and after their child's birth were identified. We defined fever in the children as clinic and emergency department visits with a fever code 7–10 days after a first dose of MCV ("MCV-associated fever"). We evaluated parental clinical conditions associated with MCV-associated fever using multivariate logistic regression analyses. After adjusting for multiple factors, including healthcare utilization, maternal fever [odds ratio (OR) = 1.19, 95% confidence interval (CI) 1.06–1.32], fever after MCV (OR = 5.90, 95% CI 1.35–25.78), respiratory infections (OR = 1.20, 95% CI 1.10–1.31), migraine (OR = 1.14, 95% CI 1.05–1.24), syncope (OR 1.14, 95% CI 1.01–1.27), and essential thrombocythemia (OR = 1.93, 95% CI 1.15–3.25) were significantly associated with MCV-associated fever. Paternal respiratory infections (OR = 1.15, 95% CI 1.05–1.27), fever associated with respiratory infections (OR = 1.47, 95% CI 1.23–1.76), and vitiligo (OR = 1.63, 95% CI 1.06–2.53) were significantly associated with MCV-associated fever. Parental clinical conditions, specifically fever alone and fever associated with respiratory infection, are associated with fever in their child 7–10 days after MCV.

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Introduction

The first dose of measles-containing vaccine (MCV), either measles-mumps-rubella (MMR) or measles-mumps-rubella-varicella (MMRV) is associated with fever 7–10 days after vaccination in children ages 1–2 years.[1–7] Fever after MCV is associated with higher antibody response,[8] nonetheless, both fever and febrile seizure are considered adverse events following vaccination and can lead to medical visits. Despite the potential immunologic advantage, fever after vaccination may affect the public's perception of vaccine safety and potentially result in parental lack of confidence, concern and reluctance to vaccinate.[9–11] However, a febrile response to infections and vaccines can provide an important immunologic response to antigenic stimuli and thus might be genetically programmed.

Factors affecting risk of fever following MCV are not well understood. In previous studies, we found that fever and febrile seizure following MCV were associated with age at vaccination, with children vaccinated after ages 15 months being at increased risk compared with those vaccinated before ages 15 months.[4] Maternal age at child's birth and race have also been associated with child's fever or febrile seizure after MCV.[12,13]

Increasingly, evidence suggests a role for genetics in risk for both febrile seizure and fever after MCV. A genome-wide association study in Denmark found two loci distinctly associated with MMR vaccine-related febrile seizures.[14] More recently, we found that children with siblings who had fever 7–10 days after MCV were three times more likely to also have fever 7–10 days after MCV.[12] Familial clustering of fever and febrile seizures after a MCV suggest that genetic factors may also play a role in the occurrence of fever after receiving a MCV.

In order to explore familial immune response patterns, we evaluated whether parental clinical conditions could predict fever in their child 7–10 days after a first dose of MCV. Establishing which parental clinical conditions are associated with fever in their children may provide information regarding the genetic programming for an individual's immune response to antigens and point to potential clinical response patterns and disease susceptibility.

Materials and methods

Study population

The study setting was Kaiser Permanente Northern California (KPNC), an integrated healthcare delivery organization that provides comprehensive care to approximately 4 million members. Members receive almost all medical care at KPNC-owned facilities, including clinics, hospitals, pharmacies, and

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laboratories. KPNC databases capture detailed information on all medical services, including vaccinations and laboratory tests, as well as on enrollment and demographics. KPNC members are similar to the broad catchment population in Northern California in terms of sociodemographic characteristics, except the extremes of income distribution are underrepresented.[15] Members receive all their routine vaccinations free of charge.

The present study included a cohort of children born at KPNC between 2009 and 2016 who received a MCV between ages 1–2 years and remained health plan member for at least 60 days after vaccination. Each child was linked with his/her mother and father, where possible, through the child's birth records for the mother and KPNC membership data and insurance account information for the father.

Outcome

The main outcome was fever in the child 7–10 days after a first dose of MCV (henceforth known as "MCV-associated fever"), identified using international classification of disease (ICD) 9 or 10 codes, or recorded body temperature during a clinic or emergency department visit.

Exposure: parental clinical conditions

Parental (maternal and paternal) clinical conditions were identified by using ICD 9 or 10 codes in both outpatient and inpatient settings. We initially identified parental clinical conditions using the "problem" list which is a set of clinical conditions for which care had been consistently sought, and subsequently included ICD codes associated with these conditions. Conditions that were present in less than 1 in 1000 mothers, as well as conditions that, when comparing mothers of children with fever with those without fever, had a prevalence ratio between 0.8 and 1 were excluded. We also excluded maternal conditions/diagnoses and procedures for which there was no biologic plausibility related to child's fever (e.g., trauma-related visits, ultrasounds, or prenatal visits).

To further investigate the genetic basis of MCV-associated fever, we explored whether parental clinical conditions were also present in their children before they received MCV and whether these conditions were also associated with MCV-associated fever using the same criteria used in mothers. Children's clinical conditions were identified using the same ICD codes used to identify parental clinical conditions.

Statistical analysis

Comparing children who had MCV-associated fever with children who did not have MCV-associated fever, we assessed the proportion of maternal clinical conditions present any time before and after their child's birth, as well as clinical conditions in children any time before the first MCV. We used chi square test for categorical variables and a T test for continuous variables. Maternal and children clinical conditions that were statistically significant at $p \leq 0.05$ in the bivariate analyses were included in multivariate logistic regression models to estimate the odds ratios of MCV-associated fever. We adjusted our results for socio-demographic factors and healthcare seeking behavior, defined by the number of ER or outpatient visits for the child between ages 7 and 12 months before the receipt of MCV. We conducted the same analysis among the subgroup of children for whom we had paternal information.

All analyses were conducted using SAS, version 9.4 (SAS Institute, Inc., Cary, North Carolina). The study was approved by the KPNC Institutional Review Board with a waiver of written informed consent because the study had no direct contact with study participants.

Results

The study included 244,125 children, who were linked to 192,253 mothers (100% of children) and 118,046 fathers (59% of children). There were 3750 children (1.54%) who had MCV-associated fever. Overall, there was no difference between parental race or age distribution between children who had fever after MCV and those who did not have fever. As we previously reported, this study confirmed that children with MCV-associated fever were more likely to be male (53.92% vs. 46.10%, p = .001), and to have had more than two clinic visits between ages 7 and 12 months (53.17% vs. 36.78%, p<0.001). Children with MCV-associated fever were more likely than children without MCV-associated fever to be preterm (9.1% vs. 7.3%, $p < 0.001$; Table 1).

In bivariate analyses, we identified 29 maternal, 13 paternal clinical conditions, and 9 in children that were significantly associated with fever (Table 2).

In a multivariate analysis, maternal fever [adjusted odds ratios (aOR) = 1.19, 95% confidence interval (CI) 1.06–1.32], maternal fever after MCV (aOR = 5.90, 95% CI 1.35–25.78). respiratory infections (aOR = 1.20, 95% CI 1.10–1.31), migraine (aOR = 1.14, 95% CI 1.05–1.24), syncope (aOR 1.14, 95% CI 1.01–1.27), and essential thrombocythemia (aOR = 1.93, 95% CI 1.15–3.25) were significantly associated with MCV-associated fever in their children (Table 3). Although not statistically significant, Addison disease (aOR = 2.90, 95% CI 0.90–9.32) had an elevated point estimate (Table 3).

Among the subgroup of children with paternal information, paternal respiratory infections (aOR = 1.15, 95% CI 1.05–1.27), fever associated with respiratory infections (aOR = 1.47, 95% CI 1.23–1.76), and vitiligo (aOR = 1.63, 95% CI 1.06–2.53) were significantly associated with MCV-associated fever in their children (Table 4).

Children who were diagnosed with febrile seizure (aOR = 3.08, 95% CI 2.44–3.90), respiratory infections (aOR = 1.30, 95% CI 1.20–1.41), respiratory failure (aOR = 2.83 (1.44–5.59), sleep disorder (aOR = 1.53, 95% CI 1.14–2.05), or gastrointestinal diseases (aOR = 1.27, 95% CI 1.17–1.38) before the first MCV were at increased risk of MCV-associated fever. Finally, children who had MCV-associated fever were more likely to have had more than two clinic visits between ages 7 and 12 months (aOR = 1.74, 95% CI 1.48–2.05) (Table 5).

Table 1. Characteristics of the study population. Children born 2009–2016. Kaiser Permanente Northern California.

	Children with fever (7–10 days) after MCV N = 3750 n (%)	Children without fever (7–10 days) after MCV N = 240375 n (%)	p value
Child's sex			0.001
Male	2022 (53.92)	122472 (50.95)	
Female	1728 (46.08)	117903 (49.05)	
Gestational age at birth			<0.001
<37 weeks (preterm)	340 (9.07)	17423 (7.25)	
≥37 weeks	2934 (78.24)	191715 (79.76)	
Missing gestational age	476 (12.69)	31240 (13.00)	
>2 visits between ages 7–12 months	1994 (53.17)	88412 (36.78)	<0.001
Maternal race			<0.001
Asian	904 (24.11)	58584 (24.37)	
Black	193 (5.15)	15371 (6.39)	
Pacific Islander	26 (0.69)	1968 (0.82)	
White	1298 (34.61)	93947 (39.08)	
Multiracial	207 (5.52)	13211 (5.50)	
Native American	19 (0.51)	979 (0.41)	
Unknown	1103 (29.41)	56318 (23.43)	
Maternal age at delivery (years)			0.007
<18	21 (0.56)	1400 (0.58)	
18–25	474 (12.64)	27996 (11.65)	
25–30	985 (26.27)	63009 (26.21)	
30–35	1400 (37.33)	86173 (35.85)	
35–40	672 (17.92)	48835 (20.32)	
≥40	198 (5.28)	12965 (5.39)	
Paternal race			<0.001
Asian	502 (13.39)	30692 (12.77)	
Black	94 (2.51)	7531 (3.13)	
Pacific Islander	16 (0.43)	1705 (0.71)	
White	803 (21.41)	59817 (24.88)	
Multiracial	49 (1.31)	3137 (1.31)	
Native American	10 (0.27)	664 (0.28)	
Unknown	709 (18.91)	38145 (15.87)	
Missing paternal information	1567 (41.80)	98684 (41.10)	
Paternal age at infant birth (years)			0.04
<18	2 (0.05)	41 (0.02)	
18–25	80 (2.13)	4957 (2.06)	
25–30	354 (9.44)	24647 (10.25)	
30–35	794 (21.17)	48903 (20.34)	
35–40	594 (15.84)	37028 (15.40)	
≥40	359 (9.57)	26115 (10.86)	
Missing paternal information	1567 (41.80)	98687 (41.10)	

MCV = measles containing vaccine

Table 2. Crude association between parental, child clinical conditions and child fever 7–10 days after Measles Containing Vaccines (MCV). Kaiser Permanente Northern California.

Risk factors	Child fever (7–10 days) after MCV N = 3721 n (%)	Child without fever (7–10 days) after MCV N = 238588 n (%)	p value
Maternal clinical conditions			
Any fever	444 (11.93)	20,836 (8.73)	<0.001
Maternal fever after MCV	2 (0.05)	18 (0.01)	0.04
Fever associated with respiratory infection	253 (6.80)	12,612 (5.29)	<0.001
Hypertension	285 (7.66)	15,392 (6.45)	0.003
Asthma	886 (23.81)	49,420 (20.71)	<0.001
Diabetes	124 (3.33)	6,442 (2.70)	0.02
Any autoimmune disease	724 (19.46)	43,791 (18.35)	0.08
Addison disease	3 (0.08)	59 (0.02)	0.03
Alopecia	324 (8.71)	16,990 (7.12)	<0.001
Respiratory infections	3,011 (80.92)	178,438 (74.79)	<0.001
Allergy	2,181 (58.61)	128,786 (53.98)	<0.001
Anemia	826 (22.20)	48,290 (20.24)	0.003
Dizziness	796 (21.39)	41,823 (17.53)	<0.001
Type 2 diabetes	121 (3.25)	6,376 (2.67)	0.03
Dysuria	701 (18.84)	36,243 (15.19)	<0.001
Endometritis	140 (3.76)	7,506 (3.15)	0.03
Herpes	523 (14.06)	30,119 (12.62)	0.009
Hyperlipidemia	212 (5.70)	11,769 (4.93)	0.03
Liver disease	129 (3.47)	6,110 (2.56)	<0.001
Migraines	903 (24.27)	45,744 (19.17)	<0.001
Obesity	1,186 (31.87)	70,250 (29.44)	0.001
Pain	741 (19.91)	37,967 (15.91)	<0.001
Polycystic ovarian syndrome	159 (4.27)	7,946 (3.33)	0.002
Arrhythmia	122 (3.28)	5,646 (2.37)	<0.001
Sleep disorder	451 (12.12)	25,924 (10.87)	0.01
Syncope	354 (9.51)	17,606 (7.38)	<0.001
Essential thrombocythemia	15 (0.40)	442 (0.19)	0.002
Vitamin deficiency	282 (7.58)	14,100 (5.91)	<0.001
Gastrointestinal disease	1,319 (35.45)	70,049 (29.36)	<0.001
Paternal clinical conditions[a]			
Any fever	192 (8.85)	8,876 (6.29)	<0.001
Fever associated with respiratory infections	166 (7.65)	6,299 (4.46)	<0.001
Any autoimmune diseases	15,967 (11.14)	277 (12.77)	0.02
Alopecia	105 (4.84)	5,343 (3.79)	0.01
Vitiligo	21 (0.97)	759 (0.54)	0.007
Respiratory infections	1,531 (70.59)	91,828 (65.07)	<0.001
Hyperlipidemia	464 (21.39)	26,436 (18.73)	0.002
Pain	299 (13.79)	17,409 (12.34)	0.04
Disease of pancreas	15 (0.69)	592 (0.42)	0.05
Sleep disorder	379 (17.47)	22,363 (15.85)	0.04
Vitamin deficiency	77 (3.55)	3,930 (2.78)	0.03
Thyroid disease	10 (0.46)	327 (0.23)	0.03
Gastrointestinal disease	570 (26.28)	33,658 (23.85)	0.009
Child clinical conditions before MCV			
Febrile seizure	77 (2.05)	1,285 (0.53)	<0.001
Asthma	182 (4.85)	7,729 (3.22)	<0.001
Epilepsy	13 (0.35)	415 (0.17)	0.01
Respiratory infections	2,648 (70.61)	141,162 (58.73)	<0.001
Allergy	503 (13.41)	26,013 (10.82)	<0.001
Herpes	118 (3.15)	5,317 (2.21)	<0.001
Respiratory failure	9 (0.24)	138 (0.06)	<0.001
Sleep disorder	47 (1.25)	1,552 (0.65)	<0.001
Gastrointestinal disorders	768 (20.48)	34,759 (14.46)	<0.001

[a]Paternal information was available for 118,046 children.

Discussion

In this study of more than 244,000 children, we found that any maternal fever, fever associated with MCV, respiratory infections, migraines, syncope, and essential thrombocythemia were significantly associated with MCV-associated fever in their children. Paternal respiratory infections, fever associated with respiratory infections and vitiligo were also significantly associated with MCV-associated fever. Overall, these results suggest that parental clinical conditions, specifically fever alone, fever associated with respiratory infection, and some autoimmune conditions were associated with fever 7–10 days after MCV in their child.

The present findings extend our previous finding that MCV-associated fever clusters in families.[12] In our previous study, we found that children whose siblings had fever after MCV were at increased risk of fever themselves after MCV. In our current study, we found an association between MCV-associated fever in the child and parents who were diagnosed

Table 3. Adjusted association between maternal clinical conditions and fever in the child 7–10 days after measles containing vaccine. Kaiser Permanente Northern California.

Maternal clinical conditions	Adjusted odds ratios (95% CI)
Any fever	**1.19 (1.06–1.32)**
Maternal fever after MCV	**5.90 (1.35–25.78)**
Respiratory infections	**1.20 (1.10–1.31)**
Addison disease	2.90 (0.90–9.32)
Alopecia	1.05 (0.93–1.18)
Dysuria	1.08 (1.00–1.18)
Herpes	1.04 (0.95–1.15)
Hyperlipidemia	1.00 (0.87–1.17)
Liver disease	1.17 (0.98–1.40)
Migraine	**1.14 (1.05–1.24)**
Arrhythmia	1.21 (1.00–1.45)
Syncope	**1.14 (1.01–1.27)**
Essential thrombocythemia	**1.93 (1.15–3.25)**
Gastrointestinal disease	1.08 (1.00–1.16)

Results were also adjusted for maternal race/ethnicity, age, child sex, child's clinical conditions, and number of child visits for fever before receipt of measles containing vaccine. Analysis included N = 244,128 children linked to their mothers (N = 192,253).

Table 4. Adjusted association between paternal clinical conditions and fever in the child 7–10 days after measles containing vaccine. Kaiser Permanente Northern California.

Paternal clinical conditions	Adjusted odds ratios (95% CI)
Any fever	1.15 (0.98–1.36)
Respiratory infections	**1.15 (1.05–1.27)**
Fever associated with respiratory infection	**1.47 (1.23–1.76)**
Hyperlipidemia	1.10 (0.99–1.23)
Alopecia	1.17 (0.96–1.43)
Vitiligo	**1.63 (1.06–2.53)**

Results were adjusted for paternal race/ethnicity, age, child's clinical conditions, and number of visits for fever for children before receipt of measles containing vaccine. Analysis included N = 118,046 children on whom we had mothers and father's information. child's clinical conditions

Table 5. Association between child clinical conditions and fever in the child 7–10 days after measles containing vaccine. Kaiser Permanente Northern California.

Child clinical conditions before MCV	Adjusted odds ratios (95% CI)
Febrile seizure	**3.08 (2.44–3.90)**
Asthma	1.10 (0.95–1.29)
Respiratory infections	**1.30 (1.20–1.41)**
Allergy	1.07 (0.97–1.18)
Herpes	1.20 (1.00–1.45)
Respiratory failure	**2.83 (1.44–5.59)**
Sleep disorder	**1.53 (1.14–2.05)**
Gastrointestinal disorders	**1.27 (1.17–1.38)**
Preterm (gestational age <37 weeks)	**1.15 (1.03–1.29)**
> 2 visits between ages 7 and 12 months	**1.74 (1.48–2.05)**

Results were also adjusted for race/ethnicity, age, and sex. Analysis included N = 244,128 children.

at any time with any fever and fever after infections. We also identified an association in the children between having fever and respiratory infections during the first year of life and being more likely to have fever after MCV. Together, these studies provide additional support to the hypothesis that there is a genetic basis for developing fever 7–10 days after MCV.

Immune reaction to vaccines depends on multiple factors, including host demographic factors such as age, sex, race as well genetic predisposition. Several previous studies reported an association between genetic and immune response to measles vaccines. About 10% of children do not develop a sufficient antibody response following MMR vaccine.[16] An early twin study reported that genetic variance in antibody level following measles vaccine was 0.49 and had a heritability of 88.5%.[17] Further studies have found associations between human leukocyte antigen alleles and immune responses to measles vaccine.[18,19] A large combined analysis of five clinical trials which evaluated the immunogenicity and safety of MMRV, and separate MMR and varicella vaccines detected an association between postvaccination fever and higher immune responses. The combined analysis found that the geometric mean of antibody titers to measles were higher in 1- to 2-year-old subjects who had a fever when compared with those subjects without fever, regardless of the measles vaccine type.[20] Additional studies have identified gene polymorphisms in key receptors of the innate immune system, including measles cellular receptors and viral pattern recognition receptors, as influencing measles vaccine responses.[21–27] Our study result that fever 7–10 days after MCV was associated with a history of having fever with a respiratory infection in both parents and children and vitiligo in fathers suggests that children's risk for MCV-associated fever may be generally related to genetic influences on familial immune responses. These patterns point to a specific immune tendency that appears affected by genetics factors and helps to establish a mechanism for future studies.

Our results should be interpreted with cautions. While some clinical conditions like infections or autoimmune conditions may be related to genetic predisposition, we do not know about how to interpret other association like maternal arrhythmia, migraine, or essential thrombocythemia with child fever after MCV. Our goal was to identify parental clinical conditions that might be associated with fever in the child after the first MCV and we found several clinical conditions. More studies are needed to confirm these findings and to investigate biological plausibility for each association. Although we carefully adjusted the results for health seeking behaviors by the number of child visits before vaccination, it is possible that the results were confounded and maybe explained by parental healthcare seeking behaviors. Furthermore, we did not confirm any of the clinical conditions via medical record reviews because of the large seize of the study population. In addition, the fever cases were limited to individuals that sought medical attention which likely represented more serious fevers. This study therefore missed mild fever and clinical conditions that did not come to medical attention. Finally, given the large screening nature of this study, our results should be considered preliminary and followed up with a more in-depth investigation of the clinical conditions we identified here.

Despites these limitations, the study has several strengths. This study was the first to investigate whether parental clinical conditions may predict fever in their child after MCV. In this study, we had access to both parents' and child's medical records which allowed us to identify clinical factors for both parents and child. Because we did not hypothesize *a priori* about the association between any specific clinical conditions and child fever after MCV, we captured all clinical conditions potentially associated with increased risk. In addition, our large sample size allowed us to detect differences that may

not have been evident in a smaller population. Finally, because we used medical record data, our results were not subject to recall bias.

Conclusion

Parental clinical conditions, specifically fever alone, fever associated with respiratory infection and immunological conditions were associated with fever in their child 7–10 days after MCV. The results in this study suggest that risk for fever is related to genetic influences on familial immune responses. Additional studies are needed to confirm our preliminary findings of an association between parental clinical factors and fever in the child after receipt of measles containing vaccine.

Disclosure of potential conflicts of interest

Dr. Klein has received research grant support from Sanofi Pasteur, Novartis, GSK, Merck, MedImmune, Pfizer, and Protein Sciences for unrelated studies. For the remaining authors none were declared.

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