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Original Contribution

Measles-Mumps-Rubella Vaccination and Asthma-like Disease in Early Childhood

Anders Hviid and Mads Melbye

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The authors evaluated the association between receipt of measles-mumps-rubella (MMR) vaccine and asthma-like disease in early childhood in a Danish nationwide cohort study ($N = 871{,}234$). Two outcomes were included: hospitalizations with asthma diagnoses and use of anti-asthma medications (for a subset of the cohort only). Poisson regression was used to estimate rate ratios according to vaccination status. MMR-vaccinated children were less often hospitalized with an asthma diagnosis (rate ratio (RR) = 0.75, 95% confidence interval (CI): 0.73, 0.78) and used fewer courses of anti-asthma medication (RR = 0.92, 95% CI: 0.91, 0.92) than unvaccinated children. This ''protective'' effect of MMR vaccine was more pronounced for hospitalizations with severe asthma diagnoses (status asthmaticus: RR = 0.63, 95% CI: 0.49, 0.82) and use of medication that was highly specific for asthma (long-acting β2-agonist inhalant: RR = 0.68, 95% CI: 0.63, 0.73). MMR vaccine was not negatively associated with anti-asthma medications often used for wheezing illnesses in early childhood (systemic β2-agonist: RR = 1.02, 95% CI: 1.01, 1.02). These results are compatible not with an increased risk of asthma following MMR vaccination but rather with the hypothesis that MMR vaccination is associated with a reduced risk of asthma-like disease in young children.

asthma; measles-mumps-rubella vaccine; vaccination; vaccines

Abbreviations: ATC, anatomic-therapeutic-chemical; CI, confidence interval; ICD, *International Classification of Diseases*; MMR, measles-mumps-rubella; UR, uses-to-users ratio.

The ''hygiene hypothesis'' suggests that early childhood exposure to microbial agents protects against atopic disease through an immunomaturing effect (1, 2). In this context, common childhood vaccines are of obvious interest, and a number of hypotheses linking childhood vaccines and atopy have been proposed (3). One suggestion is that vaccines indirectly increase the risk of atopy by preventing ''beneficial'' infections in early childhood (4). Another suggestion is that vaccines themselves have direct atopy-promoting effects—for example, by increasing immunoglobulin E levels (5) or by unbalancing the immune system (6). The majority of analytical studies have not been able to confirm an adverse effect of childhood vaccination on atopic disease, and some have even indicated a protective effect of vaccines (7, 8). However, large, well-controlled prospective studies are few, and given the importance of national vaccination programs and the possibility of vaccine safety scares (9), further research into the association between vaccines and atopic diseases is needed.

We evaluated the hypothesis of an increased risk of asthma-like disease after measles-mumps-rubella (MMR) vaccination in Denmark in a nationwide historically prospective cohort study. We evaluated both the association between MMR vaccination and hospitalizations with asthma diagnoses in early childhood and the association between MMR vaccination and use of anti-asthma medication in early childhood.

MATERIALS AND METHODS

Since April 1968, vital records on all people living in Denmark have been kept and updated daily in the Danish Civil Registration System (10). Each individual is indexed by a unique personal identification number that is also used

Correspondence to Dr. Anders Hviid, Department of Epidemiology Research, Statens Serum Institut, Artillerivej 5, DK-2300 Copenhagen S, Denmark (e-mail: aii@ssi.dk).

in other national registries. From the Civil Registration System, we obtained a cohort of all children born in Denmark from January 1, 1991, through December 31, 2003. Using the unique personal identification number, we were able to individually link information on MMR vaccination, hospitalizations with asthma diagnoses, use of anti-asthma medication (only available for children born since 1995), and potential confounders and effect modifiers to the children in the cohort.

MMR vaccination

MMR vaccination was introduced in the Danish childhood vaccination program in 1987. The MMR vaccine used in Denmark contains live attenuated Moraten measles virus, Jeryl Lynn mumps virus, and Wistar RA 27/3 rubella virus and is administered at 15 months and 12 years of age. Dates of vaccination were obtained from the National Board of Health. In Denmark, only general practitioners administer routine childhood vaccines, and the practitioners are reimbursed when reporting these vaccinations to the National Board of Health. The National Board of Health has kept a register of these reports since 1990.

Hospitalization with asthma diagnoses

Information on inpatient hospitalization with asthma diagnoses during the period from January 1, 1992, to December 31, 2004, was obtained from the Danish National Hospital Register (11). From 1990 to 1993, the *International Classification of Diseases*, Eighth Revision (ICD-8), was used, and from 1994 to 2001, the *International Classification of Diseases*, Tenth Revision (ICD-10), was used. We included the following categories of asthma diagnoses in our study: code 493.xx (ICD-8) and codes J45.x and J46.x (ICD-10). Severe asthma (status asthmaticus; ICD-8 code 493.01 and ICD-10 code J46.9) was further considered as a separate outcome (12).

Anti-asthma medication

Information on use of anti-asthma medication during the period from January 1, 1996, to December 31, 2004, was obtained from the Danish Prescription Drug Database. This registry includes detailed individual-level information on all prescriptions filled at Danish pharmacies, as well as aggregated data on hospital medication use; these are the only 2 places where prescription medication can be legally obtained in Denmark. To ensure that people are subsidized according to the total amount of money spent on prescribed medication, as dictated by Danish law, the Danish Prescription Drug Database has been built as an interactive system, where the information keyed in at the local pharmacy is immediately forwarded to a central registry at the Danish Medicines Agency. Here the patient's records are compiled for the previous year, and information is instantly returned to the pharmacy with the calculated reduction in price which should be given to the person. Therefore, the registry is considered to be of very high quality, with coverage that is virtually complete for all medication prescribed in Denmark. Information on individual-level prescriptions includes the date on which the prescription was filled and the anatomic-therapeutic-chemical (ATC) code. For analytical purposes, we considered the date of filling the prescription to be the date of use. The classes of anti-asthma medication used in this study and their ATC codes were: glucocorticoid inhalants (ATC code R03BA), short-acting β2-agonist inhalants (ATC codes R03AC02, R03AC03, and R03AC04), long-acting β2-agonist inhalants (ACT codes R03AC12 and R03AC13), systemic β2-agonists (ACT code R03CC), and other types of anti-asthma medication (all other ATC codes under R03).

Statistical analysis

Children in the cohort contributed person-time to follow-up from 1 year of age until death, disappearance/emigration, age 5 years, or December 31, 2004, whichever occurred first. Recurrence of outcome events was allowed—that is, neither asthma hospitalization nor use of anti-asthma medication terminated follow-up. To reduce unnecessary computational complexity, we counted only the first 20 events for each individual. The resulting incidence rates for asthma hospitalizations and use of anti-asthma medication were analyzed with Poisson regression (log-linear regression on the incidences using the logarithm to the follow-up time as offset), producing estimates of incidence rate ratios (hereafter called rate ratios) according to MMR vaccination status (13). MMR vaccination status was considered a time-varying variable—that is, individual children could contribute person-time as both unvaccinated and vaccinated individuals. We estimated the possible effect of MMR vaccination on asthma through 1) rate ratios comparing vaccinated children with unvaccinated children, 2) rate ratios comparing vaccinated children with unvaccinated children in subgroups defined by factors such as gender or birth weight, and 3) rate ratios comparing vaccinated children with unvaccinated children according to age at vaccination ($<$15, 15–18, 19–22, 23–26, or $\geq$27 months).

Possible confounding and effect-modifying factors

We adjusted MMR rate ratios for age and calendar period. Further information on possible confounding factors that were also adjusted for and possible MMR vaccination effect modifiers—child's sex, child's place of birth, child's birth weight, mother's country of birth, mother's age at birth of child, birth order, and infant vaccine compliance—was obtained from the Civil Registration System, the Danish Medical Birth Registry (14), and the National Hospital Register. For asthma hospitalization, we further included adjustment for infant hospitalization propensity. For study of anti-asthma medication, we further included information on both mother's and father's income in the year preceding the year of birth.

RESULTS

A total of 871,234 children (among whom 85% were MMR-vaccinated before the end of follow-up) were

included in the cohort. During 2,926,406 person-years of follow-up, we identified 26,880 asthma hospitalizations among 17,885 children. Status asthmaticus accounted for 406 hospitalizations among 354 children. The follow-up of 15,914 children was prematurely terminated because of death ($n = 5,455$), emigration ($n = 10,159$), or disappearance ($n = 300$).

A total of 600,938 children (among whom 84% were MMR-vaccinated before the end of follow-up) had information on prescription medication use. During 1,858,199 person-years of follow-up, we identified 833,424 uses of anti-asthma medication among 248,907 users (uses-to-users ratio (UR), 3.35). Steroid inhalants accounted for 315,965 uses among 67,731 users (UR, 4.66); short-acting β2-agonist inhalants accounted for 211,103 uses among 78,668 users (UR, 2.68); long-acting β2-agonist inhalants accounted for 5,445 uses among 1,363 users (UR, 4.00); systemic β2-agonists accounted for 431,672 uses among 203,865 users (UR, 2.12); and other anti-asthma medications accounted for 6,482 uses among 1,498 users (UR, 4.33). Note that when adding the number of uses across medication categories, this number exceeds the uses of ''all anti-asthma medication,'' a consequence of the 20-event counting limit per person described above in Materials and Methods. The follow-up of 12,552 children was prematurely terminated because of death ($n = 4,681$), emigration ($n = 7,710$), or disappearance ($n = 161$).

In Table 1, we present rate ratios for all asthma hospitalizations according to MMR vaccination status. We found that vaccination protected children against hospitalization, corresponding to a 25% reduction in the ''all asthma hospitalizations'' rate and a 37% reduction in the ''severe asthma hospitalization'' rate. The protective effect against all asthma hospitalizations was greatest in the youngest children, in those with the longest time spent at the hospital in infancy, in girls, in low birth weight children, in children with 1 older sibling, and in children living in rural areas. Including only asthma diagnoses in the construction of infant hospitalization propensity yielded similar rate ratios. The protective effect was greatest (rate ratio = 0.59, 95% confidence interval (CI): 0.55, 0.64) among children who had spent the most time (18 days–1 year) at the hospital for asthma in infancy, as compared with those who had spent little time ($\leq$1 day) at the hospital for asthma (rate ratio = 0.83, 95% CI: 0.80, 0.88). We further analyzed the MMR effect according to age at vaccination: Rate ratios were 0.75 (95% CI: 0.71, 0.79), 0.74 (95% CI: 0.71, 0.76), 0.84 (95% CI: 0.92, 1.01), 0.92 (95% CI: 0.84, 1.01), and 0.90 (95% CI: 0.81, 1.01) for vaccination at ages $<$15 months, 15–18 months, 19–22 months, 23–26 months, and $\geq$27 months, respectively.

In Table 2, we present rate ratios for use of anti-asthma medication according to MMR vaccination status. We found that vaccination was associated with less use of anti-asthma medication, corresponding to an 8% reduction in ''all anti-asthma medication'' use. This effect varied according to category of medication, from a 39% reduction in the use of ''other anti-asthma medications'' to no reduction in the use of systemic β2-agonists. The reduced use of all anti-asthma medication was greatest in the youngest children, in those with all infant vaccinations, in those with less affluent fathers, in boys, in children with no older siblings or only 1 older sibling, and in children living in rural areas. We further analyzed the MMR effect according to age at vaccination. These incidence rate ratios were 0.94 (95% CI: 0.93, 0.95), 0.91 (95% CI: 0.90, 0.91), 0.98 (95% CI: 0.97, 0.99), 1.00 (95% CI: 0.98, 1.01), and 1.01 (95% CI: 0.99, 1.03) for vaccination at ages $<$15 months, 15–18 months, 19–22 months, 23–26 months, and $\geq$27 months, respectively.

Further analyses were conducted using only the first asthma outcomes. In this case, follow-up was terminated after the first outcome in children with asthma outcomes. This included termination of follow-up for children with a first asthma outcome before vaccination or before 1 year of age (the start of follow-up). In this case, the asthma hospitalization rate ratio was 0.80 (95% CI: 0.77, 0.83). The rate ratio for first use of anti-asthma medication was 0.93 (95% CI: 0.92, 0.94).

Information on maternal smoking during pregnancy was available for a subgroup of children in the cohort. Among children born since 1994 whose mothers smoked during pregnancy, the rate ratio for ''all asthma hospitalizations'' was 0.69 (95% CI: 0.65, 0.72), as compared with 0.82 (95% CI: 0.78, 0.85) among children whose mothers had not smoked during pregnancy and 0.81 (95% CI: 0.72, 0.90) among children whose mothers had an unknown or unreported status for smoking during pregnancy.

Among approximately 100,000 children in the cohort who also participated in the Danish National Birth Cohort study (15), we analyzed receipt of MMR vaccine according to parental asthma and atopy. Receipt of MMR vaccine was 92% and was independent of parental asthma or parental atopy.

DISCUSSION

We evaluated the association between MMR vaccination and asthma-like disease in early childhood. Our results show that MMR-vaccinated children are less often hospitalized with asthma diagnoses and use less anti-asthma medication than unvaccinated children. This effect was most pronounced among the youngest children and children who were vaccinated age-appropriately.

At birth, the immune system is immature. The ''hygiene hypothesis'' states that infections in early childhood play an important role in maturation of the immune system and consequently the risk of developing atopy (1, 2). The hygiene hypothesis is well supported epidemiologically, but the immunologic framework remains to be established (16, 17). Measles infection has been associated with reduced risk of atopy, although findings have been contrasting (18, 19). The MMR vaccine contains live attenuated measles virus and elicits an immune response which is similar to that of natural measles infection, with both cellular and humoral immune responses.

A limited number of studies have evaluated the association between MMR vaccination and asthma and other atopic diseases. The majority of these investigators have reported no association, and a few have reported a negative association (7, 8, 20). One of the previously most extensive analytical

TABLE 1. Rate Ratios for Asthma Hospitalization According to Measles-Mumps-Rubella Vaccination Status in Danish Children, 1992–2004

	Asthma			Status Asthmaticus		
	RR[a]	95% CI	*P* Value[b]	RR[a]	95% CI	*P* Value[b]
MMR vaccination						
Yes	0.75	0.73, 0.78		0.63	0.49, 0.82	
No	1.00	Referent		1.00	Referent	
MMR vaccination (yes vs. no) according to:						
Age, years			0.0483			0.7432
1	0.73	0.70, 0.77		0.56	0.38, 0.83	
2	0.74	0.70, 0.79		0.60	0.37, 0.98	
3	0.79	0.73, 0.86		0.75	0.40, 1.39	
4	0.85	0.76, 0.95		0.81	0.41, 1.58	
Infant vaccine compliance			0.3916			0.1524
All vaccines received	0.76	0.73, 0.79		0.74	0.53, 1.02	
At least 1 missed	0.75	0.72, 0.78		0.54	0.38, 0.76	
No vaccines received	1.08	0.65, 1.81		—[c]		
Hospitalization propensity in infancy			<0.0001			0.2353
18 days–1 year	0.67	0.63, 0.70		0.66	0.45, 0.97	
2–17 days	0.77	0.74, 0.80		0.56	0.41, 0.76	
≤1 day	0.88	0.82, 0.95		0.98	0.52, 1.86	
Sex			0.0371			0.0072
Male	0.77	0.74, 0.80		0.79	0.58, 1.08	
Female	0.73	0.69, 0.76		0.45	0.31, 0.64	
Birth weight, g			0.0114			0.6083
≤2,499	0.70	0.65, 0.76		0.57	0.30, 1.10	
2,500–3,999	0.75	0.72, 0.77		0.61	0.46, 0.81	
≥4,000	0.81	0.76, 0.87		0.81	0.46, 1.41	
Birth order			<0.0001			0.0508
1	0.78	0.75, 0.82		0.66	0.46, 0.93	
2	0.70	0.67, 0.73		0.47	0.32, 0.68	
≥3	0.80	0.76, 0.85		0.96	0.59, 1.56	
Place of birth			<0.0001			0.4987
Capital, including suburbs	0.98	0.92, 1.04		0.72	0.46, 1.14	
City/town	0.72	0.69, 0.75		0.55	0.39, 0.78	
Rural area	0.69	0.66, 0.72		0.69	0.47, 1.00	

Abbreviations: CI, confidence interval; MMR, measles-mumps-rubella; RR, rate ratio.

[a] Adjusted for age, calendar period, hospitalization propensity in infancy, birth weight, place of birth, mother's country of birth, infant vaccine compliance, birth order, maternal age at birth, and child's sex.

[b] *P* value from test for homogeneity.

[c] Not estimable because there were no cases.

studies was conducted by DeStefano et al. (21). In a US cohort including 18,407 cases, the authors reported a relative risk of asthma of 0.97 (95% CI: 0.91, 1.04) for MMR vaccination. In a subanalysis, the authors took into account the possible influence of medical-care utilization bias and reported a relative risk of 0.80 (95% CI: 0.61, 1.04) for children with at least 2 medical-care encounters during the first year of life. Even though statistical significance was not achieved, this reduced relative risk compares well with our results. Roost et al. (22) conducted a cross-sectional study among approximately 1,500 Swiss children with self-reported information on asthma. Both natural measles and

TABLE 2. Rate Ratios for Use of Anti-Asthma Medication According to Measles-Mumps-Rubella Vaccination Status in Danish Children, 1996–2004

	All Anti-Asthma Medication			Steroid Inhalant			Short-acting β2-Agonist Inhalant			Long-acting β2-Agonist Inhalant			Systemic β2-Agonist			Other Anti-Asthma Medication		
	RR[a]	95% CI	*P* Value[b]	RR[a]	95% CI	*P* Value[b]	RR[a]	95% CI	*P* Value[b]	RR[a]	95% CI	*P* Value[b]	RR[a]	95% CI	*P* Value[b]	RR[a]	95% CI	*P* Value[b]
MMR vaccination																		
Yes	0.92	0.91, 0.92		0.84	0.83, 0.84		0.78	0.77, 0.79		0.68	0.63, 0.73		1.02	1.01, 1.02		0.61	0.58, 0.65	
No	1.00	Referent		1.00	Referent		1.00	Referent		1.00	Referent		1.00	Referent		1.00	Referent	
MMR vaccination (yes vs. no) according to:																		
Age, years			<0.0001			<0.0001			<0.0001			0.0300			<0.0001			<0.0001
1	0.90	0.89, 0.91		0.80	0.79, 0.81		0.75	0.74, 0.77		0.69	0.60, 0.80		1.00	0.99, 1.01		0.60	0.53, 0.67	
2	0.92	0.91, 0.93		0.84	0.82, 0.86		0.77	0.75, 0.78		0.60	0.53, 0.69		1.04	1.02, 1.06		0.52	0.47, 0.57	
3	0.96	0.94, 0.98		0.90	0.87, 0.92		0.83	0.80, 0.85		0.65	0.56, 0.75		1.06	1.03, 1.08		0.58	0.52, 0.65	
4	0.95	0.93, 0.98		0.92	0.89, 0.95		0.85	0.82, 0.88		0.80	0.70, 0.93		1.01	0.97, 1.05		0.83	0.73, 0.95	
Childhood vaccination compliance			<0.0001			<0.0001			<0.0001			<0.0001			<0.0001			0.9590
All vaccines received	0.90	0.89, 0.90		0.81	0.80, 0.82		0.76	0.75, 0.77		0.57	0.53, 0.63		0.99	0.98, 1.00		0.61	0.57, 0.66	
At least 1 missed	0.95	0.94, 0.96		0.87	0.86, 0.89		0.80	0.78, 0.81		0.86	0.77, 0.96		1.05	1.04, 1.07		0.61	0.55, 0.67	
No vaccines received	2.22	2.03, 2.42		2.35	2.05, 2.70		1.81	1.54, 2.12		5.61	2.29, 13.73		2.27	1.99, 2.59		0.67	0.27, 1.66	
Father's annual income, kroner			<0.0001			<0.0001			<0.0001			<0.0001			<0.0001			<0.0001
≤149,999	0.90	0.89, 0.92		0.84	0.82, 0.86		0.77	0.75, 0.79		0.49	0.41, 0.58		0.96	0.94, 0.98		0.58	0.51, 0.66	
150,000–349,999	0.90	0.89, 0.91		0.81	0.80, 0.82		0.76	0.75, 0.77		0.71	0.65, 0.77		1.00	0.99, 1.01		0.57	0.54, 0.61	
≥350,000	0.98	0.97, 1.00		0.92	0.90, 0.94		0.85	0.83, 0.87		0.76	0.64, 0.90		1.09	1.07, 1.10		0.90	0.78, 1.05	
Child's sex			<0.0001			<0.0001			<0.0001			0.0010			<0.0001			0.0135
Male	0.89	0.89, 0.90		0.81	0.80, 0.82		0.76	0.75, 0.77		0.74	0.67, 0.80		0.99	0.98, 1.00		0.58	0.54, 0.62	
Female	0.95	0.94, 0.96		0.89	0.87, 0.90		0.81	0.80, 0.82		0.59	0.53, 0.66		1.05	1.04, 1.06		0.67	0.61, 0.73	
Birth weight, g		0.0919				<0.0001		0.0048			0.0009				<0.0001			<0.0001
≤2,499	0.91	0.90, 0.93		0.78	0.76, 0.80		0.74	0.72, 0.77		0.63	0.50, 0.80		1.05	1.02, 1.08		0.68	0.57, 0.82	
2,500–3,999	0.92	0.91, 0.93		0.84	0.83, 0.85		0.78	0.77, 0.79		0.73	0.68, 0.80		1.02	1.01, 1.03		0.66	0.61, 0.70	
≥4,000	0.91	0.90, 0.92		0.84	0.82, 0.85		0.79	0.77, 0.81		0.55	0.48, 0.63		0.98	0.97, 1.00		0.44	0.39, 0.49	
Birth order			<0.0001			<0.0001			<0.0001			<0.0001			<0.0001			<0.0001
1	0.91	0.90, 0.92		0.89	0.88, 0.90		0.80	0.79, 0.82		0.84	0.74, 0.95		0.98	0.97, 0.99		0.71	0.65, 0.78	
2	0.91	0.90, 0.92		0.79	0.78, 0.80		0.75	0.74, 0.76		0.56	0.50, 0.61		1.03	1.02, 1.04		0.57	0.53, 0.62	
≥3	0.94	0.93, 0.95		0.83	0.82, 0.85		0.79	0.77, 0.80		0.78	0.68, 0.90		1.08	1.06, 1.10		0.55	0.49, 0.62	
Urbanization			<0.0001			<0.0001			<0.0001			0.1008			0.2310			0.0005
Capital, including suburbs	0.95	0.94, 0.96		0.93	0.92, 0.95		0.86	0.84, 0.88		0.76	0.66, 0.88		1.02	1.01, 1.04		0.68	0.60, 0.78	
City/town	0.91	0.90, 0.91		0.82	0.81, 0.83		0.75	0.74, 0.77		0.69	0.62, 0.77		1.01	1.00, 1.02		0.65	0.60, 0.71	
Rural area	0.90	0.90, 0.91		0.80	0.79, 0.81		0.76	0.75, 0.77		0.63	0.57, 0.70		1.02	1.00, 1.03		0.54	0.50, 0.59	

Abbreviations: CI, confidence interval; MMR, measles-mumps-rubella; RR, rate ratio.

[a] Adjusted for age, calendar period, income of mother, income of father, birth weight, place of birth, mother's country of birth, infant vaccine compliance, birth order, maternal age at birth, and child's sex.

[b] *P* value from test for homogeneity.

measles vaccination were reported to be negatively associated with asthma; odds ratios were 0.36 (95% CI: 0.14, 0.91) and 0.45 (95% CI: 0.21, 0.98), respectively. These results were supported by a negative association between asthma and a positive measles-specific immunoglobulin G titer (odds ratio = 0.65, 95% CI: 0.35, 1.20). Jedrychowski et al. (23) conducted a small cohort study of approximately 1,000 Polish schoolchildren. The authors reported a negative association between measles vaccination and physician-diagnosed asthma (odds ratio = 0.50, 95% CI: 0.24, 1.00).

In the context of a nationwide cohort study, the ascertainment of asthma cases is feasible almost only through nationwide registries as opposed to actual clinical review. This invites speculation on the specificity and completeness of the methods used for outcome identification. We used information on hospitalization with asthma and use of anti-asthma medication. Instead of combining this information and using it algorithmically to identify asthma cases—for example, based on number of uses of both steroid inhalants and β2-agonist inhalants within a specified time period—we chose to analyze directly and independently hospitalizations and uses of different types of anti-asthma medication. The algorithmic approach has some drawbacks, at least in this study setting, which includes the possibility of survival bias and the identification of actual asthma cases being dependent on the definition of the algorithm. While our outcomes will typically have lower specificity than those derived from an algorithmic approach, this is offset by the more detailed results with respect to asthma phenotypes obtained in our analysis. Asthma is difficult to diagnose in early childhood, and a number of different phenotypes and conditions produce asthmatic symptoms in early childhood: transient wheezing coinciding with infections in infancy and among toddlers, more persistent nonatopic wheezing in childhood with later remission, and atopic wheezing with a more chronic course of illness. We found that the MMR effect was more pronounced for hospitalization with severe asthmatic symptoms and for anti-asthma medication used for asthmatic conditions not easily controlled by more standard treatment regimens (long-acting β2-agonist inhalants and ''other anti-asthma medication''). Furthermore, there was no protective effect of MMR vaccination on the use of systemic β2-agonists. Systemic β2-agonists are mainly mixtures and are commonly used to treat transient wheezing in early childhood—for example, in the case of acute bronchitis. This minimizes the concern that the MMR effect alone relates to transient wheezing illness in early childhood instead of asthma.

In any observational study of routine vaccination, the group of unvaccinated children is a more or less selected group. We took this into account by adjusting for a wide range of possible confounding factors and by conducting a number of supplemental analyses. The uptake of MMR vaccine in our cohorts was approximately 85%, and consequently selection is less likely than it would be with a very high uptake. We specifically adjusted for receipt of infant vaccines and found that the MMR effect persisted among children vaccinated in the first year of life, further minimizing concern over selection of MMR-unvaccinated children. Maternal smoking and parental asthma/atopy are known risk factors for asthma and could, for different reasons, be associated with avoidance of vaccination. In subanalyses, we found the potential confounding effect of these factors to be negligible. We took the possibility of health-care-seeking bias and confounding by personal disease history (both all diseases and asthma alone) into account by including adjustment for hospital use in the first year of life (both all diseases and asthma alone); there was no effect on our hospitalization results. In general, health-care-seeking bias—for example, situations in which vaccinees were more likely to use anti-asthma medication—would tend to produce increased risks of asthma associated with vaccination, contrary to what we observed. While it is not possible to completely rule out remaining bias or confounding, we have examined all obvious sources and have found no indication that our findings were a result of such errors.

We identified a number of factors which modified the MMR effect. Overall, the modest differences in MMR effect and the lack of consistency across our different asthma outcomes limit the interpretability of these results. Asthma consists of a number of phenotypes, each with a highly complex genetic and environmental etiology, which we believe these results reflect.

Among children with no receipt of infant vaccines, a number of anti-asthma medication rate ratios were significantly increased. An explanation is that children with no infant vaccinations and no MMR vaccination are a highly selected group whose parents generally avoid medication. In contrast, children receiving no infant vaccines but at least 1 MMR vaccine are a group of children whose parents are less likely to be antivaccine and consequently less likely to be antimedication, hence the increased rate ratio. This is supported by the lack of a similar effect for hospitalizations, where no significant differences were found (see results for infant vaccine compliance in Table 1).

The strength of our study is the use of a nationwide cohort with prospective and independent ascertainment of exposure and outcomes, reducing the concern over selection and recall bias that is commonly found in other vaccine safety studies. Our results do not support the hypothesis of an adverse effect of MMR vaccination on asthma-like disease. Rather, they support the hypothesis that MMR vaccination is associated with a reduced risk of asthma-like disease in young children.

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Author affiliation: Department of Epidemiology Research, Statens Serum Institut, Copenhagen, Denmark (Anders Hviid, Mads Melbye).

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