

Smallpox vaccination and risk of allergy and asthma

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Asthma, rhinitis,
other respiratory
diseases

Background: It has been proposed that childhood vaccinations may influence the development of allergy. Atopy and allergic diseases have increased after routine smallpox vaccination was stopped in the 1970s.

Objective: We examined whether administration of smallpox vaccination during childhood was associated with a decreased risk of atopy, allergic rhinitis, and asthma.

Methods: The occurrence of atopy, allergic rhinitis, and asthma was studied in nearly 2000 women participating in a national birth cohort study. Detailed information on smallpox vaccination was available from school health records. Atopic status was assessed serologically by a specific response to 11 common inhalant allergens by using serum samples obtained from the women during the period 1997 to 2001. Information on allergic rhinitis and asthma was available from telephone interviews.

Results: We found no association between having been vaccinated against smallpox in childhood and risk of atopy or allergic rhinitis. Smallpox vaccination was associated with a slightly decreased risk of asthma. There was no association between age at smallpox vaccination and risk of atopy, allergic rhinitis, or asthma. Adjusting for birth cohort, sibship size, age of the woman's mother at birth, and social class in childhood did not change these results.

Conclusion: Our findings do not suggest that childhood vaccination against smallpox, even if given early in life, influences the development of atopy or allergic rhinitis. The association with asthma should be interpreted with caution and needs further study. (*J Allergy Clin Immunol* 2003;111:1227-31.)

Key words: Allergy, allergic rhinitis, asthma, atopy, epidemiology, risk factors, smallpox vaccine, vaccination

Vaccination against smallpox was in widespread use in developed countries for nearly 2 centuries up until 1980

Abbreviations used

BCG Bacille Calmette-Guérin

kU/L: Kilounits per liter

OR: Odds ratio

when the World Health Assembly declared the world free of smallpox and vaccination was stopped.¹ Recently, it has been suggested that some vaccinations may protect against the development of allergy,² whereas others may increase the risk.^{3,4} The omission of some vaccinations or the administration of others could therefore be connected with the epidemic increase in the prevalence of allergy in developed countries in recent decades.⁵⁻⁹

Although allergy has increased markedly since the 1970s, a possible association between the absence of smallpox vaccination since the late 1970s and allergy has not been examined. Smallpox vaccination in childhood might reduce the risk of becoming allergic by inducing a strong T_H1 cytokine response^{10,11} that could help prevent the balance between T_H1 and T_H2 type cytokines from skewing toward the T_H2 type associated with allergic reactions.^{12,13}

Public fear of health complications due to vaccination may undermine the confidence in present national and global immunization programs,¹⁴ and it is therefore important to critically assess the impact of routine vaccinations. Studies of smallpox vaccination have gained new interest as a result of the debate on the costs and benefits of introducing a preemptive smallpox vaccination campaign to eliminate the threat of smallpox as an agent of bioterrorism.¹⁵⁻¹⁸

We therefore investigated whether administration of smallpox vaccination during childhood was associated with a decreased risk of atopy, allergic rhinitis, and asthma by using a unique material of school health records from Copenhagen with detailed information on smallpox vaccination.

METHODS

Study population

The investigation was based on an ongoing nationwide Danish cohort study of pregnant women (The Danish National Birth Cohort).¹⁹ Women who participated in that study during the period September 1997 to October 2001 were eligible for inclusion in the present study. Furthermore, they had to have attended primary school in Copenhagen (the capital of Denmark) and to have their

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school health record identified in the Archive for School Health Records from the municipality of Copenhagen. Because all Danish residents are assigned a unique personal identification number, it was possible to link the entire cohort of pregnant women ($n = 82,257$) with a register of school health records belonging to persons born before 1978. Overall, 2269 women were identified on the basis of this linkage. Because information on vaccination had not previously been computerized, the school health records were searched manually in the archive, and 2224 (98%) were found by using information on date of birth, maiden and present names, as well as the personal identification number often written on the record.

Exposure data

The Danish compulsory smallpox vaccination was introduced in 1871 and stopped on April 1, 1977. It included all Danish children aged 0 to 7 years without contraindications against vaccination. The production of smallpox vaccine in Denmark started in 1866. The vaccine produced the last 50 years before vaccination stopped was based on the Copenhagen strain of vaccinia virus. It was available as a liquid vaccine containing more than 10^8 plaque-forming units per milliliter (PFU/mL). Vaccination was performed by various methods of scarification or with a bifurcated needle, and it has been estimated that the intradermal dose was approximately 1 microliter. Eczematous symptoms like Besnier's prurigo (atopic dermatitis) were noted as one contraindication on vaccine package leaflets dating back to the 1970s available from Statens Serum Institut (Birgitte Knudsen, personal communication, June 2002).

The Archive for School Health Records contains information from regular, mostly annual, health examinations of children who attended school in the municipality of Copenhagen between 1930 and 1990, as described elsewhere.²⁰ Detailed information about smallpox vaccination had been obtained from vaccination cards presented at school entry (average age, 7 years). In general, all children in Denmark possess a standardized vaccination card on which all vaccinations are recorded at the time they are given. Information on smallpox vaccination at school entry and during school years (age, 7 to 15 years) was recorded on the school health records by the school physician. A total of 2189 (98%) women had information on smallpox vaccination and other vaccinations available on their records; the remaining women were excluded from the study. Time of smallpox vaccination was recorded either as the exact date (87%), the month and year (6%), the year (4%), or as "yes" (3%). Women were considered unvaccinated when the school physician had indicated so or when the space for noting smallpox vaccination was left empty while information on other vaccinations were available, thus indicating that the vaccination card had been presented. Furthermore, the record provided a space for noting the presence of a medically certified exemption from smallpox vaccination, and usually the cause of exemption was also noted (in 17 of 21 cases).

Information on sibship size at school entry and age of the woman's mother at birth was available from the school health records or could be obtained from the Civil Registration System. Social class (I to V) in childhood was derived from the father's occupation recorded on the school health records at school entry.²¹ Eight women were excluded because of missing information on sibship size, leaving 2181 women in the study. Information on current occupation and height and weight before pregnancy was obtained from the women during pregnancy by using telephone interviews conducted within the National Birth Cohort Study, and information on bacille Calmette-Guérin (BCG) vaccination and pertussis whole-cell vaccination was available from the school health records.

Atopy

The atopic status of the women was determined by serologic analyses. We used serum samples obtained during the women's

pregnancy as part of the Danish National Birth Cohort study. Sera were available for 1960 (90%) of the 2181 women. The sera were stored at -30°C . Sera were analyzed for specific IgE against 11 common inhalant allergens with the Phadiatop Unicap test (Pharmacia, Copenhagen, Denmark), which examines all allergens in one pool (horse, dog, cat, grass [*Phleum pratense*], birch [*Betula verrucosa*], olive [*Olea europaea*], dust mites [*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*], herbs [*Artemisia vulgaris* and *Parietaria officinalis*], and mold fungus [*Cladosporium herbarum*]). Women with specific IgE levels of 0.35 kilounits per liter (kU/L) or greater were classified as atopic.²²

Allergic rhinitis and asthma

Information on allergic rhinitis and asthma was obtained from the women by using telephone interviews during pregnancy and was available for 1927 (88%) of the 2181 women in the study. All women had been asked whether they had ever had allergy and, if so, whether a physician had diagnosed it. Women who answered affirmatively to these 2 questions had further questions on what kind of allergy they had. Women who reported allergic rhinitis or hay fever were considered cases of allergic rhinitis. All women were also asked whether they had ever had asthma and, if so, whether a physician had diagnosed it. Those who responded affirmatively to these 2 questions were considered cases of asthma.

Statistical analyses

All risk ratios were calculated as odds ratios (ORs) by using logistic regression. Nonvaccinated women born on April 1, 1970, or later were used as reference group to assess the independent effect on risk of atopy, allergic rhinitis, and asthma of smallpox vaccination administered at age 0 to 15 years. This birth period was chosen as the optimal reference period because vaccination coverage rapidly decreased as a result of the cessation of compulsory vaccination of children aged 0 to 7 years on April 1, 1977. Hence, this group was less likely to contain many women not vaccinated because of contraindication by atopic dermatitis²³⁻²⁵ or other allergic conditions associated with this disorder. Nonvaccinated women born before April 1, 1970, were likewise treated as a separate group. In addition, all women with a medically certified exemption from smallpox vaccination, usually as a result of eczema, asthma, or allergic rhinitis or a family history of such disorders, were treated as a separate group. Finally, we assessed the independent effect of age at smallpox vaccination on risk of atopy, allergic rhinitis, and asthma among vaccinated women.

All analyses were done with and without adjustment for potential confounding by birth cohort (1953 to 1960, 1961 to 1963, 1964 to 1966, 1967 to 1969, 1970 to 1972, 1973 to 1977), sibship size (1, 2, 3, 4+), age of the woman's mother at birth (younger than 20, 21 to 24, 25 to 29, 30 to 34 years, 35 years or older, missing), and social class (I, II, III, IV, V, missing). None of these variables were significantly associated with the 3 outcomes, but they were chosen as adjustment variables because they have previously been associated with atopy, allergic rhinitis, or asthma and may also be associated with vaccination coverage.^{26,27} Variables entered into the logistic model were treated as categorical variables. *P* values were based on likelihood ratio tests, and 95% CIs were based on Wald's test. The statistical software program SAS version 6.12 (SAS Institute Inc, Cary, NC) was used for the analyses.

RESULTS

Among the 1960 women for whom sera were available, 552 (28%) were classified as atopic; among the 1927 women for whom information was available on

TABLE I. Risk of atopy according to history of smallpox vaccination

	Atopy*		
Vaccination history	Cases/all (%)	OR (95% CI)	Adjusted OR† (95% CI)
Smallpox vaccination			
No (born April 1, 1970 or later)‡	132/478 (27.6%)	1 (reference)	1 (reference)
No (born before April 1, 1970)‡	15/49 (30.6%)	1.16 (0.61-2.19)	1.29 (0.63-2.64)
No (exempted)§	9/19 (47.4%)	2.36 (0.94-5.94)	2.62 (0.99-6.91)
Yes (born April 1, 1970 or later)	327/1169 (30.0%)	1.03 (0.73-1.45)	0.98 (0.46-2.09)
Yes (born before April 1, 1970)	69/245 (28.2%)	1.02 (0.80-1.29)	1.04 (0.72-1.50)
Age at smallpox vaccination (y)			
0-1	77/265 (29.1%)	1.17 (0.81-1.71)	1.17 (0.80-1.71)
2	74/286 (25.9%)	1 (reference)	1 (reference)
3	59/185 (31.9%)	1.34 (0.89-2.02)	1.33 (0.88-2.01)
4	47/164 (28.7%)	1.15 (0.75-1.77)	1.18 (0.76-1.83)
5	47/181 (26.0%)	1.00 (0.66-1.54)	1.02 (0.66-1.58)
6	52/188 (27.7%)	1.10 (0.72-1.66)	1.13 (0.73-1.73)
7-15	26/104 (25.0%)	0.95 (0.57-1.60)	0.97 (0.57-1.66)
Unspecified**	14/41 (34.1%)	1.49 (0.74-2.98)	1.84 (0.89-3.79)

*Atopy was defined as a specific IgE level ≥ 0.35 kU/L.

†Adjusted for birth cohort, sibship size, age of the woman's mother at birth, and social class in childhood.

‡Among women born on April 1, 1970, or later, 66% were not vaccinated as opposed to 5% among women born before April 1, 1970. This difference in vaccination coverage was due to the cessation of the compulsory smallpox vaccination program on April 1, 1977, among children younger than 7 years of age.

§Medically certified exemption from smallpox vaccination. The exemption was due to eczema, asthma, and/or allergic rhinitis (n = 12), a family history of such disorders (n = 2), allergy to penicillin (n = 1), or no reason was given (n = 4).

||When grouping vaccinated women born before and after April 1, 1970, together, the adjusted OR of atopy was 1.03 (95% CI, 0.72-1.47).

¶The P value for a homogeneity test whereby we test for a differential effect of vaccination at different ages within the age span 0 to 15 years.

**Positive history of vaccination, but the age at vaccination was not specified.

allergic rhinitis and asthma, 263 (14%) had allergic rhinitis, and 165 (9%) were cases of asthma. The women were between 21 and 46 years old with an average age of 31 years (standard deviation, 4 years). Overall, the vaccination coverage was 95% for women born before April 1, 1970, and 34% for women born on April 1, 1970, or later. Among the latter group of women, vaccination coverage during the periods of birth from April 1970 to December 1971, 1972 to 1973, and 1974 to 1977 was 54%, 31%, and 7%, respectively.

Table I shows the risk of atopy according to history of smallpox vaccination. Overall, smallpox vaccination was not associated with risk of atopy compared to unvaccinated women born on April 1, 1970, or later (adjusted OR, 1.03; 95% CI, 0.72 to 1.47). The adjusted OR of atopy was 0.98 (95% CI, 0.46 to 2.09) for women born after April 1, 1970, and 1.04 (95% CI, 0.72 to 1.50) for women born before April 1, 1970. There was no differential effect of age at smallpox vaccination on the risk of atopy ($P = .85$).

Table II shows the risk of allergic rhinitis and asthma according to history of smallpox vaccination. Overall, there was no association between smallpox vaccination and risk of allergic rhinitis compared with unvaccinated women born on April 1, 1970, or later (adjusted OR, 1.12; 95% CI, 0.71 to 1.76). The adjusted OR of allergic rhinitis was 1.21 (95% CI, 0.76 to 1.92) for women born after April 1, 1970, and 0.56 (95% CI, 0.19 to 1.66) for women born before April 1, 1970. There was no differential effect of age at smallpox vaccination on the risk of allergic rhinitis ($P = .59$).

A positive history of smallpox vaccination was associated with an adjusted OR of asthma of 0.63 (95% CI, 0.34 to 1.15) for women born before April 1, 1970, and 0.24 (95% CI, 0.06 to 0.99) for women born after April 1, 1970, compared to unvaccinated women born after April 1, 1970 (Table II). The combined unadjusted OR for vaccinated women was 0.68 (95% CI, 0.48 to 0.97) compared to unvaccinated women born after April 1, 1970. Adjusting for birth cohort, sibship size, the age of the woman's mother at birth, and social class resulted in an OR of 0.55 (95% CI, 0.30 to 1.00). Further adjusting for current occupation, pre-pregnancy body mass index (weight/height²), BCG vaccination, and pertussis whole-cell vaccination did not change the estimate (OR, 0.55; 95% CI, 0.30 to 1.00). In addition, the analyses on asthma were stratified by atopic status when this was available (91%). The OR for vaccinated women with atopic asthma was 0.54 (95% CI, 0.23 to 1.31; $n_{\text{cases}} = 51$), and for women with nonatopic asthma it was 0.78 (95% CI, 0.32 to 1.88; $n_{\text{cases}} = 42$) compared to unvaccinated women born after April 1, 1970, when adjusted for all the above mentioned risk factors.

The estimates for current asthma were similar to those presented for asthma in Table II, although the CIs were wider because of fewer cases (data not shown). There was no differential effect of age at smallpox vaccination on the risk of asthma ($P = .80$), and this was regardless of whether the asthma was atopic ($P = .41$) or non-atopic ($P = .93$).

Asthma, rhinitis,
other respiratory
diseases

TABLE II. Risk of allergic rhinitis and asthma according to history of smallpox vaccination

Vaccination history	Allergic rhinitis			Asthma		
	Cases/all (%)	OR (95% CI)	Adjusted OR* (95% CI)	Cases/all (%)	OR (95% CI)	Adjusted OR* (95% CI)
Smallpox vaccination						
No (born April 1, 1970 or later)†	63/487 (12.9%)	1 (reference)	1 (reference)	50/487 (10.3%)	1 (reference)	1 (reference)
No (born before April 1, 1970)‡	8/51 (15.7%)	1.25 (0.56-2.79)	1.34 (0.55-3.26)	7/51 (13.7%)	1.39 (0.59-3.25)	1.21 (0.44-3.31)
No (exempted)‡	8/21 (38.1%)	4.14 (1.65-10.4)	4.44 (1.65-12.0)	9/21 (42.3%)	6.55 (2.63-16.3)	5.81 (2.06-16.4)
Yes (born April 1, 1970 or later)§	40/255 (15.7%)	1.25 (0.82-1.92)	1.21 (0.76-1.92)	17/255 (6.7%)	0.62 (0.35-1.11)	0.63 (0.34-1.15)
Yes (born before April 1, 1970)§	144/1113 (12.9%)	1.00 (0.73-1.37)	0.56 (0.19-1.66)	82/1113 (7.4%)	0.70 (0.48-1.01)	0.24 (0.06-0.99)
Age at smallpox vaccination (y)						
0-1	31/259 (12.0%)	0.82 (0.50-1.36)	0.84 (0.50-1.41)	14/259 (5.4%)	0.82 (0.40-1.68)	0.88 (0.42-1.83)
2	39/275 (14.2%)	1 (reference)	1 (reference)	18/275 (6.5%)	1 (reference)	1 (reference)
3	23/188 (12.2%)	0.84 (0.49-1.47)	0.87 (0.50-1.52)	18/188 (9.6%)	1.51 (0.76-2.99)	1.54 (0.77-3.08)
4	22/154 (14.3%)	1.01 (0.57-1.77)	1.09 (0.61-1.94)	12/154 (7.8%)	1.21 (0.57-2.58)	1.22 (0.56-2.65)
5	22/174 (12.6%)	0.88 (0.50-1.53)	1.00 (0.56-1.78)	12/174 (6.9%)	1.06 (0.50-2.25)	1.02 (0.47-2.22)
6	30/182 (16.5%)	1.19 (0.71-2.00)	1.40 (0.81-2.41)	12/182 (6.6%)	1.01 (0.47-2.15)	1.01 (0.47-2.21)
7-15	9/96 (9.4%)	0.63 (0.29-1.35)	0.73 (0.33-1.60)	9/96 (9.4%)	1.48 (0.64-3.41)	1.41 (0.59-3.35)
Unspecified¶	8/40 (20.0%)	1.51 (0.65-3.52)	2.14 (0.88-5.19)	4/40 (10.0%)	1.59 (0.51-4.95)	1.63 (0.50-5.31)

*Adjusted for birth cohort, sibship size, age of the woman's mother at birth, and social class in childhood.

†Among women born on April 1, 1970, or later, 66% were not vaccinated as opposed to 5% among women born before April 1, 1970. This difference in vaccination coverage was due to the cessation of the compulsory smallpox vaccination program on April 1, 1977, among children younger than 7 years of age.

‡Medically certified exemption from smallpox vaccination. The exemption was due to eczema, asthma, and/or allergic rhinitis (n = 13), a family history of such disorders (n = 3), allergy to penicillin (n = 1), or no reason was given (n = 4).

§When grouping vaccinated women born before and after April 1, 1970, together, the adjusted OR for allergic rhinitis was 1.12 (95% CI, 0.71-1.76) and for asthma it was 0.55 (95% CI, 0.30-1.00).

¶The P value for a homogeneity test whereby we test for a differential effect of vaccination at different ages within the age span 0 to 15 years.

||Positive history of vaccination, but the age at vaccination was not specified.

DISCUSSION

To our knowledge this is the first epidemiologic study on smallpox vaccination and allergy. The major long-term effect of smallpox vaccination is long-term immunity possibly lasting up to 30 years.^{28,29} The Danish smallpox vaccination program resembled that of many other developed countries, and overall our findings suggest that this did not have a long-term effect on the development of atopy and allergic rhinitis.

The present study population consisted of women who were subjected to the Danish compulsory smallpox vaccination program in childhood as well as a relatively large group of women who were not. Given this unique possibility to test the relationship between smallpox vaccination and allergy, we did not find any association with risk of atopy and allergic rhinitis when we compared all smallpox-vaccinated women with nonvaccinated women

born on April 1, 1970, or later. Because the vaccination coverage rapidly decreased as a result of the cessation of compulsory vaccination of children aged 0 to 7 years on April 1, 1977, we consider births in this period as the best reference. We also examined whether age at smallpox vaccination was associated with risk of atopy and allergic rhinitis. However, this was not the case. Our findings on atopy and allergic rhinitis therefore do not support that a strong T_H1 cytokine-stimulating vaccination like smallpox^{10,11} may prevent a skewing of the immune system toward T_H2 type immunity and thereby protect against the development of allergic disorders.

Smallpox vaccination was associated with a slightly decreased risk of asthma. This association should be interpreted with caution, because nonvaccination in the cohort born from April 1, 1970, could have been associated with allergic contraindication due to asthma, even

though exemption from vaccination was not indicated on the school records. Furthermore, the association between smallpox vaccination and reported asthma was unrelated to age at vaccination. In addition, we were not able to adjust for factors previously related to asthma such as birth weight, gestational age at birth, breast-feeding, day care in infancy, smoking habits of the subject, or smoking habits of the subject's mother during pregnancy and later, because these data were not available. We were, however, able to adjust for birth cohort, sibship size, age of the woman's mother at birth, and social class in childhood, as well as for current occupation, pre-pregnancy body mass index, BCG vaccination, and pertussis whole-cell vaccination, and this did not influence the association between smallpox vaccination and asthma. Further study is warranted to evaluate this association. Clearly, the lack of association between smallpox vaccination and atopy and allergic rhinitis argues against an allergic component association, and we are not aware of other biologic mechanisms that could explain the association with asthma.

The present study has several advantages. Information on smallpox vaccination was obtained before and independently of the blood samples and of the self-reported information on allergic rhinitis and asthma. Atopy was measured objectively by serologic testing, thereby avoiding the possible bias that accompany self- and parent-reported allergic disease. Furthermore, a number of women had a medically certified exemption from smallpox vaccination, which was mainly due to eczema, asthma, or allergic rhinitis or a family history of such disorders. These women were grouped separately in the analyses, thereby minimizing confounding by allergic contraindication.²³⁻²⁵ However, we believe that the information on exemption from smallpox vaccination was incomplete because several nonvaccinated women who were subjected to the compulsory smallpox vaccination program had no record of a certified exemption although they were obligated by law to present one. We took this into account in the analyses by separately grouping nonvaccinated women who were born before and after April 1, 1970, thereby reducing the possibility of confounding by allergic contraindication.

In conclusion, our findings do not suggest that childhood vaccination against smallpox, even if given early in life, influences the development of atopy and allergic rhinitis. However, we found that smallpox vaccination during childhood was associated with a decreased risk of asthma. This finding should be interpreted with caution and needs confirmation in future studies.

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