

the possibility that sport and exercise among adolescents may have a positive effect on their mental health deserves further investigation.

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Measles and atopy in Guinea-Bissau

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Summary

Background Epidemiological studies have led to speculation that infections in early childhood may prevent allergic sensitisation but evidence to support this hypothesis is lacking. We investigated whether measles infection protects against the development of atopy in children of Guinea-Bissau, West Africa.

Methods We conducted a historical cohort study in Bandim, a semi-rural district of Bissau, the capital of Guinea-Bissau. 395 young adults, first surveyed in 1978–80 aged 0–6 years, were followed up in 1994. Our analyses were restricted to 262 individuals still living in Bandim for whom a measles history, documented in childhood, was judged to be reliable. We defined atopy as skin-prick test positivity (≥ 3 mm weal) to one or more of seven allergens.

Findings 17 (12.8%) of 133 participants who had had measles infection were atopic compared with 33 (25.6%) of 129 of those who had been vaccinated and not had measles (odds ratio, adjusted for potential confounding variables 0.36 [95% CI 0.17–0.78], $p=0.01$). Participants

who had been breastfed for more than a year were less likely to have a positive skin test to housedust mite. After adjustment for breastfeeding and other variables, measles infection was associated with a large reduction in the risk of skin-prick test positivity to housedust mite (odds ratio for *Dermatophagoides pteronyssinus* 0.20 [0.05–0.81], $p=0.02$; *D farinae* 0.20 [0.06–0.71], $p=0.01$).

Interpretation Measles infection may prevent the development of atopy in African children.

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Introduction

The rise in allergic disease among children in the UK over the past 30 years^{1–3} remains unexplained. One hypothesis is that infections in early childhood prevent allergic sensitisation, and that successive generations of children have lost this protection as their exposure to infectious disease early in life has declined. Consequently the prevalence of atopy and concomitant allergic disease has risen.⁴ In the UK mortality rates from measles, whooping cough, and enteric infections fell nearly 100-fold in the first half of this century.⁵ Declining family size has probably contributed to this fall as severe infections in early childhood are less likely with fewer older siblings in the family.

Indirect evidence that infection in early childhood may prevent allergic disease has come from epidemiological studies using information on family size. There is strong evidence that the number of older siblings is inversely related to the prevalence of hayfever,^{4,6} although the evidence for a similar relation with eczema and asthma is

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conflicting.⁷ A study of German children in 1994 provided some support for the hypothesis that atopy might be prevented by infections at an early age. The total number of siblings was inversely related to the prevalence of atopy, as assessed by skin-test reactivity to common aeroallergens.⁸ However, there remains no direct evidence for the hypothesis that infection early in life protects against allergic sensitisation.

We examined how measles is related to the development of atopy in Guinea-Bissau, West Africa, where measles infection has been documented in a cohort of children since 1979.

Methods

In 1994 we carried out a study of 395 young adults in Guinea-Bissau, West Africa, to investigate the relation between child health, lung function, and allergy. These young adults were part of a cohort recruited for a survey of nutrition and child health in 1978. The background to the original survey has been described in detail elsewhere.⁹⁻¹¹

The cohort followed up for this study comprised 1478 children aged 0-6 years in 1978-80 and living in Bandim 1, a semi-rural district of Bissau, the capital of Guinea-Bissau. Houses in Bandim are multi-family dwellings of mud-brick and polygamy is common. The Papel is the largest of the four major ethnic groups living in the study area. In 1978, the children were measured (height, weight, and arm circumference) and background information about the type of house, age of mother, and number of family members employed was collected.

A measles epidemic occurred in 1979 (January to June) with a case-fatality rate of 25% for children younger than 3 years. In December, 1979, all traceable children who had survived were examined again, their mothers were examined (height and arm circumference), and their mothers or guardians were asked if the child had had measles. If they said "no", measles vaccination was offered to all children aged more than 6 months. Children younger than 6 months and those who missed the 1979 examination were included in a second vaccination campaign 1 year later. Before 1979 there had been no measles vaccination campaigns in Bissau. Further measles epidemics have occurred in Bandim every 2-3 years, and cases of measles have been ascertained by clinical examination or interviews with mothers during the epidemics. Information on the total number of individuals in each house was collected in a census in 1981.

395 of the 1478 children registered in the original survey were still living in Bandim 1 and agreed to participate in our study. The young adults were assessed at home in the dry season, between December, 1993, and April, 1994. Height, head circumference, and mid-upper-arm circumference were measured to the nearest millimetre with a portable stadiometer and steel tape-measure. Weight was measured with electronic scales to the nearest 100 g. Skin-prick testing was done with seven aeroallergen preparations (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, southern grass mix, aspergillus, cat, dog, and cockroach mix). These were applied, with a negative saline control and a positive histamine control (10 mg/mL), to the volar aspect of the right forearm with separate 25 gauge needles.¹² The perpendicular diameters of each weal were recorded after 10 min. One physician (CBH) carried out and measured all skin tests and was unaware of the measles history.

A positive reaction to each allergen was defined in two ways: the average diameter of the allergen weal (minus the reaction to the negative control) was 3 mm or more; or the ratio of the allergen weal diameter to the diameter of the histamine weal (after subtracting the reaction to the negative control) was at least 0.5.¹³ Participants were defined as atopic if there was one or more positive reactions by the first definition.

The mother or closest relative of the participant was interviewed about birth order, duration of breastfeeding, ethnic group, mother's education, and animals currently in the family home.

	% with atopy (n)	% positive history of measles infection (n)
Sex		
Male	18 (24/132)	50 (66/132)
Female	20 (26/130)	52 (67/130)
Current age (years)		
14-15	13 (8/62)	39 (24/62)
16-17	12 (10/81)	49 (40/81)
18-19	29 (19/66)	61 (40/66)
20-21	25 (13/52)	54 (28/52)
Month of test		
December	0 (0/8)	50 (4/8)
January	13 (12/93)	47 (44/93)
February	18 (7/40)	60 (24/40)
March	27 (20/74)	53 (39/74)
April	23 (11/47)	47 (22/47)
Mother's schooling (years)		
None	17 (30/179)	55 (99/179)
1-3	13 (5/39)	54 (21/39)
≥4	31 (12/39)	26 (10/39)
Family members employed in 1978 (n)		
1	17 (29/171)	45 (77/171)
≥2	23 (7/31)	39 (12/31)
Older siblings (n)		
0	17 (11/66)	52 (34/66)
1	26 (16/62)	42 (26/62)
2	15 (7/48)	50 (24/48)
3	10 (3/31)	55 (17/31)
≥4	20 (9/45)	56 (25/45)
Breastfeeding (months)		
≤12	29 (4/14)	71 (10/14)
13-24	17 (27/161)	44 (71/161)
≥25	18 (13/72)	63 (45/72)
Pigs kept in house		
No	22 (32/145)	50 (72/145)
Yes	13 (14/105)	50 (52/105)

Table 1: Distribution of atopy and measles infection by potential confounding variables

Mothers can recognise measles infection reliably in Guinea-Bissau^{14,15} and many cases in 1979 were confirmed by medical personnel.^{9,10} For our measles analyses we included 133 individuals in whom measles infection had been documented in 1979 or in subsequent epidemics. We relied on the mothers' 1979 reports to ascertain cases of measles before 1979. Individuals who had no documentation of measles infection were also included if the following two criteria were fulfilled: the mother had stated at interview in December, 1979, that the child had never had measles infection (a guardian's history of "no measles" was not regarded as sufficiently reliable to exclude measles infection; 108 subjects did not fulfil this criterion and were excluded); and the mother did not report measles infection when interviewed in 1994 (a further 25 people did not fulfil this criterion; measles may not have been documented because they were temporarily out of the study area at some time since 1979). The remaining 129 young adults for whom we could be most certain that past measles infection had not occurred were included in the analyses. Vaccination of these individuals is assumed on the basis of attendance at the 1979 examination.¹¹

Data were analysed by tabulation of proportions and means and by cross-tabulation of dichotomous variables. Exact confidence intervals for differences in proportions were obtained.¹⁶ The earliest anthropometric data from the 1978 and 1979 examinations (ages 0-7 years) were adjusted for age and sex within the population studied and *z*-scores were calculated by multiple linear regression.

Results

We compared the personal and background characteristics (as documented in 1978) of the 395 participants of the present survey with those from the original cohort who were not included in this survey. Participants seen in 1994 were more likely to be of the

	Odds ratio (95% CI)	
	Adjusted for age, sex, and month of test	Adjusted for other variables in table also
Measles infection		
No	1.0	1.0
Yes	0.34 (0.17–0.67)	0.36 (0.17–0.78)
Mother's schooling		
<4 years	1.0	1.0
≥4 years	1.9 (0.99–3.6)	1.9 (0.82–4.6)
Breastfeeding		
≤12 months	1.0	1.0
>12 months	0.41 (0.16–1.03)	0.47 (0.12–1.9)
Pigs kept in house		
No	1.0	1.0
Yes	0.49 (0.28–0.87)	0.67 (0.32–1.4)

Table 2: Atopy according to measles history

Papel ethnic group, to have been born in Bandim, and to have mothers who were over 30 years old in 1978 who had had 4 or more years of schooling. The two groups were similar with respect to sex distribution, childhood anthropometry, position in birth order, type of house, number of family members employed, and a history of measles infection obtained at the 1979 examination.

The age range of the 395 young adults was 14–21 years (mean, 17.8 [SD 1.9]). 80 (20.3%) of the 395 participants were atopic. The predominant positive reactions were to the dust-mite and cockroach allergens. Only four positive reactions were observed to grass, aspergillus, cat, and dog allergens. Analyses of associations of atopy with measles were restricted to 262 participants, of whom 133 had a history of measles infection and 129 had no history of measles infection and had been vaccinated. 50 (19.1%) of 262 participants included in the analysis were atopic, compared with 30 (22.6%) of 133 who were excluded because of unreliable measles histories.

Table 1 shows the distribution of atopy and measles infection according to potential confounding variables. Atopy was more common in older participants and in March and April and in participants whose mothers had 4 or more years of schooling. In a subgroup of the young adults, for whom information had been collected about family income in 1978, atopy was also more common in those from families in which two or more members were employed. Atopy was unrelated to the number of older siblings. Atopy was less common in participants who had been breastfed for more than a year and in those from homes where pigs were kept at the time of this study.

	Odds ratio (95% CI)*		
	<i>D pteronyssinus</i>	<i>D farinae</i>	Cockroach
Measles infection			
No	1.0	1.0	1.0
Yes	0.20 (0.05–0.81)	0.20 (0.06–0.71)	0.83 (0.33–2.1)
Mother's schooling			
<4 years	1.0	1.0	1.0
≥4 years	2.5 (0.60–10.4)	1.3 (0.38–4.8)	4.1 (1.6–10.9)
Breastfeeding			
≤12 months	1.0	1.0	1.0
>12 months	0.13 (0.02–0.88)	0.21 (0.04–1.1)	2.5 (0.25–23.8)
Pigs kept in house			
No	1.0	1.0	1.0
Yes	0.88 (0.24–3.2)	0.96 (0.32–2.8)	0.47 (0.17–1.3)

*Adjusted for age, sex, month of test, and other variables in table.

Table 3: Positivity to individual allergens according to measles history

There were no significant differences between atopic and non-atopic participants with respect to current height (difference 1.0 cm [95% CI –1.3 to 3.3]) and weight (difference 0.6 kg [–1.8 to 2.9]), after allowing for sex and current age. Similarly childhood measurements, mothers' measurements, ethnic group, number of individuals living in the house in childhood, season of birth, mother's age, and type of house in childhood were not significantly associated with atopy. Participants who had been breastfed for a year or less and whose mothers had less than 4 years of education were more likely to have had measles infection. Childhood anthropometry and current anthropometry were similar in those who had had measles and those who had not had measles infection.

Fewer of the young adults with a history of measles infection (17 [12.8%] of 133) than of those without a history of measles (33 [25.6%] of 129) were atopic. Table 2 shows the odds ratio for atopy by measles history after adjustment for potential confounding variables (odds ratio 0.36 [0.17–0.78], $p=0.01$). The odds ratio for 190 participants with complete information and after adjustment for the number of family members employed in 1978 was 0.29 (0.11–0.78).

The median age at the time of measles infection was 3.6 years (1.1 months–17.8 years) and the median age at vaccination was 3.0 years (4.4 months–7.6 years). 74 (62.2%) of 119 measles cases for which a date was known occurred in one epidemic in 1979. The age at which participants had measles was therefore highly correlated with current age ($r=0.995$). In the remaining 45 participants there was no independent association between age at measles and atopy. Age at vaccination was also colinear with current age ($r=0.99$).

Breastfeeding for more than a year was associated with a reduction in the odds of positivity to both housedust-mite allergens. After adjustment for breastfeeding and other variables measles infection was associated with a significant reduction in the odds of skin-test positivity to the two housedust-mite allergens (table 3). There was a non-significant reduction in the odds of skin-test positivity to cockroach allergen ($p=0.7$). Similar results were obtained when the relation between measles history and allergen positivity was examined by means of the histamine ratio criterion (adjusted odds ratios: *D pteronyssinus* 0.24 [0.11–0.53]; *D farinae* 0.43 [0.21–0.89]; cockroach 0.65 [0.35–1.2]).

Discussion

This study has shown a relation between measles and atopy in Guinea-Bissau. A documented history of measles infection was associated with a reduction in the risk of skin-test positivity to housedust mite at 14–21 years of age.

A study of the 1979 measles epidemic showed that mothers in Guinea-Bissau are able to recognise measles infection reliably.^{9,10} Serological studies have shown that, although some infections may be missed, a positive history is nearly always correct.^{14,15}

If the association found between measles and atopy in those followed up had been biased by losses from the cohort through migration, then measles infection would have to be associated with an increased risk of atopy in the migrant population, which seems unlikely. We cannot exclude the possibility that the findings were biased through differential mortality. If atopic children were more likely to die from measles infection that association

could explain why atopy was less common in participants who survived the severe epidemic of 1979. We are not aware of any evidence to support a link between atopy, or an associated genetic trait, and susceptibility to severe measles infection but this possibility merits further immunological study.

Atopy increased with current age. Studies of white people in developed countries have also shown that the rate of atopy rises between the ages of 14 and 21 years.^{17,18} We found a higher risk of atopy in participants from families with more than one income during childhood. Other studies have also found a relation between atopy and higher socioeconomic status in developed^{17,18} and developing countries.¹⁹ Atopy was more common in young adults of better-educated mothers which is consistent with findings for allergic disease in children in the UK.²⁰ Studies from developed countries have been inconclusive as to whether breastfeeding protects against atopy.²¹ Children who had been breastfed for a year or less in Bandim, although few in number, were more likely to be atopic as young adults than those breastfed for more than a year. We have confirmed this finding in a study of children aged 4–14 years in Bissau (unpublished). The number of older siblings and the total number of people in the house during childhood were not related to atopy. In western countries the number of older siblings has been used to indicate the risk of infection in early childhood. However, this is a poor indicator of infection risk in Bandim because children live in multi-family houses with no ceilings and mix continually with children from other families in the same house. This is illustrated by the lack of a relation between number of older siblings and measles infection.

A potentially confounding factor to be considered in an African population is parasitic infestation. Godfrey and Gradidge proposed²² that the high concentrations of total IgE found in heavily parasitised individuals may block mast-cell receptors for allergen-specific IgE thus preventing the clinical expression of atopy. We did not measure total IgE or faecal worm burdens in our study participants. In Bissau the level of infestation with worms and other enteric pathogens may be higher in people exposed to pigs. Pigs live intimately with the people in the houses and are a significant independent risk factor for child mortality.²³ Thus the lower risk of atopy in those who were currently exposed to pigs at home may reflect a heavier worm burden and blocking by total IgE in these individuals.

A strong relation between measles and atopy remained after adjustment for potentially confounding variables and could not be explained by nutritional status, as assessed by anthropometry during the present survey and in childhood. In this cohort health-seeking behaviour of mothers is unlikely to have been a confounding factor. Such behaviour would not have influenced the likelihood of children being vaccinated against measles because the vaccination campaigns of 1979 and 1980, the first in Bissau, were conducted house-to-house as part of the nutrition survey.

It is not clear why measles and breastfeeding were more strongly related to housedust-mite reactivity than to cockroach reactivity. Different risk factors may be important for sensitisation to different allergens depending on the timing of exposure.

One interpretation of our findings is that measles infection prevents allergic sensitisation. In-vitro work

suggests that viral and bacterial infections could prevent atopy by activation of Th1-type T cells and production of γ -interferon. This cytokine can alter the differentiation of allergen-specific T cells, otherwise destined to be of the Th2 type, towards a less atopic Th0/Th1 type.^{24,25} The initial cytokine response to measles before and during the rash is of the Th1 type although it is followed by a longer Th2-type cytokine response, which lasts for several weeks.²⁶ Experimental work by Mossman and Sad suggests that the type of T-cell response to infections may depend partly on antigen dose.²⁷

Indirect evidence has suggested that infection protects against atopy only if it occurs at a young age.^{4,6,8} Although we were limited in our analyses by collinearity between age at measles infection and current age we found no evidence to suggest that the reduction in atopy associated with measles was greater the earlier the age at infection. It is possible that measles might prevent sensitisation at any age in early childhood. There may be an extended period of maturation of T-cell response to inhalant allergens until age 5–7 years during which time the allergic response is susceptible to change and may be modifiable by environmental factors such as infections.^{28,29}

An alternative explanation for our findings is that allergic sensitisation may have been enhanced in children who received measles vaccine. However, as the young adults in this cohort were part of the first vaccination campaign in Bissau, the median age at vaccination was unusually late. There is no evidence that giving measles vaccine earlier in life, as is current policy in developed and developing countries, is associated with an increase in atopy. In a large British birth cohort, in which the majority of vaccinated children received measles vaccine at 1 year of age, no difference was found in the prevalence of allergic disease at 5 years of age between vaccinated and unvaccinated children.³⁰

A third explanation, that atopic children may have been more likely to have caught measles infection, does not seem biologically plausible. Pre-existing immunological abnormalities are unlikely to modify the risk of clinical infection because measles is a highly infectious virus and subclinical infection is rare.

As far as we know this is the first population-based study to show a reduction in atopy in relation to a specific viral infection in childhood. Our findings are consistent with the hypothesis that measles infection may prevent the development of atopy. Studies from the UK and the USA have found no relation between other respiratory infections in infancy and subsequent atopy and allergic disease in childhood^{31,32} and hospital-based studies of respiratory syncytial virus bronchiolitis are conflicting.^{33,34} However, it is possible that the effect of infections on the sensitisation process varies with the type of organism and the infective dose.^{7,27}

Further studies of atopy in developing countries, where the burden of childhood infections is still intense, may provide valuable insight into the rise in atopy that has occurred in the west.

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