

ORIGINAL PAPER

Acute infections, infection pressure, and atopy

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Summary

Background During the recent years, a new theory postulating that lack of early childhood infections would increase the prevalence rate of allergies has rapidly gained momentum. This hygiene hypothesis has been widely disseminated to the general public and it has been suggested that vaccinations would accordingly indirectly increase rates of atopy. We thus investigated associations between acute infections, infection pressure (i.e. number of daily child contacts) and atopy in one of the largest population-based medical surveys ever published in the medical literature.

Methods Almost all Finns born between 1976 and 1984 and a sample of older teenagers aged up to 19 years ($n = 5\,47\,190$) were vaccinated and questioned to establish clinical history of mumps and rubella and manifestations of atopy (rhinoconjunctivitis, eczema, and asthma) in 1982–1986. A subsample ($n = 37\,733$) including all those subjects who were vaccinated during the first 2 months of the measles, mumps, and rubella (MMR) programme were also queried information about upper respiratory infections (URIs) and infection pressure. Crude and adjusted prevalence ratios of atopy among those with infectious disease history compared with those without it were calculated.

Results The risk of URI and a history of mumps and rubella increased with the number of daily contacts. This association was apparent especially among the youngest subjects with regard to URIs whereas the proportion with histories of mumps and rubella increased with increasing infection pressure more clearly among the 6-year-olds. Atopy was not associated with daily child contacts among pre-schoolers. Children with histories of repeated URIs and MMR diseases had substantially more atopy than those with lower URI or MMR disease rates.

Conclusions Atopic subjects seem to be especially prone to clinically apparent acute respiratory tract infections, and might be in particular need of protection by immunizations. This study does not support the idea that the prevalence of atopy in affluent countries would be affected from disappearing respiratory tract infections.

Key words atopy, mumps, rubella, URI

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Introduction

The increased risk of atopic diseases in affluent societies has been claimed to result from the elimination of communicable disease in early childhood. During the past decade, people exposed to common childhood infections or under high infection pressure (e.g. members of a large family) have been reported to have fewer atopic manifes-

tations than those under lower infection pressure [1–9]. It is postulated that cell-mediated immunity responses may have altered in the absence of viral infections and tuberculosis, possibly resulting in T helper type 2(Th2)-mediated responses, which favour the manifestations of atopic diseases [1, 8]. Additional support for such arguments comes from the observation that when an only child starts attending a large day-care group before its first birthday, atopy is less likely to develop than in an only child who stays longer at home with its mother [10].

*Deceased in 2002.

These speculations about the benevolent or preventive effect of high-infection pressure during childhood on the development of atopic diseases may be ignoring [11] an important phenomenon, which suggests that atopic constitution and infection susceptibility apparently go hand-in-hand [8, 11–15]. Although this has been questioned [16]. For this report, the inter-relationships between history of various acute viral infections, infection pressure, and risk of atopy were studied in a large material accumulated during a national measles, mumps, and rubella (MMR) vaccination programme in Finland in 1982–1986. A study was recently published from the same material with respect to history of measles and atopy [11]. The purpose of this paper is to show that not only measles, but all infections of the respiratory tract are strongly positively associated with atopic status in our exceptionally large database.

Subjects and methods

Vaccinations, setting, and subjects

In Finland, since 1982, the trivalent measles, mumps, and rubella vaccine (MMR^R_{II}, Merck & Co. Inc., West Point, PA, USA distributed in Finland as Virivac^R, Statens Bakteriologiska laboratorium, Stockholm, Sweden) has been used exclusively and is administered routinely first at 14–18 months and again at 6 years. Children are vaccinated free of charge at child health-care centres. Vaccinations are voluntary. Between 1983 and 1986 children from 14 months to 6 years of age were actively MMR immunized whenever they visited mother–child health clinics. Special arrangements were made to register all MMR vaccinations in Finland between 1 November, 1982 and 30 June, 1986 when the triple vaccine was introduced. Among the targeted age groups, MMR vaccination coverage reached about 97% [17, 18].

There were 5 62 931 children born between November 1975 and June 1984 under the computerized surveillance [17, 18]. During the course of the enhanced vaccination programme, 5 47 910 children were immunized. Some of these were 'over aged' but were immunized anyway. Thus, the children 5 47 910 aged between 1 and 19 years of age had provided relevant information about MMR and allergies in the database. Non-vaccinated children aged 7–11 years had been traced and vaccinated at schools in 1985 [18]. Some children outside the targeted age groups were MMR vaccinated later on their own initiative and were registered to the database. The details of the collected data and the vaccination setting have been described [17–19].

Data collection

A public health nurse vaccinated a child or teenager and collected data by interview, including social security

number and age at vaccination. It was specifically asked and recorded whether the individual to be vaccinated had ever had physician or public health nurse-diagnosed atopic eczema, allergic rhinitis (such as hayfever) or conjunctivitis, or asthma or repeated episodes of obstructive bronchitis. Occurrence of upper respiratory infections (URIs) during the year preceding the interview (in categories 0, 1–4, 5–9, 10+), and number of usual daily contacts (in categories < 5, 5–6, 7–8, or > 8 children) were registered during the first 2 months of the programme, whereas histories of MMR and atopy were queried throughout the period of intensified MMR vaccinations in 1983–1986.

Data on URIs as well as mumps and rubella and daily child contacts were available for 37 733 14–18-month-old and 6-year-old vaccinees. Data on history of mumps and rubella and atopy alone were available on 5 47 910 vaccinees aged 14 months through 19 years, of these 28 320 had had mumps and 42 215 rubella; 52 087 had or had had eczema, 17 131 rhinitis, and 10 058 asthma. A positive history of MMR diseases increased steadily with age (Table 1 and reference [11]).

Statistical methods

The statistical significance of linear trends in the occurrence of URIs and history of mumps and rubella across the categories with increasing number of daily child contacts was assessed by χ^2 -test [20]. Allergy occurrence in large day care groups (> 8 children) was compared with small day care groups (< 5 children) in two age groups: 14–18-month-old, and 6-year-old children. Occurrence of atopic manifestations was investigated in the URI episode categories and finally averaged (adjusted) over the two age strata. Subjects with either mumps or rubella history only were compared with those with no history of MMR to

Table 1. History (%) of mumps and rubella according to age at vaccination

Age (years)	Mumps (n = 28 320)	Rubella (n = 42 215)	Number of subjects
1*	0.1	1.5	2 007 65
2	0.5	3.4	29 623
3	1.1	5.7	43 310
4	2.4	8.5	53 004
5	5.4	10.8	51 600
6*	11.3	13.7	126 303
7	15.3	15.9	21 561
8	22.1	20.4	5534
9	28.5	23.8	8220
10–14	26.5	21.8	6441
15–19	37.4	31.4	1449
All	5.2	7.7	5 47 910

*Mothers of 37 733 subjects were asked about day care and upper respiratory infections during the previous year.

Table 2. Children having no upper respiratory infections during the year preceding the interview, according to infection pressure

		Daily child contacts			
Age		1–4	5–6	7–8	≥9
14–18 months*	%	22.0	15.0	13.9	9.7
	<i>n/N</i>	2690/12 208	102/678	20/144	74/762
6 years*	%	43.6	44.2	43.1	36.3
	<i>n/N</i>	3845/8807	364/824	113/262	5105/14 048

* χ^2 for trend with 1 degree of freedom $P < 0.0001$.

Table 3. Histories of mumps and rubella according to infection pressure

History of mumps and rubella	Daily child contacts					
	Age		1–4	5–6	7–8	> = 9
Mumps	14–18 months*	%	0.16	0.15	0.00	0.26
		<i>n/N</i>	19/12 208	1/678	0/144	2/762
	6 years [†]	%	12.21	12.62	16.41	15.87
		<i>n/N</i>	1075/8807	104/824	43/262	2229/14 048
Rubella	14–18 months*	%	2.69	3.10	2.1	3.67
		<i>n/N</i>	328/12 208	21/678	3/144	28/762
	6 years [†]	%	11.38	13.23	18.32	17.29
		<i>n/N</i>	1002/8807	109/824	48/262	2429/14 048

* χ^2 for trend with 1 degree of freedom non-significant.

† χ^2 for trend with 1 degree of freedom $P < 0.0001$.

obtain the prevalence ratios (PR) of allergic diseases. The PRs were then averaged over the age strata (1, 2, 3, 4, 5, 6, 7, 8, 9, 10–14, and 15–19 years of age) by Mantel–Haenszel's method (Epiinfo version 5.01, 1993). All 95% confidence intervals for PRs were estimated according to Greenland and Robins [21].

First-order interactions with respect to urbanization (towns >1 000 000 inhabitants), age, and infection pressure were checked by comparing investigated associations over the relevant strata.

Results

The proportion of children not experiencing URIs within the year preceding the interview decreased with increasing number of child contacts, especially among the youngest children who also have higher URI rates than the older children (Table 2). Histories of mumps and rubella were also positively associated with infection pressure especially among the 6-year-olds (Table 3).

The prevalence of allergic symptoms did not differ according to child contacts among either 14–18-month-old or 6-year-old children, although asthma prevalence was about 16% lower ($P > 0.05$) among 6-year-olds in day-

Table 4. Prevalence (%) and prevalence ratio (PR) with 95% confidence interval (95% CI) of allergic manifestations according to infection pressure and age

	Daily child contacts	Age			
		14–18 months		6 years	
		%	PR (95% CI)	%	PR (95% CI)
Atopic	< 5 children*	8.6	1.00	13.4	1.00
	>9 children	8.7	1.01 (0.79–1.28)	13.8	1.03 (0.96–1.12)
Rhinoconjunctivitis	< 5 children*	1.7	1.00	6.6	1.00
	>9 children	2.6	1.53 (0.99–2.45)	7.2	1.09 (0.99–1.22)
Asthma	< 5 children*	1.7	1.00	3.7	1.00
	>9 children	1.4	0.82 (0.48–1.59)	3.2	0.86 (0.76–1.01)

*Reference category.

care groups of over eight children compared with those with five children or less (Table 4).

Prevalence of allergic manifestations increased strongly and linearly with the number of URIs (Table 5), and adjustment for daily contacts did not change the results. The prevalence of atopy among 6-year-old children with more than five URI episodes during the year preceding the interview was almost six times higher compared with those who experienced no URI episodes during the same period.

Histories of mumps and rubella were also positively associated with occurrence of atopy and after age adjustment those with only mumps or rubella had about 20–30% more atopy than those with no history of MMR (Table 6). The association was constant over age strata (data not shown).

Discussion

These results confirm, once again, the classic observation from war-time nurseries in the UK that infection pressure, i.e. size of the day-care group, is positively associated with occurrence of common childhood infections [22–24]. Hence, the fact that rubella and mumps were not dependent on infection pressure in the younger age group could result from non-apparent clinical infections among them coupled with the relatively small window of disease occurrence after maternal antibodies have waned away, might have hampered the resolution in this age group.

The results of the present study also support the notion that atopic children are more prone to clinically apparent infections [8, 11, 13–15, 25, 26]. Indeed, the positive association of various acute infections and atopy has not been quantified as clearly as in the present study.

Obviously, there is still a need for cohort follow-up studies, as our study is cross-sectional and a Danish

Table 5. Prevalence and age adjusted prevalence ratio* (APR) with 95% confidence interval (95% CI) of atopic manifestations according to upper respiratory infections (URI) among the six-year-olds

Number of URIs during the year preceding interview	Eczema		Rhinoconjunctivitis		Asthma	
	Prevalence % (n/N)	APR (95% CI)	Prevalence % (n/N)	APR (95% CI)	Prevalence % (n/N)	APR (95% CI)
0 [†]	12.0 1132/9416	1.0 (–)	4.9 462/9415	1.0 (–)	2.2 205/9421	1.0 (–)
1–4	14.6 1975/13571	1.21 1.13–1.30	7.9 1075/13554	1.62 (1.45–1.80)	3.9 529/13581	1.79 (1.53–2.10)
5+	22.9 134/585	2.13 1.82–2.50	18.8 110/584	3.84 (3.17–4.64)	12.9 76/589	5.93 (4.62–7.61)

*Mantel–Haenszel weighted averaged over 11 age strata.

[†]Reference category.**Table 6.** Crude and age adjusted prevalence ratio* (APR) with 95% confidence interval (95% CI) of atopic manifestations among vaccinees with a history of only mumps or rubella compared with vaccinees with no measles, mumps or rubella history

Atopic disease	Mumps only		Rubella only	
	Crude PR	APR (95% CI)	Crude PR	APR (95% CI)
Eczema	1.18	1.20 (1.15–1.24)	1.21	1.19 (1.15–1.22)
Rhinoconjunctivitis	1.93	1.29 (1.21–1.36)	1.72	1.28 (1.23–1.34)
Asthma	1.51	1.20 (1.10–1.30)	1.43	1.19 (1.12–1.27)

*Mantel–Haenszel weighted averaged over 11 age strata.

cohort study [27] has found a positive association of URIs and atopic dermatitis. However, in our study, in contrast to the Danish study, there was no indication that the high number of daily child contacts would decrease the rate of atopic dermatitis. In this context, however, it must be remembered that children are brought to day care earliest at 10 months of age in Finland. Thus, this material has its limitations in exploring the associations of very early infection pressure (including e.g. endotoxins) and atopic diseases. Furthermore, the study findings cannot be used to question the validity of findings that suggest that orofecal infections would make children less prone to atopy [5].

As admitting the limitations, however, it is to be noted that the analyses from this large material in totality do not support the new hygiene hypothesis, but the material behaves otherwise according expectations [22–24]. Hence, the statistically border line significant result, which indicates that the 6-year-olds would have somewhat less asthma, could be interpreted as being in line with the hygiene hypothesis. However, the fact that the prevalence of atopic manifestations do not behave sys-

tematically with respect to infection pressure coupled with the fact that asthmatics might have been removed from large day care groups would speak against this interpretation.

Memory bias might explain – in part – the strong positive association of asthma and URIs. Mothers of asthmatic children probably remember infection episodes better than mothers whose children do not have asthma, as episodes so strongly affect the well-being of their offspring.

Already, the previous results from the same material on measles and atopy [11, 28] have cast doubt on the validity of the reported inverse associations between atopic manifestations and infections, immune responses to them, or infection pressure [5–8, 10]. Such associations were increasingly reported following an influential study published in the *Lancet*, which claimed that subjects with measles history have less atopy later in life [7]. A cross-sectional German study suggested that when an only child is put in day care with other children before its first birthday, the child will have a smaller risk of allergy at the age of 5–14 years compared with those who have experienced lower infection pressure [10]. Our study does not support the German findings, although the ‘follow-up’ period in the present study was only up to 6 years of age.

The strong and systematic positive associations between acute infections and atopy found in this and in the previous study [11] coupled with the recent Norwegian cohort study findings [29] could suggest that a new theory rapidly gained support because of publication bias.

A Scottish study [8] with a considerably smaller sample size has reported results similar to ours. It found a strong positive adjusted (i.e. with respect to family size) association between rubella, varicella, mumps, and atopy when the infections were contracted before 3 years of age.

Information bias is unlikely to explain the observed associations between infections and atopy in the present study, as the data gathering in the 1980s predated discussions about the benevolent nature of early childhood infec-

tions with respect to subsequent atopy. Errors in diagnoses are unavoidable in a survey like this but would not produce bias unless errors in atopy diagnoses somehow depended on infection history, or vice versa. This is unlikely, as the new hypothesis on the origins of the contemporary asthma epidemic emerged only in the 1990s [1].

The data collected for this study as part of the national vaccination programmes are probably reasonably reliable, because acute infections and allergy are sometimes conceived of as contraindications for vaccinations. Thus, probing the vaccinees with respect to atopic manifestations was considered by the public health nurses to be integral and important part of the whole MMR programme to guarantee the safety of the vaccinated subjects. Selection bias because of mortality is also unlikely as deaths from the studied diseases are rare. A special concern in this and in the previous study on measles and atopy only [11] was the possibility that for some reason timing of vaccination was delayed among atopic children compared with non-atopic children. Under such circumstances a bias could result from MMR diseases continuing to circulate with diminishing incidence, and atopic children receiving vaccinations later having more time to catch them. However, the vaccination coverage rose similarly or even faster (catch-up age groups 2–6) among atopic children compared with non-atopic children (data not shown). Bias because of seasonality cannot have produced the observed strong positive association of URIs and atopic manifestations, as the data were collected during a short period of time (2 months).

The main uncontrolled source of confounding in this study is family size [3, 4, 8]. Again, it can be argued that a large family size would only weaken the observed positive associations, as subjects who belong to large families are subject to more acute infections but have a lower risk of atopy.

It has even been suggested that measles and acute respiratory infections might be true causes of atopy [30, 31]. On the other hand, otitis media has now been confirmed to be heritable in a convincing twin study [32]. Selection forces have probably made the ability to withstand various other infections (and vice versa) to become genetically determined. Atopy has long been known to have a strong hereditary background. Thus, joint occurrence in the same area of close proximity of a chromosome of these two hereditary determined phenomena is quite possible by mere chance.

Another possibility is gene selection. As proneness [8, 11, 13–15, 26] to infections and their severe sequelae [33–38] are probably more common among atopic than non-atopic children, the increasing rates of atopy may be at least partly because of survival, as children with atopic genes [39, 40] do not die from communicable diseases as before.

Whatever the reasons for the presumably increased rates of atopy, the discussion of the benevolent nature of early

exposure to infections with respect to atopy is probably missing important clinical and epidemiological aspects of atopic disorders. In the ongoing debate, in Scandinavia and Germany, a vaccination moratorium had been suggested, as mass immunizations, among other preventive activities, are believed by some scientists, the media, and consequently by the general public to be indirectly responsible for the increased rates of atopic allergy in society. It seems that opposite policy recommendations might be worth considering, as children with atopic constitution seem to be especially prone to acute clinically apparent infections with possible severe sequelae and thus in special need of protection by immunization.

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References

- 1 Cookson WOCM, Moffatt MF. Asthma: an epidemic in the absence of infection. *Science* 1997; **275**:41–2.
- 2 Martinez FD. Role of viral infections in the inception of asthma: could they be protective? *Thorax* 1994; **49**:1189–91.
- 3 Strachan DP. Hay fever, hygiene, and household size. *Br Med J* 1989; **299**:1259–60.
- 4 Von Mutius E, Martinez FD, Fritsch C, Nicolai T, Reitmeir P, Thieman HH. Skin test reactivity and number of siblings. *Br Med J* 1994; **308**:692–5.
- 5 Matricardi PM, Rosmini F, Ferrigno L *et al*. Cross sectional retrospective study of prevalence of atopy among Italian military students with antibodies against hepatitis a virus. *Br Med J* 1997; **314**:999–1003.
- 6 Shirakawa T, Enomoto T, Shimazu SI, Hopkin JM. The inverse association between tuberculin response and atopic disorders. *Science* 1997; **275**:77–9.
- 7 Shaheen SO, Aaby P, Hall AJ *et al*. Measles and atopy in Guinea-Bissau. *Lancet* 1996; **347**:1792–6.
- 8 Bodner C, Godden D, Seaton A. Family size, childhood infections and atopic diseases. *Thorax* 1998; **53**:28–32.
- 9 Holt PG. A potential vaccine strategy for asthma and allied atopic diseases during early childhood. *Lancet* 1994; **344**:456–8.
- 10 Krämer U, Heinrich J, Wichmann H-E. Age of entry to day nursery and allergy in later childhood. *Lancet* 1999; **353**:450–4.
- 11 Paunio M, Heinonen OP, Virtanen M, Leinikki P, Patja A, Heinonen OP. Measles history and atopic allergies: a population based, cross-sectional study. *JAMA* 2000; **283**:343–6.
- 12 Matricardi PM, Rosmini F, Riondino S *et al*. Exposure to foodborne and orofecal microbes vs. airborne viruses in relation to atopy and allergic asthma: epidemiological study. *Br Med J* 2000; **320**:412–7.
- 13 Minor TE, Baker JW, Dick EC *et al*. Greater frequency of viral respiratory infections in asthmatic children as compared with their nonasthmatic siblings. *Pediatrics* 1974; **85**:472–7.
- 14 Kraemer MJ, Richardson MA, Weiss NS *et al*. Risk factors for persistent middle-ear effusions: otitis media, catarrh, cigarette smoke exposure, and atopy. *JAMA* 1983; **249**:1022–5.

- 15 Jedrychowski W, Flak E. Atopy and low birth weight as determinants of susceptibility of children to acute respiratory tract infections (Polish; English summary). *Przegl Epidemiol* 1996; 50:315–22.
- 16 Stempel DA, Wallace WA, Henderson FW, Collier AM. Serum IgE levels and the clinical expression of respiratory illnesses. *Pediatrics* 1980; 97:185–90.
- 17 Peltola H, Karanko V, Kurki T *et al.* Rapid effect of endemic measles, mumps, and rubella of nationwide vaccination programme in Finland. *Lancet* 1986; 1:137–9.
- 18 Paunio M, Virtanen M, Peltola H *et al.* Increase of vaccination coverage by mass media and individual approach: intensified measles, mumps, and rubella prevention program in Finland. *Am J Epidemiol* 1991; 133:1152–60.
- 19 Peltola H, Heinonen OP, Valle M *et al.* The elimination of indigenous measles, mumps, and rubella by a 12-year, two-dose vaccination program. *N Engl J Med* 1994; 331:1397–402.
- 20 Further analysis of qualitative data. In: Armitage P, Berry G., eds. *Statistical methods in medical research (Chapter 12)*, (2nd Edn). Cambridge, UK: Blackwell Scientific Publications, 1987.
- 21 Greenland S, Robins JM. Estimation of a common effect parameter from sparse follow-up data. *Biometrics* 1985; 41:55–.
- 22 Allen-Williams GM. Incidence of infections in war-time day nurseries: a preliminary study. *Lancet* 1945; 249:825–6.
- 23 McLaughlin M. The physical health of children attending day nurseries. *Br Med J* 1947; i:631–4.
- 24 Menzies HF. Children in day nurseries with special reference to the child under two years old. *Lancet* 1946; ii:499–501.
- 25 Openshaw PJ, Lemanske RF. Respiratory viruses and asthma: can the effects be prevented? *Eur Respir J* 1998; 27:35–9.
- 26 Richardson VF, Larcher VF, Price JF. A common congenital immunodeficiency predisposing to infection and atopy in infancy. *Arch Dis Child* 1983; 58:799–802.
- 27 Benn CS, Melbye M, Wohlfahrt J, Björkstén B, Aaby P. Cohort study of sibling effect, infectious diseases, and risk of atopic dermatitis during first 18 months of life. *Br Med J* 2004; 328:1223–6.
- 28 Gern JE, Weiss ST. Protection against atopic diseases by measles – a rash conclusion? *J Am Med Assoc* 2000; 283:394–5.
- 29 Nafstad P, Brunekreef B, Skrandal A, Nystad W. Early respiratory infections, asthma, and allergy: 10-year follow-up of the Oslo Birth Cohort. *Pediatrics* 2005; 116:e255–62.
- 30 Imani F, Proud D, Griffin DE. Measles virus infection synergizes with IL-4 in IgE class switching. *J Immunol* 1999; 162:1597–602.
- 31 Rager KJ, Langland JO, Jacobs BL, Proud D, Marsh DG, Imani F. Activation of antiviral protein kinase leads to immunoglobulin E class switching in human B cells. *J Virol* 1998; 72:1171–6.
- 32 Casselbrant ML, Mandel EM, Fall PA *et al.* The heritability of otitis media: a twin and triplet study. *JAMA* 1999; 282: 2125–30.
- 33 Tang MLK, Kemp AS, Thorburn J. Reduced interferon-gamma secretion in neonates and subsequent atopy. *Lancet* 1994; 344: 983–5.
- 34 Warner JA, Miles EA, Jones AC *et al.* Is deficiency of interferon gamma production by allergen triggered cord blood cells a predictor of atopic eczema? *Clin Exp Allergy* 1994; 24:423–30.
- 35 Kemp M, Theander TG, Kharazami A. The contrasting roles of CD4+ T cells in intracellular infections in humans: leishmaniasis as an example. *Immunol Today* 1996; 17:13–6.
- 36 Frucht DM, Holland SM. Defective monocyte costimulation for INF-gamma production in familial disseminated Mycobacterium avium complex infection. *J Immunol* 1996; 157:411–6.
- 37 Soothill JF. Some intrinsic and extrinsic factors predisposing to allergy. *Proc T Soc Med* 1976; 69:1439.
- 38 Lipscombe RJ, Sumiya M, Hill AVS *et al.* High frequencies in African and non-African populations of independent mutations in the mannose binding protein gene. *Hum Molec Genet* 1992; 1:709–15.
- 39 Holgate ST. Asthma genetics: waiting to exhale. *Nat Genet* 1997; 15:227–9.
- 40 Laitinen T, Räsänen M, Kaprio J, Koskenvuo M, Laitinen LA. Importance of genetic factors in adolescent asthma: a population-based twin-study. *Am J Respir Crit Care Med* 1998; 157:1073–8.