Immunization and Symptoms of Atopic Disease in Children: Results From the International Study of Asthma and Allergies in Childhood

H. Ross Anderson, MD, MSc, Jan D. Poloniecki, DPhil, David P. Strachan, MD, MSc, Richard Beasley, MD, Bengt Björkstén, MD, PhD, and M. Innes Asher, MD, BSc, ChB, for the ISAAC Phase 1 Study Group

ABSTRACT

Objectives. This study tested the hypothesis that immunization is related to the prevalence of atopic disease in childhood.

Methods. We used data from the International Study of Asthma and Allergies in Childhood to perform an ecologic analysis of national and local immunization rates for tuberculosis, diphtheria and tetanus toxoids and pertussis (DTP), and measles and prevalence of atopic disease symptoms (asthma, allergic rhinoconjunctivitis, and atopic eczema).

Results. In 13- to 14-year-old children, there were significant negative associations with local birth-year immunization rates for DTP and measles but none with rates for tuberculosis. No associations were found in 6- to 7-year-old children. No associations with national immunization rates were found.

Conclusions. International variations in childhood atopic diseases are unlikely to be explained by variations in immunization. (*Am J Public Health.* 2001;91:1126–1129)

Asthma and other diseases with a strong atopic basis, such as allergic rhinitis and eczema, show marked international variation and appear to be increasing.[1–5]

In fetal and early life, the immune system is skewed toward $T_H 2$-type immunity, but after birth, it becomes progressively skewed toward $T_H 1$-type immune responses, which are essential for an effective host defense against infections.[6] Accumulating experimental and clinical evidence suggests that the conditions under which the primary encounter with ubiquitous environmental allergens and microorganisms takes place early in life may affect this normal progression from $T_H 2$- to $T_H 1$-type immunity.[7,8] Persistence of $T_H 2$-type immunity is associated with allergic antibody production (immunoglobulin E), atopy, and related atopic diseases.

One of several factors that affect the immune system in early life, and that has increased along with asthma and other allergic diseases since the 1950s, is the routine mass immunization of children against a variety of infectious diseases. The effects of immunization on the incidence of allergic disease could be positive or negative, because immunization of children could directly stimulate $T_H 1$-like immunity or indirectly prevent such immune responses by reducing the incidence of some infections. Although epidemiologic evidence can be adduced to either theory,[9–15] the larger cohort studies have tended not to support a relation. Nevertheless, the question remains important because it is undermining confidence in national and global immunization programs.[16]

We present an ecologic analysis of the relation between the prevalence of symptoms of atopic diseases in children (asthma, rhinoconjunctivitis, and atopic eczema) obtained in Phase 1 of the International Study of Asthma and Allergies in Childhood (ISAAC) and immunization data at the national and local ISAAC center levels for diphtheria and tetanus toxoids and pertussis (DTP), tuberculosis, and measles.

Methods

The methods of obtaining symptom data as part of Phase 1 of ISAAC and the world-wide results for asthma, allergic rhinoconjunctivitis, and atopic eczema symptoms have been published.[2–5] In 1995 and 1996, a standardized questionnaire was administered to 6- to 7-year-old children (parental completion) in 91 centers in 38 countries and to 13- to 14-year-old children (self-completion) in 155 centers in 56 countries. To avoid language bias, 13- to 14-year-old children in 99 centers in 41 countries were shown 5 videotaped sequences of children with clinical asthma in different situations. After each scene, children were asked to record whether their breathing had ever been like that shown in the video, and if so, whether it had in the past 12 months. Center samples comprised all or an unselected sample of schools from a defined area, with a target of 3000 children in each age group. The response rate of schools was 97% and 94%, and the response rate of children was 89% and 92%, in the young and older age groups, respectively.

The outcome variables used in the present analysis were wheezing in the past 12 months, allergic rhinoconjunctivitis in the past 12 months (sneezing, runny or blocked nose, and itchy-watery eyes without a cold or the flu), atopic eczema in the past 12 months (itchy rash in flexural area), and wheezing at rest in the past 12 months (identification with symptoms shown in videotaped scene). Prevalence was the number of positive replies as a percentage of the total number of questionnaires completed per center.

Immunization rates for tuberculosis, DTP, and measles were sought for the year

H. Ross Anderson, Jan D. Poloniecki, and David P. Strachan are with the Department of Public Health Sciences, St. George's Hospital Medical School, London, England. Richard Beasley is with the Department of Medicine, Wellington School of Medicine, University of Otago, Wellington, New Zealand. Bengt Björkstén is with the Centre for Allergy Research, Karolinska Institute, Stockholm, Sweden. M. Innes Asher is with the Department of Paediatrics, Faculty of Medicine and Health Sciences, The University of Auckland, Auckland, New Zealand.

Requests for reprints should be sent to H. Ross Anderson, MD, MSc, Department of Public Health Sciences, St. George's Hospital Medical School, Cranmer Terrace, London SW17 0RE UK (e-mail: r.anderson@sghms.ac.uk).

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that corresponded approximately to the birth years of the study groups (1982 for the 13- to 14-year-old children and 1989 for the 6- to 7-year-old children). National data were obtained from the World Health Organization Expanded Programme up to 1996 (A. Burton, personal communication, World Health Organization official estimates of immunization coverage 1980–1996, as of July 22, 1997). If data were missing for any of the relevant years, we used the mean of 1 or 2 adjacent years. Local immunization rates for the smallest geographic area containing the schools were obtained by writing to all the center collaborators (see "Acknowledgments" section), with 1 follow-up letter.

The associations between local and national immunization rates and symptom prevalence were tested with the Spearman rank correlation coefficient, and 95% confidence limits were calculated with the assumption of a bivariate normal distribution for the ranks. The analysis was done at a national level with World Health Organization rates and the average prevalence of all centers (if more than 1 in a country) and at the ISAAC center level with local immunization rates. Selected associations were examined after control for per capita gross national product (GNP) obtained from the World Health Organization Health for All database,[17] averaged over available years from 1980 to 1993. Estimates of effect size were obtained from the univariate and multivariate normal least squares regression when GNP was adjusted for.

Results

National data were available from the World Health Organization for all of the 56 countries with ISAAC centers. Local immunization data were obtained for 92 of 154 centers (60% response) (Table 1). Considerable differences were found between the national and the local rates. Regression analysis found that national rates accounted for between 11% (DTP 1989) and 68% (DTP 1982) of the variation in local rates.

The prevalence of symptoms ranged widely, with a skew toward higher rates (Table 2). The prevalence estimates for those centers that provided local immunization rates showed a mean, median, and range similar to those of the total sample, except that the symptom prevalence in those centers that provided DTP or measles data tended to be greater than in those without local data.

Of the 84 correlations examined, the only significant associations were among 13- to 14-year-old children based on center immunization data (5 of 21 analyses). In the 13- to 14-year-old group, local immunization rates indicated significant negative associations ($P<$.05) between DTP and wheezing, allergic rhinoconjunctivitis, and atopic eczema and between measles vaccination and rhinoconjunctivitis and atopic eczema but none with tuberculosis vaccination. No associations were

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TABLE 1—Local and National Immunization Rates, Percentage[a]

Vaccine	Year	No. of Centers	Minimum %	Median %	Maximum %	Mean %
Local data						
Tuberculosis	1982	32	0	87	118	69
	1989	54	0	92	123	71
DTP	1982	50	2	73	99	67
	1989	74	17	86	107	84
Measles	1982	45	0	70	106	69
	1989	74	11	87	110	82
National data						
Tuberculosis	1982	41	2	74	99	64
	1989	43	15	90	99	83
DTP	1982	43	1	61	100	60
	1989	54	26	85	99	80
Measles	1982	44	0	54	97	48
	1989	55	23	82	98	76

Note. DTP = diphtheria and tetanus toxoids and pertussis.
[a]Some rates are more than 100% because in routine public health practice, they are not based on individual-level data but on estimates of numbers of units of vaccine used and numbers of eligible children. This may lead to inaccuracies in estimating the actual number vaccinated.

TABLE 2—Prevalence of Childhood Symptoms at Centers With National Immunization Data (and Centers With Local Data in Parentheses)

Age, y	No. of ISAAC Centers (With Local Immunization Data)	Children per ISAAC Center, Median (Range)	Symptom	Minimum	Median	Maximum	Mean
				Percentage Prevalence in All Centers (With Local Immunization Data)			
6–7	91 (57)	2996 (1104, 6533)	Wheezing	0.8 (3.5)	8.7 (9.7)	32.1 (32.1)	11.7 (12.9)
	91 (57)		Rhinoconjunctivitis	0.8 (2.3)	5.9 (6.7)	14.9 (14.9)	6.6 (7.2)
	90 (57)		Eczema	0.5 (1.8)	6.8 (7.7)	18.4 (16.9)	7.1 (7.9)
13–14	154 (92)	3064 (1046, 11 400)	Wheezing	1.6 (2.6)	11.5 (12.2)	36.7 (36.7)	14.3 (15.7)
	154 (92)		Rhinoconjunctivitis	1.4 (4.0)	13.5 (14.2)	39.7 (25.5)	13.4 (13.6)
	152 (92)		Eczema	0.3 (0.8)	6.5 (7.0)	20.5 (20.5)	7.6 (8.1)
	98 (56)		Wheezing (video Q)	0.7 (1.0)	5.8 (7.2)	19.6 (19.5)	7.3 (8.4)

Note. ISAAC = International Study of Asthma and Allergies in Childhood.

TABLE 3—Effect on Prevalence (per 1000 Children per Immunization Percentage) for Those Immunizations With Statistically Significant Rank Correlation With Symptoms[a]

Vaccine	Year	Data	Symptom	Age, y	P	Spearman Rank Correlation Coefficient (95% CI)	
						Univariate Effect	Adjusted for GNP
DTP	1982	Local	Wheezing	13	.047	−0.66 (−1.72, 0.40)	−0.53 (−1.49, 0.43)
			Rhinoconjunctivitis	13	.002	−0.62 (−1.09, −0.14)	−0.60 (−1.02, −0.19)
			Eczema	13	.048	−0.37 (−0.90, 0.16)	−0.27 (−0.76, 0.21)
Measles	1982	Local	Rhinoconjunctivitis	13	.015	−0.55 (−1.10, 0.01)	−0.47 (−0.98, 0.04)
			Eczema	13	.036	−0.50 (−1.10, 0.10)	−0.42 (−0.98, 0.13)

Note. GNP = gross national product; CI = confidence interval; DTP = diphtheria and tetanus toxoids and pertussis.
[a]Linear regression coefficients before and after adjustment for per capita GNP are shown.

observed in the 6- to 7-year-old group. No statistically significant associations between symptoms and national immunization rates were found (data available on request).

Immunization rates were associated, often strongly, with a high proportion of the 34 World Health Organization Health for All indicators that ranged across economic, educational, health, and health service aspects of each country. Factors causing atopic diseases also were likely associated with some of these Health for All indicators, thereby confounding the association between immunization and symptoms of atopic disease. We used 1 indicator, per capita GNP, to explore this association. National immunization rates for DTP and measles in 1982 were positively associated with GNP (regression coefficient = 2.6, 95% confidence interval [CI] = 1.8, 3.4; regression coefficient = 1.2, 95% CI = 0.4, 2.0) per 100 children per $1000. The associations between GNP and the more limited data on local immunization rates were not significant.

Table 3 shows, for the 5 significant associations based on the rank correlation analysis, the results of linear regression with and without adjustment for GNP. Adjustment for GNP tended to slightly reduce the size of the effect estimates. After adjustment, the largest associations with local immunization rates were seen for the percentage prevalence of rhinoconjunctivitis symptoms: −0.6% (95% CI = −1.0, −0.2) per 10% of the population immunized with DTP vaccine and −0.5% (95% CI = −1.0, 0.0) per 10% of the population immunized against measles.

Discussion

Pertussis vaccine, as used worldwide at the time of this study, was a whole-cell vaccine associated with an aluminum adjuvant. Animal studies have found that this vaccine stimulates the immunoglobulin E response,[18,19] but the epidemiologic evidence that pertussis vaccine is a risk factor for atopy is inconsistent. Two

large British birth cohort studies[11,12] and a controlled trial of different types of pertussis vaccine found no evidence of an association with symptoms of atopy.[10] However, positive associations have been reported by a retrospective cohort study in an English general practice[14] and 2 other small studies.[13,15] The present study found moderate negative associations between DTP coverage and symptoms indicative of atopic disease, which decreased only slightly after control for GNP. Thus, our findings are contrary to the hypothesis that pertussis vaccine is a risk factor for atopic disease at the population level.

Live measles vaccine promotes a T_H2-type immune response in healthy adults,[20] but the available epidemiologic evidence suggests that measles immunization is not associated with an increased incidence of atopic disorders.[14,21] Infection with the wild virus produces immune responses similar to those produced by the vaccine, but epidemiologic studies have found no associations between measles infection and atopic disorders.[14,22] The weight of the evidence therefore indicates that measles immunization or infection does not increase atopic disorders, and the findings of our study confirm this at the population level.

Two Swedish studies found no association between tuberculosis vaccine given in early life and atopy.[23,24] We also found no association between tuberculosis coverage and the population prevalence of atopic disease, despite a wide range of tuberculosis vaccination rates, particularly in the birth year of the 6- to 7-year-old children.

It has been postulated that immunization might increase atopic disease either by a direct effect on the immune system or by a reduction of the burden of infection in early childhood. This worldwide ecologic study of birth period immunization rates and symptoms of atopic disease in children lends no support to this idea. Indeed, the results for DTP and measles vaccination supported a conclusion contrary to that predicted under this theory. The findings were changed little after control for GNP. This result is reassuring, because mass immuniza-

tion is an important component of disease prevention worldwide.

Because this was an ecologic study, we could not exclude associations at the individual level.[25,26] Nevertheless, the ecologic approach is appropriate for attempting to explain international variations in prevalence and for putting the findings of individual-level studies within populations in context. Furthermore, the effects of immunization may be wider on populations than on immunized individuals. □

Chile: Punta Arenas, L. Amarales; Central Santiago, I. Sanchez; South Santiago, E. Cortez; Valdivia, M. Calvo-Gil. China: Beijing, Y. Chen; Guangzhou, N.-S. Zhong. Costa Rica: M.E. Soto-Quirós. Estonia: Narva and Tallinn, M.-A. Riikjärv. Ethiopia: Jima, B. Seyoum. Finland: Kuopio, J. Pekkanen; Turku and Pori, T.A. Koivikko. France: Marseilles, D. Charpin; Montpellier, P. Godard; Pessac, A. Taytard; Strasbourg, E. Quoix; West Marne, I. Annesi. Georgia: Tiflis, A. Gamkrelidze. Germany: Greifswald, A. Kramer; Münster, U. Keil, S. Weiland. Greece: Athens, C. Gratziou. Hong Kong: (6- to 7-year-olds) Y.L. Lau; (13- to 14-year-olds) C. Lai. India: Bombay, V.A. Khatav; Chandigar, L. Kumar; Jodhpur, K.C. Jain; Kottayam, T.U. Sukumaran; New Delhi, G.R. Sethi. Italy: Ascoli Piceno, S. Bonini; Rome, F. Forastiere; Siena, E. Renzoni; Trento, S. Piffer; Verona, A. Boner. Japan: Fukuoka, N. Sankei. Kenya: Eldoret, F.O. Esamai. Kuwait: J.A. Al-Momen. Latvia: Riga, Rural Latvia, M. Leja. Lebanon: Beirut, F.M. Ramadan. Malaysia: Alor Setar, K.H. The; Ipoh, W.Y. Lim; Kota Bharu, B.S. Quah; Muar, K.W. Chum. Malta: S. Montefort. Morocco: Casablanca and Marrakesh, Z. Bouayad; Rabat, A. Bennis. New Zealand: Auckland, M.I. Asher; Bay of Plenty, C. Moyes; Christchurch, J. Pattemore; Nelson, R. Mackay; Wellington, J. Crane. Oman: Al-Khod, B.M.S. Al Riyami. Panamá: David-Panamá, G. Cukier. Peru: Lima, P. Chiarella. Philippines: Metro Manila, F. Cua-Lim. Poland: Krakow, G. Lis; Poznan, A. Breborowisc. Portugal: Funchal, Oporto, and Portimao, M. Correia; Lisbon, J.E.R. Pinto. Republic of Ireland: Dublin, L. Clancy. Romania: Cluj, D. Dumitrascu. Singapore: B.-W. Lee. South Africa: Cape Town, H. Nelson. Spain: Barcelona, R.M. Busquets; Cádiz, A.R. Asensio; Cartagena, L. García-Marcos; Castellón, A. Arnedo-Pena; Pamplona, F. Guillén Grima; Valencia, M.M.M. Suárez-Varela; Valladolid, A. Blanco Quirós. Sweden: Linköping, N.-I. Kjellman; Stockholm/Uppsala, T. Foucard. Taiwan: Taipei, K.-H. Hsieh. Thailand: Bangkok, P. Vichyanond; Chiang Mai, M. Trakultivakorn. United Kingdom: Anglia and Oxford, Northeast and Yorkshire, North Thames, North West, South and West, South Thames, Scotland, Trent, Wales, and West Midlands, H.R. Anderson; Surrey/Sussex, D. Strachan; Guernsey, D. Jeff; Jersey, C.R. Grainger. United States: Seattle, G. Redding. Uruguay: Montevideo, D. Holgado de Cuesta.

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