Influence of childhood infections and vaccination on atopy development: systematic review of the direct epidemiological evidences.

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Key Words

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hygiene hypothesis; infections; vaccination; atopy; allergy; direct evidences; epidemiological review; qualitative systematic review; systematic review; Hahnemann; Homeopathy.

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Abstract

Introduction: a theory launched 15 years ago and known as hygiene hypothesis was used to justify a common knowledge among homeopaths: *the suppression of childhood infections, also through vaccination, could lead to the development of chronic atopic diseases*. Objectives: to analyse the influence of childhood infections and vaccination on the development of atopy. Methods: qualitative systematic review of Medline (1993-2004) direct epidemiological evidences concerning the influence of childhood infections and vaccination on atopy development and discussion based on Hahnemann´s teachings. Conclusions: 1) Childhood infections do not protect against atopy, on the contrary, they increase the risk of allergic diseases, in agreement to Hahnemann´s observations which included epidemic diseases among the factors capable of stimulating the development of chronic diseases. 2) Vaccination is not a risk factor for atopy, notwithstanding the eventual allergenic effect of some specific vaccines.

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Introduction

"...it is improper and even harmful to talk or write about subjects which have not as yet been maturely developed."

S. Hahnemann[1]

Atopic dermatitis (or eczema), allergic rhinitis and asthma are the foremost clinical manifestations of atopy, the propensity of the organism to respond to common antigenic environments with a high formation level of IgE antibodies.

Atopic dermatitis which nearly always develops either in the nursing or early infancy stages and is a chronic inflammatory process of the dermis which has been infiltrated by mononuclear and lymphocyte T *helper* cells, and manifests itself by inflamed eyelids and intensely itchy eyes, erythrism and exfoliation, being that the scratching results in exudation, excoriation and liquefaction of the skin[2]. Dermatitis frequently precedes the respiratory symptoms of the atopy and has a growing prevalence in developed countries, currently of around 15% of the population[3].

In 1989, pursuing an explanation for the global increase of the prevalence of atopic diseases and considering the results that pointed towards a smaller incidence of atopy in younger brothers of numerous families, David Strachan proposed the following theory which became known as the "hygiene hypothesis":

> *"These observations…could be explained if the allergic diseases were prevented by infection in early childhood, transmitted by unhygienic contact with older siblings, or acquired prenatally … Over the past century, declining family size, improved household amenities and the higher standards of personal cleanliness have reduced the possibilities of cross-infection in young families. This may have resulted in a more widespread clinical expression of atopic disease.* [4]

Lymphocytes T *helper* (T_H) can be differentiated by certain protein products, defined as interleukins or cytokines. Romagnani and collaborators[5] isolated two sub-populations of cytokines, which they denominated as T_H1 and T_H2. Depending on the molecular stimulus, lymphocytes T_H undifferentiated (T_H0), self differentiate and self multiply themselves in one of these sub-populations.

Lymphocytes T_H1 and T_H2 manage the immune response against intracellular bacteria and helminth respectively. However, this same immune response, when inadequate, produces some of the known immunological diseases:

- T_H1: delayed hypersensitivity (example – contact dermatitis).
- T_H2: immediate hypersensitivity (example – atopic diseases)

An immunological theory attempting to explain the hygiene hypothesis was proposed in the early 90´s: *exposure to infections in the early years of life would direct the future responses of the T_H1 pattern of the life form, inhibiting the atopic illnesses mediated by the T_H2 lymphocytes* [6].

In the decade following the hygiene hypothesis, many studies investigated associations between infections in infancy and atopic diseases.

Some indirect evidence was found, suggesting that a more hygienic environment would favour the development of atopy. The most consistent associations with allergic manifestations have been[7]:

- smaller number of family members;
- larger order of birth (the oldest brother stands a higher chance of being allergic);
- higher social-economic life style;
- "urban" life style;
- more "developed" society.

The problem of these associations is that there could be factors that lead to confusion. For example, children who are raised in a farm style environment are less susceptible to atopic diseases[8]. One could try to explain this result by the theory of hygiene, that is, when born in a rural environment, the child would have more contact with animals and a bigger risk of exposure to bacteria endotoxins[9], directing future immune responses to the T_H1 pattern.

However, according to Horak and collaborators, atopic and school age children who move to farm environments, likewise begin to show a smaller cutaneous reaction to hyper-sensibility tests[10], thus suggesting that the body, at any time and not only in early childhood, can be led to a lesser allergic level due to the rural environment influence, or to the distance from allergenic factors of the urban life style.

Environment pollution is an evident urban allergen[11], but there are others subtler. Rich polyunsaturated fat, or diets poor in vitamins E or C, for instance, can be risk factors for asthma[12] [13]. Therefore, indirect evidences point to the existence of allergen factors in the Western urban life style, mainly in smaller and better provided for families.

A couple of years ago, a narrative review presented the hygiene hypothesis and its immunological theory as "scientific basis" to endorse the following observations, "empirically cited over the centuries" by "homeopathic physicians":

- *"suppression of natural manifestation of acute diseases can cause future chronic diseases"* and
- *"suppressing the manifestation of acute disease, vaccines can subsequently induce chronic diseases, with predominantly allergic symptoms (dermatitis, rhinitis, sinusitis, bronchitis, etc.)".* [14]

The objective of this article is to evaluate the validity of these propositions, that is:

- *Are infections in infancy protection factors against atopy or their clinical manifestations?*
- *Is vaccination (suppressing "benign" infections of infancy) a risk factor for the development of atopy?*

Methods

Qualitative systematic review[15] of Medline (1993-2004) direct epidemiological evidences concerning the influence of childhood infections and vaccination on atopy development.

Medline 1993-2004 data basis was searched for key words:

- hygiene hypothesis;
- infection atopy;
- infection allergy;
- ISSAC[i] infectious diseases;
- vaccination atopy;
- vaccination allergy.

A total of 2268 references were found, 407 related to hygiene hypothesis or the influence of infections and vaccination on atopy development, as indicated at table 1.

Table 1: number of references found in Medline (1993-2004) search using the keywords hygiene hypothesis, infection atopy, infection allergy, ISSAC infectious diseases, vaccination atopy, vaccination allergy.

Date	*Source*	*Key words*	*Total references*	*Specific references*
12/09/04	Medline	hygiene hypothesis	455	128
12/12/04	Medline	infection atopy	245	91
12/12/04	Medline	vaccination atopy	47	29
20/12/04	Medline	infection allergy	1195	121
20/12/04	Medline	vaccination allergy	324	37
20/12/04	Medline	ISSAC infectious diseases	2	1
			2268	407

After exclusion of repeated references, basic research and review papers, 92 original articles in English language providing direct epidemiologic evidence *pro or contra* the hygiene hypothesis were included and analyzed in this review.

[i] International Study of Asthma and Allergies In Childhood

Data were organized in three groups (some articles were classified in more than one group):

- evidence related to infection in infancy and atopy;
- evidence related to helminthes or intestinal flora and atopy;
- evidence related to vaccination and atopy.

The discussion also considered Hahnemann´s teachings on vaccination, childhood infections and chronic diseases development.

Results

Evidence related to infection in infancy and atopy

From a total of 46 articles about the influence of childhood infections on atopy development, 9 (19.6 %) indicate evidences in affirmation of the hygiene hypothesis, 2 (4,3%) present data *pro* and *contra* this theory and 35 (76.1%) against it. Data analysis is summarized at tables 2, 3 and 4.

Table 2: papers with direct evidence *pro* hygiene hypothesis found in Medline (1993-2004) search, with first Author, year of publication, design type*, number (N) of subjects (cases/controls), and quoted fragments of results or conclusions.

Author (1st)	year	design	N	quoted results or conclusions
Ceran O[16]	2004	CCTRL	67/92	recurrent tonsillitis is associated with a decline in the prevalence of asthma
Juntti H[17]	2003	CCTRL	51/51	an early RSV infection results in reduction of SPT** positivity but not of occurrence of atopic diseases
Zejda JE[18]	2003	CHT	663	no incidence of asthma in a group of 38 children who acquired measles before the follow-up started
Menendez C[19]	2002	CS	675	the proportion of children who had bronchiolitis was lower among those who had had malaria episodes than among those who had not
Lell B[20]	2001	CHT	91	children with a high exposure to P. falciparum were at lower risk of an atopic skin reaction
Wickens KL[21]	1999	CCTRL	399/398	Parent-reported rubeola infection (and possibly other similar viral exanthems) was independently associated with a decreased risk of asthma
Lewis SA[22]	1998	CHT	6350	hay fever was less common in those contracting measles infection than in those not infected… However, these effects were strongly confounded by birth order, which was closely associated with the likelihood of receiving measles vaccination and with the risk of hay fever
Calvani M[23]	1997	CS	339	EBV infection in the first years of life is associated with a lower prevalence of high IgE levels
Shaheen SO[24]	1996	CHT	395	Measles infection may prevent the development of atopy in African children.

*CHT: cohort; HCHT historical cohort; CS cross-sectional; CCTRL case control; CT clinical trial; RCT randomized controlled trial; BRCT blind randomized controlled trial; ECO ecological study; SOC series of cases.
** skin-prick test

Table 3: papers with evidence *pro* and *contra* hygiene hypothesis found in Medline (1993-2004) search, with first Author, year of publication, design type*, number (N) of subjects (cases/controls), and quoted fragments of results or conclusions.

Author (1st)	year	design	N	quoted results or conclusions
Bodner C[25]	2000	CCTRL	97/208	exposure to infections as measured by parental reports obtained at age 10-14 years and by serological tests obtained in adulthood did not influence the development of wheezing symptoms or atopic status in adulthood. However, early exposure to measles and family size may be associated with a lower risk of adult onset doctor diagnosed asthma
Bodner C[26]	1998	CS	2111	… membership of a large sibship confers some protection against atopic disease. This does not appear to be explained by the common childhood infections which show conflicting relationships with atopic disease, in that measles may have some protective effect against asthma but the more infections a child has had, the more likely he or she is to have atopic disease. The explanation of the sibship effect is likely to lie elsewhere and the fall in common childhood infections is unlikely to explain the rise in atopic disease

*CHT: cohort; HCHT historical cohort; CS cross-sectional; CCTRL case control; CT clinical trial; RCT randomized controlled trial; BRCT blind randomized controlled trial; ECO ecological study; SOC series of cases.

Table 4: papers with direct evidence *contra* hygiene hypothesis found in Medline (1993-2004) search, with first Author, year of publication, design type*, number (N) of subjects (cases/controls), and quoted fragments of results or conclusions.

Author (1st)	year	design	N	quoted results or conclusions
Vonk JM[27]	2004	CHT	597	A severe respiratory infection in the first year of life appears associated with BHR Development
Camara AA[28]	2004	CCTRL	132/65	In children under 2 years of age, infection with respiratory viruses and family history of allergy were independently associated with wheezing
Chai SK[29]	2004	CS	3610	Tuberculosis (TB) was a significant predictor of atopic symptoms… These findings are contrary to the "hygiene hypothesis"
Cohet C[30]	2004	CCTRL	1584/2539	There was little difference in the prevalence of current wheezing between the childhood infections group (prevalence = 23.5%) and the general population group (prevalence = 24.3%).
Gibbs S[31]	2004	CCTRL	307/295	Increased exposure to infection does not explain the reduced risk of AD** in second and subsequent siblings. These data cast doubt on the hygiene hypothesis…
Stipic-Markovic A[32]	2004	CS	1364	Among children who had pertussis infection the proportion of allergic children was significantly higher.
Kramer MS[33]	2004	CCTRL	819/3276 112/448	Our results do not support the hypothesis that infection protects against atopic eczema or recurrent wheezing in the first 12 months of life.
Cullinan P[34]	2003	HCHT	1250	The sibling effect was unexplained by evidence of infection with either hepatitis A or Helicobacter pylori, or by counts of infections or antibiotic prescriptions in early life.
Linneberg A[35]	2003	CCTRL	788/647	…exposure to intestinal bacterial pathogens was associated with a higher prevalence of atopy.
Jones AP[36]	2003	HCHT	402	Associations with a chest infection and a family history of atopic conditions were similarly strong predictors of eczema and rhinitis prevalence.
Nuhoglu Y[37]	2003	CS	252	Tuberculin reactivity is not inversely associated with atopy in asthmatic children.
Sidorchuk A[38]	2003	CHT	2561	Associations between EBV seropositivity and the occurrence of asthma were not apparent
Olesen AB[39]	2003	HCHT	9744	The incidence of atopic dermatitis increased after… measles infection, which is surprising in view of the hygiene hypothesis
Bager P[40]	2002	HCHT	889	The risk of atopy increased significantly with increasing number of childhood infections in the first 2 years of life

*CHT: cohort; HCHT historical cohort; CS cross-sectional; CCTRL case control; CT clinical trial; RCT randomized controlled trial; BRCT blind randomized controlled trial; ECO ecological study; SOC series of cases.
** atopic dermatitis

Table 4: (continued) papers with direct evidence *contra* hygiene hypothesis found in Medline (1993-2004) search, with first Author, year of publication, design type*, number (N) of subjects (cases/controls), and quoted fragments of results or conclusions.

Author (1st)	year	design	N	quoted results or conclusions
McKeever TM[41]	2002	CHT	29238	We found no evidence that exposure to infections reduced the incidence of allergic disease.
McKeever TM[42]	2002	HCHT	24690	Our findings suggest that exposure to antibiotics and to infections in utero is a potentially important risk factor in the development of allergic disease.
Schauer U[43]	2002	CCTRL	42/84	Severe respiratory syncytial virus bronchiolitis during the first year of life is an important risk factor for the development of recurrent wheezing and sensitisation to common allergens during the subsequent year
van der Sande MA[44]	2002	CCTRL	66/122	Severe RSV infection in early life is associated with a higher production of type 2 cytokines in Gambian children at 5 years of age
Wenzel SE[45]	2002	CCTRL	13/26	Children were also less atopic…in the respiratory syncytial virus immune globulin group than in the control group.
Chen CF[46]	2001	CS	8723	The prevalence of infectious diseases was significantly higher in children with allergic disease symptoms
Haby MM[47]	2001	CS	974	Factors which increased the risk of recent asthma were: having had a serious respiratory infection in the first 2 years of life…
Suzuki N[48]	2001	SOC – CCTRL	70 - 17/26	Infection of M. tuberculosis does not systematically upregulate Th1 cells in some patients, and is unlikely to prevent allergic disorders like asthma
Larouch V[49]	2000	CCTRL	42/42	Asthma and AHR** were found more frequently in young adults with a past history of bronchiolitis, suggesting that this type of respiratory infection may contribute to altered pulmonary function in adulthood
Paunio M[50]	2000	CS	547910	Measles and atopy occur more frequently together than expected, which does not support the hypothesis that experiencing natural measles infection offers protection against atopic disease
Hughes CH[51]	1999	CCTRL	200/200	This study has shown an association between presentation with respiratory infection during gestation and childhood asthma
Ferrari M[52]	1999	CS	1104	Exposure to SRI*** is a risk factor for asthma in the past (ie, asthma in childhood and adolescence)
Strannegård IL[53]	1998	CS	6497	Reactivity to the atypical mycobacteria M. avium and M. scrofulaceum were higher rather than lower in allergic than in nonallergic children… These findings do not support the hypothesis that early mycobacterial infections have a suppressive effect on the development of atopic disease
Sarafino EP[54]	1998	CS	121	Asthma severity was correlated with the frequencies of prior and recent respiratory Infections
Nilson [55]	1998	RCT	669	There was a positive association between whooping cough and asthma by 2 1/2 years of age
Aberg N[56]	1996	CS	2481	The strongest background factor, a family history of the diseases, was more common in children with another strong risk factor, particularly for asthma: high frequency of upper respiratory tract infection
Forster J[57]	1996	CHT	609	By the first birthday, mite sensitization could only be seen in the RSV-infected children; grass pollen sensitization was associated with RSV seropositivity
Petridou E;[58]	1995	CS	414	History of frequent infections was positively associated with IgE levels, although the relation was statistically significant only in the older age group
Sigurs N[59]	1995	CHT	140	Respiratory syncytial virus bronchiolitis during the first year of life apparently is an important risk factor for the development of asthma and sensitization to common allergens during the subsequent 2 years
Wjst M[60]	1994	CS	9484	The adjusted odds ratio for any allergic sensitization after pertussis was only slightly increased in western and in eastern Germany
Schuster A[61]	1993	SOC	25	Our results indicate that pertussis may induce IgE production in affected children.

*CHT: cohort; HCHT historical cohort; CS cross-sectional; CCTRL case control; CT clinical trial; RCT randomized controlled trial; BRCT blind randomized controlled trial; ECO ecological study; SOC series of cases.
** airway hyper-responsiveness
***serious respiratory infection

Are infections in infancy protection factors against atopy or their clinical manifestations?

Regarding the direct evidences, Table 4 presents an overwhelming data evidence against the hygiene hypothesis, which not only was not confirmed, as there are evidences that the so called "benign" infancy diseases increase the risk of atopy. The following are examples of this evidence.

McKeever and collaborators analyzed the data of more than 29 thousand children, from date of birth, investigating associations between personal infections, brother/sister infections, use of antibiotics and the occurrence of allergic diseases (asthma, eczema, and hay fever). The results revealed that exposure to infection in the early years of life did not reduce the incidence of allergic diseases. However, the use of 4 or more series of antibiotics in the 1st year of life was associated with a higher risk to these atopic diseases[41]. As a matter o fact, other studies have associated the use of antibiotics [30 62 63] or paracetamol[30] in the first years of life with future allergy.

Children who have been struck with pertussis tend to produce larger quantities of IgE or intra-dermal responses against common antigen [60,61]. Strachan himself observed a large risk of asthma in infancy in children who had previously had pneumonia or pertussis[64].

Children who had an infection transmitted by the respiratory sincicial virus with less than one (1) year of life showed a higher risk of wheezing in the 3 first years of life and increased cytokines T_H2 (IL-5 and IL-13) at 5 years old[43].

The International Study of Asthma and Allergies in Childhood (ISAAC) was founded to maximize the value of epidemiological research into asthma and allergic disease by establishing a standardized methodology and facilitating international collaboration[65] . Combining ISAAC´s questionnaires with supplementary questions about infectious diseases, Chen and collaborators studied 8723 children aged from 10 to 18 years old and found a 12-month prevalence of infectious diseases significantly higher in children with allergic disease symptoms (defined as asthma, allergic rhinitis, or atopic dermatitis)[46]. These findings oppose the idea that allergic diseases manifest in infections-suppressed individuals.

In the larger study performed investigating the occurrence of an infection and atopy, Paunio and collaborators analyzed the data of 547910 individuals, between 14 months and 19 years of age, in Finland, and compared the occurrence of atopic manifestations between those who had had measles and those who had not. The results indicated a significant prevalence towards asthma (OR = 1.67 95% CI 1.54-1.79), eczema (OR = 1.32 95% CI 1.27-1.36) and allergic- rhinitis (OR = 1.41 95% CI 1.33-1.49) in those who had had measles. The positive association between measles and atopy was evident in all ages, in those who lived in the country or those from the city and between those who had much or little contact at home or in day care centers. [50]

It was postulated[66] that epidemiologic investigations attempting to identify associations between sole infections in infancy and atopy could fail, since perhaps it could be that the total load of microbe stimulus (instead of an isolated infection) be responsible for the directing of the immune response for a T_H1 pattern, and this microbe load should also strike the body at the adequate age, called the "window of opportunity", conventionalized as the first 2 years of life[67].

To evaluate the "window of opportunity", Bager and collaborators investigated the exact year in which the measles, chicken pox, mumps and Rubella had occurred in childhood (prior to 7 years of age) and the risk of atopy in adult life, evaluated by means of RAST of 11 common respiratory antigens. The population studied included 889 pregnant women in Denmark. Infection with measles in the 1st year of life was

associated with a larger risk of atopy (OR = 3,36 95% CI 1,47-7,68) and the risk of atopy increased significantly in accordance with the increase in number of these infections in the first two years of life [40].

In another evidence against the hygiene hypothesis and against the hypothesis of "total load of microbe stimulus", Bodner and collaborators evaluated the information regarding the presence of asthma, eczema and hay fever in 2111 youngsters between the ages of 10 and 14 years old and the previous infection history of measles, mumps, rubella, chicken pox and/or pertussis, before and after 3 years of age. The results revealed a strong association between the largest number of these infections before 3 years of age and a larger risk of asthma. There was also a large increase in the risk of eczema and hay fever between the youngsters with multiple infection histories (chicken pox, mumps and rubella) in early infancy[26].

Strachan, "father of the idea", on reviewing the researches after a decade of the proposition of the hygiene hypothesis, stated:

> "*The totality of current evidence, from cross sectional and longitudinal studies of common specific and non-specific infectious illnesses in infancy and childhood offers no support to the "hygiene hypothesis".*
>
> *"There is undoubtedly something to explain, but the results of the studies which have more directly addressed infection as the explanatory factor have been disappointing and often difficult to interpret".* [68]

Evidence related to helminthes or intestinal flora and atopy

What appears to be a "new" trend between some researchers is that of understanding the intestinal flora to be a possible modulator of the immunological response[69]. The association between intestinal parasites and atopy, however, is not new. Studies on the subject date from the 70´s[70], but recent papers have been instigated by hygiene hypothesis research.

This review found 22 researches about the direct influence of helminthes or intestinal flora on atopy, pointing the majority of the results to an inverse relation, that is, individuals infested are less subjected to allergic manifestations, by not yet known immunological mechanisms.[34 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91]

The "anti-allergic" effect of helminthes is not related to any immune permanent deviation acquired in early childhood, once anthelminthic treatment of chronically infected children results in increased atopic reactivity[72]. As a matter o fact, helminthiasis provokes a T_H2 response, adding evidence against the theory that a deviation for the T_H1 response in the beginning of childhood reduces atopy risk[92]. Strachan, in a recent review, reconsidered this immunologic explanation as "somewhat simplistic" [93].

Even within the gastrointestinal habitat, the relationship host-parasite seems to influence atopy development in opposite ways: probiotics, geohelminth infections and orofecal microorganisms which are considered to be markers of poor hygiene (hepatitis A virus, *Helicobacter pylori*, and *Toxoplasma gondii*) are associated with a lower allergic sensitization, whereas exposure to intestinal bacterial pathogens (*Clostridium difficile*, *Giardia lamblia*) has been associated with a higher prevalence of atopy [35 90].

Evidence related to vaccination and atopy

From a total of 28 articles about the influence of vaccination on latter atopy development, 6 (21.4%) present results suggesting an allergenic effect of specific vaccines and 22 (78.6%) found no sensitization, or even show a protective effect of vaccination on atopy. Data is summarized at tables 5 and 6.

Table 5: papers with direct evidence indicating an allergenic effect of specific vaccines, found in Medline (1993-2004) search, with first Author, year of publication, design type*, vaccine(s) studied, number (N) of subjects (cases/controls), and quoted fragments of results or conclusions.

Author (1st)	Year	design	Vaccine	N	quoted results or conclusions
Olesen AB [39]	2003	HCHT	MMR	9744	The incidence of atopic dermatitis increased after measles, mumps and rubella vaccination.
Laubereau B [94]	2003	CS	Hib**	1943	We found little evidence for an association between Hib-vaccination and some atopic outcomes and causality cannot be ascertained.
Hurwitz EL[95]	2000	CS	DPT Tetanus	13944	DTP or tetanus vaccination appears to increase the risk of allergies and related respiratory symptoms in children and adolescents. Although it is unlikely that these results are entirely because of any sources of bias, the small number of unvaccinated subjects and the study design limit our ability to make firm causal inferences…
Farooqi IS[62]	1998	HCHT	Pertussis (whole cell	1934	Predictors of subsequent atopic disease: maternal atopy … immunisation with whole-cell pertussis vaccine… and treatment with oral antibiotics in the first two years of life…
Lewis SA[22]	1998	CHT	Measles	6350	…hay fever was more common in those given measles vaccination than in those not vaccinated (OR 1.16, 95% CI 1.03-1.31). However, these effects were strongly confounded by birth order, which was closely associated with the likelihood of receiving measles vaccination and with the risk of hay fever
Kemp T[96]	1997	CHT	DPT Polio	1242	The 23 children who received no diphtheria/pertussis/tetanus (DPT) and polio immunizations had no recorded asthma episodes or consultations for asthma or other allergic illness before age 10 years

* CHT: cohort; HCHT historical cohort; CS cross-sectional; CCTRL case control; CT clinical trial; RCT randomized controlled trial; BRCT blind randomized controlled trial; ECO ecological study; SOC series of cases.

** Haemophilus influenzae type b

Table 6: papers with direct evidence indicating no allergenic effect, or even a protective efect of specific vaccines or vaccination as a whole, found in Medline (1993-2004) search, with first Author, year of publication, design type*, vaccine(s) studied number (N) of subjects (cases/controls), and quoted fragments of results or conclusions.

Author (1st)	year	desing	Vaccine	N	quoted results or conclusions
Jedrychowski W[97]	2004	CHT	Measles	1005	Risk of allergy diagnosed by a physician in vaccinated children… was about half of that in the reference group … the same was found for asthma diagnosed by a physician and for susceptibility to respiratory infections
Stipic-Markovic A [32]	2004	CS	Pertussis	1364	Among children who received pertussis vaccine there was a significantly lower proportion of allergic than non-allergic children
Maitra A[98]	2004	CHT	Pertussis	13109	No diferences in % asthma, wheezing, atopy among fully vaccinated, partially vaccinated or non vaccinated.
Bager P[99]	2003	HCHT	BCG	2224	BCG vaccination in childhood does not influence the development of allergy or asthma .
Bager P[100]	2003	HCHT	Smallpox	2181	Our findings do not suggest that childhood vaccination against Smallpox… influences the development of atopy or allergic rhinitis.
Bernsen RM[101]	2003	HCHT	DTP + Polio	1724	Vaccinated children had a reduced risk of atopic disorders.
Grüber C[102]	2003	CHT	9 vaccines	943	Children with a higher vaccination coverage seemed to be transiently Better protected against development of atopy in the first years of life
Krause TG[103]	2003	CS	BCG	1575	The risk of atopy was the same in BCG-vaccinated compared with unvaccinated children…
Marks GB [104]	2003	HCHT	BCG	309/442	Among subjects with a family history of rhinitis or eczema, BCG vaccination was associated with a lower prevalence of current asthma
Nilsson L [105]	2003	BRCT	DTP/DT whole cell or acell.2 or 3 comp	667	Pertussis vaccination in infancy with any of these vaccines was not associated with allergic manifestations at the age of 7 years, apart from a higher prevalence of positive skin prick test results after an experimental 2-component vaccine, which is no longer in use
Cavallo GP[106]	2002	SOC	BCG	20	Total IgE and allergen-specific IgE levels were significantly decreased after BCG vaccination
Jang AS[107]	2002	CS	BCG	486	Tuberculin response due to mycobacterial infection status have no effect on AHR in schoolchildren
Anderson HR[108]	2001	CS	DTP,BCG Measles	721601	No association between BCG and atopic diseases. DTP and Measles Vaccines have negative associations with atopic diseases.
Arkwright PD[109]	2001	BRCT	BCG like procedure	41	intradermal injection of killed Mycobacterium vaccae was associated with an improvement in the severity of the dermatitis in children with moderate-to-severe disease
Grüber C[110]	2001	CHT	BCG	774	Period and lifetime prevalences of atopic dermatitis and recurrent wheezing tended to be lower in the BCG-vaccinated group early in life…
Wong GW[111]	2001	CCTRL	BCG	359/1842 424/556	The prevalence rates of asthma ever, wheeze ever, current wheeze, current rhinoconjunctivitis, and current flexural eczema were not significantly different between tuberculin positive and negative subjects
Aaby P[112]	2000	HCHT	BCG	271/53	BCG vaccination given early in infancy may prevent the development of atopy in African children
Assa'ad A[113]	2000	RCT	Pertussis Acell	51/49	A 2-component APV did not predispose to an increase of allergen-specific IgE in an adult population
Ryan EJ[114]	2000	CS	Pertussis acell.	42	…levels of IgE to common allergens and the prevalence of positive skin prick test were unaffected by the booster vaccination.
Henderson J[115]	1999	CHT	Pertussis	9444	No evidence was found that pertussis vaccination increases the risk of wheezing illnesses in young children
Nilsson L [55]	1998	RCT	Pertussis	669	We found no support for a drastic increase in allergic manifestations after pertussis vaccination.
Alm JS[116]	1997	CCTRL	BCG	216/358	Early BCG vaccination in children with atopic heredity does not seem to affect the development of atopic disease before school age

* CHT: cohort; HCHT historical cohort; CS cross-sectional; CCTRL case control; CT clinical trial; RCT randomized controlled trial; BRCT blind randomized controlled trial; ECO ecological study; SOC series of cases.

Is vaccination, suppressing "benign" infections of infancy, a risk factor for the development of atopy?

Vaccines are heterogeneous products, each one with their specific immunogenic characteristics, which should be separately analyzed. Researches that intend to investigate the global effect of immunization on atopy development normally compare results on vaccinated and non-vaccinated children. When done in small communities this tends to incur in a selection bias, since they evaluate a relatively smaller number of children who have not been vaccinated due to religious, philosophical or health reasons [55] [95] [96]. The following describes two multi-centric studies that do not follow this trend, showing that main current vaccines do not cause allergic diseases.

As already mentioned, the International Study of Asthma and Allergies in Childhood (ISAAC) is the most wide-ranging international effort on asthma and atopy research. Phase One used simple core written questionnaires for two age groups (6-7 year old children and 13-14 year old adolescents), and was completed in 156 collaborating centres, in 56 countries and a total of 721601 children participated [65]

Anderson and collaborators performed an ecological study with data taken from ISAAC to investigate eventual associations between the prevalence of atopic symptoms (asthma, allergic rhinoconjunctivitis and atopic dermatitis) in 6-7 year old children and 13-14 year old adolescents and the rate of vaccine coverage against diphtheria – tetanus – pertussis (DTP), measles and tuberculosis. In 1995 and 1996, questionnaires were filled in (by the parents) for the 6-7 year old children and by 13-14 year old adolescents. The vaccine coverage for these diseases was defined at national level with data from the WHO and, at local level, by correspondence from the research centres. The results indicated a significantly smaller atopy rate at 13-14 years old, in the youngsters that had received DPT and anti-measles vaccine. There were no associations between tuberculosis vaccine coverage and atopic diseases. The authors conclude: "International variations in childhood atopic diseases are unlikely to be explained by variations in immunization" [108] .

In an original prospective cohort, Grüber and collaborators closely followed, from birth to 5 years old, 943 children from 5 German cities, approximately 40% with a high risk of atopy (2 or more atopic family members or cord IgE ≥ 0,9 kU/L) and 60% randomly controlled, periodically investigating:

- the prevalence of asthma, rhinoconjunctivitis and atopic dermatitis (follow-up visits at 3, 6, 12, 18 months; 2, 3, 4 and 5 years);
- IgE titles (total and specifics for 9 common antigens) at birth, 1, 2, 3 and 5 years of age;
- the number of doses of each vaccine and the number of cumulative doses (counting the doses of all vaccines).

They observed:

- lower prevalence of asthma (at 1 and 3 years), atopic dermatitis (at 6 and 18 months; 3 and 5 years) and rhinoconjunctivitis (at 5 years) and lower sensitization rates and total IgE levels at all examination dates among measles/mumps (double vaccine in Germany) vaccinated children;
- smaller risk of developing atopic dermatitis up to the age of 5 years among children from families with a history of atopy and vaccinated against measles/mumps whilst, between children without a atopy family history, a statistically significant association had not occurred;
- lower prevalence rates of atopic dermatitis at most examination intervals (with statistical significance at 6 months, 2, 3 and 5 years) among rubella vaccinated children;
- tendency to lower allergic diseases prevalence at 5 years of age among pertussis-vaccinated children with statistic significance for atopic dermatitis;
- inverse relationship between pertussis doses and sensitization rate after the first birthday;
- lower risk for atopic dermatitis for children who received 3 or 4 doses of diphtheria/tetanus vaccine as compared to children who received less than 3 doses;
- inverse relationship between diphtheria/tetanus doses and sensitization rate at 2 years of age;
- no statistically significant relationship (at any age) between atopy or allergic diseases and *Haemophilus influenzae* Type b vaccination;
- no statistically significant relationship (at any age) between allergic diseases or sensitization and polio vaccination, nevertheless the obtained a higher IgE level among vaccinated children at 2 years of age, but not at 5 years

- inverse association between the cumulative dose of vaccines and atopy, that is, the larger the vaccine coverage (cumulative dose of any vaccine), lesser was the prevalence of atopic dermatitis, asthma and allergic sensitization. [102]

Other studies about associations between atopy and vaccination against pertussis, measles, tuberculosis, *Haemophilus influenzae* and smallpox are analyzed below.

Vaccination against pertussis

The vaccines against pertussis can be prepared as of suspensions of inactivated *Bordetella pertussis* (cellular vaccine) or from various combinations of the bacteria products or components, giving origin to one or more types of cellular vaccines.

The studies that investigate the association between vaccination against pertussis and atopy have revealed controversial results. According to a review performed by Grüber and his team: "*although data from animal experiments and circumstantial clinical reports suggest that pertussis vaccination can promote atopy and allergic diseases, well-controlled clinical trials do no support this hypothesis*" [117] .

Henderson and collaborators prospectively studied 9444 children, periodically evaluated from birth until 2 ½ years old, in relation to the cumulative occurrence of wheezing, vaccine status and other biological and environment indicators. The results showed that the vaccination against pertussis did not increase the risk of wheezing in any of the periods of evaluation[115].

Within a multi-centric study to investigate adverse effects of the vaccination against pertussis in Switzerland, 667 children were randomly chosen for a double-blind comparison between the occurrence of atopy and the type of vaccine administered [(cellular + DT[ii]) or (acellular with 2 components + DT) or (acellular with 5 components + DT) or (DT, as control]. Questionnaires and skin prick tests with common antigens were applied to the 7 months and to the 2 ½ year olds. At 7 years of age, the children were again

[ii] Diphtheria and Tetanus

submitted to skin tests (this time, without blinding). The cumulative incidence and the prevalence of atopic diseases were the same in the groups that received the vaccines against pertussis and DT, when compared to the group immunized with DT only. The only exception was the group vaccinated with the acellular pertussis vaccine, prepared with 2 components, which showed a larger prevalence of positive skin prick test results [105].

An historical fact must be considered when evaluating vaccination against pertussis/atopy: bearing in mind the concern of collateral neurological effects, the vaccine coverage against pertussis in Great Britain dropped from 75% to 40%, between 1974 and 1977, without any reduction in the incidence of asthma at the end of the 70´s decade, instead there was an increase in the notifications of pertussis and in the cases of death brought on by this illness[118].

Death rates due to pertussis in non-vaccinated children are not only part of the history of countries with first-rate vaccine coverage. In the 90´s decade, 103 deaths were attributed to pertussis in the USA, with a confirmed diagnosis in 101 of these cases by culture, serology, PCR, or hystopathology. Of these 103 deaths, 101 of them occurred in children, being that 96 (94%) had not received the three doses of vaccine containing the pertussis toxin, mostly because they were too young (< 4 months), since in the USA, like in Brazil, the vaccine doses are administered at 2, 4 and 6 months of age[119].

BCG

Marks and collaborators performed an historical cohort between children of 7 and 14 years of age, born in two different districts of Sydney, Australia, whose parents were Asiatic immigrants. One of these districts had regularly vaccinated immigrants´ children with BCG but the other district had not. Thus, 309 children vaccinated with BCG were compared with 442 not vaccinated in relation to parent antecedents and occurrence of atopic diseases, total IgE and RAST, specific T_H1 and T_H2 lymphocyte cytokines. The results showed an association between vaccination with BCG and a smaller prevalence of asthma between individuals with a family history of rhinitis or atopic dermatitis (OR = 0,46 95% CI 0,22-0,95) [104].

Measles (and MMR)

Paraphrasing Rall: *"It is probable that many researchers who work with MV[iii] have not actually seen a case of acute infection and, therefore, the impact of this virus on human health may seem somewhat abstract. It is thus important to begin with a sobering statistic: According to the World Health Organization, at least 40 million cases of acute MV infection occurred id 2001. Of these, over a million resulted in death, the majority of which were children in developing countries".* [120]

Strachan, in the already cited revision about the hygiene hypothesis, resumes the history about vaccination against measles and atopy: i*n Guine-Bissau, children who had measles during an epidemic showed less reactivity in the intra-dermic tests than the children who had not had the illness, but who were subsequently vaccinated against measles. This finding can be explained by a protection offered by the uncultured virus or an allergic sensibility caused by the vaccine, or furthermore, by a larger mortality rate of atopic children during an epidemic*. Nevertheless, according to Strachan, the cohort results of over 13000 British children, of which approximately half of them had been vaccinated and the other half not, evidenced the safety of the vaccine, since an evaluation at 5 years of age did not who differences in the incidence of hay fever or eczema between those immunized or not, likewise there was not a lesser incidence of these atopic manifestations in the children who had had measles. [68]

The evidences provided so far by the ISAAC[108] showing the protective effect of measles vaccination on atopy development are also tranquilizing and seem to surpass previous data on contrary [22 39].

Haemophilus influenzae

Laubereau and collaborators evaluated 1943 children between the ages of 5 and 14, investigating associations between those immunized and those not immunized against the type b (Hib) *Haemophilus influenzae* and the occurrence of atopy (RAST for 5 common air antigens, performed with 1676 children) or atopic diseases. Of the total number of children, 42% received the Hib vaccine. Results showed that the children vaccinated against the *Haemophilus* showed a slightly higher asthma risk (OR = 1,86 95% CI

[iii] Measles Virus

1,05-3,32), hay fever (OR = 1.55 95% CI 0,95-2,54), eczema (OR = 1,03 95% CI 0,70-1,50) or atopy (OR = 1,25 95% CI 0,94-1,67) for at least 1 specific IgE with com RAST >0. [94]

SmallpoX

The possible association between atopy and the extinct vaccine against smallpox was investigated by Bager and collaborators who evaluated a cohort of approximately 2000 women and relation to the vaccine status, information from the participants about rhinitis and asthma and atopic sensitivity (RAST to 11 air antigens). The authors did not obtain any whatsoever association between the anti-smallpox vaccine and the occurrence of atopy or rhinitis in adult women. The results further indicated a discreetly smaller asthma risk among those [99].

Discussion

Previous epidemiological reviews have already confirmed the association between atopy or allergic diseases and a number of lifestyle factors or the sibling effect, stressing that hygiene hypothesis failed to explain the allergy epidemic through a reduced microbial burden in early childhood [7 92 121] . Recent epidemiological reviews on vaccination and atopy also concluded that main current vaccines do not cause allergic diseases. [122 123]

Back to the homeopathic field, Hahnemann´s teachings do not endorse the observations, “empirically cited over the centuries” by “homeopathic physicians”, which consider infectious diseases in childhood as benign and protectors against future chronic diseases:

> *"Hence another adequate opportunity to observe that great epidemic diseases such as smallpox, measles, miliary rubra, scarlet fever, whooping cough, autumn dysentery and typhoid, after completing their course, especially without a meticulous homeopathic treatment, leave the organism so struck and irritated that many people who appear to have recuperated, the Psora, which was dormant and latent before, now rapidly awakens, be it in the form of eruptions similar to scabies, or be it other forms of chronic suffering…"*
>
> *S Hahnemann*[124]

As can be seen, quite to the contrary, the creator of Homeopathy evaluated epidemic diseases as important risk factors for the development of chronic diseases, including eruptions similar to scabies. Among the chronic diseases, which today we refer to as allergies, would not atopic dermatitis be an eruption similar to scabies?

Concerning vaccination, Hahnemann knew the results of the initial anti-smallpox vaccine. In more than 60 years of observation of immunized individuals, nothing was ever mentioned by him about the development of chronic diseases caused by the Jenner vaccine, but he did emphasize on the benefits provided by vaccination: "*a marking beneficial fact".* Smallpox no longer "*decimated half or three quarters of the children in the cities visited".* [125] By observing the results of smallpox immunization, Hahnemann understood vaccination as being an "anticipated homeopathic cure" [126] [127].

Criticisms about vaccination were introduced in the homeopathic publications by the English homeopath Burnett, who lived at the end of the 19th century. According to Burnett:

> *"…in vaccinating a person we are diseasing him; we communicate vaccinosis to him; if he, in addition to the vaccinosis, now gets smallpox, he is the more likely to die the worse he has the vaccinosis".* [128]

Notwithstanding current still limited knowledge relative to the immunologic memory mechanisms, in as rough way the immunologists do know that the efficiency of a vaccine depends on the capture and processing of its antigens by the dendritic cells, which present these antigens to the T cells, simultaneously stimulating the maturing of these lymphocytes into effectors or memory cells. [129]

Therefore, Burnett´s vaccine theory has no immunologic foundation. On vaccinating an individual with a certain antigen, we are not making him ill, but we are stimulating the organism to coordinate a more efficient response in case of new contact *with a similar pathogen* (as in a "anticipated homeopathic cure").

While distancing itself from Hahnemann´s initial pro-vaccination attitude, homeopathic literature multiplied prejudices in relation to the adverse effect of vaccines, which have been considered responsible from "*an increase in susceptibility of diseases in general*" [130] up to the "*social epidemic violence in the United States*" [131].

It is consensus that vaccination, as any other procedure regarding human health, is not exempt of risks or adverse effects, and that each vaccine must be evaluated by its risk/benefit rate. But, considering vaccine coverage as a whole, ample and well designed studies such as the above mentioned made by Anderson or Grüber, show vaccination as a protection factor against atopic diseases. One possible explanation for these findings is that vaccines protect against some serious infancy infections, acute diseases which are risk factors for chronic diseases development, like atopic manifestations. In the hahnemannian terminology, vaccines avoid a larger development of the *Psora* caused by epidemic diseases. This does not mean to say that a certain vaccine could not reveal allergenic effects, such as present *Haemophilus* vaccine may do.

On defending his hygiene hypothesis, Strachan considers it as "*biologically plausible explanation for the variations in allergy over time, between countries, between more and less affluent households, larger and smaller families, and by position within the family".* [68]

If different life or diet styles could explain some of those allergic variations, the fact of the first born being more susceptible to atopy than his younger brothers is a difficult biological explanation, besides the hygiene hypothesis. However, perhaps Strachan could have considered a non-biological explanation.

The possibility of psychological stressors aggravating atopic manifestations has already been established[132] [133] [134] [135] [136] [137]. Eksi and collaborators, for example, found a larger score of behaviour problems (parents quarrelling at home, unsatisfactory relationships with brothers, etc.) between asthmatic children than between controls. [138]

Perhaps inadequate (or excessive) parental care, or even the birth of the second or more children, can function as stressing experiences, harmful set-offs of atopic chronic diseases in a susceptible first born. This can be a new theory to be investigated: the “hypothesis of the stressed first born”.

Conclusions

- *Infections in infancy are not protection factors against atopy or its clinical manifestations. To the contrary, there are evidences that place these infections among the risk factors for the development of atopic diseases. These evidences confirm Hahnemann´s observations that considered epidemic diseases as harmful set-offs, capable of provoking the development of chronic diseases.*

- *Vaccination, as a whole, is not a risk factor for the development of the atopy. On the contrary, there are evidences of an inverse association between the degree of vaccine coverage and the risk of atopy and atopic diseases, notwithstanding the eventual allergenic effect of some specific vaccines.*

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