Pediatr Allergy Immunol 2002: 13: 172–176
Printed in UK. All rights reserved

Copyright © 2002 Blackwell Munksgaard

PEDIATRIC ALLERGY AND IMMUNOLOGY
ISSN 0905-6157

Review Article

Could administration of bacille Calmette-Guérin vaccination at birth protect from the development of asthma and allergic diseases in the western world? Has this question been adequately investigated?

Krishna MT, Salvi SS. Could administration of bacille Calmette-Guérin vaccination at birth protect from the development of asthma and allergic diseases in the western world? Has this question been adequately investigated?
Pediatr Allergy Immunol 2002: 13: 172–176. © 2002 Blackwell Munksgaard

Asthma and allergic diseases are disorders with a predominant Th2 immune response and there is some evidence of an inverse correlation between incidence of tuberculosis and prevalence of allergic diseases. Skewing the immune response towards a Th1 phenotype has been shown to suppress allergic inflammation. One of the ways this could be achieved is by administration of BCG vaccination early in life. Unfortunately, studies examining the protective role of BCG vaccination early in life against development of allergic diseases have shown some conflicting results and this article critically discusses the pitfalls in the currently available data. We propose that well controlled double blind placebo-controlled multi-centre study is carried out to address this important question and if this study shows a favourable outcome simple measures such as offering BCG vaccination early in life could help reduce prevalence of allergic diseases.

Mamidipudi T. Krishna and Sundeep S. Salvi
University of Southampton, Southampton, UK

Key words: allergy; asthma; BCG vaccine; prevention

Dr M. T. Krishna, Medical Specialties (RCMB Division), Level D, Center Block, Southampton General Hospital, Tremona Road, Southampton SO16 6YD, UK
Tel.: (023) 80794155
Fax: (023) 80701771
E-mail: mtkrishna@yahoo.com

Accepted 23 October 2001

The rising prevalence of asthma in western countries

There is now little doubt that the rising global prevalence of asthma is linked to several factors, including indoor environment, western lifestyle, pet ownership, diet, and early sensitization to allergens. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee reported a world-wide variation in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema (1). They reported some striking differences in the prevalence of these allergic disorders in 13–14-year-old children from different countries. For asthma, the highest 12-month prevalences of self-reported symptoms from written questionnaires were 17–37% in the UK, 27–33% in New Zealand, 25–34% in Australia and 30% in Ireland, and the lowest were 1% in Indonesia, 2% in Albania, 1–10% in Ethiopia, 1–17% in India, 7% in Pakistan, and 6% in Uzbekistan. The key message from this world-wide study was that the prevalence rates of asthma were highest in English-speaking developed countries.

Most studies thus far have focused on risk factors for the development of atopic disorders, but less is known about factors that could protect from the development of asthma and allergic diseases.

Th1/Th2 paradigm: An inverse association between tuberculosis and asthma

Research in the last decade has highlighted the key role played by T helper (Th) cells in orchestrating the chronic mucosal inflammation in asthmatic airways (2). Th cells have been broad-

ly categorized into two subtypes based on their antagonistic cytokine profile (3). Whilst Th1 cells preferentially produce interleukin (IL)-2, interferon-γ (IFN-γ), and tumour necrosis factor-β (TNF-β), and are implicated in the development of delayed (type-IV) hypersensitivity reactions in chronic granulomatous diseases such as tuberculosis, leprosy, and sarcoidosis, Th2 cells produce IL-4, -5, -9 and -13, but not IFN-γ and IL-2 (3). Whilst IL-4 and -13 are important in inducing isotype switching of B cells to immunoglobulin E (IgE) synthesis (3), IL-5 increases survival, maturation, and activation of eosinophils (4), a key inflammatory cell in asthma. Furthermore, IL-13 has been shown to have additional biological properties, including the ability to induce mucosal inflammation, epithelial damage, eosinophil influx, bronchial hyper-responsiveness (BHR), and smooth muscle hypertrophy – all characteristic features of asthma (5). There is also recent evidence to link IL-9 as a candidate gene for asthma. IL-9 has been associated with IgE synthesis, BHR, and mucin production (6–9). Whilst Th2 cytokines drive the allergic inflammation, IFN-γ has a strongly protective influence preventing such a response (2–5).

It has now been generally accepted that asthma and allergic diseases are disorders with a predominant Th2 immune response, and a few studies have shown that alleviation of symptoms from allergic rhinitis could be achieved by tilting the immune response towards a Th1 phenotype or by suppressing the Th2 immune response (10,11). There is also indirect evidence from epidemiological studies that an inverse association exists between tuberculin responses and skin-prick test (SPT) positivity (12). More recently, some studies have highlighted the protective effect of mycobacterial infections, *Mycobacterium tuberculosis* (MTB) in particular, in the development of allergic diseases. An epidemiologic analysis was conducted to investigate the relationship between tuberculosis notification rates and the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema in 85 centres from 23 countries in which standardized data were available (13). These essentially comprised countries in Europe, as well as the USA, Canada, Australia, and New Zealand. Tuberculosis notification rates were significantly inversely associated with the lifetime prevalence of wheeze and asthma. An increase in the tuberculosis notification rates of 25 per 100 000 was associated with an absolute decrease (by 4.7%) in the prevalence of wheeze. Symptoms of allergic rhinoconjunctivitis in the previous 12 months were also inversely associated with tuberculosis notification rates. Moreover, it has been shown that infection with *M. tuberculosis* significantly suppresses the Th2 immune response (14). The bulk of this evidence prompts us to consider safe and simple methods by which development of a predominant Th2 immune response can be suppressed early in life, thereby blocking the development of allergic diseases.

Pregnancy is characterized by Th2 predominance. This is an essential prerequisite for a successful outcome as the Th2 environment prevents fetal-allograft rejection. IL-4 and IL-13 are produced in the human amniotic epithelium in the first and third trimesters and in the second trimester, respectively (15,16). The concentration of IL-10 has been shown to be higher in the amniotic fluid of atopic women as opposed to non-atopic women (17). Furthermore, a reduced cell-mediated immune state has been described in pregnancy (18), which is attributed to a reduction in natural killer (NK) cell activity. Additionally, IFN-γ, a Th1 cytokine, is an abortifactant whose effect may be mediated through activation of NK cells; clearly such an environment is undesirable for maintaining pregnancy (19). However, fetal peripheral blood mononuclear cells (PBMC) still produce some IFN-γ to counteract the effects of the Th2 environment produced by the placenta and/or mother (20).

Although the development of atopy in the newborn is determined by a multitude of factors, including genetic predisposition, intra-uterine exposure to allergen, maternal atopic status, and passive exposure to cigarette smoke, an intense Th1 stimulus at birth, such as bacille Calmette-Guérin (BCG) vaccination, could be protective by facilitating the switch back to a Th1 state at a time when the Th2 environment from the placental unit has just been withdrawn.

This area of asthma and allergy has been extremely difficult to address in epidemiological studies because of several confounding variables influencing the disease process, including those that could predispose to allergy (housing, genetic influence, maternal smoking during pregnancy, early life sensitization, etc.) (21) and those that could potentially protect from the development of allergic disease (the 'Hygiene Hypothesis', poor sanitation, recurrent infections, large family size, diet, breast-feeding, etc.) (22).

Is there a case for vaccination with BCG early in life to prevent the development of asthma?

Based on the Th1/Th2 paradigm it is tempting to speculate that modulation of the immature immune system early in life towards a Th1 immune response could protect from develop-

ment of allergic disease. There are some recent epidemiologic- and laboratory-based human and animal studies that indirectly support this view. A recent epidemiologic study by Illi and co-workers (23) has clearly demonstrated that recurrent mild upper respiratory virus infections early in life protect against the development of asthma, and the authors suggest that this could occur by tilting the immune system towards a Th1 phenotype. A similar phenomenon has been demonstrated using vaccination with *M. vaccae* in an allergen-challenge model of human asthma (24). In this study, prior administration of *M. vaccae* to sensitized mild asthmatics significantly attenuated the development of an allergen-induced late asthmatic response and IL-5 production *in vitro* by PBMC (24). Moreover, allergen-specific immunotherapy, which has been used successfully in the treatment of allergic rhinitis, has been shown to act by suppressing the Th2 immune response, and indeed this is associated with a significant reduction in symptoms and BHR (6,7,25). In a similar approach, Savolainen and co-workers (26) have shown that in patients with allergic rhinitis, priming of PBMCs *in vitro* by tuberculin significantly increased the gene expression and protein levels of IFN-γ in a dose-dependent manner, and this was associated with a significant decrease in the gene expression and protein levels of Th2 cytokines, including IL-4 and IL-13. Studies in animal models support the view regarding a protective effect of BCG vaccination early in life. Administration of BCG vaccination to Th2-susceptible newborn BP2 mice blocked allergic inflammation and BHR (27) in response to ovalbumin. In a similar study, Tukenmez and co-workers have shown that preimmunization with *M. bovis* and *M. vaccae* in newborn ovalbumin-sensitized mice inhibits IgE production in response to aerosolized allergen (28). The observations made in the studies described above strongly support the view that inducing a predominant Th1 immune response in early life could potentially prevent the development of asthma later in life.

Applying the above observations in the context of developing countries, we would like to draw attention to a potentially important factor that could also account (at least in part) for the lower prevalence of allergic disease in developing countries, as reported in the ISAAC study. As per the current World Health Organization (WHO) guidelines for global immunization (29), BCG vaccination is administered at birth in all developing countries that have a high incidence of *M. tuberculosis*, as a specific measure to prevent primary complex during childhood. Indeed, as reported in the ISAAC study, these countries correspondingly have the lowest prevalence rates for allergic diseases, including asthma and rhinitis. In contrast, in countries with the highest prevalence rates for allergic disease, BCG vaccination is administered at school-leaving age (14–15 years), by which time allergic disease has already manifested. Furthermore, as per the British Thoracic Society (BTS) guidelines for treatment and prevention of *M. tuberculosis* (30), BCG vaccination is offered at birth to all children born to Asian parents in the UK. This could, at least in part, explain the lower prevalence rate for asthma amongst Asian children in Britain when compared to white Caucasian children (31).

Few studies have attempted to investigate the protective effect of BCG vaccination early in life and the results have been conflicting. At the present time it is still unclear whether or not administration of BCG vaccine early in life is protective against allergic diseases (32,33). In the present issue of *Pediatric Allergy and Immunology*, Grüber et al. (34) carried out an epidemiological analysis in German preschool children with different ethnic backgrounds, and reported that administration of BCG vaccination in the neonatal period demonstrated a weak, but protective, effect against the development of asthma, but not atopic eczema and hay fever. Their data indicate that BCG vaccination may be associated with a 15% reduction in the risk for development of asthma. The results of this study are not entirely consistent with other studies carried out in Europe, Africa, and Japan. The possible reasons for these inconsistencies are discussed below. A retrospective analysis from health records of children in Guinea-Bissau, West Africa, has clearly demonstrated that vaccinating African children early in life significantly reduces the prevalence of atopy, as demonstrated by SPT positivity to common airborne allergens later in life (33). In addition, this study also demonstrated that the greatest reduction in atopy was achieved in those children who were vaccinated during the first week of life. However, similar studies from Holland and Sweden have been disappointing, but these studies were largely hampered by a small sample size. In a recent study, a protective effect of early BCG vaccination was demonstrated for symptoms of wheeze, atopic sensitization, and allergic rhinitis only up to the first 24 months of life, but the effect was not sustained thereafter (35). Again, one of the drawbacks of this study was that it was not sufficiently powered to detect a difference. Furthermore, several factors may have contributed to what could be regarded as

conflicting evidence among the Japanese, African, and European BCG studies:

1 None of these studies were double-blind and placebo-controlled.

2 The vaccine strains and doses used differed. The BCG Tokyo strain 172 used in the Japanese study differs biochemically from the Copenhagen strain used in the Swedish and German studies. Differences in the immunogenicity of different strains have been described and these have been primarily attributed to the genetic characteristics of the BCG strains and their capacity to survive in the host (36–38), but no direct comparison of the immunogenicity of the Danish and Japanese strains in humans is presently available. The Japanese vaccine was administered at a 10-fold higher dose to achieve comparable indurations evoked by the Copenhagen strain 1331. Data from the WHO indicate that four main strains account for more than 90% of the vaccines currently in use worldwide: the French Pasteur strain 1173 P2 (used in 14 countries for their own production); the Danish strain 1331; the Glaxo strain 1077 (derived from the Danish strain); and the Tokyo strain 172. Despite attempts of the WHO to standardize production and vaccine characteristics (by using stabilization and lyophilization) the concentration ranges from 50 000 to 3 million live particles per dose, according to the strain used (39).

3 Age at vaccination varied between 0–180 and 1–343 days, respectively, in the Swedish (32) and German studies (35). This might have potentially influenced the outcome in the European studies because the African study showed that the greatest reduction in atopy was observed in children who had been vaccinated during the first week of life. It has been suggested that in order to influence the function of allergen-specific T lymphocytes, the Th1 activation induced by BCG would have to take place before, or at the time of, first exposure and sensitization to allergens.

Conclusion

There is little doubt that the complex interaction between several environmental and genetic factors, lifestyle, and natural infections early in life lead to the development of allergic diseases. There is also indirect evidence to support the idea of an inverse association between the incidence of tuberculosis and prevalence of allergic diseases. Also, skewing the immune response towards a Th1 phenotype leads to the suppression of biomarkers of allergic inflammation, and this is associated with attenuated physiological responses to allergen challenge in sensitized asthmatics. Clearly, the results reported from studies thus far are inconsistent and it is unclear at the present time whether or not early vaccination with BCG has any protective effect against the development of allergic disease. Most of the currently available data regarding the potential protective effect of vaccination with BCG early in life on the development of allergic disease have come from retrospective analysis of health records and have been limited by small sample size, lack of standardization of BCG vaccine strain and dosage, and potential bias as a result of lack of randomization. Separately and importantly, administration of BCG vaccination at birth would also reduce the incidence of tuberculosis in the western world, which has seen a rising trend in the last two decades.

We propose that prospective multi-centre, randomized placebo-controlled studies, using a standardized BCG vaccine, are urgently needed to examine this hypothesis. If this approach is successful, simple measures such as revision of the current schedule for BCG vaccination would not only reduce the prevalence of allergic disease but also result in a huge economic benefit for western countries where allergic diseases are on the increase and imposing a huge financial burden on the health service.

References

1. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Lancet 1998: 351: 1225–32.
2. Robinson DS, Hamid Q, Ying S, et al. Predominant TH2-like BAL T cell population in asthma. N Engl J Med 1992: 326: 295–304.
3. Mosmann TR, Coffman RL. TH1 and TH2 cells: different patterns of lymphokine secretion lead to different functional properties. Annu Rev Immunol 1989: 7: 145–73.
4. Shi HZ, Li CQ, Qin SM, Xie ZF, Liu Y. Effect of inhaled IL-5 on the number and activity of eosinophils in circulation from asthmatics. Clin Immunol 1999: 103: 463–7.
5. Zhu Z, Homer RJ, Wang Z, et al. Pulmonary expression of interleukin-13 causes inflammation, mucus hypersecretion, subepithelial fibrosis, physiological abnormalities, and eotaxin production. J Clin Invest 1999: 103: 779–88.
6. Bhathena PR, Combair SA, Holroyd KJ, Erzurum SC. Interleukin-9 receptor expression in asthmatic airways *in vivo*. Lung 2000: 178: 149–60.
7. Louahed J, Toda M, Jen J, et al. Interleukin-9 upregulates mucin expression in airways. Am J Respir Cell Mol Biol 2000: 22: 649–56.
8. Shimbara A, Christodoulopoulos P, Soussi-Gounni A, et al. IL-9 and its receptor in allergic and non-allergic lung disease: Increased expression in asthma. J Allergy Clin Immunol 2000: 105 **(1 Part 1)**: 108–15.
9. Nicolaiden NC, Holroyd KJ, Ewart SL, et al. Interleukin-9: a candidate gene in asthma. Proc Natl Acad Sci USA 1997: 94: 13175–80.

10. Durham SR, Walker SM, Varga EM, et al. Long-term clinical efficacy of grass-pollen immunotherapy. N Engl J Med 1999: 341: 468–75.
11. Varney VA, Hamid QA, Gaga M, et al. Influence of grass pollen immunotherapy on cellular infiltration and cytokine mRNA expression during allergen-induced late-phase cutaneous responses. J Clin Invest 1993: 92: 644–51.
12. Shirakawa T, Enomoto T, Shimazu S, Hopkin JM. The inverse association between tuberculin responses and atopic disorder. Science 1997: 275: 77–9.
13. von Mutius E, Pearce N, Beasley R, et al. International patterns of tuberculosis and the prevalence of symptoms of asthma, rhinitis, and eczema. Thorax 2000: 55: 449–53.
14. Ohrui T, Zayasu K, Sato E, Matsui T, Sekizawa K, Sasaki H. Pulmonary tuberculosis and serum IgE. Clin Exp Immunol 2000: 122: 13–5.
15. Jones CA, Williams KA, Finley-Jones JF, Hart HA, Harty PH. Interleukin-4 production by human amnion epithelial cells and regulation of its activity by glycosa amino glycan binding. Biol Reprod 1995: 52: 839–47.
16. Williams TJ, Jones CA, Miles EA, Warner JO, Warner JA. Fetal and neonatal interleukin-13 production during pregnancy and at birth and subsequent development of atopic symptoms. J Allergy Clin Immunol 2000: 105: 951–9.
17. Warner JA, Jones CA, Jones AC, et al. Immune responses during pregnancy and the development of allergic disease. Pediatr Allergy Immunol 1997: 8: 5–14.
18. Weinberg ED. Pregnancy-associated depression of cell-mediated immunity. Rev Infect Dis 1984: 6: 814–31.
19. Robertson SA, Mayrhofer G, Seamark RF. Uterine epithelial cells synthesise granulocyte–macrophage colony-stimulating factor (GM-CSF) and IL-6 in pregnant and non-pregnant mice. Biol Reprod 1992: 46: 1064–79.
20. Warner JA, Warner JO. Early life events in allergic sensitisation. Br Med Bull 2000: 56: 883–93.
21. von Mutius E. The rising trends in asthma and allergic disease. Clin Exp Allergy 1998: 28 (Suppl. 5): 45–9;50–1.
22. Strachan DP. Family size, infection and atopy: the first decade of the 'hygiene hypothesis'. Thorax 2000: 55 (Suppl. 1): S2–10.
23. Illi S, von Mutius E, Lau S, et al. Early childhood infectious diseases and the development of asthma up to school age: a birth cohort study. BMJ 2001: 322: 390–5.
24. Camporota L, Corkhill A, Long H, et al. Effects of intra-dermal injection of SRL-172 (killed *Myobacterium vaccae* suspension) on allergen-induced airway responses and IL-5 generation by PBMC in asthma. Am J Respir Crit Care Med 2000: 161: A477.
25. Grembiale RD, Camporota L, Naty S, Tranfa CM, Djukanovic R, Marsico SA. Effects of specific immunotherapy in allergic rhinitic individuals with bronchial hyperresponsiveness. Am J Respir Crit Care Med 2000: 162: 2048–52.
26. Savolainen J, Nieminen K, Waris M, Makela MJ, Terho EO. Tuberculin-primed PBMC fail to produce TH2-type cytokines. Allergy 2000: 55: 895–6.
27. Nahori M, Lagranderie M, Lefort J, et al. Effects of *Mycobacterium bovis* BCG on the development of allergic inflammation and bronchial hyperresponsiveness in hyper-IgE BP2 mice vaccinated as newborns. Vaccine 2001: 19: 1484–95.
28. Tukenmez F, Bahceciler NN, Barlan IB, Basaran MM. Effect of pre-immunization by killed *Mycobacterium bovis* and *vaccae* on immunoglobulin E response in ovalbumin sensitized newborn mice. Pediatr Allergy Immunol 1997: 8: 53–8.
29. World Health Organization. Global Programme for Vaccines and Immunization. Immunization Policy. Geneva: WHO, 1995.
30. Control and prevention of tuberculosis in the United Kingdom: code of practice 2000. Joint Tuberculosis Committee of the British Thoracic Society. Thorax 2000: 55: 887–901.
31. Pararajasingam CD, Sittampalam L, Damani P, Pattemore PK, Holgate ST. Comparison of the prevalence of asthma among Asian and European children in Southampton. Thorax 1992: 47: 529–32.
32. Alm JS, Lilja G, Pershagen G, Scheynius A. Early BCG vaccination and development of atopy. Lancet 1997: 350: 400–3.
33. Aaby P, Shaheen SO, Heyes CB. Early BCG vaccination and reduction in atopy in Guinea-Bissau. Clin Exp Allergy 2000: 30: 644–50.
34. Grüber C, Meinlschmidt G, Bergmann R, Wahn U, Stark K. Is early BCG vaccination associated with less atopic disease? An epidemiological study in German pre-school children with different ethnic backgrounds. Pediatr Allergy Immunol 2002: 13: 178–182.
35. Grüber C, Kulig M, Bergmann R, Guggenmoos-Holzmann I, Wahn U and The MAS-90 Study Group. Delayed hypersensitivity to tuberculin, total immunoglobulin E, specific sensitization, and atopic manifestation in longitudinally followed early bacille Calmette-Guérin-vaccinated and nonvaccinated children. Pediatrics 2001: 107: e36.
36. Abou-Zeid C, Smith I, Grange J, Steele J, Rook G. Subdivision of daughter strains of bacille Calmette-Guérin (BCG) according to secreted protein patterns. J Gen Microbiol 1986: 132: 3047–53.
37. Fomukong NG, Dale JW, Osborn TW, Grange JM. Use of gene probes based on the insertion sequence IS 986 to differentiate between BCG vaccine strains. J Appl Bacteriol 1992: 72: 126–33.
38. Lagranderie MRR, Balazuc AM, Deriaud E, Leclerc CD, Gheorghi M. Comparison of immune responses of mice immunized with five different *Mycobacterium bovis* BCG vaccine strains. Infect Immun 1996: 64: 1–9.
39. Milstein JB, Gibson JJ. Quality control of BCG vaccine by the WHO: a review of factors that may influence vaccine effectiveness and safety. Bull World Health Organ 1990: 68: 93–108.