

Potential health effects from non-specific stimulation of the immune function in early age: The example of BCG vaccination

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There is increasing, but still inconsistent evidence that vaccinations and childhood infections may play a role in the normal maturation of the immune system, and in the development and balance of immune regulatory pathways, both of which might impact health later in life. This review covers the epidemiological evidence regarding the role of *Bacillus Calmette-Guérin* (BCG) vaccination on the following inflammatory or autoimmune diseases: asthma and allergic diseases, Crohn's disease (CD), insulin-dependent diabetes mellitus (IDDM), and specific cancers. The literature is more comprehensive for asthma and allergic diseases, with 16 studies reporting the absence of an association while seven rather suggest a protective effect of BCG. We found insufficient evidence on CD to conclude at this point. Overall, the evidence for IDDM based on four studies leans towards no association, although some effects were observed in population subsets. Five epidemiological investigations provide evidence on a possible link with cancer incidence or mortality at various sites, with indications of both increased and decreased risks. Given the potential public health implications, it is imperative to acquire a better understanding of how BCG vaccination could influence the development of such chronic health conditions in the population.

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The immune response has profound repercussions on health. This can be easily demonstrated by considering the plethora of health problems associated with immunosuppression. Whether it is acquired or induced, immunosuppression has been associated, so far, with excess risks of viral and bacterial infections, and with several virally-linked neoplasia such as Kaposi sarcoma (1), cervical cancer (2), and lymphoproliferative disorders (3). More generally, immunity also plays a critical role in diseases which result from an autoimmune response (e.g., lupus, insulin-dependent diabetes mellitus) and conditions related to an inflammatory process (e.g., Crohn's disease, asthma).

The damage caused by pathogens such as viruses, bacteria, or by chemicals triggers the

immune system to induce an inflammatory process, most notably via the complex interactions between several T-cell populations, including T helper (T_H) and regulatory T (T_{reg}) cells. Upon their activation during infection, the T_H cells can be categorized in two subgroups which differ in the cytokines they produce. The T_H1 cells produce pro-inflammatory cytokines [interleukin (IL)-1, IL-2, γ -interferon (IFN- γ), tumour necrosis factor (TNF)- α], and are involved in delayed hypersensitivity reactions such as in tuberculosis (TB), leprosy, sarcoidosis (4). T_H2 cells produce a distinct repertoire of cytokines, including IL-4, -5, -9, -10, and IL-13. The consequences of inducing T_H1 vs. T_H2 cells are biologically significant; whereas the secretion of T_H1 cytokines leads to cell-mediated

immunity, the production of a predominantly T_H2 response will favour an antibody-dependent immune response. Inflammation mediated by the T_H1 response normally resolves itself by negative feedback brought about by the T_H2 cytokines on the T_H1 cytokines. The production of T_H2 cytokines follows closely that of the T_H1 , ensuring that a balance is achieved. In chronic inflammation, this balance is lost, either because of the persistence of T_H1 cytokines or through lack of T_H2 negative feedback (5). The production of immunosuppressive cytokines, such as IL-10, by T_{reg} also contributes to the suppression of T_H1 responses. Inflammation is generally part of the healing process, but may have negative consequences if it becomes chronic. For several cancers, chronic inflammation either because of viral infection or from other sources seems to be one of the steps in the carcinogenic process (5). Inflammation is also thought to be part of the mechanism linking hyperlipidemia to atherosclerosis (6).

In contrast, allergic inflammation as observed in allergies and asthma is driven by the T_H2 lymphocytes. Following an initial contact with antigen-presenting cells, most notably with antigen-loaded dendritic cells, this subset of T-cells is activated and via specific receptors leads to the secretion of cytokines that promote airway inflammation. The release of IL-4 will induce the production of high levels of immunoglobulin E (IgE) by B cells while further favouring the development of T_H2 cells. Other cytokines, such as IL-5 and IL-9, will promote the recruitment of eosinophils and mast cells, respectively, while IL-13 will favour hyperplasia of goblet cells and hypersecretion of mucus (7, 8). This cascade of signals is, however, highly susceptible to the regulatory activity of T_{reg} s, which control T_H activity via direct cell-cell contact and secretion of other immunoregulatory cytokines, such as IL-10 and TGF- β (9, 10). The hypothesis most consistently proposed in relation to the recent rise in allergic disease and asthma in industrialized countries thus relates to the development of the immune response. The hygiene hypothesis postulates that the decrease in exposure to infectious diseases has resulted in the absence of shifting of the immune system's initial T_H2 (allergic) response to a T_H1 (non-allergic) response (11), leading to the lack of a normal process called immune deviation (12). One must, however, keep an open mind that this simplistic T_H1 vs. T_H2 paradigm may hide some yet unknown mechanisms, as recently suggested by studies showing that infections in the lungs with pathogens can elicit a strong T_H1 response

mimicking in several ways tissue damage and symptoms observed in allergic inflammation (13). However, the mechanisms by which a decreased exposure to microbial agents early in life would result in favouring a T_H2 response are still controversial and possibly implicate regulatory mechanisms, most notably those mediated by T_{reg} populations (14).

Immune modulation

There are a number of exogenous exposures which can modulate the immune response, including medications (e.g., anti-inflammatory, immunosuppressive drugs) as well as prophylactic and therapeutic vaccines. The *Bacillus Calmette-Guérin* (BCG) vaccine is an example of such exogenous modulators of the immune response. The BCG is a non-pathogenic strain of attenuated live *Mycobacterium bovis*, which was first used in the 1920s to vaccinate neonates, children, and adults to protect them against tuberculosis (TB). BCG vaccination stimulates macrophages, which in turn induce the production of cytokines by T_H1 lymphocytes. The resulting production of INF- γ is known to have an inhibitory effect on T_H2 responses. By such a stimulation, the immune response is balanced towards a T_H1 rather than a T_H2 response (15). As a result of its immunostimulatory potential, BCG is used in immunotherapy for certain stages of superficial bladder cancer (16). Its effect occurs through non-specific pathways, e.g., by stimulation of macrophages and tumour cytotoxic natural killer (NK) cells (17, 18).

Influence of the immune response on health

There exist plausible immunological underlying mechanisms that could explain beneficial and detrimental associations between the cellular immune response and several chronic diseases. The mechanisms are complex and not yet clear, but epidemiological studies have suggested that markers of immune stimulation may be associated with increased or decreased risk of several health conditions such as asthma, autoimmune disorders, atherosclerosis and cancer.

We will herein provide a qualitative review of the epidemiological literature for and against hypotheses of an effect of early immune stimulation on selected chronic diseases characterized by inflammatory or autoimmune processes. We will use the BCG vaccination as one example of non-specific immune stimulation in early age. Immunization with BCG can serve as a useful model to assess the impact of early-life

stimulation of T_H1 cells, because of its demonstrated T_H1 immunostimulatory effects (19) and its administration often occurring in the early months of life. Our aim is to provide a general overview of the epidemiological literature focusing on the influence of BCG vaccination on the following inflammatory or autoimmune diseases: asthma and allergic diseases, Crohn's disease (CD), insulin-dependent diabetes mellitus (IDDM), and specific cancers.

Asthma and allergic diseases

Asthma and allergic diseases such as atopy and allergic rhinitis have been extensively studied in relation to BCG vaccination. Several reasons justify this scientific interest. Animal models have convincingly showed that BCG immunization hampers T_H2 responses through an inhibition of the secretion of IL-4, IL-5, IgE, and immunoglobulin G1 (IgG1) (20–24). There is also the possibility that BCG could induce antigen-specific immune suppression by inducing high levels of IL-10. *In vitro* culture of lymphocytes from individuals stimulated with the purified protein derivative (PPD) resulted in the production of high levels of IL-10 among PPD-anergic subjects (25). IL-10 is an anti-inflammatory cytokine playing an important role against the development of allergic and asthmatic disease. The fact that increased IL-10 synthesis by T-cells has been shown to be beneficial in the treatment of asthma and allergy supports the hypothesis that IL-10-producing T_{reg} cells play an important role in controlling the development of allergic inflammation (26, 27). In fact, an eventual hope for the treatment of allergic airway disease is to design therapies that stimulate endogenous antigen-specific T_{reg} cell function or that induce *de novo* T_{reg} activity. Interestingly, a threefold increase in the number of circulating T_{reg} in patients with TB as compared with healthy controls was documented, concomitant to an elevated level of IL-10 and TGF β -1 (28). The ability of IL-10 to inhibit pro-inflammatory cytokine production, major histocompatibility complex class II expression, maturation, and antigen-presenting function of dendritic cells, as well as its ability to suppress IgE-induced cytokine production by mast cells are among the numerous mechanisms by which this cytokine can inhibit asthma (29). As for TGF β , a pleiotropic cytokine with significant anti-inflammatory and immunosuppressive properties, its role in the control of T_H2 response in airway inflammation remains under discussion. Indeed, although this cytokine is well known to inhibit T-cell proliferation (30) and

that mice lacking a functional TGF β receptor type II (TGF β RII) at the surface of their T-cells develop severe autoimmune diseases (31), mice lacking this molecule still suppress their target cells (32). However, as reduced expression of TGF β correlates with a stronger inflammatory response and mucus production in an experimentally-induced asthma model (33), it is likely that the secretion of TGF β by T_{reg} plays a yet undefined role in the regulation of T_H response in airway inflammation. Depletion of T_{reg} in peripheral blood monocytic cells also increased the number of *Mycobacterium tuberculosis* antigen-specific IFN- γ -producing T-cells in patients with TB, further supporting the hypothesis that T_{reg} cells contribute to the suppression of T_H1 -type immune responses (28).

In a critical review of the epidemiological literature on the association between early-life microbial exposure and prevention of allergic disease based on the hygiene hypothesis, Kemp and Björkstén underline the fact that some studies have shown protection among those exposed to microbial agents early in life, but have been limited in terms of assessing whether these agents act via a lack of immune deviation in early childhood (12). Studies have suggested a decreased risk of allergic diseases and asthma among those with recurrent mild upper respiratory viral infections in childhood (34, 35) and with day care attendance used as a proxy for early exposure to infectious agents (36, 37). Table 1 provides a summary of epidemiological studies focussing on the association between BCG vaccination or a positive tuberculin response (a marker of T_H1 -mediated acquired immunity) and the risk of asthma and allergic diseases. Among the 23 studies identified, most were generally consistent with the absence of such associations (38–47) or an effect limited to a subgroup only (48–53). Nevertheless, a protective effect was noted in seven studies (54–60). There was substantial variation in terms of population, size, study design, BCG strains and doses, adjustment variables, although these factors did not appear to predict the direction of the associations. Exposures considered included either BCG vaccination *per se*, most often assessed through parental report, vaccination records, presence of BCG scar or, conversely, tuberculin reactivity measured by standard tuberculin skin tests. Outcomes comprised a wide range of conditions ascertained by self-report and clinical evidence, e.g., serology and skin-prick test. BCG vaccination was perinatal in most studies. In populations vaccinated at another time point, no association emerged

Table 1. Epidemiological studies addressing BCG vaccination or tuberculin reactivity in relation to asthma and allergic diseases

Author, year (reference)	Country	Study design	No. of subjects	Exposure	Age at BCG vaccination (yr)	BCG strain/dose*	Outcome	Comments
Inverse association								
Shirakawa et al., 1997 (54)	Japan	RC	867	Tuberculin test	Birth, 6, 12	Tokyo 172 10 ⁶ CFU	Atopy, asthma, eczema	Inverse association
Aaby et al., 2000 (55)	Guinea-Bissau	RC	400	BCG	Birth	n.a.	Rhinitis Atopy	No association No association if exposure defined by BCG scar
Sarinho et al., 2000 (56)	Brazil	CC	134 cases and 134 controls	BCG scar diameter	n.a.	n.a.	Asthma	
Bager et al., 2003 (57)	Denmark	RC	2176	BCG	At school entry	n.a.	Asthma Atopy, allergic rhinitis	Inverse association No association
Garcia-Marcos et al., 2005 (58)	Spain	RC	9590	BCG	Birth	Copenhagen 1331 10 ⁵ bacteria	Asthma, hay fever, atopic dermatitis	No association between age at BCG and any outcome
Martignon et al., 2005 (59)	France	RC	718	BCG	Birth	n.a.	Asthma, atopic diseases	Borderline statistical significance
Obihara et al., 2005 (60)	South Africa	CS	337	Tuberculin test	Birth	n.a.	Allergic rhinitis	Inverse association with allergic rhinitis symptoms, but not with skin-prick test
No association								
Alm et al., 1997 (38)	Sweden	RC	574	BCG	< 6 months	Copenhagen 1331 0.05 ml	Atopy	
Stranegård et al., 1998 (48)	Sweden	CS	6497	BCG, tuberculin test	≤ 1	n.a.	Allergy, atopic dermatitis, allergic rhinoconjunctivitis, asthma	Weak negative association in immigrants
Omenaas et al., 2000 (39)	Norway	CS	574	Tuberculin test	14	n.a.	Total and specific serum IgE	
Yilmaz et al., 2000 (40)	Turkey	CC	538 cases and 198 controls	Tuberculin test	Birth, 6, 12	Copenhagen 1077, Pasteur, and French 3–15 × 10 ⁶ CFU/ml	Atopy	
Grüber et al., 2001 (41)	Germany	PC	774	BCG	Birth	Copenhagen 1331 10 ⁵ bacteria	Atopic dermatitis, recurrent wheezing, allergic rhinitis. Total serum IgE	
Anderson et al., 2001 (42)	Several	E	92 centres (ISAAC)	BCG rates	n.a.	n.a.	Atopic dermatitis, recurrent wheezing, allergic rhinitis. Rates of wheezing, allergic rhinoconjunctivitis, atopic eczema	
Wong et al., 2001 (43)	China	CS	2201	Tuberculin test	Birth, 7–10	Glaxo	Wheezing, rhinoconjunctivitis, flexural eczema, asthma, atopy	
Grüber et al., 2002 (49)	Germany	RC	38,808	BCG	Birth	Copenhagen 1331 10 ⁵ bacteria	Atopic dermatitis, asthma, hay fever	Strong inverse association among immigrants
Jentoft et al., 2002 (44)	Norway	CS	386	Tuberculin test	14	Bergen, Copenhagen	Asthma symptoms, lung function, bronchial responsiveness	
Pahari et al., 2002 (45)	UK	CS	329	BCG and tuberculin test	n.a.	n.a.	Asthma diagnosis, wheezing, night cough	
Krause et al., 2003 (46)	Greenland	CS	1575	BCG	Birth	Copenhagen 1331	Atopy	No association between age at BCG and atopy

Table 1. Continued

Author, year (reference)	Country	Study design	No. of subjects	Exposure	Age at BCG vaccination (yr)	BCG strain/dose*	Outcome	Comments
Marks et al., 2003 (50)	Australia	RC	751	BCG	Birth	CSL derived from Glaxo	Atopy, hay fever, eczema, asthma	Lower prevalence of asthma among BCG-vaccinated subjects with family history of allergic diseases
Ota et al., 2003 (47)	The Gambia	CS	507	BCG, tuberculin test	n.a.	n.a.	Atopy	Inverse association between tuberculin response and current allergic symptoms. No association between age at BCG and any outcome
Annus et al., 2004 (51)	Estonia	RC	723	BCG, tuberculin test	Birth, 7	Soviet 5–15 × 10 ⁵ bacteria/0.05 mg	Atopy, symptoms of asthma, allergic rhinitis, eczema	Inverse association between tuberculin response and current allergic symptoms. No association between age at BCG and any outcome
Townley et al., 2004 (52)	Thailand Argentina Turkey	PC	1704	Tuberculin test	Birth	Thai Red Cross, Pasteur 1173 P2	Atopy, allergic diseases, eczema, hay fever, asthma	Inverse association between tuberculin test and allergic diseases in Thailand and Turkey
Da Cunha et al., 2004 (53)	Brazil	CS	1612	BCG	Birth, at school	Pasteur Moreau R10 0.1 ml	Asthma, allergies	Inverse association with asthma in subjects presenting a history of allergy and sneezing

BCG, Bacillus Calmette-Guérin; CC, case-control; CFU, colony-forming units; CS, cross-sectional; E, ecological; n.a., not available; PC, prospective cohort; RC, retrospective cohort.

*Information, if available, as reported in the publication.

between age at vaccination and any of the outcomes considered. Ethnicity has been suggested as an effect modifier (61), possibly as a result of differences in genetic susceptibility as well as in early-life microbial exposures (50). Overall, our review suggests that, despite the number of studies already conducted, the effect of early-life T_H1 stimulation on allergic diseases and asthma remains incompletely elucidated, as was previously suggested based on earlier literature (62).

Crohn's disease

Crohn's disease is an inflammatory disease of the gastrointestinal tract, of mostly unknown aetiology. It is generally thought to result from a complex combination of genetic, environmental, and immunological factors. Familial aggregation and racial variations have pointed to genetic factors and indeed some were identified (63). The *NOD2* gene encodes for an intracellular receptor for bacterial lipopolysaccharides, which in turn activates NFκB, a transcription factor that enhances the production of inflammatory mediators. The *NOD2* gene product may confer susceptibility to CD by one or both of these mechanisms: (i) alteration of the recognition of microbial pathogens; (ii) overactivation of NFκB in monocytes (64). Impaired innate immunity, leading to a delayed recruitment of neutrophils at sites of bacterial penetration, could result in bacterial persistence and in the development of chronic inflammation (65). The recent rise in incidence observed in several countries is compatible with a dual involvement of environmental and genetic factors (66). Exposure to infections during childhood has been investigated in relation to the development of CD. Results have been inconsistent, some studies suggesting a protective effect of childhood infections (67, 68), others suggesting an increased risk of CD among children more exposed to pathogens (69–72). A lack of exposure to parasitic infections in childhood may be responsible for a reduced T_H2 immune response unable to counterbalance the chronic uncontrolled inflammatory reaction with an overly strong and lasting T_H1 immune response in CD (73, 74). This would suggest that not only the timing of infections in childhood, but also the type of infections need to be considered in further epidemiological studies. A study focussing on *Mycobacterium avium* subspecies *paratuberculosis* (MAP) as a risk factor for CD showed a seemingly protective effect of BCG vaccination on infection with MAP (75).

The epidemiological evidence specifically addressing the association between immunization with BCG and CD is very sparse. We could identify only one such study. In this case-control study conducted in France on 222 cases and 222 matched controls, BCG vaccination was associated with an approximately threefold increase in risk of CD, with a dose-response according to the number of BCG immunization doses per subject. Although the point estimates were imprecise, these results remained after adjustment for several factors including family history of inflammatory bowel diseases (76). CD is predominantly driven by a T_H1 immune response (73). The early-life modulation of the immune system towards the T_H1 pathway by BCG vaccination could be one of the several factors eventually leading to an increased risk of CD.

Insulin-dependent diabetes mellitus

Insulin-dependent diabetes mellitus, or type 1 diabetes, is an autoimmune condition in which insulin-producing pancreatic islets β cells undergo immune-mediated destruction. Autoreactive T-cells are thought to target autoantigens within the β cells (77). In experimental immunostimulation therapies, some agents such as macrophage activators (78), Freund's adjuvant (79–81), and BCG (82, 83) have prevented the onset of IDDM in mice or rats seemingly by tipping an autoimmune response towards a non-destructive T_H2 response. In humans, it has been hypothesized that early-age BCG vaccination would be associated with the risk of IDDM (84). Epidemiological studies on BCG vaccination in relation to IDDM are summarized in Table 2. The few studies conducted to date provided no consistent evidence of an association. However, in one study, the lower proportion of birth-vaccinated IDDM cases diagnosed at a very young age as compared with non-vaccinated cases suggested a possible temporary boost of the immune function after vaccination (85). Conversely, another study reported a higher cumulative risk of IDDM in BCG-vaccinated children, among those positive for islet autoantibodies (86). In a descriptive study, BCG vaccination was associated with a lower prevalence of autoantibodies among vaccinated IDDM cases (87).

Cancer

A decade ago, infectious agents were first recognized as human carcinogens according to the IARC Monographs Programme on the Evaluation of Carcinogenic Risks to Humans. In 1994,

Table 2. Epidemiological studies addressing BCG vaccination in relation to IDDM

Author, year (reference)	Country	Study design	No. of subjects	Exposure	Age at BCG vaccination (yr)	Outcome	Comments
Descriptive							
Sanjeevi et al., 2002 (87)	India	CS	91 IDDM cases	BCG	n.a.	GAD65 and IA-2 antibodies	No comparison of antibody positivity by BCG status in subjects without IDDM. Difference in proportion of antibody-positive subjects between BCG vaccinated and non-vaccinated was –46% ($p < 0.001$) for GAD65 and –39% ($p < 0.001$) for IA-2
No association							
Dahlquist and Gothefors, 1995 (114)	Sweden	RC	408,678	BCG	Birth	IDDM	Later onset of IDDM among BCG-vaccinated (series B)
Parent et al., 1997 (85)	Canada	CC	Series A: 93 cases, 2,093 controls Series B: 249 cases, 431 controls	BCG	77% under 1	IDDM	Higher cumulative risk of IDDM in BCG-vaccinated children, among those positive for autoantibodies
Huppamm et al., 2005 (86)	Germany	PC	1212	BCG	Birth	IDDM, islet autoantibodies (IAA, GADA, 1A-2A)	

BCG, Bacillus Calmette-Guérin; CC, case-control; GAD65, GADA, glutamic acid decarboxylase autoantibody; IA-2, 1A-2A, tyrosine phosphatase autoantibodies; IAA, insulin autoantibodies; IDDM, insulin-dependent diabetes mellitus; n.a., not available; PC, prospective cohort; RC, retrospective cohort.

two of this programme's monographs were devoted to infectious agents, one focussing on hepatitis viruses (88), the other on schistosomes, liver flukes and *Helicobacter pylori* (89). There are now about a dozen infectious agents considered as being carcinogenic, several of which are viruses.

Aside from specific infectious agents, there was and still is debate over whether more general immune factors come to play in promotion or protection against cancer. Burnet and Thomas proposed, under the immunosurveillance hypothesis, that immunosuppression increased cancer risk through the lack of normal elimination of aberrant cells, allowing them to progress into neoplastic lesions (90). Experimental evidence showing that athymic nude mice did not experience increased cancer incidence (91) and early studies of transplant recipients, among whom a few but not many cancers were in excess (92, 93), did not strongly support the hypothesis. Recent experimental evidence has revived the debate over the immunosurveillance hypothesis when it was shown that the immune system, through the action of lymphocytes and IFN- γ , could prevent the development of tumours and influence their immunogenicity (94). New models also suggest that tumour neoplastic progression and malignant conversion depend on a fine balance between pro- and anti-inflammatory reactions resulting from the cytokines produced by the T_H1 and T_H2 subsets of T-cells in the peritumoural environment (5).

Associations between markers of early immune stimulation and some malignancies, predominantly leukaemias and lymphomas, have been observed in epidemiological investigations. Among these markers were factors such as neonatal and childhood vaccinations, day care attendance, childhood infections, birth order and number of siblings (37, 95–99). Studies focussing on BCG vaccination and cancer are summarized in Table 3. In the early 1970s, a decreased leukaemia mortality rate among individuals who had received neonatal BCG vaccination was reported (100, 101). This report triggered several reactions in the scientific community: some criticizing the methods (102, 103), others cautiously presenting somewhat convergent results (104, 105). These results were reproduced in a few countries (106). In two large clinical trials, BCG vaccination was associated with increased incidence of lymphosarcoma and Hodgkin's disease (107), and with stomach, kidney, and lymphopoietic cancers (lymphosarcoma, lymphoma, Hodgkin's disease and leukaemia) (108). Several authors have underlined the fact that in studies

Table 3. Epidemiological studies on the association between BCG vaccination and cancer

Author, year (reference)	Country	Study design	No. of subjects	Exposure	Age at BCG vaccination (yr)	Outcome	Comments
Inverse association							
Davignon et al., 1970, erratum 1971 (100, 101)	Canada	RC	~1.9 million	BCG	Most at birth	Leukaemia mortality regrouping lymphoid, myeloid, and monocytic	Several comments to the editor on this article (102–105)
Krone et al., 2003 (110)	Six European countries and Israel	CC	603 cases and 627 controls	BCG	Variable	Melanoma incidence	
Kölmel et al., 2005 (112)	Six European countries and Israel	PC	542 melanoma cases	BCG	Variable	Death	F/U of cases from the case-control study by Krone et al. (2003)
Positive association							
Snider et al., 1978 (107)	Puerto Rico	CT	77,972	BCG	Most 10–18	Incidence: Lymphosarcoma and Hodgkin's disease All cancers	Excess among those 7–15 yr at vaccination No association
Kendrick and Comstock, 1981 (108)	USA	CT	34,767	BCG	Most 5–19	Incidence: Stomach cancer Kidney cancer Lymphosarcoma, lymphoma, Hodgkin's disease and leukaemia All cancers	Positive association Positive association Positive association No association

BCG, Bacillus Calmette-Guérin; CC, case-control; CT, clinical trial; F/U, follow-up; PC, prospective cohort; RC, retrospective cohort.

suggesting a protective effect, the BCG vaccine was administered neonatally (107–110). More recently, results from a European multi-centre population-based case-control study suggested that BCG vaccination was associated with a decreased incidence of melanoma (111), and with better melanoma survival (112). Some have hypothesized that the effect of BCG on immune maturation, especially in neonates, would confer a protection against leukaemia and melanoma (106, 109, 113).

Conclusion

In summary, there is increasing, but still inconsistent evidence that vaccinations and childhood infections may play a role in the normal maturation of the immune system, and in the development and balance of immune regulatory pathways. Several epidemiological studies have focussed on a possible link between BCG vaccination and the development of asthma and allergic diseases, but this issue remains unclear. Much fewer investigations have addressed chronic diseases just as pertinent because of their inflammatory and autoimmune characteristics, such as IDDM, CD, and cancer. Despite null results in a majority of studies, the evidence for an association observed in some populations deserves to be further explored.

There appear to be several chronic conditions for which a modulation of the immune function could play an aetiological role. Altogether, this raises the possibility that common or related immunological mechanisms could be involved in the development of these seemingly different conditions. The study of BCG vaccination and of other well-documented sources of immune stimulation in the early years of life has the potential to contribute crucial knowledge on the complex influences that might have a long-term impact on chronic diseases. Further population health studies are needed to shed more light on the role of the immune function and its modulation on health and disease. Although such a research area is currently considered to be a potentially fertile research avenue, there remain considerable knowledge gaps to be filled. The general hypothesis of a role of the immune maturation and function in the development of chronic diseases has hardly been tested in the context of population-based studies. And this is largely because of the paucity of markers of the immune function in the population. Given the potential public health implications, it is imperative to acquire a better understanding of the role of the modulation of the immune function in the

aetiology of such chronic health conditions in the population.

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