Arch Pediatr Infect Dis. 2016 April; 4(2):e30180. doi: 10.5812/pedinfect.30180.

Published online 2016 April 1. **Review Article**

BCG Vaccination as a Prevention Strategy, Threats and Benefits

Fariba Shirvani,[1] Abdollah Karimi,[1] and Maryam Rajabnejad[1,*]

[1]Pediatric Infections Research Center, Mofid Children's Hospital, Shahid Beheshti University of Medical Sciences, Tehran, IR Iran

[*]*Corresponding author*: Maryam Rajabnejad, Pediatric Infections Research Center, Mofid Children's Hospital, Shahid Beheshti University of Medical Sciences, Tehran, IR Iran. Tel: +98-2122226941, Fax: +98-2122226941, E-mail: mrajabnejad2@yahoo.com

Received 2015 July 25; **Revised** 2016 January 13; **Accepted** 2016 January 13.

Abstract

Context: Tuberculosis is still one of the deadliest communicable diseases.
Objectives: Nine million people worldwide developed TB in 2013, and 1.5 million people died from it, 360000 of which were HIV positive. Although the disease is controllable by means of diagnostic and treatment measures, the death toll from the disease is still high, and efforts to combat it must be accelerated.
Data Sources: Data compiled from 202 countries in the Global Tuberculosis Report 2014 showed that TB is present in all regions of the world.
Study Selection: Higher numbers of tuberculosis cases were diagnosed in 2013 in comparison with previous reports, indicating that diagnoses and reports of new cases may be improved by stringent data collection.
Data Extraction: A special note to the 2014 report highlighted the progress of drug resistant TB during the last two decades.
Results: Worldwide, a proportion of new cases with multidrug-resistant TB (MDR-TB) were reported at 3.5% in 2013 without a significant change compared with recent years. Interestingly, higher levels of resistance and poor treatment outcomes are of major concern in some parts of the world. Due to this concern, special attention is focused on prevention rather than treatment. On the other hand, the effectiveness of an existing vaccine (BCG) is increasingly questionable.
Conclusions: It has the potential to cause disseminated infection, and an increasing number of immunocompromised patients prone to disease and the suboptimal preventive potency of this vaccine suggest the need for a global attempt to review its benefits and disadvantages.

Keywords: Tuberculosis, BCG Vaccine, Strategy

1. Context

In 2013, 6.1 million TB cases were reported to WHO; 5.7 million were newly diagnosed, and 0.4 million were already in the treatment phase (1). BCG vaccination is used as a preventive measure of disseminated and life-threatening mycobacterium tuberculosis infection, and it is injected intradermally in newborn infants at birth in endemic regions of the world.

Mycobacterium bovis based Bacille Calmette Guerin (BCG) was originally used as an oral vaccine in the 1930s. The movement from oral administration to intradermal injection began in the 1960s. Mycobacterium Bovis originally infects the gastrointestinal tract of cattle and humans naturally. The BCG based vaccine can provide stimulation of both innate and acquired immunity (2). The BCG vaccine was first introduced in Iran in 1947 in the Institute Pasteur, and the use of the vaccination began. Currently, Intradermal injectable and Intravesical BCG formulations are available (3).

In the last decades, the overall incidence of TB in industrialized countries has decreased, and based on the concern for adverse effects following BCG immunization, modifications of BCG policies may be beneficial. With the prevalence levels of tuberculosis at around 30 sputum smear positive per 100,000, a BCG program could be beneficial; however, when prevalence falls to 15 per 100,000, the advantage of BCG vaccination must be carefully assessed. If it is below 5 per 100,000, the vaccinations may lead to an excess of adverse effects per each prevented case (4).

2. Objectives

To describe:

1) BCG vaccination protocol in our country from birth and the possibility of disseminated infection in patients with special underlying immunologic problems

2) Diagnostic protocol of patients with disseminated BCG infection.

3) Immunodeficiency disorders and other conditions with a predisposition to disseminated BCG infection

4) Treatment program in disseminated BCG infection

5) Other preventive measures (vaccine trials) to prevent mycobacterium tuberculosis infection

6) Review case reports of patients with BCG infection (clinical manifestation, age, diagnosis, underlying disease, parental consanguinity, treatment, outcome).

3. Data Sources

To obtain a complete set of data, we searched PubMed and Cochrane collaboration and EMBASE for articles published in English with no time limitation on the date until March 2015. MESH terms accessed via PubMed were used for searching the Medline electronic bibliographical database.

We used common search terms on Persian sites to retrieve information about the history of BCG vaccination in Iran as well as English language sources.

4. Study Selection

We did not include a "methodological filter" (study type filter) for our search strategy. BCG complications and BCGosis (disseminated disease) were searched for throughout the literature, and articles were selected for their relevance to the analysis of underlying disorders. Immunodeficiency was added to the search items to improve the selection power of underlying disorders in patients with BCG complications. Additional references were selected through the identification of citations in the retrieved articles.

5. Data Extraction

We used independent extraction by multiple observers. After data acquisition, a systematic strategy for data classification and the categorization of findings in a meaningful manner was performed.

6. Results

6.1. BCG Vaccination Protocol in Iran

Most experts agree on the effectiveness of the BCG vaccine. Various countries have developed very different BCG vaccination policies. The United Kingdom has a universal BCG vaccination program, while others (Canada and United states) recommend it only for high-risk groups. In Canada, different policies are used across provinces in which some provinces undergo mass vaccination programs and others do not. BCG vaccination policies also vary by number of doses, age, and method of administration. Vaccination policies have changed in countries over time. Since 1921, when the original BCG vaccine strain was developed, different vaccine strains were introduced and are currently being used. Genetic differences between BCG vaccine variants may cause different immunogenicity and effects on TST results. The database of global BCG vaccination policies and practices, a database containing BCG information from each country across all world regions (http:// www.bcgatlas.org/), includes valuable information of different countries' BCG vaccination policies. In our country, the current BCG vaccination is recommended at birth to all newborn infants, but a booster dose is not recommended. Booster vaccinations were done at 4-6 years of age, but the practice ended in 1999. Because this vaccine is used in all newborn infants, infant with all types of T cell deficiencies are prone to its complications of disseminated BCG infection (5).

6.2. Definition of BCG Infection

BCG vaccination in immunocompetent individuals is completely safe, and its immunogenicity begins approximately 12 weeks after vaccination. Post vaccination granuloma formation without evidence of disseminated BCG infection accompanied by a negative finding in PCR confirms the occurrence of active immunity. Mature hepatic granuloma with no evidence of the involvement of other organs was found as an Immunologic response to BCG vaccination that may occur in healthy children after BCD vaccination (6). There are various symptoms described by different authors for patients with BCG infection, but a definitive diagnosis was described by Bernatowska et al. who described the clinical status of BCG infection as systemic symptoms such as fever, loss of weight, delay in linear growth, and 2 or more areas of the body involved beyond the site of BCG vaccination. Identification of Mycobacterium bovis is done by culture, a standard PCR, and histopathological changes with granuloma formation. Areas of involvement are the lymph node, skin, soft tissue, lung, spleen, liver, and bones. If PCR is positive for mycobacterium complex or if there are typical histopathological changes and the diagnosis is confirmed by a negative PCR and/or culture results, then the diagnosis may be changed to probable and possible cases (7). In a study by Sadeghi-Shanbestari et al. in Tabriz, the inclusion criteria of patients with disseminated BCG infections were lymphadenitis or an abscess or fistula in the BCG vaccination site or another site with 2 or more of following signs: fever higher than 38.5 c for more than two weeks, anemia with hemoglobin less than 10, recurrent or persistent oral candidiasis, hepathosplenomegaly, bone disease (pain or arthritis), weight loss, recurrent or persistent diarrhea, and parent and family history of immunodeficiency (8).

6.3. Clinical Manifestation of Patients With Disseminated BCG Infection

Clinical suspicion of disseminated BCG infection is important in the early diagnosis of underlying immunodeficiency and the implementation of a treatment plan. If a child with a history of consanguineous parents and a BCG scar as evidence of birth vaccination has a clinical dilemma of prolonged or intermittent fever (high and low grade), fatigue, weakness, pallor, cough, long-term vesicular, raised maculopapular, petechia, purpural, pustular skin lesions, Ichtiosis, resistant oral candidiasis, lymphadenopathy near the BCG site with fistulization, mediastinal, and/or generalized lymphadenopathy without a response to antibiotics and other treatment modalities, this infection is a possibility (9, 10).

6.4. Laboratory Tests Necessary for Diagnostic Evaluation

Confirmation of Mycobacterium Bovis infection is the mainstay of diagnosis. Clinical specimens such as a lymph node biopsy, bone marrow aspiration, liver biopsy, gastric lavage and BAL or pus extracted from cold abscesses are used for acid fast staining, culture, and PCR preparation. A drug sensitivity test can be used for better therapeutic results. After confirmation of infection by Mycobacterium Bovis or a probable diagnosis with strong clinical suspicion, a CBC, liver function tests, and Serum Immunoglobin levels (IgG, IgM, IgA) are evaluated. An HIV test, CD19, CD3, CD56, CD3CD4, CD3CD8, and NBT (Nitrobluetetrazolium) are performed, and if negative, then confirmatory DHR (Dihydrorhedamine Test) and Isohemaglutinin antibody measurements are prescribed. In cases of suspicion of Human Lymphocytic Haemophagositic Syndrome, Cholesterol, Triglyceride, Fibrinogen, and CD 25 (Soluble IL2α) tests are recommended. Based on other clinical and laboratory manifestations of patients, other tests can be used for evaluation. Genetic deficiencies in Mendelian susceptibility to mycobacterial diseases are IFN-δ receptor 1/2 deficiencies, IL-12/23 receptor β1 chain deficiency, IL-12p40 deficiency, STAT1 deficiency, and LZ-NEMO deficiency. In general, focusing on a simple CBC in a child with oral candidiasis, hepathosplenomegaly, skin rashes, fever, poor weight gain, and a history of family members' deaths due to recurrent or chronic infections accompanied by parental consanguinity can be a good diagnostic guide in these children. Checking for a history of stillbirth or early death due to severe infections in the patient's siblings and other relatives from consanguine and non-consanguine parents and an evaluation for immunodeficiency are recommended (11, 12).

6.5. BCG Infection and Immunodeficiency

The incidence rate of disseminated BCG infection in vaccinated children is 0.06-1.56 cases per million vaccinated cases (6). Casanova JL 1995 studied 1951,39 cases and identified 108 cases of disseminated BCG infection with SCD (Severe Combined Immunodeficiency). Eleven cases had chronic granulomatous disease, 4 cases had AIDS, and 1 case had complete Di George syndrome. Three cases were not matched with a specific immunodeficiency, and 50 cases were defined as idiopathic. For 7 of 24 parents for whom information was available, consanguinity was found, so genetic immune response irregularity is an important factor in these patients (13). The incidence of disseminated BCG infection following BCG vaccination amongst children with HIV infections has been estimated to be as high as 992 per 100,000 with a mortality rate of 81% (14). The recommendation of the world health organization (WHO) is a full contraindication to BCG vaccination in HIV-infected infants, and in countries with a high incidence of tuberculosis, infants at risk for HIV infection should be tested for HIV prior to vaccination (15). In a study designed by Monajemzadeh M, PCR examination was performed on 21 pathologic specimens from patients with a histopathologic diagnosis of mycobacterial infection in 2004 (Tehran). For detection of BCG, mycobacterium TB, or other mycobacterial infections, the specimens were from the lymph nodes, liver, spleen, appendix, and lungs. Four cases had SCID, 3 cases had no immunodeficiency, and information was not accessible for the others. Twelve cases were positive for BCG infection, 2 for mycobacterium tuberculosis, and 1 for non-mycobacterium tuberculosis infection. The other cases were negative. The mean age of children assessed was 20 months (16). BCG infection complication may also affect BMT patients with a primary immunodeficiency, and there was a study in Turkey that reported on a child with SCID T-B+ who had a generalized infection due to BCG and underwent an effective treatment plan after BMT (17). Case reports of BCG infection are shown in the Tables 1 and 2, and the clinical manifestations and diagnostic evaluations are reviewed (Tables 1 and 2).

6.6. Important Types of Immunodeficiency With Disseminated BCG Infection as a Clinical Presentation

6.6.1. Severe Combined Immunodeficiency (SCID)

In regions that require a BCG vaccination program at birth, neonates with T and B cell immunodeficiency may suffer from disseminated BCG infection. These infants are unlikely to recover from this disease, and their chance for survival may decrease to a low level. SCID is a type of immunodeficiency with both B cell and T cell types of deficiency. Children with this type of immunodeficiency may

Table 1. [Part 1] Brief Explanation of Cases With Disseminated BCG Infections

Author	Source	Year of Publication	Age, mo	History of Consanguineous Marriage in Parents	Organs Involved	Number of Cases	Type of Immunodeficiency	Diagnosis Documentation	Treatment	Outcome
Jouanguy et al. (18)	Paris	1996	2.5 (girl)	Consanguinity	Cachexia, granulomatous dermatitis, hepathosplenomegaly, lymph node enlargement, diffuse pneumonitis, multiple osteolytic regions, fever	1	INF δ R1 deficiency by mutation analysis	Ill-defined granuloma, acid fast bacilli, PCR mycobacterium bovis	Antituberculosis and δ interferrone	Death
Karimi et al. (9)	Iran/Mazandaran	2002	11	In 7 cases	Lung, skin, liver, spleen, lymph node, bone	8	7 = SCID1 1 = CGD2	Positive Zeil Nelson stain	RIZE3 or RISE4 and δ interferone, GCSF	3 death
Kinciogullari et al. (17)	Ankara/Turkay	2002	7 (girl)	Consanguinity	Spina ventosa, hepatosplenomegaly,fever 4 weeks after BMT	1	T-B + SCID	Positive Zeil Nelson stain, PCR positive for mycobacterium complex	RIS and Clofazimine after relapse amikacin and ciprofloxacin was added	Cure
Huang et al. (19)	Taiwan	2006	8 (boy)	NA	Fever for two weeks, skin lesions, cough , FTT, unhealed ulcer on deltoid	1	SCID.T + B + NK-, missense mutation in IL2Rγ gene	Numerous acid fast bacill and positive PCR for BCG	RIZ and IVIG6	Death
Liberek et al. (20)	Poland	2006	4 (boy)	NA	Paleness, Hepathosplenomegaly, lymphadenitis	1	(IFN-δr1 def. By flocytometry	Lymph node biopsy caseating granuloma	RIS	Death
Alborzi et al. (21)	Shiraz/Iran	2007	28 (girl)	NA	naprolonged fever, hepathosplenomegaly, different abscesses	1	Normal	Granulma in biopsy Mycobacterium bovis in PCR	IR	Cure
Rezai et al. (22)	Tehran	2008	5 -72 (3 females, 12 males)	NA	Fever,weight loss, osteomyelitis, skin lesions, hepathosplenomegaly, lymphadenopathy	15	4 SCID, 1CVID, 2CGD, 1HIV, remaining unknown	Histopathologic finding of acid fast bacilli	RISE, INFG	6 Death
Tajima et al. (6)	Japan	2008	5 (girl)	NA	Asymptomatic, found dead in bed, due to extensive milk aspiration	1	Normal	Granuloma formation with acid fast bacilli and neg PCR for mycobacterium	NA	Death
Gadiri et al. (23)	Iran/Kermanshah	2009	NA	NA	Fistulized lymphadenopathy, osteomyelitis, splenomegaly	2	NA	Granuloma in liver biopsy, Zeil nelson stain of PUS, culture pos for M.bovis	RIE and Clarythromycin and δ interferone	2 cure
Sadeghi-Shanbestar et al. (8)	Iran/Tabriz	2009	< 1 y	6	Axillary lymphadenopathy, oral and diffuse candidiasis, recurrent diarrhea, splenomegaly	8	8 = SCID	Acid fast bacilli in two or more sites (BM,Lymph node, Gastric wash)	NA	8 death
Sohail et al. (24)	Pakistan/Islamabad	2009	11 (male)	Consanguinity	Swelling in right axilla with oozing, lethargy, breathing difficulty, FTT, brain involvement	1	SCID (T-B-NK+) byflocytometry	NA	RIZE and meropenem and cotrimoxazole, amikacin, ofloxacin, dexamethazone	Death

suffer from serious fever and prolonged viral and bacterial infections. Once these patients are infected with BCG, they can lose the chance for a bone marrow transplantation, which can be performed as soon as possible after birth. SCID is sub-classified into three main subcategories based on the different peripheral lymphocyte immune phenotyping, such as T_B_NK + SCID (absent circulating T- and B-cells but NK cells present), T_B + NK+ (absent circulating T-cells but B- and NK cells present), and T_B + NK_ (absent circulating T- and NK cells but B-cells present) (30).

The underlying genetic defects in SCID cannot always be detected because of the high cost and poor prognosis

Table 2. [Part 2] Brief Explanation of Cases With Disseminated BCG Infections

Author	Source	Year of Publication	Age, mo	History of Consanguineous Marriage in Parents	Organs Involved	Number of Cases	Type of Immunodeficiency	Diagnosis Documentation	Treatment	Outcome
Sadeghi-Shabestari and Rezaei (11)	Tabriz/Iran	2009	2 - 62	7 cases	Fever-diarrhea-cough-lymphadenopathy-weight loss-FTT-hepathosplenomegaly-oral candidiasis	11	7SCID-1CGD-1MSMD7-2 IL12R bidef	Acid fast bacilli in smear-culture of mycobacterium bovis	4 drugs but not named	8 death
Bacalhau et al. (25)	Poertugal	2011	5 (boy)	Not	Three days of fever, cough, oral trash, bil pulmonary rales, hepathosplenomegaly, recurrent infections	1	SCID, mutation in IL-2-IL2RG gene	PCR for BCG	RIE, levofloxacin, linezolide, BMT	Cure
Norozi et al. (26)	Tehran	2011	5 (boy)	Consanguinity	Diarrhea, fever 2 weeks before, axillary lymphadenopsthy, hepathosplenomegaly, paleness, FTT	1	SCID T-B + NK-	Pathology pneumocystis pneumonia, culture and PCR was Mycobacterium Bovis	Anti TB, cotrimoxazole, antifungal, IVIG	Death
Shahmohammadi et al. (27)	Mazandaran /Iran	2012	24	One had consanguinity	Fever, weight loss, axillary lymphadenopathy and fistulization, skin lesions	2	NA	Granuloma formation in biopsy	One case RISE and δINF	Cure
Shirvani et al. (28)	Tehran	2012	4 (old boy)	Consanguinity	Prolonged cough and fever, skin purple rashes, hepatosplenomegaly, FTT	1	T- B + NK-SCID and HLH8	Positive PCR	isoniazide, rifampin, ethambutol, clarithromycin, ciprofloxacin, cotrimoxazole, gancyclovir, amphotricin B, IVIG, Gma Interferon, amphotericin B	Death
Al-Mousa H (29)	Saudi Arabia	2014	5 (old girl)	Consanguinity	Recurrent chest infection, diarrhea, lymphadenopathy, scattered macular rash over entire body, ulcer and discharge at the site of BCG vaccination	1	T-B-NK + SCID	Positive smear with acid fast bacilli, positive culture	Isoniazide, Rifampin, ethambutol, ciprofloxacin, clarithromycin, HSCT	Cure

of patients and the reduced hope of finding family members for a cure. If it could be performed, gc deficiency and JAK3 deficiency could be suspected in patients with T_-B + NK_SCID regarding the associated phenotypic abnormalities. CD3, CD45, and IL7-Ra deficiencies may be suspected in patients with T_B + NK + SCID and RAG1/2, and Artemis deficiencies may be found in patients with T_B_-NK + SCID. SCID cases may have immune system deregulation after uncontrolled disseminated infection (8). A case report of a 5.5-month-old girl with prolonged fever, hepathosplenomegaly and axillary draining, adenopathy, and paraaortic adenopathy had high ESR, anemia, thrombocytopenia, elevated ferritin, and hypertriglyceridemia with the diagnosis of Hemophagocytic Hystiocytosis and SCID (31).

6.7. Mendelian Susceptibility to Mycobacterial Diseases (MSMD)

Cytokines and specially interferon-gamma have a large responsibility in the regulation of immune response to Baclle Calmette-Guerine (BCG). In a study by Parvaneh et al. thirty patients with BCG adenitis and 30 age and sex-matched healthy children with a history of BCG vaccination in the first two days of life from Fars/Iran were examined for the detection of Polymorphism at position +874 of the IFN-δ gene. The minor allele (T) was significantly lower in patients with BCG adenitis, which means that lower interferon production is mainly responsible for an unusual reaction to the BCG vaccine (32).

MSMD is a group of genetically heterogeneous disorders. Six autosomal (IFNGR1, IFNGR2, IL12B, IL12RB1, IRF8, and STAT1) and 2 X-linked (CYBB, NEMO) genes in MSMD-causing mutations were found. Since 1996, the investiga-

tion of Allelic heterogeneity revealed up to 15 genetic disorders with complete and partial defects and dominant and recessive traits and complete defects with and without protein production. With the exception of CYBB, MSMD-causing genes encode molecules involved in the IL-12-IFN-γcircuit (33). These rare disorders have been diagnosed in over 220 patients from over 43 countries worldwide with inborn errors of the IL-12/23-IFN-gamma circuit (34).

In the following section, we briefly describe the important types of MSMD.

6.8. IFN δ R1 and IFN δ R2 Deficiency

Interferon- δ, which is produced by T cells and is a natural killer of cells, may induce macrophage for production of interleukin-1 and TNF-α. These molecules enhance antigen presentation and increase nitric oxide and reactive-oxygen intermediates production. INF δ is a cytokine and induces cellular activation and has two binding sites as IFN δ R1 and a chromosome 21-encoded transmembrane accessory factor called IFNδR2. Two chains of each molecule activate intracellular parts such as JAK1 and JAK2. This results in the phosphorylation of tyrosine at position 457 of the interferon-g receptor 1 chain, which may result in the production of a binding site for Stat 1a (signal transduction and activation of transcription protein), leading to subsequent dissociation of Stat 1a from the interferon-δ-receptor complex. This stat translocates in the nucleus, and by inducing interferon δ-inducible genes, it results in their transcription and phosphorylation of cytosol components to make several proteins. Patients with IFN δ R1 deficiency have more than 30 currently recognized mutations and have a poor prognosis with different mycobacterial, CMV, and Herpes Virus 8 infections. They may die in childhood, and the most common treatment is homozygote stem cell transplantation (18, 35). A case report in 1997 examined a 3-year-old child with unrelated parents and a history of lymphadenopathy, wasting, fever, and hepathosplenomegaly. Her three sisters and one brother died previously because of severe infections. She had a liver biopsy, and the result of its culture was M. smigata. Two null mutations of the IFN- δ -Rl gene were identified by genetic investigation, and a flow cytometry analysis with an antibody to IFN- δ -R1 could not detect the receptor on the peripheral lymphocytes and monocytes. She did not respond to therapy and died. IFN δ R2 deficiency is very rare. This molecule interacts with IFN δ -IFN δ R1 complex, and its complete deficiency is accompanied by early onset mycobacterial disease and poorly defined multibacillary granulomas with a poor prognosis for survival (36).

6.9. STAT1 Deficiency

It is obvious that Stat-1 is critical for the signaling of IFN-δ and IFN-α in humans. Without Stat-1, IFNs are not able to induce intracellular 1 (gamma activating factors GAF), ISGF3 (interferon-stimulated gene factor 3) (ISGF3) activation, and HLA class II cell surface expression, so the production of IL-12, IFN-δ, and TNF-α are defective (37).

IFN-δ stimulates the homodimerization and phosphorylation of Stat-1 (gamma activating factors GAF). This results in GAF homodimers and ISGF-3 heterotrimers transferring to the nucleus. If IFN-responsiveness is intact, they act as gene transcription factors and bind to cis-acting regulatory sequences in DNA (gamma activating sequences (GAS)) and interferon stimulated response elements (ISRE), respectively. Mutations in Stat-1 result in susceptibility to mycobacteria and viruses due to impaired IFN-δ - and IFN-α/βmediated immunity, respectively (38).

6.10. IL-12p40 Deficiency

IL p40 is a unique but known AR cytokine defect. This defect may have originated from a mutation in Iran dating 600 years ago and 875 years ago in Saudi Arabia. It occurs in populations with a high prevalence of consanguinity (32). The IL12β gene is composed of eight exons, and its mRNA is produced only in IL-12-producing antigen-presenting cells. IL-12 comprises two disulfide-linked subunits: p35 and p40. The p40 subunit may also be associated with the p19 subunit to form IL-23. Binding of IL-12 to a heterodimeric receptor consisting of two chains (IL-12Rβ1 and IL-12Rβ2) expressed on NK and T lymphocytes induces the production of large amounts of IFN-δ. IL-23 binds to a heterodimeric receptor (IL-12Rβ1 and IL-23R) and induces IFN- δ, and to greater extent, IL-17.

All IL-12p40-deficient patients vaccinated with BCG have suffered from BCG disease. One IL-12p40-deficient patient from Saudi Arabia with BCGosis and S. paratyphi C disease also had tuberculosis. Surprisingly, high proportions of these patients are infected with salmonella. Half of the cases were infected with Salmonella, which was often accompanied by mycobacterial disease. One child who was not vaccinated with BCG developed a recurrent and disseminated infection caused by non-typhoidal Salmonella. A similar observation was made for the more numerous IL-12Rβ1-deficient patients, half of whom also suffered from salmonellosis. In contrast, few cases ($\sim$6%) of Salmonella infection were observed among MSMD patients bearing mutations affecting the IFN-δ signaling pathway and isolated Salmonella infections have never yet been reported in patients with IFN-δ -signaling defects. These observations suggest that IL-12/IL-23 plays a key role in protective immunity against Salmonella, probably via IFN-

δ -independent mechanisms (39). In patients with non-typhoidal, extraintestinal salmonellosis, the physicians should check for IL-12p40 and IL-12Rβ1 deficiencies (33).

6.11. IL-12Rβ_1 Deficiency

The IL12RB1 gene contains 17 exons encoding a gp130-like protein formed by an extracellular N terminal immunoglobulin (Ig)-like domain, a transmembrane domain, and an intracellular domain. Functional IL-12 receptors are expressed primarily on activated T and NK cells. High-affinity IL-12 binding and complete signaling needs co-expression of IL-12Rβ1 and IL-12Rβ2. Another function of IL-12Rβ1 is its combination with IL-23R to constitute the IL-23R complex for IL-23 signaling. IL-12 and IL-23 will activate Janus kinase 2 (Jak2) and Tyk2 and several Stat proteins as well; however, IL-12 and IL-23 strongly induce the phosphorylation of Stat-4 and Stat-3, respectively (40). Interleukin-12 receptor β1 (IL-12Rβ1) deficiency is a rare autosomal recessive disorder, and its penetrance is not always complete. Mycobacterial disease and salmonellosis are the most frequent infectious diseases in patients with IL-12Rβ1 deficiency. Other infectious phenotypes have only rarely been observed in one patient each. A disseminated disease caused by a facultative intracellular dimorphic fungus, Paracoccidioides brasiliensis, has been reported in one IL-12Rβ1-deficient patient (41), which was probably due to a difference in exposure to the pathogens. Approximately 12% of the IL-12Rβ1 deficient individuals are asymptomatic, and some of them do not develop the disease until later in life, so a large range of the age at first infection (from 1 week to 31.7 years) may result (42). Because of the role of IL-12-IFN-γcircuit in the elimination of intracellular pathogens in tuberculosis, severe BCG, and non-tuberculosis mycobacterium, these patients may have chronic infections with these organisms. Currently, these types of immunodeficiencies are referred to as IL12-12/23-INF δ circuits. Other rare infections are Nocardia and Paracoccidiomyces infections. Severe diseases by non-typhoidal, and to a lesser extent, thyphoidal Salmonella serotypes, is common (43).

6.12. HIV and BCG Coinfection

HIV-infected children may receive BCG vaccination after birth when their HIV status has not been diagnosed yet and they are asymptomatic. Disseminated BCG infection may be diagnosed between 5 and 36 months of age. Various symptoms occur in these children, such as weight loss, lymphadenitis, cardiomyopathy, hepatomegaly, and fever, and they will not grow at an optimal rate mentally or physically. Other opportunistic infections, including M. avium/intracellulare and pneumocystis carirni are usually present (44). Mycobacterial infection could promote immunodeficiency, so with an HIV infection, the HIV viral load increases in patients with active tuberculosis (45). Thus, in the case of HIV positive children, BCG infection may accelerate the HIV status. The diagnosis of BCG infection in these cases may be problematic in cases with no specific clinical signs and poor availability of molecular diagnostic tests.

6.13. Treatment Program in Disseminated BCG Infection

Since almost all cases of disseminated BCG infections may have an underlying immunodeficiency, different protocols are used for the treatment of these patients. Because of the known resistance of BCG to Pirazinamide, this drug is not used in the treatment program of BCG osis. An in vivo study on the resistance to pyrazinamide on a few strains of BCG adenitis in Iranian children and the BCG strain used for vaccination (institute Pasteur of IRAN) by Fahimzad A showed that increasing the concentration of Pyrazinamide added to other anti-mycobacterial drugs inhibited the growth of organisms (46). Drugs that are used in combination and different time periods are Isoniazide, Rifampicin, Streptomycin, Ethambutol, Fludarabine, Busulfan, and Cyclosporine. Anti-timosit globulin, IFNγ, and HSCT are other treatment options for these children. If drugs are used judiciously in combination with HSCT, the prognosis of survival in patients may rise accordingly (27). Regarding the basic immunologic problems in these patients, BMT is the best treatment strategy (47).

6.14. New Vaccines for Control of Global TB Infection

There are three reasons to explain why TB has not been adequately controlled. First, diagnostic technology cannot optimally differentiate cases of latent M tuberculosis infection and infectious TB disease. Second, anti-tuberculosis drug treatment is a long process, and in the case of poor consumption, it may result in multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains. The third is the efficacy of BCG vaccination. Evidence derived from 60 years of control trials with the BCG vaccine shows that the protective efficacy of the vaccine against TB is variable. Based on this information, different vaccine trials have sought to address the new protective tool to control TB infection and disease. After 90 years of BCG global vaccine introduction, mycobacterial infection is not controlled adequately. On the other hand, experts in HIV infection have voiced considerable doubt in the birth BCG vaccination in high risk neonates. Currently, because of the low effect of BCG on the control of pulmonary TB, this vaccine is not used in the UK or the USA (48).

6.15. Vaccine Trial in Prevention of Mycobacterium Tuberculosis Infection

BCG has been part of the Expanded Program of Immunization since 1970. It prevents milliary and meningeal TB in children, but its effect on the prevention of pulmonary TB is inadequate in all age groups in high endemic regions. The current BCG vaccine's largest obstacle is the lack of protection in adults because of waning immunity in childhood. A booster vaccination is used in some countries, but its cost effectiveness against infection is variable. Different vaccines are used as pre/post or therapeutic methods with different components in the prevention of disseminated disease and treatment modality in patients with disseminated BCG infection. Currently, two types of the BCG vaccine, rBCG and an rMtb deletion, are currently under investigation. Sub-unit vaccines are used for the induction of immunity to a single or multiple immunodominant antigens divided into adjuvanted recombinant proteins or viral vector systems (49).

6.16. Development of MVA85A

Modified Vaccinia Ankara (MVA) is an attenuated strain of vaccinia virus that was given to more than 100,000 people during the smallpox eradication campaign. MVA85A, which is the live, non-replicating, recombinant strain of MVA, expresses antigen 85A. The first step in the trial of this vaccine was implemented on animals. The phase 1 clinical trial was done on mice, guinea pigs, non-human primates, and cattle, and the goal was the detection of the boosting effect of this vaccine after BCG infection. The first-human trial of MVA85A was done in healthy, BCG vaccine-naïve, M tuberculosis-uninfected adults in the UK, and the safety was evaluated in BCG vaccine-primed adults. The other vaccinated groups were adults latently infected with M tuberculosis in the UK and in Africa with a higher mycobacterial load from the environment and HIV patients. More than 2,000 individuals (47 latently infected with M tuberculosis and 108 HIV-infected groups) have received MVA85A in 19 clinical trials. MVA85A was found to be safe and well tolerated with no evidence of immunologic adverse effects in any trials to date. This vaccine may act as an adjuvant to routine BCG vaccination. The principle target populations for MVA85A are infants with a history of BCG vaccinations at birth, adolescents and young adults with waning immunity, and those affected by childhood BCG and adult HIV cases. Another important issue for any new vaccine is being effectively incorporated into administration with vaccines in the current vaccination program for immunization (EPI) (48). The outcome of the MVA85A phase IIb vaccine trial showed disappointing and questionable results because gene expression was shut down (49).

7. Conclusions

The protective effect of the BCG vaccine appears to vary according to geography and the vaccine strain (19, 50). Patients with different primary and acquired immunodeficiencies may acquire invasive BCG infection in different time periods after vaccination. The potential efficacy of this vaccine against severe Mycobacterial disease in immunocompetent hosts should be reevaluated because of its disadvantages in immunocompromised patients. Being aware of immunologic status in high risk vaccine recipients may prevent unwanted results.

References

1. World Health Organization. . Global Tuberculosis Report 2014. Executive summary 2014. Available from: http://www.who.int/tb/publications/global_report/gtbr14_executive_summary.pdf?ua=1.
2. Schreiber F, Huo Z, Giemza R, Woodrow M, Fenner N, Stephens Z, et al. An investigation of clinical and immunological events following repeated aerodigestive tract challenge infections with live Mycobacterium bovis Bacille Calmette Guerin. *Vaccine.* 2010;**28**(33):5427–31. doi: 10.1016/j.vaccine.2010.06.005. [PubMed: 20558246].
3. Imen Pharmed. . History of BCG vaccine production in IRAN 2014. Available from: http://ipiranian.ir.
4. Manissero D, Lopalco PL, Levy-Bruhl D, Ciofi Degli Atti ML, Giesecke J. Assessing the impact of different BCG vaccination strategies on severe childhood TB in low-intermediate prevalence settings. *Vaccine.* 2008;**26**(18):2253–9. doi: 10.1016/j.vaccine.2008.02.038. [PubMed: 18400344].
5. Zwerling A, Behr MA, Verma A, Brewer TF, Menzies D, Pai M. The BCG World Atlas: a database of global BCG vaccination policies and practices. *PLoS Med.* 2011;**8**(3):eee1001012. doi: 10.1371/journal.pmed.1001012. [PubMed: 21445325].
6. Tajima Y, Takagi R, Nakajima T, Kominato Y. An infant with asymptomatic hepatic granuloma probably caused by bacillus Calmette-Guerin (BCG) vaccination found incidentally at autopsy: a case report. *Cases J.* 2008;**1**(1):337. doi: 10.1186/1757-1626-1-337. [PubMed: 19019255].
7. Bernatowska EA, Wolska-Kusnierz B, Pac M, Kurenko-Deptuch M, Zwolska Z, Casanova JL, et al. Disseminated bacillus Calmette-Guerin infection and immunodeficiency. *Emerg Infect Dis.* 2007;**13**(5):799–801. doi: 10.3201/eid1305.060865. [PubMed: 18044052].
8. Sadeghi-Shanbestari M, Ansarin K, Maljaei SH, Rafeey M, Pezeshki Z, Kousha A, et al. Immunologic aspects of patients with disseminated bacille Calmette-Guerin disease in north-west of Iran. *Ital J Pediatr.* 2009;**35**:42. doi: 10.1186/1824-7288-35-42. [PubMed: 20030825].
9. Karimi A, Nategian A, Mamishi S. Report of 8 cases of disseminated BCG in patients vaccinated in Children Medical Center (1998-2002) Tehran/IRAN. *Mazandaran Sci Res J.* 2004;**13**(38):67–75.
10. Gonzalez B, Moreno S, Burdach R, Valenzuela MT, Henriquez A, Ramos MI, et al. Clinical presentation of Bacillus Calmette-Guerin infections in patients with immunodeficiency syndromes. *Pediatr Infect Dis J.* 1989;**8**(4):201–6. [PubMed: 2654859].
11. Sadeghi-Shabestari M, Rezaei N. Disseminated bacille Calmette-Guerin in Iranian children with severe combined immunodeficiency. *Int J Infect Dis.* 2009;**13**(6):e420–3. doi: 10.1016/j.ijid.2009.02.008. [PubMed: 19403320].
12. Casanova JL, Jouanguy E, Lamhamedi S, Blanche S, Fischer A. Immunological conditions of children with BCG disseminated infection. *Lancet.* 1995;**346**(8974):581. [PubMed: 7658805].
13. Casanova JL, Blanche S, Emile JF, Jouanguy E, Lamhamedi S, Altare F, et al. Idiopathic disseminated bacillus Calmette-Guerin infection: a

French national retrospective study. *Pediatrics.* 1996;**98**(4 Pt 1):774–8. [PubMed: 8885960].
14. Azzopardi P, Bennett CM, Graham SM, Duke T. Bacille Calmette-Guerin vaccine-related disease in HIV-infected children: a systematic review. *Int J Tuberc Lung Dis.* 2009;**13**(11):1331–44. [PubMed: 19861003].
15. Hesseling AC, Johnson LF, Jaspan H, Cotton MF, Whitelaw A, Schaaf HS, et al. Disseminated bacille Calmette-Guerin disease in HIV-infected South African infants. *Bull World Health Organ.* 2009;**87**(7):505–11. [PubMed: 19649364].
16. Monajemzadeh M, Shahsiah R, Zarei A, Alamooti AA, Mahjoub F, Mamishi S, et al. Frequency of bacille Calmette-Guerin (BCG) and Mycobacterium tuberculosis in tissue biopsy specimens of children vaccinated with BCG. *Am J Clin Pathol.* 2010;**133**(1):102–6. doi: 10.1309/AJCPXLZPRHX9L0YG. [PubMed: 20023264].
17. Ikinciogullari A, Dogu F, Ciftci E, Unal E, Ertem M, Reisli I, et al. An intensive approach to the treatment of disseminated BCG infection in a SCID patient. *Bone Marrow Transplant.* 2002;**30**(1):45–7. doi: 10.1038/sj.bmt.1703578. [PubMed: 12105777].
18. Jouanguy E, Altare F, Lamhamedi S, Revy P, Emile JF, Newport M, et al. Interferon-gamma-receptor deficiency in an infant with fatal bacille Calmette-Guerin infection. *N Engl J Med.* 1996;**335**(26):1956–61. doi: 10.1056/NEJM199612263352604. [PubMed: 8960475].
19. Huang LH, Shyur SD, Weng JD, Huang FY, Tzen CY. Disseminated Cutaneous Bacille Calmette-Guérin Infection Identified by Polymerase Chain Reaction in a Patient with X-linked Severe Combined Immunodeficiency. *Pediatr Dermatol.* 2006;**23**(6):560–3.
20. Liberek A, Korzon M, Bernatowska E, Kurenko-Deptuch M, Rytlewska M. Vaccination-related Mycobacterium bovis BCG infection. *Emerg Infect Dis.* 2006;**12**(5):860–2. doi: 10.3201/eid1205.050107. [PubMed: 16710956].
21. Alborzi A, Mostafavi N. Retroperitoneal abscess due to disseminated Bacille Calmette-Guerin infection. *Jpn J Infect Dis.* 2007;**60**(6):392–3. [PubMed: 18032842].
22. Rezai MS, Khotaei G, Mamishi S, Kheirkhah M, Parvaneh N. Disseminated Bacillus Calmette–Guerin Infection after BCG Vaccination. *J Trop Pediatr.* 2008;**54**(6):413–6.
23. Gadiri K, Afsharian M, Vazizi S, Mansori F, Namdari M. Two cases of disseminated BCG infection in Kermanshah and review of literature. *Kordestan Med Univ J.* 2007;**12**:91–6.
24. Sohail S, Afzal M, Anwar V, Shama Q. Disseminated Bacille Calmette-Guerin (BCG) disease in an infant with severe combined immunodeficiency. *J Coll Physicians Surg Pak.* 2014;**24 Suppl 3**:S259–61. [PubMed: 25518795].
25. Bacalhau S, Freitas C, Valente R, Barata D, Neves C, Schafer K, et al. Successful Handling of Disseminated BCG Disease in a Child with Severe Combined Immunodeficiency. *Case Rep Med.* 2011;**2011**:527569. doi: 10.1155/2011/527569. [PubMed: 22110512].
26. Norouzi S, Movahedi Z, Mamishi S, Monajemzadeh M, Rezaei N. Disseminated BCG as a unique feature of an infant with severe combined immunodeficiency. *Turk J Pediatr.* 2011;**53**(3):328–32. [PubMed: 21980818].
27. Shahmohammadi S, Saffar MJ, Rezai MS. BCG-osis after BCG vaccination in immunocompromised children: Case series and review. *J Pediatr Rev.* 2014;**2**(1):62–74.
28. Shirvani F, Chavoshzadeh Z, Arjmand R, Karimi A. Four-Month-Old Boy With Fever, Hepatosplenomegaly and Diffuse Pulmonary Infiltrations. *Arch Clin Infect Dis.* 2012;**7**(2):72–4.
29. Al-Mousa H. An infant with disseminated bacillus Calmette-Guerin infection (BCGitis). *Int J Pediatr Adolescent Med.* 2014;**1**(2):89–92.
30. Deeks SL, Clark M, Scheifele DW, Law BJ, Dawar M, Ahmadipour N, et al. Serious adverse events associated with bacille Calmette-Guerin vaccine in Canada. *Pediatr Infect Dis J.* 2005;**24**(6):538–41. [PubMed: 15933565].
31. Ghanaie R, Shiari R, Karimi A, Armin S, Fahimzad A, Shiva F, et al. A case series report of Iranian children Hemophagocytic Lymphohistiocytosis syndrome. *Arch Pediatr Infect Dis.* 2013;**1**(1):31–5.
32. Parvaneh N, Pourakbari B, Daneshjoo KH, Ashraf H, Salavati A, Mamishi S. Polymorphism in the First Intron of Interferon-Gamma Gene (+874T/A) in Patients with BCG Adenitis. *Iranian J Publ Health.* 2009;**38**(3):12–6.
33. Prando C, Samarina A, Bustamante J, Boisson-Dupuis S, Cobat A, Picard C, et al. Inherited IL-12p40 deficiency: genetic, immunologic, and clinical features of 49 patients from 30 kindreds. *Medicine (Baltimore).* 2013;**92**(2):109–22. doi: 10.1097/MD.0b013e31828a01f9. [PubMed: 23429356].
34. Filipe-Santos O, Bustamante J, Chapgier A, Vogt G, de Beaucoudrey L, Feinberg J, et al. Inborn errors of IL-12/23- and IFN-gamma-mediated immunity: molecular, cellular, and clinical features. *Semin Immunol.* 2006;**18**(6):347–61. doi: 10.1016/j.smim.2006.07.010. [PubMed: 16997570].
35. Newport MJ, Huxley CM, Huston S, Hawrylowicz CM, Oostra BA, Williamson R, et al. A mutation in the interferon-gamma-receptor gene and susceptibility to mycobacterial infection. *N Engl J Med.* 1996;**335**(26):1941–9. doi: 10.1056/NEJM199612263352602. [PubMed: 8960473].
36. Pierre-Audigier C, Jouanguy E, Lamhamedi S, Altare F, Rauzier J, Vincent V, et al. Fatal disseminated Mycobacterium smegmatis infection in a child with inherited interferon gamma receptor deficiency. *Clin Infect Dis.* 1997;**24**(5):982–4. [PubMed: 9142806].
37. Chapgier A, Wynn RF, Jouanguy E, Filipe-Santos O, Zhang S, Feinberg J, et al. Human complete Stat-1 deficiency is associated with defective type I and II IFN responses in vitro but immunity to some low virulence viruses in vivo. *J Immunol.* 2006;**176**(8):5078–83. [PubMed: 16585605].
38. Dupuis S, Jouanguy E, Al-Hajjar S, Fieschi C, Al-Mohsen IZ, Al-Jumaah S, et al. Impaired response to interferon-alpha/beta and lethal viral disease in human STAT1 deficiency. *Nat Genet.* 2003;**33**(3):388–91. doi: 10.1038/ng1097. [PubMed: 12590259].
39. Happel KI, Dubin PJ, Zheng M, Ghilardi N, Lockhart C, Quinton LJ, et al. Divergent roles of IL-23 and IL-12 in host defense against Klebsiella pneumoniae. *J Exp Med.* 2005;**202**(6):761–9. doi: 10.1084/jem.20050193. [PubMed: 16157683].
40. Trinchieri G. Interleukin-12 and the regulation of innate resistance and adaptive immunity. *Nat Rev Immunol.* 2003;**3**(2):133–46. doi: 10.1038/nri1001. [PubMed: 12563297].
41. Fieschi C, Dupuis S, Catherinot E, Feinberg J, Bustamante J, Breiman A, et al. Low penetrance, broad resistance, and favorable outcome of interleukin 12 receptor beta1 deficiency: medical and immunological implications. *J Exp Med.* 2003;**197**(4):527–35. [PubMed: 12591909].
42. Rosenfeldt V, Paerregaard A, Valerius NH. Disseminated infection with Bacillus Calmette-Guerin in a child with advanced HIV disease. *Scand J Infect Dis.* 1997;**29**(5):526–7. [PubMed: 9435049].
43. MacLennan C, Fieschi C, Lammas DA, Picard C, Dorman SE, Sanal O, et al. Interleukin (IL)-12 and IL-23 are key cytokines for immunity against Salmonella in humans. *J Infect Dis.* 2004;**190**(10):1755–7. doi: 10.1086/425021. [PubMed: 15499529].
44. van de Vosse E, Haverkamp MH, Ramirez-Alejo N, Martinez-Gallo M, Blancas-Galicia L, Metin A, et al. IL-12Rbeta1 deficiency: mutation update and description of the IL12RB1 variation database. *Hum Mutat.* 2013;**34**(10):1329–39. doi: 10.1002/humu.22380. [PubMed: 23864330].
45. Halsey NA, Henderson DA. HIV infection and immunization against other agents. *N Engl J Med.* 1987;**316**(11):683–5. doi: 10.1056/NEJM198703123161108. [PubMed: 3821800].
46. Fahimzad SA, Ghasemi M, Shiva F, Ghadiri K, Navidinia M, Karimi A. Susceptibility Pattern of Bacille Calmette-Guerin Strains Against Pyrazinamide and Other Major Anti-Mycobacterial Drugs. *Arch Pediatr Infect Dis.* 2015;**3**(1 TB).
47. Heyderman RS, Morgan G, Levinsky RJ, Strobel S. Successful bone marrow transplantation and treatment of BCG infection in two patients with severe combined immunodeficiency. *Eur J Pediatr.* 1991;**150**(7):477–80. [PubMed: 1915499].

48. Meyer J, McShane H. Global progress in tuberculosis vaccine development. *Clin Med.* 2012;**12**(Suppl 6):s17–20.
49. Andersen P, Kaufmann SH. Novel vaccination strategies against tuberculosis. *Cold Spring Harb Perspect Med.* 2014;**4**(6) doi: 10.1101/cshperspect.a018523. [PubMed: 24890836].
50. Venkataswamy MM, Goldberg MF, Baena A, Chan J, Jacobs WJ, Porcelli SA. In vitro culture medium influences the vaccine efficacy of Mycobacterium bovis BCG. *Vaccine.* 2012;**30**(6):1038–49. doi: 10.1016/j.vaccine.2011.12.044. [PubMed: 22189700].