Chapter 20
BCG Immunization: Efficacy, Limitations, and Future Needs

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Abbreviations

BCG	Bacille Calmette–Guérin
BMRC	British Medical Research Council
CI	Confidence interval
HCW	Healthcare workers
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
IUATLD	International Union against Tuberculosis and Lung Disease
NRAMP	Natural resistance-associated macrophage protein
TB	Tuberculosis
UNICEF	United Nations Children's Fund
USPHS	United States Public Health Service
WHO	World Health Organization

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20.1 Historical Background

Bacille Calmette–Guérin (BCG), a live attenuated vaccine, is one of the oldest vaccines in the world. The original BCG strain was lost during World War I (1914–1918) (Lagrange 1984). Derived from a virulent strain of *Mycobacterium bovis* through 230 subcultures over 13 years by French investigators Calmette and Guérin (Sakula 1983), the first dose of BCG was orally given to a human volunteer in 1921 (Calmette 1931a; Weill-Hallé and Turpin 1925). The safety of BCG was severely challenged when contaminated BCG killed 72 children in Germany from 1929 to 1930 (Calmette 1931b; Lange; 1930; Moegling; 1935).

With early evidence for efficacy among student nurses in Norway (Heimbeck 1936), BCG was increasingly used in Europe. The demonstration of high efficacy of BCG against tuberculosis (TB) in trials initiated by the British Medical Research Council (BMRC) in the 1950s led to routine BCG vaccination in the majority of the world (WHO 1972; Hart and Sutherland 1977). Since BCG was incorporated into the Expanded Program on Immunization's (EPI) infant vaccination schedule in 1974, use of BCG has globally expanded.

Owing to the lack of protection shown in BCG trials conducted by the United States Public Health Service (USPHS) in the early 1950s (Comstock and Palmer 1966), the USA has adopted a policy of selective BCG vaccination among high-risk populations and based their TB control strategy partly on rapid diagnosis and early treatment of TB disease and partly on preventive treatment of infected individuals (CDC 1996). The Netherlands has followed suit.

20.2 Global Use of BCG

As the only licensed vaccine against TB, BCG is one of the most widely used vaccines in the world. In the 1990s, approximately 100 million children received BCG vaccine every year (WHO 1997). Based on WHO/UNICEF estimates, global coverage of BCG vaccination during infancy further increased from 81 % in 1990 to 88 % in 2009 (WHO 2010b). More than 120 million doses are now used every year (Ritz et al. 2008).

BCG vaccination policies vary across different countries by the BCG strain (Ritz and Curtis 2009) as well as the vaccination schedule (Brewer et al. 1995). Four BCG strains account for more than 90 % of the vaccines currently in use: Pasteur-1173 P2, Copenhagen-1331, Glaxo-1077, and Tokyo-172. The Pasteur strain is currently the international reference strain of vaccine (Milstien and Gibson 1990). BCG vaccination schedules can be classified into four main groups (Fine et al. 1999): vaccination once only at birth, vaccination once only in childhood or adolescence, multiple doses involving boosters, and selective vaccination among high-risk groups. Vaccination once only at birth is the schedule currently recommended by the WHO EPI) and practiced in most countries. A study by Ritz and Curtis found that

44 % of countries reportedly used more than one BCG strain within a 5-year period (Ritz and Curtis 2009). To help clinical interpretation of diagnostic tests as well as the design and evaluation of new TB vaccines, Zwerling and coworkers have created the first searchable online database of global BCG vaccination policies and practices which also captures any applicable changes (Zwerling et al. 2011).

BCG vaccination policies have changed with TB incidence. To improve cost-effectiveness, nine countries have shifted from universal to selective BCG vaccination in response to declining TB incidence rates: Spain in 1981; Denmark in 1986; Austria in 1990; Germany in 1998; and Isle of Man, Slovenia, UK, Finland, and France between 2005 and 2007 (Zwerling et al. 2011). According to the International Union against Tuberculosis and Lung Disease (IUATLD), universal BCG vaccination may be stopped when an efficient notification system is in place with one of the following conditions: (1) the average annual notification rate of smear-positive pulmonary TB is less than 5 per 100,000, (2) the average annual notification rate of tuberculous meningitis in children under 5 years of age is less than 1 per 10 million population over the previous 5 years, or (3) the average annual risk of tuberculous infection is less than 0.1 % (IUATLD 1994).

Over 30 countries have stopped BCG revaccination as increasing evidence demonstrated lack of additional protection (Zwerling et al. 2011).

BCG vaccination policies have also changed as a result of HIV infection. Being live attenuated, BCG can cause invasive and disseminated BCG disease among the immunocompromised, especially HIV-infected subjects. Before 2007, WHO recommended routine vaccination in TB-endemic countries in the absence of symptoms of HIV infection (WHO 2004). Since 2007, in response to evidence of an unacceptably higher risk of disseminated BCG disease among HIV-infected vaccinees (WHO 2007a), WHO has recommended that BCG vaccination of HIV-infected children be discontinued in TB-endemic countries (WHO 2007b). The IUATLD has suggested that neonatal BCG vaccination in TB-endemic areas be continued until programs are in place for selective deferral of BCG vaccination in infants exposed to HIV (Hesseling et al. 2008).

20.3 Efficacy of BCG

Most of the variations regarding global use of BCG across different countries may have stemmed from the partial and variable efficacy of BCG.

20.3.1 Initial Experience and Historical Cohort Trials

With preliminary evidence for the utility of BCG in protecting against TB among student nurses in the 1930s (Heimbeck 1936) and American Indians in the 1940s (Aronson 1948a, b), BMRC and USPHS set up major trials in the early 1950s to

further evaluate the efficacy of BCG against TB. Instead of drawing conclusive evidence for the protective efficacy of BCG, BMRC and USPHS demonstrated completely opposing findings. The use of Copenhagen strain against tuberculin-negative adolescents in BMRC trials efficaciously protected against TB, whereas the Park or Tice strains given to tuberculin-negative subjects by the USPHS demonstrated little protection. Two hypotheses were put forward to explain the discrepancy. One attributed the differences to variation between BCG strains (Hart 1967). The other considered environmental factors, especially environmental mycobacteria (Palmer and Long 1966). To evaluate these hypotheses, a large trial involving all age groups started in 1968 to compare two well-established BCG strains ("Paris/Pasteur" vs. "Danish/Copenhagen") in the Chingleput area of South India, where there is a high prevalence of environmental mycobacteria. A companion trial in an area in northern India with little environmental mycobacterial exposure was conceived but unfortunately aborted due to political unrest. The Chingleput trial revealed no evidence for the efficacy of either vaccine against pulmonary TB (Baily 1980; ICMR/WHO Scientific Group 1980). This set the scene for a series of clinical trials (WHO 1972; Bettag et al. 1964; Comstock et al. 1974, 1976; Comstock and Webster 1969; Frimodt-Moller et al. 1973; Rosenthal et al. 1961; Stein and Aronson 1953; Tripathy 1987; Vandiviere et al. 1973) and observational studies (Blin et al. 1986; Camargos et al. 1988; Canetti et al. 1972; Jin et al. 1989; Miceli et al. 1988; Murtagh 1980; Orege et al. 1993; Padungchan et al. 1986; Pönnighaus et al. 1992; Rodrigues et al. 1991; Shapiro et al. 1985; Tidjani et al. 1986; Wunsch Filho et al. 1990) that evaluated the efficacy of BCG in different populations of the world.

20.3.2 Efficacy and Impact of BCG Vaccination

Most studies were conducted among participants initially vaccinated during infancy and young childhood rather than adulthood. Vaccine efficacy rates are generally greatest within the few years following vaccination and most consistent against serious forms of TB in infants and young children (CDC 1996; Rieder 2008). Data are too few for evaluating the protective efficacy of BCG against other forms of extrapulmonary TB. On the other hand, the protective efficacy of BCG vaccination against pulmonary TB is highly heterogeneous with efficacy estimates ranging from below 0 % to approximately 80 % across clinical trials and observational studies (WHO 1972; Bettag et al. 1964; Blin et al. 1986; Comstock et al. 1974, 1976; Comstock and Webster 1969; Frimodt-Moller et al. 1973; Miceli et al. 1988; Orege et al. 1993; Putrali et al. 1983; Pönnighaus et al. 1992; Rodrigues et al. 1991; Shapiro et al. 1985; Stein and Aronson 1953; Tripathy 1987; Vandiviere et al. 1973).

The protective efficacy of BCG against TB has been evaluated by several meta-analyses (Brewer 2000; Colditz et al. 1994, 1995). For BCG vaccination during infancy, the summary protective efficacy was 65 % (95 % confidence interval (CI) 12–86 %) against death from TB, 64 % (95 % CI, 30–82 %) against TB meningitis, 78 % (95 % CI 58–88 %) against disseminated TB, 83 % (95 % CI 58–93 %) against

laboratory-confirmed TB, 74 % (95 % CI, 62–83 %) against any TB case when estimated from randomized controlled trials, and 52 % (95 % CI 38–64 %) against any TB case when estimated from case–control studies (Colditz et al. 1995). These findings corroborated summary protective effects of BCG against severe forms of TB demonstrated by another meta-analysis (Rodrigues et al. 1993): 86 % (95 % CI 65–95 %) against miliary or meningeal TB according to randomized controlled trials and 75 % (95 % CI 61–84 %) according to case–control studies.

Assuming that TB meningitis is approximately 1 % of the annual risk of infection, it has been estimated that every 12,500–16,667 BCG vaccinations during infancy will prevent one case of TB meningitis among children under 5 years (Fine et al. 1999). Assuming an annual risk of infection from 0.5 to 1 %, a risk of primary disease from 1 to 5 %, and that BCG vaccination in infancy confers 50 % protection against childhood TB, it has been estimated that 267–2667 vaccinations will prevent one case of childhood TB (Fine et al. 1999).

Observed findings regarding BCG efficacy may suggest that BCG is particularly effective in preventing hematogenous spread of *Mycobacterium tuberculosis* (Balasubramanian et al. 1994; Marsh et al. 1997), but not so efficient in preventing the establishment of lung infection following exposure (Sutherland and Lindgren 1979). However, there is increasing evidence from observational studies that BCG can also reduce the risk of infection (Diel et al. 2011; Eisenhut et al. 2009; Eriksen et al. 2010; Leung et al. 2015; Roy et al. 2014; Soysal et al. 2005) and aid bacillary clearance during treatment of pulmonary disease (Jeremiah et al. 2010).

Besides differences in methodology (Rieder 2008), a number of hypotheses have been proposed to explore the highly variable efficacy of BCG against pulmonary TB (Fine et al. 1999; Lambert et al. 2009; Rieder 2008). These include differences in the BCG vaccine, the virulence between *M. tuberculosis* strains, and the stages in the TB epidemic. There are also variations in host factors such as nutritional status, exposure to environmental mycobacteria, ultraviolet light exposure, and genetics underlying susceptibility. Table 20.1 summarizes the arguments for and against such hypotheses. Although there is still no consensus, partial protection conferred by environmental mycobacterial exposure may offer a biologically plausible explanation that partly addresses why BCG efficacy tends to be higher in temperate regions than tropical regions and, in particular, rural areas with greater exposure to environmental mycobacteria.

20.3.3 Efficacy of BCG Revaccination

In addition to neonatal BCG vaccination, many countries have a tradition of repeated BCG vaccination (Fine et al. 1999). Some administer multiple doses of BCG at infancy, school entry, and graduation, whereas some (as in Hungary and Russia) have recommended up to five doses of BCG from birth to 30 years of age. Although it is debatable whether the protective effect of BCG against pulmonary disease may last more than 15 years after vaccination (Sterne et al. 1998), studies in Malawi,

Table 20.1 Hypotheses regarding variable efficacy of BCG vaccination (Fine et al. 1999; Lambert et al. 2009; Rieder 2008)

Hypothesis	Arguments for	Arguments against
Differences in vaccine strains	BCG strains provided variable protection in the rabbit (Dannenberg et al. 2000) and guinea pig models (Smith et al. 1979). Based on animal studies of immunogenicity, Pasteur-1173 P2 and Copenhagen-1331 have been labeled "strong" and Glaxo-1077 and Tokyo-172 "weak"	The Chingleput trial showed that neither the Pasteur nor the Copenhagen strain was efficacious (WHO 1979; Indian Council of Medical Research (ICMR) 1999; Baily 1980)
		Shift from Japan and Glaxo to Paris and Danish vaccines in Indonesia and Columbia suggested that the Pasteur and Copenhagen vaccines might be less protective (Comstock 1988), but another trial in Hong Kong suggested that the Pasteur vaccine might be more protective than the Glaxo vaccine (ten Dam 1993)
Differences in vaccine doses	Variable doses given by multipuncture devices might have variable BCG doses, thereby leading to variable efficacy of BCG in trials involving multipuncture administration (Bettag et al. 1964; Comstock and Webster 1969; Frimodt-Moller et al. 1973; Rosenthal et al. 1961)	The Chingleput trial demonstrated no difference in BCG efficacy between two doses with 10-fold difference (Baily 1980)
Different exposure to environmental mycobacteria	In guinea pig TB models, exposure to different environmental mycobacteria and BCG conferred variable protection (Palmer and Long 1966)	Not all findings are consistent with masking of BCG protection by environmental mycobacteria (Fine 1995)
	In murine TB models, airborne infection with *M. avium* complex conferred similar protection against TB as the Danish BCG strain (Orme and Collins 1984)	
	In murine TB models, timing of exposure to *M. vaccae* before BCG affected sensitization by BCG (Brown et al. 1985)	
	Exposure to environmental mycobacteria might partly explain why BCG given earlier in life afforded larger protection in the Chingleput trial (Indian Council of Medical Research (ICMR) 1999)	
	In Puerto Rico, BCG conferred less protection in rural areas with higher exposure to environmental mycobacteria (Comstock and Edwards 1972)	
	There may be higher exposure to environmental mycobacteria in tropical regions. The protective efficacy of BCG against pulmonary TB in children is generally lower in tropical than temperate regions (Colditz et al. 1995; Putrali et al. 1983; Shapiro et al. 1985; Tripathy 1987)	

Difference in ultraviolet light exposure	The sensitivity of BCG bacilli and dermal Langerhans cells to UV may partly explain a tendency for lower protection in tropical regions (Fine 1995; Wilson et al. 1995)	This does not explain why BCG has conferred more protection against leprosy than TB in the same population (Pönnighaus et al. 1992; Tripathy 1983)
Genetic differences underlying host susceptibility	Vitamin D receptor, interferon receptor polymorphisms, NRAMP, HLA-DR, HLA-DQ, and other genes that control immune mechanisms influence susceptibility to TB (Bellamy et al. 1998; Brahmajothi et al. 1991; Goldfeld et al. 1998; Jouanguy et al. 1996, 1997; Khor et al. 2010). Thus, different genetic makeups may partly account for the variable efficacy of BCG	None yet published
Nutritional differences between study populations	Poor nutritional status is expected to impair cellular immune mechanism and hence the protective efficacy of BCG (Rieder 2008)	BCG conferred high levels of protection among poorly nourished native American children than well-nourished British adolescent (Hart and Sutherland 1977)
		This does not explain why BCG has conferred more protection against leprosy than TB in the same population (Pönnighaus et al. 1992; Tripathy 1983)
Difference in virulence between *M. tuberculosis* strains	Assuming that less virulent strains can confer protection against TB but induce false-negative tuberculin skin test, the protective effect of BCG vaccination among infected but tuberculin-negative subjects is masked (Rieder 2008)	Masking of protective effect is likely incomplete, but some BCG trials have demonstrated no protection at all (Rieder 2008)
Different stages in the TB epidemic	Assuming that the protective effect of BCG is masked by primary infection and exogenous reinfection, BCG is expected to offer less protection in places with higher risk of TB infection (Smith et al. 2000; ten Dam and Pio 1982)	Despite a declining risk of infection in the UK, BCG still conferred a persistently high level of protection (Rodrigues et al. 1991)

Brazil, Chile, Hong Kong, and other countries have suggested the lack of additional protection from BCG boosters (Karonga Prevention Trial Group 1996; Dantas et al. 2006; Rodrigues et al. 2005; Sepulveda et al. 1992; Springett and Sutherland 1994; Tala-Heikkilä et al. 1998). Over 30 countries have ceased BCG revaccination, whereas 16 still administer BCG boosters (Zwerling et al. 2011). A lack of additional protection from BCG revaccination may be partly explained by a diluting effect from continuous exposure to TB and environmental mycobacteria (Fine 1995).

20.3.4 Efficacy of BCG Vaccination Among Healthcare Workers (HCW)

It is contentious whether BCG may confer appreciable protection against TB among HCW. Assuming a workplace incidence of TB infection greater than 0.06 % per year, a decision analysis involving tuberculin-negative HCW showed that treatment of LTBI decreased the number of TB cases by 9 %, whereas BCG vaccination decreased the number by 49 % (Marcus et al. 1997). Another decision analysis among HCW exposed to multidrug-resistant TB (MDR-TB) also suggested that BCG was beneficial (Stevens and Daniel 1996). However, a review by Brewer and Colditz (1995) suggested that methodological flaws in the published literature would preclude a meta-analysis of efficacy of BCG among HCW. The United States CDC has suggested that BCG be considered among tuberculin-negative HCW when there is a high risk of exposure to multidrug-resistant TB and the risk cannot be effectively contained by comprehensive TB infection control measures (CDC 1997).

20.3.5 Efficacy of BCG Against Other Mycobacterial Diseases

BCG has been shown to confer protection against leprosy (Abel et al. 1990; Brown et al. 1968; Fine 1988; Fine et al. 1986; Lwin et al. 1985). The cessation of BCG vaccination was followed by a higher incidence of peripheral lymphadenitis due to environmental mycobacteria in Sweden (Romanus et al. 1995) and *M. avium* in the Czech Republic (Trnka et al. 1994). It has been postulated that infection with one species of mycobacterium triggers a cellular immune response that acts more swiftly in killing other mycobacteria subsequently encountered.

20.4 Need for Better Vaccines

BCG is insufficient for protecting against pulmonary TB, which contributes to the main public health burden of TB. A highly efficacious vaccine may be required for improving TB treatment efficacy and combating drug-resistant TB. HIV infection

has fuelled the TB epidemic. Matched case–control studies suggest that HIV infection may abrogate the protective effect of BCG against extrapulmonary TB (Arbeláez et al. 2000). A safer and more effective TB vaccine is needed for HIV-infected subjects.

Four types of candidate TB vaccines have been proposed on the basis of a comprehensive TB vaccination strategy (Lambert et al. 2009): (1) a priming vaccine that induces the host immunity in preparation for subsequent boosters, (2) a boosting vaccine that enhances the immunity induced by the priming vaccine, (3) a vaccine for postexposure administration among healthy adolescents or adults, and (4) a therapeutic vaccine that can increase TB treatment efficacy or shorten TB treatment duration.

Reflecting new approaches in vaccinology, candidate TB vaccines can be classified into several categories (Lambert et al. 2009): (1) live attenuated vaccines (such as recombinant or recombinant attenuated *M. tuberculosis*), (2) live vectored subunits (such as adenovirus or Modified Vaccinia Ankara), (3) recombinant proteins in adjuvants, (4) DNA vaccines, and (5) whole-cell killed mycobacteria (such as *M. vaccae*).

Without safer and more effective vaccines alongside better tools for the diagnosis and treatment of TB, it may be difficult to meet the Millennium Development Goals of halving the global TB prevalence and death rates by 2015 relative to their levels in 1990 and eliminating TB as a public health problem by 2050 (WHO 2010a). Modeling studies have demonstrated that neonatal vaccination with a preexposure vaccine that is 60 % effective would reduce 39 % of the TB incidence by 2050 in southern Asia (Abu-Raddad et al. 2009). The same model shows that mass vaccination with such a preexposure vaccine can achieve a much bigger impact on TB transmission and prevent 84 % new cases (85.9 million) and 81 % deaths (14.5 million) (Abu-Raddad et al. 2009).

By April 2009, the development pipeline for TB vaccines had included seven candidates tested in humans, including two nonreplicating viral-vectored vaccines in Phase IIb trial in infants and in HIV-infected adults (Beresford and Sadoff 2010). By the end of 2010, 10 vaccine candidates had entered different phases of trials (5 in Phase I, 2 in Phase II, 2 in Phase IIb, and 1 in Phase III trials) (WHO 2010a). By August 2014, a total of 15 vaccine candidates were in clinical trials, including recombinant BCGs, attenuated *M. tuberculosis* strains, recombinant viral-vectored platforms, protein/adjuvant combinations, and mycobacterial extracts (WHO 2014).

20.5 Future Perspectives

TB vaccine development is onerous and challenging. Although the deciphering of the whole genome of *M. tuberculosis* (Cole et al. 1998) and the significant progress on sequencing that of BCG have facilitated the development of better vaccines, it is by no means easy to evaluate the efficacy of new vaccines in developing countries in the presence of confounding factors that can boost the host immunity, such as TB disease, BCG vaccination, and environmental mycobacteria.

Major obstacles include (1) major gaps in scientific knowledge: inadequate understanding of natural host immunity and bacillary latency, the lack of surrogate markers for vaccine-induced immunity in humans, and a dearth of more natural nonhuman primate models of TB infection; (2) underfunding of expensive TB research work; and (3) the need for sustained political commitment in making future vaccines affordable, accessible, and available in areas that need them most (Beresford and Sadoff 2010).

Science alone is inadequate for combating TB (Beresford and Sadoff 2010; Migliori et al. 2007). Concerted efforts are required to integrate scientific advancement and political mobilization to ensure that substantial TB-related morbidity and mortality can be effectively avoided by mass vaccination campaigns using better TB vaccines.

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