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Correcting the record on BCG before we license new vaccines against tuberculosis

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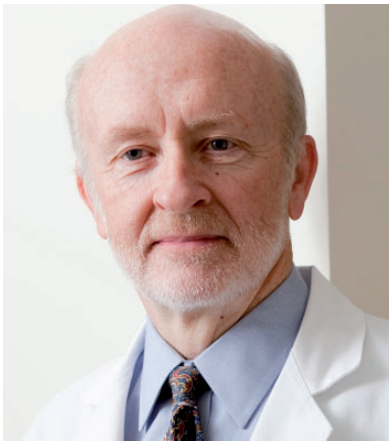
Introduction

Global eradication of tuberculosis by 2035 will require the development of an improved vaccine strategy.[1] At least 14 vaccine candidates have entered clinical trials, including vaccines targeted for priming infants and vaccines targeted for boosting protection in adolescents and adults.[2] As efficacy data from human trials become available, it will be important to interpret those results with a critical and contemporary understanding of the efficacy of the currently available vaccine, Bacille calmette Guerin (BCG). Numerous misinterpretations regarding BCG persist as summarised in Table 1.

Existing reviews on the efficacy of BCG have not focused explicitly on how new priming and new boosting vaccines in development might compare to BCG.[3,4] Nor do they consider relevant data on natural human immune protection against tuberculosis, heterologous protection against tuberculosis, trials of other mycobacterial vaccines and recent epidemiologic studies on the role of infection with non-tuberculous mycobacteria. All of these issues are relevant to the assessment of new tuberculosis vaccines in development and will be the focus of this commentary. Because there is an emerging consensus that the variations in the efficacy of BCG are not due to the differences in BCG strains, that issue will not be addressed here.[5] BCG is associated with numerous local and systemic side effects, a problem that might be addressed with newer less reactogenic vaccine candidates, another issue which will not be addressed here.

Efficacy of BCG prime in mycobacteria-naïve infants

BCG is administered routinely at birth in tuberculosis-endemic countries. Thus, the efficacy of new priming vaccines for infants should be judged against the efficacy of BCG in prospective trials performed in mycobacteria-naïve infants. Four such trials were conducted in over 4000 infants before chemotherapy was widely available and thus include both disease due to tuberculosis and death as endpoints. Collectively, these trials showed that the efficacy of BCG was 73% against disease and 87% against death (Table 2). New priming vaccines in development should either demonstrate greater efficacy or comparable efficacy with reduced side effects. It is important to note that there has never been a randomised controlled trial of BCG immunisation among mycobacteria-naïve infants in a tropical location. Only 0.6% of participants in the South India trial were infants, and case ascertainment in this group was judged to be inadequate.[4,6]



Duration of efficacy of BCG prime

Three studies provided accurate data on the long-term efficacy of BCG. A prospective trial in the United States among Native Americans was conducted among individuals who received lifetime medical care at the same federal healthcare facilities. In the first 12 years of this trial, efficacy against disease was 67% and had fallen to 54% ten years later. Average efficacy against disease was 52% over 50 years, and disease was predominantly pulmonary.[11] A prospective trial of BCG in the United Kingdom showed efficacy of

84% in the first five years and had fallen to 59% at 10–15 years.[12] A retrospective study based on a national database in Norway showed that the efficacy of BCG against pulmonary tuberculosis was 67% at ten years, 63% at 20 years and had fallen to levels that were not statistically significant at 30 and 40 years. Average efficacy over 40 years was 49%.[13] Collectively these reports indicate that BCG has long-term efficacy against pulmonary tuberculosis but that efficacy begins to wane at approximately 20 years.

Heterologous immunity and the efficacy of BCG boosters in adolescents and adults

Two large prospective trials have demonstrated that BCG boosters administered to adolescents or adults previously immunised with BCG failed to provide increased protection against tuberculosis.[14,15] Two theories have been advanced to explain this finding: masking and blocking. The masking theory holds that the failure of BCG boosters is due to the fact that many adolescents and adults are already mycobacteria-experienced. This can result from prior infection with environmental non-tuberculous mycobacteria, which confers 'heterologous protection' against tuberculosis or from prior latent tuberculosis infection, which confers homologous protection against tuberculosis.[16,17] The theory is that the efficacy of BCG may be masked by the protection already present in the mycobacteria-experienced placebo group. The blocking theory, supported by an animal model, posits that prior mycobacterial immunity blocks replication of BCG and consequently its efficacy.[18]

Blocking is a phenomenon that could reduce or eliminate the efficacy of live tuberculosis vaccine boosters. Masking is likely to present a challenge to all types of tuberculosis vaccine boosters under development by requiring a high level of vaccine efficacy to exceed the naturally acquired immunity from prior non-tuberculous mycobacteria or tuberculosis infection present in many adolescents and adults in a control group. However, an inactivated whole cell mycobacterial vaccine booster has been shown effective in a recent Phase 3 clinical trial.[19]

Table 1. BCG and new vaccines against tuberculosis: alternative facts.

1. The efficacy of BCG is 50%
2. The duration of BCG efficacy is 10–15 years
3. BCG prevents disseminated tuberculosis and tuberculous meningitis but not pulmonary tuberculosis
4. BCG is ineffective in southern latitudes due to high background rates of infection with non-tuberculous mycobacteria
5. Live BCG is the only vaccine against tuberculosis to have shown efficacy in humans
6. New vaccines against tuberculosis should be based exclusively on antigens from *Mycobacterium tuberculosis*

The myth regarding infections with non-tuberculous mycobacteria in the tropics

Reviews on the efficacy of BCG in different regions of the world continue to state the unsupported contention that infections due to non-tuberculosis mycobacteria are more common in tropical regions and therefore mask the efficacy of BCG. Further, the meaning of 'non-tuberculous mycobacteria infections are more common in the tropics' is often unclear. Is this phrase intended to refer to wider distribution of non-tuberculous mycobacteria in the environment, to a higher rate of asymptomatic non-tuberculous mycobacteria infection in healthy persons based on non-tuberculous mycobacteria skin testing or to a higher incidence of symptomatic, culture-positive non-tuberculous mycobacteria disease? In fact, none of these measures is more common in the tropics.

Table 2. Efficacy of BCG prime in mycobacteria-naïve infants.

Reference	Location	Participants (n)	Efficacy – disease	Efficacy – death
Aronson[7]	Western United States	232	59%	100%
Ferguson and Simes[8]	Montreal	609	80	78
Rosenthal et al.[9]	Chicago	451	74	100
Rosenthal et al.[10]	Chicago	3381	72	84
Total		4673	73	87

The highest rate of non-tuberculous mycobacteria isolation from environmental sources has been reported from Finland, where 100% of soil samples collected across a country-wide band of latitude were positive for non-tuberculous mycobacteria.[20] In an international epidemiologic study that used identical methods for isolating non-tuberculous mycobacteria from natural and potable water, slightly higher rates of isolation were found in northern than southern latitudes.[21] A study of potable water in the United States and Finland found that up to 40% of recirculating hot water systems were colonised with non-tuberculous mycobacteria.[22] Availability of domestic hot water is typically more limited in lower income countries in the tropics than in industrialised northern countries.

Skin test studies in asymptomatic healthy adults support widespread prior non-tuberculous mycobacteria infection throughout the world. We conducted studies in patients with culture-positive pulmonary disease due to non-tuberculous mycobacteria or tuberculosis showing that dual skin tests with purified protein derivative and an non-tuberculous mycobacteria antigen could distinguish non-tuberculous mycobacteria and tuberculosis infections with a high degree of specificity.[23] We then applied dual skin testing with the same antigens to healthy individuals in northern and southern hemispheres and found no difference in the rates of asymptomatic non-tuberculous mycobacteria infection.[24] Studies of antibody to *Mycobacterium avium* antigens in the non-BCG immunised persons in the United Kingdom and tuberculin skin test negative persons in the United States indicated that a high percentage of the population in northern regions has experienced asymptomatic infection with non-tuberculous mycobacteria.[25,26] This is not unexpected given the frequency of potable water colonisation described above.

Finally, when comparable methods have been employed to detect symptomatic culture-positive disease due to non-tuberculous mycobacteria in the northern and southern hemispheres, non-tuberculous mycobacteria infections have been more common in the north. Before the widespread availability of antiretroviral therapy for HIV, anecdotal data suggested that disseminated infection with *M. avium* did not occur in African populations with HIV. Our group conducted blood culture studies on 566 AIDS patients at the same stage of immunosuppression in the United States, Finland, Zaire and Trinidad. Using identical methods, we detected *M. avium* bacteremia in 20% of patients in Finland and the United States versus 2–8% in Kenya and Trinidad.[27]

Although there are numerous species of non-tuberculous mycobacteria which may have different effects on protection against tuberculosis, these environmental, skin test, antibody and blood culture studies establish that, by any definition, 'infections' due to non-tuberculous mycobacteria are common worldwide, and not more common in the tropics than in other regions (Table 3). The myth that 'non-tuberculous mycobacteria infections are more common in the tropics' should be eliminated from discussions of the efficacy of BCG in southern latitudes.

Efficacy of BCG prime in mycobacteria-experienced adolescents and adults

As noted above, adults and adolescents throughout the world have high rates of prior infection with

Table 3. Infections due to non-tuberculous mycobacteria (NTM) are not more common in the tropics.

Environmental isolates	Soil	100% (n=47) from Finland positive for NTM[20]
	Water	35% from US and Finland positive for NTM, 10% from DRC and Kenya positive for NTM[21]
	Potable water	45% of hospital water from US and Finland positive for NTM[22]
Asymptomatic infection, healthy individuals	Skin tests	Similar rates of NTM positivity in US, Finland, Kenya and Trinidad[24]
	Antibody	Increasing IgG to *M. avium* with age among tuberculin-negative US children[25]
	Antibody	Increasing IgG to *M. avium* with age among BCG-negative UK children[26]
Symptomatic disease, AIDS patients	Blood culture	*M. avium* bacteremia rates 10–20% in Finland and US vs. 2–8% in Kenya and Trinidad[27]

non-tuberculous mycobacteria. In tuberculosis-endemic regions, adolescents and adults also have high rates of latent infection with *Mycobacterium tuberculosis*. Tuberculin skin testing has been used in trials of BCG priming in adolescents and adults to exclude those who are already mycobacteria-experienced. However, since antibody to mycobacterial antigens is detectable in many persons with negative tuberculin skin tests, it is likely that only a minority of adolescents and adults, including those who are tuberculin-negative, are truly mycobacteria-naïve in any region of the world. Trials with live BCG that have failed to show efficacy in adolescents and adults reflect the effects of masking and blocking or both.[3]

There are two trials that have demonstrated efficacy in participants beyond the age of infancy where prior mycobacterial experience could have been a potential issue. A trial in the United Kingdom in which BCG efficacy was high was conducted in individuals age 14–15 years and excluded 28% who were tuberculin skin test positive.[12] These two features may have effectively reduced the rate of prior mycobacterial exposure to a level that did not interfere with induction of an immune response. The US trial in Native Americans in which BCG efficacy was high was conducted in children with a mean age of seven years and excluded 50% of participants who reacted to high-dose tuberculin.[7] As in the UK trial, these exclusion criteria would have reduced the number of participants with prior mycobacterial experience.

Other mycobacterial vaccines that have been shown effective in humans

In one of the earliest examples of a controlled clinical trial, a multiple dose series of inactivated *Mycobacterium bovis* was shown to be effective in the prevention of tuberculosis among over 400 patients newly admitted to a psychiatric hospital in Jamaica. Alternate patients were assigned to vaccine or no vaccine; efficacy was 42% against disease.[28] Single-dose, live *Mycobacterium microti*, a member of the *M. tuberculosis* complex, was shown to be effective in a large randomised clinical trial in the United Kingdom. Over 10,000 individuals received *Mycobacterium microti*, and the efficacy was 73% at 10–15 years.[12] Two inactivated whole cell vaccines were administered to over 100,000 children during the 1950s in Italy. These vaccines were not evaluated in prospective trials but were judged to be effective in preventing both tuberculosis disease and death: Anatuberculina Integrale Petragnani, a formalin killed mix of avian, bovine and human strains, and Vaccino Diffondente Salvioli, consisting of heat-killed tubercle bacilli.[29] More recently, a multiple dose series of an inactivated whole cell vaccine derived from a non-tuberculous mycobacterium, SRL172, was shown to be 39% effective in a Phase 3 randomised controlled trial among 2013 HIV-infected patients in Tanzania.[19]

These vaccine data can be considered along with epidemiologic studies to summarise what is currently known about human immune protection against tuberculosis. Single-dose live mycobacterial vaccines are effective, and multiple-dose whole cell inactivated mycobacterial vaccines are effective. Epidemiologic studies cited above confirm that natural infection with non-tuberculous mycobacteria or with *M. tuberculosis* also confer protection. Thus, known examples of human immune protection against tuberculosis all involve exposure to the whole organism and include evidence of heterologous protection within the mycobacterial genus, observations that offer a promising path forward for tuberculosis vaccine development. Unfortunately, recent policy positions on tuberculosis vaccine development interpret the failure of a protein subunit vaccine booster[30] to mandate a return to molecular antigen discovery and improved animal models.

Correcting the record on BCG

The studies cited here indicate that BCG priming is highly effective against pulmonary tuberculosis and provides substantial protection for at least 20 years and lower levels of protection for up to 50 years. BCG is most effective when administered to mycobacteria-naïve infants. Since there are no randomised controlled trials of BCG immunisation among mycobacteria-naïve infants in southern latitudes, there is no evidence that BCG is any less effective in the south. Infections with environmental non-tuberculous mycobacteria are common worldwide and may be less common in tuberculosis-endemic countries in the southern hemisphere (Table 4).

The efficacy of priming vaccines designed to improve on BCG should be judged against the efficacy of BCG in the four prospective trials conducted in mycobacteria-naïve infants. Side effects of new priming vaccines should also be compared to those of BCG, an issue that is not considered in detail here.

Given the significant efficacy of BCG priming vaccines for at least 20 years, development of an effective BCG booster for adolescents and adults should be the main priority in vaccine development. Modelling indicates that a BCG booster will have a much greater effect on global tuberculosis incidence than an improved BCG prime in the next few decades.[31]

Table 4. BCG and new vaccines against tuberculosis: the facts.

1. BCG as a prime is >70% effective in mycobacteria-naïve infants
2. BCG as a prime is highly effective for 20 years, with lower levels of efficacy demonstrable for 50 years.
3. BCG as a prime is effective against pulmonary tuberculosis
4. There are no data to support a geographical differences in the efficacy of a BCG prime in mycobacteria-naïve infants
5. Multiple live and inactivated whole cell vaccines have been shown effective in the prevention of tuberculosis in humans
6. Data on heterologous immunity supports the development of vaccines based on any species within the genus *Mycobacteria*

The efficacy of boosting vaccines in adolescents and adults previously immunised with BCG should be compared against those of unboosted individuals in cohorts matched for duration of immunisation since the BCG prime. If blocking is the basis for the failure of live BCG boosters, then other live mycobacterial vaccine boosters may be subject to the same effect. Multiple whole cell vaccines within the mycobacterial genus have been shown to be effective against tuberculosis in humans and should be an important focus in clinical trials of investigational vaccines.

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References

1. Dye C, Glaziou P, Floyd K and Raviglione M. Prospects for tuberculosis elimination. *Annu Rev Public Health* 2013; 34: 271–286.
2. Kaufmann SH, Weiner J and von Reyn CF. Novel approaches to tuberculosis vaccine development. *Int J Infect Dis* 2017; 56: 263–267.
3. Colditz GA, Brewer TF, Berkey CS, Wilson ME, Burdick E, Fineberg HV, et al. Efficacy of BCG vaccine in the prevention of tuberculosis: meta-analysis of the published literature. *JAMA* 1994; 271: 698–702.
4. Clemens JD, Chuong JJ and Feinstein AR. The BCG controversy: a methodological and statistical reappraisal. *JAMA* 1983; 249: 2362–2369.
5. Mangtani P, Abubakar I, Ariti C, Beynon R, Pimpin L, Fine PE, et al. Protection by BCG vaccine against tuberculosis: a systematic review of randomized controlled trials. *Clin Infect Dis* 2014; 58: 470–480.
6. Trial of BCG vaccines in South India for tuberculosis prevention. *Indian J Med Res* 1979; 70: 349–363.
7. Aronson JD. Protective vaccination against tuberculosis with special reference to BCG vaccination. *Am Rev Tuberc* 1948; 58: 255–281.
8. Ferguson RG and Simes AB. BCG vaccination of infant Indians in Saskatchewan. *Tubercle* 1949; 30: 5–11.
9. Rosenthal SR, Loewinsohn E, Graham ML, Liveright D, Thorne MG and Johnson V. BCG vaccination in tuberculous households. *Am Rev Respir Dis* 1960; 84: 690–704.
10. Rosenthal SR, Loewinsohn E, Graham ML, Liveright D, Thorne MG, Johnson V, et al. BCG vaccination against tuberculosis in Chicago: a twenty year study statistically analyzed. *Pediatrics* 1961; 28: 622–641.
11. Aronson NE, Santosham M, Comstock GW, Howard RS, Moulton LH, Rhoades ER, et al. Long-term efficacy of BCG vaccine in American Indians and Alaska natives: a 60-year follow-up study. *JAMA* 2004; 291: 2086–2091.
12. Hart PD and Sutherland I. BCG and vole bacillus vaccines in the prevention of tuberculosis in adolescence and early adult life. *Brit Med J* 1977; 2: 293–295.
13. Nguipdop-Djomo P, Heldal E, Rodrigues LC, Abubakar I and Mangtani P. Duration of BCG protection against tuberculosis and change in effectiveness with time since vaccination in Norway: a retrospective population-based cohort study. *Lancet Infect Dis* 2016; 16: 219–226.
14. Rodrigues LC, Pereira SM, Cunha SS, Genser B, Ichihara MY, de Brito SC, et al. Effect of BCG revaccination on incidence of tuberculosis in school-aged children in Brazil: the BCG-REVAC cluster-randomised trial. *Lancet* 2005; 366: 1290–1295.
15. Anonymous. Randomised controlled trial of single BCG, repeated BCG, or combined BCG and killed *Mycobacterium leprae* vaccine for prevention of leprosy and tuberculosis in Malawi. Karonga Prevention Trial Group. *Lancet* 1996; 348: 17–24.
16. Fine PEM. Variation in protection by BCG: implications of and for heterologous immunity. *Lancet* 1995; 346: 1339–1345.
17. Andrews JR, Noubary F, Walensky RP, Cerda R, Losina E and Horsburgh CR. Risk of progression to active tuberculosis following reinfection with

Mycobacterium tuberculosis. *Clin Infect Dis* 2012; 54: 784–791.
18. Brandt L, Cunha JF, Olsen AW, Chilima B, Hirsch P, Appleberg R, et al. Failure of the *Mycobacterium bovis* BCG vaccine: some species of environmental mycobacteria block multiplication of BCG and induction of protective immunity to tuberculosis. *Infect Immun* 2002; 70: 672–678.
19. von Reyn CF, Mtei L, Arbeit RD, Waddell R, Cole B, Mackenzie T, et al. Prevention of tuberculosis in Bacille Calmette-Guerin-primed, HIV-infected adults boosted with an inactivated whole-cell mycobacterial vaccine. *AIDS* 2010; 24: 675–685.
20. Iivanainen EK, Martikainen PJ, Raisanen ML and Katila ML. Mycobacteria in boreal coniferous forest soils. *FEMS Microbiol Ecol* 1997; 23: 325–332.
21. von Reyn CF, Waddell RD, Eaton T, Arbeit RD, Maslow JN, Barber TW, et al. Isolation of *Mycobacterium avium* complex from water in the United States, Finland, Zaire, and Kenya. *J Clin Micro* 1993; 31: 3227–3230.
22. Ristola M, Arbeit R, von Reyn CF and Horsburgh C Jr. Isolation of Mycobacterium avium from potable water in homes and institutions of patients with HIV infection in Finland and the United States. *Biomed Res Int* 2015; 2015: 1–3.
23. von Reyn CF, Green PA, McCormick D, Huitt G, Marsh B, Magnusson M, et al. Dual skin testing with *M. avium* sensitin and PPD: an open study in patients with *Mycobacterium avium* complex infection or tuberculosis. *Clin Infect Dis* 1994; 19: 15–20.
24. von Reyn CF, Barber TW, Arbeit RD, Sox CH, O'Connor GT, Brindle RJ, et al. Evidence of previous infection with *M. avium* among healthy subjects: an international study of dominant mycobacterial skin test reactions. *J Infect Dis* 1993; 168: 1553–1558.
25. Fairchok MP, Rouse JH and Morris SL. Age-dependent humoral responses of children to mycobacterial antigens. *Clin Diagn Lab Immunol* 1995; 2: 443–447.
26. Pilkington C, Costello AMd, Rook GAW and Stanford J. Development of IgG responses to mycobacterial antigens. *Arch Dis Child* 1993; 69: 644–649.
27. von Reyn CF, Arbeit RD, Tosteson ANA, Ristola MA, Barber TW, Waddell R, et al. The international epidemiology of disseminated *Mycobacterium avium* complex infection in AIDS. *AIDS* 1996; 10: 1025–1032.
28. Opie EL, Flahiff EW and Smith HH. Protective inoculation against human tuberculosis with heat-killed tubercle bacilli. *Am J Hyg* 1939; 29: 155–164.
29. Weiss DW. Vaccination against tuberculosis with non-living vaccines. I. The problem and its historical background. *Am Rev Respir Dis* 1959; 80: 676–688.
30. Tameris MD, Hatherill M, Landry BS, Scriba TJ, Snowden MA, Lockhart S, et al. Safety and efficacy of MVA85A, a new tuberculosis vaccine, in infants previously vaccinated with BCG: a randomised, placebo-controlled phase 2b trial. *Lancet* 2013; 381: 1021–1028.
31. Knight GM, Griffiths UK, Sumner T, Laurence YV, Gheorghe A, Vassall A, et al. Impact and cost-effectiveness of new tuberculosis vaccines in low- and middle-income countries. *Proc Natl Acad Sci U S A* 2014; 111: 15520–15525.