

# Should BCG vaccination be continued in resource limited countries?

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## Introduction

Tuberculosis, (TB) is one of the major causes of death from a single infectious agent worldwide. It is likely that 95% of the more than eight million new cases of TB and 99% of two million deaths annually occur in middle- and low-income countries.<sup>1,2</sup> Tuberculosis is responsible for 25% of all avoidable deaths in resource limited countries.<sup>2</sup>

Because of the widely varying prevalence of TB in different areas of the world, the World Health Organization (WHO) published the incidence of the disease in 6 separate regions, illustrated in Table 1.<sup>3</sup>

In addition, about 480 000 people got multidrug resistant TB (MDR-TB) in 2013, universally.<sup>4</sup> The emergence of MDR strains (especially in HIV patients), highlights the proper control and eliminating transmission of TB infection.<sup>5</sup>

**Table 1** Minimum, Maximum and Mean Tuberculosis rate worldwide

| Who Region                         | Minimum Tb Rate Per 100000 Population/ Country | Maximum Tb Rate Per 100000 Population/ Country | Mean Tb Rate in Region | Median Tb Rate in Region |
|------------------------------------|--|--|------------------------|--------------------------|
| African region (AFRO)              | 21/Mauritius                                   | 1382/Swaziland                                 | 420.85                 |                          |
| American region (AMRO))            | 6.9/Turks and Caicos Island sd                 | 206/Haiti                                      | 42.08                  |                          |
| Eastern Meditranian Region (EMRO)  | 1.8/United Arab Emirate                        | 619/Djibouti                                   | 22                     |                          |
| European Region (EURO)             | 1.5/San Marino                                 | 194/Greenland                                  | 54                     |                          |
| South Eastern Asian Region (SEARO) | 40/Maldives                                    | 492/Timor-leste                                | 121.83                 |                          |

The mortality rate in human immunodeficiency virus (HIV)-infected patients with TB is twice that of HIV-infected patients without TB.<sup>6-8</sup>

In 2013, almost 78million people were infected with the HIV and about 39million people died of this infection. About 0.8% of adults aged 15-49years are living with HIV worldwide. In Sub-Saharan Africa nearly 1 in every 20 adults is living with HIV. People who are infected with HIV are 26 to 31 times more likely to get TB disease.<sup>4</sup>

Accordingly, we would like to highlight the importance of TB prevention, the advantages and disadvantages of the current vaccine and the policy for its recommendation in different epidemiological situations.

## Current vaccine, reasons for discontinuing BCG vaccination in most industrial countries

Bacille Calmette Guerin (BCG), the currently used vaccine was produced in 1921 and is still the only available vaccine against Tb.<sup>9</sup>

First dose of BCG is injected to neonates as part of expanded program for immunization and, since its first usage in 1921, became the most commonly used vaccine in history with almost 4billion doses used worldwide.<sup>10</sup>

It should be considered that changes in epidemiological pattern of disease and decrease in its incidence have produced changes in BCG

vaccination policy in different countries. According to the BCG world Atlas, among the 180 countries with available data, 157 countries currently administer mass BCG vaccination (many countries have begun BCG vaccination program since 1940s-1960s), while 23 countries have either stopped BCG vaccination (due to a reduction in TB incidence, like Spain, Denmark, Austria and Germany), or never recommended universal BCG immunization and use a selective vaccination program of "at risk" groups (19 countries like USA, Netherlands).<sup>11</sup>

Although, there is no evidence that BCG decreases the risk of becoming infected with Mycobacterium tuberculosis, but it can prevent severe form of disease in younger ages. According to National Institute for Health and clinical Excellence systematic review, the protective efficacy of BCG for annual incidence of tuberculosis and prevention against pulmonary TB in vaccinated versus not vaccinated infants are 77% and 74%, respectively, which decline with increasing age.<sup>11</sup>

BCG vaccine strains differ from each other and from the original BCG first used in 1921. These genetic differences affect antigenic proteins, and lead to differences in efficacy too. Ritz and Curtis found that 44% (83/188) of countries reported using various BCG strains over an interval of only 5years.<sup>12</sup>

Varying estimates of its efficacy in preventing pulmonary tuberculosis have been reported in different trials from 0% announced by Chingleput in South India to 80% in the UK Medical research Council report. Steadily, high estimates of efficacy has been reported for preventing severe disease in infants.<sup>13,14</sup>

The duration of protection against pulmonary TB is also variable, on an average lasts about 10years.<sup>15</sup>

Unfortunately, “boosting” the protection gained by first BCG vaccination cannot be achieved by subsequent shots later in life. New strategies to offer protection beyond early childhood are needed.<sup>10</sup>

Another problem with BCG is, while BCG vaccination is essential in countries with significant HIV prevalence, BCG should not be used in HIV positive or unknown HIV status with suspected symptoms consistent with HIV.<sup>16</sup>

The most common complications of BCG vaccine include inoculation site abscess and local lymphadenitis. Although BCG complications are rare, great variations in rates of adverse reactions have been reported that can be attributed to the inoculation techniques, BCG strain, number of vaccination and diagnostic setting.<sup>17</sup>

Following adverse effects are reported after BCG administration:

- Local ulcers and regional lymphadenitis: 4-30 per 1000 vaccinated infants
- Osteomyelitis: 0.1 to 30 per 100,000 doses
- Disseminated BCG infection: 1 per 1000,000 doses
- Death: 0.02 per million doses

As mentioned, different BCG vaccination policies exist in different countries. Vaccination schedule also have been changed within and across countries over the years, reflecting changes in evidence, health policy, increasing or decreasing TB incidence, and HIV incidence.

Accordingly there should be a policy for BCG vaccination recommendation in different countries.

## Re-introduction of BCG

According to BCG world atlas, there is no country which has re-introduce BCG vaccination universally, due to HIV re-emergence or other causes.<sup>11</sup>

## WHO recommendation on BCG injection according to the annual risk of Tb infection

### WHO recommendation on Use of BCG vaccine in high burden vs. low burden countries

In highly endemic setting for tuberculosis (Tb) or where there is high risk of exposure to Tb, a single dose of vaccine should be injected to all newborns.<sup>18</sup> (which protects against severe forms of disease like miliary Tb and meningitis in infants).<sup>19</sup> An infant that had not received the BCG dose soon after birth can be given a dose until 12months of age, after that no dose should be given.<sup>20</sup>

In low-burden setting, the WHO Position Paper on BCG vaccine states<sup>21</sup> recommendation may be chosen to restrict BCG vaccination only to neonates, infants or tuberculin-negative older children of high-risk groups for Tb exposure. In some low- burden settings intensified case detection and early treatment are used in place of vaccination.

As an increasing number of industrialized countries are eager to continue their BCG vaccination policy during the coming years, the International Union Against Tuberculosis and Lung Disease has developed criteria outlining “low endemicity”. To change from general to selective BCG vaccination, an efficient warning system must be available, in addition to the following criteria:

- An average yearly notification rate of smear-positive pulmonary Tb cases below 5 per 100000; or
- An average yearly notification rate of tuberculosis meningitis in children aged under five years less than 1 per 10million population during recent five years; or
- An average annually risk of Tb infection below 0.1%<sup>22</sup>.

Annual rate of TB infection (ARI) is a good indicator for showing TB trends in a community, although it is usually obtained from surveys among non-vaccinated children. As many countries use mass BCG vaccination, an important question should be answered: Is ARI of value in communities with routine BCG vaccination too?

Chadha et al.,<sup>23</sup> explored the feasibility of estimation ARI among BCG vaccinated children with two different techniques and concluded that the distribution of tuberculin reaction among BCG vaccinated and unvaccinated children is similar, so the ARI could be estimated using vaccinated children.<sup>23</sup> Gopi et al.,<sup>24</sup> reached similar results too.<sup>24</sup> But, Kumari et al.,<sup>25</sup> measured ARI and found it to be significantly higher in children with BCG scars compared with no scar group. They could not separate vaccinated and unvaccinated children.<sup>25</sup>

## BCG in adolescents and adults

As there is no evidence that revaccination with BCG affords any additional protection, general revaccination is not recommended.<sup>10,26</sup>

However, given the serious consequences of emerging multidrug-resistant disease and the low reactogenicity of the vaccine, BCG vaccination may be considered for all HIV-negative, unvaccinated, tuberculin-negative persons who are in a mandatory close exposure to multidrug-resistant tuberculosis (e.g. health care workers in facilities still lacking of proper TB infection control measures in place).<sup>16</sup>

## Do new vaccines meet the needs?

A comprehensive approach is needed, to follow the Global Plan to Stop TB, 2006–2015, “effective TB vaccines will be an essential component of any strategy to eliminate tuberculosis (TB) by 2050”<sup>12</sup> and to reach the new End TB goals of a 95% reduction in TB deaths and a 90% reduction in TB cases by 2035. This approach includes new and more effective vaccines, as well as improved diagnostics and treatment.<sup>10</sup>

Unfortunately, BCG is not completely protective against disease in infants and is unreliable against adult pulmonary TB. It provides some protection against severe forms of pediatric TB. Latent tuberculosis infection (LTBI) in adults and adolescents accounts for most of the disease burden, and transmission, worldwide. New, effective and safe vaccines, are urgently needed to prevent TB in all age groups, and against all forms of disease and infection, including LTBI and drug-resistant strains(which can be found in those with HIV).<sup>24</sup>

There are about 15 Tb vaccines in clinical trials include protein or adjuvant, viral vectored, mycobacterial whole cell or extract, attenuated Mtb and recombinant live vaccines. MTBVAC, Crucell Ad35/MVA85A, AdAg85A, ID93+GLA-SE,DAR 901 and TB/FLU-04L in phase I trials, VPM 1002,Crucell Ad35/AERAS-402 and H1/H56/H4+1 in phase II trials while two other vaccines including MVA85A and M72+AS01E are in phase IIb trials and one vaccine M.vaccae is in phase III clinical Trial.<sup>27</sup>

According to nature of Mtb, different vaccines should be produced to implement various strategies to control the disease worldwide:

- Vaccines for prevention of infection that can be administered prior to MTb exposure,
- Vaccines that can be given after exposure to MTB to reduce disease incidence and transmission (to people who have Latent Tuberculosis Infection),
- Vaccines that can be injected after treatment of MTB disease to prevent reactivation and transmission.

Besides, an immunotherapeutic vaccine for patients with active Tb in conjunction with therapy, for shortening the duration of the treatment and reducing recurrence rates.<sup>10</sup>

Sixteen different TB vaccine candidates include five based on whole cell mycobacteria and the remainder as various sub-unit based, are currently in clinical trials, with a few approaching or currently in proof-of concept ( three are in Phase IIb)<sup>11</sup> studies in the field, and many in preclinical development. In sub- unit based vaccines, Mtb antigens are expressed as recombinant proteins that are either expressed with adjuvants or presented in recombinant viral vectors. Many of them employ a prime-boost strategy to complement the existing immune response to BCG.<sup>10</sup>

The major blocks in TB vaccine production to date have been the lack of an immunological correlate of protection, it means that protection in preclinical challenge models does not reflect efficacy, so a human challenge model is needed and continued research in these areas is essential.<sup>10</sup>

## Conclusion

BCG has limited efficacy in prevention pulmonary disease which is the main cause of transmission .Its even lower efficacy beyond infancy, decrease in TB incidence before emergence of HIV, and its complications that in some cases may be fatal led to changes in BCG administration policy from mass injection to either its omission from vaccination schedule or its administration in special high risk groups only.

- a. A comprehensive approach is needed to provide BCG vaccine policy for different countries.
- b. Many variables should be considered, for example; TB annual risk, BCG cost-effectiveness not only in different ages but also for various forms of disease and infection, and according to the strain available in that region and HIV rate in each country and availability of a new vaccine.
- c. A precise surveillance should be held in all countries to calculate the average rate of smear-positive pulmonary TB cases, tuberculosis meningitis in children aged under five years and annual risk of tuberculosis infection.
- d. Until new vaccines with a higher efficacy against TB and with an option of being effective in different age groups, become available, it seems prudent that in countries with a high incidence of TB, BCG vaccination should be a part of the routine immunization program. Which should be administered to all infants at birth?
- e. While in areas with a low endemicity, BCG vaccination should be offered only in selected cases, i.e. infants and tuberculin negative children and health care workers at a high risk of exposure at home or in the community.

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## Conflicts of interest

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