Spotlight

IFAKARA HEALTH INSTITUTE
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Search for a New TB Vaccine

Key Points

- TB is a major burden in Tanzania and other African countries
- Existing TB vaccines are not effective in preventing TB in adults
- Alternative vaccine candidates are under development
- Among these, the H1/IC31 candidate vaccine is being tested and IHI is among institutions involved in this research
- Phase II of the study is currently ongoing in Bagamoyo

Introduction

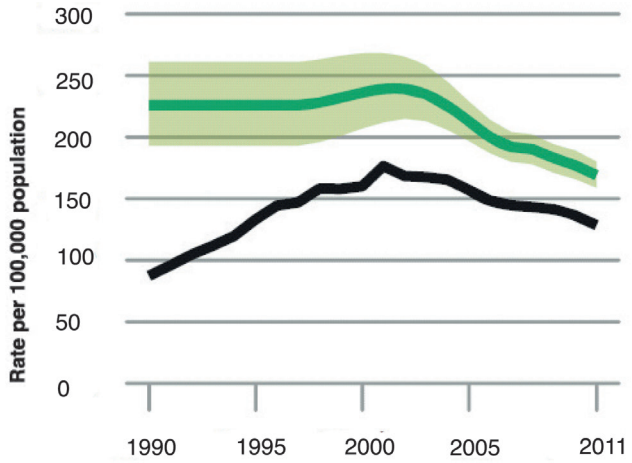
In 2010, tuberculosis (TB) infected 8.8 million people of whom almost one in five died. TB is caused by various strains of *Mycobacterium tuberculosis* bacteria, is spread from person to person through the air.

TB deaths occur predominantly in poor countries. Tanzania is among the top 22 high-burden countries, which collectively account for about 80% of global TB cases. TB tends to affect mostly young adults, in their most productive years.

In 2010, the incidence of TB in Tanzania was estimated to be as high as 281 infected people for every 100,000 Tanzanians, according to WHO data and the disease killed 13 for every 100,000 Tanzanians in 2010. At least 12 people die of TB each day in Tanzania. Although prevalence of TB has been declining (see Figure 1 below), TB remains a major burden for Tanzania.

Multi-drug resistant TB (MDR-TB), a main threat to TB control, accounted for an estimated 1.1% of new TB cases in Tanzania, in 2010.

Figure 1: Case notification and estimated TB incidence rate



Trends in case notification rates (new and relapse cases, all forms) (black) and estimated TB incidence rates (green). Shaded areas represent uncertainty bands.
Source: WHO, Global tuberculosis report 2012.

There is thus a growing impetus to improve existing TB vaccines and devise new and more effective ones. The only licensed TB vaccine, the Bacille Calmette Guerin (BCG) is very effective against severe and disseminated forms of TB among children. However, because BCG-induced protection wanes within a decade, its efficacy among adults is variable. The Ifakara Health Institute (IHI) is among the global partners in this search for an effective TB vaccine. This Spotlight discusses alternative TB vaccine candidates and specifically highlights IHI's involvement in this work.

BCG

The BCG vaccine was developed between 1906 and 1919 by Boquet, Calmette, and Guérin, hence the name. The vaccine is a live, but weakened form of the bacteria that causes TB, and works by stimulating the body's defense mechanisms against the bacteria. BCG has recorded more than 4 billion safe administrations at a cost of US $0.1 - US $0.2 per dose of product. Given to over 90% of children today, BCG is the most widely-used vaccine in the world. The vaccine protects against severe forms of tuberculosis in newborns and young children. However, the present regimen of BCG vaccination has little or no effect when administered to adults. This has lead towards a push to search for alternatives.

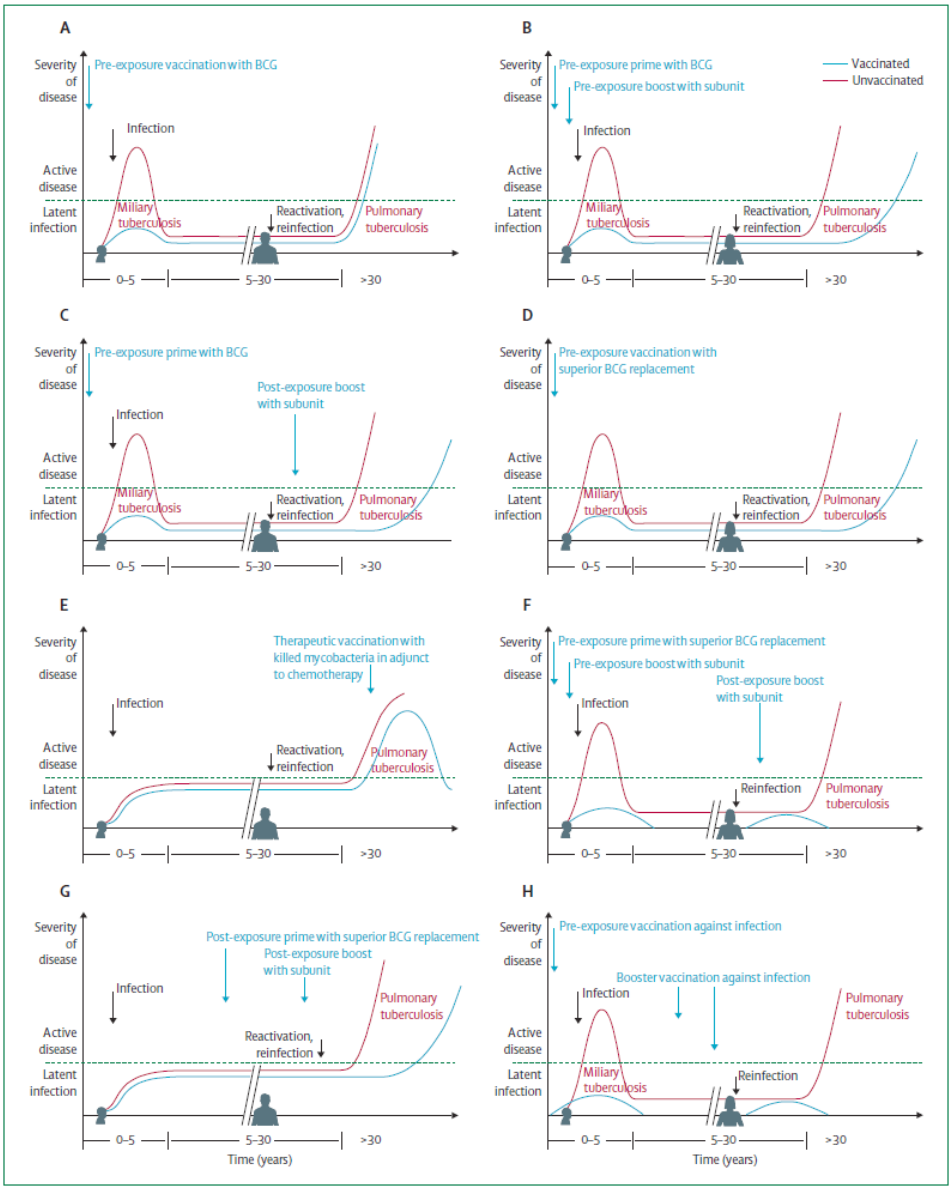
Alternatives to BCG

New vaccine candidates need to induce a more efficient immunity than that achieved by BCG. What is needed is a new vaccine which targets and contains TB bacteria and prevents reactivation of the disease at some later stage. Current global vaccination strategies being tested involve vaccination with a viable vaccine, that either "boosts" the immune system's ability to neutralize TB bacteria or as replacement for BCG. Present vaccination candidates only reduce the initial amount of TB bacteria in one's body. The rest of the TB bacteria are simply contained (see Figure 2 below).

The underlying mechanism of action of present vaccine candidates is to stimulate the body's immune system's capabilities to fight TB bacteria. There are many types of vaccines currently under development. These include live mycobacterial vaccines, DNA-based vaccines and subunit vaccines.

Living mycobacterial vaccines pose significant health risks in HIV-infected individuals. Although this can be addressed, significant regulatory barriers imposed on genetically modified organisms have impeded efficient development of these vaccines. DNA vaccines have so far been disappointing in stimulating the body's immune response and protection in model studies. Not surprisingly, then, three of the most advanced vaccines are all subunit vaccines.

Figure 2: Different Vaccination Strategies (Source: Kaufmann, et al., 2010)



Present strategy: (A) pre-exposure vaccination with BCG protects against early childhood tuberculosis but does not eradicate Mycobacterium tuberculosis. Future vaccination strategies: (B) pre-exposure boost with subunit vaccine in children primed with BCG to prevent tuberculosis in early childhood and to delay tuberculosis disease outbreak in adults; (C) post-exposure boost with subunit vaccine in adults who had been primed with BCG during early childhood to delay tuberculosis disease outbreak in adults; D) pre-exposure vaccination with superior BCG replacement to prevent tuberculosis in early childhood and to delay tuberculosis disease outbreak in adults; (E) therapeutic vaccination in adjunct to chemotherapy in patients with active tuberculosis; (F) heterologous prime-boost vaccination with superior BCG replacement and subunit vaccine, to achieve sterile eradication; (G) heterologous prime-boost vaccination in individuals with latent infection by prime with superior BCG replacement and subunit vaccine boost to prevent tuberculosis disease outbreak; and (H) pre-exposure vaccination to prevent stable infection with M tuberculosis.

Subunit vaccines

These vaccines work by improving our bodies' ability to identify and neutralize TB bacteria. Subunit vaccine approach builds on the concept of stimulating the immune response to a number of selected antigens delivered in the form of recombinant antigens. The Statens Serum Institut (SSI) in Denmark has duplicated and evaluated 250 of these antigens from TB bacteria. They have selected a few, most promising, in stimulating the body's immune response against TB bacteria. Some of these antigens have demonstrated protective efficacy in animals.

These efforts constitute, among the most prominent vaccine candidates, the HI/IC31 candidate vaccine (a combination of SSI's Ag85B-ESAT-6 and Intercell's IC31®). The H1/IC31® candidate vaccine enhances the recipient's immune response. It is among the most promising for low-income settings and is safe for HIV-infected individuals. See an overview of candidates in Figure 3 below.

Figure 3: Vaccine Candidates in Clinical Trials, Globally (Source: Kaufmann, et al., 2010)

	Description	Developmental stage	Sponsor or funder
MVA85A	Attenuated strain of vaccinia expressing Ag85A	Phase 1 completed and phase 2 continuing; phase 2b in infants started	Wellcome Trust, Aeras, Emergent BioSolutions
rBCG30	BCG overexpressing Ag85B	Phase 1 completed	University of California, Los Angeles; Aeras
AERAS-402	Non-replicating Ad35 expressing Ag85A, Ag85B, and TB10.4	Phases 1 and 2 continuing	Aeras
AdAg85A	Non-replicating Ad5 expressing Ag85A	Phase 1	McMaster University
M72	Recombinant fusion (Mtb39 and Mtb32) in AS02 and AS01 adjuvant systems	Phases 1 and 2 completed; additional trials continuing	GlaxoSmithKline, Aeras, Tuberculosis Vaccine Initiative
H1-IC31	Recombinant fusion of Ag85B-ESAT-6 in IC31 adjuvant	Phase 1 completed	Statens Serum Institut, Tuberculosis Vaccine Initiative
H1-CAF01	Recombinant fusion of Ag85B-ESAT-6 in CAF01 adjuvant	Phase 1 continuing	Statens Serum Institut, Tuberculosis Vaccine Initiative
H4-IC31 (AERAS-404)	Recombinant fusion of Ag85B-TB10.4 in IC31 adjuvant	Phase 1 completed	Statens Serum Institut, Aeras
rBCGΔUreC:Hly (VPM1002)	BCG with an endosome escape mechanism	Phase 1 completed	Vakzine Projekt Management, Tuberculosis Vaccine Initiative, Max Planck Institut
RUTI	Detoxified *M tuberculosis* in liposomes	Phase 1 completed	Archivel Farma
M vaccae	Inactivated *M vaccae*	Phase 3 completed	National Institutes of Health

MVA=modified vaccinia Ankara. Ag=antigen. Ad=adenovirus. AS=adjuvant system. ESAT-6=early secretory antigenic target 6. CAF=cationic adjuvant formulation. Hly=haemolysin. *11 new tuberculosis vaccines that have gone into clinical trials. Two of them, MVA85A and AERAS-402 *Mycobacterium vaccae*, have gone into phase 2 trials and one, *M vaccae*, has completed a phase 3 trial.

Hope for the future

Given that TB killed as many as 6900 Tanzanians in 2010 alone, all hopes hinge on the success of global efforts to find an effective alternative TB vaccine. IHI is conducting the first randomized, double-blind, clinical phase II trial evaluating the H1/IC31 vaccine candidate's ability to enhance the body's immune response against TB bacteria and safety of two doses of the vaccine, in HIV-positive individuals. The trial is conducted in collaboration with SSI, Aurum Institute, Swiss Tropical and Public Health Institute, and the South African TB Vaccine Initiative. Dr. Klaus Reither leads IHI's efforts in the H1/IC31 TB vaccine candidate study in Bagamoyo working together with Elirehema Mfinanga, Humphrey Shao, and Khadija Said. Their work is still ongoing. IHI hopes to continue along this line of work in collaboration with other institutions.

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