Comparative vaccine pipeline against Tuberculosis: VPM1002, H1/IC31®, H56/IC31® and RUTI®

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Tuberculosis (TB) is an infectious disease caused by the bacillus *Mycobacterium tuberculosis* (Mtb) that ranks as the second leading cause of death from an infectious disease worldwide. Efforts to develop new diagnostics, drugs and vaccines have intensified during the past decade. A bibliographic analysis of the current status in research and development aiming to briefly describe, evaluate and compare four novel vaccine candidates is attempted in this review.

Where are we?

In 2012:
8.6M new cases
1.3M deaths

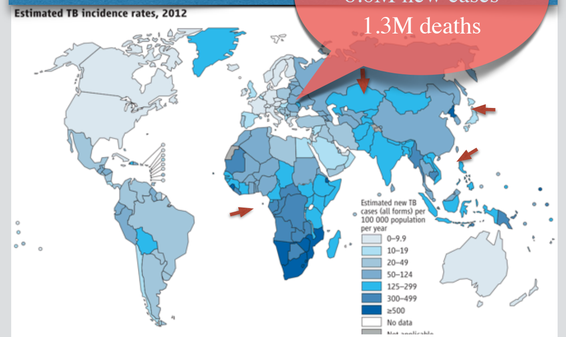


Figure 1. Global estimated TB incidence rates, 2012. Source taken from Stop TB Partnership[1].

- 1/3 of the world's population are infected.
- Leading killer of people with HIV.
- Treatment:
  - Too long
  - Ineffective against resistant strains (MDR, XDR, TDR)
- Difficult early diagnosis.
- Inconsistence efficacy of the only vaccine available, BCG (*see discussion*) [1, 2, 3, 4].

Where do we need to go?

Stop TB Partnership targets [1, 5]:

- By 2015: Reduce prevalence and death rates by 50%
- By 2050: Reduce the global incidence of active TB cases to <1 case per 1M population per year (=eradication)

Development of new diagnostics, drugs and vaccines are urgently needed as well as better biomarker correlates of immunity.

Analysis of four of the state-of-the-art candidate vaccines

Name	Type	Route of administration	Strategy	Immune response triggered	Target population	Safety profile	Development stage	Sponsors
VPM1002	Live recombinant BCG (rBCG) with an endosome escape mechanism through lysteriolysin expression and urease C deletion	Intradermal injection	Prime (Pre-exposure); BCG replacement	Stimulation of antigen-specific CD4 and improved CD8 T cell responses; Th17 cells activation; Humoral response induction; Polyantigenic	—	No safety concerns; safe and well tolerated (Absence of severe adverse effects)	Phase I completed; ongoing Phase IIa	Vakzine Projekt Management (VPM), Tuberculosis Vaccine Initative (TBVI), Max Planck Institute, Statens Serum Institute (SSI)
H1/ IC31	Protein-adjuvant fusion of Ag85B-ESAT-6 in IC31	Intramuscular injection (deltoid muscle / arm)	Prime-boost (Pre-exposure)	Stimulation of strong and long-lasting Th1 cellular response; Pauciantigenic; No humoral response stimulation	Adolescents; adults	No safety concerns; local adverse events in high dose adjuvanted vaccine	Phase I completed; ongoing Phase IIa	Statens Serum Institute (SSI), Tuberculosis Vaccine Initiative (TBVI), European and Developing Countries Clinical Trial Partnership (EDCTP), Intercell
H56/ IC31	Protein-adjuvant fusion of Ag85B-ESAT-6-Rv2660c in IC31	Intramuscular injection	Prime-boost; Immunotherapy (pre- and post-exposure)	Stimulation of strong multifunctional CD4 T cell responses; Limitation of reactivation of LTBI; Pauciantigenic	Adolescents; adults	—	Phase I completed; ongoing Phase I/IIa	Statens Serum Institute (SSI), Aeras, Intercell
RUTI	Non-live detoxified *M. tuberculosis* in liposomes	Subcutaneous	Immunotherapy*; Boost (post- and pre-exposure) *Adjunct to LTBI INH prophylaxis	Mixed Th1, Th2, Th3 response towards latency antigens; Humoral response induction; Polyantigenic	HIV+; adults; LTBI diagnosed	No hypersensitivity observed	Phase I completed; ongoing Phase IIa	Archivel Farma, S.L.

Table 1. Comparative evaluation of VPM1002, H1, H56, and RUTI® as candidate vaccines in current clinical development [6, 7].

Future vaccines are based in 3 different approaches: (1)Prime, (2)Boost, and (3)Immunotherapy.

Priming vaccines aim to replace the actual BCG, by either attenuation or by complementing it with new Ags.

Boosting vaccines seek to extend prime protection by subsequent boosting vaccination(s).

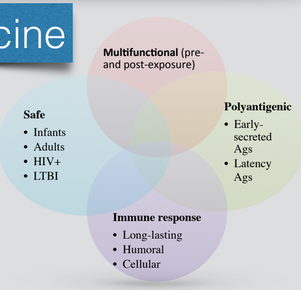
Immunotherapeutic vaccines aspire to shorten treatment by synergizing with chemotherapy if there is active TB or LTBI.

Discussion

Product name	Strengths	Limitations
BCG	Protection against miliary TB and meningeal TB; Cheaply produced	Not effective against pulmonary TB and most forms of extrapulmonary TB; Durability protection unclear; Cannot be boosted with repeated vaccination; Contraindicated for use in immunocompromised individuals; Can cause BCGitis (local infection) and BCGosis (systemic disease)
VPM1002	Superior protection than BCG (even against high virulence isolates); Induction of CD8+ T cell response; Activation of Th17 cells subset; Humoral response	*Hly* inclusion toxin gene may cause additional regulatory scrutiny for safety; Hygromycin resistance marker included in the construct
H1/IC31	Superior protection than BCG; Long lasting CD4+ Th1 response (>2.5 years)	No humoral response triggered; Local vaccine-related reactions in high dose adjuvanted vaccine; Presumptive interference with QuantiFERON
H56/IC31	Superior protection than BCG and H1; Improved prevention of reactivation and improved long-term containment of LTBI; Strong multifunctional CD4+ T cell response; Effective vaccination also after exposure	No detectable CD8+ T cells response; No humoral response triggered
RUTI	Induction of CD8+ T cell response; Humoral response; Could also be used as a booster and soon after recent infections	Does not decrease bacterial load directly; As potent as BCG; Dose dependent local adverse reactions (mild)

Table 2. Strengths and limitations comparison between the described vaccines and the old BCG [6, 7].

Ideal vaccine



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