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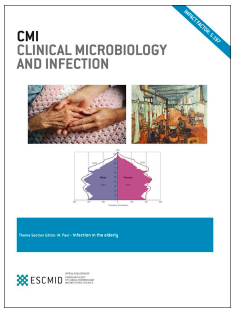

Tuberculosis prevention: current strategies and future directions

Anca Vasiliu, Leonardo Martinez, Rishi K. Gupta, Yohhei Hamada, Tara Ness, Alexander Kay, Maryline Bonnet, Martina Sester, Stefan H.E. Kaufmann, Christoph Lange, Anna Maria Mandalakas

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TUBERCULOSIS PREVENTION

- GRAPHICAL ABSTRACT -

BURDEN OF INFECTION

It is estimated that one in four people is infected with *M. tuberculosis* worldwide

TRANSMISSION CONTROL

M. tuberculosis transmission risk is influenced by host, pathogen, and environment, with increased risk from close, prolonged exposure in poorly ventilated settings.

VACCINATION

BCG

The BCG vaccine is the only licensed and widely used vaccine for tuberculosis prevention in humans, but its effectiveness is limited to young children.

Novel Vaccine Candidates

Subunit vaccines are composed of few antigens considered relevant for protection (M72:AS01E vaccine candidate has shown a total efficacy of 54%)

Whole cell vaccines comprise many *M. tuberculosis* antigens.

mRNA vaccines have entered the clinical trial pipeline in 2023 and phase 1 trials are ongoing.

TESTS OF LATENT INFECTION

Tests routinely used in clinical care include the tuberculin skin test (TST) and blood-based interferon-gamma release assays (IGRA).

Novel skin tests using *M. tuberculosis* specific antigens have been explored as alternatives to the TST and showed similar performance as IGRA or TST.

PREVENTIVE TREATMENT

Tuberculosis preventive treatment (TPT) reduces the risk of tuberculosis by 60-90%. Shorter regimens are now recommended with better adherence and fewer side effects.

For pregnant women, regimens based on rifampicin are preferred.

For contacts of MDR/RR-TB, a daily regimen including a fluoroquinolone for six months is recommended.

CLEAN VERSION

Tuberculosis prevention: current strategies and future directions

Manuscript category: Narrative Review

Authors: Anca Vasiliu[1], Leonardo Martinez[2], Rishi K. Gupta[3], Yohhei Hamada[4], Tara Ness[1], Alexander Kay[1], Maryline Bonnet[5], Martina Sester[6], Stefan H. E. Kaufmann[7,8,9], Christoph Lange[1,10,11,12], Anna Maria Mandalakas[1,10,11]

Affiliations:

1. Baylor College of Medicine, Department of Pediatrics, Global TB Program, Houston, TX, USA.
2. Department of Epidemiology, School of Public Health, Boston University, Boston, Massachusetts
3. Institute of Health Informatics, University College London, London, United Kingdom
4. Institute for Global Health, University College London, London, United Kingdom
5. University of Montpellier, TransVIHMI, IRD, INSERM, Montpellier, France
6. Department of Transplant and Infection Immunology, Saarland University, Homburg, Germany
7. Max Planck Institute for Infection Biology, Berlin, Germany
8. Max Planck Institute for Multidisciplinary Sciences, Göttingen, Germany
9. Hagler Institute for Advanced Study, Texas A&M University, College Station, USA
10. Division of Clinical Infectious Diseases, Research Center Borstel, Borstel, Germany
11. German Center for Infection Research (DZIF), Partner Site Hamburg-Lübeck-Borstel-Riems, Borstel, Germany
12. Respiratory Medicine and International Health, University of Lübeck, Lübeck, Germany

Corresponding author: Anca Vasiliu, Baylor College of Medicine, Department of Pediatrics, Global TB Program, Houston, TX, USA, anca.vasiliu@bcm.edu, tel: +33652727749

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Abstract

Background: An estimated one fourth of the world's population is infected with *Mycobacterium tuberculosis*, and 5–10% of those infected develop tuberculosis in their lifetime. Preventing tuberculosis is one of the most underutilized but essential components of curtailing the tuberculosis epidemic. Moreover, current evidence illustrates that tuberculosis manifestations occur along a dynamic spectrum from infection to disease rather than a binary state as historically conceptualized. Elucidating determinants of transition between these states is crucial to decreasing the tuberculosis burden and reaching the END-TB Strategy goals as defined by the World Health Organization (WHO). Vaccination, detection of infection, and provision of preventive treatment are key elements of tuberculosis prevention.

Objective: This review provides a comprehensive summary of recent evidence and state-of-the-art updates on advancements to prevent tuberculosis in various settings and high-risk populations.

Sources: We identified relevant studies in the literature and synthesized the findings to provide an overview of the current state of tuberculosis prevention strategies and latest research developments.

Content: We present the current knowledge and recommendations regarding tuberculosis prevention, with a focus on *M. bovis* Bacille-Calmette-Guérin (BCG) vaccination and novel vaccine candidates, tests for latent infection with *M. tuberculosis*, regimens available for tuberculosis preventive treatment (TPT) and recommendations in low- and high-burden settings.

Implications: Effective tuberculosis prevention worldwide requires a multipronged approach that addresses social determinants, improves access to tuberculosis detection and to new short TPT regimens. Robust collaboration and innovative research are needed to reduce the global burden of tuberculosis and develop new detection tools, vaccines, and preventive treatments that serve all populations and ages.

Background

The World Health Organization (WHO) reported an alarming 10.6 million cases of tuberculosis in 2021 (1). Indirect evidence suggests that one fourth of the world's population is estimated to be infected with *Mycobacterium tuberculosis* (2), and 5–10% of those infected develop tuberculosis in their lifetime (3). There is a paradigm shift in our understanding of tuberculosis natural history - instead of perpetuating a binary classification of latent *M. tuberculosis* infection (LTBI) and active tuberculosis, a dynamic spectrum of physiological states including incipient, subclinical, and active disease is now recognized (4,5). Once infected with *M. tuberculosis,* the host immune response may eliminate the infection, contain the infection through immune response, or progress to subclinical, and thereafter active disease (4–7) (Figure 1). Given that current diagnostic tests are unable to distinguish between these stages and produce both false positive and false negative results, the development of specific detection methods and targeted interventions to prevent disease progression and transmission are of paramount importance.

This review provides a comprehensive summary of recent evidence and state-of-the-art updates on advancements to prevent tuberculosis in various settings and high-risk populations.

Determinants of *M. tuberculosis* transmission

The risk of *M. tuberculosis* transmission is driven by a combination of host, pathogen, and environmental determinants. The main host-related factor is high bacillary load, as evidenced by a positive GeneXpert MTB/RIF, or cavitary disease (8,9), and exposure occurring in close proximity and for extended periods (10,11). Regarding pathogen-related factors, genomic sequencing has revealed that distinct lineages possess varying degrees of virulence, thereby influencing their potential for transmission(12–14). Next-generation sequencing now supports population level surveillance of tuberculosis by comparing the DNA sequences from patient isolates(15) and from environmental sources such as wastewater samples (16) to provide insight into transmission dynamics (17). The main

environmental determinant that increases the risk of *M. tuberculosis* transmission is overcrowding, as experienced in healthcare facilities(18), orphanages(19), prisons (20) and informal settlements(21). The main prevention strategies currently available are vaccines (BCG or novel vaccine candidates still in the pipeline), identification of *M. tuberculosis* infection, and preventive treatment.

BCG vaccination

Bacillus Calmette-Guérin (BCG) vaccine remains the only licenced and widely used vaccination for tuberculosis prevention in humans (22,23). BCG is effective in young children and mainly against severe forms of tuberculosis.

An individual-participant meta-analysis synthesized data from 26 studies including 68,552 participants. The studies were restricted to those with BCG vaccination at birth with the primary aim to investigate the age-specific impact of BCG vaccination on all forms of tuberculosis (24). The overall effectiveness of BCG vaccination was of 18% (95% confidence interval (CI), 9–26); however, effectiveness was only seen in young children <5 years, suggesting novel vaccines are needed to prevent tuberculosis in older populations. BCG was protective against tuberculosis in those with a positive test of infection.

Whether BCG revaccination provides protection against tuberculosis has been debated for decades(25,26). The Chingleput BCG vaccination trial (conducted in 1968) had shown no overall protection against active tuberculosis at 15 years in adults and limited protection in children(27). A re-analysis of this study shows that among 2,890 and 1,546 participants of all ages in the BCG revaccination and placebo arms, the incidence of tuberculosis at 15 years post-vaccination was lower in the BCG revaccination arm (190 versus 296 cases per 100,000 population; Hazard Ratio, 0.64; 95%CI, 0.46-0.89)(28).

Better tuberculosis vaccines and innovative strategies are urgently needed in order to overcome the current tuberculosis crisis. Important evidence is expected from an ongoing phase III BCG pre-travel study and a phase IIb booster BCG revaccination study; unfortunately, both studies include only adults.

Novel tuberculosis vaccines

After a long standstill, several tuberculosis vaccines are in development and at least a dozen candidates are currently moving through the clinical trial pipeline (see Table 1) (22,29–31).

T lymphocytes which activate effector cells of innate immunity are critical for protection against tuberculosis induced by natural infection. Although antibodies participating in protective immunity activate secondary effector mechanisms (32), this activation itself is apparently insufficient. Neutralizing antibodies specific for protective antigens which could prevent infection with *M. tuberculosis* have not been identified. As a corollary, vaccine research and development is hampered by the lack of correlates of protection (33). General agreement exists that Th1 type CD4 T cells play a critical role in the protective immune response to *M. tuberculosis*. They are likely supported by IL-17 producing CD4 T-cells, unconventional T-cells, and CD8 T-cells which secrete cytokines and express cytolytic activity (34). Pre-exposure vaccination involves administering a vaccine to individuals without exposure to *M. tuberculosis*, or without a detectable immune response to specific antigens. Post-exposure vaccination involves vaccinating individuals who have been exposed to *M. tuberculosis* or have risk of developing tuberculosis due to recent exposure, and aims to prevent the development of tuberculosis or reduce its severity.

Vaccine candidates in clinical trials comprise subunit vaccines and whole cell vaccines. Subunit vaccines serve as boosters for individuals vaccinated at birth and are composed of few antigens considered relevant for protection. Attenuated live whole cell vaccines serve as boosters or replacements for*BCG*. Whole cell vaccines comprise a plethora of *M. tuberculosis* antigens. Inactivated vaccines are often composed of atypical mycobacteria which share numerous antigens with *M. tuberculosis*. Booster vaccines are administered either pre-exposure, in the absence of LTBI, or post-exposure, if evidence of LTBI exists. Replacement vaccines target neonates prior to exposure with *M. tuberculosis*.

Several vaccine trials are ongoing. Notably, the M72:AS01$_E$ vaccine candidate has shown a total efficacy of 54% (95% CI 2.1-74.2) to prevent pulmonary tuberculosis in participants who received at least one dose(35). The DAR-901 vaccine, an inactivated whole cell vaccine, was studied for the prevention of LTBI in 667 healthy Tanzanian adolescents; the primary efficacy outcome was time to IGRA conversion. The vaccine candidate did not show a significant effect on new IGRA positivity or persistent LTBI - efficacy rates of 3% [95%CI 13.9-17.7] and 4% [95%CI 12.1-18.5], respectively(36). However, lack of a direct and accurate measure of LTBI limits our ability to assess the effectiveness of vaccines designed to prevent infection(37). Two live vaccines, MTBVAC and VPM1002, are based on *M. tuberculosis* and BCG, respectively. MTBVAC is an attenuated deletion mutant of *M. tuberculosis* lacking two independent virulence gene loci: phoP (transcription factor for several virulence factors) and fadD26 (involved in lipid synthesis). These deletions affect expression of hundreds of gene products including virulence factors. VPM1002 is a BCG vaccine in which the urease C gene has been replaced by the listeriolysin gene to strengthen attenuation and immunogenicity. The latest innovations in the vaccine area are mRNA vaccines which have entered phase I clinical trials (Table 1). These vaccines target the 1) healthy BCG-vaccinated and tuberculosis-infected people and 2) non-BCG vaccinated and non-tuberculosis infected people. There is insufficient knowledge to predict their potential efficacy.

Detecting latent *M. tuberculosis* infection

Test platforms routinely used in clinical care include the tuberculin skin test (TST) or blood-based interferon-γ (IFN-γ) release assays (IGRA) (37). The TST relies on the induction of a skin-test reaction after *in vivo* stimulation with tuberculin purified protein derivative. Commercial IGRA tests are based on IFN-γ production after specific stimulation of whole blood or peripheral blood mononuclear cells with two *M. tuberculosis* antigens, ESAT-6 and CFP-10. These antigens are encoded in the region of difference 1 (RD1) present in the *M. tuberculosis* and *M. bovis* genome and absent in BCG and most

environmental mycobacteria. Stimulation-induced IFN-γ is detected by either an ELISA, an ELISPOT assay, or flow cytometry. IGRAs are cross-reactive with only a few non-tuberculous mycobacteria but not with *M. bovis*, and are therefore more specific compared with TST (37). IGRAs include negative and positive controls to assess validity and general immune function; thus, GRAs are preferred in patients with immunodeficiency (38). It is important to note that CD4 depletion in people living with HIV (PLHIV) may diminish test reliability (39) and the ability of ELISPOT-based assays to correct for the number of lymphocytes in the sample may preserve test reliability (40). Based on established cut-off values, a positive result in exposed patients and patients at high risk of developing active tuberculosis represents an indication for preventive treatment. Neither IGRAs nor the TST differentiate LTBI from disease (41). The use of IGRAs in low resource settings is prohibitive by its high price. TST requires cold chain and the patient to come to the health facility 48-72 hours after test placement for induration reading. Although quantitative information is not used routinely, tuberculosis incidence is higher among individuals with larger TST indurations or IGRA-levels (42). The predictive value of IGRAs was shown to be higher than TST in low incidence countries (43,44), whereas predictive utility of both tests is rather low in high burden countries (45). The performance of TST tends to be better in younger populations; nevertheless, for IGRAs no clear trend was identified in a meta-analysis (45) mainly due to one study where IGRAs performed poorer in children (46). Therefore, newer generation tests are needed to better identify individuals who would benefit from TPT. Novel skin-tests using *M tuberculosis*-specific antigens (RD1 antigens) have been explored as alternatives and showed similar performance as IGRAs or TST (47) namely similar specificity to IGRA, and higher sensitivity than TST in children and in PLHIV (48–50).

Promising experimental approaches to differentiate between LTBI and tuberculosis exist based on altered cytokine expression profiles (51–53) or enrichment of specific T cells from blood into pleural fluid or bronchoalveolar lavage (54–56). Whole blood signatures comprising different numbers of transcripts have been explored. Although whole-blood transcriptional signatures have demonstrated the potential to identify individuals at risk of developing tuberculosis, these individuals are mostly

184 those who will develop incipient and subclinical disease (52,53,57). The CORTIS trial analysed the
185 diagnostic performance of a signature comprising 11 transcripts (RISK11) (58). The signature identified
186 active tuberculosis and confirmed its potential to predict progression to incident tuberculosis.
187 However, when study participants were randomized to receive preventive chemotherapy based on
188 the RISK11 signature, this did not reduce progression to tuberculosis. While further studies are needed
189 to define clinical applications, these novel test principles will have potential to better identify the
190 states along the tuberculosis spectrum.
191
192 **Tuberculosis preventive treatment (TPT)**
193 Tuberculosis preventive treatment (TPT) recommended after exposure to tuberculosis is considered
194 secondary prophylaxis. When recommended in PLHIV as part of a comprehensive package of HIV care
195 regardless of tuberculosis exposure in high burden settings, TPT is considered primary prophylaxis.
196 Shorter recommended regimens can reduce the risk of tuberculosis development by 60-90% (Table 2)
197 and are preferred due to their association with higher completion rates . The shortest recommended
198 regimen is one month of rifapentine and isoniazid daily(59). Studies demonstrate that rifamycin-
199 containing regimens have similar efficacy to 6 or 9 months of isoniazid monotherapy (61–63) and 3-
200 month daily rifampicin is associated with a lower risk of hepatotoxicity(60,62). Although low TPT
201 coverage may be associated with acquired drug resistance, increased TPT coverage reduces acquired
202 drug resistance.(64).
203 The choice of regimen should be based upon the availability of medicines and formulations, the risk
204 of adverse events, use of concomitant medications, and patients' preferences. Notably, rifapentine is
205 not available word-wide including countries within the European region of the WHO(65). Further, the
206 cost of rifapentine can be a barrier, particularly in high-burden countries with resource constraints.
207
208 *TPT in pregnant women and young children*

Data on the use of rifapentine in pregnant women and children <2 years are limited (3). One randomized controlled trial reported a higher risk of adverse pregnancy outcomes in women who were given isoniazid monotherapy during pregnancy compared to those who started therapy postpartum, whereas the same signal was not observed in observational studies (66,67). Rifampicin is generally considered safe and might be the preferred option for pregnant women. The timing of TPT should be discussed with pregnant women, considering their two-fold increased risk of tuberculosis late in pregnancy and the post-partum period. Further, maternal tuberculosis is associated with a six-fold increased risk of poor outcome in the neonate.

TPT in MDR/RR-tuberculosis

Among individuals in close contact with people with multidrug/rifampicin-resistant tuberculosis (MDR/RR-tuberculosis), the WHO recommends daily fluoroquinolone (levofloxacin or moxifloxacin) for six months alone or in combination with other agents like ethionamide or ethambutol(3), although the recommendation was based on limited evidence. Two RCTs of daily levofloxacin alone for six months in contacts of MDR/RR-tuberculosis are expected to report results in 2023 (68–70). For other types of drug resistance, the evidence on TPT is lacking.

Recommendations in low-burden settings

In accordance with the END-TB Strategy, low tuberculosis incidence countries (incidence rate <10/100,000 population) strive towards elimination (<1/100,000) by 2035 (71,72). In addition to ensuring effective treatment for people with tuberculosis, active case finding and LTBI screening among risk-groups are key to achieving this ambitious goal (72). Screening may focus on close contacts of index cases with pulmonary tuberculosis, though contacts of extra-pulmonary cases are also at risk (73).

Tuberculosis disproportionately affects specific populations in low-incidence settings, particularly recent migrants from high burden countries, people undergoing immunosuppressive therapy, and

PLHIV (74–76). These groups, along with individuals recently exposed to tuberculosis, should be prioritized for active case finding and LTBI screening.

New-entrant screening may identify people at the point of entry in the destination country, or at pre-immigration screening, and is complemented by retrospective identification of people within two to five years of arrival (77). For migrants, the risk of tuberculosis is known to decline with time since exposure or migration (78), highlighting that active tuberculosis/LTBI screening should be performed rapidly after arrival to maximise benefits. In the absence of tuberculosis, a discussion of the individual benefits and risks of preventative therapy can be supported using the personalized risk predictor tool PERISKOPE-TB, which incorporates IGRA/TST results and individual risk factors (like age, HIV status, history of contact, country of birth, date of migration, solid organ recipient) (78). In parallel to efforts implemented within low-incidence countries, it is critical and cost-effective to support tuberculosis control efforts in high-burden settings, thereby contributing towards global progress and further reducing the risk of disease among recent entrants(79).

Recommendations in high-burden settings

Tuberculosis high incidence settings (incidence rate >100/100,000 population) carry a disproportionate burden of tuberculosis and are often within low- and middle-income countries. The tuberculosis epidemic in these settings is fuelled by socioeconomic determinants; poverty, malnutrition, and hunger increase susceptibility to LTBI, active tuberculosis, and severity of clinical outcomes(80–82). A recent cluster randomized controlled trial estimated that provision of nutritional supplementation to 30 households would prevent one incident tuberculosis case(83). Tuberculosis control can only be achieved by coordinated interventions related to social structural determinants, as well as timely diagnosis and support throughout the treatment. Several social and financial support strategies have been proposed to improve tuberculosis treatment adherence, including conditional cash transfers, which improved treatment completion rates(84). Nevertheless, a meta-analysis of

interventions using cash incentives has shown little to no effect on the number of people that are cured or complete tuberculosis treatment.

Evidence from high-burden settings has shown a 3-fold increase in LTBI measured using TST/IGRAs in tuberculosis-affected households compared with tuberculosis-free households. Notably, RCTs demonstrate benefits of TPT regardless of TST/IGRA results in PLHIV(85). Further, the results of an individual participant meta-analysis in PLHIV have demonstrated the utility of C-reactive protein alone and chest radiograph combined with symptom screening to effectively screen for tuberculosis(86). The WHO symptom screen in household contacts had a pooled sensitivity of 89% (52%-98%), and a specificity of 69% (51%-83%)(87). In young children, symptom screening and treating, without testing for LTBI, represents the most cost-effective strategy(88). Therefore, the WHO recommends prioritizing TPT initiation in children under 5 who are household contacts of a person with bacteriologically confirmed tuberculosis, or in PLHIV(3). TPT can be initiated in this population without the need for LTBI testing or a chest radiograph and through symptom-based exclusion of tuberculosis (89). However, improved technologies like portable radiographs and computer aided detection (CAD) could play a crucial role in improving tuberculosis detection(90); unfortunately, CAD technologies have not been effectively evaluated in children.

Conclusion

Effective prevention of tuberculosis requires a multi-prong approach including novel vaccines, improved tests offering accuracy for each stage on the tuberculosis continuum, and shorter and accessible preventive treatment regimens. While low-burden countries strive for elimination and narrowly combat tuberculosis primarily in migrants, high-burden settings still face numerous challenges and transmission ubiquitously plagues many high-risk groups. Robust collaboration and innovative research are needed to reduce the global burden of tuberculosis and develop new detection tools, vaccines, and treatment regimens that serve all populations.

Transparency declaration

Conflict of Interest S.H.E.K. is co-applicant of a patent for TB biomarkers, and coinventor and coholder of a patent for the TB vaccine, VPM1002, which has been licensed to Vakzine Projekt Management GmbH, Hannover/Germany and Serum Institute for India Ltd., Pune/India. C.L. reports personal fees from INSMED, Gilead, GSK and Janssen for lecturing at sponsored symposia outside of the presented work. M.S. has received grants for investigator-initiated studies by Astellas and Biotest, and travel support and honoraria from Biotest, Moderna, MSD, Qiagen, Takeda outside the presented work.

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569 Table 1: Major TB vaccine candidates in clinical development
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TB Protein: adjuvant formulations			
Name	**Composition**	**Most advanced clinical stage**	**Representative clinical trial number**
H56:IC31	Fusion protein of 2 antigens: IC31 as adjuvant [1)]	Phase IIb ongoing	NCT03512249
ID93:GLA-SE	Fusion protein of 4 antigens: GLA-SE as adjuvant [2)]	Phase IIb ongoing	NCT03806686
M72:AS01$_E$	Fusion protein of 2 antigens: AS01$_E$ as adjuvant [3)]	Phase IIb completed	NCT01755598
AEC:BC02	Combination of 3 protein antigens: BC02 as adjuvant [4)]	Phase IIa ongoing	NCT05284812
GamTBvac	Combination of 3 protein antigens: CpG as adjuvant [5)]	Phase III ongoing	NCT04975737
Mtb-antigen encoding mRNA vaccines			
BNT164a1 / BNT164b1	mRNA expressing multiple Mtb antigens in lipid nanoparticles	Phase I ongoing	NCT05547464 NCT 05537038
TB antigen expressing viral vectors			
ChadOx1.85A/MVA85A	ChadOx1 as carrier for prime, MVA as carrier for boost, both expressing same antigen [6)]	Phase IIa ongoing	NCT00480558
TB/FLU-04L	Non-replicating influenza virus expressing 2 antigens [7)]	Phase I completed	NCT02501421
Inactivated whole cell vaccines			
Immuvac	Killed *M. indicus pranii*	Phase III ongoing	CTRI/2019/01/017026
RUTI	Killed detoxified *M. tuberculosis*	Phase IIb ongoing	NCT04919239
DAR-901	Killed *M. obuense*	Phase IIb completed	NCT02712424
Viable attenuated whole cell vaccines			

MTBVAC	Genetically attenuated *M. tuberculosis* [8)]	Phase III for children and Phase IIa for adolescents and adults ongoing	NCT04975178
VPM1002	Genetically enhanced BCG [9)]	Three phase III trials ongoing for (i) HIV-exposed/unexposed neonates, (ii) adolescent and adult household contacts; (iii) cured TB patients undergoing recurrence	NCT04351685

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572 [1)] IC31 adjuvant: cationic peptide with a TLR-9 agonist.
573 [2)] GLA-SE: oil-in-water emulsion with TLR-4 agonist.
574 [3)] $AS01_E$: liposome with TLR-4 agonist.
575 [4)] BC02: CpG adjuvant in aluminum hydroxide.
576 [5)] CpG adjuvant.
577 [6)] Chimpanzee adenovirus (ChadOx1) as prime and modified vaccinia Ankara (MVA) as boost both expressing same antigen.
578 [7)] Non-replicating influenza virus expressing 2 antigens.
579 [8)] 2 independent gene deletions (phoP and fadD26) in Mtb.
580 [9)] Exchange of urease C by listeriolysin gene in BCG.

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Table 2. TB preventive treatment regimens

Regimen	Dose*	Comments
4 months of daily rifampicin	Age 10 years & older: 10 mg/kg/day Age <10 years: 15 mg/kg/day (range, 10–20 mg)	• Less hepatotoxicity than isoniazid monotherapy: 1.8% for 6H vs 0.3% for 4R (62) • Less than 0.01 difference in confirmed tuberculosis when comparing rifampin and isoniazid after 28 months of follow-up (60). • Potent inducer of the cytochrome P450 enzyme system and can reduce concentrations of certain drugs (e.g. warfarin and protease inhibitors) significantly.**
3 months of daily rifampicin plus isoniazid	Isoniazid: Age 10 years & older: 5 mg/kg/day Age <10 years: 10 mg/kg/day (range, 7–15 mg) Rifampicin: Age 10 years & older: 10 mg/kg/day Age <10 years: 15 mg/kg/day (range, 10–20 mg)	• Hepatotoxic risk not significantly different from 6H (OR 0.83, 95%CI 0.49-1.42)(91). • Paediatric fixed dose formulations available; might be the preferred option in young children. • Potent inducer of the cytochrome P450 enzyme system and can reduce concentrations of certain drugs significantly (e.g. warfarin and protease inhibitors).**
3 months weekly rifapentine plus isoniazid (12 doses)	Age 2-14 years: Differ by weight-band (See the WHO guidelines*) Age > 14 years: Rifapentine 900 mg + Isoniazid 900 mg	• Less hepatotoxicity than isoniazid monotherapy: 1.5% for 3HP vs 5.5% for 6H (in HIV-positive)[2] and 0.4% for 3HP vs 2.7% for 9H (in HIV-negative)(63). • There was a difference of 24% in TB occurrence in the 3HP group versus the isoniazid group (61) • Systemic drug reactions appear to be more common than others: 3.5% for 3HP vs 0.4% for 9H(92). • Limited data in pregnant women and children < 2 years. • Potent inducer of the cytochrome P450 enzyme system and can reduce concentrations of certain drugs significantly (e.g. warfarin and protease inhibitors).**
1 month of daily rifapentine*** plus isoniazid (28 doses)	Age ≥13 years (regardless of weight band) Isoniazid, 300 mg/day Rifapentine, 600 mg/day	• Hepatotoxicity less or similar to 9H: 2% for 1HP vs 3% for 9H(59). • No hypersensitivity reactions in 1496 participants in one RCT(59). • There were 2% of TB cases in both isoniazid and 1HP group after 3.3 years (57) • Limited evidence in children < 13 years. One prospective cohort study (n= 408) reported its' safety in 2-19 years(93). • Potent inducer of the cytochrome P450 enzyme system and can reduce concentrations of certain drugs significantly (e.g. warfarin and protease inhibitors).**

6 or 9 months of daily isoniazid	Age 10 years & older: 5 mg/kg/day Age <10 years: 10 mg/kg/day (range, 7–15 mg)	• Less preferred to rifamycin-containing regimens.
6 months of daily levofloxacin	Age >14 years, by body weight: < 46 kg, 750 mg/day; >45 kg, 1g/day Age <15 years (range, approx. 15–20 mg/kg/day), by body weight: • 5–9 kg: 150 mg/day; • 10–15 kg: 200–300mg/day; • 16–23 kg: 300–400mg/day; • 24–34 kg: 500–750mg/day	• Regimens should be developed for other types of drug resistance

6H: 6 months of daily isoniazid; 9H: 9 months of daily isoniazid; 4R: 4 months of daily rifampicin; 3HP: 3 months weekly rifapentine plus isoniazid; 1HP: one month of daily rifapentine plus isoniazid.
*Based on WHO consolidated guidelines on tuberculosis. Module 1: prevention – tuberculosis preventive treatment.
**Detailed information is available elsewhere (e.g. https://reference.medscape.com/drug-interactionchecker)
***Rifapentine is not currently available in many European countries(65)