

1 **CLEAN VERSION**

2 **Tuberculosis prevention: current strategies and future directions**

3
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32 **Abstract**

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

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

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

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

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

55

56 **Background**

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

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

71

72 **Determinants of *M. tuberculosis* transmission**

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

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

85

86 **BCG vaccination**

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

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

97 Whether BCG revaccination provides protection against tuberculosis has been debated for
98 decades(25,26). The Chingleput BCG vaccination trial (conducted in 1968) had shown no overall
99 protection against active tuberculosis at 15 years in adults and limited protection in children(27). A re-
100 analysis of this study shows that among 2,890 and 1,546 participants of all ages in the BCG
101 revaccination and placebo arms, the incidence of tuberculosis at 15 years post-vaccination was lower
102 in the BCG revaccination arm (190 versus 296 cases per 100,000 population; Hazard Ratio, 0.64;
103 95%CI, 0.46-0.89)(28).

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

107

108 **Novel tuberculosis vaccines**

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

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

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

132 Several vaccine trials are ongoing. Notably, the M72:AS01_E vaccine candidate has shown a total
133 efficacy of 54% (95% CI 2.1-74.2) to prevent pulmonary tuberculosis in participants who received at
134 least one dose(35). The DAR-901 vaccine, an inactivated whole cell vaccine, was studied for the
135 prevention of LTBI in 667 healthy Tanzanian adolescents; the primary efficacy outcome was time to
136 IGRA conversion. The vaccine candidate did not show a significant effect on new IGRA positivity or
137 persistent LTBI - efficacy rates of 3% [95%CI 13.9-17.7] and 4% [95%CI 12.1-18.5], respectively(36).
138 However, lack of a direct and accurate measure of LTBI limits our ability to assess the effectiveness of
139 vaccines designed to prevent infection(37). Two live vaccines, MTBVAC and VPM1002, are based on
140 *M. tuberculosis* and BCG, respectively. MTBVAC is an attenuated deletion mutant of *M. tuberculosis*
141 lacking two independent virulence gene loci: *phoP* (transcription factor for several virulence factors)
142 and *fadD26* (involved in lipid synthesis). These deletions affect expression of hundreds of gene
143 products including virulence factors. VPM1002 is a BCG vaccine in which the urease C gene has been
144 replaced by the listeriolysin gene to strengthen attenuation and immunogenicity. The latest
145 innovations in the vaccine area are mRNA vaccines which have entered phase I clinical trials (Table 1).
146 These vaccines target the 1) healthy BCG-vaccinated and tuberculosis-infected people and 2) non-BCG
147 vaccinated and non-tuberculosis infected people. There is insufficient knowledge to predict their
148 potential efficacy.

149

150 **Detecting latent *M. tuberculosis* infection**

151

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

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

179 Promising experimental approaches to differentiate between LTBI and tuberculosis exist based on
180 altered cytokine expression profiles (51–53) or enrichment of specific T cells from blood into pleural
181 fluid or bronchoalveolar lavage (54–56). Whole blood signatures comprising different numbers of
182 transcripts have been explored. Although whole-blood transcriptional signatures have demonstrated
183 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 world-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*

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

217

218 *TPT in MDR/RR-tuberculosis*

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

225

226 **Recommendations in low-burden settings**

227 In accordance with the END-TB Strategy, low tuberculosis incidence countries (incidence rate
228 <10/100,000 population) strive towards elimination (<1/100,000) by 2035 (71,72). In addition to
229 ensuring effective treatment for people with tuberculosis, active case finding and LTBI screening
230 among risk-groups are key to achieving this ambitious goal (72). Screening may focus on close contacts
231 of index cases with pulmonary tuberculosis, though contacts of extra-pulmonary cases are also at risk
232 (73).

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

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

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

248

249 **Recommendations in high-burden settings**

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

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

262 Evidence from high-burden settings has shown a 3-fold increase in LTBI measured using TST/IGRAs in
263 tuberculosis-affected households compared with tuberculosis-free households. Notably, RCTs
264 demonstrate benefits of TPT regardless of TST/IGRA results in PLHIV(85). Further, the results of an
265 individual participant meta-analysis in PLHIV have demonstrated the utility of C-reactive protein alone
266 and chest radiograph combined with symptom screening to effectively screen for tuberculosis(86).

267 The WHO symptom screen in household contacts had a pooled sensitivity of 89% (52%-98%), and a
268 specificity of 69% (51%-83%)(87). In young children, symptom screening and treating, without testing
269 for LTBI, represents the most cost-effective strategy(88). Therefore, the WHO recommends prioritizing
270 TPT initiation in children under 5 who are household contacts of a person with bacteriologically
271 confirmed tuberculosis, or in PLHIV(3). TPT can be initiated in this population without the need for
272 LTBI testing or a chest radiograph and through symptom-based exclusion of tuberculosis (89).

273 However, improved technologies like portable radiographs and computer aided detection (CAD) could
274 play a crucial role in improving tuberculosis detection(90); unfortunately, CAD technologies have not
275 been effectively evaluated in children.

276

277 **Conclusion**

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

285

286 **Transparency declaration**

287 **Conflict of Interest** S.H.E.K. is co-applicant of a patent for TB biomarkers, and coinventor and
288 coholder of a patent for the TB vaccine, VPM1002, which has been licensed to Vakzine Projekt
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302

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568

569 Table 1: Major TB vaccine candidates in clinical development
570

<i>TB Protein: adjuvant formulations</i>			
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
<i>Mtb-antigen encoding mRNA vaccines</i>			
BNT164a1 / BNT164b1	mRNA expressing multiple Mtb antigens in lipid nanoparticles	Phase I ongoing	NCT05547464 NCT 05537038
<i>TB antigen expressing viral vectors</i>			
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
<i>Inactivated whole cell vaccines</i>			
Immuvac	Killed <i>M. indicus pranii</i>	Phase III ongoing	CTRI/2019/01/017026
RUTI	Killed detoxified <i>M. tuberculosis</i>	Phase IIb ongoing	NCT04919239
DAR-901	Killed <i>M. obuense</i>	Phase IIb completed	NCT02712424
<i>Viable attenuated whole cell vaccines</i>			

MTBVAC	Genetically attenuated <i>M. tuberculosis</i> 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

571

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.

581

582

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)	<ul style="list-style-type: none"> • 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)	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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)	<ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> • 5–9 kg: 150 mg/day; • 10–15 kg: 200–300mg/day; • 16–23 kg: 300–400mg/day; • 24–34 kg: 500–750mg/day 	<ul style="list-style-type: none"> • 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)