Literature Review

Levofloxacin as Tuberculosis Preventive Therapy for Household Contacts of Drug-Resistant Tuberculosis: Global Evidence and Implementation in Indonesia

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Abstract

Drug-resistant (DR) tuberculosis (TB), including multidrug-resistant (MDR) and rifampicin-resistant (RR) TB, remains a major global public health problem. This narrative review aims to summarize evidence regarding the effectiveness and safety of levofloxacin as tuberculosis preventive therapy (TPT) among household contacts of DR-TB patients and its implementation in Indonesia. The clinical spectrum of TB spans from infection to active disease, the progression of which can be prevented through TPT. Drug resistance in TB develops through genetic mutations. Levofloxacin (Lfx) exerts antimycobacterial activity by inhibiting the deoxyribonucleic acid (DNA) gyrase enzyme. The Vietnam Quinolones for MDR-TB Trial (VQUIN) demonstrated an incidence rate ratio of TB disease of 0.55 (95% confidence interval [CI]=0.19–1.62) in the Lfx group compared with the placebo group. In the Tuberculosis Child Multidrug-Resistant Preventive Therapy (TB-CHAMP) study, the hazard ratio for TB disease was 0.44 (95% CI=0.15–1.25) in the Lfx group compared with placebo. Although neither trial individually achieves statistical significance in reducing TB incidence, a meta-analysis of both studies revealed a significant relative reduction in cumulative TB incidence of 0.41 (95% CI=0.18–0.92) in the Lfx group compared with placebo. The administration of Lfx was associated with low-grade musculoskeletal adverse events (risk ratio=6.36; 95% CI=4.30–9.42). Overall, daily administration of Lfx for six months is recommended as the standard TPT regimen for DR-TB, particularly among household contacts of MDR/RR-TB cases.

Keywords: drug-resistant tuberculosis, household contact, levofloxacin, tuberculosis preventive therapy

INTRODUCTION

Drug-resistant (DR) tuberculosis (TB) persists as a major threat to public health worldwide because some people have a persistent immune response to *Mycobacterium tuberculosis* (*M. tuberculosis*) that is associated with a higher risk of progression to active disease. It is further estimated that, worldwide, approximately 3 per 1,000 individuals have latent MDR-TB infection, with a prevalence estimated to be twice as high among

individuals aged <15 years.[1]

According to the Global Tuberculosis Report 2024 released by the World Health Organization (WHO), an estimated 400,000 (95% uncertainty interval [UI]=360,000–440,000) patients were diagnosed with multidrug-resistant (MDR) TB or rifampicin-resistant (RR) TB worldwide in 2023. The proportion of MDR/RR-TB was estimated at 3.2% (95% UI=2.5–3.8%) among incident TB cases and 16% (95% UI=9.0–24%) among individuals with prior TB treatment. Indonesia accounted for 7.4% of new MDR/RR-TB cases globally in 2023, placing it third among those with the highest incidence of MDR/RR-TB.[2]

In 2024, WHO included MDR/RR-TB in the priority list of antibiotic-resistant bacterial pathogens due to its high burden of morbidity and mortality, long-term impact on health systems, as well as the cost and complexity of the public health response.[3,4] This makes drug resistance a major challenge to ending the global TB epidemic.

The risk of TB infection and disease is found to be higher among TB contacts, where individuals who have been in contact with TB patients.[5,6] Tuberculosis preventive therapy (TPT), including for contacts of MDR/RR-TB, is the key public health measure available to lower the risk of progression from infection to active disease.[2,7,8]

The End TB Strategy, announced by WHO in 2015 to eliminate TB by 2035, for the first time incorporated the diagnosis and management of TB infection, including among household contacts of MDR/RR-TB cases, as part of essential interventions. However, no specific management recommendations were provided other than close monitoring for the development of active TB disease among MDR/RR-TB contacts for a minimum of two years. This was due to the lack of scientific evidence identified through systematic literature reviews to support specific recommendations for the prevention of DR-TB as a public health intervention.[4]

Two large randomized controlled trials were conducted to evaluate the efficacy of TPT among contacts of MDR/RR-TB, namely the Vietnam Quinolones for MDR-TB Trial (VQUIN) and the Tuberculosis Child Multidrug-Resistant Preventive Therapy (TB-CHAMP) study, which informed the WHO's latest consolidated guidelines on TPT published in 2024. One of the strong recommendations in the updated WHO consolidated guidelines is the use of daily levofloxacin (Lfx) for six months as the preferred TPT regimen for contacts of MDR/RR-TB.[7]

Therefore, this narrative review summarizes global evidence regarding the effectiveness and safety of Lfx as TPT among household contacts of DR-TB patients, as well as its implementation in Indonesia.

METHODS

This article is a narrative literature review that was conducted using PubMed, Scopus, and Google Scholar databases,

with the inclusion criteria being published from 2015 onwards and using combinations of the keywords: "drug-resistant tuberculosis", "multidrug-resistant tuberculosis", "tuberculosis preventive therapy", "levofloxacin", "household contacts", and "latent tuberculosis infection".

International guidelines from the World Health Organization (WHO) and national Indonesian tuberculosis guidelines were also reviewed. Priority was given to articles with randomized controlled trials, meta-analyses, and recent guideline documents relevant to preventive therapy for household contacts of DR-TB.

CLINICAL SPECTRUM OF TB

For pragmatic purposes in clinical practice and public health, patients are commonly classified into latent TB infection and active (pulmonary) TB disease.[9] Latent TB infection is defined as a condition that occurs after exposure to *M. tuberculosis*, in which infection is established and an immune response develops to control the pathogen, rendering it in a quiescent state.[9,10] Latent TB infection is asymptomatic and non-transmissible.[9,10]

Meanwhile, active pulmonary TB disease is characterized by respiratory symptoms (persistent cough, hemoptysis) and systemic symptoms (fever, fatigue, loss of appetite, and weight loss). Pulmonary TB is transmissible and can be confirmed by microbiological diagnostic testing.[9]

Following exposure to *M. tuberculosis*, approximately 30% of close contacts or individuals who have been exposed to a patient with TB become infected.[10–12] Among those infected, 5–10% will progress to active TB disease within the first year after infection, while the remaining 95% will enter latent TB infection.[12]

After the first year, approximately 3–5% of individuals with latent TB infection will subsequently develop active TB disease. In contrast, the remaining 95% will maintain latent infection throughout their lifetime.[12] Figure 1 illustrates the proportion of outcomes among individuals exposed to *M. tuberculosis* through close contact with TB patients.

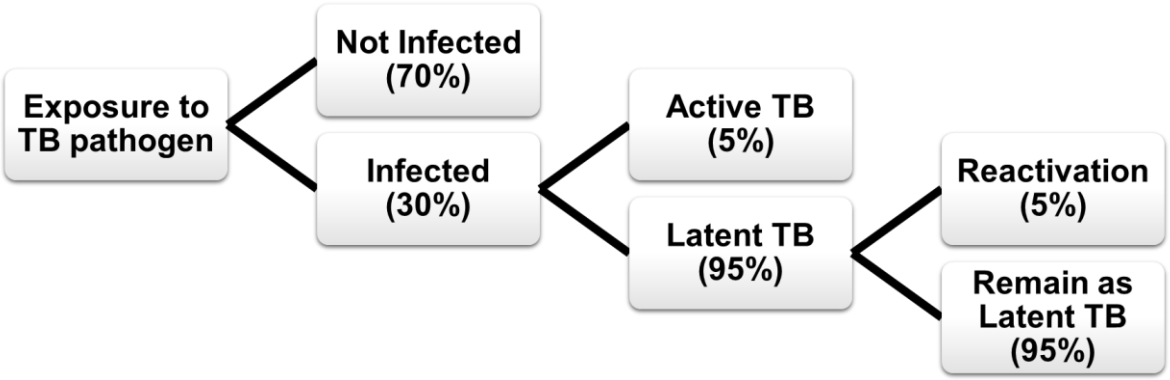

Figure 1. Outcomes in individuals exposed to *M. tuberculosis*[12]

Some individuals can eliminate *M. tuberculosis* through innate immune responses or adaptive immune responses without T-cell activation or the formation of memory T cells. In this group, TST or interferon-γ release assay (IGRA) results are negative. Other individuals can eliminate *M. tuberculosis* and develop memory T-cell responses, resulting in positive TST or IGRA results. There is no risk of TB transmission or evidence supporting the benefit of TPT in this group.[9]

If *M. tuberculosis* is not successfully eliminated, the organism may persist in a dormant state, resulting in TB infection that can be identified through positive TST or IGRA findings. In this stage, TPT plays an important role in reducing the risk of progression to active TB disease.[9]

There is also an intermediary stage within the TB disease spectrum, subclinical TB, which is represented by individuals do not report recognized TB-related symptoms but exhibit radiological and/or microbiological abnormalities consistent with TB. Because bacillary burden is often low, sputum acid-fast bacilli (AFB) smears may be negative despite positive culture or molecular test results.[9,13,14] Consequently, subclinical TB may be missed by symptom-based screening alone and is more likely to be identified through active case-finding strategies incorporating chest radiography.[11]

The subsequent clinical spectrum is active TB disease, which is usually accompanied by symptoms such as cough, fever, and weight loss, and can be confirmed by sputum AFB smear microscopy, culture, and molecular WHO-recommended rapid diagnostic test (mWRD). Individuals with subclinical TB as well as those with active TB disease should be treated with standard anti-tuberculosis drug (ATD) regimens consisting of an intensive phase with four drugs followed by a continuation phase with two drugs.[9,11]

Therefore, an understanding of the clinical spectrum of TB disease is essential for establishing an accurate diagnosis and providing appropriate management.[11] Table 1 summarizes the clinical spectrum of TB disease.

Table 1. Clinical spectrum of TB disease[9]

Parameter	Infection eliminated		Latent TB infection	Subclinical TB disease	Active TB disease
	With innate immune response	With acquired immune response			
TST	Negative	Positive	Positive	Positive	Usually, positive
IGRA	Negative	Positive	Positive	Positive	Usually, positive
Culture	Negative	Negative	Negative	Intermittently positive	Positive
AFB smear	Negative	Negative	Negative	Usually, negative	Positive or negative
Infectious status	No	No	No	Sporadically	Yes
Symptoms	None	None	None	Mild or none	Mild to severe
Preferred treatment	None	None	TPT	ATD	ATD

Note: TB=tuberculosis; TST=tuberculin skin test; IGRA=interferon-γ release assay; AFB=acid-fast bacilli; TPT=tuberculosis preventive therapy; ATD=anti-tuberculosis drugs

PATHOGENESIS OF DRUG RESISTANCE IN TB

According to the WHO, DR-TB is classified into five categories:[2]

1) isoniazid-resistant TB, defined as TB resistant only to isoniazid;
2) rifampicin-resistant TB (RR-TB), defined as TB resistant only to rifampicin;
3) multidrug-resistant TB (MDR-TB), defined as TB resistant to both rifampicin and isoniazid;
4) pre–extensively drug-resistant TB (pre-XDR-TB), defined as TB resistant to rifampicin and any fluoroquinolone (one class of second-line ATD); and
5) extensively drug-resistant TB (XDR-TB), defined as TB resistant to rifampicin, plus any fluoroquinolone and at least one of either bedaquiline or linezolid.

Since the first clinical trial of ATD involving human subjects in 1948, the phenomenon of drug resistance in TB has been described. Subsequently, each time a new ATD has been introduced into clinical practice, drug-resistant strains of *M. tuberculosis* have emerged and spread widely, typically within a decade.[9]

There are two main mechanisms of drug resistance in TB. The first mechanism is target modification, for example is mutation of the *M. tuberculosis* ribonucleic acid (RNA) polymerase, which confers resistance to rifampicin.[9,15] The second mechanism is defective enzymatic conversion of prodrugs into their active forms, with a representative example being resistance to isoniazid.[9]

As a prodrug, isoniazid requires activation by a catalase enzyme encoded by the katG gene to be converted into its active form and inhibit mycolic acid synthesis in *M. tuberculosis*. This inhibitory process is facilitated by nicotinamide adenine dinucleotide hydrogen (NADH)-dependent enoyl–acyl carrier protein (ACP) reductase encoded by the inhA gene. Mutations in the katG or inhA genes constitute the principal molecular mechanisms of isoniazid resistance.[16]

In relation to the natural course of TB disease, the development of drug resistance in TB occurs through two mechanisms, acquired resistance and transmitted resistance. Acquired resistance refers to the intrapatient evolution of drug resistance, which usually arises from poor treatment adherence or problems related to drug diffusion within the body. Transmitted resistance occurs when an individual is infected with *M. tuberculosis* that is genetically resistant to ATD.[15]

For more than a decade, the estimated proportion of MDR/RR-TB among new TB cases has remained at approximately 3–4%, whereas among previously treated TB cases it has remained in the range of 18–21%. This indicates that the substantial burden of DR-TB is largely driven by ongoing transmission. Thus, contact investigation and the provision of TPT for contacts of DR-TB are critically vital.[15]

MECHANISM OF ACTION OF LFX IN TB

As a 3rd-generation fluoroquinolone antibiotic, Lfx targets the intracellular metabolism of *M. tuberculosis*. This drug

inhibits the enzyme DNA gyrase, which is essential for bacterial DNA replication. In *M. tuberculosis*, DNA gyrase is the only topoisomerase that serves as a drug target. Enzyme DNA gyrase is an A_2B_2 protein, consisting of two A-subunits and two B-subunits. Inhibition of DNA gyrase at any subunit results in blockade of DNA replication, suppression of cell division, and ultimately cell death, both in replicating and non-replicating *M. tuberculosis*.[17,18]

The antimycobacterial activity of Lfx depends on its molecular affinity for the target enzyme and efflux pumps, as well as on the permeability of the *M. tuberculosis* cell wall, which is inherently low. This fluoroquinolone antibiotic exhibits excellent early bactericidal activity, enabling rapid killing of TB bacilli during the initial phase of treatment. In addition, Lfx has high sterilizing activity, as it can eliminate residual bacteria after the initial treatment phase, including persistent subpopulations of *M. tuberculosis* whose metabolic states render them less susceptible to drug-mediated killing.[17,18]

EVALUATION OF THE EFFICACY OF LFX AMONG CONTACTS OF MDR/RR-TB

The VQUIN Study

The VQUIN study by Fox et al was a randomized, double-blind, placebo-controlled phase-3 clinical trial conducted across 10 provinces in Vietnam between 2016 and 2019. It evaluated the efficacy and safety of a six-month daily Lfx regimen (6Lfx; 10–15 mg/kg for adults, 15–20 mg/kg for children) compared with a matched placebo among household contacts of all ages living with bacteriologically confirmed MDR/RR-TB index patients.[7,8]

A total of 2,041 participants with documented *M. tuberculosis* infection (positive TST) in the absence of active disease were randomized in a 1:1 ratio. Follow-up assessments for active TB incidence were systematically performed through symptom screening and chest radiography at months 6, 12, 18, 24, and 30.[7,8]

Out of 1,995 participants who completed the 30-month follow-up, bacteriologically confirmed active TB disease developed in 6 participants (0.6%) in the Lfx group and 11 participants (1.1%) in the placebo group. This yielded an incidence rate ratio of 0.55 (95% confidence interval [CI]=0.19–1.62), demonstrating a 45% reduction in TB incidence that did not reach statistical significance due to the unexpectedly low number of overall TB events during follow-up.[7,8]

Regarding safety, mild-to-moderate (grade 1–2) adverse events were significantly higher in the Lfx group (31.9%) than in the placebo group (13.0%) (risk difference=18.9%; 95% CI=14.2–23.6; P<0.001), leading to early treatment discontinuation in 7.4% of the intervention cohort, although no grade 3–4 events or deaths were drug-related.[7,8]

The TB-CHAMP Study

The TB-CHAMP study by Hesseling et al was a randomized, double-blind, placebo-

controlled trial conducted in five provinces in South Africa between 2017 and 2023. It evaluated a 24-week daily Lfx regimen (15–20 mg/kg) against a matched placebo specifically among pediatric and adolescent household contacts (predominantly aged <5 years) exposed to adult pulmonary MDR-TB index patients.[7,19]

A total of 922 eligible children confirmed to be free of active TB disease at baseline were randomized. Efficacy and safety endpoints were monitored through regular clinical visits at weeks 4, 8, 12, 16, 24, 48, and 72, utilizing rigorous symptom monitoring, weight evaluation, and targeted microbiological investigations.[7,19]

In the modified intention-to-treat (mITT) population (n=916) assessed at week 48, active TB disease developed in 5 of 451 children (1.1%) in the Lfx group compared with 12 of 465 children (2.6%) in the placebo group. This corresponded to a hazard ratio (HR) of 0.44 (95% CI=0.15–1.25; P=0.12), showing a substantial clinical effect size that mirrored the VQUIN study, but similarly missed individual statistical significance due to wide confidence intervals driven by low baseline event rates.[7,19]

However, daily Lfx demonstrated excellent tolerability in this pediatric population. Grade ≥3 adverse events did not differ significantly (HR=0.52; 95% CI=0.16–1.71; P=0.29) between the arms (0.9% in Lfx vs. 1.7% in placebo), and treatment discontinuation due to toxicity occurred in only 1.3% of the Lfx group and 0.2% of the placebo group (HR=5.00; 95% CI=0.61–41.32; P=0.14).[7,19]

Critical Synthesis of The VQUIN and TB-CHAMP Studies

A critical comparison of the VQUIN and TB-CHAMP studies provides important clinical insights arising from differences in study design and target populations. Although both studies evaluated the 6Lfx intervention and demonstrated comparable reductions in active TB incidence among household contacts of MDR/RR-TB, neither study individually achieved statistical significance. A major shared limitation was the overestimation of baseline TB incidence during sample size calculation, resulting in underpowered cohorts because of lower-than-expected event rates during follow-up.[8,19]

Differences in tolerability profiles were also observed between the two studies. In the VQUIN study, which predominantly included adults, mild-to-moderate adverse events were relatively common and contributed to treatment discontinuation in 7.4% of participants.[8] In contrast, the pediatric-focused TB-CHAMP trial demonstrated favorable tolerability of daily Lfx in young children, with low rates of toxicity-related discontinuation (1.3%) and no evidence of musculoskeletal cartilage toxicity.[19]

These findings have important implications for clinical practice and programmatic implementation. First, they support the feasibility of implementing 6Lfx as a programmatic preventive strategy for household contacts of MDR/RR-TB, particularly with pediatric formulations that may improve adherence and tolerability. Second, the studies highlight the

importance of pooled individual participant data meta-analysis in overcoming the limited statistical power of individual trials and supporting current DR-TPT recommendations.[8,19]

Nevertheless, important evidence gaps remain, particularly regarding pregnant and breastfeeding women, who were not included in either trial. Therefore, limited trial-based safety data in routine clinical practice continue.

Meta-Analysis of Two Clinical Trials of Lfx as Preventive Therapy for DR-TB

The role of TPT is crucial in protecting individuals with latent TB infection from progression to active TB disease and in reducing further transmission. However, scientific evidence from clinical trials evaluating TPT among individuals exposed to MDR/RR-TB patients remains limited. Although two phase 3 clinical trials have evaluated Lfx as TPT for MDR-TB in adults and children, i.e., the VQUIN and TB-CHAMP studies, but the reductions in TB incidence observed in both trials did not reach statistical significance.[20]

Consequently, Duong et al conducted a meta-analysis of these two trials to evaluate the efficacy and safety of Lfx as TPT for MDR-TB. This meta-analysis employed standard individual participant data (IPD) methods to estimate the overall treatment effect, as well as Bayesian methods to estimate efficacy within each trial with greater precision.[20]

The primary efficacy endpoint of the meta-analysis was the incidence of bacteriologically confirmed or clinically diagnosed TB disease up to week 54 after randomization. Safety endpoints included:[20]

1) grade ≥3 AEs from treatment initiation through 21 days after the last dose of study drug;
2) drug-related grade ≥3 AEs;
3) serious AEs occurring up to 21 days after the last dose of study drug;
4) treatment discontinuation due to AEs of any grade; and
5) five prespecified AE domains of special interest, including musculoskeletal effects (arthritis, arthralgia, or tendinitis) occurring at any time from treatment initiation.

Bayesian methods were used to estimate the efficacy of Lfx in the VQUIN population by "borrowing" information from TB-CHAMP, and vice versa.[20] This approach enhanced statistical power compared with analyses of each trial alone.

Overall, by week 54, TB disease occurred in 8 participants in the Lfx group compared with 21 participants in the placebo group. The relative difference in cumulative TB incidence was 0.41 (95% CI=0.18–0.92; P=0.03).[18] Administration of Lfx was not associated with an increased risk of grade ≥3 AEs (risk ratio [RR]=1.07; 95% CI=0.70–1.65).[20]

However, the incidence of musculoskeletal AEs of any grade was higher in the Lfx group than in the placebo group (RR=6.36; 95% CI=4.30–9.42). Post hoc analysis demonstrated that musculoskeletal AEs did not occur in children aged <10 years. Nearly all musculoskeletal AEs were grade 1 (62%)

or grade 2 (35%).[20]

The meta-analysis of the VQUIN and TB-CHAMP studies demonstrated that Lfx was significantly associated with a relative reduction of approximately 60% in TB incidence among adults and children who were household contacts of MDR-TB patients. In addition, Lfx as TPT for MDR-TB was associated with an increased incidence of low-grade AEs, particularly musculoskeletal AEs (RR=6.36; 95% CI=4.30–9.42; P<0.001).[20]

Early treatment discontinuation due to AEs occurred more frequently in the Lfx group than in the placebo group (RR=6.32; 95% CI=3.43–11.63; P<0.001). Nevertheless, most AEs leading to early treatment discontinuation were of low severity. Further evaluation is required to better define the risk–benefit balance, tolerability, and cost-effectiveness of MDR-TB preventive therapy across different populations.[20]

CONTACT INVESTIGATION AMONG CONTACTS OF DR-TB

Contact investigation is an activity conducted to enhance TB case detection through the early and systematic identification of individuals who have been in contact with a source of TB infection.[21] In cases of DR-TB, contact investigation is useful for identifying individuals who are indicated for DR-TB preventive therapy (DR-TPT). Contact investigation also serves as a means of active case finding for DR-TB patients, both adults and children.[22]

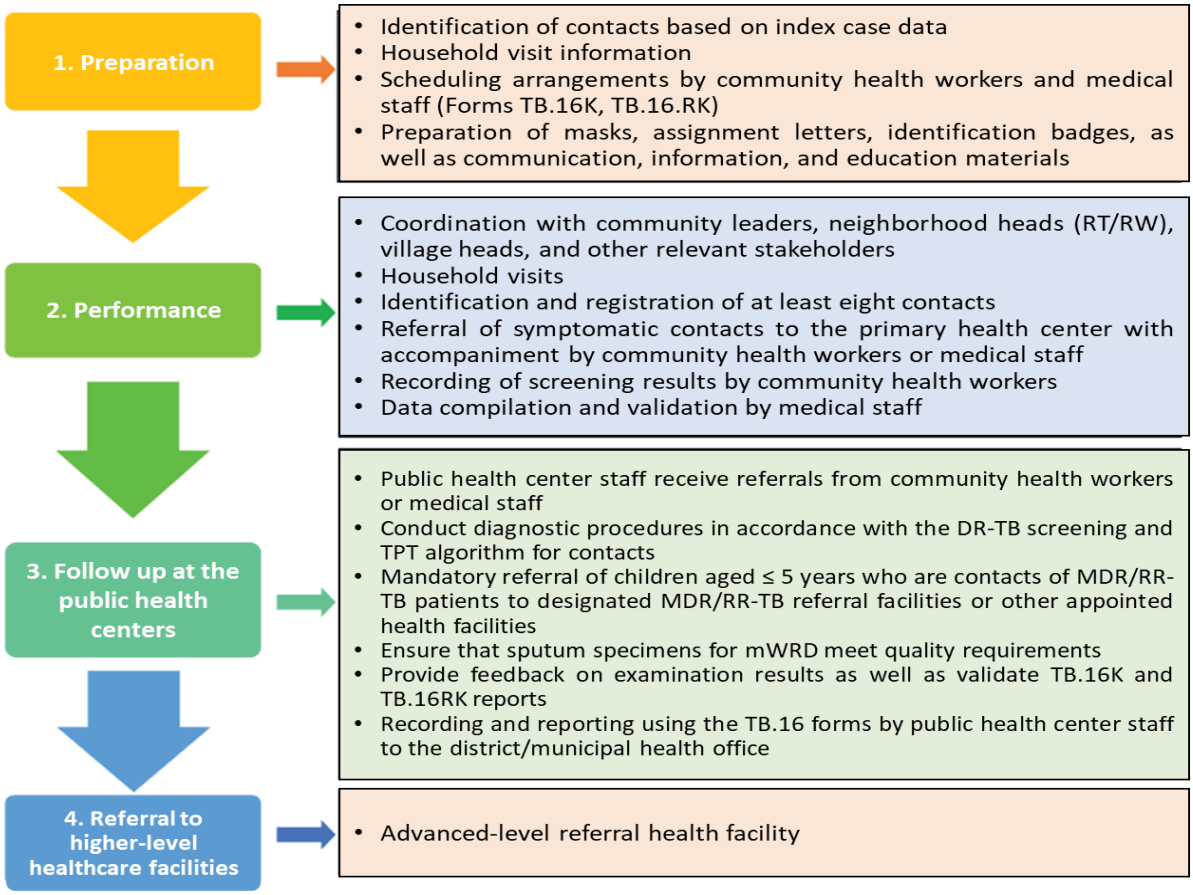

Figure 2. Series of contact investigation activities in DR-TB cases[22]

As in cases of drug-susceptible TB, the principles of contact investigation among contacts of DR-TB also refer to the 2020 Technical Guidelines for the Management of Latent TB Infection, the 2023 Technical Guidelines for the Management of TB in Children and Adolescents, and the Regulation of the Minister of Health of the Republic of Indonesia Number 67 of 2016 on Tuberculosis Control.[22] The series of contact investigation activities in DR-TB cases is illustrated in Figure 2.

Contact investigation can be conducted at both the community level and healthcare facility level. At the community level, contact investigation is carried out by community health volunteers accompanied by primary healthcare center staff. At the healthcare facility level, contact investigation is conducted by physicians together with other healthcare workers. The implementation of contact investigation involves collaboration between healthcare providers and community members, such as health volunteers, directly observed treatment (DOT) supporters, educators, and peers selected by the primary healthcare center.[22]

These selected community members receive training, orientation, official assignment letters, and identification cards from the head of the primary healthcare center. During contact investigation activities, proper recording and reporting must be carried out using TB.01 forms (TB patient treatment cards for index cases) and TB.16K forms (contact examination forms).[22]

PRINCIPLES OF TPT FOR CONTACTS OF DR-TB

The algorithm for screening and TPT among DR-TB contacts is presented in Figure 3. Symptom screening should be performed for individuals who are household contacts of DR-TB patients. If there are no TB symptoms and the contact is aged <5 years, the individual may be given DR-TPT directly, provided there are no contraindications. If there are no TB symptoms and the contact is aged ≥5 years, a chest X-ray should be performed.[23]

If the chest X-ray is suggestive of TB, an mWRD should be conducted.[23] If the mWRD result is negative or testing cannot be performed, diagnosis and follow-up should be determined by the physician based on the patient's clinical condition, with possible diagnoses being either clinical TB or non-TB. If diagnosed as clinical TB, the contact should be managed as a TB patient.[7,23]

For asymptomatic household contacts of DR-TB aged ≥5 years, if the chest X-ray is not suggestive of TB or is entirely unavailable, immunological testing via TST or IGRA is no longer required under the latest simplified guidelines. The clinical protocol routes these individuals directly to contraindication screening. In the absence of clinical contraindications (such as acute hepatic injury or severe neuropathy), a standard DR-TPT regimen should be immediately initiated. This streamlined pathway has eliminated diagnostic barriers.[7,23]

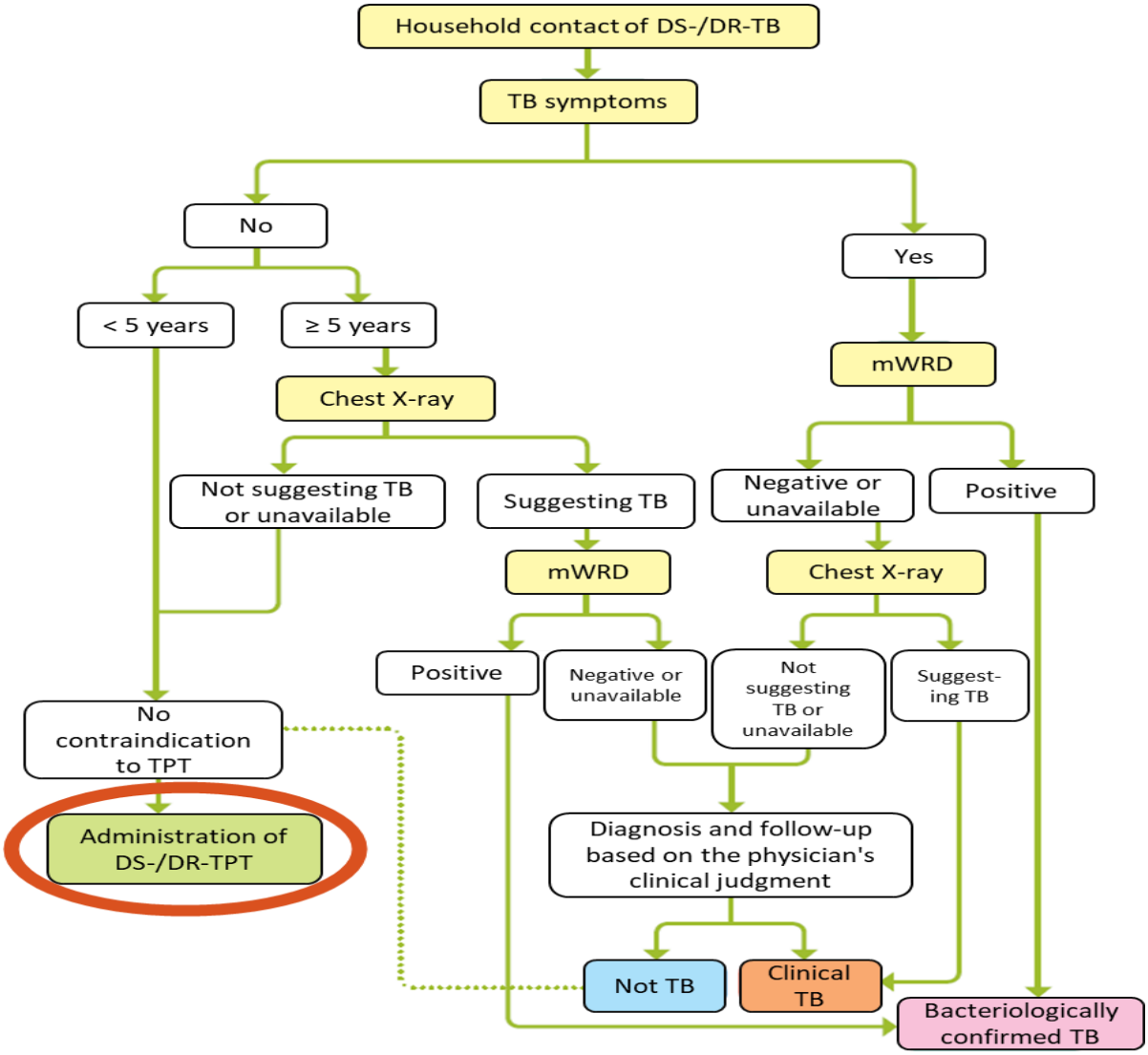

Figure 3. Screening and TPT algorithm for DR-TB contacts[23]

For household contacts of DR-TB presenting TB symptoms, an mWRD must be promptly performed. If the result is positive, the contact is managed as a bacteriologically confirmed TB case, and the drug resistance profile guides the appropriate anti-TB treatment regimen.[7,23]

Conversely, if the mWRD result is negative or unavailable, a chest X-ray should be conducted. If the chest X-ray is suggestive of TB, the contact undergoes clinical evaluation by a physician to differentiate between clinically diagnosed TB and a non-TB status. However, if the chest X-ray is not suggestive of TB or remains unavailable, the presence of active TB disease is reasonably ruled out. The contact is routed directly to TPT contraindication screening to safely initiate DR-TPT, following the same recommendation described previously for non-TB individuals.[7,23]

As for the standard recommended DR-TPT regimen, which is 6Lfx, it consists of daily administration for six months.[7,11,22] The Lfx dose should be adjusted based on the contact's age and body weight. For contacts aged <15 years, the Lfx dose range for TPT is 15–20 mg/kg body weight

per day. A 100 mg dispersible tablet formulation of Lfx is available for children. For contacts aged ≥15 years, the Lfx dose is 750 mg/day for body weight ≤45 kg, or 1 g/day for body weight >45 kg.[11] Levofloxacin can be administered with or without food.[24] Table 2 summarizes the Lfx dosing for DR-TPT.

Table 2. Dosing of Lfx for DR-TPT[11]

Age	Body weight (kg)	Dose (mg/day)
<15 years	5 - <10	150
	10 - <16	200-300
	16 - <24	300-400
	24 - <35	500-750
≥15 years	≤45	750
	>45	1,000

If drug susceptibility testing (DST) of the index case shows fluoroquinolone resistance, indicating a pre-XDR-TB case, the Lfx regimen cannot be used, and the clinical expert team should determine TPT. If DST of the index case reveals resistance to fluoroquinolones and at least one additional Group A drug (bedaquiline or linezolid), the index case is classified as an XDR-TB case.[22]

Although there are no established recommendations for TPT regimens for contacts of XDR-TB cases, the principle is to use an ATD regimen that does not include fluoroquinolones and to prioritize the use of novel drugs such as delamanid or bedaquiline. Therefore, further research is needed to identify optimal TPT regimens for contacts of XDR-TB patients.[22]

Several general principles apply to the administration and monitoring of TPT among DR-TB contacts. Patients or their parents must receive counseling before TPT initiation and provide informed consent. Close monitoring for adverse drug reactions (ADRs) is essential. During the first two months, the drug susceptibility results of the index DR-TB case should be reviewed to detect possible resistance to fluoroquinolones or other second-line ATDs. Coordination between hospital and primary healthcare staff is required to monitor DST results of the index case.[22]

During TPT administration, if TB symptoms develop, immediate re-evaluation should be performed to determine whether the contact has developed TB disease. Examples of ADRs that require monitoring include gastrointestinal disturbances, cardiac rhythm abnormalities, and headache. After completing TPT, DR-TB contacts should undergo clinical observation and follow-up every six months for at least two years. Follow-up assessments include evaluation of TB symptoms and body weight. If TB symptoms appear before the scheduled follow-up, the individual should promptly return to the DR-TB healthcare facility.[22]

COVERAGE OF TPT AMONG CONTACTS OF DR-TB IN INDONESIA

According to the 2020–2024 National Strategy for Tuberculosis Control in Indonesia, the target coverage of TPT among household contacts in Indonesia was set at 58% by 2023.[25] Unfortunately, based on the 2023 Tuberculosis Control Report published by the Ministry of Health of the Republic of Indonesia in 2024, the national coverage of TPT among household

contacts had reached only 2.6%. Although this coverage remains far below the target, an increasing trend in TPT coverage among household contacts in Indonesia has been observed from 2020 to 2023, as shown in Figure 4. The highest TPT coverage was reported in Banten Province (10.1%), while the lowest was observed in Papua Pegunungan Province (0.0%). No province in Indonesia achieved the targeted TPT coverage in 2023.[26]

Several TPT regimens are used for contacts of drug-susceptible TB, including 3HP, daily isoniazid and rifampicin for three months (3HR), daily isoniazid for six months (6H), and 1HP. The 2023 Tuberculosis Control Report indicated that the DR-TPT regimen 6Lfx, with a proportion of 1.91%, ranked fourth among the most commonly used TPT regimens in Indonesia. The proportion of the 6Lfx regimen was only one rank higher than that of the 1HP regimen (0.06%), which has not yet been included in the national TPT program and is still in the piloting phase.[26]

Regarding treatment outcomes, TPT recipients are considered to have completed treatment if they have taken at least 80% of the prescribed preventive therapy according to the duration of the regimen used. TPT completion rates among household contacts in Indonesia are reported in cohort analyses based on the number of TPT recipients reported one year earlier.[26]

In 2023, the treatment completion proportion for the DR-TPT 6Lfx regimen was 75.52%. The 6Lfx regimen was associated with the highest proportions of loss to follow-up, treatment discontinuation due to adverse events, and not evaluated outcomes, at 15.1%, 7.29%, and 2.08%, respectively. Nevertheless, no cases of treatment failure or death were reported among recipients of the DR-TPT 6Lfx regimen.[26]

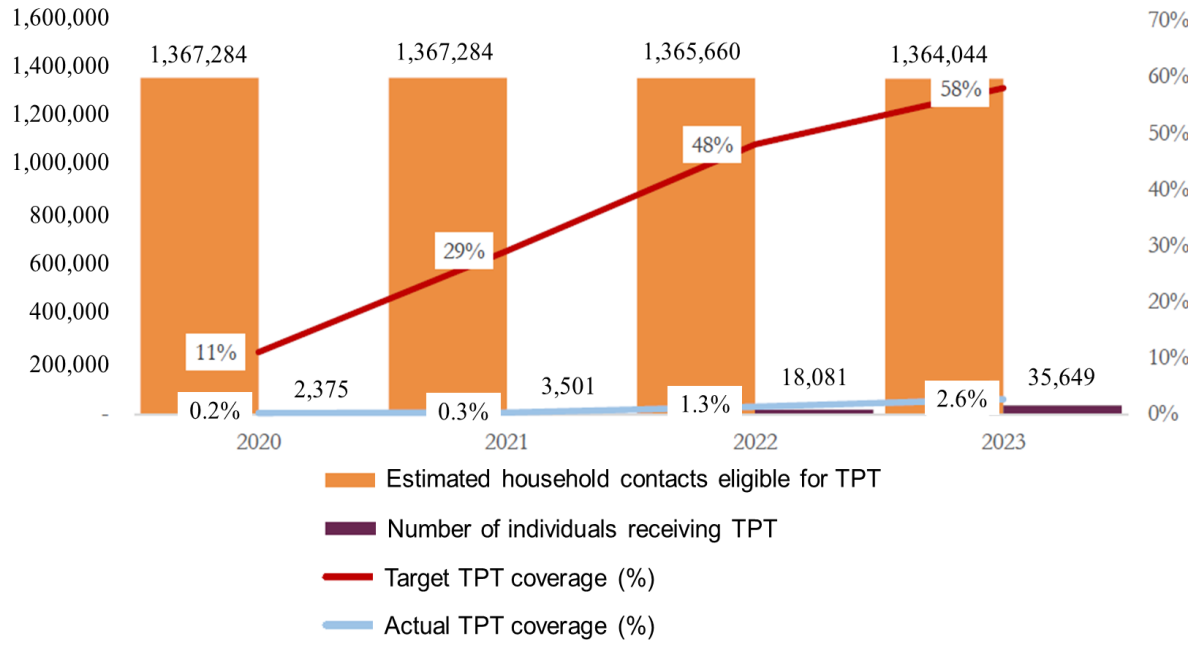

Figure 4. National coverage of TPT provision among household contacts in Indonesia, 2020–2023[26]

CONCLUSION

Robust clinical evidence from the VQUIN and TB-CHAMP trials, further strengthened by a recent individual participant data meta-analysis, demonstrates that the 6Lfx regimen significantly reduces the cumulative incidence of tuberculosis among household contacts exposed to MDR/RR-TB. This preventive regimen has shown an acceptable safety profile, with adverse events predominantly limited to mild and manageable musculoskeletal symptoms. Consequently, 6Lfx is currently recommended as the standard DR-TPT regimen for eligible household contacts across age groups.

Programmatically, active and integrated contact investigation remains a key component for excluding active TB disease and identifying candidates for preventive therapy. However, DR-TPT coverage in Indonesia remains below national targets, highlighting the need to strengthen implementation strategies, optimize healthcare delivery, and improve access to preventive care.

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