

**PHILIPPINE CLINICAL PRACTICE
GUIDELINES
FOR THE DIAGNOSIS AND TREATMENT
OF ADULT TUBERCULOSIS:
2021 UPDATE**

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Philippine College of Chest Physicians (PCCP)

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Association of Philippine Medical Colleges Foundation Inc (APMC)

Culion Foundation

Samahan ng Lusog Baga (*TB Patients' Group*)

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Philippine College of Occupational Medicine (PCOM)

Philippine College of Radiology (PCR)

Philippine College of Physicians (PCP)

Philippine Hospital Association (PHA)

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Philippine Neurological Association (PNA)

Philippine Tuberculosis Society Inc (PTSI)

TB Heals (*TB Patients' Group*)

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FUNDING AGENCY: DOH-AHEAD Program through PCHRD

CLINICAL PRACTICE GUIDELINE FOR TUBERCULOSIS

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COMMONLY USED ABBREVIATIONS

| | |
|----------|--|
| C | - Ciprofloxacin |
| CPG | - Clinical Practice Guidelines |
| CXR | - Chest x-ray |
| DOH | - Department of Health |
| DOT | - Directly Observed Therapy |
| DSSM | - Direct Sputum Smear Microscopy |
| DRTB | - Drug Resistant Tuberculosis |
| DST | - Drug Susceptibility Testing |
| E | - Ethambutol |
| EPTB | - Extrapulmonary tuberculosis |
| HIV | - Human Immunodeficiency Virus |
| H/INH | - Isoniazid |
| IGRA | - Interferon Gamma Release Assay |
| LAMP | - Loop-mediated isothermal amplification |
| Lo | - Levofloxacin |
| MDRTB | - Multi-Drug Resistant Tuberculosis |
| M | - Moxifloxacin |
| MTB/RIF | - Mycobacterium tuberculosis/Rifampicin |
| NTP-MOP | - National Tuberculosis Program Manual of Procedures |
| a. | - Ofloxacin |
| Pa | - Pretomanid |
| PI | - Protease inhibitor |
| PTB | - Pulmonary Tuberculosis |
| R/RIF | - Rifampicin |
| RR | - Rifampicin Resistance |
| RR-TB | - Rifampicin Resistant Tuberculosis |
| RFP/P | - Rifapentine |
| NNS | - Number needed to screen |
| NTPS | - National TB Prevalence Survey |
| S/STM | - Streptomycin |
| TB | - Tuberculosis |
| TB – MAC | - Tuberculosis Medical Advisory Committee |
| TST | - Tuberculin Skin Test |
| WHO | - World Health Organization |
| Z | - Pyrazinamide |

EXECUTIVE SUMMARY

Following the 2018 Manual for CPG Development [7] by the DOH as the main guide for updating the 2016 CPG for Tuberculosis, the results of over three years of search and review of evidence, consultations, consensus gathering, feedback from stakeholders, the 2021 TB CPG Task Force presents **Table 1 below to summarize the key findings of the 2021 Updates of the Clinical Practice Guidelines for the Diagnosis, Management and Prevention of TB in Adults in the Philippines**. Listed are the statements and strength of recommendations and the quality of evidence behind them.

Table 1. Summary of Recommendations of 2021 Update of TB CPGs

| Recommendations | Strength of Recommendation | Quality of Evidence |
|--|----------------------------|---------------------|
| 1. Among asymptomatic adults with risk factors for pulmonary tuberculosis, screening via chest x-ray has a 93.8% sensitivity and is recommended to identify individuals warranting further bacteriologic work-up. | Strong | Moderate |
| 2. Among asymptomatic adults without risk factors for pulmonary tuberculosis, there is NO evidence demonstrating the accuracy of chest x-ray. However, because of the high prevalence of TB locally and considering that ~10% of bacteriologically confirmed TB had neither risk factors or symptoms, a chest x-ray is recommended as a screening tool for identifying individuals warranting further bacteriologic work-up. | Strong | Moderate |
| 3. Xpert® is a more accurate test (Sn 0.74-1.00; Sp 0.82-0.99; LR+ 21.8, LR- 0.04) compared to DSSM (Sn 0.26-0.86; Sp 0.84-0.98; LR+ 10.8, LR- 0.49) and is recommended as the initial diagnostic test of choice for pulmonary TB. | Strong | High |
| 4. TB LAMP is as accurate as GeneXpert® in the diagnosis of pulmonary TB (Sn = 0.78 (95% CI 0.81-0.83); Sp = 0.98 (95% CI 0.96-0.93); LR+ = 58.2, LR- = 0.24). Due to its ability to detect rifampicin resistance, GeneXpert® is still the recommended diagnostic test of choice. In areas where Xpert is unavailable and the risk of resistance is low, TB LAMP may be used. | Weak | Very low |

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| 5. Sputum culture with drug susceptibility testing is recommended to detect resistance to other anti-TB drugs, when Xpert MTB/RIF shows rifampicin resistance. | Strong | Moderate |
| 6. Among adults clinically diagnosed with extrapulmonary TB (EPTB) based on radiologic/imaging findings, bacteriologic workup (i.e. GeneXpert® and TB culture) in addition to histopathology are recommended for the diagnosis. | Strong | Low |
| 7. There is no evidence for or against recommending empiric treatment among patients with negative bacteriologic tests but with clinical signs and symptoms of TB. Empiric treatment may be recommended for HIV-positive patients. | Weak | Very low |
| 8. Among patients with PTB, Xpert Ultra may be used in lieu of Xpert MTB/RIF as the initial test in adults with presumptive PTB. | Strong | High |
| 9. Among patients with presumptive EPTB, Xpert MTB/RIF Ultra is non-inferior to and replaces Xpert® MTB/RIF in establishing diagnosis of EPTB. | Strong | Low |
| 10a. Among adults newly diagnosed to have rifampicin-susceptible pulmonary tuberculosis, 2HRZE/4HR is still the recommended treatment regimen. | Strong | High |
| 10b. The inclusion of fluoroquinolone is not recommended. | Strong | High |
| 11a. In patients who require TB retreatment with confirmed rifampicin susceptibility by rapid drug susceptibility testing, the Category II regimen should no longer be prescribed. (WHO 2017 Good practice statement) | Good practice statement | N/A |
| 11b. On the basis of the availability of rapid drug susceptibility testing for rifampicin, the standard first-line treatment regimen of 2HRZE/4HR is recommended. Revisions in the drug regimen should be made based on the results of full drug susceptibility testing. If rifampicin resistance is present, referral to a facility for the evaluation of drug-resistant TB is recommended. | Good practice statement | N/A |

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| 12a. A shortened regimen of moxifloxacin, clofazimine, ethambutol and pyrazinamide in 40 weeks supplemented by kanamycin, isoniazid and prothionamide in the first 16 weeks among MDR/RR pulmonary tuberculosis may be recommended. | Conditional | Moderate |
| 12b An all-oral bedaquiline-containing regimen of 9–12 months duration is recommended in eligible patients with confirmed MDR/RR-TB who have not been exposed to treatment with second-line TB medicines used in this regimen for more than 1 month, and in whom resistance to fluoroquinolones has been excluded. | Conditional | Very low |
| 13. Among non-HIV adult household/close contacts of patients with active TB (regardless of bacteriologic status), either a tuberculin skin test or an interferon-gamma release assay (IGRA) may be used to screen for latent tuberculosis infection (LTBI). | Conditional | Very low |
| 14a. Among non-HIV adults diagnosed to have LTBI, isoniazid given once daily for 6 months is recommended for the treatment of LTBI among non-HIV adult patients. | Strong | Moderate |
| 14b. Rifampicin given once daily for 4 months or rifampicin + isoniazid given once daily for 3 to 4 months may be considered as alternative treatments for LTBI. | Conditional | Low to moderate |
| 14c. Directly observed therapy with Rifapentine + Isoniazid for 12 doses weekly may also be considered. | Conditional | Low |
| 15a.1. Triage of people with TB signs and symptoms, or with TB disease is recommended to reduce <i>M. tuberculosis</i> transmission to healthcare workers (including community health workers), persons attending healthcare facilities or other persons in settings with a high risk of transmission. | Conditional | Very low |
| 15a.2. Separation or isolation of people with presumed or documented infectious TB is recommended to reduce <i>M. tuberculosis</i> transmission to healthcare workers or other persons attending healthcare facilities. | Conditional | Very low |

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| 15a.3. Prompt initiation of effective TB treatment of people with TB disease is recommended to reduce <i>M. tuberculosis</i> transmission to healthcare workers, persons attending health care facilities or other persons in settings with a high risk of transmission. | Strong | Very low |
| 15a.4. Respiratory hygiene (including cough etiquette) in people with presumed or confirmed TB is recommended to reduce <i>M. tuberculosis</i> transmission to healthcare workers, persons attending healthcare facilities or other persons in settings with a high risk of transmission. | Strong | Low |
| 15b.1. Upper-room germicidal ultraviolet (GUV) systems are recommended to reduce <i>M. tuberculosis</i> transmission to healthcare workers, persons attending health care facilities, or other persons in settings with a high risk of transmission. | Conditional | Moderate |
| 15b.2. Ventilation systems (including natural, mixed-mode, mechanical ventilation and recirculated air through high-efficiency particulate air [HEPA] filters) are recommended to reduce <i>M. tuberculosis</i> transmission to healthcare workers, persons attending healthcare facilities or other persons in settings with a high risk of transmission. | Conditional | Very low |
| 15c.1. Particulate respirators, within the framework of a respiratory protection program, are recommended to reduce <i>M. tuberculosis</i> transmission to healthcare workers, persons attending healthcare facilities or other persons in settings with a high risk of transmission. | Conditional | Very low |
| 16. Among patients with TB-HIV co-infection, rifampicin-containing regimens are comparable to non-rifampicin based regimens in terms of effectiveness and safety. | Weak | Very low |
| 17. Among HIV patients with TB co-infection who are on rifampicin-based regimens, caution should be exercised when increasing the dose of lopinavir/ritonavir. Increasing the dose may increase the risk of adverse events without reducing virologic failure. | Weak | Very low |

Table 2. Comparison of 2016 Statement with the New 2021 Recommendations

| | 2016 Statement | 2021 Recommendation |
|---|---|---|
| QUESTIONS ON SCREENING | | |
| Q1. Among adults with no symptoms but with risk factors , how accurate is screening by chest x-ray in identifying individuals warranting further bacteriologic work-up? | Together with a good clinical history, a good quality chest xray film is needed to initially guide the clinician in the identification of presumptive PTB for further bacteriologic confirmation. | Among asymptomatic adults with risk factors for pulmonary tuberculosis, screening via chest x-ray has a 93.8% sensitivity and is recommended to identify individuals warranting further bacteriologic work-up. |
| Q2. Among adults with no symptoms and no risk factors, how accurate is screening by chest x-ray in identifying individuals warranting further bacteriologic work-up? | | Among asymptomatic adults without risk factors for pulmonary tuberculosis, there is NO evidence demonstrating the accuracy of chest x-ray. However, because of the high prevalence of TB locally and considering that ~10% of bacteriologically confirmed TB had neither risk factors or symptoms, a chest x-ray is recommended as a screening tool for identifying individuals warranting further bacteriologic work-up. |
| QUESTIONS ON DIAGNOSIS | | |
| Q3. Among adults with presumptive pulmonary TB (PTB), how accurate is Sputum Xpert MTB/Rif compared to sputum DSSM in establishing diagnosis of Pulmonary TB? | Initial diagnostic test among presumptive TB pooled sensitivity of 89% and specificity of 99% | Xpert® is a more accurate test (Sn 0.74-1.00; Sp 0.82-0.99; LR+ 21.8, LR- 0.04) compared to DSSM (Sn 0.26-0.86; Sp 0.84-0.98; LR+ 10.8, LR- 0.49) and is recommended as the initial diagnostic test of choice for pulmonary TB. |
| Q4. Among adults with presumptive PTB, how accurate is Sputum TB LAMP compared to Xpert MTB/Rif in establishing initial diagnosis of Pulmonary TB? When is the sputum TB LAMP a preferred test over Xpert MTBRif? | No mention | TB LAMP is as accurate as GeneXpert® in the diagnosis of pulmonary TB (Sn = 0.78 (95% CI 0.81-0.83); Sp = 0.98 (95% CI 0.96-0.93); LR+ = 58.2, LR- = 0.24). Due to its ability to detect rifampicin resistance, GeneXpert® is still the diagnostic test of choice. In areas where Xpert is unavailable and the risk of resistance is low, TB LAMP may be used. |

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| Q5. Among adults with presumptive pulmonary TB (PTB), should sputum TB culture with drug susceptibility testing (DST) be done with Xpert MTB/Rif? | TB culture remains the gold standard for TB Diagnosis. If available, sputum TB 16tandar can be requested in the diagnostic workup of TB specifically in ruling out NTM | Sputum culture with drug susceptibility testing is recommended to detect resistance to other anti-TB drugs, when Xpert MTB/RIF shows rifampicin resistance. |
| Q6. Among adults clinically diagnosed with EPTB based on imaging studies, should further bacteriologic workup be done versus histopathology alone to establish diagnosis of EPTB? | Similar to PTB, diagnostic bacteriologic confirmation of EPTB includes direct microscopy, TB culture and Xpert MTB/Rif. | Among adults clinically diagnosed with EPTB based on radiologic/imaging findings, bacteriologic workup (i.e. GeneXpert® and TB culture) in addition to histopathology are recommended for the diagnosis. |
| Q7. Among adults whose bacteriologic workup for active TB disease is negative, how effective is empiric treatment based on physician's clinical judgement in achieving treatment success and reducing relapse and mortality? | No mention | There is no evidence for or against recommending empiric treatment among patients with negative bacteriologic tests but with clinical signs and symptoms of TB. Empiric treatment may be recommended for HIV-positive patients. |
| Q8. Among adults with presumptive pulmonary TB (PTB), how accurate is Sputum Xpert MTB/Rif compared to sputum Xpert Ultra in establishing diagnosis of Pulmonary TB? | No mention | Among patients with PTB, Xpert Ultra may be used in lieu of Xpert MTB/RIF as the initial test in adults with presumptive PTB. |
| Q9. Among adults with presumptive extrapulmonary TB (EPTB), how accurate is Xpert MTB/Rif compared to Xpert Ultra in establishing diagnosis of extrapulmonary TB? | No mention | 9. Among patients with presumptive EPTB, Xpert MTB/RIF Ultra is non-inferior to and replaces Xpert® MTB/RIF in establishing diagnosis of EPTB. |

QUESTIONS ON TREATMENT OF TB

| | | |
|--|---|---|
| Q10. Among adults newly diagnosed to have rifampicin-susceptible PTB, is standard 2HRZE/4HR still the recommended treatment regimen to optimize treatment success/ completion and reduce | 2HRZE/4HR (Category 1) for PTB and EPTB except maninges, bones or joints. | 10a. Among adults newly diagnosed to have rifampicin-susceptible PTB, 2HRZE/4HR is still the recommended treatment regimen. |
|--|---|---|

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|--|---|---|
| risk for treatment failure, relapse, and mortality compared to HRZE plus fluoroquinolone? | | 10b. The inclusion of fluoroquinolone is not recommended. |
| Q11. Among adults who need retreatment for tuberculosis with known susceptibility to rifampicin, is the standard 2HRZE/4HR the recommended regimen to optimize treatment success/ completion and reduce risk for treatment failure, relapse and mortality compared to 2HRZES/1HRZE/5HRE or immediate referral to PMDT? | All retreatment cases should be immediately be referred to the nearest Xpert MTB/Rif facility for rifampicin susceptibility testing. Category II regimen (2HRZES/HRZE/5HRE) should only be given among confirmed Rifampicin sensitive retreatment cases or in circumstances where Xpert MTB/Rig services cannot be performed | 11a. In patients who require TB retreatment with confirmed rifampicin susceptibility by rapid drug susceptibility testing, the Category II regimen should no longer be prescribed. (WHO 2017 Good practice statement) 11b. On the basis of the availability of rapid drug susceptibility testing for rifampicin, the standard first-line treatment regimen of 2HRZE/4HR is recommended. Revisions in the drug regimen should be made based on the results of full drug susceptibility testing. If rifampicin resistance is present, referral to a facility for the evaluation of drug-resistant TB is recommended. |
| Q12. Among persons with multi-drug resistant or rifampicin resistant-TB, is the standard shortened regimen as effective as WHO conventional multi-drug or rifampicin-resistant regimens? | All DR-TB patients should be managed under programmatic setting. Management of DR TB involves the use of second line drugs that are more expensive, less effective and more toxic for at least 18 months. Management outside the proper framework will only lead to further drug resistance. | 12a. A shortened regimen of moxifloxacin, clofazimine, ethambutol and pyrazinamide in 40 weeks supplemented by kanamycin, isoniazid and prothionamide in the first 16 weeks among MDR/RR pulmonary tuberculosis may be recommended. 12b An all-oral bedaquiline-containing regimen of 9–12 months duration is recommended in eligible patients with confirmed MDR/RR-TB who have not been exposed to treatment with second-line TB medicines used in this regimen for more than 1 month, and in whom resistance to fluoroquinolones has been excluded. |

QUESTIONS ON DIAGNOSIS AND MANAGEMENT OF LATENT TB

| | | |
|---|---|---|
| Q13. Should non-HIV adult household/close contacts of active TB cases (regardless of bacteriologic status) with no active disease undergo the interferon gamma release assay (IGRA) or tuberculin skin test (TST) to identify latent TB? Is IGRA more accurate than standard TST? | Tuberculin skin test (TST) is the preferred screening test for LTBI in resource limited setting like the Philippines. | Among non-HIV adult household/close contacts of patients with active TB (regardless of bacteriologic status), either a tuberculin skin test or an interferon-gamma release assay (IGRA) may be used to screen for latent tuberculosis infection (LTBI). |
| Q14. Will treatment of latent TB infection (LTBI) of non-HIV adults diagnosed to have LTBI, using any of 9H, 6H, 3-4HR, 4R or 12 doses weekly INH-Rifapentine vs no treatment be effective in reducing the risk for conversion of latent TB to active TB? | Isoniazid 300mg daily for 6 months under supervised treatment is the recommended regimen for LTBI. | 14a. Among non-HIV adults diagnosed to have LTBI, isoniazid given once daily for 6 months is recommended for the treatment of LTBI among non-HIV adult patients. 14b. Rifampicin given once daily for 4 months or rifampicin + isoniazid given once daily for 3 to 4 months may be considered as alternative treatments for LTBI. 14c. Directly observed therapy with Rifapentine + Isoniazid for 12 doses weekly may also be considered. |

QUESTIONS ON PREVENTION AND INFECTION CONTROL FOR TB

| | | |
|--|---|--|
| Q15. Among high risk or special settings, what are the recommended measures to prevent transmission of TB? | Isolation is recommended for the ff cases: Bacteriologically confirmed PTB not started or are in early stages of TB treatment Presumptive DRTB or known MDR/XDR TB Documented HIV/ADIS cases or those with strong clinical evidence for HIV/AIDS | 15a.1. Triage of people with TB signs and symptoms, or with TB disease is recommended. 15a.2. Separation or isolation of people with presumed or documented infectious TB 15.a.3 Prompt Initiation of TB Treatment 15.a.4 Respiratory hygiene 15.b.1 Upper-room germicidal ultraviolet (GUV) systems are recommended 15b.2. Ventilation systems (including natural, mixed-mode, mechanical ventilation and recirculated air through high- |
|--|---|--|

| | | |
|--|--|--|
| | | efficiency particulate air [HEPA] filters) are recommended. 15c.1. Particulate respirators are recommended. |
|--|--|--|

QUESTIONS ON TB-HIV COINFECTION

| | | |
|---|------------|--|
| Q16. Among patients with TB-HIV co-infection, how effective and safe are rifampicin-containing regimens in terms of clinical cure and adverse reactions compared to non-rifampicin based regimens? | No mention | 16. Among patients with TB-HIV co-infection, rifampicin-containing regimens are comparable to non-rifampicin based regimens in terms of effectiveness and safety. |
| Q17. Among patients with TB-HIV co-infection who are on second line ART (lopinavir-ritonavir) and rifampicin-based regimen, should the dose of ART (lopinavir-ritonavir) be boosted or not to reduce clinical failure and adverse events? | No mention | 17. Among HIV patients with TB co-infection who are on rifampicin-based regimens, caution should be exercised when increasing the dose of lopinavir/ritonavir. Increasing the dose may increase the risk of adverse events without reducing virologic failure. |

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INTRODUCTION

Tuberculosis (TB) continues to be the leading cause of death from an infectious disease globally.[1] In the 2019 Global TB report [2], the Philippines now ranks 4th among high TB-burden countries with an incidence rate of 554 per 100, 000 population. The recent 2016 National TB Prevalence Survey (NTPS) also reported alarmingly high TB prevalence rates at 434 per 100,000 (95% C.I. 350–518) and 1,159 per 100,000 (95% C.I. 1,016–1,301), respectively, for smear positive and bacteriologically confirmed TB among those age ≥15 years old.[3]

In 2014, the World Health Organization (WHO) declared the urgent need to unite and accelerate efforts to end TB in the next 20 years.[4] This new global strategy envisions a world free of TB with zero deaths, zero disease and zero suffering due to TB by the year 2035. To achieve these ambitious goals, the End TB Strategy calls on all countries to embody specific principles, actions and strategies. The End TB Strategy has three pillars which highlight the following: (1) patient-centered care for all people with TB; (2) the use of bold policies and supportive systems; and (3) innovations and research. To successfully implement the End TB Strategy, the cascade of care (also called the continuum of care) model will be adapted by countries to assure and evaluate patient retention across sequential stages of TB care. [5] The supportive systems in the pillars should be able to navigate patients seamlessly through the screening, diagnosis, treatment, prevention and control of TB, whether in public or private healthcare. Additionally, the Department of Health (DOH) has plans to transform the healthcare delivery system to follow the Universal Health Care (UHC) model by January 2020. It is in this context that the 2021 Clinical Practice Guidelines (CPG) TB Update was developed.

Objectives of the 2021 TB CPG Update

This TB CPG has the following objectives:

- 1) To update the 2016 Philippine Clinical Practice Guidelines on TB in Adults with recent medical evidence (2015 -2020) in light of new developments at the global level and contextualized to the national setting;
- 2) To guide clinicians and other TB personnel regarding the current standards of care related to the screening, diagnosis, treatment and prevention of TB among both immunocompetent and high-risk adult clinical groups in the Philippines;
- 3) To harmonize with and complement the most recent NTP-MOP on TB.
- 4) To reduce practice variability among public and private health practitioners and improve detection, treatment and other clinical outcomes in adult patients diagnosed with tuberculosis.

Scope and Target Population of Update: New Evidence since the 2016

This document is **intended to update the 2016 Philippine Clinical Practice Guidelines** on the Diagnosis, Treatment and Prevention of TB [6]. Therefore, reference to the 2016 CPG is still advised for issues which are stable, well-grounded on strong evidence and continues to be current acceptable practice. On the other hand, the new 2021 CPG TB Update addresses identified issues where previous unresolved questions or controversies were present and now reports new findings which form the basis for new recommendations affecting current practices on TB care.

Additionally this 2021 update realigns the Philippine CPG with the End TB strategy's successful continuum of care, as well as DOH's National TB Program (NTP) 6th Manual of Procedures (MOP) which was released in 2020. It thus reduces the differences in processes between the previous CPG and the current MOP.

The 2021 Update is also intended to prepare TB health providers with guidance aligned to the Republic Act. No. 11223, also known as the Universal Health Care (UHC) Act,

Being an update, publications which were included in the previous 2006 and 2016 versions of the Philippine CPG were not reiterated anymore. Thus the evidence reviewed in this document are from publications and other materials which have been released from 2015 to 2019.

This 2021 Update covers only the Management, Diagnosis and Treatment of the adult population in the country. Best practices among both immunocompetent and immunocompromised individuals in the adult population are discussed.

Intended Users of this Update:

This document is intended for practicing clinicians and other healthcare professionals involved in the holistic care of adult patients with presumptive or confirmed TB. These include physicians of all specialties, nurses, medical technologists and other paramedical staff caring for TB patients, as well as other health practitioners indirectly involved in TB care such as program managers, hospital administrators, educators, policy makers, diagnostic and therapeutic product developers and similar professionals. This update was written for use in both private and public health systems. Details of the available evidence have been painstakingly included here for greater understanding of medical and paramedical students, trainees and other practitioners of modern medicine.

Developments and Challenges Encountered during the COVID-19 Pandemic

While most of the preliminary work on the evidence review and consensus were completed pre-pandemic, the occurrence of the COVID-19 in 2020 led to the major delay in the public consultations and presentations to stakeholders, necessary steps in CPG development.

METHODOLOGY

The process outlined in the 2018 Manual for CPG Development [7] by the DOH was followed including preparation and prioritization of key clinical questions, appraisal and synthesis of evidence, development of recommendations, external review and revision, and dissemination.

Following the international standards and the DOH Manual for CPG Development [1], this 2021 TB CPG Update was operationalized in four phases: 1) preparation and prioritization, 2) CPG generation, 3) CPG appraisal, and 4) implementation.

I. Preparation, Prioritization and Organization of the Process

Steering Committee. In the preparation and prioritization phase, the Steering Committee for the TB CPG Update was convened on the second quarter of 2019. It was composed of five members, all of whom were clinicians and a past or present president of any of the main proponent professional societies (PhilCAT, PSMID, PCCP) and/or were lead chairpersons in the previous versions of the 2006 and 2016 TB CPGs. The Steering Committee was tasked to oversee the 2021 guideline development process. It set the CPG objectives, scope, target audience, and clinical questions. In consultation with their respective professional societies and other relevant groups, the committee identified and prioritized key clinical questions in a meeting held on November 19, 2019. They listed the burning key issues to be included in the TB CPG update. They also identified and formed the working groups who would be involved in creating the evidence base and finalizing the recommendations for each clinical question.

II. Evidence Generation and Synthesis

Technical Working Group. Immediately after, the Technical Working Group (TWG) was formed consisting of six committees working on 1) screening; 2) diagnosis; 3) treatment; 4) prevention and control of TB; 5) drug resistant TB; and 6) latent TB.

Each committee commissioned evidence review experts (ERE) who searched, appraised, and synthesized relevant published or unpublished local and/or foreign medical studies from 2015 to 2019.

Formulation of Clinical Questions. The Steering Committee formulated the guideline questions structured in PICO format (population, intervention, comparator - control, and outcome). A complete list of the guideline questions in PICO format is presented in Table 3 below.

Table 3. List of Questions Identified by the Steering Committee to be Urgent and Relevant to the current practice of Tuberculosis Care.

| |
|--|
| QUESTIONS ON SCREENING |
| 1. Among adults with no symptoms but with risk factors , how accurate is screening by chest x-ray in identifying individuals warranting further bacteriologic work-up? |
| 2. Among adults with no symptoms and no risk factors, how accurate is screening by chest x-ray in identifying individuals warranting further bacteriologic work-up? |
| QUESTIONS OF TB DIAGNOSIS |
| Q3. Among adults with presumptive pulmonary TB (PTB), how accurate is Sputum Xpert MTB/Rif compared to sputum DSSM in establishing diagnosis of Pulmonary TB? |
| Q4. Among adults with presumptive pulmonary TB (PTB), how accurate is Sputum TB LAMP compared to Xpert MTB/Rif in establishing initial diagnosis of Pulmonary TB? When is the sputum TB LAMP a preferred test over Xpert MTB/ Rif? |
| Q5. Among adults with presumptive pulmonary TB (PTB), should sputum TB culture with drug susceptibility testing (DST) be done with Xpert MTB/Rif? |
| Q6. Among adults clinically diagnosed with extrapulmonary TB (EPTB) based on imaging studies, should further bacteriologic workup be done versus histopathology alone to establish diagnosis of EPTB? |
| Q7. Among adults whose bacteriologic workup for active TB disease is negative, how effective is empiric treatment based on physician's clinical judgement in achieving treatment success and reducing relapse and mortality? |
| Q8. Among adults with presumptive pulmonary TB (PTB), how accurate is Sputum Xpert MTB/Rif compared to sputum Xpert Ultra in establishing diagnosis of Pulmonary TB? |
| Q9. Among adults with presumptive extrapulmonary TB (EPTB), how accurate is Xpert MTB/Rif compared to Xpert Ultra in establishing diagnosis of extrapulmonary TB? |
| QUESTIONS ON TREATMENT OF TB |
| Q10. Among adults newly diagnosed to have rifampicin-susceptible PTB, is standard 2HRZE/4HR still the recommended treatment regimen to optimize treatment success/ completion and reduce risk for treatment failure, relapse, and mortality compared to HRZE plus fluoroquinolone? |
| Q11. Among adults who need retreatment for tuberculosis with known susceptibility to rifampicin, is the standard 2HRZE/4HR the recommended regimen to optimize treatment success/ completion and reduce risk for treatment failure, relapse and mortality compared to 2HRZES/1HRZE/5HRE or immediate referral to PMDT? |
| Q12. Among persons with multi-drug resistant or rifampicin resistant-TB, is the standard shortened regimen as effective as WHO conventional multi-drug or rifampicin-resistant regimens? |

DIAGNOSIS AND MANAGEMENT OF LATENT TB

Q13. Should non-HIV adult household/close contacts of active TB cases (regardless of bacteriologic status) with no active disease undergo the interferon gamma release assay (IGRA) or tuberculin skin test (TST) to identify latent TB? Is IGRA more accurate than standard TST?

Q14. Will treatment of latent TB infection (LTBI) of non-HIV adults diagnosed to have LTBI, using any of 9H, 6H, 3-4HR, 4R or 12 doses weekly INH-Rifapentine vs no treatment be effective in reducing the risk for conversion of latent TB to active TB?

PREVENTION AND INFECTION CONTROL FOR TB

Q15. Among high risk or special settings, what are the recommended measures to prevent transmission of TB?

TB-HIV COINFECTION

Q16. Among patients with TB-HIV co-infection, how effective and safe are rifampicin-containing regimens in terms of clinical cure and adverse reactions compared to non-rifampicin based regimens?

Q17. Among patients with TB-HIV co-infection who are on second line ART (lopinavir-ritonavir) and rifampicin-based regimen, should the dose of ART (lopinavir-ritonavir) be boosted or not to reduce clinical failure and adverse events?

Search Strategy, Evidence Selection and Data Synthesis. The EREs for each of the six committees started to search the evidence based on their specific assigned questions. An independent literature searches were systematically performed by the designated ERE for each guideline question. Electronic search was conducted in at least two databases such as Cochrane Database, MEDLINE via PubMed, HERDIN, and clinical trial registries up to November 2019. Other databases such as CENTRAL and Google Scholar were searched when needed. Relevant local databases and websites of medical societies were also utilized in the search. Keywords were based on PICO (MeSH and free text) set for each question. In general the search terms "tuberculosis", "TB", "Kochs Disease", "Koch's Disease", "Koch Disease", "Mycobacterium tuberculosis infection" combined with pertinent keywords based on the question listed in Table 3. Related articles were also examined. Unpublished data were also sourced, especially from local researches. Assistance from librarians, clinical epidemiologists, and statisticians was sought.

The criteria for inclusion of evidence into the data synthesis include the following: directness, methodological validity, results, and applicability of each article. RevMan, STATA, and GRADEPro were used for the quantitative synthesis of important clinical outcomes for each question. The Quality of Evidence was assessed using the GRADE approach. (2)

Creation of the Evidence Summaries The EREs assessed the quality of evidence as high, moderate, low or very low based on methodologic quality of the studies, directness of the evidence, heterogeneity of the study results, precision of the estimates of effect of critical outcomes and publication bias according to the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach seen in Table 4 .[8] When relevant, existing CPGs were appraised and adapted. Together with the committee members, they summarized the evidence, and drafted the initial recommendations.

The evidence summaries were then prepared for presentation to the consensus panel members to finalize the recommendations.

Table 4. Basis for Assessing the Quality of the Evidence using GRADE Approach

| Certainty of Evidence | Interpretation |
|--|--|
| High | We are very confident that the true effect lies close to that of the estimate of the effect |
| Moderate | We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different |
| Low | Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect |
| Very Low | We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect |
| Factors that lower quality of the evidence are: | |
| <ul style="list-style-type: none"> ● Risk of bias ● Important inconsistency of results ● Some uncertainty about directness ● High probability of reporting bias ● Sparse data/Imprecision ● Publication bias | |
| Additional factors that may increase quality are: | |
| <ul style="list-style-type: none"> ● All plausible residual confounding, if present, would reduce the observed effect. ● Evidence of a dose-response gradient ● Large effect | |

III. Development of Evidence-based Recommendations by Consensus

Creation of the CPG Consensus Panel. Simultaneously, the Consensus Panel was also formed. The Steering Committee convened the Consensus Panel (CP), considering possible conflicts of interests of each panel member. To ensure fairness and transparency, the composition was guided by the DOH manual (1). The key stakeholders included policymakers, patient advocates, and physicians. Thus, the 2021 CPG Consensus Panel was composed of representatives invited from relevant professional societies, academic institutions, agencies, and patient groups (Samahan ng Lusog Baga and TB Heals). Each stakeholder group had at least one key representative and backup member to anticipate possible unforeseen absences. The conflicts of interest of the panel members were declared and assessed by the Steering Committee.

The consensus panel representatives were tasked to review the evidence summaries and develop recommendations during the *en banc* meeting. In the meeting, they prioritized critical and important outcomes; discussed necessary considerations revolving around the recommendations and voted on each recommendation and its strength.

Formulation of the Recommendations. Draft recommendations were formulated based on the quality of evidence, trade-offs between benefit and harm, cost-effectiveness, applicability, feasibility, equity, resources and uncertainty due to research gaps.

The strength of each recommendation (i.e. strong or weak) was determined by the panel considering all the factors mentioned above. Strong recommendation means that the panel is “confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects” while weak recommendation means that the “desirable effects of adherence to a recommendation probably outweigh the undesirable effect but is not confident.” (4)

En Banc Meeting for Consensus Development. On December 7, 2019, the evidence summaries with draft recommendations were presented to the multidisciplinary Consensus Panel, which also included representatives of TB patients (Samahan ng Lusog Baga and TB Heals). This was held at the Function Room of the Mezzanine of Tropicana Suites, LM Guerrero, Malate, Manila. After the evidence was presented by the technical working teams for each of the clinical guideline questions, each of the panelists, including the TB patients, were encouraged to raise their queries, feedback, concerns and other issues. The panelists deliberated on the direction and strength of the recommendations based on the balance between desirable and undesirable effects, quality of evidence, patients’ values and preferences, cost and access to tests or interventions, and potential implications to patients, clinicians, and policy makers, as outlined in the GRADE approach. They then voted for or against each of the draft recommendations and rated the strength of the recommendations as strong, weak or conditional. To reach consensus, statements should have received at least 70% votes from the consensus panel members. Major or minor reservations were addressed through discussion.

The recommendation for each question and its strength was determined through voting. A consensus decision was reached if 75% of all CP members agreed. (2) If consensus was not reached in the first voting, questions, and discussions were encouraged. Two further rounds of voting on an issue were conducted. Evidence-based draft recommendations were also revised based on input arrived at by consensus in the *en banc* discussions.

Managing Conflicts of Interest. The Steering Committee (SC) facilitated the whole CPG formulation process, but their members had no direct participation in assessing and synthesizing the evidence, generating the evidence summaries and evidence-based draft recommendations of the Evidence Review Experts, and voting on final recommendations during the *en banc* consensus panel review. They invited the relevant organization to nominate individuals who can become part of the consensus panel.

Each nominee was required to fill out and sign a declaration of interest form and submit their curriculum vitae. The SC screened the nominees for any possible conflict of interest that may bias their decisions. Those with significant potential COI based on the decision of the COI Committee were not allowed to vote during the *en banc* meeting but fully participated in the panel discussions. See Annex E.

External Review. The second draft which was the product of the consensus meeting was routed for external review by four independent external reviewers who were also present during the consensus panel meeting. Each reviewed the draft guidelines on the content, clarity, acceptability, applicability and feasibility of the recommendations. Their feedback was taken into consideration by the steering committee prior to finalizing the CPG

The draft was finalized by the steering committee for presentation to stakeholders and future users in medical conferences. The final recommendations are summarized in Table 1. The finalized draft was presented in public for further feedback. It was first presented in full during the 2020 PSMID Annual Convention, and subsequently in the 2021 Philippine College of Physicians Annual Convention, both of which targeted the expected end-users of the guidelines. Comments and questions were encouraged and considered in the finalization of the draft.

Up to this point in the CPG development, the CPG team has worked independently of the funding body (DOH)..

Submission to the Department of Health for Approval. The final recommendations were first submitted in April 2023 and then re-submitted on November 2023 to answer comments of reviewers.

Guideline Dissemination. The updated guidelines are being disseminated to all training institutions for implementation. As soon as approved, electronic version will be uploaded in the websites of PSMID, PhilCAT and PCCP. Printed copies of the guidelines will also be distributed to medical societies as well as for posting online for wider coverage.

Guideline Monitoring and Updating. A standard presentation portfolio has been created for easy access and easier dissemination. Its use will be monitored by committees within the PhilCAT, the PSMID and training institutions under the PCP. Percent compliance to the 2021 TB CPG will be monitored through health facilities with training residency and fellowship programs. Programs found to have 70% compliance or lower will undergo re-orientation by any of main professional societies. On the other hand, the compliance to the mandatory notification can be monitored using the ITIS.

Because of the dynamic and vigorous TB research taking place, there is always new information which needs to be appraised and shared. The next update of the TB CPGs is set to begin starting 2024. The Steering Committee has started the discussion about how the CPG could be updated in a more efficient manner. The template of the COVID-19 Living Guidelines where the evidence is reviewed almost as soon as it becomes available, and recommendations are made accordingly appears to address the concerns about timeliness and relevance of CPGs. Thus, the approach to maintain the TB CPG as a Living Guideline is preferred and likely to be pursued in the next several years.

Sponsorship and Funding. The development of this guideline was funded by the Philippine Department of Health (DOH). Supplementary budget for printing has been approved by the PBSP.

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Quick Guide to Users of this Update On How To Interpret The Evidence

A. Interpreting Evidence on Screening Program

Note: This quick guide on how to read evidence on diagnostic tests will be helpful for Questions 1 and 2.

The criteria for evaluating screening programs are:

1. The burden of illness must be high.
2. The tests must be accurate.
3. Early treatment must be more effective than late treatment.
4. Diagnostic tests and early treatment must be safe.
5. The cost of the screening strategy must be commensurate to the potential benefit.

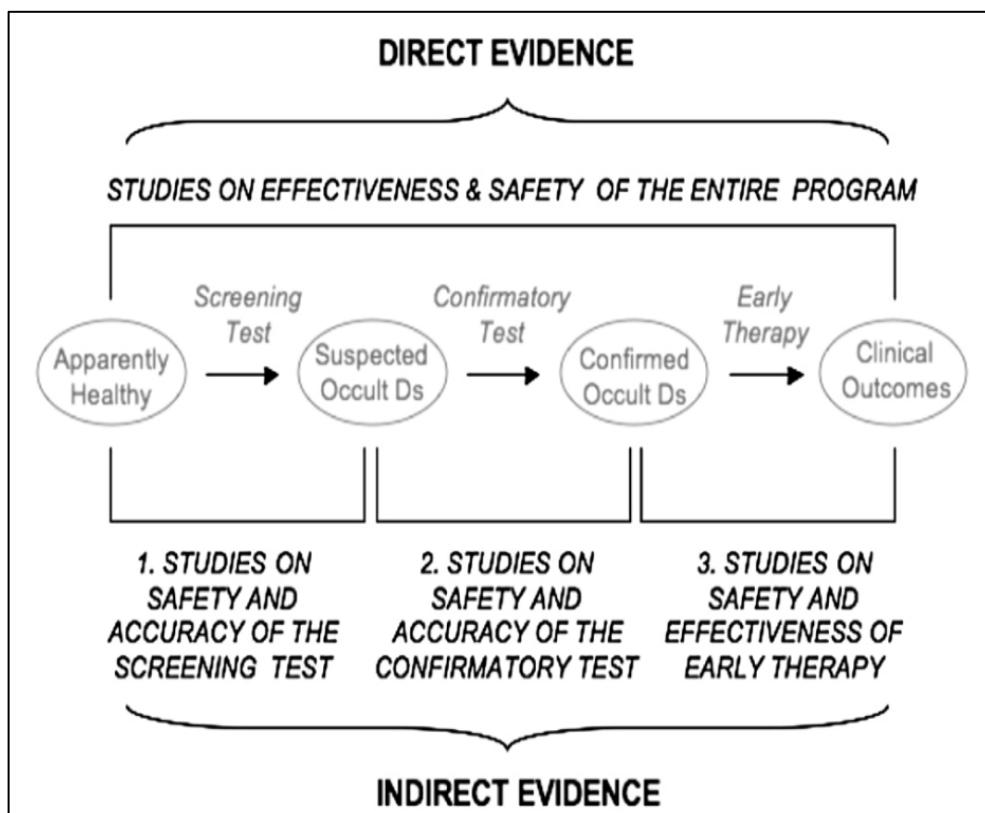


Figure 1. Admissible evidence for evaluation of a screening program³

³ Adapted from Dans AL, Dans LF and Silvestre MA. Painless Evidence – Based Medicine. 2nd edition. 2016.

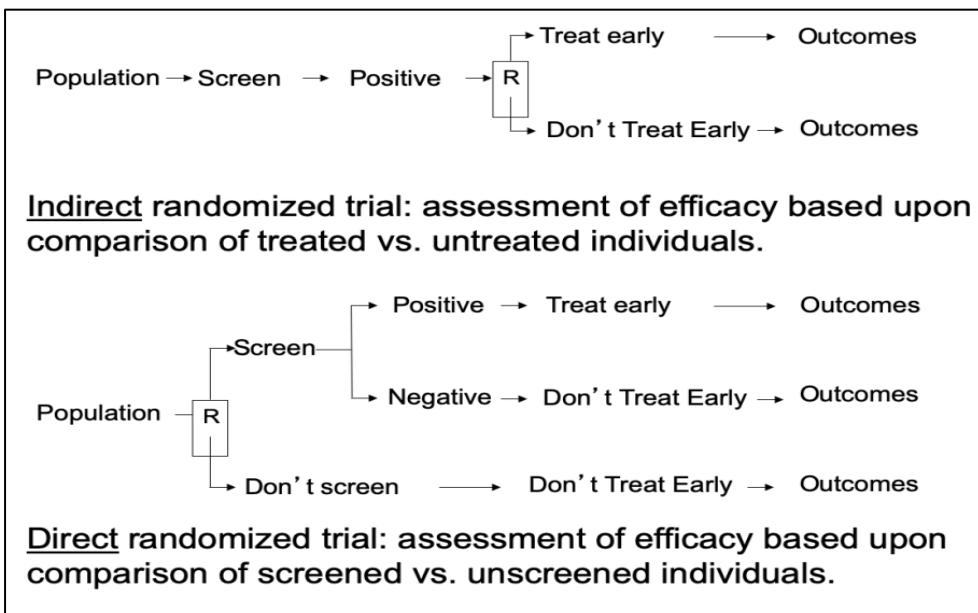


Figure 2. Indirect (A) and direct (B) trials of the effectiveness of screening¹

B. Interpreting Evidence on Diagnosis

Note: This quick guide on how to read and interpret evidence on diagnostic tests will be helpful for Questions 3 to 9.

There are four conventional ways of determining how accurate a test is. These measures are adequate when comparing results of two tests using a 2 x 2 table.

- **Sensitivity (sn)** refers to the proportion of persons with disease who correctly have a positive test.
- **Specificity (sp)** refers to the proportion of persons with no disease who correctly have a negative test.
- **Positive predictive value (PPV)** is the proportion of persons with a positive test who correctly turn out to have disease
- **Negative predictive value (NPV)** is the proportion of persons with a negative test who correctly turn out to have no disease

Table 5. Interpreting likelihood ratios (LRs)

| Likelihood ratio | Likelihood of disease | Grade of likelihood |
|------------------|-----------------------|--|
| LRs > 1.0 | INCREASE | LR<3.0 (close to 1.0) – weakly positive LR=3.0-10.0 – moderately positive LR>10.0 is strongly positive |
| LRs < 1.0 | DECREASE | LR >0.3 (close to 1.0) – weakly negative LR=0.3-0.1 – moderately negative LR<0.1 strongly negative |

However, if we need to evaluate a test with multi-level results, we need a “2 x n” table and compute for ***likelihood ratio (LR)***. LR is a measure of how much the likelihood of the disease changes given a test result.

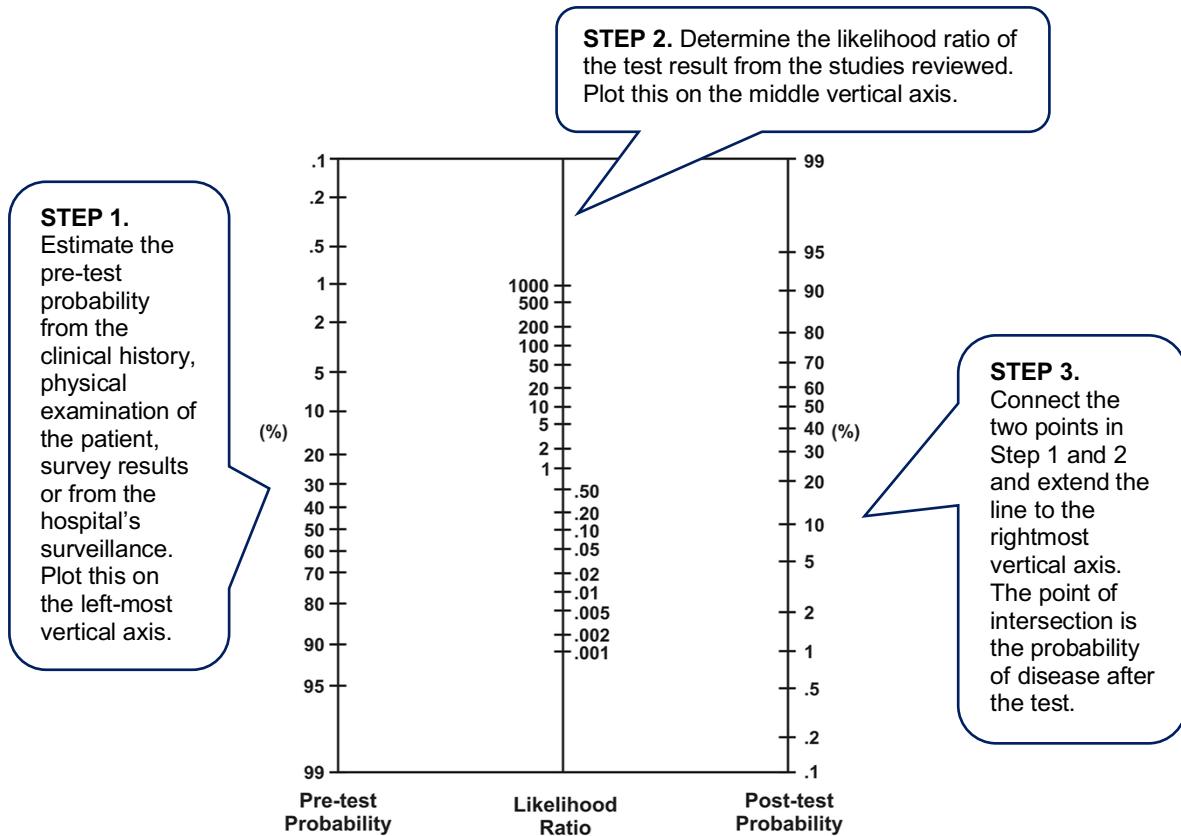


Figure 3. Using Bayes nomogram for estimating post-test probability

C. Interpreting Evidence on Therapy

Table 6. Ways of expressing effectiveness

| Outcome | Summary of result within each group | Comparison of results between two groups |
|--|---|--|
| Dichotomous (e.g. lived or died, BP controlled or not) | Proportion (e.g. deaths per 100 patients) | Relative risk reduction, absolute risk reduction (ARR), relative risk (RR) (see Table 4) |
| | Rate (e.g. deaths per 100 patients) | Hazard ratio = rate in treatment / rate in control |
| Continuous (e.g. blood pressure in mmHg, quality of life on a scale of 0 to 1) | Mean (e.g. mean blood pressure) | Mean difference = mean in control – mean in treatment group |

Instructions: When researchers express the effect of treatment using the relative risk reduction, absolute risk reduction, or relative risk, they often provide a range of

possibilities rather than a single estimate. This range of possibilities is called a ‘95% Confidence Interval (95% CI)’ to mean ‘we are 95% sure that the true effect of a drug lies in this range’. Table 4 below shows examples of the usefulness of interpreting 95% CIs.

Table 7. Interpreting 95% Confidence Intervals (Cis)

| Measure of effectiveness and interpretation of estimates | Interpreting 95% Confidence Intervals (Cis) | | | |
|--|--|---|--|---|
| | Superior (treatment surely better than control) | Inferior (treatment surely worse than control) | Inconclusive (more studies needed) ¶ | Equivalent (treatments are equal) ¶ |
| Relative risk (RR)§ = R_t / R_c <1.0 Treatment beneficial =1.0 Treatment no effect >1.0 Treatment harmful | Both ends of 95% CI <1.0 | Both ends of 95% CI >1.0 | 95% CI wide; straddles 1.0 | 95% CI narrow; straddles 1.0 |
| | Example: RR = 0.7 [95% CI: 0.6, 0.8] | Example: RR = 2.4 [95% CI: 1.8, 3.2] | Example: RR = 1 [95% CI: 0.2, 5.3] | Example: RR = 1 [95% CI: 0.9, 1.1] |
| Absolute Risk Reduction (ARR) = $R_c - R_t$ (usually in %) >0% Treatment beneficial =0% Treatment no effect <0% Treatment harmful | Both ends of 95% CI >0% | Both ends of 95% CI <0% | 95% CI straddles 0%; either end is far from 0% | 95% CI straddles 0%; either end is close to 0% |
| | Example: ARR = 2% [95% CI: 1%, 3%] | Example: ARR = -3% [95% CI: -7%, -1%] | Example: ARR = 1% [95% CI: -20%, 32%] | Example: ARR = 0.2% [95% CI: -0.1%, 0.5%] |

¶ In both inconclusive and equivalent results, the 95% CI interval straddles the point of no effect (ARR = 0% or RR = 1.0). One end reflects the worst possible harm, while the other end reflects the best possible benefit. The only difference is that, in equivalence, either end is close to “no effect” (i.e. any benefit is ignorable, and any harm is ignorable too). Consider the ends of the 95% CI to make sure there is agreement that the benefits and harms are ignorable.

§ R_c is the rate of the outcomes in the Control group; R_t is the rate of the outcome in the Treatment group

Note: The interpretations in this table only hold if the dichotomous events are expressed as adverse rather than desirable events, e.g. death rather than survival, treatment failure rather than cure, or disease rather than disease-free. When dichotomous outcomes are expressed as desirable events, the interpretation of benefit and harm is reversed.

Instructions: The balloons below label the most important parts of the forest plot. Go through these labels and familiarize yourself with the anatomy of the graph and understand what the forest plot can signify.

Review : Hypothetical example

Comparison: 01 Gym-based fitness regimen (treatment) vs Home-based fitness regimen (control)

Outcome : 02 Failure to get a modelling contract

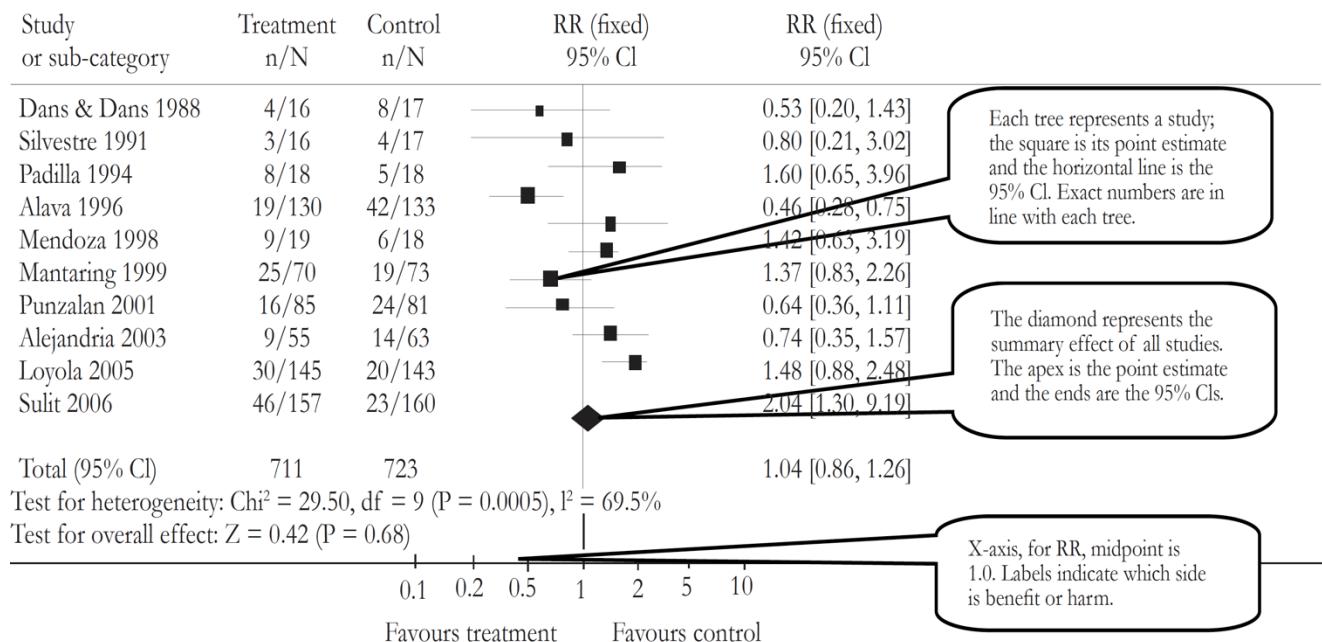


Figure 4. How to interpret forest plots

GRADE APPROACH IN ASSESSING THE LEVEL OF QUALITY OF EVIDENCE

(GRADE: Grading of Recommendations Assessment, Development and Evaluation; modified from WHO Handbook in Guideline Development, 2014)

These quality ratings apply to the body of evidence assessed for the research question, not to individual studies. Evidence based on randomized controlled trials is initially given a high-quality rating, while evidence from observational studies is given a low-quality rating. The level is then adjusted according to the following criteria.

Box 1. Standard criteria for grading of evidence⁴

| Domain | Grade | Characteristic |
|---|---|--|
| STUDY DESIGN | 0 | All randomized controlled trials |
| | -1 | All observational studies |
| STUDY DESIGN LIMITATIONS | 0 | Most of the pooled effect provided by studies, with low risk of bias ("A") |
| | -1 | Most of the pooled effect provided by studies with moderate ("B") or high ("C") risk of bias. Studies with high risk of bias weighs <40% |
| | -2 | Most of the pooled effect provided by studies with moderate ("B") or high ("C") risk of bias. Studies with high risk of bias weighs ≥40% |
| | <p><i>Note:</i> <i>Low risk of bias (no limitations or minor limitations) – "A"</i> <i>Moderate risk of bias (serious limitations or potentially very serious limitations including unclear concealment of allocation or serious limitations, excluding limitations on randomization or concealment of allocation) – "B"</i> <i>High risk of bias (limitations for randomization, concealment of allocation, including small blocked randomization (<10) or other very serious, crucial methodological limitations) – "C"</i></p> | |
| INCONSISTENCY | 0 | No severe heterogeneity ($I^2 < 60\%$ or $X^2 < 0.05$) |
| | -1 | Severe, non-explained, heterogeneity ($I^2 \geq 60\%$ or $X^2 < 0.05$) If heterogeneity could be caused by publication bias or imprecision due to small studies, downgrade only for publication bias or imprecision (i.e. the same weakness should not be downgraded twice) |
| INDIRECTNESS | 0 | No indirectness |
| | -1 | Presence of indirect comparison, population, intervention, comparator, or outcome |
| IMPRECISION | 0 | The confidence interval is precise according to the figure below. The total cumulative study population is not very small (i.e. sample size is more than 300 participants) and the total number of events is more than 30. |
| | | |
| | -1 | One of the above-mentioned conditions is not fulfilled. |
| | -2 | The two above-mentioned are not fulfilled. |
| <p><i>Note: If the total number of events is less than 30 and the total cumulative sample size is appropriately large (e.g. above 3000 patients, consider not downgrading the evidence). If there are no events in both control and control groups, the quality of evidence in the specific outcome should be regarded as very low.</i></p> | | |
| PUBLICATION BIAS | 0 | No evident asymmetry in the funnel plot or less than five studies to be plotted. |
| | -1 | Evident asymmetry in funnel plot with at least five studies |

2. Dans Al, Dans LF and Silvestre MA. Painless Evidence – Based Medicine. 2nd edition. 2016.

Table 8. Quality of evidence in GRADE

| Quality Level | Definition |
|-----------------|---|
| High | We are very confident that the true effect lies close to that of the estimate of the effect. |
| Moderate | We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. |
| Low | Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of effect. |
| Very Low | We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect. |

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**RESULTS:
UPDATED RECOMMENDATIONS
For Tuberculosis in Adults
2021**

UPDATES ON SCREENING FOR TUBERCULOSIS

Q1: AMONG ADULTS WITH NO SYMPTOMS BUT WITH RISK FACTORS OF TUBERCULOSIS⁵, HOW ACCURATE IS SCREENING BY CHEST X-RAY IN IDENTIFYING INDIVIDUALS WARRANTING FURTHER BACTERIOLOGIC WORK-UP?

RECOMMENDATION

Among asymptomatic adults with risk factors for pulmonary tuberculosis (PTB), the chest x-ray (CXR) is an accurate screening tool with a 93.8 % sensitivity and is recommended to identify individuals warranting further bacteriologic work-up. (Strong recommendation, moderate-quality evidence)

REMARKS

Despite the absence of clinical studies directly addressing the question, the consensus panel still recommends using CXR as a screening test among asymptomatic adults due to its high sensitivity. This current recommendation is also consistent with existing guidelines and reports from the WHO regarding TB screening. The 6th MOP recommends annual CXR among those consulting in health facilities, including targeted workplaces, communities, and congregate settings. Steps must be taken to make good quality CXR more accessible in health facilities across the country.

Voting: 15/15 Agree

SUMMARY OF EVIDENCE

There were no studies that directly assessed the accuracy of CXR compared to other diagnostic methods (e.g. culture, Xpert® MTB/RIF, LAMP, LPA) for screening asymptomatic patients with risk factors.

A TB prevalence survey in Kenya (HIV-prevalence, 14.9%) showed that the presence of any abnormality on CXR had a sensitivity of 94% (95% CI 88–98; 92% in HIV-infected and 100% in HIV-uninfected) and a specificity of 73% (95% CI 68–77; not specified as to HIV status).[1] However, the study did not stratify patients into symptomatic and asymptomatic patients. Table Q1.1 summarizes the diagnostic performance of different screening methods employed in this study, including CXR.

⁵ Risk factors include: healthcare workers, contacts of TB patients, those ever treated for TB (i.e., with history of previous TB treatment), people living with HIV (PLWHIV), elderly (>60 years old), diabetics, smokers, urban and rural poor, all those with immunosuppressive medical conditions, congregate settings.

Table Q1.1. Diagnostic accuracy of CXR and other TB screening methods⁶

| Screening strategy (strategy # as in Table 1) | TB cases with positive screen | Participants without TB with positive screen | Sensitivity(%) (95%CI*) | Specificity(%) (95%CI) | PPV(%) (95%CI) | AUC [†] |
|---|-------------------------------|--|-------------------------|------------------------|----------------|------------------|
| Total N | 123 | 20,443 | | | | |
| 1. Cough ≥2 weeks [§] | 64 | 2,200 | 52 (41–63) | 89 (88–90) | 2.8 (2.0–3.2) | 0.71 |
| in HIV-positive | 36 | | 69 (56–83) | | | |
| in HIV-negative | 20 | | 41 (25–57) | | | |
| in HIV-unknown | 8 | | 36 (17–59) | | | |
| 2. Any symptom of any duration or severity [§] | 111 | 13,878 | 90 (84–95) | 32 (30–34) | 0.8 (0.6–1.0) | 0.61 |
| in HIV-positive | 50 | | 96 (87–100) | | | |
| in HIV-negative | 40 | | 82 (68–91) | | | |
| in HIV-unknown | 21 | | 95 (77–100) | | | |
| 8. CXR – any abnormality** | 113 | 5,229 | 94 (88–98) | 73 (68–77) | 2.1 (1.5–2.7) | 0.83 |
| in HIV-positive | 47 | | 92 (81–98) | | | |
| in HIV-negative | 48 | | 100 (93–100) | | | |
| in HIV-unknown | 18 | | 86 (68–100) | | | |
| 11. Cough ≥2 weeks or any CXR abnormality [§] | 119 | 8,702 | 97 (92–99) | 57 (55–60) | 1.4 (1.1–1.7) | 0.79 |
| in HIV-positive | 52 | | 100 (93–100) | | | |
| in HIV-negative | 49 | | 100 (93–100) | | | |
| in HIV-unknown | 18 | | 82 (60–95) | | | |

CI = Confidence Interval CXR = Chest radiograph.

*Where the design effect was ≤1 CI's were not adjusted for cluster design but binomial exact CI presented.

†AUC = Area under the receiver operating characteristic curve.

§Denominator for HIV-positive n = 52, HIV-negative n = 49, HIV-unknown n = 48.

**3 cases did not have a CXR, 1HIV+, 1HIV-, 1HIVunknown, so denominators are 120, 51, 48 and 21 respectively. For specificity: 1347 missing records.

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Another systematic review investigated the number needed to screen (NNS) to detect a case of active TB among different risk groups.[2] Of the many combinations of components of a screening algorithm (Table Q1.2), the presence of CXR in the algorithm consistently resulted in a lower NNS. NNS was lower when CXR was used as the primary screening tool (NNS = 27) or as a component of the screen (NNS = 37). In contrast, higher NNS values were found in strategies that used symptom screening alone (NNS = 142) or did not use CXR imaging (NNS = 73). Furthermore, this review [2] also showed that using CXR versus not using CXR yielded lower NNS among HIV/AIDS (8 vs. 54), household contacts (17 vs. 54), and homeless subjects (67-70 vs. 455) (Table Q1.3).

Table Q1.2. Crude median and weighted mean NNS for different screening algorithms*

| Screening algorithm | Overall | Low & moderate incidence | Moderate & high incidence |
|---------------------------------------|----------------------------------|------------------------------------|-------------------------------|
| CXR in primary screen | 70 (22-282) 148 (2-11,019) | 112 (39-573) 127 (3-11,019) | 27 (9-106) 204 (2-3,189) |
| No CXR in primary screen | 143 (34-1,112) 212 (3-30,865) | 302 (54-61,729) 343 (3-30,865) | 73 (24-285) 188 (3-6,355) |
| CXR in primary or secondary | 94 (27-415) 149 (2-11,019) | 145 (45-1,202) 203 (2-2,189) | 37 (12-144) 180 (2-30,865) |
| Symptom screen only as primary screen | 156 (42-773) 319 (3-30,865) | 713 (57-30,030) 713 (15-30,865) | 142 (40-601) 308 (3-6,355) |

*Adapted from Shapiro et al. (2013). CXR = chest x-ray

⁶ Source: p.6, Table 4, 1. van't Hoog AH, Meme HK, Laserson KF, Agaya JA, Muchiri BG, Githui WA, et al. Screening strategies for tuberculosis prevalence surveys: the value of chest radiography and symptoms. PLoS One. 2012;7(7):1–9.

Note: Numbers given in table are crude median NNS (IQR) (top row) and weighted mean NNS and (range of NNS) (bottom row) from the studies included in each category. ND=not defined

Table Q1.3. NNS Using CXR versus No CXR among Risk Groups*

| Risk factors | Incidence of TB | Purpose of screen | NNS (95% CI) | |
|--------------------|---------------------------|--|--------------------------------|--------------|
| | | | With CXR | Without CXR |
| HIV/AIDS | medium and high incidence | | 8 | 54 |
| Household contacts | medium and high incidence | primary or secondary screen | 17 (2-155) | 54 (5-568) |
| Drug users | | | 54 (5-108) | |
| Homeless | | primary screen among other screening tools | 67 (33-1,778) 70 (33-1,778) | 455 (22-590) |

*Adapted from Shapiro et al. (2013) data

The NNS presented may provide guidance in setting priorities in the local context, especially in settings where resources are limited, and TB incidence is high. Prioritizing the screening of risk groups with low NNSs may be useful for patients in the HIV clinic, elderly, household contacts of patients with TB, and drug users (Table Q1.4).

Table Q1.4. NNS of risk groups*

| Risk group | NNS range |
|---|-----------|
| HIV-infected (including VCT attendees) | 10-37 |
| Elderly/nursing homes, etc. | 7-45 |
| Household contacts | 17-25 |
| Drug users | 20 |
| Persons with diabetes | 35 |
| Miners | 36 |
| Pregnant women and GYN clinic attendees | 36-39 |
| Community-wide screening (high-incidence) | 100 |

*Adapted from Shapiro et al. (2013) data

The 2016 NTPS showed that the proportion of TB cases among individuals with diabetes mellitus was higher (8%) compared to non-cases (4%) ($P<0.001$). [3] There were also more cases of TB identified among those with a history of smoking (67%) compared to non-cases (39%) ($P<0.001$) (Table Q1.5). However, they did not perform subgroup analysis for these risk groups to determine the accuracy of using CXR in asymptomatic individuals. The survey concluded that risk groups should be targeted, and further studies on cost-effectiveness of CXR screening among these high-risk groups is recommended.

Table Q1.5. Risk factors for TB cases compared to non-cases, 2016 NTPS, Philippines

| Characteristics | Survey TB cases n = 466 | | Non-cases n = 46,223 | | Total participants N = 46,689 | |
|--------------------------|----------------------------|----------------|-------------------------|----------------|----------------------------------|----------------|
| | No. | % ^a | No. | % ^a | No. | % ^a |
| Diabetes mellitus | | | | | | |
| Yes | 38 | 8.2 | 1,828 | 4.0 | 1,866 | 4.0 |
| No | 428 | 91.8 | 44,395 | 96.0 | 44,823 | 96.0 |
| Smoking | | | | | | |
| Yes | 313 | 67.2 | 18,222 | 39.4 | 18,535 | 39.7 |
| No | 153 | 32.8 | 27,975 | 60.5 | 28,128 | 60.2 |
| Don't know | 0 | 0.0 | 26 | 0.1 | 26 | 0.1 |
| Total | 466 | 100.0 | 46,223 | 100.0 | 46,689 | 100.0 |

^aColumn percentage

Chest radiography is a good screening tool for PTB because of its high sensitivity (87 to 98%).[4] Due to its low specificity (46% to 89%), however, CXR screening should be followed by a rapid, highly sensitive and specific test to confirm TB diagnosis.

Based on the WHO TB operational guide, systematic screening for TB needs to properly target high-risk groups and consider epidemiological, social and health-systems contexts.[5] The profile of the risk group can influence the choice of algorithm since accuracy of certain tools is affected by underlying biological factors associated with certain risk factors (e.g. CXR, Xpert® MTB/RIF, and sputum-smear microscopy have lower sensitivity among people living with HIV).[4]

The WHO End TB Strategy includes systematic screening for active TB in high-risk groups highlighting the need for early TB diagnosis. WHO strongly recommends systematic screening for active TB among household contacts and other contacts of people with TB (NNS 17, 89 studies), people living with HIV (NNS 10, 74 studies), and people exposed to silica (NNS 36, 8 studies). Systematic screening for active TB should be considered in people in prisons and other penitentiary institutions, in people with an untreated fibrotic CXR lesion, in geographically defined subpopulations with extremely high levels of undetected TB, in a highly endemic country (e.g., 100 per 100,000 population or higher), and in subpopulations with very poor access to health care. [6]

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Q2: AMONG ADULTS WITH NO SYMPTOMS AND NO RISK FACTORS, HOW ACCURATE IS TB SCREENING BY CHEST X-RAY IN IDENTIFYING INDIVIDUALS WARRANTING FURTHER BACTERIOLOGIC WORK-UP?

RECOMMENDATION

There is no evidence that demonstrates the accuracy of the CXR (98.2% Sn, 71.4% Sp, +LR 3.44, -LR 0.03) as a screening tool among asymptomatic adults without TB risk factors. However, because of the high prevalence of TB locally and considering that based on the NTPS ~10% of bacteriologically confirmed TB ($n=466$) had no risk factors and no symptoms ($n=121$), CXR is recommended as a screening tool for identifying individuals warranting further bacteriologic work-up. (Strong recommendation, moderate-quality evidence)

REMARKS

The panel made this recommendation to improve case detection and provide guidance for TB screening in health facilities and in the workplace since TB incidence in the country is high. [1,2] Currently, WHO has no strong recommendation regarding the use of CXR for asymptomatic individuals without risk factors in the general population, but advocates screening people living in highly endemic areas (i.e. > 1% TB prevalence). Early detection of TB to reduce the severity of illness and to minimize spread of infection is a pillar of the “End TB” strategy of the WHO. The 6th MOP recommends CXR as the primary screening tool for active case finding in congregate settings, targeted communities and workplaces.

Concerns about access, cost, film quality for analog type x-ray, unnecessary exposure to radiation (although negligible), turn-around times and standardized reading need to be addressed to implement this.

Voting: 14/14 agree (1 person left at the time of the voting)

SUMMARY OF EVIDENCE

Review of published literature from 2015 to 2019 using the search terms “tuberculosis, pulmonary”[Mesh], screening, adult, chest radiography, chest x-ray, symptom, and asymptomatic” yielded 17 articles. Without the 5-year restriction, an additional 37 articles published before the year 2015 were retrieved. Pooled estimates in studies cited by WHO [3] and another systematic review [4] showed that CXR had a higher sensitivity for detecting PTB in the general population compared to symptom screening (Table Q2.1).

Table Q2.1. Pooled sensitivity and specificity of chest radiograph as a screening tool for pulmonary TB in the general population

| | Population HIV prevalence/region (No. of participants) | Reference test | Quality of evidence | Sensitivity % (95% CI) | Specificity % (95% CI) |
|--|---|--|---------------------|------------------------|------------------------|
| CXR, any abnormality (3 studies) | Combined 72,065 | Sputum culture or sputum-smear microscopy, or both | Moderate | 97.8 (95.1 – 100.0) | 75.4 (72.0 – 78.8) |
| CXR, TB-related abnormality (5 studies) | Combined 163,646 | Sputum culture or sputum-smear microscopy, or both | Low | 86.8 (79.2 – 94.5) | 89.4 (86.7 – 92.0) |

However, these studies were not designed to evaluate the diagnostic accuracy of CXR as a screening tool specifically among asymptomatic individuals not belonging to high-risk groups. Only indirect evidence regarding the possible use of CXR in this population may be derived from some studies. For example, in one prevalence survey conducted in Cape Town, South Africa, 9 of 780 asymptomatic individuals were bacteriologically positive for TB, with 6 of 9 patients showing TB-related abnormalities on CXR [5]. Another prevalence survey in Western Kenya reported 48 (1.2%) TB cases among 3,852 asymptomatic participants, with no TB cases seen among the 15,893 asymptomatic participants with normal CXR results. [6] In a cross-sectional study in Vietnam, case yield was higher for screening by CXR (90.5%) compared to symptom screening by interview (37.9%).[7] Lastly, a retrospective study in Vaud Canton, Switzerland, compared the bacteriological and clinical presentation of the actively screened TB cases by CXR with other patients detected by passive screening. [8] More asymptomatic patients were found among actively screened patients (49.3%; 95% CI 37.4-61.2) compared to passively screened patients (17.6%; 95% CI 10.3-24.9). Among patients with culture confirmed PTB, 42.2% (95% CI 27.2-57.2) of actively screened patients had no symptoms compared to 13% (95% CI 5.31-20.7) of passively screened patients.[8]

Data from the 2016 NTPS showed that among the survey cases with CXR findings suggestive of TB (Table Q2.2), majority (67.5%, 276/409) were negative by symptom screening. Only 133 (28.5%) of the survey cases were positive for both symptoms and CXR.[1]

Of the 437 available CXRs, 409 (93.6%) were interpreted as suggestive of TB. Chest x-ray screening alone identified 98.2% (430/438) cases compared to 32.2% (150/466) identified by symptom screening alone; screening for TB cases using symptoms alone would have missed one- to two-thirds of bacteriologically confirmed PTB cases. [1]

Table Q2.2. Distribution of negative symptoms and CXR central reading among microbiologically confirmed survey cases, NTPS 2016, Philippines.

| Screening symptoms | CXR (central reading) | Smear-positive survey cases (N = 173) | | Bacteriologically confirmed survey cases (N = 466) | |
|---|-----------------------|---------------------------------------|------|--|------|
| | | Number | % | Number | % |
| Positive ^a | Positive | 79 | 45.7 | 133 | 28.5 |
| Positive ^a | Negative | 2 | 1.2 | 6 | 1.3 |
| Negative but with other symptoms ^b | Positive | 56 | 32.4 | 168 | 36.0 |
| Negative but with other symptoms ^b | Negative | 2 | 1.2 | 17 | 3.6 |
| Negative | Positive | 21 | 12.1 | 108 | 23.2 |
| Negative | Negative | 1 | 0.6 | 5 | 1.1 |

^a Positive for screening symptoms of cough for at least two weeks at the time of the interview and/or blood in sputum (hemoptysis) in the past month

^b Negative but with other symptoms i.e. fever, weight loss, night sweats

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UPDATES ON DIAGNOSIS OF TUBERCULOSIS

Q3: AMONG ADULTS WITH PRESUMPTIVE PULMONARY TB (PTB), HOW ACCURATE IS SPUTUM XPERT® MTB/RIF COMPARED TO SPUTUM DSSM IN ESTABLISHING THE DIAGNOSIS OF PTB?

RECOMMENDATION

Xpert® MTB/RIF is a more accurate test (Sn 0.74-1.00; Sp 0.82-0.99; LR+ 21.8, LR- 0.04) compared to direct sputum smear microscopy (DSSM) (Sn 0.26-0.86; Sp 0.84-0.98; LR+ 10.8, LR- 0.49) and is recommended as the initial diagnostic test of choice for PTB. (**Strong recommendation, high-quality evidence**)

REMARKS AND CONSENSUS ISSUES

The consensus panel recommends the use of Xpert® MTB/RIF as the initial diagnostic test for the diagnosis of PTB. Unlike DSSM, Xpert® MTB/Rif is a more sensitive test and has the added benefit of determining rifampicin resistance (RR). Xpert® MTB/RIF testing is a useful tool for early diagnosis of TB and multi-drug resistant TB (MDRTB).

Voting: 15/15 agree

SUMMARY OF EVIDENCE

Xpert® MTB/RIF is an automated, cartridge-based nucleic acid amplification test for TB. It detects *M. tuberculosis* as well as the mutation that confers RR. The assay provides results directly from specimens in less than 2 hours.

Search terms included ("GeneXpert") OR ("Nucleic Acid Amplification Techniques"[Mesh]) AND (("Tuberculosis"[Mesh]) OR "tuberculosis")
Based on 4 high-quality studies [1-4] comparing the sensitivities and specificities of Xpert® MTB/RIF and DSSM, with TB culture as a reference standard, the following parameters were derived (Table Q3.1):

Table Q3.1. Comparison of Diagnostic Accuracy Estimates Between Xpert® MTB/RIF and DSSM

| Diagnostic Performance Measures | Xpert® MTB/RIF | DSSM |
|---------------------------------|------------------|------------------|
| Sensitivity | | |
| Range | 0.74-1.00 | 0.26-0.86 |
| Pooled/Summary (CI 95%) | 0.96 (0.69-1.00) | 0.54 (0.29-0.77) |
| Specificity | | |
| Range | 0.82-0.99 | 0.84-0.98 |
| Pooled/Summary (CI 95%) | 0.96 (0.84-0.99) | 0.95 (0.89-0.98) |
| Likelihood Ratios | | |
| LR+ (CI 95%) | 21.8 (5.2-91.6) | 10.8 (7.6-15.4) |
| LR- (CI 95%) | 0.04 (0.00-0.42) | 0.49 (0.29-0.83) |

Xpert® MTB/RIF had a better sensitivity, with a pooled estimate of 96%, compared to DSSM at 54%. This means that Xpert® MTB/RIF identifies more true positive cases and less false positive cases of PTB compared to DSSM. Both Xpert® MTB/RIF and DSSM had comparable specificities and had similar yields for true negative cases.

The likelihood of PTB increases 21.8 times with a positive Xpert® MTB/RIF result compared to DSSM, with a likelihood of 10.8 times with a positive result. In contrast, a negative Xpert® MTB/RIF decreases the likelihood of PTB by 0.04 times, as compared to a negative sputum smear, which decreases the likelihood by 0.49.

Favorable qualities of the Xpert® platform include automaticity of the process, consistent quality, and the diagnostic utility to simultaneously detect RR. DSSM can still be used for TB diagnosis in resource-limited settings with no access to Xpert® MTB/RIF testing. Recognized limitations of DSSM include requirements for higher specimen volume (5-10mL) compared to Xpert® MTB/RIF (1mL) and laboratory expertise to minimize technique-related concerns including smear preparation and interpretation. The NTP MOP 6th ed. States that the use of Xpert MTB/RIF assay is the primary diagnostic test for TB in the Philippines replacing DSSM, and that smear-positive specimens by DSSM will require further Xpert® MTB/Rif testing for rapid determination of RR.

The WHO included Xpert® MTB/RIF in its policy framework for implementing TB diagnostics in 2015, citing its advantages over sputum microscopy [6]. Access to Xpert® MTB/RIF and cost are factors to be considered in the utilization of this test. In the past few years, the Philippine DOH has embarked on the rollout of rapid TB testing utilizing the Xpert® MTB/RIF to detect TB and drug resistant TB. From just 84 Xpert® machines in 2014, there are now 488 Xpert® machines distributed in various government TB treatment centers. The rollout is further augmented by optimized specimen transport process to address access to free Xpert® MTB/RIF testing.

To address the concerns regarding Xpert® MTB/RIF testing access in private healthcare institutions, a national platform to access concessional pricing through consortium has been established to offer reduced and uniform pricing to patients.

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Q4: AMONG ADULTS WITH PRESUMPTIVE PULMONARY TB (PTB), HOW ACCURATE IS SPUTUM TB LAMP COMPARED TO XPERT® MTB/RIF IN ESTABLISHING THE INITIAL DIAGNOSIS OF PTB? WHEN IS SPUTUM TB LAMP PREFERRED OVER XPERT® MTB/RIF?

RECOMMENDATION

TB LAMP is as accurate as GeneXpert® in the diagnosis of PTB ($Sn = 0.78$ (95% CI 0.81-0.83); $Sp = 0.98$ (95% CI 0.96-0.93); $LR+ = 58.2$, $LR- = 0.24$). Due to its ability to detect RR, GeneXpert® is still the recommended diagnostic test of choice. In areas where GeneXpert® is unavailable and the risk of resistance is low, TB LAMP may be used. **(Weak recommendation, Very low-quality evidence)**

REMARKS AND CONSENSUS ISSUES

The inability of TB-LAMP to detect RR, as well as its limited availability in the country were identified by the panel as key issues. TB LAMP has recently been made available in the Philippines for TB testing in a few government and private laboratories. The NTP MOP 6th ed. Policy statement on TB LAMP is for this test to be used as an alternative diagnostic test if Xpert® MTB/RIF is inaccessible [1]. Unlike Xpert® MTB/RIF, TB LAMP cannot detect RR. As such, for patients with positive TB-LAMP results, follow-up testing using rapid molecular tests that detect RR should still be done. This limitation may contribute to delays in treatment initiation for individuals who tested positive and are suspected to have resistance.

Voting: 15/15 agree

SUMMARY OF EVIDENCE

PubMed was used for the search with the search terms "TB LAMP" or "tuberculosis LAMP", "Xpert" or "Genexpert" or "Cepheid", "Pulmonary TB" or "PTB" or "pulmonary tuberculosis."

Loop-mediated isothermal amplification (LAMP) is a manual molecular assay that amplifies DNA independent of room temperature. A commercial assay that employs the LAMP technique to detect tuberculosis, TB-LAMP has logistical advantages compared to Xpert® MTB/RIF. It does not require air conditioning, has less need for infrastructure, and less maintenance costs. The results of TB-LAMP can be read by the naked eye or under ultraviolet light after 15 to 60 minutes. TB-LAMP can process 14 samples in 1-1.5 hours, up to 70 samples per day, compared to 16 tests per working day for Xpert® MTB/RIF. These properties make TB-LAMP a viable option for barangay health centers to replace DSSM. However, unlike Xpert® MTB/RIF, TB-LAMP cannot detect RR.

A 2019 meta-analysis and systematic review which included 13 studies ($n=5,099$) explored the diagnostic accuracy of TB-LAMP in the diagnosis of PTB. [2] Six studies performed Xpert® MTB/RIF and TB-LAMP on the same participants ($n = 2,837$) but used different reference standards (Table Q4.1). Of 2,837 participants eligible for inclusion in the analysis, 1,075 (38%) qualified for Standard 1 status across four studies; 1,809 (64%) qualified for Standard 2 across 6 studies, and 2,772 (98%) qualified for Standard 3 across eight studies.

Table Q4.1. Reference standards used by Shete (2019) [2]

| STANDARD | WITH TB | NO TB |
|----------|---|--|
| 1 | | No positive and at least 2 negative cultures performed on 2 different sputum samples |
| 2 | at least 1 positive culture confirmed to be MTB by speciation testing | No positive and at least 2 negative cultures performed on at least 1 sputum sample |
| 3 | | No positive and at least 1 negative culture |

Table Q4.2 shows the pooled sensitivities and specificities of Xpert® MTB/RIF and TB-LAMP across the three reference standards in this review. The pooled sensitivity of TB-LAMP was lower than that of Xpert® MTB/RIF. The specificities of all three tests were similar. In head-to-head comparisons, TB-LAMP appeared to be less sensitive than the Xpert® MTB/RIF, but the difference in sensitivity was not statistically significant. The evidence profile for this PICO question is reported in Appendix Q4 (Table Q4.3, Table Q4.4, and Table Q4.5). These results were similar to the findings of a recent meta-analysis conducted in China.[3]

Table Q4.2. Accuracy of TB-LAMP and the Xpert® MTB/RIF assay*

| Reference standard ^a | Pooled sensitivity ^b | Pooled specificity ^b |
|---------------------------------|---------------------------------|---------------------------------|
| TB-LAMP | | |
| Standard 1 | 78.0 (66.6 – 86.4) | 98.9 (97.4 – 99.6) |
| Standard 2 | 74.1 (64.1 – 82.2) | 98.8 (96.8 – 99.6) |
| Standard 3 | 75.8 (63.2 – 85.0) | 98.2 (96.0 – 99.2) |
| Xpert® MTB/RIF | | |
| Standard 1 | 81.1 (70.6 – 88.5) | 98.2 (95.9 – 99.2) |
| Standard 2 | 80.4 (73.4 – 85.9) | 97.4 (94.9 – 98.7) |
| Standard 3 | 84.0 (75.6 – 90.0) | 97.2 (94.4 – 98.6) |

* Source: Shete PB, Farr K, Strnad L, Gray CM, Cattamanchi A. Diagnostic accuracy of TB-LAMP for pulmonary tuberculosis: a systematic review and meta-analysis. BMC Infect Dis. 2019;19(268):1–11.

^a Data were restricted to study participants for whom there were valid results for both TB-LAMP and the Xpert® MTB/RIF assay and cases in which testing was performed on non-frozen specimens

^b Values are percentages (95% confidence intervals).

Several limitations were identified in this review. First, there was a lack of a consistent reference standard which could have resulted in misclassification of patients depending on what standard was used. Second, conflicts of interest could not be ruled out as most of the studies were conducted by national government organizations sponsored by the manufacturers of the test. Third, these studies were conducted in areas where individuals underwent extensive training. Lastly, the results may have been confounded by operational issues or by the inclusion of patients with HIV.

Even in the absence of these methodological issues, TB-LAMP still exhibits the major disadvantage of not being able to detect RR. Thus, its use is limited for screening and it cannot replace Xpert® MTB/RIF especially in an area with high TB endemicity and rising MDR-TB cases.

A 2016 policy guidance from WHO described an unpublished cost-effectiveness study comparing Xpert® MTB/RIF and TB-LAMP conducted in Malawi and Vietnam. [4] Findings from this study showed that TB-LAMP was potentially more cost-effective than smear microscopy in areas where setting up a laboratory containing Xpert® MTB/RIF poses logistic challenges.

The weighted average per-test cost of TB-LAMP and Xpert® MTB/RIF ranged from US\$ 13.78 to 16.22 and US\$ 19.17 to 28.34 respectively, when they were used as routine diagnostic tests at all peripheral-level laboratories in both countries. [3] The first-year expenditure required for implementation at peripheral laboratories with a medium workload (10–15 sputum smear microscopy tests per day) in Vietnam was US\$ 26,917 for TB-LAMP and US\$ 43,325 for the Xpert® MTB/RIF assay.

In the cost-effectiveness analyses, TB-LAMP improved case-detection rates and was cost-effective when compared with WHO's willingness-to-pay threshold levels. As a test performed at peripheral laboratories, TB-LAMP is generally a cheaper and more affordable alternative molecular test to the Xpert® MTB/RIF assay. The findings of the cost-effectiveness analysis also demonstrated that TB-LAMP is potentially a cost-effective alternative to DSSM in settings where the Xpert® MTB/RIF assay cannot be implemented due to its infrastructure requirements (e.g. continuous power supply). However, given the inability of TB-LAMP to detect RR-TB and its suboptimal sensitivity for detecting TB among persons living with HIV, policymakers must cautiously evaluate the operational feasibility and cost considerations prior to introducing this technology in their countries.

A local cost-effectiveness study is recommended.

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APPENDIX Q4

GRADE Evidence Profiles

Table Q4.3. Accuracy of TB-LAMP compared to Xpert® MTB/RIF MTB/RIF in establishing initial diagnosis of PTB among adults with presumptive PTB (Reference Standard 1)

Question: Should TB LAMP vs. Xpert MTB be used to diagnose Pulmonary TB (standard 1) in adults?

| TB LAMP | | Xpert MTB | | | | | | | Prevalences | | 1% | 5% | 15% | |
|---|---------------------------------|--|---|--------------|----------------------|-------------|------------------|----------------------------------|------------------|------------------------------|------------------|------------------------------|----------------------|--|
| Sensitivity | 0.78 (95% CI: 0.71 to 0.83) | Sensitivity | 0.81 (95% CI: 0.71 to 0.89) | | | | | | | | | | | |
| Specificity | 0.98 (95% CI: 0.96 to 0.99) | Specificity | 0.98 (95% CI: 0.96 to 0.99) | | | | | | | | | | | |
| Outcome | # of studies (# of patients) | Study design | Factors that may decrease certainty of evidence | | | | | Effect per 1,000 patients tested | | | | | Test accuracy CoE | |
| | | | Risk of bias | Indirectness | Inconsistency | Imprecision | Publication bias | TB LAMP | Xpert MTB | TB LAMP | Xpert MTB | TB LAMP | Xpert MTB | |
| True positives (patients with Pulmonary TB (standard 1)) | 4 studies 1075 patients | cross-sectional (cohort type accuracy study) | very serious ^a | not serious | serious ^b | not serious | none | 8 (7 to 8) | 8 (7 to 9) | 39 (36 to 42) | 41 (35 to 44) | 117 (107 to 124) | 122 (106 to 133) | |
| | | | | | | | | 0 fewer TP in TB LAMP | | 2 fewer TP in TB LAMP | | 5 fewer TP in TB LAMP | | |
| False negatives (patients incorrectly classified as not having Pulmonary TB (standard 1)) | | | | | | | | 2 (2 to 3) | 2 (1 to 3) | 11 (8 to 14) | 9 (6 to 15) | 33 (26 to 43) | 28 (17 to 44) | |
| | | | | | | | | 0 fewer FN in TB LAMP | | 2 more FN in TB LAMP | | 5 more FN in TB LAMP | | |
| True negatives (patients without Pulmonary TB (standard 1)) | 4 studies 1075 patients | cross-sectional (cohort type accuracy study) | very serious ^a | not serious | serious ^b | not serious | none | 971 (947 to 982) | 972 (949 to 982) | 932 (909 to 942) | 933 (911 to 942) | 834 (813 to 843) | 835 (815 to 843) | |
| | | | | | | | | 1 fewer TN in TB LAMP | | 1 fewer TN in TB LAMP | | 1 fewer TN in TB LAMP | | |
| False positives (patients incorrectly classified as having Pulmonary TB (standard 1)) | | | | | | | | 19 (8 to 43) | 18 (8 to 41) | 18 (8 to 41) | 17 (8 to 39) | 16 (7 to 37) | 15 (7 to 35) | |
| | | | | | | | | 1 more FP in TB LAMP | | 1 more FP in TB LAMP | | 1 more FP in TB LAMP | | |

Explanations:

- a. Failure to perform mycobacterial culture on at least two sputum samples, failure to use liquid culture or because liquid culture contamination rates were outside the acceptable range of 5-12%
- b. Significant heterogeneity I²: 61 – 78%; P <0.03

Table Q4.4. Accuracy of TB-LAMP compared to Xpert® MTB/RIF in establishing initial diagnosis of PTB among adults with presumptive PTB (Reference Standard 2)

Question: Should TB LAMP vs. Xpert MTB be used to diagnose Pulmonary TB (standard 2) in adults?

| TB LAMP | | Xpert MTB | | | | | | | Prevalences | | 1% | 5% | 15% | | | | | | | | | | | | |
|---|-----------------------------|----------------------------|--|---|--------------|----------------------|-------------|------------------|----------------------------------|------------------|------------------------------|------------------|------------------------------|----------------------|------------------|--|--|--|--|--|--|--|--|--|--|
| Sensitivity | 0.76 (95% CI: 0.70 to 0.81) | Sensitivity | 0.80 (95% CI: 0.73 to 0.86) | | | | | | | | | | | | | | | | | | | | | | |
| Specificity | 0.98 (95% CI: 0.96 to 0.99) | Specificity | 0.97 (95% CI: 0.95 to 0.99) | | | | | | | | | | | | | | | | | | | | | | |
| Outcome | | Study design | | Factors that may decrease certainty of evidence | | | | | Effect per 1,000 patients tested | | | | | Test accuracy CoE | | | | | | | | | | | |
| | | | | Risk of bias | Indirectness | Inconsistency | Imprecision | Publication bias | TB LAMP | Xpert MTB | TB LAMP | Xpert MTB | TB LAMP | Xpert MTB | | | | | | | | | | | |
| True positives (patients with Pulmonary TB (standard 2)) | | 6 studies 1809 patients | cross-sectional (cohort type accuracy study) | very serious ^a | not serious | serious ^b | not serious | none | 8 (7 to 8) | 8 (7 to 9) | 38 (35 to 41) | 40 (37 to 43) | 114 (105 to 122) | 121 (110 to 129) | ⊕○○○ VERY LOW | | | | | | | | | | |
| | | | | | | | | | 0 fewer TP in TB LAMP | | 2 fewer TP in TB LAMP | | 7 fewer TP in TB LAMP | | | | | | | | | | | | |
| False negatives (patients incorrectly classified as not having Pulmonary TB (standard 2)) | | | | | | | | | 2 (2 to 3) | 2 (1 to 3) | 12 (9 to 15) | 10 (7 to 13) | 36 (28 to 45) | 29 (21 to 40) | | | | | | | | | | | |
| | | | | | | | | | 0 fewer FN in TB LAMP | | 2 more FN in TB LAMP | | 7 more FN in TB LAMP | | | | | | | | | | | | |
| True negatives (patients without Pulmonary TB (standard 2)) | | | | | | | | | 970 (950 to 980) | 964 (940 to 977) | 931 (912 to 941) | 925 (902 to 938) | 833 (816 to 842) | 828 (807 to 839) | | | | | | | | | | | |
| | | | | | | | | | 6 more TN in TB LAMP | | 6 more TN in TB LAMP | | 5 more TN in TB LAMP | | | | | | | | | | | | |
| False positives (patients incorrectly classified as having Pulmonary TB (standard 2)) | | | | | | | | | 20 (10 to 40) | 26 (13 to 50) | 19 (9 to 38) | 25 (12 to 48) | 17 (8 to 34) | 22 (11 to 43) | | | | | | | | | | | |
| | | | | | | | | | 6 fewer FP in TB LAMP | | 6 fewer FP in TB LAMP | | 5 fewer FP in TB LAMP | | | | | | | | | | | | |

Explanations:

- a. Failure to perform mycobacterial culture on at least two sputum samples, failure to use liquid culture or because liquid culture contamination rates were outside the acceptable range of 5-12%
- b. Significant heterogeneity $I^2: 61 - 78\%; P < 0.03$

Table Q4.5. Accuracy of TB-LAMP compared to Xpert® MTB/RIF in establishing initial diagnosis of PTB among adults with presumptive PTB (Reference Standard 3)

Question: Should TB LAMP vs. Xpert MTB be used to diagnose Pulmonary TB (standard 3) in adults?

| TB LAMP | | Xpert MTB | | Prevalences | | | | | | | | | | | | | | | | | |
|---|-----------------------------|----------------------------|---|---------------------------|-------------|----------------------|-------------|------|---|----------------------------------|----------------------------------|------------------|------------------|------------------|------------------|----------------------|--|--|--|--|--|
| Sensitivity | 0.80 (95% CI: 0.70 to 0.88) | Sensitivity | 0.84 (95% CI: 0.76 to 0.90) | 1% | 5% | 15% | | | | | | | | | | | | | | | |
| Specificity | 0.98 (95% CI: 0.96 to 0.99) | Specificity | 0.97 (95% CI: 0.94 to 0.99) | | | | | | | | | | | | | | | | | | |
| True positives (patients with Pulmonary TB (standard 3)) | | 8 studies 2772 patients | cross-sectional (cohort type accuracy study) | very serious ^a | not serious | serious ^b | not serious | none | Factors that may decrease certainty of evidence | | Effect per 1,000 patients tested | | | | | Test accuracy CoE | | | | | |
| | | | | | | | | | TB LAMP | Xpert MTB | TB LAMP | Xpert MTB | TB LAMP | Xpert MTB | | | | | | | |
| | | | | | | | | | 8 (7 to 9) | 8 (8 to 9) | 40 (35 to 44) | 42 (38 to 45) | 120 (105 to 131) | 126 (113 to 135) | | | | | | | |
| | | | | | | | | | 0 fewer TP in TB LAMP | 2 fewer TP in TB LAMP | 6 fewer TP in TB LAMP | | | | ⊕○○○ VERY LOW | | | | | | |
| False negatives (patients incorrectly classified as not having Pulmonary TB (standard 3)) | | | | | | | | | 2 (1 to 3) | 2 (1 to 2) | 10 (6 to 15) | 8 (5 to 12) | 30 (19 to 45) | 24 (15 to 37) | | | | | | | |
| | | | | | | | | | 0 fewer FN in TB LAMP | 2 more FN in TB LAMP | 6 more FN in TB LAMP | | | | | | | | | | |
| | | | | | | | | | 967 (951 to 977) | 962 (935 to 976) | 928 (913 to 938) | 923 (897 to 937) | 830 (817 to 839) | 826 (802 to 838) | | | | | | | |
| | | | | | | | | | 5 more TN in TB LAMP | 5 more TN in TB LAMP | 4 more TN in TB LAMP | | | | ⊕○○○ VERY LOW | | | | | | |
| True negatives (patients without Pulmonary TB (standard 3)) | | | | | | | | | 23 (13 to 39) | 28 (14 to 55) | 22 (12 to 37) | 27 (13 to 53) | 20 (11 to 33) | 24 (12 to 48) | | | | | | | |
| | | | | | | | | | 5 fewer FP in TB LAMP | 5 fewer FP in TB LAMP | 4 fewer FP in TB LAMP | | | | | | | | | | |
| | | | | | | | | | 967 (951 to 977) | 962 (935 to 976) | 928 (913 to 938) | 923 (897 to 937) | 830 (817 to 839) | 826 (802 to 838) | | | | | | | |
| | | | | | | | | | 5 more TN in TB LAMP | 5 more TN in TB LAMP | 4 more TN in TB LAMP | | | | | | | | | | |
| False positives (patients incorrectly classified as having Pulmonary TB (standard 3)) | | | | | | | | | 23 (13 to 39) | 28 (14 to 55) | 22 (12 to 37) | 27 (13 to 53) | 20 (11 to 33) | 24 (12 to 48) | | | | | | | |
| | | | | | | | | | 5 fewer FP in TB LAMP | 5 fewer FP in TB LAMP | 4 fewer FP in TB LAMP | | | | | | | | | | |
| | | | | | | | | | 967 (951 to 977) | 962 (935 to 976) | 928 (913 to 938) | 923 (897 to 937) | 830 (817 to 839) | 826 (802 to 838) | | | | | | | |
| | | | | | | | | | 5 more TN in TB LAMP | 5 more TN in TB LAMP | 4 more TN in TB LAMP | | | | | | | | | | |

Explanations:

- a. Failure to perform mycobacterial culture on at least two sputum samples, failure to use liquid culture or because liquid culture contamination rates were outside the acceptable range of 5-12%
- b. Significant heterogeneity I²: 61 – 78%; P <0.03

Q5: AMONG ADULTS WITH PRESUMPTIVE PTB, SHOULD SPUTUM TB CULTURE WITH DRUG SUSCEPTIBILITY TESTING (DST) BE DONE WITH XPERT® MTB/RIF?

RECOMMENDATION

- a. Sputum culture with DST is recommended to detect resistance to other anti-TB drugs, when Xpert® MTB/RIF shows RR. (***Strong recommendation, moderate-quality evidence***)
- b. There is no evidence for or against concurrent testing with Xpert® MTB/RIF and sputum culture with DST in patients with presumptive PTB.

REMARKS AND CONSENSUS ISSUES

The second recommendation regarding concurrent testing was made as Xpert® MTB/RIF and TB culture are usually ordered at the same time in healthcare settings where both tests may be available. The TB MOP 6th ed. States that patients with Xpert® MTB/RIF results showing RR and who are considered high risk for DRTB, should submit two sputum samples for the following: 1) rapid molecular testing using line probe assay for determination of first-line and second-line drug resistance and 2) TB culture with phenotypic DST for first-line and second-line anti-TB drugs. [1]

Voting: 14/14 agree

SUMMARY OF EVIDENCE

There were no studies that directly compared the use of Xpert® MTB/RIF alone with Xpert® MTB/RIF and sputum culture with DST at the operational level (i.e in service provision to patients). All studies encountered to date determined the accuracy of Xpert® MTB/RIF in detecting TB using sputum culture as the standard reference. The evidence profile for this PICO question is reported in Appendix Q5 (Table Q5.2). Other studies investigated the ability of Xpert® MTB/RIF to detect RR. [2-4,6,7] This is particularly important especially in areas like the Philippines where the incidence of TB is ≥20/100 000 and DRTB is ≥2%. [5]

The 2016 NTPS involving 61,466 individuals aged ≥15 years showed that 1,159 individuals per 100,000 (95% CI 1,016-1,301) were bacteriologically positive for PTB. Under field conditions, Xpert® MTB/RIF detected 1.7 times more *M. tuberculosis* cases than sputum culture. [5]

Table Q5.1 Summary of studies on Xpert® MTB/Rif to detect rifampicin resistance.

| STUDY | STUDY DESIGN | POPULATION | REFERENCE STANDARD | SENSITIVITY % (95%CI) | SPECIFICITY % (95% CI) |
|--------------------------|---|--|--|-----------------------|------------------------|
| Horne, 2018 (USA) | Meta-analysis with 95 studies combined, 48 of which addressed Xpert® MTB/Rif RR detection | 8020 participants, respiratory specimens | Culture-based Drug Susceptibility Testing/ MTBDRplus | 96 (95.0-96.9) | 98 (97.6-98.3) |
| Lin Fan, 2018 (China) | Prospective Cohort | 256 smear-negative suspected TB cases (ages 11-89) 1625 sputum samples (out of 2241 various respiratory specimen collected) | DST | 100 (95.8-100) | 100 (29.2-100) |
| Feliciano, 2019 (Brazil) | Retrospective | 85 culture-positive PTB patients, 37 newly diagnosed and 48 previously treated (ages 13-82) | Phenotypic DST and/or WGS | 94.68 (90.4-97.4) | 97.8 (97.0-98.6) |
| Pandey, 2017 (Nepal) | Cross-sectional study | | Drug Susceptibility testing | 98.57 (92.3-99.9) | 100 (78.2-100) |

In the same survey, RR was detected in 29 of the 397 Xpert® MTB-positive specimens. Of these, 3 were susceptible by DST and 10 were concordant with Xpert® MTB/RIF. Rifampicin resistance rate by DST was 5.7% (13/397), of which 9 were both rifampicin (RIF) + isoniazid (INH) resistant. 17 of the 81 previously treated for TB were positive for RR by Xpert®. Hence, previous TB treatment was significantly associated with RR by Xpert®MTB/RIF (OR 8.2; 95% CI 3.8-18).

WHO recommended that DST should still be performed to detect resistance to anti-TB agents other than RIF and INH and to monitor progress of treatment.[8] Similar recommendations were echoed by the NTPS report. [5]

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APPENDIX Q5

Table Q5.2. Grade Pro Summary of Findings for Xpert® MTB/RIF and DST.

▼ Should GeneXpert MTB/Rif be used to diagnose MTB drug resistance in presumptive pulmonary tuberculosis? Bottom panel Explanations

i Source of data: from single study pooled across studies range from studies

| | | | | | | | | | | | |
|--|--------------------------------|--|-----------------------|-----------------------|------------------------|----------------------|-------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|----------|
| Sensitivity | 0.96 (95% CI: 0.95 to 0.97) | Effect per 1,000 | | | | | | | | | |
| Specificity | 0.98 (95% CI: 0.98 to 0.98) | Prevalences i 2% 21% 22% | | | | | | | | | |
| Factors that may decrease certainty of evidence | | | | | | | | | | | |
| Outcome | No of studies (No of patients) | Study design | i Risk of bias | i Indirectness | i Inconsistency | i Imprecision | i Other considerations | Effect per 1,000 patients tested | Test accuracy CoE | | |
| True positives (patients with MTB drug resistance) | 51 studies 2118 patients | cross-sectional (cohort type accuracy study) | serious ^a | serious | not serious | not serious | strong association | 19 (19 to 19) 1 (1 to 1) | 202 (199 to 204) 8 (6 to 1 1) | 211 (209 to 213) 9 (7 to 1 1) | MODERATE |
| False negatives (patients incorrectly classified as not having MTB drug resistance) | | | | | | | | | | | |
| True negatives (patients without MTB drug resistance) | 51 studies 7631 patients | cross-sectional (cohort type accuracy study) | serious ^a | serious ^b | | | | 960 (960 to 960) 20 (20 to 20) | 774 (774 to 774) 16 (16 to 16) | 764 (764 to 764) 16 (16 to 16) | - |
| False positives (patients incorrectly classified as having MTB drug resistance) | | | | | | | | | | | |

^a The majority of the studies were observational.

^b There was comparison between DST and Xpert® but DST is the standard reference and hence there was no study that directly addressed the query.

^c The prevalence rates of 2%, and 21% were based on the local prevalence of newly diagnosed and previously diagnosed cases of RR.

^d The 22% was the prevalence derived from the pooled data of the 51 studies.

Q6: AMONG ADULTS CLINICALLY DIAGNOSED WITH EXTRAPULMONARY TB (EPTB) BASED ON IMAGING STUDIES, SHOULD FURTHER BACTERIOLOGIC WORKUP BE DONE VERSUS HISTOPATHOLOGY ALONE TO ESTABLISH DIAGNOSIS OF EPTB?

RECOMMENDATION

Among adults clinically diagnosed with extrapulmonary TB (EPTB) based on radiologic/imaging findings, bacteriologic workup (i.e.Xpert® MTB/RIF and TB culture) in addition to histopathology are recommended for the diagnosis. **(Strong recommendation, low-quality evidence)**

REMARKS

Despite the low certainty of evidence, the guideline panel decided to strongly recommend performing bacteriologic workup (at least using Xpert® MTB/RIF) to reduce the variability in practice observed among clinicians. In the 2016 version of this guideline, Xpert® MTB/RIF was already recommended as the preferred initial diagnostic test for bacteriologic confirmation of EPTB. The NTP MOP 6th ed. Also states as policy that for patients suspected to have EPTB, body fluid or biopsy samples that are appropriate for Xpert® MTB/RIF testing shall be obtained for bacteriologic confirmation. Healthcare workers should be aware of the requirements for collection, storage and processing of extrapulmonary specimens for bacteriologic confirmation. [1]

Voting: 15/15 agree

SUMMARY OF EVIDENCE

Despite a systematic search of major databases, no studies were found directly evaluating the effect of additional bacteriological evaluation on TB detection for adult patients diagnosed with EPTB on the basis of strong clinical evidence and radiologic findings.

However, the search yielded a single-center prospective study from Pakistan that evaluated TB diagnosis based on microbiological and histopathological findings among patients suspected clinically to have tuberculous lymphadenitis (TBLA). [2] Results of this study showed that among 297 included patients, 89.6% had histopathology suggestive of TB and there was microbiologic evidence of TB in 32.6% by Xpert® MTB/RIF, 26.6% by TB culture, and 12.5% by AFB smear positivity. The histopathology findings among those with positive microbiologic evidence of TB ranged from acute suppurative or necrotizing inflammation to chronic granulomatous inflammation, caseation necrosis, or reactive lymphoid hyperplasia.

Table Q6.1. Test characteristics using histopathology as reference standard

| Test | Sensitivity % | Specificity % | LR+ | LR- | AUC, % (95% CI)* |
|-------------|---------------|---------------|------|------|------------------|
| AFB smear | 12.7 | 93.4 | 1.92 | 0.93 | 51.5 (43.2-59.8) |
| AFB culture | 30.7 | 90.2 | 3.13 | 0.77 | 60.7 (53.1-68.3) |
| GeneXpert® | 33.2 | 85.0 | 2.21 | 0.79 | 59.5 (51.7-67.4) |

*AUC-area under the curve, measures overall diagnostic accuracy

The accuracy of Xpert® MTB/RIF was also determined compared to culture positivity for *Mycobacterium tuberculosis* (MTB). The sensitivity, specificity, positive and negative likelihood ratio of Xpert® MTB/RIF were as follows: 65.7%, 80.4%, 3.35, and 0.43, respectively. The overall diagnostic accuracy using area under the curve (AUC) was 51.5% (43.2-59.8).

A recently published systematic review and meta-analysis determined the accuracy of Xpert® MTB/RIF compared with culture in people with presumptive EPTB. [2] Across the different types of specimens, pooled Xpert® MTB/RIF sensitivity varied from 31% in pleural tissue to 97% in bone or joint fluid, and more than 80% in urine, bone, or joint fluid and tissue samples. Pooled Xpert® MTB/RIF specificity had less variation: 82% for bone or joint tissue to ≥ 98% in cerebrospinal fluid, pleural fluid, urine and peritoneal fluid.

Xpert® MTB/RIF pooled sensitivity and specificity (95% credible interval) compared to culture in cerebrospinal fluid were 71.1% (60.9% to 80.4%) and 98.0% (97.0% to 98.8%), respectively (29 studies, 3774 specimens; moderate level of evidence). The positive and negative likelihood ratios were 35.55 and 0.29, respectively. (Appendix Q6, Table Q6.2a)

Xpert® MTB/RIF pooled sensitivity and specificity (95% credible interval) compared to culture in pleural fluid were 50.9% (39.7% to 62.8%) and 99.2% (98.2% to 99.7%), respectively (27 studies, 4006 specimens; low level of evidence). The positive and negative likelihood ratios were 63.62 and 0.49, respectively. (Appendix Q6, Table Q6.2b)

Xpert® MTB/RIF pooled sensitivity and specificity (95% credible interval) compared to culture in urine were 82.7% (69.6% to 91.1%) and 98.7% (94.8% to 99.7%), respectively (13 studies, 1199 specimens; moderate level of evidence). The positive and negative likelihood ratios were 63.63 and 0.18, respectively. (Appendix Q6, Table Q6.2c)

Recommendations from Other Clinical Practice Guidelines

- As per the WHO, the basis of EPTB diagnosis should be one of the following: one culture-positive specimen, or positive histology, or strong clinical evidence consistent with active EPTB.
- EPTB presentation often varies with an extremely wide spectrum of signs and symptoms dependent on the organs affected, aggressiveness of disease and host

immune response. [3] Also, EPTB is often pauci-bacillary, and the sites of infection are difficult to access for specimen collection for diagnostic work-up (i.e., microscopy, histology, culture or molecular tests). [3] Currently, there is no available and reliable single rule-out test (i.e., test with minimal or absent false-negative results) in the diagnosis of EPTB. Thus, the diagnosis of EPTB is often made in the context of integrating several non-specific findings from different forms of investigations. [3]

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Table Q6.2 (a-c) Summary of Findings on the Diagnostic Performance of Xpert MTB/RIF

Table Q6.2a Summary of Findings on the Diagnostic Performance of Xpert MTB/RIF in CSF

SUMMARY OF FINDINGS

Summary of findings 1. Xpert® MTB/RIF in cerebrospinal fluid

Participants: patients presumed to have TB meningitis

Prior testing: patients who received Xpert testing may first have undergone a health examination (history and physical examination) and possibly a chest radiograph

Role: replacement test for usual practice

Settings: primarily tertiary care centres (the index test was often run in reference laboratories)

Index (new) test: Xpert

Studies: cross-sectional studies

Limitations: participants were evaluated exclusively as inpatients at a tertiary care centre, or, if the clinical setting was not reported, Xpert was performed at a reference laboratory rather than at primary care facilities and local hospitals

Pooled sensitivity (95% CrI): 71.1% (60.9 to 80.4); **pooled specificity (95% CrI):** 98.0% (97.0 to 98.8)

| Test result | 1000 people tested for TB using Xpert® MTB/RIF (95% CrI) | | | Number of participants (studies) | Certainty of the evidence (GRADE) |
|--|--|------------------|-------------------|----------------------------------|-----------------------------------|
| | Prevalence of 1% | Prevalence of 5% | Prevalence of 10% | | |
| True-positives (patients with TB meningitis) | 7 (6 to 8) | 36 (30 to 40) | 71 (61 to 80) | 433 (29) | ⊕⊕⊕⊕ Moderate ^{a,b} |
| False-negatives (patients incorrectly classified as not having TB meningitis) | 3 (2 to 4) | 14 (10 to 20) | 29 (20 to 39) | | |
| True-negatives (patients without TB meningitis) | 970 (960 to 978) | 931 (922 to 939) | 882 (873 to 889) | 3341 (29) | ⊕⊕⊕⊕ High |
| False-positives (patients incorrectly classified as having TB meningitis) | 20 (12 to 30) | 19 (11 to 28) | 18 (11 to 27) | | |

Abbreviations: CrI: credible interval; TB: tuberculosis.

The median prevalence in the included studies was 10%. We also included other plausible prevalence estimates for the target condition.

Credible limits were estimated based on those around the point estimates for pooled sensitivity and specificity. The results presented in this table should not be interpreted in isolation from results of the individual included studies contributing to each summary test accuracy measure. These are reported in the main body of the text of the review.

^aAs assessed by QUADAS-2, for the reference standard domain only four studies (14%) had unclear risk of bias because specimens underwent decontamination. We did not downgrade.

^bThe wide CrI around true-positives and false-negatives may lead to different decisions depending on which credible limits are assumed. We downgraded one level.

GRADE certainty of the evidence

High: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

The results presented in this table should not be interpreted in isolation from results of the individual included studies contributing to each summary test accuracy measure.

Table Q6.2b Summary of Findings on the Diagnostic Performance of Xpert MTB/RIF in Pleural Fluid

Summary of findings 2. Xpert® MTB/RIF in pleural fluid

Participants: patients presumed to have pleural TB

Prior testing: patients who received Xpert testing may first have undergone a health examination (history and physical examination) and possibly a chest radiograph

Role: replacement test for standard practice, which may include more invasive tests, such as pleural biopsy

Settings: primarily tertiary care centres (the index test was often run in reference laboratories)

Index (new) test: Xpert

Reference standard: solid or liquid culture

Studies: cross-sectional studies

Limitations: in most studies, participants were evaluated at a tertiary care centre, or if the clinical setting was not reported, Xpert was performed at a reference laboratory

Pooled sensitivity (95% CrI): 50.9% (39.7 to 62.8); **pooled specificity (95% CrI):** 99.2% (98.2 to 99.7)

| Test result | 1000 people tested for TB using Xpert®MTB/RIF (95% CrI) | | | Number of participants (studies) | Certainty of the evidence (GRADE) |
|---|---|-------------------|-------------------|----------------------------------|-----------------------------------|
| | Prevalence of 10% | Prevalence of 15% | Prevalence of 25% | | |
| True-positives (patients with pleural TB) | 25 (20 to 31) | 76 (60 to 94) | 127 (99 to 157) | 606 (27) | ⊕⊕○○ Low ^{a,b} |
| False-negatives (patients incorrectly classified as not having pleural TB) | 25 (19 to 30) | 74 (56 to 90) | 123 (93 to 151) | | |
| True-negatives (patients without pleural TB) | 942 (933 to 947) | 843 (835 to 847) | 744 (736 to 748) | 3399 (27) | ⊕⊕⊕⊕ High |
| False-positives (patients incorrectly classified as having pleural TB) | 8 (3 to 17) | 7 (3 to 15) | 6 (2 to 14) | | |

Abbreviations: CrI: credible interval; TB: tuberculosis.

The median prevalence in the included studies was 15%. We also included other plausible prevalence estimates for the target condition.

^aAs assessed by QUADAS-2, for the reference standard domain, ten studies (37%) had unclear risk of bias because specimens underwent decontamination. We did not downgrade.

^bFor individual studies, sensitivity estimates ranged from 10% to 100%. We could not explain heterogeneity by study quality or other factors. We downgraded two levels for inconsistency.

GRADE certainty of the evidence

High: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

The results presented in this table should not be interpreted in isolation from results of the individual included studies contributing to each summary test accuracy measure.

Table Q6.2c Summary of Findings on the Diagnostic Performance of Xpert MTB/RIF in Urine

Summary of findings 3. Xpert® MTB/RIF in urine

Participants: patients presumed to have genitourinary TB

Prior testing: patients who received Xpert testing may first have undergone a health examination (history and physical examination) and possibly a chest radiograph

Role: replacement test for standard practice, which may include more invasive tests, such as biopsy of affected organs

Settings: primarily tertiary care centres (the index test was often run in reference laboratories)

Index (new) test: Xpert

Reference standard: solid or liquid culture

Studies: cross-sectional studies

Limitations: in most studies, participants were evaluated at a tertiary care centre, or if the clinical setting was not reported, Xpert was performed at a reference laboratory

Sensitivity: 82.7% (69.6 to 91.1); **specificity:** 98.7% (94.8 to 99.7)

| Test result | 1000 people tested for TB using Xpert®MTB/RIF (95% CrI) | | | Number of participants (studies) | Certainty of the evidence (GRADE) |
|---|--|---------------------|----------------------|-------------------------------------|-----------------------------------|
| | Prevalence of 2% | Prevalence of 7% | Prevalence of 15% | | |
| True-positives (patients with genitourinary TB) | 17 (14 to 18) | 58 (49 to 64) | 124 (104 to 137) | 73 (13) | ⊕⊕⊕ Moderate ^{a,b} |
| False-negatives (patients incorrectly classified as not having genitourinary TB) | 3 (2 to 6) | 12 (6 to 21) | 26 (13 to 46) | | |
| True-negatives (patients without genitourinary TB) | 967 (929 to 977) | 918 (882 to 927) | 839 (806 to 847) | 1126 (13) | ⊕⊕⊕ Moderate ^c |
| False-positives (patients incorrectly classified as having genitourinary TB) | 13 (3 to 51) | 12 (3 to 48) | 11 (3 to 44) | | |

Abbreviations: CrI: credible interval; TB: tuberculosis.

The median prevalence in the included studies was 7%. We included what we considered to be plausible prevalence estimates for the target condition.

^aAs assessed by QUADAS-2, for the reference standard domain only four studies (31%) had unclear risk of bias because specimens underwent decontamination.

^bFor individual studies, sensitivity estimates ranged from 0% to 100%. We thought that the small number of culture-positives in studies could explain some, but probably not all, of the variation in sensitivity results. We downgraded one level.

^cThe wide CrI around true-negatives and false-positives may lead to different decisions depending on which credible limits are assumed. We downgraded one level.

GRADE certainty of the evidence

High: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

The results presented in this table should not be interpreted in isolation from results of the individual included studies contributing to each summary test accuracy measure.

Q7: AMONG ADULTS WHOSE BACTERIOLOGIC WORKUP FOR ACTIVE TB DISEASE IS NEGATIVE, HOW EFFECTIVE IS EMPIRIC TREATMENT BASED ON A PHYSICIAN'S CLINICAL JUDGEMENT IN ACHIEVING TREATMENT SUCCESS AND REDUCING RELAPSE AND MORTALITY?

RECOMMENDATION

There is no evidence for or against recommending empiric anti-TB treatment based on a physician's clinical judgment among patients with negative bacteriologic tests, but with clinical signs and symptoms of TB. However, empiric treatment may be considered for HIV-positive patients. (**Weak recommendation, very low-quality evidence**)

REMARKS

Physicians treat patients with anti-TB medications based solely on clinical diagnosis with no bacteriologic evidence of TB. However, there is limited information regarding the outcome of patients who are empirically treated for TB. Due to the paucity of studies addressing this question, as well as the low quality of the evidence available, the guideline panel is unable to make any recommendations for this specific clinical scenario. The panel recognizes that there is a knowledge gap that should be addressed by future research conducted on this specific population. Further studies should include a description of patient characteristics (e.g., symptomatic, non-responsive to antibiotics) to facilitate valid comparisons with participants in other studies.

In the NTP MOP 6th ed., TB suspects with negative bacteriologic tests are evaluated by the health facility physician who shall decide on the diagnosis based on best clinical judgment, and if needed, initiate treatment with anti-TB medications. The patient can be also referred to the TB Medical Advisory Committee (TB MAC). [1] The panel, however, recommends empiric TB treatment among HIV-positive patients whose bacteriologic workup for TB is negative. This was based on one observational study among severely ill HIV patients with smear negative PTB. The study showed that patients who were empirically treated with anti-TB medications based on clinical decision had better 8 week mortality outcomes after starting treatment, compared to no treatment.

Voting: 15/15 agree

SUMMARY OF EVIDENCE

Based on one cohort study with a low risk of bias, smear negative PTB suspect patients who were not given treatment had a better mortality outcome at 6 months after the 1st consultation, compared to those who were given empiric TB treatment (Figure Q7.1). This was observed for both HIV-positive and HIV-negative subgroups. [1]

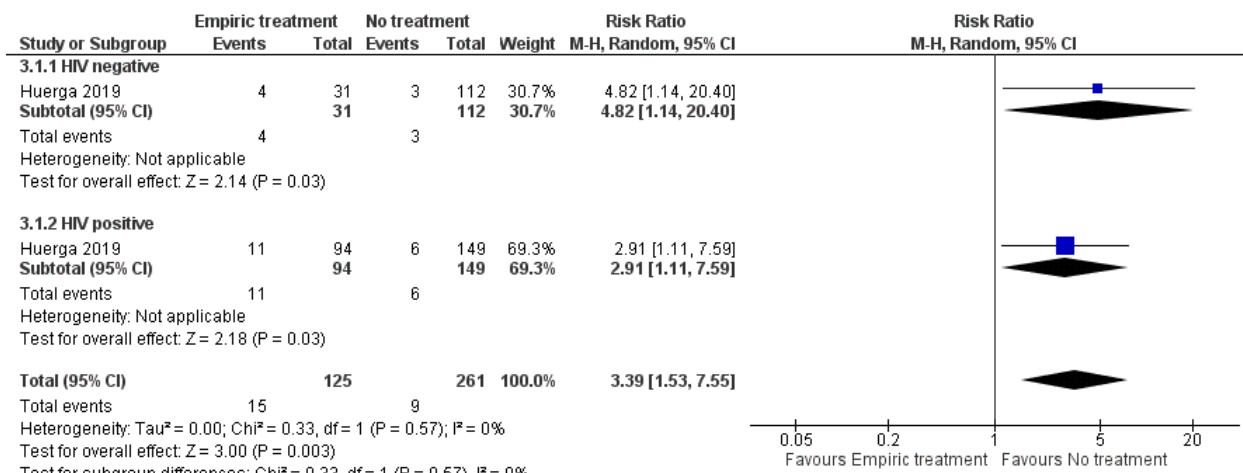


Figure Q7.1 Empiric treatment vs. no treatment in smear-negative patients

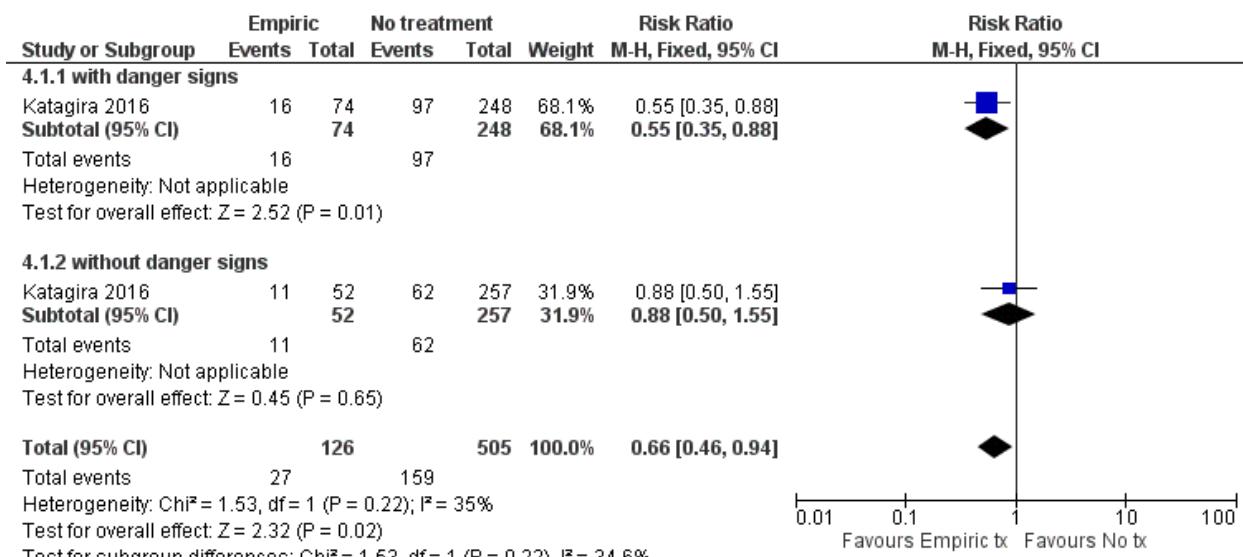


Figure Q7.2 Empiric treatment vs. No Treatment Among HIV patients

Based on a single observational study with a low risk of bias, empiric treatment based on clinical decision of smear-negative, severely-ill HIV patients had better mortality outcome at 8 weeks versus those were not given treatment (Figure Q7.2).[3] Severely ill was described as a subgroup of HIV patients with 3 danger signs like fever (axillary temperature >39°C), tachycardia (pulse>120 beats per minute), or tachypnea (respiratory rate >30 breaths per minute). For HIV patients without warning signs, there was no difference in outcomes between empiric treatment or no treatment (Table Q7.2, Appendix Q7).

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3. Katagira W, Walter ND, Boon S Den, Kalema N, Ayakaka I, Vittinghoff E, et al. Empiric TB treatment of severely ill patients with HIV and presumed pulmonary TB improves survival. *J Acquir Immune Defic Syndr.* 2016;72(3):297–303.

APPENDIX Q7

Table Q7.1 Summary of Evidence on Treatment versus no Treatment for PTB

Author(s): M. Abat

Question: No treatment compared to treatment of bacteriologically confirmed PTB for PTB in bacteriologically negative patients

Setting: Western Kenya

Bibliography: Huerga H, Ferlazzo G, Wanjala S, Bastard M, Bevilacqua P, Ardizzone E, et al. Mortality in the first six months among HIV-positive and HIV-negative patients empirically treated for tuberculosis. BMC Infect Dis. 2019;19(132):1-11.

| Certainty assessment | | | | | | | No of patients | | Effect | | Certainty | Importance |
|---|-----------------------|--------------|---------------|----------------------|-----------------------------|----------------------|----------------|--|----------------------------|---|-----------|------------|
| No of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | No treatment | treatment of bacteriologically confirmed PTB | Relative (95% CI) | Absolute (95% CI) | | |
| Mortality at 6 months after 1st consultation | | | | | | | | | | | | |
| 1 | observational studies | not serious | not serious | serious ^a | serious ^b | none | 9/261 (3.4%) | 16/184 (8.7%) | RR 0.45 (0.17 to 1.17) | 48 fewer per 1,000 (from 72 fewer to 15 more) | | VERY LOW |
| Mortality at 6 months after 1st consultation – HIV negative | | | | | | | | | | | | |
| 1 | observational studies | not serious | not serious | not serious | very serious ^{b,c} | none | 3/112 (2.7%) | 1/49 (2.0%) | RR 1.31 (0.14 to 12.31) | 6 more per 1,000 (from 18 fewer to 231 more) | | VERY LOW |
| Mortality at 6 months after 1st consultation – HIV positive | | | | | | | | | | | | |
| 1 | observational studies | not serious | not serious | serious ^d | not serious | none | 6/149 (4.0%) | 15/135 (11.1%) | RR 0.36 (0.14 to 0.91) | 71 fewer per 1,000 (from 96 fewer to 10 fewer) | | VERY LOW |

CI: Confidence interval; RR: Risk ratio

Explanations

- a. mix of HIV and non-HIV patients
- b. CI straddles unity
- c. wide CI
- d. HIV patients

Table Q7.2 Summary of Evidence on Empiric Treatment versus No Treatment for HIV patients

Author(s): M. Abat

Question: Empiric treatment compared to no treatment in severely ill HIV patients for PTB in bacteriologically negative patients

Setting: Kampala, Uganda

Bibliography: Katagira W, Walter ND, Boon S Den, Kalema N, Ayakaka I, Vittinghoff E, et al. Empiric TB treatment of severely ill patients with HIV and presumed pulmonary TB improves survival. J Acquir Immune Defic Syndr. 2016;72(3):297–303.

| Certainty assessment | | | | | | | No of patients | | Effect | | Certainty | Importance |
|---|-----------------------|--------------|---------------|----------------------|----------------------|----------------------|-------------------|---|---------------------------|---|--|------------|
| No of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Empiric treatment | no treatment in severely ill HIV patients | Relative (95% CI) | Absolute (95% CI) | | |
| Mortality at 8 weeks after starting treatment | | | | | | | | | | | | |
| 1 | observational studies | not serious | not serious | serious ^a | not serious | none | 27/126 (21.4%) | 159/505 (31.5%) | RR 0.66 (0.46 to 0.94) | 107 fewer per 1,000 (from 170 fewer to 19 fewer) |  VERY LOW | |
| Mortality at 8 weeks after starting treatment – with danger signs | | | | | | | | | | | | |
| 1 | observational studies | not serious | not serious | serious ^a | not serious | none | 16/74 (21.6%) | 97/248 (39.1%) | RR 0.55 (0.35 to 0.88) | 176 fewer per 1,000 (from 254 fewer to 47 fewer) |  VERY LOW | |
| Mortality at 8 weeks after starting treatment – without danger signs | | | | | | | | | | | | |
| 1 | observational studies | not serious | not serious | serious ^a | serious ^b | none | 11/52 (21.2%) | 62/257 (24.1%) | RR 0.88 (0.50 to 1.55) | 29 fewer per 1,000 (from 121 fewer to 133 more) |  VERY LOW | |

CI: Confidence interval; RR: Risk ratio

Explanations

a. HIV patients

b. straddles unity

Q8: AMONG ADULTS WITH PRESUMPTIVE PULMONARY TB (PTB), HOW ACCURATE IS SPUTUM XPERT® MTB/RIF COMPARED TO SPUTUM XPERT ULTRA IN ESTABLISHING DIAGNOSIS OF PULMONARY TB?

Compared with Xpert MTB/RIF, Xpert Ultra had higher sensitivity and lower specificity for PTB. Recognizing the minimal trade off with Xpert Ultra, it is non-inferior to, and may be used in lieu of Xpert MTB/Rif as the initial test in adults with presumptive PTB. (**Strong Recommendation, high quality evidence**)

REMARKS

Xpert MTB/Rif Ultra is currently provided in selected private hospitals and laboratories, and soon in government facilities. DOH has recently released guidance for the interpretation for Xpert MTB/Rif Ultra.

SUMMARY OF EVIDENCE

Xpert Ultra sensitivity was slightly higher at 88%, (CI 85% to 91%) compared to Xpert MTB/RIF at 85% (CI 82% to 88%); however, Xpert Ultra specificity was slightly lower at 96% (CI 94% to 97%) versus Xpert MTB/RIF at 98% (CI 97% to 98%) [1].

Table Q8.1 Pooled sensitivity and specificity of Xpert MTB/Rif and Xpert Ultra as diagnostic tool for PTB

| Test | Number of participants (studies) | Quality of evidence | Sensitivity | Specificity |
|---------------|----------------------------------|---------------------|----------------|----------------|
| Xpert MTB/Rif | 10, 409 (70 studies) | High | 85% (82 to 88) | |
| | 26,828 (70 studies) | High | | 98% (97 to 98) |
| Xpert Ultra | 462 (1 study) | Moderate | 88% (85 to 91) | |
| | 977 (1 study) | Moderate | | 96% (94 to 97) |

Studies included in the analysis for Xpert MTB/Rif had median tuberculosis prevalence of 26% and are applicable to settings with higher tuberculosis prevalence such as the Philippines.

Xpert Ultra was developed to improve Xpert MTB/Rif sensitivity especially among smear-negative and HIV-associated TB. One study reported that the limit of detection using Xpert MTB/Rif of 112.6 CFU/ml increased to 15.6 CFU/ml using Xpert Ultra [2]. It is worth noting that Xpert Ultra added a new result category, “trace call”, corresponding to the lowest MTB burden detection [3].

A WHO Technical Experts Group agreed that Xpert Ultra was non-inferior to Xpert MTB/Rif assay for the detection of rifampicin resistance. It also recognized that it has higher sensitivity than Xpert MTB/Rif particularly in smear-negative culture-positive specimens and in specimens from HIV-infected patients. However, this increase in sensitivity results in a slightly lower specificity in a higher TB burden setting as Xpert Ultra also detects non-replicating or non-viable bacilli present particularly in patients with recent history of TB.

In the 2020 WHO Consolidated guidelines for diagnostics, repeat testing with Xpert Ultra for patients with “trace call” result was not conditionally recommended since evidence was insufficient at that time.

Special mention was given regarding the use of Xpert Ultra in adults with signs and symptoms of PTB, with a prior history of TB and an end of treatment within the last 5 years – the lower threshold for bacillary detection by Xpert Ultra might be associated with a high false-positive rate. As such, this was only given a conditional recommendation due to the low certainty for test accuracy in these clinical scenarios [4].

Algorithm for the Interpretation of Xpert MTB/Rif Ultra Results

Adapted from *GLI Planning for country transition to Xpert MTB/RIF Ultra Cartridges (2017)*
downloadable at http://www.stoptb.org/wg/gli/assets/documents/GLI_ultra.pdf

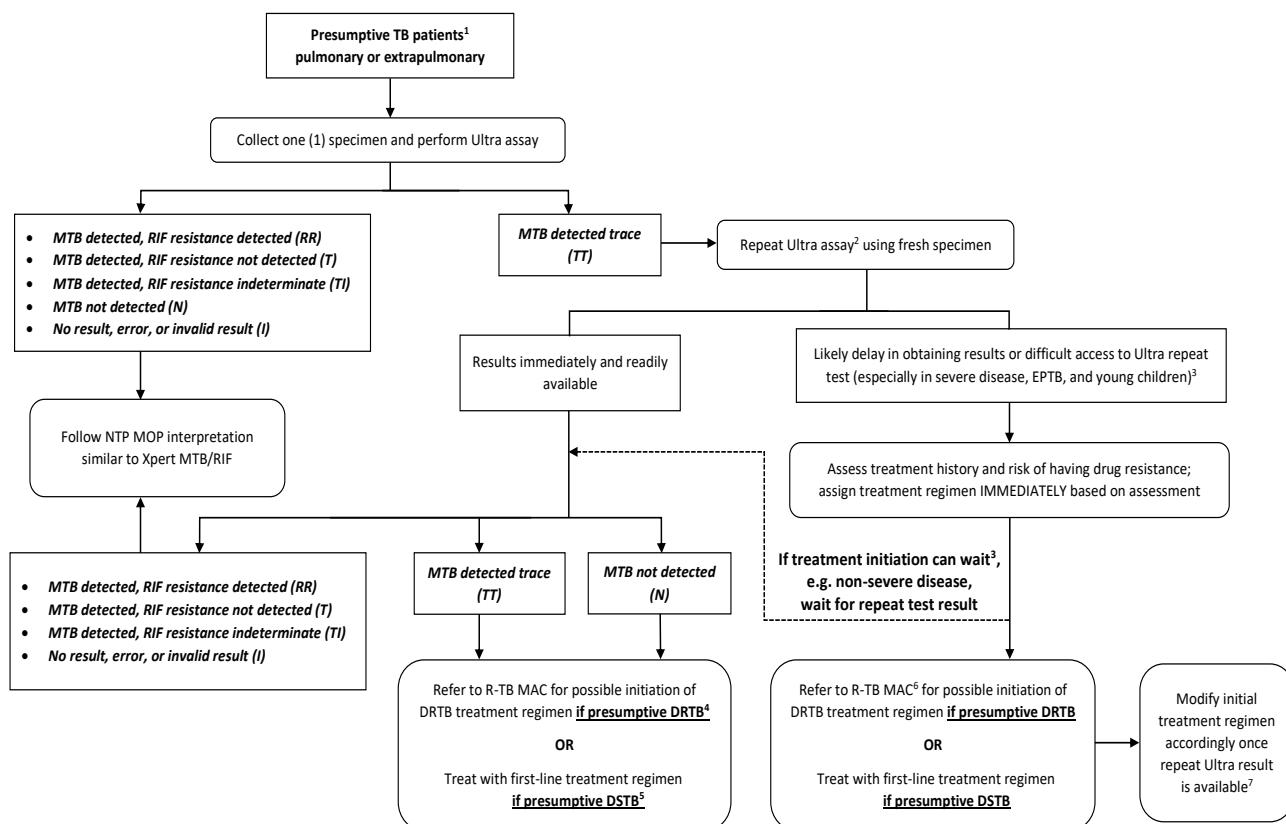


Figure Q8.1. Algorithm for the Interpretation of Xpert MTB/Rif Ultra Results

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Q9: AMONG ADULTS WITH PRESUMPTIVE EXTRAPULMONARY TB (EPTB), HOW ACCURATE IS XPERT® MTB/RIF COMPARED TO XPERT® ULTRA IN ESTABLISHING DIAGNOSIS OF EXTRAPULMONARY TB?

RECOMMENDATION

In general, among patients with presumptive EPTB, Xpert MTB/RIF Ultra is non-inferior to, and may replace Xpert MTB/RIF in establishing diagnosis of EPTB. (**Strong recommendation, low quality of evidence**)

TB meningitis

Strong recommendation, low certainty of evidence for test accuracy for Xpert Ultra.

TB lymphadenitis (both lymph node biopsy and lymph node aspirate)

Conditional recommendation, low certainty of evidence for Xpert Ultra

EPTB – Others

For other specimens such as pleural fluid, peritoneal fluid, pericardial synovial fluid, and urine, conditional recommendation, insufficient evidence for Xpert Ultra.

SUMMARY OF EVIDENCE

Due to challenges encountered in obtaining extrapulmonary specimens and technical limitations of conventional bacteriological diagnosis, a mix of both microbiologic and composite reference standards are used in literature for extrapulmonary TB. A recently published Cochrane review in 2021 included studies until January 2020 [1], evaluating Xpert MTB/RIF Ultra and Xpert MTB/RIF assays for extrapulmonary tuberculosis and rifampicin resistance in adults.

Sensitivity varied across specimens while for most specimens, specificity remained high.

In 2017, WHO commissioned a non-inferiority analysis [2] of Xpert Ultra compared with Xpert MTB/Rif. Based on the results of this study, WHO recommended that use of Xpert MTB/Rif be applied to Xpert Ultra as well. This was reiterated in the updated consolidated guidelines of 2020 [3].

TB meningitis (CSF)

Six studies [1-6] were included with n= 475. The pooled sensitivity for Xpert Ultra was 89.4% (95% CI, 79.1-95.6) and pooled specificity was 91.2% (83.2-95.7). There was low certainty of evidence, and it was downgraded for imprecision.

For Xpert MTB/Rif, 30 studies in one review [1] were included with 3395 subjects. Pooled sensitivity was 71.1% (95% CI, 62.8-79.1) and pooled specificity was 96.9% (95% CI, 95.4-98) with moderate certainty of evidence. This was also downgraded for imprecision.

Overall, for CSF samples, Xpert Ultra had higher sensitivity but lower specificity compared to Xpert MTB/Rif.

Pleural fluid

For Xpert Ultra, four studies [6-9] were included with 398 subjects. The pooled sensitivity was 75% (95% CI, 58-86.4) and pooled specificity was 87% (95% CI, 63.1-97.9) with very low certainty of evidence. This was downgraded for indirectness, inconsistency and imprecision.

For Xpert MTB/Rif, 25 studies were included in one review [1], with a total of 3065 subjects. The pooled sensitivity was 49.5% (95% CI, 39.8-59.9) and pooled specificity was 98.9% (95% CI, 97.6-99.7) with moderate certainty of evidence. Downgraded for indirectness, inconsistency and imprecision.

There were no studies that directly compared Xpert Ultra vs. Xpert MTB/Rif using pleural fluid samples.

Lymph node aspirate

Against composite reference standard

For Xpert ultra, only 1 study [10] was included with 73 subjects. Sensitivity was 70% (95% CI, 51-85) and specificity was 96.4 (95% CI, 91.3-98.6) with very low certainty of evidence. This was downgraded for indirectness and imprecision.

For Xpert MTB/Rif, four studies [1, 11-14] were included with 670 subjects. Pooled sensitivity was 81.6% (95% CI, 61.9-93.3) and pooled specificity was 96.4 (85% CI, 91.3-98.6) with low certainty of evidence. This was downgraded for risk of bias and indirectness.

For other EPTB specimens, there were sparse subjects and trials.

The higher sensitivity of Xpert Ultra is due to its low TB detection limit and is found in specimens with low numbers of bacilli, especially in smear-negative, culture-positive specimens. However, because of this, the Ultra may be more prone to detecting small numbers of non-replicating or non-viable bacilli present. This may give rise to false positive results in TB detection. Rifampicin resistance detection is not similarly affected.

The Perez-Risco study [7] used different types of specimens: sterile fluids, nonsterile fluids, lymph nodes, abscess aspirates, and tissues. The highest sensitivity was obtained in samples of lymph nodes (94.1%), and nonsterile fluids (93.7%), followed by tissue specimens (86.6%), stool material (80%), abscess aspirates (64.7%) and sterile fluids (60.5%)

More studies on Xpert Ultra with standardized sampling collection will be helpful to inform future practice.

Recommendations from other CPGs:

In 2020 the WHO recommended the use in all settings of Xpert® MTB/RIF Ultra as a replacement for the Xpert® MTB/RIF cartridge.

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UPDATE ON TREATMENT OF TUBERCULOSIS

Q10: AMONG ADULTS NEWLY DIAGNOSED WITH RIFAMPICIN-SUSCEPTIBLE PTB, IS STANDARD 2HRZE/4HR STILL THE RECOMMENDED TREATMENT REGIMEN TO OPTIMIZE TREATMENT SUCCESS/COMPLETION AND REDUCE THE RISK OF TREATMENT FAILURE, RELAPSE, AND MORTALITY COMPARED TO HRZE PLUS FLUOROQUINOLONE?

RECOMMENDATION

- a. Among adults newly diagnosed with rifampicin susceptible PTB, 2HRZE/4HR is still the recommended treatment regimen. (**Strong recommendation, high-quality evidence**)
- b. The inclusion of fluoroquinolone as part of the primary regimen for rifampicin susceptible PTB is not recommended. (**Strong recommendation, high-quality evidence**)

REMARKS

A member of the guideline panel suggested adding the phrase “as long as subject to close bacteriological monitoring” to recommendation 10a due to the observed increase in INH resistance among patients (estimated at 10-15%). Relapse rates have also increased sharply, matching INH resistance. Monitoring sputum samples (i.e. sputum at 5 months) was also suggested. Neither the substitution nor addition of fluoroquinolone to the primary regimen were recommended as they do not offer any additional benefit. **Voting: 14/15 agree, 1/15 abstain**

SUMMARY OF EVIDENCE

Search strategy used the PubMed and search terms: ("smear negative") OR ("bacteriologically negative") OR ("sputum negative") OR ("sputum smear negative") OR (smear negative) OR (sputum negative) OR (bacteriologically negative)) AND ("Tuberculosis"[Mesh]) AND ((empiric treatment") OR ("decision to treat") OR (empiric treatment) OR (decision to treat))

Based on high level of evidence [1,2], fluoroquinolone-containing regimens did not show superiority over standard 2HRZE/4HR on the following outcomes – treatment failure, serious adverse events and all-cause death. However, compared with HRZE alone, moxifloxacin-containing regimens significantly increased sputum conversion for patients with newly diagnosed PTB.

A network meta-analysis of 12 randomized controlled trials involving 6,465 newly diagnosed, sputum positive adult patients was reviewed. [1] The regimens compared were HRZE, RZE+Moxifloxacin (MRZE), HRZ+Moxifloxacin (HRZM), HRZ+Gatifloxacin (HRZG), HRZ+Ofloxacin (HRZO), HR+Ciprofloxacin (HRC), HRZE+Moxifloxacin (HRZEM), and HRZE+Levofloxacin (HRZELo). All studies included reported sputum conversion by the eighth week using Löwenstein-Jensen solid culture method. HRZEM (OR 4.96; 95% CI 2.83-8.67), MRZE (OR 1.48; 95% CI 1.19-1.84) and HRZM (OR 1.32; 95% CI 1.08-1.62) had higher sputum conversion rates than the HRZE regimen. HRZM (OR 1.29; 95% CI 1.04-1.59) and MRZE (OR 1.27; 95% CI 1.07-1.50) regimens also had higher conversion rates than HRZE using the liquid medium. In contrast, HRC (OR 0.39; 95% CI 0.19-0.77) and HRZO (OR 0.47; 95% CI 0.24-0.92) had lower conversion rates compared to HRZE.

The meta-analysis did not show significant differences in treatment failure for MRZE (OR 0.72; 95% CI 0.04-14.58), HRZM (OR 0.46; 95% CI 0.06-3.30) and HRZG (OR 0.27; 95% CI 0.02-3.88). The difference in all-cause mortality by the end of treatment and during the intensive phase was likewise not statistically significant. The most common adverse events noted were gastrointestinal, neurological, skin and appendages, cutaneous and urinary system disorders, but no statistical differences were found among them by the end of treatment and during the two-month intensive phase: MRZE (OR 0.87, 95% CI 0.60–1.25) and HRZM (OR 0.83, 95% CI 0.55–1.26).[1]

Another meta-analysis including 9 studies examined the effectiveness and safety of moxifloxacin in addition to the recommended regimen for the treatment of TB. [2] The results showed that adding moxifloxacin during the first 2 months of drug treatment for TB increased sputum conversion compared to the recommended regimen alone (OR 1.895; 95% CI 1.355-2.651, $p = 0.000$). Moreover, the moxifloxacin-containing regimen reduced TB relapse after treatment (OR 0.516; 95% CI 0.342-0.920, $p = 0.022$), suggesting that the introduction of moxifloxacin into the recommended regimen reduced TB relapse after treatment. No significant difference was noted in terms of adverse events (OR 1.001; 95% CI 0.855-1.172, $p = 0.989$).

Appendix Q10 shows the summary of findings table for the results discussed above.

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APPENDIX Q10

Table Q10.1 Summary of Certainty of Evidence on Moxifloxacin + recommended regimen compared to recommended regimen for newly diagnosed TB

Authors: Tan, Carol

Question: Moxifloxacin + recommended regimen compared to recommended regimen for newly diagnosed TB

Setting:

Bibliography: Xu P, Chen H, Xu J, et al. Moxifloxacin is an effective and safe candidate agent for tuberculosis treatment: a meta-analysis. Int J Infect Dis. 2017;60:35-41. doi:10.1016/j.ijid.2017.05.003

| No. of studies | Study design | Certainty assessment | | | | | No. of patients | | Effect | | Certainty | Importance |
|----------------|--------------|----------------------|---------------|--------------|-------------|----------------------|------------------------------------|---------------------|-------------------|-------------------|-----------|------------|
| | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Moxifloxacin + recommended regimen | Recommended regimen | Relative (95% CI) | Absolute (95% CI) | | |

Sputum conversion (assessed with: 2 or more consecutive negative sputum cultures detected at the endpoint of treatment)

| | | | | | | | | | | | | |
|---|----------------------|-------------|-------------|-------------|-------------|------|--|--|------------------------|---|-----------|----------|
| 9 | 78 standardiz trials | not serious | not serious | not serious | not serious | none | | | OR 1.90 (1.35 to 2.65) | 2 fewer per 1,000 (from 3 fewer to 1 fewer) | ⊕⊕⊕⊕ HIGH | CRITICAL |
|---|----------------------|-------------|-------------|-------------|-------------|------|--|--|------------------------|---|-----------|----------|

Recurrence of TB (follow up: mean 12 months; assessed with: recurrence during 1 year after treatment was collected)

| | | | | | | | | | | | | |
|---|----------------------|-------------|-------------|-------------|-------------|------|--|--|------------------------|---|-----------|--|
| 3 | 78 standardiz trials | not serious | not serious | not serious | not serious | none | | | OR 0.56 (0.34 to 0.92) | 1 fewer per 1,000 (from 1 fewer to 0 fewer) | ⊕⊕⊕⊕ HIGH | |
|---|----------------------|-------------|-------------|-------------|-------------|------|--|--|------------------------|---|-----------|--|

CI: Confidence interval; **RR:** Risk ratio

Table Q10.2 Summary of evidence of Fluoroquinolones in Newly Diagnosed TB.

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| Outcomes | Impact | No. of participants (studies) | Certainty of the evidence (GRADE) |
|---|--|-------------------------------|-----------------------------------|
| Week-8 Sputum Negativity Assessed with: Löwenstein-Jensen solid culture method Follow up: range 2 months to 30 months | HRZEM (OR 4.96; 95% CI 2.83-8.67) HRZELo (OR 1.85; 95% CI 0.71-4.79) MRZE (OR 1.50; 95% CI 1.21-1.86) HRZM (OR 1.37; 95% CI 1.13-1.66) HRC (OR 0.39; 95% CI 0.19-0.77) HRZO (OR 0.47; 95% CI 0.24-0.92) HRZG (OR 1.23; 95% CI 0.97-1.57) | (7 RCTs) | ⊕⊕⊕⊕ HIGH |
| Week 8 Sputum Negativity Assessed with: Liquid medium | HRZM (OR 1.29; 95% CI 1.04-1.59) MRZE (OR 1.27; 95% CI 1.05-1.53) HRZG (OR 1.43; 95% CI 0.69-2.95) HRZO (OR 0.84; 95% CI 0.39-1.78) | (4 RCTs) | ⊕⊕⊕⊕ HIGH |
| Secondary outcome: Treatment failure by the end of treatment Assessed with: defined as continued or recurrent positive sputum cultures (culture confirmed) and evaluated by the end of treatment | MRZE (OR 0.72; 95% CI 0.04-14.58) HRZM (OR 0.46; 95% CI 0.06-3.30) HRZG (OR 0.27; 95% CI 0.02-3.88) | (3 RCTs) | ⊕⊕⊕⊕ HIGH |
| Secondary outcome: Serious adverse events by the end of treatment Assessed with: grade 3 and higher adverse events including death according to the modified version of criteria from National Institute of Allergy and Infectious Diseases, Division of AIDS | MRZE (OR 0.65; 95% CI 0.30-1.44) HRZM (OR 1.15; 95% CI 0.60-2.19) HRZG (OR 0.91; 95% CI 0.22-3.80) | (3 RCTs) | ⊕⊕⊕⊕ HIGH |
| Secondary outcome: Serious adverse events during intensive phase Assessed with: grade 3 and higher adverse events including death according to the modified version of criteria from National Institute of Allergy and Infectious Diseases, Division of AIDS | HRZM (OR 0.38; 95% CI 0.08-1.84) HRZO (OR 0.39; 95% CI 0.09-1.58) HRZELo (OR 0.53; 95% CI 0.14-1.91) MRZE (OR 0.75; 95% CI 0.45-1.25) HRZG (OR 1.42; 95% CI 0.59-3.44) | (5 RCTs) | ⊕⊕⊕⊕ HIGH |
| Death from all cause by the end of treatment | HRZG (OR 0.32; 95% CI 0.02-4.36) HRZM (OR 1.01; 95% CI 0.34-3.04) MRZE (OR 1.19; 95% CI 0.24-6.05) | (3 RCTs) | ⊕⊕⊕⊕ HIGH |
| Death from all cause during intensive phase | HRZO (OR 0.19; 95% CI 0.01-4.03) HRZELo (OR 0.58; 95% CI 0.07-4.53) HRZM (OR 0.61; 95% CI 0.03-13.15) MRZE (OR 0.80; 95% CI 0.35-132.49) HRZG (OR 0.98; 95% CI 0.10-9.50) | (5 RCTs) | ⊕⊕⊕⊕ HIGH |
| New outcome | | (0 studies) | - |

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and relative effect of the intervention (and its 95% CI).

CI: Confidence interval; OR: network odds ratio

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

UPDATE ON SUSPECTED OR CONFIRMED MDR TUBERCULOSIS

Q11: AMONG ADULTS WHO NEED RETREATMENT FOR TUBERCULOSIS WITH KNOWN SUSCEPTIBILITY TO RIFAMPICIN BY XPERT® TESTING, IS THE STANDARD 2HRZE/4HR THE RECOMMENDED REGIMEN TO OPTIMIZE TREATMENT SUCCESS/ COMPLETION AND REDUCE RISK FOR TREATMENT FAILURE, RELAPSE AND MORTALITY COMPARED TO 2HRZES/1HRZE/5HRE OR IMMEDIATE REFERRAL TO PROGRAMMATIC MANAGEMENT OF DRUG-RESISTANT TB (PMDT)?

RECOMMENDATION

- b. In patients who require TB retreatment with confirmed rifampicin susceptibility by rapid DST, the Category II regimen should no longer be prescribed. (**WHO 2017 Good practice statement**)
- c. On the basis of the availability of rapid DST to RIF, the standard first-line treatment regimen (2HRZE/4HR) is recommended. Revisions in the drug regimen should be made based on the results of the full DST. If RR is present, referral to a facility specialized in the care of drug-resistant TB should be made. (**Good practice statement**)
- d. This statement supersedes the previous 2016 CPG recommendation on Category II treatment regimen for retreatment cases.

REMARKS

We provide an update to the recommendation in the 2016 version of this guideline regarding the preferred treatment regimen for re-treatment cases. Rapid DST for drugs other than RIF should be done to inform the choice of the treatment regimen. However, rapid DST may not always be available in health facilities. In such cases, physicians are suggested to start Category I empiric treatment regimen while awaiting results of a rapid and/or full DST.

Voting: 15/15 agree, 2 rounds

SUMMARY OF EVIDENCE

There were no RCTs comparing HRZE vs. HRZES or immediate referral to PMDT for retreatment cases. The 2017 WHO Guidelines for treatment of DST and patient care [1] was adapted to answer this clinical question. The guideline was appraised using the AGREE tool and obtained an overall quality rating of 6/7.

The good practice statement from the 2017 WHO Guidelines was based on a systematic review of 20 studies on clinical outcomes of the WHO Category II empiric treatment regimen. The median treatment success rate was 68%, which was below the WHO target of 85%. The use of streptomycin (STM) further increased adverse events (e.g. ototoxicity, nephrotoxicity). The addition of a single drug to a previously ineffective regimen (e.g., HRZE) also did not improve treatment success rate. A GRADE recommendation could not be formulated based on evidence; thus, the WHO guideline development group (GDG) drafted a good practice statement instead.

The results of a More recent systematic review by Cohen et al.[2] support the WHO recommendation above. This review evaluated the clinical outcomes of a TB retreatment regimen for both microbiologically confirmed and unconfirmed cases. There were 39 studies, which were mostly (33/39) retrospective cohorts. Majority were performed in Asia (predominantly in India) and Africa. Significant heterogeneity was noted between studies ($I^2 = 0.95$), which precluded calculation of a pooled estimate. Treatment success rates ranged from 27% to 92%. Only 2/39 (5%) studies met the WHO target of 85% treatment success. The treatment success rate was <75% in 29 (74%) studies, and <50% in 4 studies (Appendix Q11.1). The low rates of treatment success in the majority of the studies do not favor the Category II regimen.

In 2005, Saravia et al did a comparative retrospective cohort of Category I failures in Lima, Peru. [3] Patients received either one of two regimens: Strategy A was a Category II regimen; if that regimen failed, an 18-month standardized regimen including second-line drugs was used. Strategy B was a pilot protocol that included DST and empiric treatment regimen (ETR) for MDR-TB. If DST results showed resistance to only INH and RIF, the ETR was continued unchanged. If DST results showed resistance to other drugs, the patient received an individualized treatment regimen (ITR) tailored to the susceptibility profile of the infecting strain. Strategy B was 3x more likely than Strategy A to cure patients (79% vs. 38%; RR 2.9; 95% CI 1.7-5.1). Strategy B was 5x more likely to cure patients than the Category II regimen alone (79% vs. 15%; RR 5.2; 95%CI 3.0-9.2).

In the Philippine setting, a retrospective cohort analysis of PTB patients from two data sets from the National Drug Resistance Survey and the PMDT was done by Lew et al. [4] This analysis looked at outcomes of Category I and II regimens in mono- and poly-resistant tuberculosis cases in the Philippines and linked drug resistance patterns with treatment outcomes. Among 138 Category II patients, 92 were INH-resistant (66.7%), 9 were either EMB- or STM-resistant, and 37 were poly-resistant. The Category II regimen produced poor outcomes: 59.4% (95% CI 49.2-68.9) treatment success in mono-resistant and 40.5% (95% CI 25.2-57.8) treatment success in poly-resistant cases (Appendix Q11.2).

Recommendations from the 6th MOP:

The DOH-NTP 6th MOP recommends the following regimens for drug-susceptible and drug-resistant PTB or EPTB (Table 11.1). A TB MAC shall be established per region to provide clinical expertise and guidance on the diagnosis of clinically diagnosed DRTB

and management of difficult DSTB and DRTB cases. All regions have been trained on all oral MDRTB regimens and are currently transitioning to programmatic implementation in treatment centers, satellite treatment centers, and health centers implementing i-DOTS (integrated delivery of TB services) for both DS and DRTB using patient-centered care.

Table Q11.1 NTP 6th MOP Treatment Regimens for Drug-Susceptible and Drug-Resistant TB

| Regimen Name | Regimen |
|--|---|
| <u>Regimen 1: New or Retreatment</u> | 2HRZE/4HR |
| PTB or EPTB (except CNS, bones, joints) with MTB/Rif sensitive or intermediate results on Xpert; smear-positive; TB LAMP positive; or clinically diagnosed (MTB not detected, or bacteriologic testing not done) | |
| <u>Regimen 2: New or Retreatment</u> | 2HRZE/10HR |
| EPTB of CNS, bones, joints with MTB/Rif sensitive or intermediate results on Xpert; smear-positive; TB LAMP positive; or clinically diagnosed (MTB not detected, or bacteriologic testing not done) | |
| <u>Regimen 3: Standard Short All Oral Regimen (SSOR)</u> | 4-6 months of Lfx-Bdq(6)-Cfz-Pto-Z-E-Hhd; 5 months of Lfx-Cfz-Z-E |
| <u>Regimen 4: Standard Long All Oral Regimen for FQ Susceptible (SLOR FQ-S)</u> | 6 months of Lfx-Bdq-Lzd-Cfz 12-14 months of Lfx-Lzd-Cfz |
| <u>Regimen 5: Standard Long All Oral Regimen for FQ Resistant (SLOR FQ-R)</u> | 6 months of Bdq-Lzd-Cfz-Cs-Dlm; 12-14 months of Lzd-Cfz-Cs |
| <u>Individualized Treatment Regimen (ITR)</u> | Construct to have at least 4-5 likely effective drugs |

LEGEND: Amikacin (Am), Bedaquiline (Bdq), Clofazimine (Cfz), Cycloserine (Cs), Delamanid (Dlm), Ethambutol I, Imipenem-cilastatin (Imp-cln), Isoniazid (H), Isoniazid high dose (Hhd)Levofloxacin (Lfx), Linezolid (Lzd), Meropenem (Mpm), Moxifloxacin (Mfx), p-aminosalicylic acid (PAS), Prothionamide (Pto), Pyrazinamide (Z), Rifampicin(R), Streptomycin (S),

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APPENDICES Q11.1 [2]

Table Q11.2 Studies describing Outcomes of TB Retreatment Regimen

| Author, year | Country | Study design | n | Success rate | | Population under study |
|---|-----------------------------|----------------|------------------|----------------|---|------------------------|
| | | | | % | | |
| Studies conducted in Asia | | | | | | |
| Abeygunawardena, 2014 ¹⁰ Bam, 2007 ¹¹ | Sri Lanka Nepal | RC RC | 160 118 | 82 92 | All patients registered at a district chest clinic Smear-positive patients being treated for TB at refugee camps | |
| Becx-Bleumink, 1999 ¹² | Indonesia | PC | 239 | 87 | Smear-positive patients prospectively enrolled in a pilot of ambulatory treatment | |
| Burugina Nagaraja, 2011 ¹³ | India | RC | 202 | 34 | Patients from TB registration centres in seven districts who had failed treatment | |
| Chandrasekaran, 2007 ¹⁴ | India | RC | 699 | 43 | Smear-positive patients from all TB registration centres in one district | |
| Chughtai, 2013 ¹⁵ | Pakistan | RC | 12 656 | 78 | All patients registered for treatment of pulmonary TB across the country | |
| Deepa, 2013 ¹⁶ | India | RC | 1 077 | 67 | Smear-positive patients registered at all TB centres in one state | |
| Halim, 2006 ¹⁷ Kumar, 2010 ¹⁸ Kumar, 2014 ¹⁹ | Indonesia India India | RC RC PC | 107 133 38 | 70 64 55 | All patients registered at a central hospital All patients registered at centres in one district All HIV-positive patients treated for failure, relapse or default at a research centre | |
| Mehra, 2008 ²⁰ | India | RC | 517 | 70 | Patients treated for failure and relapse TB at a single urban chest clinic | |
| Mukherjee, 2009 ²¹ | India | RC | 234 | 68 | Smear-positive patients registered at a regional TB unit | |
| Mukhopadhyay, 2011 ²² | India | RC | 140 | 69 | All patients registered two TB units in one district (one urban, one rural) | |
| Pardeshi, 2007 ²³ Sarpal, 2014 ²⁴ | India India | RC RC | 507 545 | 66 81 | Smear-positive patients registered in one district All patients registered in one district | |
| Sisodia, 2006 ²⁵ Srinath, 2011 ²⁶ | India India | RC RC | 2 215 5 365 | 74 76 | Smear-positive patients registered in four districts All patients registered in one state | |
| Vasudevan, 2014 ²⁷ | India | RC | 133 | 67 | All patients registered in one district | |
| Win, 2012 ²⁸ | Myanmar | RC | 3 643 | 73 | All patients registered across the country | |
| Studies conducted in Africa | | | | | | |
| Akpabio, 2011 ²⁹ | South Africa | RC | 388 | 27 | All patients with pulmonary TB registered at a regional TB hospital | |
| Bohler, 2005 ³⁰ | Sudan | RC | 62 | 68 | Smear-positive patients registered at five TB management units in IDP camps | |
| Bachmann, 2010 ³¹ Berhe, 2012 ³² | South Africa Ethiopia | CT RC | 1 385 22 | 62 64 | All patients prospectively enrolled into the PALSA trial Smear-positive patients registered in 10 rural and five urban districts | |
| Dooley, 2011 ³³ | Morocco | RC | 291 | 73 | Smear or culture-positive patients registered at nine urban TB clinics | |
| Gninafon, 2004 ³⁴ | Benin | RC | 236 | 78 | Smear-positive patients registered at a large urban referral hospital | |
| Ige, 2011 ³⁵ Jones-Lopez, 2011 ³⁶ | Nigeria Uganda | RC PC | 127 288 | 74 77 | All patients starting treatment at a university hospital Smear-positive patients treated as in-patients at a TB referral centre | |
| Munoz-Sellart, 2010 ³⁷ Nakanwagi-Mukwaya, 2013 ³⁸ | Ethiopia Uganda | RC RC | 338 105 | 66 46 | All patients registered at seven health centres All relapse, failure and default patients registered at three regional referral hospitals | |
| Ottmani, 2006 ³⁹ | Morocco | RC | 14 635 | 71 | All bacteriologically confirmed cases registered across the country | |
| Salaniponi, 2003 ⁴⁰ | Malawi | RC | 741 | 65 | Smear-positive patients registered at non-private health facilities | |
| Takarinda, 2012 ⁴¹ Twanya, 2011 ⁴² Wahome, 2013 ⁴³ | Zimbabwe Malawi Kenya | RC RC RC | 225 411 46 | 72 67 61 | All patients registered in one district All patients registered across the country All health care workers working at a referral hospital | |
| Studies conducted in other regions | | | | | | |
| Espinal, 2000 ⁴⁴ | Multicentre | PC | 876 | 57 | DR-TB survey in Dominican Republic, Hong Kong SAR, China, Italy, Russia, Korea and Peru | |
| Furin, 2012 ⁴⁵ | Georgia | RC | 6 633 | 58 | All patients registered for anti-tuberculosis treatment across the country | |
| McGreevy, 2012 ⁴⁶ Ponce, 2012 ⁴⁷ | Haiti Peru | RC CT | 153 111 | 78 71 | All patients registered at a TB-HIV referral centre Smear-positive patients registered in three districts | |
| Sevim, 2002 ⁴⁸ | Turkey | RC | 47 | 83 | Relapse and default patients registered at one referral clinic | |

TB = tuberculosis; RC = retrospective cohort; PC = prospective cohort; HIV = human immunodeficiency virus; CT = clinical trial; PALSA = Practical Approach to Lung Health in sub-Saharan Africa; IDP = internally displaced persons; DR-TB = drug-resistant TB; SAR = special administrative region.

Appendix Q11.2 [4]

Table Q11.3 Treatment outcomes among Monoresistant, polyresistant and Combined Resistance Patients treated with Category 1 or Category II regimens

| Treatment outcomes by drug resistance profile | Category 1 | | Category 2 | | P value |
|---|------------|--------------------|------------|------------------|---------|
| | n | % (95%CI) | n | % (95%CI) | |
| Monoresistance | 235 | | 101 | | |
| Success | 206 | 87.7 (82.6–91.4) | 60 | 59.4 (49.2–68.9) | <0.001 |
| Cured | 174 | 74.0 (67.9–79.4) | 41 | 40.6 (31.1–50.8) | |
| Completed | 32 | 13.6 (9.63–18.8) | 19 | 18.8 (12–28.1) | |
| Failed | 5 | 2.13 (0.786–5.17) | 13 | 12.9 (7.3–21.4) | |
| Defaulted | 16 | 6.81 (4.07–11) | 13 | 12.9 (7.3–21.4) | |
| Died | 6 | 2.55 (1.04–5.74) | 8 | 7.93 (3.73–15.5) | |
| Transferred out | 2 | 0.851 (0.148–3.37) | 7 | 6.93 (3.07–14.2) | |
| Polyresistance | 53 | | 37 | | |
| Success | 41 | 77.4 (63.5–87.3) | 15 | 40.5 (25.2–57.8) | |
| Cured | 37 | 69.8 (55.5–81.3) | 10 | 27.0 (14.4–44.4) | |
| Completed | 4 | 7.55 (2.45–19.1) | 5 | 13.5 (5.08–29.6) | |
| Failed | 6 | 11.3 (4.69–23.7) | 16 | 43.2 (27.5–60.4) | |
| Defaulted | 6 | 11.3 (4.69–23.7) | 6 | 16.2 (6.77–32.7) | |
| Died | 0 | 0 (0–8.42) | 0 | 0 (0–11.7) | |
| Transferred out | 0 | 0 (0–8.42) | 0 | 0 (0–11.7) | |
| Mono- + polyresistance | 288 | | 138 | | |
| Success | 247 | 85.8 (81.1–89.5) | 75 | 54.3 (45.7–62.8) | <0.001 |
| Cured | 211 | 73.3 (67.7–78.2) | 51 | 37.0 (29–45.6) | |
| Completed | 36 | 12.5 (9.02–17) | 24 | 17.4 (11.7–25) | |
| Failed | 11 | 3.82 (2.02–6.93) | 29 | 21.0 (14.7–28.9) | |
| Defaulted | 22 | 7.64 (4.96–11.5) | 19 | 13.8 (8.7–20.9) | |
| Died | 6 | 2.08 (0.85–4.7) | 8 | 5.8 (2.72–11.5) | |
| Transferred out | 2 | 0.694 (0.12–2.76) | 7 | 5.07 (2.24–10.6) | |

CI = confidence interval.

Q12: AMONG PERSONS WITH MULTI-DRUG RESISTANT (MDR TB) OR RIFAMPICIN RESISTANT-TB (RR TB), IS THE STANDARD SHORTENED TREATMENT REGIMEN AS EFFECTIVE AS THE WHO CONVENTIONAL MULTI-DRUG, OR RR REGIMENS?

DRAFT RECOMMENDATION

A shortened regimen of moxifloxacin, clofazimine, ethambutol and pyrazinamide in 40 weeks supplemented by kanamycin, isoniazid and prothionamide in the first 16 weeks among MDR or RR TB may be recommended (***Conditional recommendation, moderate-quality evidence***) Oral bedaquiline-containing regimen of 9–12 months duration is recommended in eligible patients with confirmed MDR/RR-TB who have not been exposed to treatment with second-line TB medicines used in this regimen for more than 1 month, and in whom resistance to fluoroquinolones has been excluded. (***Conditional recommendation, very low certainty in the evidence***)

REMARKS

The guideline panel decided to wait for the results of other ongoing trials before making any recommendation. There are now newer studies showing adverse effects for certain drugs (e.g. kanamycin, capreomycin).

The Panel recommends that all patients with RR TB or MDR TB be referred to the nearest MDRTB clinic for initiation of appropriate MDR TB regimen. (***Best practice statement***)

If the clinician so desires, he/she can present the patient's case to the National or Regional TB MAC whenever applicable during their regular meetings. (***Best practice statement***)

Please refer to **Annex X** for the complete directory and process of referral to the Regional TB MAC in the country.

SUMMARY OF EVIDENCE

After a systematic search of two databases (e.g., MEDLINE and ClinicalTrial.gov), only one randomized clinical trial was found comparing the efficacy of a shortened regimen compared to the standard long regimen among MDR TB patients.[1] The STREAM (Standard Treatment Regimen of Anti-Tuberculosis Drugs for Patients with MDR TB) trial was an open-label, randomized, multi-center international parallel non-inferiority trial involving 424 adults with RR PTB. The trial evaluated the effectiveness of a 40-week regimen over an 80-week regimen as prescribed by the 2011 WHO guideline. The short regimen included moxifloxacin (high dose), clofazimine, ethambutol, and pyrazinamide administered over a 40-week period, supplemented by kanamycin (injectable), isoniazid,

and prothionamide in the first 16 weeks, while the long regimen was the WHO-approved MDR TB regimen. [1]

Results showed that a short regimen of 9-11 months did not significantly differ from a long duration regimen of 20-24 months in terms of the following outcomes -- favorable status (RR 1.01; 95% CI 0.91-1.13), mortality (RR 1.31; 95% CI 0.62-2.74), and serious adverse events (RR 0.85; 95% CI 0.65-1.10). Favorable status was defined as negative cultures for *M. tuberculosis* at 132 weeks, with no intervening positive culture or previous unfavorable response. An unfavorable outcome was defined by the initiation of two or more drug therapies that were not included in the assigned regimen, treatment extension beyond the permitted duration, death from any cause, a positive culture from one of the two most recent specimens, or no visit at 76 weeks or later. The study, however, excluded patients with previous exposure to fluoroquinolones and second-line agents, known resistance to fluoroquinolones, and pregnant and breastfeeding individuals.

Khan et al. assessed the effectiveness and safety of shortened MDR TB regimens using individual patient data and aggregate meta-analysis.[2] They included five prospective observational studies (3 published, 2 unpublished) which included 796 MDR TB patients. Out of 796 patients, 669 were successfully treated with a pooled success rate of 83% (95% CI 71.9-90.3). However, 4 out of 5 of the studies did not include the patients who had previous exposure to second-line agents.

The updated WHO 2020 consolidated guidelines on MDR TB recommends that a shorter all-oral bedaquiline-containing regimen of 9–12 months duration is recommended in eligible patients with confirmed MDR/RR-TB who have not been exposed to treatment with second-line TB medicines used in this regimen for more than 1 month, and in whom resistance to fluoroquinolones has been excluded. [3] The WHO also does not recommend giving the short-course treatment to children as well as pregnant and breastfeeding women as these patients were not included in the STREAM trial.

The American Thoracic Society guideline has not made a recommendation either for or against the standardized shorter-course regimen compared with the longer individualized regimens, but instead recommends trials using regimens that include the novel oral agents and exclude the injectables. [4]

Since the publication of this first clinical trial on MDR TB, the WHO MDR TB guideline has changed to recommending an all-oral regimen based on observational studies. Several clinical trials on all oral regimens are underway.

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Table Q12.1 Summary of Evidence on Shortened Regimen compared to Long Duration for Multiple-Drug Resistant TB

Author(s): Ian Theodore Cabaluna

Question: Shortened Regimen compared to Long Duration for Multiple-Drug Resistant TB

Setting: Ethiopia, Mongolia, South Africa and Vietnam

Bibliography: Nunn A et al. A Shorter Regimen for Rifampin-Resistant Tuberculosis. New England Journal of Medicine. 2019;381(11):e22.

| Certainty assessment | | | | | | | No of patients | | Effect | | Certainty | Importance |
|----------------------|--------------|--------------|---------------|--------------|-------------|----------------------|-------------------|---------------|-------------------|-------------------|-----------|------------|
| No of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Shortened Regimen | Long Duration | Relative (95% CI) | Absolute (95% CI) | | |

Favorable status (defined as cultures negative for *M. tuberculosis* at 132 weeks, with no intervening positive culture or previous unfavorable response which include by initiation of two or more drug therapies that were not included in the assigned regimen, treatment extension beyond the permitted duration, death from any cause, a positive culture from one of the two most recent specimens, or no visit at 76 weeks or later

| | | | | | | | | | | | | |
|---|------------------|-------------|-------------|-------------|-------------|------|----------------|-----------------|------------------------|--|-----------|--|
| 1 | randomised trial | not serious | not serious | not serious | not serious | none | 99/124 (79.8%) | 193/245 (78.8%) | RR 1.01 (0.91 to 1.13) | 8 more per 1,000 (from 71 fewer to 102 more) | ⊕⊕⊕⊕ HIGH | |
|---|------------------|-------------|-------------|-------------|-------------|------|----------------|-----------------|------------------------|--|-----------|--|

Time to an unfavorable outcome (follow up: 132)

| | | | | | | | | | | | | |
|---|------------------|-------------|-------------|-------------|----------------------|------|------------------|------|--|--------------------------------|---------------|--|
| 1 | randomised trial | not serious | not serious | not serious | serious ^a | none | 253 participants | | HR 1.06 (0.65 to 1.72) [Time to an unfavorable outcome] | -- per 1,000 -rom -- to --) | ⊕⊕⊕○ MODERATE | |
| | | | | | | | - | 0.0% | | -- per 1,000 -rom -- to --) | | |

All-cause mortality (follow up: 132 weeks)

| | | | | | | | | | | | | |
|---|------------------|-------------|-------------|-------------|----------------------|------|---------------|--------------|------------------------|---|---------------|--|
| 1 | randomised trial | not serious | not serious | not serious | serious ^a | none | 24/282 (8.5%) | 9/141 (6.4%) | RR 1.31 (0.62 to 2.74) | 20 more per 1,000 (from 24 fewer to 111 more) | ⊕⊕⊕○ MODERATE | |
|---|------------------|-------------|-------------|-------------|----------------------|------|---------------|--------------|------------------------|---|---------------|--|

Time to death (follow up: 132 weeks)

| | | | | | | | | | | | | |
|---|------------------|-------------|-------------|-------------|----------------------|------|---|------|---|--------------------------------|---------------|--|
| 1 | randomised trial | not serious | not serious | not serious | serious ^a | none | | | HR 1.38 (0.64 to 2.96) [Time to death] | -- per 1,000 -rom -- to --) | ⊕⊕⊕○ MODERATE | |
| | | | | | | | - | 0.0% | | -- per 1,000 -rom -- to --) | | |

Serious Adverse Event (follow up: 132 weeks)

| | | | | | | | | | | | | |
|---|-------------------|-------------|-------------|-------------|----------------------|------|----------------|----------------|------------------------|--|---------------|--|
| 1 | randomised trials | not serious | not serious | not serious | serious ^a | none | 91/282 (32.3%) | 53/141 (37.6%) | RR 0.85 (0.65 to 1.10) | 46 fewer per 1,000 (from 112 fewer to 29 more) | ⊕⊕⊕○ MODERATE | |
|---|-------------------|-------------|-------------|-------------|----------------------|------|----------------|----------------|------------------------|--|---------------|--|

CI: Confidence interval; RR: Risk ratio; HR: Hazard Ratio

Explanations

a. Wide confidence interval

UPDATES ON MANAGEMENT OF LATENT TUBERCULOSIS

Q13: SHOULD NON-HIV ADULT HOUSEHOLD/CLOSE CONTACTS OF ACTIVE TB CASES (REGARDLESS OF BACTERIOLOGIC STATUS) WITH NO ACTIVE DISEASE UNDERGO THE INTERFERON GAMMA RELEASE ASSAY (IGRA) OR TUBERCULIN SKIN TEST (TST) TO IDENTIFY LATENT TB INFECTION (LTBI)? IS IGRA MORE ACCURATE THAN STANDARD TST?

RECOMMENDATION

- a. Children aged ≥ 5 years, adolescents and adults who are household contacts of people with bacteriologically confirmed PTB who are found not to have active TB by an appropriate clinical evaluation or according to national guidelines may be given TB preventive treatment. (***Conditional recommendation, low certainty in the estimates of effect***)
- b. Either a tuberculin skin test (TST) or an interferon-gamma release assay (IGRA) may be used to screen for latent tuberculosis infection (LTBI) among non-HIV close contacts of patients with active TB. Cost, availability, and the need for other resources have to be considered when deciding which test to use. (***Weak recommendation, very low-quality evidence***).

REMARKS

In the 2016 version of this CPG, IGRA was recommended prior to the treatment of LTBI among those starting biological agents. Other risk groups who could potentially benefit from IGRA could not be answered in this question.

Voting: 14/14 agree

The 6th NTP MOP recommends that TST or IGRA shall not be required prior to initiation of preventive treatment in the following eligible individuals: (a) Persons living with HIV (PLHIV); (b) Children less than 5 years old who are household contacts of bacteriologically confirmed PTB; and (c) Individuals aged 5 years and older who are household contacts of bacteriologically confirmed PTB with other TB risk factors.

SUMMARY OF EVIDENCE

We reviewed the literature for evidence on the utility of IGRA and TST in predicting progression to active TB among non-HIV close contacts of active TB cases.

We searched MEDLINE since inception, with no language restrictions, for articles on diagnostic accuracy/predictive utility using the following search terms: “latent tuberculosis”[MESH]; “tuberculin test”[MESH] OR “tuberculin skin test” OR Mantoux test;

“interferon-gamma release tests”[MESH] OR “QuantiFERON-TB” OR “T.SPOT.” We identified, retrieved, and reviewed several relevant systematic reviews [1-4], then manually searched their reference lists for relevant studies. We also reviewed the evidence profile of the latest WHO guidelines on LTBI. [5]

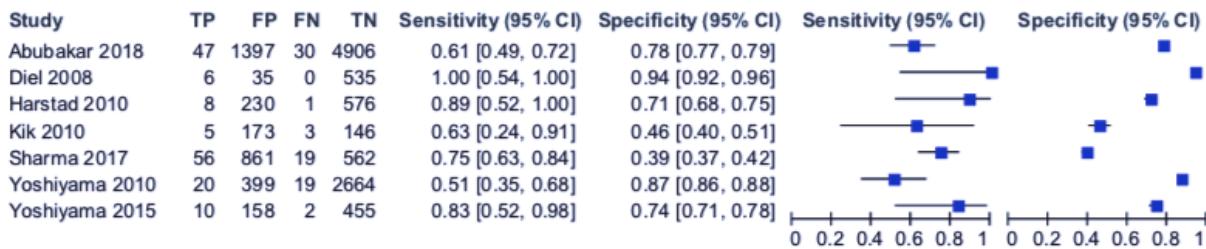
Based on very low-quality evidence, IGRA and TST can accurately identify non-HIV close contacts of active TB cases that may progress to active TB.

Several prospective cohort studies assessed the accuracy of IGAs and TST in identifying non-HIV close contacts of active TB cases that may progress to active TB within 2 years and would therefore be candidates for chemoprophylaxis. Most of the studies were done in low-burden, high to middle-income countries, and included adult and pediatric close household contacts of identified active TB patients or immigrants from high-burden countries (Table Q13.1). Index tests included IGAs (QuantiFERON Gold TB, T-SPOT.TB, ELISPOT, and ESAT-6), and TST with different cutoff values (5mm, 10mm, 15mm). In all the studies, progression to active TB was considered the marker of LTBI. Determination of active TB varied across studies, with some requiring confirmation by culture, and others utilizing clinical criteria that included radiographic and histopathologic evidence of TB and treatment response as determined by a physician.

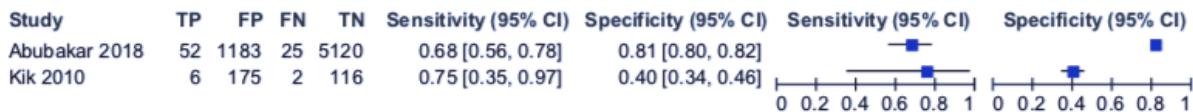
Table Q13.1. Characteristics of Included Studies

| Study | Country | Study Population | Index Tests |
|----------------|-------------|---------------------------------------|---------------------|
| Abubakar 2018 | UK | contacts or migrants from high burden | QFT, T-SPOT.TB, TST |
| Diel 2008 | Germany | immunocompetent close contacts | QFT, TST |
| Harstad 2010 | Norway | recent migrants, asylum seekers | QFT, TST |
| Kik 2010 | Netherlands | immigrants who are close contacts | QFT, T-SPOT.TB, TST |
| Yoshiyama 2010 | Japan | household or work contacts | QFT |
| Yoshiyama 2015 | Japan | household or work contacts | QFT |
| Sharma 2017 | India | close household contacts | QFT, TST |
| Hill 2008 | Gambia | household contacts | ELISPOT |
| Doherty 2002 | Ethiopia | household contacts | in-house ELISA |

QFT



T-SPOT.TB



ELISA

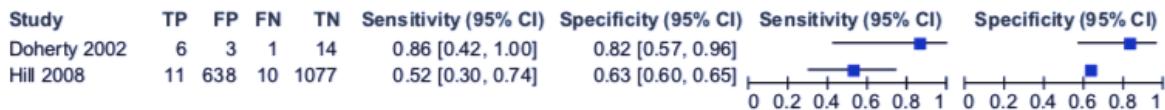
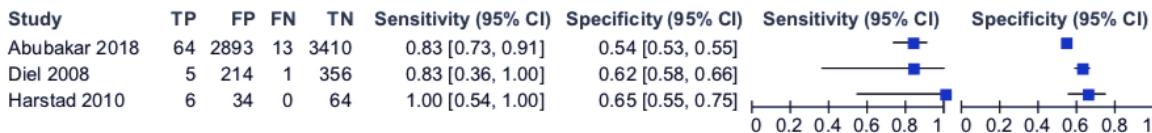
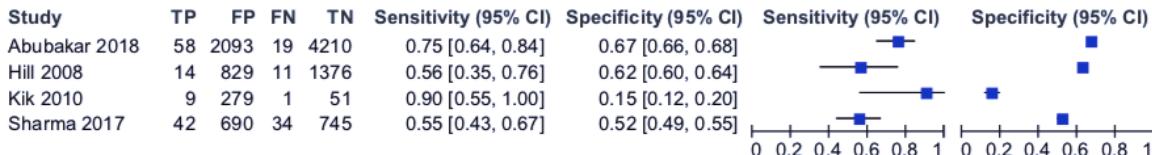


Figure Q13.1. Forest Plot of Sensitivity and Specificity of IGRAs

TST 5mm



TST 10mm



TST 15mm

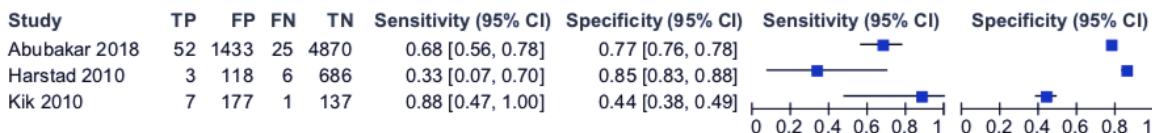


Figure Q13.2. Forest Plot of Sensitivity and Specificity of Tuberculin Skin Test

Tuberculin Skin Test (TST)

A total of 6 studies [6-11] investigated the accuracy of TST in predicting progression to active TB among patients with LTBI: 3 for TST \geq 5mm, 4 for TST \geq 10mm, and 3 for TST \geq 15mm. Sensitivity ranged from 0.33 (95% CI 0.07-0.70) to 1.00 (95% CI 0.54-1.00), while specificity ranged from 0.15 (95% CI 0.12-0.20) to 0.85 (95% CI 0.83-0.88). The sensitivity and the specificity estimates for each study are shown in Table Q13.2. Due to the significant variability across studies, estimates of sensitivity and specificity were not pooled.

Comparison of IGRA and TST

There are significant overlaps in the confidence intervals of the sensitivity of IGRA and TST in all of the studies. Some studies showed a better specificity for IGRA compared to TST, but the differences were marginal. [6-7,10] There was no substantive advantage of one test over the other in terms of identifying patients with LTBI who would progress to active TB. Hence, other considerations such as cost and availability may determine the choice of screening test LTBI for non-HIV close contacts of patients with active TB.

Table Q13.2. Side-by-Side Comparison of Sensitivity and Specificity of Index Tests

| Study | Index Test | IGRA | | TST | |
|---------------|------------|------|---------------------|-------|---------------------|
| | | Sn | Sp (95% CI) | Sn | Sp (95% CI) |
| Abubakar 2018 | QFT | Sn | 0.61 (0.49 to 0.72) | 5mm | 0.83 (0.73, 0.91) |
| | | Sp | 0.78 (0.77 to 0.79) | | 0.54 (0.53, 0.55) |
| | T-SPOT | Sn | 0.68 (0.56 to 0.78) | 10 mm | 0.75 (0.64 to 0.84) |
| | | Sp | 0.81 (0.80 to 0.82) | | 0.67 (0.66 to 0.68) |
| | T-SPOT | Sn | | 15 mm | 0.68 (0.56 to 0.78) |
| | | Sp | | | 0.77 (0.83 to 0.88) |
| Diel 2008 | QFT | Sn | 0.94 (0.52 to 1.00) | 5 mm | 0.83 (0.36 to 1.00) |
| | | Sp | 0.71 (0.68 to 0.75) | | 0.62 (0.58 to 0.66) |
| | QFT | Sn | 0.89 (0.52 to 1.00) | 5 mm | 1.00 (0.54 to 1.00) |
| | | Sp | 0.71 (0.68 to 0.75) | | 0.65 (0.55 to 0.75) |
| Harstad 2010 | QFT | Sn | | 15 mm | 0.33 (0.07 to 0.70) |
| | | Sp | | | 0.85 (0.83 to 0.88) |
| | ELISA | Sn | 0.52 (0.30 to 0.74) | 10 mm | 0.56 (0.35 to 0.76) |
| | | Sp | 0.63 (0.60 to 0.65) | | 0.62 (0.60 to 0.64) |
| Kik 2010 | QFT | Sn | 0.63 (0.24 to 0.91) | 10 mm | 0.90 (0.55 to 1.00) |
| | | Sp | 0.46 (0.40 to 0.51) | | 0.15 (0.12 to 0.20) |
| | T-SPOT | Sn | 0.75 (0.35 to 0.97) | 15 mm | 0.88 (0.47 to 1.00) |
| | | Sp | 0.40 (0.34 to 0.46) | | 0.44 (0.38 to 0.49) |
| Sharma 2017 | QFT | Sn | 0.75 (0.63 to 0.84) | 10 mm | 0.55 (0.43 to 0.67) |
| | | Sp | 0.39 (0.37 to 0.42) | | 0.52 (0.49 to 0.55) |

Recommendations of Other Guidelines:

- **Philippine TB Guidelines 2016** [15]: TST is the preferred screening test for LTBI in a resource-limited setting like the Philippines. (**Strong recommendation, low quality evidence**)

2018 WHO LTBI Guidelines [5]: Either TST or IGRA can be used to test for LTBI. (**Strong recommendation, very low quality evidence**)

- 2020 WHO Consolidated Guidelines On Tuberculosis: Tuberculosis Preventive Treatment [16]: Either a TST or IGRA can be used to test for LTBI. (***Strong recommendation, very low certainty in the estimates of effect***)

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APPENDIX Q13

Table Q13.3 Summary of Certainty of Evidence: Interferon Gamma Release Assay (IGRA) Or Tuberculin Skin Test (TST) for Latent Tuberculosis

| Nº of studies (Nº of patients) | Study design | Factors that may decrease certainty of evidence | | | | | Test accuracy CoE |
|-----------------------------------|---|---|----------------------|----------------------|-------------|-------------------|----------------------|
| | | Risk of bias | Indirectness | Inconsistency | Imprecision | Publication bias | |
| 11 studies 13,323 patients | Observational study (Prospective cohort) | serious ^a | serious ^b | serious ^c | not serious | none ^d | ⊕○○○ VERY LOW |

a. Not all confounders controlled for; Lack of independence between index test and confirmatory test (i.e. confirmation of incident active TB); Some studies used clinical criteria rather than microbiologic confirmation for diagnosis of TB

b. Some studies included children; some studies included both immigrants from high burden settings, not just those who are close contacts of persons with active TB

c. Study settings varied according to disease burden

d. There are ongoing longitudinal studies, specifically for IGRAAs.

Q14: WILL TREATMENT OF LATENT TB INFECTION (LTBI) OF NON-HIV ADULTS DIAGNOSED TO HAVE LTBI, USING ANY OF 9H, 6H, 3-4HR, 4R OR 12 DOSES WEEKLY INH-RIFAPENTINE (RFP) VS. NO TREATMENT BE SAFE AND EFFECTIVE IN REDUCING THE RISK OF CONVERSION OF LTBI TO ACTIVE TB?

RECOMMENDATIONS

- a. Among non-HIV adults diagnosed to have LTBI, INH given once daily for 6 months is recommended for the treatment of latent TB infection among non-HIV adult patients. (***Strong recommendation, moderate quality of evidence***)
- b. RIF given once daily for 4 months or RIF+INH given once daily for 3 to 4 months may be considered as alternative treatments for latent TB infection. (***Conditional recommendation, low to moderate quality of evidence***)
- c. Directly observed therapy with RFP + INH 12 doses weekly may also be considered. (***Conditional recommendation, low quality of evidence***)

REMARKS

Outcomes were expanded to include safety and not just the conversion of LTBI to active TB. It is important to note that these recommendations are based on the available evidence regarding hepatotoxicity, completion rates, and efficacy—drug resistance was not included.

Voting: 14/14 agree

The 6th MOP recommends the following treatment regimens for LTBI:

Table Q14.1 Treatment Recommendations of the 6th MOP for LTBI

| <i>TB Preventive Treatment Regimen (TPT)</i> | <i>Indications</i> |
|---|--|
| 6H (Isoniazid daily) | Currently available under the program |
| 3HP (Isoniazid, Rifapentine weekly) | Weekly dosing for 3 months Contraindicated in pregnant and <2 years old |
| 3HR (Isoniazid, Rifampicin daily) | Preferred for children if 3HP not available |
| 4R (Rifampicin daily) | Preferred for adults if 3HP not available |

SUMMARY OF EVIDENCE

We searched MEDLINE since inception, with no language restrictions, for articles on the effectiveness and safety of treatments for LTBI using the following search terms: “Latent Tuberculosis”[MESH] OR “latent tuberculosis”; “Isoniazid”[MESH] OR isoniazid; “Rifampin”[MESH] OR (“rifapentine”[Supplementary concept] OR rifapentine) OR “rifamycins”[MESH]; randomized controlled trial [pt], meta analysis [pt]. To identify additional articles for safety, we added (“Hepatitis”[MESH] OR “Chemical and Drug Induced Liver Injury”[MESH]) to our search. We retrieved relevant meta-analyses and systematic reviews and checked their reference lists for other potentially relevant articles. We also reviewed the evidence tables and references of the 2018 WHO guidelines on LTBI. [1]

Efficacy

Based on low to moderate quality of evidence, INH monotherapy given for 6 months, RIF monotherapy given for 4 months, combination INH + RIF given for 3 to 4 months, and combination INH and RFP 12 doses given weekly are effective in preventing active TB among non-HIV patients with LTBI when compared with placebo.

In a meta-analysis of 11 randomized controlled trials including 73,375 participants, INH given for 6 months, or 12 months reduced the risk of progression to active TB by 60% (RR 0.40; 95% CI 0.31;0.52) over two years or longer when compared to placebo. [2] Two studies including 14,145 participants showed that INH given for 6 months is effective (RR 0.44; 95% CI 0.27;0.73) in preventing active TB. [2] This is consistent with the findings of two network meta-analyses that assessed the comparative effectiveness of treatments for LTBI [3, 4].

No studies directly compared the other treatment regimens with placebo or no treatment. Indirect comparisons of the different LTBI treatments with placebo were reported in two network meta-analyses. [3, 4] Zenner et al. [4] included a total of 61 randomized controlled trials, while Pease et al. [3] included 30 trials in which patients had confirmed LTBI and reported rate ratios to account for differences in follow-up across studies. In addition, Pease et al. [3] also compared completion rates across the different LTBI treatments. Despite these differences, findings on efficacy were consistent between the 2 network meta-analyses.

The overall quality of the included studies in both network meta-analyses was rated low to moderate. Risk of bias was rated down due to unclear allocation concealment and blinding in most trials. Both meta-analyses also included studies on children, patients with HIV, and countries with both low and high TB burden.

Table Q14.1 shows the odds ratios of the different treatments for LTBI compared to no treatment. [4] INH monotherapy, RIF monotherapy or in combination with INH, and INH/RFP combination therapy were shown to be effective in preventing active TB. The data suggest that RIF or RFP-containing treatments may be more effective than INH

monotherapy, but strong conclusions cannot be made because the confidence intervals across all treatments overlapped significantly.

Table Q14.2. Efficacy in terms of prevention of TB vs. no treatment
(Zenner et al., 2017)

| Treatment | Total number of participants | Prevention of active TB OR (95% CrI) |
|-------------------------|------------------------------|---|
| INH 6 months | 18,084 | 0.40 (0.26 to 0.60) |
| INH 9 months | 6,350 | 0.46 (0.22 to 0.95) |
| INH/RPT 12 doses weekly | 4,726 | 0.36 (0.18 to 0.73) |
| INH/RIF 3 to 4 months | 1,833 | 0.33 (0.20 to 0.54) |
| RIF 4 months | 1,068 | 0.25 (0.11 to 0.57) |

Note: INH, isoniazid; RPT, rifapentine; RIF, rifampicin; CrI, credible intervals

Pease et al. [3] also compared treatment completion, defined as 80% to 100% medication consumption, across the different LTBI treatments (Figure 1). [3] The results showed that a 3- to 4-month course of treatment was 3 to 4 times more likely to be completed than a 12-month course of placebo (Table Q14.2).

Table Q14.3. Efficacy in terms of treatment completion vs. placebo 12 months
(Pease et al., 2017)

| Treatment | Total # of Participants | Treatment completion OR (95% CrI) |
|-------------------------|-------------------------|--------------------------------------|
| INH 6 months | 8,837 | 1.49 (0.73 to 2.89) |
| INH 9 months | 4,323 | 1.64 (0.57 to 4.45) |
| INH/RMP 3 to 4 months | 1,103 | 3.14 (1.43 to 6.77) |
| INH/RPT 12 doses weekly | 4,520 | 3.58 (1.40 to 8.83) |
| RIF 3 to 4 months | 476 | 3.95 (1.15 to 13.72) |

Note: INH, isoniazid; RPT, rifapentine; RIF, rifampicin; CrI, credible intervals

Safety

Based on moderate quality of evidence, preventive treatment with INH increases the risk for hepatotoxicity compared to placebo. The risk for hepatotoxicity was lower for RIF monotherapy compared to INH monotherapy. There is limited data on the safety of the other treatment regimens compared to placebo.

One large study including 10,874 participants from Eastern Europe showed that the risk for hepatotoxicity in patients receiving INH was 5.5 times higher than those receiving placebo (RR 5.54; 95% CI 2.56;12.00). [2] However, absolute event rates were low—only 7 out of 6,990 participants (0.1%) who received INH and 77 out of 3,884 participants (2.0%) who received placebo reported hepatotoxicity.

A meta-analysis of 5 randomized controlled trials including 1,774 adults and children showed a lower risk for hepatotoxicity, defined as significant elevations in liver

transaminase levels, among patients who received RIF monotherapy compared to INH monotherapy (RR 0.15; 95% CI 0.07;0.35, I² 16%). [5] However, there was no significant difference in the rates of hepatotoxicity between combination RIF and INH and INH alone (RR 0.88; 95% CI 0.43;1.81). [5]

Table Q14.3 shows the odds ratios for hepatotoxicity of the different LTBI treatment regimens. [4] The data suggest that the risk for hepatotoxicity is lower in RIF only, RIF/INH combination, and RFP/INH combination therapies compared to INH monotherapy. This is consistent with the findings of a systematic review on adverse events of LTBI treatment by Pease et al. [6], which reported median rates for hepatotoxicity to be below 7.0% for all treatment regimens (Table Q14.4). However, these results should be interpreted with caution because of significant between-study variability and limited overall reporting of adverse events. It should also be noted that RFP/INH combination therapy was administered through DOT in all the studies that included this treatment regimen.

Table Q14.4. Hepatotoxicity vs. no treatment (Zenner et al., 2017)

| Treatment | Total number of participants | Hepatotoxicity OR (95% CrI) |
|-------------------------|------------------------------|-----------------------------|
| RMP 4 months | 1,068 | 0.14 (0.02 to 0.81) |
| INH/RPT 12 doses weekly | 4,726 | 0.52 (0.13 to 2.15) |
| INH/RIF 3 to 4 months | 1,833 | 0.72 (0.21 to 2.37) |
| INH 6 months | 18,084 | 1.10 (0.40 to 3.17) |
| INH 9 months | 6,350 | 1.70 (0.35 to 8.05) |

Note: INH, isoniazid; RPT, rifapentine; RIF, rifampicin; CrI, credible intervals

Table Q14.5. Rates of hepatotoxicity in nonrandomized studies (Pease et al., 2018)

| Treatment | Total number of participants | Hepatotoxicity Median % (min-max) |
|-------------------------|------------------------------|-----------------------------------|
| RMP 4 months | 2,346 | 0.01% (0 to 2.0%) |
| INH/RPT 12 doses weekly | 2,826 | 1.1% (0 to 3.9%) |
| INH/RIF 3 to 4 months | 1,000 | 5.1% (1.0 to 20%) |
| INH 9 months | 8,432 | 3.1% (0 to 9.0%) |
| INH 6 months | 1,817 | 6.3% (0 to 13.3%) |

Note: INH, isoniazid; RPT, rifapentine; RIF, rifampicin; CrI, credible intervals

Recommendations from other guidelines:

Philippine TB Guidelines 2016

- INH 300 mg daily for 6 months under supervised treatment is the recommended regimen for LTBI (**Strong recommendation, moderate quality of evidence**)
- Pyridoxine at a dose of 25 mg/day is recommended to prevent peripheral neuropathy. (**Strong recommendation, low quality of evidence**)

2018 WHO Guidelines:

- INH monotherapy for 6 months is recommended for treatment of LTBI in both adults and children in countries with high and low TB incidence. (**Strong recommendation, high-quality evidence. Existing recommendation**)
- RFP and INH weekly for 3 months may be offered as an alternative to 6 months of isoniazid monotherapy as preventive treatment for both adults and children in countries with a high TB incidence. (**Conditional recommendation, moderate-quality evidence. New recommendation**)

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APPENDIX Q14

Table 14.6.Summary of Certainty of Evidence for Treatment of LTBI

Authors: Palileo, L.

Question: INH compared to no treatment or placebo for latent tuberculosis infection among non-HIV

Setting:

Bibliography: Smieja M, Marchetti C, Cook D, Smaill FM. Isoniazid for preventing tuberculosis in non-HIV infected persons. *Cochrane Database of Systematic Reviews* 1999, Issue 1. Art. No.: CD001363. doi: 10.2002/14651858.CD001363.

| Certainty assessment | | | | | | | Summary of findings | | | | |
|---|--------------|---------------|----------------------|----------------------|------------------|-------------------------------|------------------------------|------------------|-----------------------------------|-----------------------------------|---|
| No of participants (studies) Follow-up | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Overall certainty of evidence | Study event rates (%) | | Relative effect (95% CI) | Anticipated absolute effects | |
| | | | | | | | With no treatment or placebo | With INH | | Risk with no treatment or placebo | Risk difference with INH |
| Active TB | | | | | | | | | | | |
| 73375 (11 RCTs) | not serious | not serious | serious ^a | not serious | none | ⊕⊕⊕○ MODERATE | 557/33113 (1.7%) | 239/40262 (0.6%) | RR 0.40 (0.31 to 0.52) | 17 per 1,000 | 10 fewer per 1,000 (from 12 fewer to 8 fewer) |
| Extrapulmonary TB | | | | | | | | | | | |
| 44636 (4 RCTs) | not serious | not serious | serious ^a | not serious | none | ⊕⊕⊕○ MODERATE | 28/22257 (0.1%) | 9/22379 (0.0%) | RR 0.34 (0.16 to 0.71) | 1 per 1,000 | 1 fewer per 1,000 (from 1 fewer to 0 fewer) |
| TB Deaths | | | | | | | | | | | |
| 25714 (2 RCTs) | not serious | not serious | serious ^a | serious ^b | none | ⊕⊕○○ LOW | 10/9396 (0.1%) | 3/16318 (0.0%) | RR 0.29 (0.07 to 1.18) | 1 per 1,000 | 1 fewer per 1,000 (from 1 fewer to 0 fewer) |
| Safety: Hepatitis | | | | | | | | | | | |
| 10874 (1 RCT) | not serious | not serious | serious ^c | not serious | none | ⊕⊕⊕○ MODERATE | 7/6990 (0.1%) | 77/3884 (2.0%) | RR 5.54 (2.56 to 12.00) | 1 per 1,000 | 5 more per 1,000 (from 2 more to 11 more) |

CI: Confidence interval; RR: Risk ratio

a. Studies mostly in low burden settings

b. Wide confidence interval

c. Studies done in European countries—there might be important differences in risk for INH toxicity between study population and Filipinos given physiologic differences in metabolising INH.

GRADE TABLE

| Certainty assessment | | | | | | | Certainty |
|----------------------|---|----------------------|---------------|----------------------|----------------------|----------------------|---------------------|
| Nº of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | |
| 61 | randomized trials | serious ^a | not serious | serious ^b | not serious | none | ⊕⊕○○ LOW |
| 30 | randomized trials | serious ^a | not serious | serious ^b | not serious | none | ⊕⊕○○ LOW |
| 61 | randomized trials | serious ^a | not serious | serious ^b | serious ^c | none | ⊕○○○ VERY LOW |
| 78 | observational studies and randomized trials | serious ^d | not serious | serious ^b | serious ^c | none | ⊕○○○ VERY LOW |

a. Unclear risk of bias for allocation concealment and blinding for many studies

b. Studies included both adult and pediatric populations, HIV and non-HIV patients, and high and low burden countries.

c. Small number of events, wide confidence intervals

d. limited control of confounders, ascertainment bias

UPDATE ON INFECTION CONTROL OF TUBERCULOSIS

Q15: AMONG HIGH RISK OR SPECIAL SETTINGS, WHAT ARE THE RECOMMENDED MEASURES TO PREVENT TRANSMISSION OF TB?

RECOMMENDATIONS

Administrative Controls

- **Recommendation 1:** Triage of people with TB signs and symptoms, or with TB disease, is recommended to reduce *M. tuberculosis* transmission to health workers (including community health workers), persons attending health care facilities or other persons in settings with a high risk of transmission. (*Conditional recommendation based on very low certainty in the estimates of effects*)
- **Recommendation 2:** Respiratory separation / isolation of people with presumed or demonstrated infectious TB is recommended to reduce *M. tuberculosis* transmission to health workers or other persons attending health care facilities. (*Conditional recommendation based on very low certainty in the estimates of effects*)
- **Recommendation 3:** Prompt initiation of effective TB treatment of people with TB disease is recommended to reduce *M. tuberculosis* transmission to health workers, persons attending health care facilities or other persons in settings with a high risk of transmission. (*Strong recommendation based on very low certainty in the estimates of effects*)
- **Recommendation 4:** Respiratory hygiene (including cough etiquette) in people with presumed or confirmed TB is recommended to reduce *M. tuberculosis* transmission to health workers, persons attending health care facilities or other persons in settings with a high risk of transmission. (*Strong recommendation based on low certainty in the estimates of effects*)

Environmental Controls

- **Recommendation 5:** Upper-room germicidal ultraviolet (GUV) systems are recommended to reduce *M. tuberculosis* transmission to health workers, persons attending health care facilities or other persons in settings with a high risk of transmission. (*Conditional recommendation based on moderate certainty in the estimates of effects*)
- **Recommendation 6:** Ventilation systems (including natural, mixed-mode, mechanical ventilation and recirculated air through high-efficiency particulate air [HEPA] filters) are recommended to reduce *M. tuberculosis* transmission to health workers, persons attending health care facilities or other persons in settings with

a high risk of transmission (***Conditional recommendation based on very low certainty in the estimates of effects***)

Respiratory Protection

- **Recommendation 7:** Particulate respirators, within the framework of a respiratory protection program, are recommended to reduce *M. tuberculosis* transmission to health workers, persons attending health care facilities or other persons in settings with a high risk of transmission. (***Conditional recommendation based on very low certainty in the estimates of effects***)

REMARKS

The panel unanimously voted to adapt the recommendations from the 2019 WHO guidelines on tuberculosis infection prevention and control. N95 masks may be recommended considering the high TB burden in the Philippines, but cost and treatment setting must be considered. **Voting: 13/13 agree**

SUMMARY OF EVIDENCE

Search terms used were "guidelines" AND "tuberculosis" AND "infection" and "prevention" AND "control. This yielded four (4) results, which included two (2) guidelines; one published by the WHO in 2019 and one (1) from Center for Disease Control and Prevention (CDC) in 2005. [1,2]. We performed a critical group appraisal of the two guidelines using the Appraisal of Guidelines Research and Evaluation (AGREE) II instrument. Overall assessment of the WHO and CDC guidelines using the AGREE II instrument yielded scores of 83% and 50%, respectively

Currency survey since the end of search date of the WHO guidelines in 2018 did not yield any pertinent additional studies.

The 2005 CDC guideline for preventing transmission of tuberculosis in health-care settings has identified the following characteristics of patients with TB disease that increases the risk for infectiousness:

- presence of cough;
- cavitation on chest radiograph;
- positive acid-fast bacilli (AFB) sputum smear result;
- respiratory tract disease with involvement of the larynx (substantially infectious);
- respiratory tract disease with involvement of the lung or pleura (exclusively pleural involvement is less infectious);
- failure to cover the mouth and nose when coughing;
- incorrect, lack of, or short duration of anti-tuberculosis treatment; and

- undergoing cough-inducing or aerosol-generating procedures (e.g., bronchoscopy, sputum induction, and administration of aerosolized medications)

In addition, they also listed the probability of increased risk for transmission of *M. tuberculosis* as a result of various environmental factors, such as:

- exposure to TB in small, enclosed spaces.
- inadequate local or general ventilation that results in insufficient dilution or removal of infectious droplet nuclei.
- recirculation of air containing infectious droplet nuclei.
- inadequate cleaning and disinfection of medical equipment.
- improper procedures for handling specimens.

Both the updated 2019 WHO guideline on tuberculosis infection prevention and control and the 2005 CDC guideline for preventing tuberculosis in healthcare settings have enumerated measures to prevent transmission of TB that involves administrative control, environmental control, and respiratory protection.

The 2019 WHO guidelines include respiratory hygiene (including cough etiquette) in people with presumed or confirmed TB to reduce *M. tuberculosis* transmission to health workers, persons attending health care facilities, or other persons in settings with a high risk of transmission. The 2019 WHO guidelines do not present interventions directed to household settings, given that there was no directly applicable evidence that fulfilled the inclusion criteria for this systematic evaluation of data. However, some considerations pertinent to households are mentioned, where applicable (i.e. respiratory hygiene and respiratory protection) under implementation considerations (Table 1, WHO 2019 Annex 4, PICO 2).

Zayas et al. evaluated the effect of cough etiquette on the chain of transmission of infectious respiratory diseases. [3] Participants in this study performed a voluntary cough while covering their mouth and nose with their hands, sleeve/arm, tissue, or while wearing a surgical mask. Droplets released were quantitatively characterized to assess how effective the maneuvers were in controlling the cough aerosol jet. The study showed that cough etiquette maneuvers did not fully interrupt the chain of transmission of infectious respiratory diseases.

Recommendations from the 2019 WHO guidelines include prompt initiation of effective TB treatment of people with TB disease to reduce *M. tuberculosis* transmission to health workers, persons attending health care facilities, or other persons in settings with a high risk of transmission. Evidence continues to mount showing that delays in initiation of effective TB treatment increase the probability of forward transmission of the disease (Table 2, WHO 2019 Annex 4, PICO 1). [4,5]

The recommendations given in the 2019 WHO guidelines on TB-specific interventions are components of a comprehensive hierarchy of controls, which in turn is a component

of the overall framework of infection prevention and control (IPC) practices and depends on the adoption of a multimodal strategy. Thus, the adoption of several elements needs to be integrated.

Looking at the effect of triage on the incidence of LTBI and TB disease among health workers, a systematic search yielded 15 observational studies from secondary and tertiary health care facilities, of which 73% were carried out in low TB burden settings. [6] A total of six studies [7,8,9,10,11,12] measuring the effect of triage on the incidence of LTBI alone among health workers in all settings were included in the analysis (Table 3, WHO 2019 Annex 4, PICO 1).

Estimates of reduction of TB incidence in high TB burden settings, calculated from crude pooled data, seemed to indicate very slight or no reduction in TB incidence (crude incidence rate ratio [IRR]: 0.98) among health workers after the implementation of triage within a set of composite IPC measures (WHO 2019, Annex 3). These studies seemed to indicate that there is a 12.6% absolute risk reduction (crude estimate combining data from two studies) in the number of active TB disease cases in persons attending health care settings with the use of triage (in combination with other IPC measures) compared to similar populations in settings where triage was not implemented.

In an additional study reporting on the use of isolation (an infection control audit at 121 primary health care facilities in South Africa), the authors reported slightly increased odds of developing smear-positive TB (unadjusted odds ratio [OR]: 1.09; 95% confidence interval [CI] 0.99–1.19) in health workers for a unit increase in the administrative audit tool score, where a higher score equates to better administrative control measures. [13] However, the 2019 WHO guideline review showed that isolation of TB patients seemed to have an inconspicuous effect or no effect on the risk of active TB disease among health workers, as indicated earlier (Table 4, WHO 2019 Annex 4, PICO 2).

Multiple studies suggest that the decline in healthcare-associated transmission observed in specific institutions is associated with rigorous implementation of infection IPC measures. [1]

Primary environmental controls consist of controlling the source of infection by using local exhaust ventilation (e.g., hoods, tents, or booths) and diluting and removing contaminated air by using general ventilation. Secondary environmental controls consist of controlling the airflow to prevent contamination of air in areas adjacent to the source (All rooms) and cleaning the air by using high efficiency particulate air (HEPA) filtration or UVGI.

A systematic review assessing the effectiveness of GUV systems yielded a total of five included studies [9,14,15,16,17], of which three evaluated IPC interventions involving health workers [9,14,15] (Table 5, WHO 2019, PICO 3). A meta-analysis could not be performed, owing to differences in outcome measurement and heterogeneity among the interventions.

Use of respiratory protection can further reduce the risk of exposure of HCWs to infectious droplet nuclei that have been expelled into the air by a patient with infectious TB disease. A systematic review assessing the effectiveness of respiratory protection in reducing the risk of *M. tuberculosis* transmission yielded a total of nine studies [7,9,10,11,14,15,18,19,20] (Table 6, WHO 2019, annex 4 PICO). The systematic search also identified four studies [9,11,14,20] in which respirators were used as part of a broader respiratory protection program. No included studies focused on the implementation of respiratory protection programs in non-health care congregate settings. The included studies provided heterogeneous results on the effect of such programs to protect health workers from acquiring TB infection or developing TB disease. The reduction in TST conversion ranged from a 4.3% absolute reduction (with the introduction of particulate respirators and fit-testing as part of a respiratory protection program) to a 14.8% reduction.

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APPENDIX Q15 GRADE Profiles

Table Q15.1 Respiratory hygiene to reduce TB transmission to HCWs (WHO 2019 Annex 4, PICO 2)

Author(s): University of Sydney
 Date: 27-29 March 2018
 Question: Can respiratory hygiene (or cough etiquette) in people with presumed or confirmed TB reduce TB transmission to healthcare workers in healthcare or other congregate settings to reduce TB transmission when compared to settings where these interventions are not implemented?
 Setting: International

| N° of studies | Study design | Certainty assessment | | | | | Impact | Certainty | Importance |
|--|-----------------------|----------------------|---------------|---------------------------|-------------|--|---|--|------------|
| | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | | | |
| Reduction in LTBI incidence/prevalence - all settings (n=2) | | | | | | | | | |
| 2 ¹² | observational studies | serious ^a | not serious | very serious ^b | not serious | all plausible residual confounding would suggest spurious effect, while no effect was observed | Two studies were included. Heterogeneity in the interventions precluded meta-analysis. The two studies both found a reduction in TST conversions in the intervention compared to control group. In Roth (n=725), a composite intervention including surgical mask use by patients (comparing two hospitals in the intervention arm to two in the control arm) reduced TST conversions by between 4.1 and 12.4 conversions per 1,000 person months. In Yanai 2003, a composite intervention including patient masks was associated with a decrease in TST conversions from 13/77 (16.9%) to 2/96 (2.1%) – a decrease of 14.8%. ^{12c} |  VERY LOW | CRITICAL |
| Reduction in TB incidence/prevalence (n=2) | | | | | | | | | |
| 2 ¹² | observational studies | serious ^a | not serious | serious ^b | not serious | all plausible residual confounding would suggest spurious effect, while no effect was observed | Two studies were included. Heterogeneity in the interventions precluded meta-analysis. In these two studies, surgical mask use by patients was a part of a composite intervention. They both found a reduction in TB in the intervention compared to control group. In Barnes 2002, the use of surgical masks by patients as a part of a composite intervention of 13 components reduced the TB notification rate from 100/2697 (3.7%) to 96/2979 (3.2%). In Yanai 2003, a composite intervention including patient masks was associated with a decrease in TB cases from 30/4357 (0.7%) to 19/4780 (0.4%), a reduction in 0.29 cases/100 person years. Therefore, both studies were associated with a decrease in TB cases. ^{12c} |  VERY LOW | CRITICAL |

Ci: Confidence interval; RR: Risk ratio

Explanations

- a. The one included study had a high risk of bias (confounding relating to secular trends, non-randomised group allocation, lack of allocation concealment, no adjustment for confounding).
- b. Differences in intervention (applicability). The comparator and interventions are poorly described. The intervention is a composite intervention including engineering, respiratory protection and administrative controls, of which cough hygiene is one component (downgraded by one level).
- c. No single effect estimate/meta-analysis was possible due to heterogeneity of outcomes.

References

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Table Q15.2 Respiratory hygiene to reduce TB transmission to other persons (WHO 2019 Annex 4, PICO 2)

Author(s): University of Sydney
 Date: 27-29 March 2018
 Question: Can respiratory hygiene (or cough etiquette) in people with presumed or confirmed TB reduce TB transmission to other persons attending healthcare settings when compared to transmission to the same populations in settings with no intervention or different interventions?
 Setting: International

| N° of studies | Study design | Certainty assessment | | | | | N° of patients | Effect | Certainty | Importance |
|--|-----------------------|--------------------------|---------------|----------------------|-------------|--|----------------|---------------|---------------|---|
| | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | | | | |
| Reduction in LTBI incidence/prevalence (n=1) (Animal study, surgical mask use by patient with TB) | | | | | | | | | | |
| 1 ¹² | observational studies | not serious ^b | not serious | serious ^c | not serious | strong association | 36/90 (40.0%) | 69/90 (76.7%) | not pooled | see comment |
| Reduction in TB incidence/prevalence (n=1) | | | | | | | | | | |
| 1 ¹² | observational studies | serious ^c | not serious | serious ^c | not serious | strong association all plausible residual confounding would suggest spurious effect, while no effect was observed | 0/44 (0.0%) | 25/90 (28.9%) | not pooled | see comment |
| Reduction in TB incidence/prevalence in people living with HIV (n=1) | | | | | | | | | | |
| 1 ¹² | observational studies | serious ^c | not serious | serious ^c | not serious | strong association all plausible residual confounding would suggest spurious effect, while no effect was observed | 0/44 (0.0%) | 25/90 (28.9%) | not estimable |  LOW |

Ci: Confidence interval; RR: Risk ratio

Explanations

- a. Dharmadhikari 2012 measured the effect of surgical mask use by MDR-TB patients upon TST conversion in guinea pigs. The mask use was associated with a substantial reduction in infection 68/90 (76.6%) to 36/90 (40.0%), a reduction by 36.6% in guinea pigs. The reviewers assessed that indirectness was an important concern, given differences between humans and guinea pigs. This led to downgrading the quality of evidence by one point. A steady rise in infection risk over the study period, indicating a dose-response relationship with the duration of exposure. This led to upgrading the quality assessment by one. Therefore, this was rated as low quality evidence.
- b. The blinding of the individuals reporting the outcomes was not stated.
- c. The biology of latent TB infection in guinea pigs is different than that in humans. Therefore there is a serious concern of indirectness (Downgraded by one level).
- d. Moro 2000 (n= 134) study evaluated the effect of surgical mask use for prevention of transmission of MDR-TB, with the outcome of MDR-TB. In this study, surgical mask use by patients was a part of a composite intervention. There was a reduction of 29% in the incidence of TB between the intervention group (0/44 (0%)) and the control group (2/90 (29%)).
- e. The included study has a high risk of bias (confounding relating to secular trends, non-randomised group allocation, lack of allocation concealment, no adjustment for confounding).
- f. The comparator and interventions are poorly described. The interventions comprise multiple simultaneous components, including engineering, respiratory protection and administrative controls (downgraded by one level).

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Table Q15.3 Prompt initiation of effective treatment of TB patients to reduce transmission (WHO 2019 Annex 4, PICO 1)

Author(s): TB Centre, London School of Hygiene & Tropical Medicine
 Date: 27–29 March 2018
 Question: Can effective treatment of patients with TB disease reduce TB transmission to HCWs (including community HCWs) when compared to transmission to the same populations in settings where treatment is not yet administered?
 Setting: International

| No of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Effective treatment | Treatment – [delayed or] not DST-based | Relative (95% CI) | Absolute (95% CI) | Certainty | Importance |
|---|-----------------------|---------------------------|----------------------|---------------------------|---------------------------|----------------------|---------------------|--|-------------------|----------------------------------|--|------------|
| Reduction in LTBI incidence/prevalence in all settings | | | | | | | | | | | | |
| 4 (2,244) | observational studies | very serious ^a | serious ^d | very serious ^a | very serious ^b | none | 42/3081 (1.4%) | 155/3260 (4.8%) | RR 0.29 (- to -) | 34 fewer per 1,000 (from - to -) |  VERY LOW | CRITICAL |
| Reduction in LTBI incidence/prevalence in low TB burden settings | | | | | | | | | | | | |
| 4 (2,244) | observational studies | very serious ^a | serious ^d | very serious ^a | very serious ^b | none | 42/3081 (1.4%) | 155/3260 (4.8%) | RR 0.29 (- to -) | 34 fewer per 1,000 (from - to -) |  VERY LOW | CRITICAL |
| Reduction in LTBI incidence/prevalence in high TB burden settings - not measured | | | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - | - | - |
| Reduction in LTBI incidence/prevalence in primary care - not measured | | | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - | - | - |
| Reduction in LTBI incidence/prevalence in secondary/tertiary care | | | | | | | | | | | | |
| 4 (2,244) | observational studies | very serious ^a | serious ^d | very serious ^a | very serious ^b | none | 42/3081 (1.4%) | 155/3260 (4.8%) | RR 0.29 (- to -) | 34 fewer per 1,000 (from - to -) |  VERY LOW | CRITICAL |
| Reduction in active TB incidence/prevalence in all settings - not measured | | | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - | - | CRITICAL |

CI: Confidence interval; RR: Risk ratio

Explanations

- a. Please note that the study included by Weibel et al. does not describe, specifically, the implementation of treatment based on drug susceptibility, but only describes the introduction of drug susceptibility testing. We have assumed that the results of testing were then used to inform treatment.
- b. Please note that meta-analysis was not conducted - pooled estimates and measures of effect are crude estimates.
- c. There are design specific issues to these studies. Mainly, it is not possible to ascertain the effect of the intervention in question as the intervention is grouped with other interventions, which presents a serious risk of bias. There is also a serious design issue with the study by Wenger et al., as the intervention only differs slightly between before and after (3 agents vs. 4 agents). Though studies were not designed specifically to answer our question, the way they are designed does not give us confidence in the results of interest.
- d. Some inconsistency exists. In the study by Jarvis, in particular, certain results are reported as unavailable, but the site of origin of these results is not specified, so this cannot be accounted for in analysis. In addition, in the study by Weibel et al., overall denominators for at-risk individuals are provided, but not the time period for which these individuals were at risk, reducing confidence in the estimates of risk.
- e. Indirectness is severe and from many sources: population, intervention, and comparators (please see assessment of directness for details).
- f. Serious imprecision exists. For a dichotomous outcome all studies have fewer than 110 cases (range 10–104). Sample sizes are also low in three studies (range 65–650; the exception is Weibel et al. with a sample size of 4,329).

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Table Q15.4 Prompt initiation of effective treatment of TB patients to reduce transmission (WHO 2019 Annex 4, PICO 1)

Author(s): TB Centre, London School of Hygiene & Tropical Medicine
 Date: 27–29 March 2018
 Question: Can effective treatment of patients with TB disease reduce TB transmission to other persons attending healthcare settings when compared to transmission to the same populations in settings where treatment is not yet administered?
 Setting: International

| No of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Effective treatment | Treatment – [delayed or] not DST-based | Relative (95% CI) | Absolute (95% CI) | Certainty | Importance |
|---|-----------------------|----------------------|--------------------------|---------------------------|----------------------|----------------------|---------------------|--|-------------------|----------------------------------|--|------------|
| Reduction in LTBI incidence/prevalence in all settings (n = 0 studies) - not measured | | | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - | - | - |
| Reduction in active TB incidence/prevalence in all settings (n = 1 study) | | | | | | | | | | | | |
| 1 (1) | observational studies | serious ^a | not serious ^d | very serious ^a | serious ^b | none | 5/193 (2.6%) | 19/216 (8.8%) | RR 0.295 (- to -) | 62 fewer per 1,000 (from - to -) |  VERY LOW | CRITICAL |
| Reduction in active TB incidence/prevalence in low TB burden settings (n = 1 study) | | | | | | | | | | | | |
| 1 (1) | observational studies | serious ^a | not serious ^d | very serious ^a | serious ^b | none | 5/193 (2.6%) | 19/216 (8.8%) | RR 0.295 (- to -) | 62 fewer per 1,000 (from - to -) |  VERY LOW | CRITICAL |
| Reduction in active TB incidence/prevalence in high TB burden settings (n = 0 studies) - not measured | | | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - | - | - |
| Reduction in active TB incidence/prevalence in primary care (n = 0 studies) - not measured | | | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - | - | - |
| Reduction in active TB incidence/prevalence in secondary/tertiary care (n = 1 study) | | | | | | | | | | | | |
| 1 (1) | observational studies | serious ^a | not serious ^d | very serious ^a | serious ^b | none | 5/193 (2.6%) | 19/216 (8.8%) | RR 0.295 (- to -) | 62 fewer per 1,000 (from - to -) |  VERY LOW | CRITICAL |
| Reduction in active TB incidence/prevalence in HIV-negative individuals (n = 0 studies) - not measured | | | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - | - | - |
| Reduction in active TB incidence/prevalence in HIV-positive individuals (n = 1 study) | | | | | | | | | | | | |
| 1 (1) | observational studies | serious ^a | not serious ^d | very serious ^a | serious ^b | none | 5/193 (2.6%) | 19/216 (8.8%) | RR 0.295 (- to -) | 62 fewer per 1,000 (from - to -) |  VERY LOW | CRITICAL |

CI: Confidence interval; RR: Risk ratio

Explanations

- a. Please note that meta-analysis was not conducted - all summary estimates and measures of effect are crude estimates.
- b. No significant difference in the treatment in the before and after groups (1.5 vs. 2.0 drugs given before vs. after; range 0–4 in both periods; $p = 0.2$). Exposure is also different for between before and after groups.
- c. As there is only one study included we cannot comment on heterogeneity of results between studies.
- d. Authors describe "expanded use of antituberculous drugs" in "after" period, but no description of time to treatment; therefore unable to assess for difference compared with delayed treatment administration.
- e. Small numbers of cases in both arms. Overall number of exposed individuals = 409 ($n = 216$ before; $n = 193$ after).

References

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Table Q15.5 Triage of people with TB signs to reduce transmission (WHO 2019 Annex 4, PICO 1)

| No of studies | Study design | Certainty assessment | | | | | No of patients | | Effect | | Certainty | Importance |
|---|------------------------------------|----------------------|--------------------------|---------------------------|----------------------|----------------------|-------------------|-------------------|---------------------|-------------------------------------|-----------|------------|
| | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Triage | No triage | Relative (95% CI) | Absolute (95% CI) | | |
| Reduction in LTBI incidence/prevalence in all settings* | | | | | | | | | | | | |
| 6 | observational studies ^b | serious ^b | not serious | very serious | serious ^b | none | 1966/24852 (7.9%) | 1350/9547 (14.0%) | RR 0.57 (- to -) | 60 fewer per 1,000 (from - to -) | VERY LOW | CRITICAL |
| Reduction in LTBI incidence/prevalence in low TB burden settings* | | | | | | | | | | | | |
| 5 | observational studies ^b | serious ^b | not serious | very serious | serious ^b | none | 206/22035 (0.9%) | 322/8045 (4.0%) | RR 0.23 (- to -) | 31 fewer per 1,000 (from - to -) | VERY LOW | CRITICAL |
| Reduction in LTBI incidence/prevalence in high TB burden settings* | | | | | | | | | | | | |
| 1 14 | observational studies ^b | serious ^b | not serious ^b | serious ^b | not serious | none | 1760/2817 (62.5%) | 1028/1602 (64.2%) | RR 0.97 (- to -) | 19 fewer per 1,000 (from - to -) | VERY LOW | CRITICAL |
| Reduction in LTBI incidence/prevalence in primary care - not measured | | | | | | | | | | | | |
| Reduction in LTBI incidence/prevalence in secondary/tertiary care* | | | | | | | | | | | | |
| 6 | observational studies ^b | serious ^b | not serious | very serious | serious ^b | none | 1966/24852 (7.9%) | 1350/9547 (14.0%) | RR 0.57 (- to -) | 60 fewer per 1,000 (from - to -) | VERY LOW | CRITICAL |
| Reduction in active TB incidence/prevalence in all settings* | | | | | | | | | | | | |
| 2 | observational studies ^b | serious ^b | not serious | very serious ^b | serious ^b | none | 110/6216 (1.8%) | 129/7161 (1.8%) | RR 0.98 (- to -) | 0 fewer per 1,000 (from - to -) | VERY LOW | CRITICAL |
| Reduction in active TB incidence/prevalence in low TB burden settings | | | | | | | | | | | | |
| 1 * | observational studies ^b | not serious | not serious ^b | not serious | serious ^b | none | | | RR 0.32 (- to -) | 0 fewer per 1,000 (from - to -) | VERY LOW | CRITICAL |
| Reduction in active TB incidence/prevalence in high TB burden settings* | | | | | | | | | | | | |
| 2 | observational studies ^b | serious ^b | not serious | very serious ^b | serious ^b | none | 110/6216 (1.8%) | 129/7161 (1.8%) | RR 0.98 (- to -) | 0 fewer per 1,000 (from - to -) | VERY LOW | CRITICAL |
| Reduction in active TB incidence/prevalence in primary care - not measured | | | | | | | | | | | | |
| Reduction in active TB incidence/prevalence in secondary/tertiary care* | | | | | | | | | | | | |
| 2 | observational studies ^b | serious ^b | not serious | very serious ^b | serious ^b | none | 110/6216 (1.8%) | 129/7161 (1.8%) | RR 0.98 (- to -) | 0 fewer per 1,000 (from - to -) | VERY LOW | CRITICAL |

CI: Confidence interval; RR: Risk ratio

Explanations

- a. Please note: The total number of studies measuring the effect of triage on the incidence of LTBI in all settings was 10. Four studies were excluded from the summary analysis (certainty estimates and crude summaries of findings [meta-analysis was NOT conducted]) because they did not report results in a format suitable for aggregation. These were (first author, year published): 1) Baussano, 2007; 2) Blumberg, 1998; 3) Louther, 1997; and 4) Yanai, 2003. Please see separate footnotes that summarise the results of these studies.
- b. Study reporting outcome, but not included in summary assessments. Baussano, 2007: Incidence rate of 151 conversions of 104,039 person-years before TBIC intervention were implemented, vs. 42 TST conversions per 4463 person-years after implementation (crude rate ratio 0.38 after vs. before).
- c. Study reporting outcome, but not included in summary assessments. Blumberg, 1998 (some overlap with 1995 paper): TST conversion rate of 5.8/100 person-years in 1992 (pre-intervention) to 1.0/100 person-years from 1993–1997 (after the intervention was implemented); crude incidence rate ratio 0.18, after vs. before [derived from data presented]; authors report a p-value comparing the two time periods: <0.001.
- d. Study reporting outcome, but not included in summary assessments. Yanai, 2003: TST conversions from 3.3 per 100 person-years (95% CI 3.3–15.3) before the implementation of TBIC measures (in 1995–1997) to 6.4 per 100 person-years (95% CI 5.5–11.4) and 2.2 per 100 person-years (95% CI 0.5–1.1), after implementation, in 1998 and 1999, respectively. Unadjusted rate ratio 0.9 (95% CI 0.4–2.3) for 1998 vs. 1995–1997, and 0.03 (95% CI 0.01–0.2) for 1999 vs. 1995–1997, respectively).
- e. Definitions of triage varied widely between the six studies: Bangsberg - "all patients known HIV+, with HIV risk factors, or homelessness presenting with pneumonia/evidence of TB were isolated on presentation at the emergency room"; Blumberg 1995 - "expanded respiratory isolation policy"; Holzman - not defined; Roth - "rapid diagnosis and treatment"; Weibel - "revised policy (based on CDC guidelines) for isolation [CDC 1994: 'in hospitals and other inpatient facilities, any patient suspected of having or known to have infectious TB should be placed in a TB isolation room']"; and Wenger - "higher index of suspicion for TB and stricter application of isolation criteria".
- f. Study reporting outcome, but not included in summary assessments. Louther, 1997: 7.2 TST conversions per 100 person-years before the implementation of infection control measures, compared with 3.3 per 100 person-years after the implementation (crude rate ratio 0.46 [derived from data presented]; authors report p-value comparing the two groups: 0.001).
- g. A mix of before/after, during/after, and prospective and retrospective cohort studies.
- h. All studies are observational. Several studies have high risk of bias, with loss to follow-up, or incomplete ascertainment and/or reporting of outcomes of interest.
- i. Indirectness exists in the wide variation in types of triage and the descriptions of their implementation, as well as the implementation of a large number of infection control measures at one time. Please see assessment of directness for details.
- j. Low number of events (<300) in almost all studies and two studies (Bangsberg and Wenger) have fewer than 20 events. The exception is the study by Roth et al., which has a total of 2,872 events.
- k. Please note: The total number of studies estimating the effect of triage on the incidence of LTBI in low TB burden settings was eight. Three studies were excluded from the summary analysis (certainty estimates and crude summaries of findings [meta-analysis was NOT conducted]) because they did not report results in a format suitable for aggregation. These were (first author, year published): 1) Baussano, 2007; 2) Blumberg, 1998; and 3) Louther, 1997. Please see separate footnotes that summarise the results of these studies.
- l. Definitions of triage varied widely between the five studies: Bangsberg - "all patients known HIV+, with HIV risk factors, or homelessness presenting with pneumonia/evidence of TB were isolated on presentation at the emergency room"; Blumberg 1995 - "expanded respiratory isolation policy"; Holzman - not defined; Weibel - "revised policy (based on CDC guidelines) for isolation [CDC 1994: 'in hospitals and other inpatient facilities, any patient suspected of having or known to have infectious TB should be placed in a TB isolation room']"; and Wenger - "higher index of suspicion for TB and stricter application of isolation criteria".
- m. All studies have small numbers of events (<300; two had >20 events) and moderate overall sample sizes (except for Blumberg et al.).
- n. Please note: The total number of studies estimating the effect of triage on the incidence of LTBI in high TB burden settings was one. One study was excluded from the summary analysis (certainty estimates and crude summaries of findings [meta-analysis was NOT conducted]) because it did not report results in a format suitable for aggregation. This was (first author, year published): 1) Yanai, 2003. Please see the separate footnote that summarises the results of this study.
- o. High loss to follow-up.
- p. Cannot comment on inconsistency as data from only one study included.
- q. Very different definitions of triage used, population not well described, differences in background risk, and triage implemented along with other infection control measures. Please see assessment of directness for details.
- r. Please note: The total number of studies measuring the effect of triage on the incidence of LTBI in secondary/tertiary care settings was 10. Four studies were excluded from the summary analysis (certainty estimates and crude summaries of findings [meta-analysis was NOT conducted]) because they did not report results in a format suitable for aggregation. These were (first author, year published): 1) Baussano, 2007; 2) Blumberg, 1998; 3) Louther, 1997; and 4) Yanai, 2003. Please see separate footnotes that summarise the results of these studies.
- s. Please note: The total number of studies measuring the effect of triage on the incidence of TB disease in all settings was four. Two studies were excluded from the summary analysis (certainty estimates and crude summaries of findings [meta-analysis was NOT conducted]) because they did not report results in a format suitable for aggregation. These were (first author, year published): 1) Jacobson, 1957; and 2) O'Hara, 2017. Please see separate footnotes that summarise the results of these studies.
- t. Study reporting outcome, but not included in summary assessments. Jacobson, 1957: Incidence rate of 78 episodes of TB disease among health care workers in 38,331 person-years in the control group (1942–51, before the intervention was implemented) to 12 episodes in 18,229 person-years after implementation of triage (1952–55, crude incidence rate ratio 0.32, after vs. before).
- u. Definitions of triage differed between the two studies: Harries - "priority to patients with chronic cough; rapid collection of sputum specimens" and Yanai - "triage/isolation and expedited diagnosis training for health care workers".
- v. Study reporting outcome, but not included in summary assessments. O'Hara, 2017: Unadjusted odds ratio (OR) for TB disease in HCW at facilities with a higher administrative score was 0.94 (95% CI 0.87–1.02; p = 0.12). Adjusted OR (adjusted for environmental score, PPE score, administrative score, and number of TB patients) 0.97 (95% CI 0.80–1.04; p = 0.36).
- w. Under-reporting of outcomes in at least one study, poor reporting of loss to follow-up.
- x. Very serious indirectness exists in terms of the population studied and the nature and implementation of the intervention. Please see assessment of directness for details.
- y. Small numbers of events in both studies.
- z. Small number of outcomes in before (n = 78) and after (n = 12) periods.
- aa. Please note: The total number of studies measuring the effect of triage on the incidence of TB disease in high TB burden settings was three. One study was excluded from the summary analysis (certainty estimates and crude summaries of findings [meta-analysis was NOT conducted]) because it did not report results in a format suitable for aggregation. This was (first author, year published): 1) O'Hara, 2017. Please see the separate footnote that summarises the results of this study.
- bb. Please note: The total number of studies measuring the effect of triage on the incidence of TB disease in secondary/tertiary care settings was four. Two studies were excluded from the summary analysis (certainty estimates and crude summaries of findings [meta-analysis was NOT conducted]) because they did not report results in a format suitable for aggregation. These were (first author, year published): 1) Jacobson, 1957; and 2) O'Hara, 2017. Please see separate footnotes that summarise the results of these studies.

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Table Q15.6 Triage of people with TB signs to reduce to reduce transmission (WHO 2019 Annex 4, PICO 1)

Author(s): TB Centre, London School of Hygiene & Tropical Medicine
 Date: 27-29 March 2018
 Question: Can triage of people with TB signs, symptoms or with confirmed TB disease, reduce TB transmission to other persons attending healthcare settings when compared to transmission to the same populations in settings with no intervention or different interventions?
 Setting: International

| Nº of studies | Study design | Certainty assessment | | | | | Nº of patients | | Effect | | Certainty | Importance |
|---|-----------------------|----------------------|---------------|---------------------------|----------------------|----------------------|----------------|----------------|-------------------|-----------------------------------|-----------|------------|
| | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Triage | No triage | Relative (95% CI) | Absolute (95% CI) | | |
| Reduction in LTBI incidence/prevalence in all settings (n = 8 studies) - not measured | | | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - | - | - |
| Reduction in active TB incidence/prevalence in all settings (n = 2 studies) | | | | | | | | | | | | |
| 2 ^{1a} | observational studies | serious ^b | not serious | very serious ^c | serious ^d | none | 5/237 (2.1%) | 45/306 (14.7%) | RR 0.143 (- to -) | 126 fewer per 1,000 (from - to -) | | VERY LOW |
| Reduction in active TB incidence/prevalence in low TB burden settings (n = 2 studies) | | | | | | | | | | | | |
| 2 ^{1a} | observational studies | serious ^b | not serious | very serious ^c | serious ^d | none | 5/237 (2.1%) | 45/306 (14.7%) | RR 0.143 (- to -) | 126 fewer per 1,000 (from - to -) | | VERY LOW |
| Reduction in active TB incidence/prevalence in high TB burden settings (n = 0 studies) - not measured | | | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - | - | - |
| Reduction in active TB incidence/prevalence in primary care (n = 0 studies) - not measured | | | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - | - | - |
| Reduction in active TB incidence/prevalence in secondary/tertiary care (n = 2 studies) | | | | | | | | | | | | |
| 2 ^{1a} | observational studies | serious ^b | not serious | very serious ^c | serious ^d | none | 5/237 (2.1%) | 45/306 (14.7%) | RR 0.143 (- to -) | 126 fewer per 1,000 (from - to -) | | VERY LOW |
| Reduction in active TB incidence/prevalence in HIV-negative individuals (n = 0 studies) - not measured | | | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - | - | - |
| Reduction in active TB incidence/prevalence in HIV-positive individuals (n = 2 studies) | | | | | | | | | | | | |
| 2 ^{1a} | observational studies | serious ^b | not serious | very serious ^c | serious ^d | none | 5/237 (2.1%) | 45/306 (14.7%) | RR 0.143 (- to -) | 126 fewer per 1,000 (from - to -) | | VERY LOW |

CI: Confidence interval, RR: Risk ratio

Explanations

- a. Please note that meta-analysis was *not* conducted - all summary estimates and measures of effect are crude estimates.
- b. Serious risk of bias, probable to alter the results: exposure is different for each study between before and after groups, and not a clear differentiation of intervention vs. no intervention.
- c. Multiple interventions were introduced at the same time. In addition, 'triage' was poorly defined in both studies, as targeting people with "respiratory disease and fever" but with no mention of expedited diagnosis, or as an "increased index of suspicion for TB" without description of how this was implemented. Please see also assessment of directness.
- d. Both studies had small sample sizes. The total at-risk population was 543; a total 50 events were included.

References

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Table Q15.7 Respiratory isolation of people with TB signs to reduce to reduce transmission (WHO 2019 Annex 4, PICO 1)

Author(s): TB Centre, London School of Hygiene & Tropical Medicine
 Date: 27-29 March 2018
 Question: Can respiratory isolation/separation of people with presumed or demonstrated infectious TB reduce TB transmission to HCWs (including community HCWs) when compared to transmission to the same populations in settings with no intervention or different interventions?
 Setting: International

| No of studies | Study design | Certainty assessment | | | | | No of patients | | Effect | | Certainty | Importance |
|--|-----------------------|---------------------------|--------------------------|---------------------------|----------------------|----------------------|-----------------------|--------------------------|------------------------|---|-----------|------------|
| | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Respiratory isolation | No respiratory isolation | Relative (95% CI) | Absolute (95% CI) | | |
| Reduction in LTBI incidence/prevalence in all settings | | | | | | | | | | | | |
| 12 ^{1a} | observational studies | very serious | not serious | very serious | serious ^b | none | 2413/91397 (2.6%) | 1914/40097 (4.8%) | RR 0.55 (- to -) | 21 fewer per 1,000 (from - to -) | | VERY LOW |
| Reduction in LTBI incidence/prevalence in low TB burden settings | | | | | | | | | | | | |
| 11 ^{1a} | observational studies | very serious ^b | not serious | very serious | serious ^b | none | 653/88580 (0.7%) | 885/38495 (2.3%) | RR 0.32 (- to -) | 16 fewer per 1,000 (from - to -) | | VERY LOW |
| Reduction in LTBI incidence/prevalence in high TB burden settings | | | | | | | | | | | | |
| 1 ^{1a} | observational studies | serious ^b | not serious ^b | serious ^b | not serious | none | 1760/2817 (62.5%) | 1028/1602 (64.2%) | RR 0.97 (- to -) | 19 fewer per 1,000 (from - to -) | | VERY LOW |
| Reduction in LTBI incidence/prevalence in primary care - not measured | | | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - | - | - |
| Reduction in LTBI incidence/prevalence in secondary/tertiary care | | | | | | | | | | | | |
| 12 ^{1a} | observational studies | very serious | not serious | very serious | serious ^b | none | 2413/91397 (2.6%) | 1914/40097 (4.8%) | RR 0.55 (- to -) | 21 fewer per 1,000 (from - to -) | | VERY LOW |
| Reduction in active TB incidence/prevalence in all settings | | | | | | | | | | | | |
| 2 ^{1a} | observational studies | serious ^b | not serious | very serious ^b | serious ^b | none | 110/6216 (1.8%) | 129/7161 (1.8%) | RR 0.98 (- to -) | 0 fewer per 1,000 (from - to -) | | VERY LOW |
| Reductions in active TB incidence/prevalence in low TB burden settings - not measured | | | | | | | | | | | | |
| 2 ^{1a} | observational studies | serious ^b | not serious | very serious ^b | serious ^b | none | 110/6216 (1.8%) | 129/7161 (1.8%) | RR 0.98 (- to -) | 0 fewer per 1,000 (from - to -) | | VERY LOW |
| Reductions in active TB incidence/prevalence in high TB burden settings | | | | | | | | | | | | |
| 2 ^{1a} | observational studies | serious ^b | not serious | very serious ^b | serious ^b | none | 110/6216 (1.8%) | 129/7161 (1.8%) | RR 0.98 (- to -) | 0 fewer per 1,000 (from - to -) | | VERY LOW |
| Reductions in active TB incidence/prevalence in primary care | | | | | | | | | | | | |
| 1 ^{1a} | observational studies | very serious ^b | not serious ^b | very serious ^b | serious ^b | none | | | OR 1.09 (0.99 to 1.19) | 1 fewer per 1,000 (from 1 fewer to 1 fewer) | | VERY LOW |
| Reductions in active TB incidence/prevalence in secondary/tertiary care | | | | | | | | | | | | |
| 2 ^{1a} | observational studies | serious ^b | not serious | very serious ^b | serious ^b | none | 110/6216 (1.8%) | 129/7161 (1.8%) | RR 0.98 (- to -) | 0 fewer per 1,000 (from - to -) | | VERY LOW |

CI: Confidence interval, RR: Risk ratio, OR: Odds ratio

Explanations

- a. PLEASE NOTE: The total number of studies measuring the effect of isolation on the incidence of LTBI in all settings was 19. Seven studies were excluded from the summary analysis (certainty estimates and crude summaries of findings [meta-analysis was NOT conducted]) because they did not report results in a format suitable for aggregation. These were (first author, year published): 1) Baussano, 2007; 2) Blumberg, 1998; 3) Bryan, 1983; 4) da Costa, 2009; 5) Louther, 1997; 6) Slinkowitz, 1996; and 7) Yanai, 2003. Please see separate footnotes that summarise the results of these studies.
- b. STUDY REPORTING OUTCOME BUT NOT INCLUDED IN SUMMARY ASSESSMENTS. Baussano, 2007: incidence rate of TST conversions of 106/4034 person-years before TBIC interventions were implemented, vs. 42 TST conversions per 4463 person-years after implementation (crude rate ratio 0.36 after vs. before).
- c. STUDY REPORTING OUTCOME BUT NOT INCLUDED IN SUMMARY ASSESSMENTS. Blumberg, 1998; some overlap with 1995 paper): TST conversion rate of 5.98/100 person-years in 1992 (pre-intervention) to 1.09/100 person-years from 1993-1997 (after the intervention was implemented; crude incidence rate ratio 0.18, after vs. before [derived from data presented]; authors report a p-value comparing the two time periods: <0.001).
- d. STUDY REPORTING OUTCOME BUT NOT INCLUDED IN SUMMARY ASSESSMENTS. Bryan, 1983: TST conversion of 4.5% in 1976, before the implementation of TBIC measures, vs. 5.1%, 1.5%, 0.85%, and 0.59% in the four years after implementation (crude risk ratio 1.13, 0.33, 0.19, and 0.13 for 1977-1981, respectively).
- e. STUDY REPORTING OUTCOME BUT NOT INCLUDED IN SUMMARY ASSESSMENTS. da Costa, 2009: TST conversions incidence rate from 5.8 per 1,000 person-months (95% CI 4.9-6.7), to 3.7 per 1,000 person-months (95% CI 2.8-4.6); rate ratio 0.46 (95% CI 0.23-0.69) after vs. before, p = 0.005, adjusted rate ratio (adjusted for exposure and occupation) 0.24 (95% CI 0.10-0.54).
- f. STUDY REPORTING OUTCOME BUT NOT INCLUDED IN SUMMARY ASSESSMENTS. Slinkowitz, 1996: TST conversion in 0%, 8.0%, and 5.1% of bronchoscopists in hospitals without IC measures and zero TB patients, 1-5 TB patients, and ≥6 TB patients, vs. 3.3%, 8.3%, and 5.7% in hospitals with the same numbers of TB patients but which had implemented four IC measures (crude risk ratio 1.04 and 1.12 [IC vs. no IC] for hospitals with 1-5 TB patients and ≥6 TB patients, respectively). In other HCW, TST conversion in 0.49%, 0.64%, and 0.78% in hospitals with the same numbers of TB patients but which had implemented four IC measures (crude risk ratio 1.08, 1.08, and 1.18 [IC vs. no IC] for hospitals with 1-5 TB patients and ≥6 TB patients, respectively).
- g. STUDY REPORTING OUTCOME BUT NOT INCLUDED IN SUMMARY ASSESSMENTS. Yanai, 2003: TST conversions from 8.3 per 100 person-years (95% CI 5.3-15.3) before the implementation of TBIC measures (in 1995-1997) to 6.4 per 100 person-years (95% CI 1.5-11.1) and 2.3 per 100 person-years (95% CI 0-4.1) after implementation, in 1998 and 1999, respectively. Unadjusted rate ratio 0.9 (95% CI 0.4-2.2) for 1998 vs. 1995-1997 and 0.03 (95% CI 0.01-0.2) for 1999 vs. 1995-1997, adjusted rate ratio 0.4 (95% CI 0.1-1.6) and 0.01 (95% CI 0-0.04) for 1998 and 1999 vs. 1995-1997, respectively).
- h. STUDY REPORTING OUTCOME BUT NOT INCLUDED IN SUMMARY ASSESSMENTS. Louther, 1997: 7.2 TST conversions per 100 person-years before the implementation of infection control measures, compared with 3.3 per 100 person-years after the implementation (crude rate ratio 0.45 [derived from data presented], authors report p-value comparing the two groups: 0.001).
- i. Most studies included here have a high or unclear risk of bias. All are observational studies, some with high rates of loss to follow-up (e.g., Roth), low or unclear levels of participation, or incomplete reporting of outcomes (e.g., Blumberg). Two studies do not report results correctly or have missing results.
- j. Indirectness was primarily through the implementation of multiple infection control measures together with isolation. Please see assessment of directness for details.
- k. Precision exists; all except two studies (Fridkin and Roth) have fewer than 300 outcomes and three studies (Bangsberg, Behman, and Wenger) have fewer than 20 outcomes.
- l. PLEASE NOTE: The total number of studies measuring the effect of isolation on the incidence of LTBI in low TB burden settings was 16. Five studies were excluded from the summary analysis (certainty estimates and crude summaries of findings [meta-analysis was NOT conducted]) because they did not report results in a format suitable for aggregation. These were (first author, year published): 1) Baussano, 2007; 2) Blumberg, 1998; 3) Bryan, 1983; 4) Louther, 1997; and 5) Slinkowitz, 1996. Please see separate footnotes that summarise the results of these studies.
- m. Most studies included here have a high or unclear risk of bias. All are observational studies, some with incomplete reporting of outcomes (e.g., Blumberg), and two studies do not report results correctly or have missing results.
- n. PLEASE NOTE: The total number of studies measuring the effect of isolation on the incidence of LTBI in high TB burden settings was three. Two studies were excluded from the summary analysis (certainty estimates and crude summaries of findings [meta-analysis was NOT conducted]) because they did not report results in a format suitable for aggregation. These were (first author, year published): 1) da Costa, 2009 and 2) Yanai, 2003. Please see separate footnotes that summarise the results of these studies.
- o. High proportions were lost to follow-up; those lost to follow-up may have been at higher risk of disease (more likely to be physicians).
- p. Cannot comment on inconsistency as data from only one study are included.
- q. PLEASE NOTE: The total number of studies measuring the effect of isolation on the incidence of LTBI in secondary/tertiary care settings was 19. Seven studies were excluded from the summary analysis (certainty estimates and crude summaries of findings [meta-analysis was NOT conducted]), because they did not report results in a format suitable for aggregation. These were (first author, year published): 1) Baussano, 2007; 2) Blumberg, 1998; 3) Bryan, 1983; 4) da Costa, 2009; 5) Louther, 1997; 6) Slinkowitz, 1996; and 7) Yanai, 2003. Please see separate footnotes that summarise the results of these studies.
- r. PLEASE NOTE: The total number of studies measuring the effect of isolation on the incidence of active TB disease in all settings was four. Two studies were excluded from the summary analysis (certainty estimates and crude summaries of findings [meta-analysis was NOT conducted]) because they did not report results in a format suitable for aggregation. These were (first author, year published): 1) Claassens, 2013 and 2) O'Hara, 2017. Please see separate footnotes that summarise the results of these studies.
- s. STUDY REPORTING OUTCOME BUT NOT INCLUDED IN SUMMARY ASSESSMENTS. Claassens, 2013: Unadjusted odds ratio for smear-positive TB among health care workers in facilities where administrative controls were implemented vs. facilities without (or with fewer) administrative controls 1.09 (95% CI 0.99-1.19), p = 0.07.
- t. STUDY REPORTING OUTCOME BUT NOT INCLUDED IN SUMMARY ASSESSMENTS. O'Hara, 2017: Unadjusted odds ratio (OR) for TB disease in HCW at facilities with a higher administrative score was 0.94 (95% CI 0.87-1.02; p = 0.12). Adjusted OR (adjusted for environmental score, PPE score, miscellaneous score, and number of TB patients) 0.97 (95% CI 0.90-1.04; p = 0.36).
- u. Under-ascertainment of outcome in at least one study. All studies implemented isolation/spatial separation in addition to a number of other TBIC interventions; the effect of isolation/separation on the outcome of interest cannot be determined. Poor reporting of loss to follow-up.
- v. Very serious indirectness exists, for populations studied and in the nature of and fidelity to the intervention. Please see assessment of directness for details.
- w. Both studies had fewer than 200 events; one had fewer than 100 events.
- x. PLEASE NOTE: The total number of studies measuring the effect of isolation on the incidence of active TB disease in high TB burden settings was four. Two studies were excluded from the summary analysis (certainty estimates and crude summaries of findings [meta-analysis was NOT conducted]) because they did not report results in a format suitable for aggregation. These were (first author, year published): 1) Claassens, 2013 and 2) O'Hara, 2017. Please see separate footnotes that summarise the results of these studies.
- y. Please note that the odds ratio quoted for this study is for the development of smear-positive TB among healthcare workers at facilities classified by their implementation of infection control measures (i.e., the authors reported slightly increased odds of developing smear-positive TB in healthcare workers in facilities where administrative controls were implemented compared with facilities without or with fewer administrative controls).
- z. High likelihood of under-ascertainment or outcome (smear-positive disease in HCW), as only routine records used, without verification or any additional efforts to estimate numbers of cases. In addition, high variability in implementation intervention across different facilities, with isolation only implemented in ~50% of facilities. Most importantly, the study used the facilities as the base unit for assessing risk of TB disease (so reduced TB incidence to a binary of any/ no HCW developing TB at a particular facility) - individual HCW data not assessed.
- aa. Indirectness is severe. Please see assessment of directness for details.
- bb. Small effect seen, and in the opposite direction to expected. Confidence interval is narrow, but crosses 1.
- cc. PLEASE NOTE: The total number of studies measuring the effect of isolation on the incidence of active TB disease in secondary/tertiary care settings was three. One study was excluded from the summary analysis (certainty estimates and crude summaries of findings [meta-analysis was NOT conducted]) because it did not report results in a format suitable for aggregation. This was (first author, year published): 1) O'Hara, 2017. Please see the separate footnote that summarises the results of this study.

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Table Q15.8 Respiratory isolation of people with TB signs to reduce transmission (WHO 2019 Annex 4, PICO 1)

Author(s): TB Centre, London School of Hygiene & Tropical Medicine
 Date: 27-29 March 2018
 Question: Can respiratory isolation / separation of people with presumed or demonstrated infectious TB reduce TB transmission to other persons attending healthcare settings when compared to transmission to the same populations in settings with no intervention or different interventions?
 Setting: International

| Certainty assessment: | | | | | | | N° of patients | | Effect | | Certainty | Importance | | |
|---|-----------------------|----------------------|---------------|---------------------------|----------------------|----------------------|-----------------------|--------------------------|-------------------|------------------------------------|------------------|------------|--|--|
| N° of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Respiratory isolation | No respiratory isolation | Relative (95% CI) | Absolute (95% CI) | | | | |
| Reduction in LTBI incidence/prevalence in all settings (n = 0 studies) - not measured | | | | | | | | | | | | | | |
| Reduction in active TB incidence/prevalence in all settings (n = 2 studies; n = 543 individuals at risk) | | | | | | | | | | | | | | |
| 2 ^{a,b} | observational studies | serious ^b | not serious | very serious ^b | serious ^d | none | 5/237 (2.1%) | 45/306 (14.7%) | RR 0.143 (- to -) | 126 fewer per 1,000 (from -- to -) | ⊕○○○ VERY LOW | CRITICAL | | |
| Reduction in active TB incidence/prevalence in low TB burden settings (n = 0 studies; n = 543 individuals at risk) | | | | | | | | | | | | | | |
| 2 ^{a,b} | observational studies | serious ^b | not serious | very serious ^b | serious ^d | none | 5/237 (2.1%) | 45/306 (14.7%) | RR 0.143 (- to -) | 126 fewer per 1,000 (from -- to -) | ⊕○○○ VERY LOW | CRITICAL | | |
| Reduction in active TB incidence/prevalence in high TB burden settings (n = 0 studies; n = 0 individuals at risk) - not measured | | | | | | | | | | | | | | |
| Reduction in active TB incidence/prevalence in primary care (n = 0 studies; n = 0 individuals at risk) - not measured | | | | | | | | | | | | | | |
| Reduction in active TB incidence/prevalence in secondary/tertiary care (n = 2 studies; n = 543 individuals at risk) | | | | | | | | | | | | | | |
| 2 ^{a,b} | observational studies | serious ^b | not serious | very serious ^b | serious ^d | none | 5/237 (2.1%) | 45/306 (14.7%) | RR 0.143 (- to -) | 126 fewer per 1,000 (from -- to -) | ⊕○○○ VERY LOW | CRITICAL | | |
| Reduction in active TB incidence/prevalence in HIV-negative individual (n = 0 studies; n = 0 individuals at risk) - not measured | | | | | | | | | | | | | | |
| Reduction in active TB incidence/prevalence in HIV-positive individual (n = 2 studies; n = 543 individuals at risk) | | | | | | | | | | | | | | |
| 2 ^{a,b} | observational studies | serious ^b | not serious | very serious ^b | serious ^d | none | 5/237 (2.1%) | 45/306 (14.7%) | RR 0.143 (- to -) | 126 fewer per 1,000 (from -- to -) | ⊕○○○ VERY LOW | CRITICAL | | |

CI: Confidence interval; RR: Risk ratio

Explanations

- a. Please note that meta-analysis was not conducted - all summary estimates and measures of effect are crude estimates.
- b. Serious risk of bias, probable to alter the results: exposure is different for each study between before and after groups; also isolation measures were in effect before and then more so after. Not a clear differentiation of intervention vs. no intervention.
- c. Multiple interventions were introduced at the same time.
- d. Both studies had small sample sizes. The total at-risk population was 543; a total 50 events were included.

References

1. Moro ML, Errante I, Infuso A, Sodano L, Gori A, Orceca CA, Salamina G, D'Amico C, Besozzi G, Caggese L. Effectiveness of infection control measures in controlling a nosocomial outbreak of multidrug-resistant tuberculosis among HIV patients in Italy. *Int J Tuberc Lung Dis*; 2000.
2. Stroud LA, Tokars JI, Greico MH, Crawford JT, Culver DH, Edlin BR, Sordillo EM, Woodley CL, Giligan ME, Schnieder N, Williams J, Jarvis WR. Evaluation of infection control measures in preventing the nosocomial transmission of multidrug-resistant Mycobacterium tuberculosis in a New York city hospital. *Infect Control Hosp Epidemiol*; 1995.

Table Q15.9 Use of Germicidal Ultraviolet irradiation to reduce transmission of TB among healthcare workers (WHO 2019 Annex 4, PICO 3)

| Certainty assessment: | | | | | | | Impact | | | | Certainty | Importance | | |
|---|-----------------------|----------------------|---------------|---------------------------|-------------|--|---|--------------------|-------------------|-------------------|------------------|------------------|----------|--|
| N° of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Upper room UVGI | No upper room UVGI | Relative (95% CI) | Absolute (95% CI) | | | | |
| Reduction in LTBI incidence/prevalence (n=3) | | | | | | | | | | | | | | |
| 3 ^{a,c} | observational studies | serious ^b | not serious | very serious ^b | not serious | all plausible residual confounding would suggest spurious effect, while no effect was observed | Three studies in humans evaluated this outcome. In Fella, a composite outcome including UVGI was associated with a reduction in TST conversion from 41/303 (13.5%) in the intervention group to 21/446 (4.7%) in the control group – a reduction of 8.8%. In Yanai 2003, a composite intervention including patient masks was associated with a decrease in TST conversions from 13/77 (16.9%) to 2/86 (2.1%) – a decrease of 14.8%. There was no evidence of heterogeneity. In Weibel 1992, mechanical ventilation, in combination with other engineering measures, was associated with a reduction in TST conversions from 982/221 (4.4%) to 62/108 (0.28%), a reduction of 4.1%. Heterogeneity in the interventions precluded meta-analysis. | | | | | ⊕○○○ VERY LOW | CRITICAL | |
| Reduction in TB incidence/prevalence (n=1) | | | | | | | | | | | | | | |
| 1 ^{a,c} | observational studies | serious ^b | not serious | very serious ^b | not serious | all plausible residual confounding would suggest spurious effect, while no effect was observed | 19/4780 (0.4%) | 30/4357 (0.7%) | not pooled | see comment | ⊕○○○ VERY LOW | CRITICAL | | |

CI: Confidence interval

Explanations

- a. The included studies have a high risk of bias (confounding relating to secular trends, non-randomised group allocation, lack of allocation concealment, no adjustment for confounding).
- b. Differences in intervention (applicability). The comparator and interventions are poorly described. The interventions comprise multiple simultaneous components, including engineering, respiratory protection and administrative controls (downgraded by one level).
- c. Only one study evaluated this outcome. In Yanai 2003, a composite intervention including patient masks was associated with a decrease in TB cases from 30/4357 (0.7%) to 19/4780 (0.4%), a reduction in 0.29 cases/100 person years.

References

1. Fella P, Rivera P, Hale M, Squires K. Dramatic increase in tuberculin skin test conversion rate among employees at a hospital in New York City. *Am J Infect Control*; 1995.
2. Yanai H, Limpakarnjanarat K, Uthaivoravut W, Mastro TD, Mori T, Tappero JW. Risk of Mycobacterium tuberculosis infection and disease among health care workers, Chiang Rai, Thailand. *Int J Tuberc Lung Dis*; 2003.
3. Weibel SF, French AL, Bush P, DeGuzman D, Weinstein RA. Protecting health care workers from tuberculosis: a 10-year experience. *Am J Infect Control*; 2009.

Table Q15.10 Use of Germicidal Ultraviolet irradiation to reduce transmission of TB to others (WHO 2019 Annex 4, PICO 3)

Author(s): University of Sydney
 Date: 27-29 March 2018
 Question: Can upper room GUV reduce TB transmission in persons in TB care or others in high TB transmission risk settings when compared to transmission to the same populations in settings with no intervention or different interventions?
 Setting: International

| Certainty assessment | | | | | | | Impact | Certainty | Importance |
|--|-------------------|--------------|--------------------------|----------------------|-------------|----------------------|---|-----------|------------|
| N° of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | | | |
| Reduction in LTBI incidence/prevalence (n=0) in humans | | | | | | | | | |
| 0 | | | | | | | | - | Critical |
| Reduction in TB incidence/prevalence (n=0) in humans | | | | | | | | | |
| 0 | | | | | | | | - | Critical |
| Reduction in LTBI incidence/prevalence (animal studies) (n=2) | | | | | | | | | |
| 2 ^a | randomised trials | not serious | not serious ^b | serious ^c | not serious | none | Two animal studies were included, measuring infection in guinea pigs arising from exhausted air from patient wards. Both studies showed a reduction in infection with use of UVGI. The measured absolute reductions were 25.5% (Esmoibe), 46.7% (Mphaphlele). | ⊕⊕⊕○ | Moderate |
| Reduction in TB incidence/prevalence (animal studies) (n=1) | | | | | | | | | |
| 1 ^d | randomised trials | not serious | not serious ^e | serious ^f | not serious | none | One animal study was included. This was conducted in guinea pigs, exposed to air from patients with TB. In this study, UVGI was associated with a reduction in TB on autopsy of 5%. | ⊕⊕⊕○ | Moderate |

CI: Confidence interval

Explanations

- a. The direction and magnitude of the effect was consistent across the studies. One study (Mphaphlele) involved two study periods, where the rate of infectiousness differed based upon the location of the exhaust outlet in the room. The data were pooled in the final analysis. The direction of the effect was the same in both time periods.
- b. These three studies evaluated tuberculin skin test conversion among guinea pigs exposed to air removed from tuberculosis wards. Differences in the nature of transmission to guinea pigs, compared to humans, are likely to be significant (Downgraded one level).
- c. The direction and magnitude of the effect was consistent across the studies.
- d. These studies were conducted among guinea pigs (3 studies) and rabbits (1 study). Tuberculosis was diagnosed by autopsy. Differences in the nature of transmission to animals and the measurement of the outcome (autopsy diagnosed disease) compared to humans are likely to be significant (Downgraded one level).

References

1. Mphaphlele M, Dhammadikari AS, Jensen PA, Rudnick SN, van Reenen TH, Pagano MA, Leuschner W, Sears TA, Milonova SP, van der Walt M, Stoltz AC, Weyer K, Nardell EA. Institutional Tuberculosis Transmission Controlled Trial of Upper Room Ultraviolet Air Disinfection: A Basis for New Dosing Guidelines. *Am J Respir Crit Care Med*; 2015.
2. Esmoibe AR, Moore DAJ, Gilman RH, Navicopa M, Ticona E, Mitchell B, Noakes C, Martinez C, Sheen P, Ramirez R, Quino W, Gonzalez A, Friedland JS, Evans CA. Upper-Room Ultraviolet Light and Negative Air Ionization to Prevent Tuberculosis Transmission. *Plos Medicine*; 2009.

Table Q15.11 Use of particulate respirators to reduce TB transmission (WHO 2019, Annex 4 PICO 4)

Author(s): University of Sydney
 Date: 27-29 March 2018
 Question: Can the use of particulate respirators reduce TB transmission in healthcare workers in TB care or other high TB transmission risk settings when compared to transmission to the same populations in settings with no intervention or different interventions?
 Setting: International

| Certainty assessment | | | | | | | Impact | Certainty | Importance | |
|--|-----------------------|----------------------|---------------|---------------------------|-------------|--|---|----------------|-------------------|-------------------|
| N° of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | | | | |
| Reduction in LTBI incidence/prevalence (n=9) | | | | | | | | | | |
| 9 ^{a,b,c,d,e,f,g,h,i,j,k,l,m,n,o,p,q,r,s,t,u,v,w,x,y,z} | observational studies | serious ^b | not serious | very serious ^b | not serious | all plausible residual confounding would suggest spurious effect, while no effect was observed | Nine studies examined the effect of particulate respirators upon TST conversion. These studies produced effects in the same direction (reducing infection), however the magnitude of the effect varied considerably between settings. Concerns around confounding due to multiple interventions, and heterogeneity of the interventions, means that the findings were not meta-analyzed. Bangsberg 1997 compared the effect of respiratory masks fitted tightly against usual, prior to the introduction of a new mask, control group. Comparing the period 13.3% to 25.5% (0.4%) to six months after (11.0% to 11.0% in Dec 1993) there was a 1% increase in conversion. Comparing the same control period (0% in Jun 1993) to the period 6-12 months after (0% in Jun 1993) there was no difference. Given the low event numbers, these findings were not of significance. Second, Bausmann found that staff respiratory protection was associated in a reduction in TST conversion from 26.3/1000 person years to 5.4 / 1000 person years – a reduction of 16.9 / 1000 person years. Third, Blumberg 1995 showed a composite intervention with a particulate respirator was associated in a reduction of TST conversion from 0.935 (13.3%) to 255/153 (0.4%), a 2.3% reduction. Fourth, 1995 showed that particulate respirators were associated with a reduction in TST conversion from 41/203 (13.5%) to 21/446 (4.7%), a reduction of 8.8%. Dust fume respirators had no effect. Maloney 1995 showed a composite intervention including molded surgical masks was associated with a reduction in TST conversion from 15/90 (16.7%) to 4/78 (5.1%), a reduction by 11.5%. In Yanai 2003, a composite intervention including mixed mode ventilation was associated with a decrease in TST conversions from 13/77 (16.9%) to 2/98 (2.1%) – a decrease of 14.8%. Roth 1995 showed a composite intervention including respirator for health workers, including a reduction in TST conversion from 1/100 (1%) to 1/24 (4.2%) conversions per 1,000 persons. Welbel 2009 saw a 4.1% reduction in TST conversions, as part of a composite intervention. da Costa 2009 showed a reduction of 1.9 TST conversions per month, as a part of a composite intervention. | ⊕⊕⊕○ | Very Low | Critical |
| Reduction in TB incidence/prevalence (n=1) | | | | | | | | | | |
| 1 ^{a,b,c,d,e,f,g,h,i,j,k,l,m,n,o,p,q,r,s,t,u,v,w,x,y,z} | observational studies | serious ^b | not serious | very serious ^b | not serious | all plausible residual confounding would suggest spurious effect, while no effect was observed | Use of particulate respirators | No use | Relative (95% CI) | Absolute (95% CI) |
| | | | | | | | 19/4780 (0.4%) | 30/4357 (0.7%) | not pooled | see comment |

CI: Confidence interval

Explanations

- a. The included studies have a high risk of bias (confounding relating to secular trends, non-randomized group allocation, lack of allocation concealment, no adjustment for confounding).
- b. Differences in intervention (applicability). The comparator and interventions are poorly described. The interventions comprise multiple simultaneous components, including engineering, respiratory protection and administrative controls (downgraded by one level).
- c. Only one study evaluated this outcome. In Yanai 2003, a composite intervention including use of staff particulate respirators was associated with a decrease in TB cases from 30/4357 (0.7%) to 19/4780 (0.4%), a reduction in 0.29 cases/100 person years.

References

1. Maloney SA, Pearson ML, Gordon MT, Del Castillo R, Boyle JF, Jarvis WR. Efficacy of control measures in preventing nosocomial transmission of multidrug-resistant tuberculosis to patients and health care workers. *Am Intern Med*; 1995.
2. Fella P, Rivers P, Holt M, Squires K, Sepkowitz K. Dynamic increases in tuberculin skin test conversion rates among employees at a hospital in New York City. *Am J Infect Control*; 1995.
3. Bausmann H, Baur M, Corso A, Mariano D, Barocelli AP, Taglia M, Casco V, Picone P, Arribalzaga V. Risk of tuberculosis conversion among healthcare workers and the adoption of preventive measures. *Occup Environ Med*; 2007.
4. Yanai H, Lingskampranee K, Uthaiwirat W, Masto TD, Mori T, Tanyeroji JW. Risk of Mycobacterium tuberculosis infection and disease among health care workers, Chiang Rai, Thailand. *Int J Tuberc Lung Dis*; 2003.
5. Roth VR, Garrett DO, Leder K, Ksiazek TG, Schuchat A, Martinez EAS, Brink N, Larson WR. A multicenter evaluation of tuberculin skin test positivity and conversion among health care workers in Brazilian hospitals. *Int J Tuberc Lung Dis*; 2005.
6. Blumberg HM, Starr M, Erwin M, Basham R, Schulman JA. Risk of house staff tuberculin skin test conversion in an area with a high incidence of tuberculosis. *Clin Infect Dis*; 1998.
7. Bangsberg DR, Crowley K, Moss A, Dokkin JF, McGregor C, Neu HC. Reaction in tuberculin skin-test conversions among medical house staff associated with improved tuberculosis infection control practices. *Infect Control Hosp Epidemiol*; 1997.
8. Welbel SF, French AL, Bush P, DeGuzman D, Weinstein RA. Protecting health care workers from tuberculosis: a 10-year experience. *Am J Infect Control*; 2009.
9. da Costa P, Trajman A, Mello FC, Goudinho S, Silva MA, Garrel D, Ruffino-Neto A, Kretsch AL. Administrative measures for preventing Mycobacterium tuberculosis infection among healthcare workers in a teaching hospital in Rio de Janeiro, Brazil. *J Hosp Infect*; 2009.

Table Q15.12 se of particulate respirators to reduce TB transmission (WHO 2019, Annex 4 PICO 4)

Author(s): University of Sydney

Date: 27-29 March 2018

Question: Can the use of particulate respirators reduce TB transmission in persons in TB care or other high TB transmission risk settings when compared to transmission to the same populations in settings with no intervention or different interventions?

Setting: International

| N° of studies | Study design | Certainty assessment | | | | | N° of patients | Effect | | | Certainty | Importance |
|---|-----------------------|----------------------|---------------|---------------------------|-------------|---|----------------|--------------------------------|---------------|-------------------|------------------|------------|
| | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | | Use of particulate respirators | No use | Relative (95% CI) | | |
| Reduction in LTBI incidence/prevalence (n=0) | | | | | | | | | | | | |
| 0 | | | | | | | | | | | - | CRITICAL |
| Reduction in TB incidence/prevalence (n=1) | | | | | | | | | | | | |
| 1 ^a | observational studies | serious ^b | not serious | very serious ^c | not serious | strong association all plausible residual confounding would suggest spurious effect, while no effect was observed | 0/44 (0.0%) | 26/90 (28.9%) | not pooled | see comment | ⊕○○○ VERY LOW | CRITICAL |
| Reduction in TB incidence/prevalence in people living with HIV (n=1) | | | | | | | | | | | | |
| 1 ^a | observational studies | serious ^b | not serious | very serious ^c | not serious | strong association all plausible residual confounding would suggest spurious effect, while no effect was observed | 0/44 (0.0%) | 26/90 (28.9%) | not estimable | | ⊕○○○ VERY LOW | CRITICAL |

CI: Confidence interval

Explanations

- a. Moro 2000 evaluated the effect of mask use by people entering isolation rooms (including visitors). Surgical masks were used. At the same time, high-risk pentamidine use (a risk for increased cough and transmission) was also ceased. The effect of this intervention reflects a combination of multiple components. Incident MDR-TB reduced from 26/90 (29%) to 0/44 (0%) during the period after the intervention began. The reduction in MDR-TB incidence was 10.6 / 1,000 patient days. Confounding factors are likely, and the effect cannot only be attributed to the respiratory protection program.
- b. The included study has a high risk of bias (confounding relating to secular trends, non-randomised group allocation, lack of allocation concealment, no adjustment for confounding).
- c. The intervention comprises multiple simultaneous components, including engineering, respiratory protection and administrative controls (downgraded by one level).

References

1. Moro ML, Errante I, Infuso A, Sodano L, Gori A, Orcese CA, Salamina G, D'Amico C, Besozzi G, Caggesse L. Effectiveness of infection control measures in controlling a nosocomial outbreak of multidrug-resistant tuberculosis among HIV patients in Italy. *Int J Tuberc Lung Dis*; 2000.

UPDATE ON MANAGEMENT OF TB-HIV COINFECTION

Q16: AMONG PATIENTS WITH TB-HIV CO-INFECTION, HOW EFFECTIVE AND SAFE ARE RIFAMPICIN-CONTAINING REGIMENS IN TERMS OF CLINICAL CURE AND ADVERSE REACTIONS COMPARED TO NON-RIFAMPICIN BASED REGIMENS?

RECOMMENDATION

Among patients with TB-HIV co-infection, RIF-containing regimens are comparable to non-RIF based regimens in terms of effectiveness and safety. (***Weak recommendation, very low-quality evidence***)

REMARKS

Anti-retroviral treatments for HIV patients need to be specified as these drugs may have potential interactions with RIF. **Voting: 15/15 agree**

SUMMARY OF EVIDENCE

Search terms for this question included Free text: tuberculosis, HIV, human immunodeficiency virus, AIDS, acquired immunodeficiency syndrome, rifampicin, rifampin and Mesh terms: Tuberculosis, HIV, Acquired Immunodeficiency Syndrome, Rifampin.

Based on very low level of evidence, there is no significant difference between RIF-containing regimens and non-RIF containing regimens in terms of effectiveness and safety.

There were 2 RCTs comparing RIF-containing regimens and non-RIF-based regimens. A randomized controlled trial in 2015 included 207 treatment-naive smear-positive adult patients with PTB, 40 of whom had HIV co-infection. [1] Of the 207, 181 were DS-TB, and 26 were MDR TB. Patients with HIV were eligible if their CD4 count was greater than 200 cells per μ l and they had no AIDS-defining illness besides TB. Drug susceptible patients were randomized to receive 8 weeks of MPa100Z (moxifloxacin, 100 mg pretomanid, pyrazinamide), MPa200Z, or HRZE. Patients with MDR TB were not randomized because they were not eligible for HRZE therapy. Subgroup analysis for patients with TB-HIV co-infection was not done.

Overall results showed that MPa200Z had significantly greater bactericidal activity than HRZE in terms of decreasing the colony forming unit (CFU) counts of TB. There was no significant difference in the time to culture positivity and adverse events among the treatment groups. The most common adverse events were hyperuricemia in 59 patients (29%), nausea in 37 patients (18%) and vomiting in 25 patients (12%).

Another randomized controlled trial in 2010 included 69 treatment-naive, drug-sensitive, sputum smear-positive, adult patients with PTB, 10 of whom had HIV co-infection.[2] Individuals with HIV infection under antiretroviral treatment or with a CD4 cell count of $\leq 300 \times 10^6/\text{liter}$ were excluded, as were those with bacilli resistant to RIF. Patients were randomized to receive pretomanid monotherapy at 200 mg, 600 mg, 1000 mg, 1200 mg or standard treatment HRZE. Subgroup analysis for patients with TB-HIV co-infection was not done.

Overall results showed no significant difference in bactericidal activity among the treatment groups, as measured by the CFU counts and time to culture positivity. Higher number of adverse events was observed in patients given higher Pa doses. There were 2 serious adverse events (hemoptysis), 1 from the Pa200 group and 1 from the HRZE group.

Pooling of data for the bactericidal activity of non-RIF containing drugs could not be done due to differences in reporting of results (e.g., mean daily change in CFU in 1 study, actual CFU counts at the end of the time period in another study). Based on qualitative evaluation, pretomanid monotherapy and MPa100Z have comparable bactericidal activity to RIF-containing regimens as measured by CFU counts of TB and time to culture positivity. MPa200Z had significantly greater bactericidal activity compared to RIF containing regimens as measured by CFU counts.

In terms of adverse events, the summary of results are shown in Table Q16.1.

Table Q16.1. Summary of Results for Rifampicin Containing Regimens*

| Outcome | Measure of treatment effect | 95% CI | Interpretation | Basis |
|----------------------|-----------------------------|-----------|-----------------|--------|
| Total adverse events | RR = 0.93 | 0.81-1.06 | Not significant | 2 RCTs |

*Please refer to appendix to view forest plots of combined studies.

Data pooled from both RCTs show no significant difference in adverse events between RIF containing and non-RIF containing regimens.

Given these findings, both RIF-containing regimens and non-RIF containing regimens may be considered for the treatment of patients with TB-HIV co-infection.

REFERENCES:

1. Dawson R, Diacon AH, Everitt D, van Niekerk C, Donald PR, Burger DA, et al. Efficiency and safety of the combination of moxifloxacin, pretomanid (PA-824), and pyrazinamide during the first 8 weeks of antituberculosis treatment: a phase 2b, open-label, partly randomised trial in patients with drug-susceptible or drug-resistant pulmonary tuberculosis. Lancet. 2015;385:1738-1747.
2. Diacon AH, Dawson R, Hanekom M, Narunsky K, Maritz SJ, Venter A, et al. Early bactericidal activity and pharmacokinetics of PA-824 in smear-positive tuberculosis patients. Antimicrobial Agents and Chemotherapy. 2010;54(8):3402-3407.

APPENDIX Q16



Figure Q16.1 Total adverse events (The treatment groups with varying doses of pretomanid were grouped together as non-rifampicin containing)

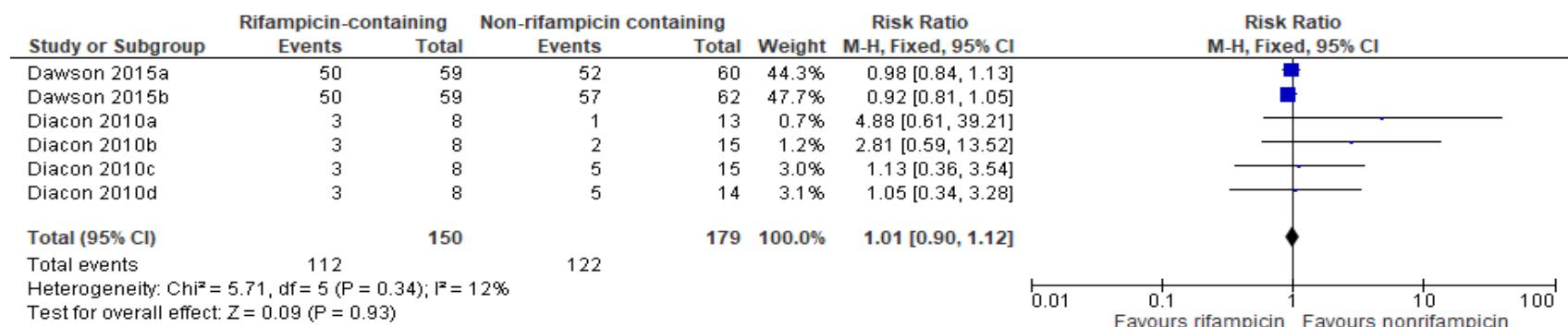


Figure Q16.2 Total adverse events (The treatment groups with varying doses of pretomanid were separated and compared to HRZE)

Author(s): Tan-Lim, CC

Date: 22 November 2019

Question: Among patients with TB-HIV co-infection, how effective and safe are rifampicin-containing regimens in terms of clinical cure and adverse reactions compared to non-rifampicin based regimens?

Setting: Dawson 2015 – South Africa and Tanzania; Diacon 2010 – South Africa

Bibliography:

1. Dawson R, Diacon AH, Everitt D, van Niekerk C, Donald PR, Burger DA, et al. Efficiency and safety of the combination of moxifloxacin, pretomanid (PA-824), and pyrazinamide during the first 8 weeks of antituberculosis treatment: a phase 2b, open-label, partly randomised trial in patients with drug-susceptible or drug-resistant pulmonary tuberculosis. Lancet. 2015;385:1738-1747.
2. Diacon AH, Dawson R, Hanekom M, Narunsy K, Maritz SJ, Venter A, et al. Early bactericidal activity and pharmacokinetics of PA-824 in smear-positive tuberculosis patients. Antimicrobial Agents and Chemotherapy. 2010;54(8):3402-3407.

Table Q16.2 Summary of certainty of Evidence re TB-HIV coinfection

| | | Quality Assessment | | | | | | | Summary of Findings | | |
|----------------|--------------|-----------------------------------|---------------------------|---------------|---------------------------|-------------|----------------|------------------|-----------------------------------|------------|--|
| Outcomes | Study Design | Participants | Risk of Bias | Inconsistency | Indirectness | Imprecision | Reporting Bias | Over-all Quality | OR/RR or MD | Importance | |
| Clinical cure | 2 RCTs | 276 (50 with TB-HIV co-infection) | Serious ^a | Not serious | Very serious ^b | Not serious | Not serious | ⊕○○○ Very Low | Not pooled due to inadequate data | Critical | |
| Adverse events | 2 RCTs | 276 (50 with TB-HIV co-infection) | Very serious ^c | Not serious | Serious ^d | Not serious | Not serious | ⊕○○○ Very Low | RR = 0.93 (95% CI 0.81, 1.06) | Critical | |

^a Serious risk of bias due to differences in baseline characteristics of treatment groups. Although blinding was not done, outcome was assessed using microbiologic techniques

^b Very serious indirectness due to inclusion in both RCTs of HIV-positive and HIV-negative patients, and use of surrogate outcome (CFU counts) in place of clinical outcome (cure)

^c Very serious risk of bias due to differences in baseline characteristics of treatment groups and lack of blinding which would affect reporting and detection of adverse events

^d Serious indirectness due to inclusion in both RCTs of HIV-positive and HIV-negative patient

Q17: AMONG PATIENTS WITH HIV ON LOPINAVIR-RITONAVIR (LPV/r) AND ARE RECEIVING RIFAMPICIN-BASED REGIMENS FOR TB CO-INFECTION, SHOULD THE DOSE OF ART (LOPINAVIR-RITONAVIR) BE INCREASED (BOOSTED OR DOUBLED) TO REDUCE VIROLOGIC FAILURE AND ADVERSE EVENTS?

RECOMMENDATION

Among patients with TB-HIV co-infection who are on RIF-based regimens, caution should be exercised when increasing the dose of LPV/r. Increasing the dose may increase the risk of adverse events without reducing virologic failure. (**Weak recommendation, very low-quality evidence**)

REMARKS

Current evidence suggests that increasing the dose offers no clear benefit but increases the possibility of harm. The panel also suggests to replace clinical failure with virologic failure as one of the outcomes, because RIF, when used with protease inhibitors (PIs), substantially decreases the levels of PIs. Issues regarding the applicability of the boosted doses used in the cited studies were raised. It is not also possible to determine which among boosted vs. double dose produces better outcomes from the studies reviewed.

Voting: 1st round – 6/15 agree, 3/15 abstain, 6/15 disagree; 2nd round – 8/15 agree, 3/15 abstain, 4/15 disagree; 3rd round – 13/15 agree, 2 abstain

SUMMARY OF EVIDENCE

Medline, Cochrane Library and Trip Database were used to search using Free text: “tuberculosis”, “HIV, human” “immunodeficiency virus”, AIDS, acquired immunodeficiency syndrome, ritonavir, lopinavir” Meshterms used were: Tuberculosis, HIV, Acquired Immunodeficiency Syndrome, Lopinavir, Ritonavir

Based on very low level of evidence, LPV/r should not be given as a boosted dose among patients with TB-HIV co-infection on RIF-based TB regimens due to significantly increased risk of adverse events with no significant difference in clinical failure.

There are 4 cohort studies[1-4] that evaluated the effect of boosted doses of lopinavir/ritonavir (LPV/r) among patients given concurrent RIF for treatment of TB. The prospective study [2] and one of the retrospective studies [1] compared boosted dose LPV/r (400mg/400mg BID) to double dose LPV/r (800mg/200mg BID). The other 2 retrospective cohort studies [3,4] compared boosted dose to standard dose LPV/r

(400mg/100mg BID). All cohort studies reported virologic failure and adverse events necessitating treatment modification as outcomes.

One retrospective cohort study [1] used a historical cohort as the control group. However, numerical data on the outcome of this historical cohort was not provided. Thus, the results of this study could not be pooled into the meta-analysis. This study compared boosted dose to double dose LPV/r. There was virologic failure in 3 out of 25 patients given double dose LPV/r. The authors reported that these results are similar to the overall rate of second line treatment failure observed among patients requiring second-line antiretroviral therapy in their setting. In terms of safety, 3 out of 25 patients (12%) given double dose LPV/r experienced adverse events necessitating treatment discontinuation. The historical control group given boosted dose LPV/r had significantly higher adverse events (47%, p value = 0.024),

There were also 2 pharmacokinetic studies on the effect of LPV/r when given as boosted dose among patients with TB-HIV coinfection and treated with RIF based regimens. [5,6] These studies had no control group; hence, results could also not be pooled into the meta-analysis. The 2014 study [6] reported that 3 out of 5 patients had detectable viral load at the end of the study, while the 2019 study [5] reported that 1 out of 11 had <1.0 decrease in viral load at the end of the study. The earlier study [6] had 3 dropouts due to adverse events noted after LPV/r initiation. The more recent one [5] had no dropouts due to adverse events, but 1 out of 11 patients developed a severe adverse event (marked elevation of transaminases).

The summary of results is shown in Table Q17.1.

Table Q17.1. Summary of Results

| Outcome | Measure of Treatment Effect | 95% CI | Interpretation | Basis |
|--|-----------------------------|-------------|-----------------|------------------|
| Virologic failure: Boosted dose vs. non-boosted dose (Fig Q17.1) | OR = 0.76 | 0.23, 2.51 | Not significant | 3 cohort studies |
| Virologic failure: Boosted dose vs. standard dose (Fig Q17.2) | OR = 0.60 | 0.13, 2.8 | Not significant | 2 cohort studies |
| Adverse events necessitating treatment modification: Boosted dose vs. non-boosted dose (Fig Q17.3) | OR = 7.05 | 1.86, 26.63 | Significant | 3 cohort studies |
| Adverse events necessitating treatment modification: Boosted dose vs. standard dose (Fig Q17.4) | OR = 6.38 | 1.47, 27.70 | Significant | 2 cohort studies |

*Please refer to appendix to view forest plots of combined studies

Data pooled from the 3 cohort studies [2-4] show that there is no significant difference in virologic failure between boosted doses of LPV/r and non-boosted doses (standard or double dose) of LPV/r. Subgroup analysis on boosted dose compared to standard dose of LPV/r similarly shows no significant difference in virologic failure, based on 2 cohort studies [3,4].

In terms of adverse events, boosted doses of LPV/r is associated with significantly higher risk of adverse events compared to non-boosted doses of LPV/r, based on 3 cohort studies [2-4]. Based on subgroup analysis of 2 cohort studies [3,4] on boosted dose compared to standard dose of LPV/r, there is a significant increase in adverse events among those given boosted doses compared to those given standard doses of LPV/r. The most common reported adverse events reported were elevation in transaminase levels.

Given these findings, LPV/r should not be given as boosted dose among patients with TB-HIV co-infection taking RIF-based TB regimens. There is no significant difference in virologic failure, but there is a significantly higher risk of adverse events.

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2. Decloedt EH, Maartens G, Smith P, Merry C, Bango F, McIlleron H. The Safety, Effectiveness and Concentrations of Adjusted Lopinavir/Ritonavir in HIV-Infected Adults on Rifampicin-Based Antitubercular Therapy. *PLoS One.* 2012;7(3):e32173.
3. L'homme RF, Nijland HM, Gras L, Aarnoutse RE, van Crevel R, Boeree M, et al. Clinical experience with the combined use of lopinavir/ritonavir and rifampicin. *AIDS.* 2009;23(7):863-865.
4. Murphy RA, Marconi VC, Gandhi RT, Kuritzkes DR, Sunpath H. Coadministration of Lopinavir/Ritonavir and Rifampicin in HIV and Tuberculosis Co-Infected Adults in South Africa. *PLoS One.* 2012;7(9):e44793.
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6. Schmaltz CS, Costa MM, Cattani VB, Pinto DP, Liporage J, Benjamin A, et al. Pharmacological Interaction of Lopinavir/Ritonavir 800/200 mg BID and Rifampicin in Subjects Presenting Tuberculosis with Contraindication for an Efavirenz containing Antiretroviral Regimen. *J AIDS Clin Res.* 2014;5:10.

APPENDIX Q17

Author(s): Tan-Lim, CC **Date:** 23 November 2019

Question: Among patients with TB-HIV co-infection who are on second line ART (lopinavir-ritonavir) and rifampicin-based regimen, should the dose of ART (lopinavir-ritonavir) be boosted or not to reduce clinical failure and adverse events?

Setting: South Africa

Bibliography:

- Decloedt EH, Maartens G, Smith P, Merry C, Bango F, McIlheron H. The Safety, Effectiveness and Concentrations of Adjusted Lopinavir/Ritonavir in HIV-Infected Adults on Rifampicin-Based Antitubercular Therapy. *PLoS One.* 2012;7(3):e32173.
- L'homme RF, Nijland HM, Gras L, Aarnoutse RE, van Crevel R, Boeree M, et al. Clinical experience with the combined use of lopinavir/ritonavir and rifampicin. *AIDS.* 2009;23(7):863-865.
- Murphy RA, Marconi VC, Gandhi RT, Kuritzkes DR, Sunpath H. Coadministration of Lopinavir/Ritonavir and Rifampicin in HIV and Tuberculosis Co-Infected Adults in South Africa. *PLoS One.* 2012;7(9):e44793.

Table 17.2 Summary of Certainty of Evidence for TB-HIV

| | | Quality Assessment | | | | | | | Summary of Findings | | |
|------------------|------------------|--------------------|----------------------|---------------|----------------------|----------------------|----------------|------------------|---|------------|--|
| Outcomes | Study Design | Participants | Risk of Bias | Inconsistency | Indirectness | Imprecision | Reporting Bias | Over-all Quality | OR/RR or MD | Importance | |
| Clinical failure | 3 Cohort studies | 81 | Serious ^a | Not serious | Serious ^b | Serious ^c | Not serious | ⊕○○○ Very Low | OR = 0.76 (95% CI 0.23, 2.51) | Critical | |
| Adverse events | 3 Cohort studies | 81 | Serious ^a | Not serious | Not serious | Not serious | Not serious | ⊕○○○ Very Low | OR = 7.05 (95% CI 1.86, 26.63) | Critical | |

^a Serious risk of bias because cohort studies did not match the 2 groups for all variables associated with the outcome and did not do statistical adjustment

^b Serious indirectness due to reporting of outcome as virologic failure instead of clinical failure

^c Serious imprecision due to wide confidence intervals

APPENDIX Q17

Author(s): Tan-Lim, CC **Date:** 23 November 2019

Question: Among patients with TB-HIV co-infection who are on second line ART (lopinavir-ritonavir) and rifampicin-based regimen, should the dose of ART (lopinavir-ritonavir) be boosted or not to reduce clinical failure and adverse events?

Setting: South Africa

Bibliography:

1. Decloedt EH, Maartens G, Smith P, Merry C, Bango F, McIlheran H. The Safety, Effectiveness and Concentrations of Adjusted Lopinavir/Ritonavir in HIV-Infected Adults on Rifampicin-Based Antitubercular Therapy. *PLoS One.* 2012;7(3):e32173.
2. L'homme RF, Nijland HM, Gras L, Aarnoutse RE, van Crevel R, Boeree M, et al. Clinical experience with the combined use of lopinavir/ritonavir and rifampicin. *AIDS.* 2009;23(7):863-865.
3. Murphy RA, Marconi VC, Gandhi RT, Kuritzkes DR, Sunpath H. Coadministration of Lopinavir/Ritonavir and Rifampicin in HIV and Tuberculosis Co-Infected Adults in South Africa. *PLoS One.* 2012;7(9):e44793.

Table Q17.3 Summary of Certainty of Evidence for TB-HIV

| | | Quality Assessment | | | | | | | Summary of Findings | | |
|------------------|------------------|--------------------|----------------------|---------------|----------------------|----------------------|----------------|------------------|---------------------|---|----------|
| Outcomes | Study Design | Participants | Risk of Bias | Inconsistency | Indirectness | Imprecision | Reporting Bias | Over-all Quality | OR/RR or MD | Importance | |
| Clinical failure | 3 Cohort studies | 81 | Serious ^a | Not serious | Serious ^b | Serious ^c | Not serious | | ⊕○○○ Very Low | OR = 0.76 (95% CI 0.23, 2.51) | Critical |
| Adverse events | 3 Cohort studies | 81 | Serious ^a | Not serious | Not serious | Not serious | Not serious | | ⊕○○○ Very Low | OR = 7.05 (95% CI 1.86, 26.63) | Critical |

^a Serious risk of bias because cohort studies did not match the 2 groups for all variables associated with the outcome and did not do statistical adjustment

^b Serious indirectness due to reporting of outcome as virologic failure instead of clinical failure

^c Serious imprecision due to wide confidence intervals

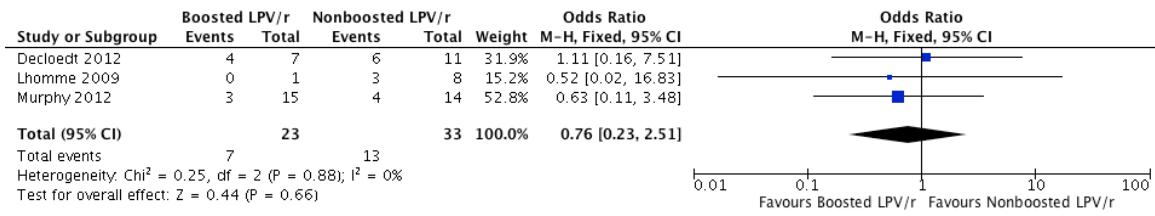


Figure Q17.1 Effects of boosted doses compared to nonboosted doses of LPV/r on virologic failure

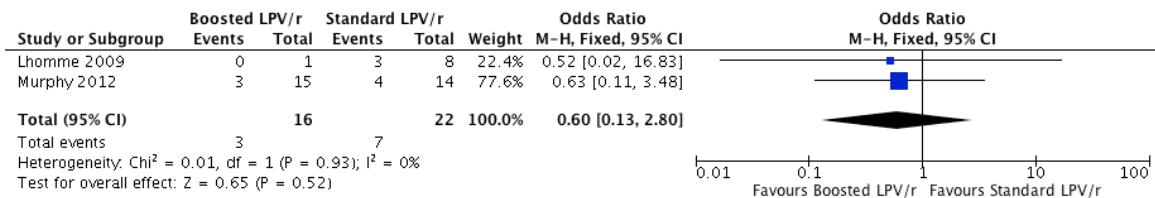


Figure Q17.2 Effects of boosted doses compared to standard doses of LPV/r on virologic failure

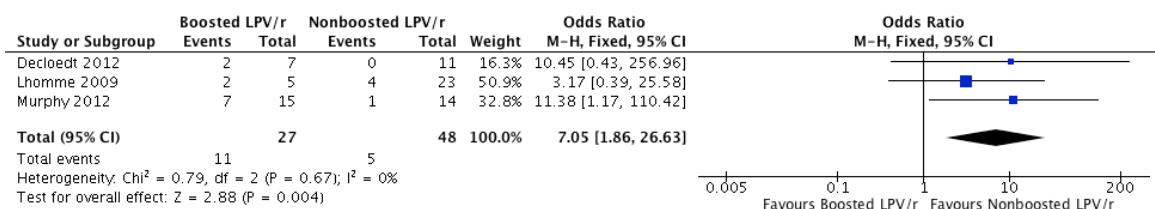


Figure Q17.3 Adverse events experienced by patients on boosted doses compared to nonboosted doses of LPV/r

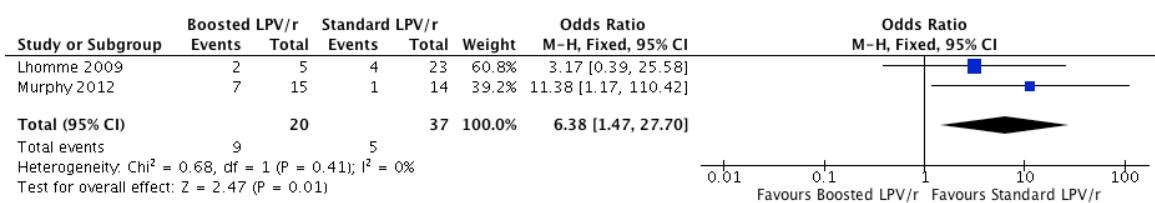


Figure Q17.4 Adverse events experienced by patients on boosted doses compared to standard doses of LPV/r

SPECIAL UPDATE ON MANDATORY TB NOTIFICATION

A. FREQUENTLY ASKED QUESTIONS ON MANDATORY TB NOTIFICATION

What is mandatory TB notification?

Mandatory TB notification is a process of requiring all health care providers and facilities, both public and private, providing part or all TB services such as diagnosis, treatment and prevention, to report to the DOH every person with TB using format and processes designed for this purpose.

What is the legal basis for the mandatory TB notification?

Republic Act (RA) 10767 (Section 12) mandates that “all public & private health centers, hospitals and facilities observe the national protocol on TB management and notify DOH of all TB cases as prescribed under the Manual of Procedures of the National TB Program.” Its Implementing Rules and Regulations (IRR) Section 8.1 requires that current TB notification system be revised to cover all service providers, not only those that are considered part of an established TB service delivery network, to ensure that all persons diagnosed and treated are reported, including its outcome, according to the requirements of the MOP.

Why do we need to notify TB cases?

TB is a notifiable disease and a major public health problem. This will bolster case finding, help ensure high quality TB management in both public and private sectors and assess progress towards TB disease elimination goals. This is an important component of an improved surveillance system.

What is required to notify?

The physician or healthcare provider or medical facility needs to register manually using the TB Service Provider Information Sheet for doctors or health facilities or electronically through URL itis.doh.gov.ph/register.

How does one notify a patient with TB?

Once registered, physicians notify patients diagnosed or initiated treatment with TB, following case definitions prescribed in the 6th MOP. Notification can be done (1) manually by filling out the TB Case Notification Form; (2) through the ITIS Lite website by visiting URL itis.doh.gov.ph/mandatorynotification; or (3) via the ITIS Lite mobile notification app (android or IOS). The app requires a smartphone or tablet that runs IOS or Android operating systems, reliable internet connection at least 1 mbps to install the app and to sync encoded cases.

Notification is done by (1) direct encoding in ITIS or ITIS Lite by the physician; (2) collected by a trained hospital point person, (3) referred to a TB Clinic for notification, or (4) encoded by a TB Notification Officer assigned to the physician.

When do I need to notify?

Notification shall be done at 3 time points: (1) upon diagnosis, whether treatment is initiated or not, referred to another provider for treatment, or even when patient refused treatment; (2) upon initiation of treatment; and (3) once treatment outcomes is known. Double notification will be filtered by the system.

Reporting is done at the end of each month. Zero reporting is also required if no TB cases are seen for the month.

Is patient consent required in mandatory TB notification?

Patient consent is not required in mandatory TB notification, but the patient needs to be informed about the physician's responsibility and purpose to notify as mandated by law, following procedures consistent with the Data Privacy Act of 2012. This aims to protect the right to information privacy while ensuring free flow of mandated information through fair, secure and lawful data collection and processes.

How are patient data utilized?

The designated TB Notification Officer by the NTP Coordinator will review and analyze ITIS-generated reports. All Rural Health Units and Health Centers and their designated TB Notification Officers at the municipality, city, provincial and regional levels shall be responsible in the collection, consolidation and analysis of TB notification reports.

Why is it taking too long to proceed during my first login in ITIS Lite?

During the first login, the app is syncing all previous TB notification cases encoded in the web. This is to ensure that the same data will be available to you whether using mobile or web version. A slow internet connection is also a factor.

Is the mobile app secure to store patient information?

The application is designed to handle personal sensitive information such as patient demographics. Some of the security features of ITIS Lite are: (1) app logs out a user every 15 minutes of inactivity; (2) app requires username and password every session; (3). Local database on mobile device is encrypted; and (4) DOH can blacklist a device for malicious activities.

Can I use more than one ITIS Lite account on my mobile device?

No. If you have installed the app on your mobile device and have already logged in, the app automatically downloads data from the DOH to your mobile device. As

of the moment, it will not be possible for another ITIS Lite user to use your device to notify.

Why does my TB Notification turn from orange to white color in ITIS Lite?

When one notifies a case to DOH, the initial orange color signifies that data entered have been saved on the mobile device. It turns to white if saved data have been successfully submitted and received by DOH, which automatically happens whenever a reliable internet connection is available.

For immediate technical assistance related to mandatory TB notification:

For Assistance on Mandatory TB Notification

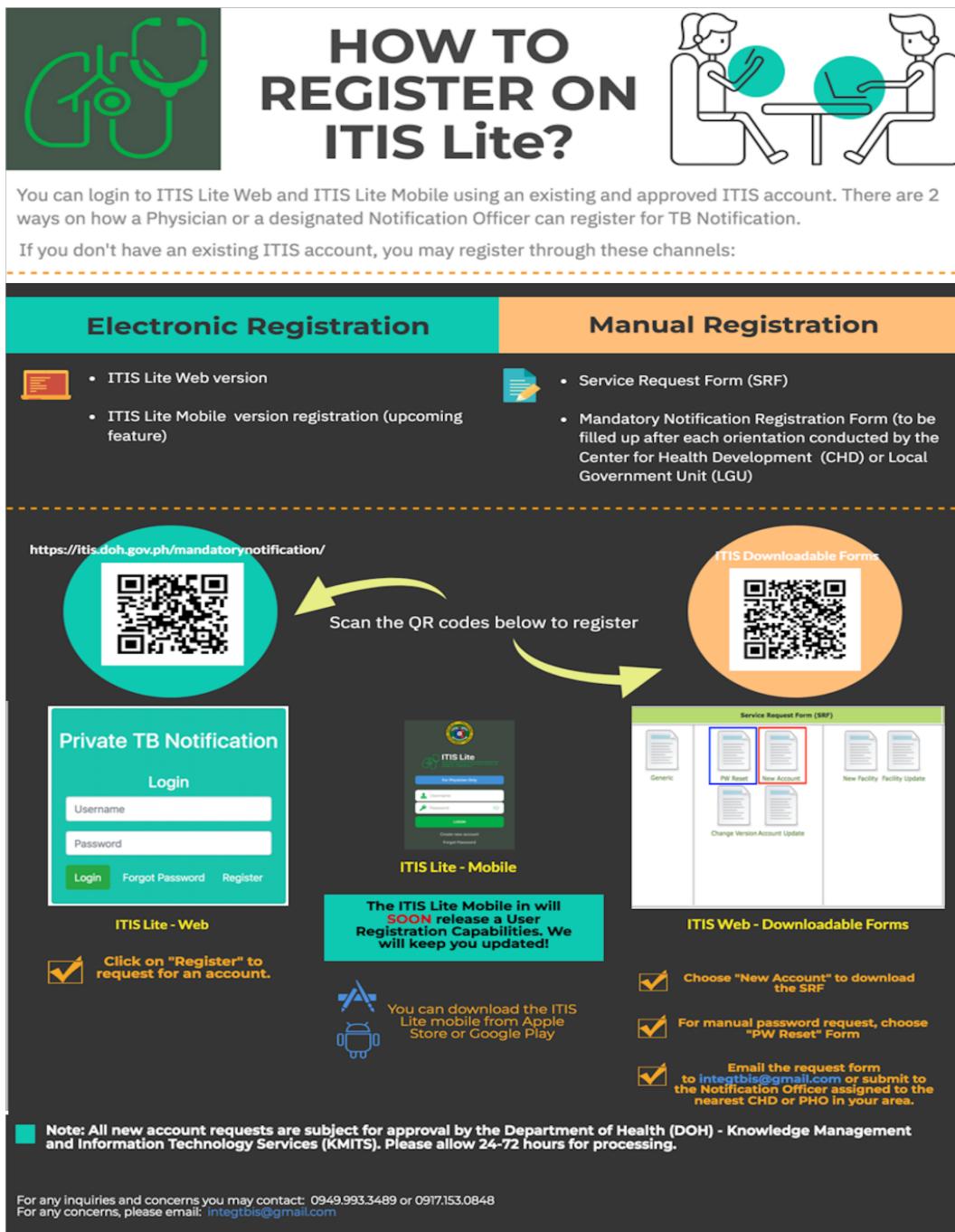
Landline: (02) 8651-7800 local 1941

Mobile: (0949) 993-3489 SMART;
(0917) 815-0469 GLOBE

Email: integtbis@gmail.com

Box 2: Contact Details for Technical Assistance related to Mandatory TB Notification

B: STEP BY STEP PROCESS TO REGISTER AS A PHYSICIAN NOTIFIER



HOW TO REGISTER ON ITIS Lite?

You can login to ITIS Lite Web and ITIS Lite Mobile using an existing and approved ITIS account. There are 2 ways on how a Physician or a designated Notification Officer can register for TB Notification.

If you don't have an existing ITIS account, you may register through these channels:

| Electronic Registration | Manual Registration |
|--|--|
| <ul style="list-style-type: none">ITIS Lite Web versionITIS Lite Mobile version registration (upcoming feature) | <ul style="list-style-type: none">Service Request Form (SRF)Mandatory Notification Registration Form (to be filled up after each orientation conducted by the Center for Health Development (CHD) or Local Government Unit (LGU)) |

<https://itis.doh.gov.ph/mandatorynotification/>

Scan the QR codes below to register

ITIS Lite - Web

ITIS Lite - Mobile

The ITIS Lite Mobile in will **SOON** release a User Registration Capabilities. We will keep you updated!

ITIS Downloadable Forms

ITIS Web - Downloadable Forms

Choose "New Account" to download the SRF

For manual password request, choose "PW Reset" Form

Email the request form to integtbis@gmail.com or submit to the Notification Officer assigned to the nearest CHD or PHO in your area.

Note: All new account requests are subject for approval by the Department of Health (DOH) - Knowledge Management and Information Technology Services (KMTS). Please allow 24-72 hours for processing.

For any inquiries and concerns you may contact: 0949.993.3489 or 0917.153.0848
For any concerns, please email: integtbis@gmail.com

Figure 5. How to Register on ITIS Lite

C: ADMINISTRATIVE ORDER 2020-0057 ON MANDATORY TB NOTIFICATION



Republic of the Philippines
Department of Health

OFFICE OF THE SECRETARY

DEC 01 2020

ADMINISTRATIVE ORDER
No. 2020 - 0057

SUBJECT: Guidelines on Mandatory Tuberculosis (TB) Notification

I. RATIONALE

TB ranked fifth among the top ten leading causes of mortality based on the 2017 Philippine Health Statistics. The 2016 National TB Prevalence Survey revealed that around one million Filipinos have TB and the burden remains unabated in the last ten years. The World Health Organization had estimated that around 599,000 new TB cases develop every year. Yet only 68% were notified to DOH, thus, around 189,000 are still "missing". For the past two decades, NTP had engaged them through the public-private mix DOTS initiative but many are still unengaged, hence, many cases remained unreported to NTP.

Section 8 of the Implementing Rules and Regulations issued by the Department of Health (DOH) on May 5, 2017 for Republic Act No. 10767 entitled Comprehensive Tuberculosis (TB) Elimination Plan Act stipulated that "all public and private health care providers shall report all detected TB cases in accordance with the guidelines issued by the National TB Control Program (NTP)". Making TB a notifiable disease recognizes that it is a major public health problem in the Philippines requiring an improved surveillance system.

In 2017, DOH had launched the 2017-2022 Philippine Strategic TB Elimination Plan: Phase 1 (PhilSTEP1) towards TB elimination that in general aims to reach, treat and protect TB patients. This was further detailed in the Updated PhilSTEP1 2020 – 2023 wherein TB cases reported through mandatory TB notification was included as a major program indicator to monitor TB elimination efforts in the country. Mandatory TB notification will bolster case finding, help ensure high quality TB management in both the public and private sectors, and assess progress towards TB disease elimination goals.

TB as an infectious disease for elimination is a notifiable disease that requires mandatory reporting. Mandatory reporting refers to the obligatory reporting of a condition to local or state authorities as required for notifiable diseases as stipulated in Republic Act 11332 or the Mandatory Reporting of Notifiable Diseases and Health Events of Public Health Concern Act".

The TB notification system being managed by NTP is the Integrated TB Information System (ITIS), an electronic case-based recording and reporting platform. However, it mostly captures TB cases seen and reported by the public health facilities including hospitals and few private health care providers.

Figure 6. First Page of the AO 2020-0057

D: PROCESS OF REFERRAL TO THE TB MEDICAL ADVISORY COMMITTEE (TB-MAC)

Who can be referred to the TB-MAC?

Difficult or challenging cases of TB that cannot be resolved or decided upon at the health facility or individual physician level can be referred to the Regional TB Medical Advisory Committee (R-TBMAC). The patient being referred should be notified in ITIS/ITIS Lite before referral.

Who can refer to the Regional TB-MAC?

Any physician or facility can refer their patients to the R-TBMAC. Referring physician may be requested to either respond to queries by email or present to the committee via online meeting platform. Recommendations will be provided within 24-48 hours or elevated to the national TB MAC with recommendations within 24-48 hours.

How to refer to the Regional TB-MAC?

Referral can be via email, e-TBMAC website or mobile app. An active ITIS or ITIS Lite Account is required when using the web or mobile app. The following information need to be provided:

- TB Treatment Enrolment and Case Management form sent by email or recorded in ITIS/ITIS Lite if using web or mobile app.
- Medical abstract with pertinent diagnostic work-up results

The eTBMAC platform can be accessed through the web (<https://etbmac.doh.gov.ph>) or mobile app (for iOS and android) and log-in using ITIS/ITIS Lite credentials. Referring doctor will choose “Health Care Worker” option to access the landing page that displays the enrollment, case management, and treatment outcome modules. Select the module consistent with reason for referral.

To refer a case, click the “Create new” button and provide all relevant information about the patient being referred. TB case number is not required for the enrolment module where case being referred are pending registration, except for case management and treatment outcome modules. Upload relevant imaging (jpeg, png or pdf file) and provide additional remarks on the appropriate sections. Once all information is provided, click the “Create new enrollment” button if for enrollment or “Create new case” if for case management and treatment outcome. The status of referral can be viewed by clicking the specific module and reviewing the tabs under each module. For more information, check the link https://youtube.com/channel/UCmgUwrmSlo6iZuu_iUU2QCQ/videos.

Please refer to the directory of national and regional TB MAC

| AREA | EMAIL |
|--|-------------------------------|
| National | ntbmacph@gmail.com |
| CAR | ntpleprosy.idccar@gmail.com |
| Ilocos Region | r1tbmac@gmail.com |
| Cagayan Valley | cvtbmac2@gmail.com |
| Central Luzon | ro3tbmac@gmail.com |
| NCR-North - <i>Caloocan, Malabon, Navotas, Valenzuela, Pasig, Taguig, Marikina, Quezon City, Pateros</i> | tbmacnernorth@gmail.com |
| NCR-South - <i>Manila, San Juan, Mandaluyong, Pasay, Las Pinas, Muntinlupa, Paranaque, Makati</i> | tbmacsouthncr@gmail.com |
| CaLaBaRZon | pmdt4a@gmail.com |
| MiMaRoPa | mimaropa.tbmac@gmail.com |
| Bicol | bicoltbmac@gmail.com |
| Western Visayas | tbmacwesternvisayas@gmail.com |
| Central Visayas | tbmacregion7@gmail.com |
| Eastern Visayas | region8tbmac@gmail.com |
| Zamboanga Peninsula | r9tbmac@gmail.com |
| Northern Mindanao | tbmacregionx@gmail.com |
| Davao | rtbmac11@gmail.com |
| SOCCSKSARGEN | rtbmac.xii@gmail.com |
| CARAGA | caragatbmac.13@gmail.com |
| BARMM | BARMMtbmac@yahoo.com |

ANNEXES

**(Each member of the CPG team was required to
complete his/her own
Declarations of Conflicts of Interest)**

ANNEX A
SUMMARY OF AFFILIATIONS, EXPERTISE and CONFLICTS OF INTEREST OF
STEERING COMMITTEE

| NAME | EXPERTISE | Affiliations | COI declared | DISPOSITION |
|---------------------------|---|---|---|--------------------|
| REGINA P. BERBA MD | Infectious Diseases Clinical Epidemiology | PhilCAT PSMID UP PGH The Medical City | Past National Chair PhilCAT | Allowed |
| MARISSA M. ALEJANDRIA, MD | Infectious Diseases Clinical Epidemiology | PSMID UP PGH The Medical City | Board Member of PSMID | Allowed |
| VINCENT M. BALANAG, MD | Pulmonary Medicine Clinical Epidemiology | PhilCAT PCCP Lung Center of the Philippines | Medical Director of Lung Center Philippines | Allowed |
| JUBERT P. BENEDICTO, MD | Pulmonary Medicine | PhilCAT PCCP UP PGH Lung Center of the Philippines | Past National Chair PhilCAT | Allowed |
| LALAINA L. MORTERA, MD | Pulmonary Medicine | PhilCAT PCCP | Past National Chair PhilCAT | Allowed |

ANNEX B
SUMMARY OF AFFILIATIONS, EXPERTISE and CONFLICTS OF INTEREST OF
TECHNICAL WORKING GROUP

| NAME | EXPERTISE | Affiliation | COI Declared | DISPOSITION |
|---------------------------------|--|---|--|----------------|
| EVELYN SALIDO MD | Internal Medicine Rheumatology Clinical Epidemiology | UP NIH | None | Allowed |
| MARIO M. PANALIGAN, MD | Infectious Diseases Clinical Epidemiology | PSMID | None | Allowed |
| ROWENA GENUINO, MD | Dermatology Clinical Epidemiology | UP PGH Makati Medical Center Manila Doctors Hospital | None | Allowed |
| ADELAINE J. LOPEZ, MD | Infectious Diseases | PSMID | None | Allowed |
| MONICA PIA REYES-MONTECILLO, MD | Infectious Diseases | PSMID PCP Westlake MC Unihealth Southwoods Hosp TMC South Luzon Qualimed Hospital Sta Rosa Calamba MC Univ of Perpetual Help MC- Binan | None | Allowed |
| JANICE CAMPOS-CAOILI, MD | Infectious Diseases | PSMID PhilCAT Makati Medical Center | Board Member of PhilCAT and PSMID | Allowed |
| MARC EVANS ABAT, MD | Internal Medicine Geriatrics | PCP | None | Allowed |
| ALDRICH IVAN LOIS BUROG, MD | Clinical Epidemiology | | None | Allowed |

| | | | | |
|--------------------------------|--|---|---------------------------------|----------------|
| GINA ANTONINA EUBANAS, MD | | | None | Allowed |
| BRYAN ALBERT LIM, MD | Infectious Diseases | PSMID | None | Allowed |
| KATHRYN ROA, MD | Infectious Diseases | PSMID | None | Allowed |
| GELZA MAE ZABAT, MD | Infectious Diseases | PSMID PMA PCP St. Luke's MC UERMMC Philippine Heart Center; EAMC Commonwealth Hosp & MC | None | Allowed |
| JEMELYN U. GARCIA, MD | Infectious Diseases | PSMID RITM | None | Allowed |
| IAN THEODORE CABALUNA, MD | | UP NIH | None | Allowed |
| GINA ANTONINA EUBANAS, MD | Dermatologist Clinical Epidemiologist | Philippine Dermatology Society | | Allowed |
| KAREN MARIE R. GREGORIO, MD | Infectious Diseases | PSMID | None | Allowed |
| MARC EVANS ABAT, MD | Internal Medicine Geriatrics Medicine | PCP Phil College of Geriatric Medicine UP PGH The Medical City Manila Doctors Hospital Cardinal Santos MC | None | Allowed |
| STEPHANIE CAROL TAN-LIM, MD | | | None | Allowed |
| MA. TARCELA S. GLER, MD | Infectious Diseases | PSMID Makati Medical Center | PI in study TB Reach | Allowed |

| | | | | |
|---------------------------------|-----------------------|---|--|----------------|
| JUBERT P. BENEDICTO, MD | Pulmonary Medicine | PCCP PhilCAT UP PGH Lung Center Phil | Past PhilCAT National Chair | Allowed |
| MITZIE MARIE M. CHUA | Infectious Diseases | PSMID | None | Allowed |
| DEBORAH IGNACIA DAVID-ONA, MD | Hypertension Medicine | PCP St Lukes Medical Center | None | Allowed |
| MARIETTO L. PARTOSA, JR., MD | Pulmonary Medicine | PCCP | None | Allowed |
| MA. KRIELEDA KARLENE G. TAN, MD | Pulmonary Medicine | PCCP UP PGH | None | Allowed |
| RALPH ELVI M. VILLALOBOS, MD | Pulmonary Medicine | PCCP UP PGH | None | Allowed |
| LIA PALILEO VILLANUEVA, MD | Adult Medicine | PCP UP PGH | None | Allowed |
| EVALYN A. ROXAS, MD | Infectious Diseases | PSMID PHICS UP PGH UP CPH Ospital ng Maynila Manila Med | Past President PHICS College Secretary UP CPH | Allowed |
| KINGBHERLY L. LI, MD | Infectious Diseases | PSMID PCP PHICS Chinese General Hosp and MC | Board member PHICS | Allowed |
| MARISSA J. NEPOMUCENO, MD | Infectious Diseases | PSMID PCP Manila Med- Med | None | Allowed |
| ISSA RUFINA S. TANG, MD | Infectious Diseases | PSMID PCP Phil Orthopedic Center LCP | None | Allowed |

| | | | | |
|--|-----------------------------------|--|-------------|----------------|
| | | Pasig COVID-19 Referral Ctr NKTI De Los Santos Medical Ctr | | |
| HOWELL H. BAYONA MD (technical Writer) | Speech language pathologist | St Lukes Medical Center Global City Philippine Society of Speech Pathology | None | Allowed |

ANNEX C
SUMMARY OF DECLARATION OF CONFLICTS OF INTERESTS OF
CONSENSUS PANEL MEMBERS

| NAME | REPRESENTATIVE | DECLARATION OF CONFLICT OF INTEREST | DISPOSITION BY STEERING COMMITTEE |
|------------------------|--|--|-----------------------------------|
| Elizabeth V. Cadena | Philippine Tuberculosis Society | Investment PI in research | Allowed |
| Rogelio V. Dazo JR | Philippine Medical Association | None to declare | Allowed |
| Allan Fabella | DOH | Adviser to National TB Prevalence Survey | Allowed |
| Ann Marie Garfin | DOH (National TB Program) | National TB Program manager | Allowed |
| Karl Evans Henson | Philippine Society of Microbiology and Infectious Diseases | None to declare | Allowed |
| Arthur Dessi Roman | Philippine Society of Microbiology and Infectious Disease | Board member PSMID Medical Specialist of Research Institute of Tropical Medicine | Allowed |
| Maria Encarnita Limpin | Philippine College of Physicians | Consulting for Pascual Pharma for Acetimax Secretary of the Philippine College of Physicians Executive director on Action on Smoking and Health, Philippines | Allowed |
| Imelda Mateo | Philippine College of Physicians | Regent of Philippine College of Physicians Treasure of Philippine College of Chest Physician Vice-president on Action on Smoking and Health, Philippines | Allowed |

| | | | |
|--------------------------|---|-----------------------------|---------|
| Raquel Evangelista-Lopez | Philippine Association of Family Physicians | None to declare | Allowed |
| Paul Leandrey Ygusguiza | Philippine Association of Family Physicians | None to declare | Allowed |
| Lorraine Anne Obana | TB Heals | None to declare | Allowed |
| Augusto Sablan Jr. | Philippine College of Chest Physicians | None to declare | Allowed |
| Julie Christie Visperas | Philippine College of Chest Physicians | None to declare | Allowed |
| Amelia Sarmiento | Philippine Coalition Against TB (PhilCAT) | Executive Director, PhilCAT | Allowed |
| Aileen David-Wang | CHEST Philippines | None to declare | Allowed |

ANNEX D
SUMMARY OF DECLARATION OF CONFLICTS OF INTERESTS OF
EXTERNAL REVIEWERS

| NAME | AFFILIATION | DECLARATION OF CONFLICT OF INTEREST | DISPOSITION |
|------------------------------------|----------------------------------|--|--------------------|
| CAMILO ROA MD | PhilCAT PCCP | NONE | Allowed |
| MARY ANN LANSANG MD | University of the Philippines | NONE | Allowed |
| RAJENDRA PRASAD HUBRAJ YADAV MD | WHO | NONE | Allowed |
| TAUHIDUL ISLAM MD | WPRO | NONE | Allowed |

