

# Tuberculosis Infection Control Operational Research Protocols

## Study questions:

1. Do IGRA conversions among HCWs have a stronger association with risk factors for recent TB exposure than TST conversions?
2. Does the introduction of a minimum TB-IC package decrease transmission of TB from patients to HCWs?
3. Does reducing delays in the diagnosis and treatment for TB reduce the risk for transmission of TB to HCWs?
4. Does voluntary re-assignment of HIV-infected HCWs, allowing for other factors including ARVs, IPT, infection control measures, significantly reduce TB disease among HIV infected HCWs?

## Surveillance protocol for latent TB infection

**OR Appendix 1** includes recommended procedures, definitions and a standardized questionnaire to collect the appropriate information for on-going surveillance for latent TB infection among HCWs. These protocols can be modified to fit the local context; however, the more standardized the procedures the more comparable the results will be to similar studies. This protocol may be utilized to address study questions 1-4.

## Surveillance protocol for active TB disease

**OR Appendix 2** includes recommended procedures, definitions and a standardized questionnaire to collect appropriate information for on-going surveillance for active TB disease among HCWs. These protocols can be modified to fit the local context; however, the more standardized the procedures the more comparable the results will be to similar studies. This protocol may be utilized to address study questions 2-4.

## Assessing minimum TB-IC requirements and supplementary TB-IC measures in healthcare facilities

**OR Appendix 3** includes a questionnaire to assess whether minimum TB-IC requirements are in place in health facilities. Also includes a section with additional supplementary measures which can be tailored to the health facility's additional measures. Assessment of this minimum package should be done at least on a bi-annual basis to acquire a standardized snapshot of selected important TB-IC measures in healthcare facilities.

## Assessing risk levels for HCWs of physical and functional areas in a health facility

**OR Appendix 4** includes a conceptual framework on how to categorize low versus high risk TB transmission areas and functions within a facility. This categorization can be modified, if needed, to fit the facility-specific risk assessment.

## *Operational Research Study 1: Tuberculin skin testing (TST) versus interferon-gamma release assays (IGRA) for measuring the annual risk of TB infection (ARTI) in HCWs.*

**Context:** Traditionally, the tuberculin skin test (TST) has been used for estimating the ARTI in HCWs<sup>1</sup>. HCWs with TST conversions are considered recently infected and at risk for progressing to TB disease. It is therefore recommended that they be offered isoniazid preventive therapy. However, the TST has limitations in accuracy and reliability<sup>2</sup>.

Interpretation of TST boosting, conversions and reversions is challenging<sup>3</sup>.

Newly available IGRAs are more specific than TST and are not affected by prior BCG vaccinations<sup>4</sup>. Because these assays are ex-vivo, boosting is not a concern with repeated IGRA testing. Although IGRAs may be useful for diagnosing TB infection, there is considerable uncertainty around their use

1 Centers for Disease Control and Prevention. Guidelines for preventing the transmission of Mycobacterium tuberculosis in health-care settings, 2005. MMWR. 2005;54(No.RR-17):1-141.

2 American Thoracic Society (2000) Targeted tuberculin testing and treatment of latent tuberculosis infection. Am J Respir Crit Care Med 161: S221-247

3 Menzies D (1999) Interpretation of repeated tuberculin tests. Boosting, conversion, and reversion. Am J Respir Crit Care Med 159: 15-21.

4 Pai M, Zwerling A, Menzies D (2008) Systematic review: T-cell-based assays for the diagnosis of latent tuberculosis infection: an update. Ann Intern Med 149: 177-184.

in serial testing<sup>5</sup>. IGRA conversions and reversions are documented<sup>6,7,8</sup>, and there is no consensus on how to define conversions with IGRAs. Prognosis of IGRA conversions and reversions are unknown. In medium to high burden settings, it is not clear if IGRAs are better for measuring ARTI than TST.

**Hypothesis:** IGRAs are better capable of identifying new TB infection due to occupational exposure than TST.

**Study design:** Prospective serial testing design. All consenting HCWs will be screened by two-step TST at baseline and one of the commercially available IGRAs. A questionnaire will be used to collect data such as demographics, prior TB disease, HIV status, BCG status, and occupational exposure profile of the HCWs at baseline (e.g. duration of employment, direct contact with TB patients, nature of work). After 12 months, the HCWs will undergo repeat TST and IGRA to document conversions (new infections). A repeat questionnaire will be used to ascertain TB exposure between the baseline and year 1 testing.

**Study setting:** A healthcare facility which manages patients with TB.

**Study outcomes:** TST and IGRA conversion rates will be used to estimate ARTI in HCWs. Analysis will focus on whether the ARTI estimates differ substantially for the two tests, and whether IGRA conversions have a stronger association with recent TB exposure than TST conversions.

### **Study population and methods:**

Study tools: A surveillance system for latent TB infection (OR Appendix 1) should be utilized for data collection.

Inclusion criteria: Ideally, all HCWs will be included. If this is not feasible because of large numbers, then HCWs working in locations that are considered high risk for TB exposure (e.g. internal medicine, infectious diseases, pulmonology, microbiology, radiology, nursing, TB or DOTS clinic) can be preferentially included. HCWs include trainees who are at risk of TB exposure (e.g. nursing students, residents, interns).

Exclusion criteria: Any HCW who had positive prior TST, or a major adverse reaction to the TST, or bacteriologically confirmed history of TB disease.

Estimated number of participants and sampling: All HCWs in the healthcare facility will be invited to participate. However, to precisely estimate ARTI, a sample size of at least 500 HCWs will be ideal. Assuming an ARTI of 5%, if 500 HCWs are serially tested, then the ARTI will be estimated with a 95% CI of 3 - 7%.

Enrollment procedure: If a periodic (annual or more frequent) TST screening program is already ongoing for detection of LTBI, then HCWs can be enrolled via the occupational health and safety/ employee health program. Otherwise, all HCWs will be invited to participate in the study, which will involve (bi-)annual screening using TST and IGRA for detection of LTBI and administration of (bi-) annual, standardized questionnaire (OR Appendix 1) over the study period.

Data analysis: Analyses will involve: a) estimation and comparison of conversion rates with both TST and IGRA; and b) association between TB exposure factors - as collected with the questionnaire - and test results. Logistic regression will be used to study association between TST or IGRA conversion (using various definitions for conversions), and between TST/IGRA and the exposure/risk factors. If IGRA conversion correlates more strongly with the exposure gradient, that should be seen in the magnitude of the odds ratios and the c-statistic (area under the receiver operating curve (ROC) for the model, which is a measure of diagnostic accuracy). A secondary analysis can be done to assess factors associated with discordant conversion results (e.g. TST conversion, but no conversion with IGRA).

Minimum duration: 1 year

Requirements: 1) a trained person who can place and read the TST; 2) a phlebotomist for blood draw;

5 Pai M, O'Brien R (2007) Serial testing for tuberculosis: can we make sense of T cell assay conversions and reversions? PLoS Med 4: e208.

6 Pai M, Joshi R, Dogra S, Mendiratta DK, Narang P, et al. (2006) Serial testing of health care workers for tuberculosis using interferon-gamma assay. Am J Respir Crit Care Med 174: 349-355.

7 van Zyl-Smit RN, Pai M, Peprah K, Meldau R, Kieck J, et al. (2009) Within-subject Variability and Boosting of T Cell IFN-g Responses Following Tuberculin Skin Testing. Am J Respir Crit Care Med 180: 49-58.

8 Pai M, Joshi R, Dogra S, Zwerling AA, Gajalakshmi D, et al. (2009) T-cell assay conversions and reversions among household contacts of tuberculosis patients in rural India. Int J Tuberc Lung Dis 13: 84-92.

3) a laboratory that is capable to performing the IGRA assays.

Clinical follow-up: All HCWs with TST conversions must be offered IPT, after ruling out active TB disease. All HCWs with TB symptoms must be worked up for active TB disease. HIV testing can also be offered to HCWs found to have active TB.

### **Potential limitations and challenges:**

A major challenge will be to include and follow-up of the required number of HCWs, and ensuring that repeat tests are done as per schedule. If a healthcare facility employs only a small number of HCWs, then ARTI estimates are likely to be highly imprecise. To some extent, this may be overcome by doing a multi-center study with more than one healthcare facility included in the same area or region. If a multi-center study is done, then care should be taken to follow the same protocol and testing procedures at all sites (training and standardization will be required, and, ideally, IGRA testing should be done in one central laboratory). Another limitation is the lack of consensus on how to define IGRA conversions - so, one of the study objectives is to explore which conversion definition has the best correlation with markers of TB exposure. Lastly, if HCWs do not agree to get HIV tested, then the impact of HIV on TST and IGRA results will not be determined.

### ***Operational research study 2: Effects of a minimum TB-IC package on TB in HCWs***

**Context:** The risk of getting TB is increased in HCWs in low and middle income countries (LMIC) compared to the general population. In high TB incidence settings, this poses a significant occupational health problem. In many healthcare facilities in LMIC, it is not feasible to implement expensive technology, such as negative pressure isolation rooms. However, also affordable and relatively easy to implement TB-IC measures are expected to reduce TB transmission considerably already. In this light, we define a minimum TB-IC package, which is based on grade of evidence and feasibility of implementation in LMIC:

1. Implementation of outpatient triage for cough,
2. Collection of sputum outdoors or in separate, sufficiently ventilated rooms,
3. Adequate ventilation in other consultation/examination areas, waiting areas and TB wards,
4. Cohorting or isolation of TB patients in separate inpatient TB wards.

**Hypothesis:** the introduction of a minimum TB-IC package compared to the situation where this minimum package is not available will decrease transmission of TB from patients to HCWs.

**Study design:** Prospective, multi-center pre- and post-intervention study (quasi-experimental). The primary study outcomes (TB infection and TB disease in HCWs) will be assessed before and after a minimum TB-IC package is implemented in healthcare facilities. If health facilities already have routine screening of and a registration system in place for TB infection and TB disease in health workers, this registration system can be used to compare the study outcomes in different time period. If such a routine screening and registration system is not in place, these data should be collected before implementation and compared to after implementation. However, usually the duration of time before implementation will be too small in a single HCF to reach sufficient statistical power to be able to show an effect. Therefore, a multi-center study should be implemented. This may also give the possibility to assess effects of differences in additional TB-IC measures besides the minimum package.

**Intervention:** The intervention should be a multi-tiered approach aimed to introduce TB-IC measures in the healthcare facilities. The first step is to install an IC committee which will make a TB-IC plan. Assessment of whether the minimum set of TB-IC measures is in place, should be done utilizing OR Appendix 3.

**Study setting:** Health care facilities which manage TB patients in settings with medium or high burden of TB.

**Study outcomes:** As study outcome parameters the following impact indicators will be used:

- Incidence of TB infection in health workers
- Incidence of TB disease in health workers

## **Study population and methods:**

Study tools: A surveillance system for latent TB infection and active TB disease (OR Appendix 1 & 2) as well as the minimum TB-IC assessment (OR Appendix 3), should be utilized for data collection for this study.

Inclusion criteria: Ideally, all HCWs will be included. If this is not feasible because of large numbers, then HCWs working in locations that are considered high risk for TB exposure (e.g. internal medicine, infectious diseases, pulmonology, microbiology, radiology, nursing, TB or DOTS clinic) can be preferentially included. HCWs includes trainees who are at risk for TB exposure (e.g. nursing students, residents, interns).

Exclusion criteria: Any HCW who had positive prior TST or had a major adverse reaction to the TST.

Estimated number of participants and sampling: All health workers in the healthcare facility will be invited to participate. However, to be able to show a reduction in annual risk of infection (ARTI) from 6% to 3%, 750 health workers need to be included both before and after implementation of the minimum TB-IC package. The TB disease endpoint will need more HCWs than the infection endpoint. If 1% of HCWs get TB disease per year; one will need 5000 HW in both the pre-intervention and post-intervention period to show a reduction to 0.5%.

Enrollment procedure: If a periodic (annual or more frequent) TST screening program is already ongoing for detection of LTBI, then HCWs can be enrolled via the occupational health and safety/ employee health program. Otherwise, all HCWs will be invited to participate in the study, which will involve (bi-)annual screening using TST for detection of LTBI (for those already undergoing TST through occupational health and safety/employee health, enrollment would enable access to records) and administration of (bi-)annual, standardized questionnaires over the study period.

Data analysis: The effect of the minimum TB-IC package on conversion rates and TB disease rate will be analyzed by comparing ARTI's and TB disease rates among HCW before and after implementation of the entire minimum TB-IC package with the chi-square test. Also, conversion and TB disease rates can be compared with survival analysis. Exclude those with TB disease history as well for measurement of TB infection

Minimum duration: two periods of one year, the first period before and the second period after implementation of the minimum TB-IC package. As it is not ethical to delay implementation because a baseline measurement is required, screening should be implemented as a first step. TST conversion rates and TB disease rates among HCW during and after implementation can then be compared.

Requirements: full-implementation of active screening for TB infection and disease among HCWs. A study coordinator should be appointed and have the capacity to collect, enter, analyze and report findings on the TB-IC situation in the facilities over time, and TB infection and TB disease among HCW in a systematic manner.

Clinical follow-up: HCWs with conversion by TST should be considered for preventive therapy.

## **Potential limitations and challenges:**

A major challenge will be to include and follow-up of the required number of HCWs, and ensuring that repeat tests are done as per schedule. If a healthcare facility employs only a small number of HCWs, then ARTI estimates are likely to be highly imprecise. To some extent, this may be overcome by doing a multi-center study with more than one healthcare facility included in the same area or region. If a multi-center study is done, then care should be taken to follow the same protocol and testing procedures at all sites (training and standardization will be required).

## ***Operational research study 3: Impact of reduction of diagnostic and treatment delays among patients with TB/MDR-TB on transmission among HCWs.***

**Context:** A delay in the diagnosis and treatment of patients with active TB prolongs the period of infectiousness and thereby increases the risk of exposure to persons with whom the infected person comes into contact. Diagnostic delays are a result of both patient delay, the time from which the person initially experiences symptoms consistent with TB to the time he or she presents to the healthcare system; and healthcare system delay, the time from which the person initially presents to either an informal or formal healthcare provider to the time the person is diagnosed with active TB disease. Once diagnosed, patients may experience additional delays between the time of diagnosis and the time at which appropriate treatment for TB disease is initiated, often due to availability of medicines or in the case of drug-resistant or MDR-TB, awaiting laboratory results for drug



susceptibility testing. Patients who experience extended delays are at risk for increased morbidity and mortality from TB, and patients with more severe disease may be more likely to transmit disease to others. HCWs in settings with a high prevalence of TB are at an increased risk for acquiring infection through occupational exposure. Patient delay, healthcare system delay, and treatment delay all have the potential to further amplify this risk, since patients who experience such delays are more likely to be un- or inadequately treated and in the late and more infectious stages of disease. In inpatient settings it is possible that a delayed diagnosis of TB in a patient admitted for other reasons may jeopardize the health of HCWs, particularly if infection control measures for respiratory protection are not utilized. Further, if a person with TB presents repeatedly to an outpatient setting without receiving a proper diagnosis, HCWs are at risk of repeated interactions with an infectious case.

**Hypothesis:** Reductions in diagnostic delays for TB patients will translate to less risk for the acquisition of TB infection and TB disease among HCWs.

**Study Design:** Prospective, multi-center, pre- post- intervention study (quasi-experimental). The primary study outcome, incidence of TB infection and TB disease among HCWs, will be assessed before and after an intervention aimed to reduce diagnostic delays for TB patients, after adjusting for level of occupational and non-occupational/community TB exposure, relevant socio-demographic and health characteristics of HCWs, and infection control measures.

**Intervention:** The intervention should be a multi-tiered approach aimed at reducing the diagnostic delays of TB patients serviced by the healthcare facilities and treatment delays within the healthcare facilities. The intervention would likely include community outreach and education to increase awareness in community members; education and collaboration with private practitioners, traditional healers, and other non-public settings where patients may initially seek healthcare; educating and utilizing tools to improve timely, accurate diagnosis of TB in public health settings; improving access to accurate, timely TB and DR-TB diagnostics (i.e. by improving turn-around times); strengthening communications between laboratories and clinicians; and providing clinicians with clear guidance for the management of TB patients.

**Study Setting:** Health care facilities which manage patients with TB, in a setting with a medium or a high burden of TB.

**Study Outcomes:** As study outcome parameters the following impact indicators will be used:

- Incidence of LTBI in health workers
- Incidence of TB disease in health workers

### **Study Population and methods:**

Study tools: A surveillance system for latent TB infection and active TB disease (OR Appendix 1 and 2) as well as the minimum TB-IC assessment (OR Appendix 3), should be utilized for data collection for this study. The following additional information to questionnaires in OR Appendix 1-2 should be collected based on medical records of TB patients at the healthcare facilities:

- TB symptoms.
- DST results.
- Onset (date) of symptoms consistent w/ TB disease.
- Date(s) and details about previous healthcare encounters (both formal and informal – incl. traditional healers, private physicians) for current episode of symptoms.
- Number of outpatient visits to facility during period with TB symptoms.
- Dates of admission to and discharge from facility.
- Date of start of treatment.
- Dates of smear examination and results (quantitative) (to assess infectiousness and estimate time of smear conversion) If the facilities do not typically ask patients about onset of symptoms and seeking care prior to the visit when TB is diagnosed, then this study may involve having to implement procedures at the facility to routinely ask patients about this.

To attempt to control for potential changes in community exposure, surveillance data on smear-positive TB cases from the study catchment area should be analyzed in the models e.g. quarterly, bi-annual or annual incidence rates.

**Inclusion criteria:** Ideally, all HCWs will be included. If this is not feasible because of large numbers, then HCWs working in locations that are considered high risk for TB exposure (e.g. internal medicine, infectious diseases, pulmonology, microbiology, radiology, nursing, pediatrics, TB or DOTS clinic) can be preferentially included. HCWs includes trainees who are at risk for TB exposure (e.g. nursing students, residents, interns).

**Exclusion criteria:** HCWs that have a previously positive TST indicating LTBI or previous TB disease.

**Estimated number of participants and sampling:** All health workers in the healthcare facility will be invited to participate. However, to be able to show a difference in annual risk of infection (ARTI) from 6% to 3%, 750 health workers need to be included both before and after implementation of the intervention measures to reduce diagnostic delays. The TB disease endpoint will need more HCW than the infection endpoint. If 1% of HCW get TB disease per year; one will need 5000 HW in both the pre-intervention and post-intervention period to show a reduction to 0.5%.

**Enrollment procedure:** If a periodic (bi-annual or more frequent) TST screening program is already ongoing for detection of LTBI, then HCWs can be enrolled via the occupational health and safety/employee health program. Otherwise, all HCWs will be invited to participate in the study, which will involve (bi-)annual screening using TST for detection of LTBI (for those already undergoing TST through occupational health and safety/employee health, enrollment would enable access to records) and administration of (bi-)annual, standardized questionnaires over the study period.

**Data analysis:** The impact of the intervention aimed to reduce diagnostic delays will be assessed by comparing rates of TB infection and TB disease among HCWs before and after the intervention, after controlling for HCW and patient characteristics, occupational and non-occupational exposures, and infection control measures.

For all - calculate time from diagnosis to initiation of TB treatment

For DR-TB: time from diagnosis/sputum collection to initiation of appropriate therapy (based on DST results, if available).

**Minimum duration:** Two periods of one year, the first period before and the second period after implementation of the intervention aimed at reducing diagnostic delays.

**Requirements:** full-implementation of active screening for TB infection and disease among HCWs, and measurement of diagnostic delays before and after the intervention. A study coordinator should be appointed and have the capacity to collect, enter, analyze and report findings on the TB-IC situation in the facilities over time, and TB infection and TB disease among HCW in a systematic manner.

**Potential limitations and challenges:** A major challenge will be to minimize losses to follow-up among HCWs enrolled, particularly if there is a high rate of staff turnover over the period of study. It will be necessary to ensure that standardized procedures and forms are used to collect data from all sites. One of the other key challenges is that the intervention may not effectively reduce diagnostic delays, and therefore would compromise the primary objective of the study. Previous studies demonstrating effective interventions for reducing diagnostic delays for TB patients is limited, and the reasons for diagnostic delays are both multi-factorial and differ according to the public health infrastructure, and the political, geographic, and cultural context. Before the current study is implemented, it is critical that any intervention implemented to reduce diagnostic delays be piloted to establish effectiveness. To control for potential changes in community transmission, local surveillance data on smear-positive cases may be placed in the model; however, if the quality of the data is unreliable e.g., data analysis of this factor will be less meaningful. Finally, because the study time will take place over 2-3 years, there is the potential that other interventions or temporal changes may be implemented that may impact rates of TB infection and TB disease in HCWs (e.g. enhanced infection control measures, changes in policies/guidelines, new diagnostics, media, etc). It will be critical to try to capture all potentially relevant factors throughout the study. Analytic techniques can be used to account for these factors to some extent, but it is likely that any major temporal changes will have effects that are unmeasured and unknown.

***Operational research study protocol 4: Effect of opting out of high TB risk work environments on TB disease incidence among HIV-infected HCWs.***

**Context:** Persons living with HIV/AIDS who are also dually infected with Mtb have exponential rates of TB incidence compared to HIV-uninfected and latently infected persons. Rapid progression of nosocomial hospital epidemics with high case fatality rates have been observed among HIV-infected persons. Isoniazid preventive therapy is now recommended for HIV-infected persons by WHO and has been shown to reduce the risk of progression to active TB disease among HIV-infected

persons; however, the uptake in middle-high TB burden and low-middle income countries has been sub-optimal to date. The provision of anti-retrovirals to HIV-infected persons and concomitant immunoreconstitution has also shown an effect of reducing TB disease but not to the level of HIV un-infected persons. Infection control measures have also been able to reduce TB transmission in healthcare facilities. One potential administrative measure for further reducing risk of infection or re-infection among HIV-infected HCWs is by reducing their exposure via voluntary re-assignment of tasks and/or ward. This potential intervention has not been evaluated in a systematic way for its effectiveness in reducing TB incidence among HIV-infected HCWs. While ideally HIV+ workers would be safer to be limited to work in low risk areas, the reality in many high burden TB and HIV settings is that this is not feasible due to high proportion HIV+ HCWs in combination with a general HCW shortage, individual human rights of HIV+ workers to make informed decisions of the occupational risks they are willing to take in balance with employers' obligations to make the best efforts to protect them, potential perceived or real threat by HIV+ HCWs for unjust professional demotion or dismissal in some highly stigmatized settings, and HIV stigma that averts HIV testing and HIV disclosure in a work setting. This study attempts to evaluate how to best minimize risk of TB disease among HIV+ HCWs controlling for practical realities in many healthcare facilities.

**Hypothesis:** The introduction of voluntary re-assignment to lower risk work settings for HIV-infected HCWs compared to the situation where voluntary re-assignment is not offered or not taken up will significantly decrease TB incidence among HIV-infected HCWs

**Study design:** Prospective, multi-center cohort study. Evaluation of TB disease incidence rates among HIV-infected HCWs who voluntarily re-assign to lower risk areas. Over a 3 year study period, multiple centers should actively screen all HCWs in their facilities for latent TB infection and active TB disease on a bi-annual basis and collect information on HIV, TB exposure, IPT, ART use and immunosuppression. Staff working in high risk TB areas who are HIV-infected should be offered voluntary re-assignment to other lower TB risk working areas. Incidence of TB disease among cohorts of HIV-infected HCWs (with and without voluntary re-assignment) will be compared to cohorts of HIV negative workers, controlling for potential TB exposure in the facilities and in the community as well as infection control measures within the facilities.

**Study setting:** Health care facilities which manage patients with TB, in a setting with a medium or a high burden of TB and a medium or high burden of HIV

Study outcomes: As study outcome parameter the following impact indicator will be used:

- TB disease among any person working in a healthcare facility

### **Study population and methods:**

Study tools: A surveillance system for latent TB infection and active TB disease (OR Appendix 1 & 2) as well as the minimum TB-IC assessment (OR Appendix 3), should be utilized for data collection for this study. In addition, for this particular study the following will be required for routine collection:

- Information on relocation of HCW from areas from higher to lower exposure to infectious TB. This list is not exhaustive of all physical and functional areas (such as housekeeping or physio-therapy) and procedures in a health facility, but the main risk areas and procedures of most health facilities are likely included here. These classifications may be changed based on a study site specific risk assessment (see OR Appendix 4 on physical and functional area risk assessment) specific to HCW risk (excluding potential risk to patients and visitors). For the purposes of an analytic framework for potential risk to HCWs:
  - Very high risk location and procedures could include, for example,: MDR-XDR-TB wards, TB culture, DST and molecular testing facilities, sputum induction areas, indoor sputum collection areas;
  - Higher risk locations and procedures could include, for example, TB wards (inpatient and outpatient), intensive care and internal medicine inpatient wards, respiratory therapy departments, intubation areas, bronchoscopy service areas;
  - High-medium risk includes, for example, x-ray service departments, outpatient department (waiting room and consultation room), emergency/urgent care departments, ARV clinics;
  - Medium-low risk may include pediatric wards (physically separated from adult

- patients), maternity wards (with average stay that is short e.g., 1-2 days), maternity and pediatric outpatient services, surgery departments (unless known TB patients or suspects have chest surgery), administrative areas with limited patients;
- Lower risk includes, for example, administrative areas where no patients are located and AFB sputum microscopy centers (where sputum collection is not conducted inside the laboratory, sputum is not centrifuged, and no culture, DST nor molecular testing are conducted for TB).
- Local quarterly surveillance data on new smear-positive cases detected in the study catchment area for inclusion in the statistical model to control for potential fluctuations in community transmission.

**Inclusion criteria:** HCW working in HCF

HCW is defined as any worker regardless of profession within a healthcare facility

**Exclusion criteria:** HCW unwilling to participate in screening for TB infection and disease

Estimated number of participants and sampling: To compare the risk of TB disease among HIV+ HCW during and outside assignment in high TB risk areas, assuming 1. that 33% of HIV+ HCW work in high risk areas (i.e. ratio low:high=0.5:1), 2. an annual risk of TB disease to be 2.5% in those working in high risk areas (i.e. median time to TB disease=52 months), 3. an accrual time during which individuals are recruited of 12 months, 4. follow-up time of 2 years after recruitment, and 5. a hazard ratio of 1.5, one would need to include at least 525 HIV+ HCW to be able to determine a difference in TB disease risk at 95% confidence level and with 80% power.

**Enrollment procedure:** If a periodic screening is ongoing and routine, participants can be enrolled into the study via the occupational health and safety program or employee health clinic. If such a periodic screening does not exist, it will be necessary to set this up for the purposes of the study. The occupational health and safety program or other identified staff health program should also offer voluntary re-assignment to HIV-infected workers who are working in high risk TB areas.

**Consent:** Written informed consent will be required from all HCWs.

**Data analysis:**

This study should be analyzed with survival analysis. HCWs will be followed over time based on their IPT, HIV, ART, CD4 status, occupation within the facility, re-assignment status, and other factors. They will be censored either if they develop TB, they discontinue working at the facility for reasons other than TB disease, they die, or they reach the end of the study period without developing active TB disease. HIV unknown HCWs should be analyzed separately. If a HCW converts HIV status, they should be switched to the HIV positive follow-up group within the context of statistical analysis. In a high HIV and TB prevalent setting, the minimum number of participants in the study to achieve adequate statistical power is estimated to be 525 HIV+ staff enrolled. However, because the prevalence of HIV infection and TB disease is highly variable between countries, a power sample size calculation should be done specific for each study.

**Minimum duration:** 2-3 years

**Requirements:** Full-implementation of active screening for latent TB infection and TB disease among HCWs, preferably including HIV screening and monitoring among HIV-positive HCWs. A work reassignment program should be in place, which provides an opportunity for HIV+ HCW for relocation from positions where exposure to untreated TB is high to a lower risk position. A study coordinator should be appointed and have the capacity to collect, enter, analyze and report findings in a systematic manner.

**Clinical follow-up:** Clinical decisions for treatment of TB (both preventive and active disease) will be based on national protocols or clinic specific protocols.

## **Potential limitations and challenges:**

Due to stigma, many HCWs may not uptake voluntary HIV testing and counseling within their health facility workplace. If such results are largely missing, this will limit the power of the study. However, missing value imputations i.e. special analyses for predicting HIV status when missing and sensitivity analyses may be utilized when evaluating the potential missing data for HIV status. Unknown HIV status should be analyzed separately. Some HCWs may opt-out of working in high risk settings while



others may choose to remain. The acceptability of opting out among HIV+ HCWs and the feasibility of opting out in countries with high HIV prevalence and a shortage of HCWs is not assessed in this proposal; however, this may be a useful expanded study in parallel with the measurement from this proposal of the effectiveness of opting out. Undiagnosed infectious TB cases may be in any setting in a healthcare facility making the concept of high risk vs. medium-low risk blurry. However, the literature suggest that some areas of healthcare facilities have higher rates of transmission and the definition of high risk vs. medium-low risk areas is therefore a logical surrogate for potentially prolonged exposure than exceptional periodic exposure. Local analyses specific to the study catchment area may also be utilized to further define high vs. medium-low risk areas including a TB risk assessment. Further, the statistical model may include a variable regarding which departments the HCW was located. This study will be limited by the availability and completeness of the study data set. Further, some bias may be introduced by utilizing multiple healthcare facilities for comparison, particularly if the burden of TB is higher in some health care facilities and the extent of implementation of a minimum infection control package is different in distinct facilities. The proposed statistical analysis, however, can also control for this factor to an extent.

## **OR Appendix 1: Protocol and Questionnaire for surveillance of latent TB infection – (Modify for specific study setting as needed).**

**The questionnaire can be utilized for operational research protocols 1-4. For each protocol utilizing this questionnaire, the following standard procedures and definitions are recommended:**

### **Procedures**

**Enrollment procedure:** If a periodic TST screening program is already ongoing, then HCWs can be enrolled via the occupational health and safety (or employee health clinic) program. If not, then special arrangements will have to be made to recruit HCWs. Clinical decisions about IPT will be made on the basis of serial TST results (because it is considered standard of care).

**Consent:** Written informed consent will be required from all HCWs before screening for TB infection.

**Database:** If not available, a database should be set up to record results of (bi-)annual screening of health workers for TST conversion and the questionnaire information.

**TST:** Participants will undergo TST using the Mantoux method. 2 TU of PPD RT23 (tuberculin bioequivalent to 5 TU of PPD-S) will be injected in the volar aspect of the forearm. 48 to 72 hours later, the transverse diameter of the induration will be demarcated using the ballpoint pen method and measured in millimeters by trained readers. Participants whose initial TST is positive (10 mm+) will be referred for medical evaluation. Participants whose initial TST is negative (0-9 mm), will undergo a second TST, 1 - 2 weeks later on the opposite forearm, using the same testing protocol to elicit the booster phenomenon [two-step TST protocol].

For Operational Research Protocol 1 Only:

IGRA: Two commercial IGRAs are available: QuantiFERON-TB Gold In Tube (Cellestis, Carnegie, Australia) and T-SPOT.TB (Oxford Immunotec, Abingdon, UK). Whichever assay is selected, it should be performed according to the manufacturer's recommendations.

### **Definitions**

**TST conversions:** baseline TST <10 mm and follow-up TST of >10 mm, with an increase of 10 mm over the baseline induration size (ATS/CDC/IDSA definition)<sup>9</sup>.

For Operational Research Protocol 1 Only:

**IGRA conversions:** a baseline negative IGRA result which becomes positive at repeat testing;

9 American Thoracic Society (2000) Targeted tuberculin testing and treatment of latent tuberculosis infection. Am J Respir Crit Care Med 161: S221-247

however, this definition has been shown to result in a high conversion rate. More stringent definitions have been proposed 6-8 and will be explored in the study.

### Questionnaire administration

Each participants will have a questionnaire completed by a HCW or a data manager on demographics (age, sex, race, education, etc.), medical history (e.g. diabetes, HIV, immunosuppressive conditions), treatment for previous LTBI/disease, non occupational (e.g. household contact) and occupational TB exposure (e.g. work location, job title, year of training, duration of employment, contact with TB patients). HIV testing is at the discretion of participants and their healthcare providers (VCT and confidentiality must be ensured and HIV+ patients will need to be referred for evaluation). During repeat testing, participants will complete short questionnaires on exposures since the previous survey. The medical information on TST results should be filled in by the healthcare provider or data manager.

### Potential additional resources

**Administrative records** from facility on all HCWs, their hire dates, if and when they left the organization or died, transferred to another department, changed positions.

----- To be filled once -----

Health Facility: \_\_\_\_\_ Date: \_\_\_\_\_ / \_\_\_\_ /20\_\_\_\_

#### Staff Member Details

Name: \_\_\_\_\_ Written informed consent: ☐ Yes ☐ No  
Date of birth: \_\_\_\_ / \_\_\_\_ /19\_\_\_\_ Personal unique number (e.g. staff number): \_\_\_\_\_  
Gender: ☐ Male ☐ Female  
Job title: ☐ Medical Doctor ☐ Nurse ☐ Other, namely: \_\_\_\_\_  
Total number of years of formal education: \_\_\_\_\_  
Of which total number of years of formal medical training: \_\_\_\_\_  
Employed in this facility since: \_\_\_\_ / \_\_\_\_ /19\_\_\_\_  
Total number of years working in any healthcare facility, including employment at this facility: \_\_\_\_\_  
Type of employment: ☐ administrative ☐ custodial ☐ laboratory ☐ patient-care  
Current work location(s): \_\_\_\_\_  
(if more than one, which is the main location: \_\_\_\_\_)

----- to be filled every follow-up appointment and compiled with previously filled forms -----

Date: \_\_\_\_\_  
Personal Unique Number: \_\_\_\_\_  
Name: \_\_\_\_\_  
Change in work location within facility: ☐ Yes ☐ No If yes, current location(s): ..  
\_\_\_\_\_  
Date of employment termination at this health facility (if applicable): \_\_\_\_ / \_\_\_\_ /20\_\_\_\_

#### Medical History

Diabetes: ☐ Yes ☐ No  
Other immunosuppressive condition: ☐ Yes ☐ No -> which condition: \_\_\_\_\_  
\_\_\_\_\_

History of TB prophylaxis: ☐ Yes ☐ No -> in which year:

History of bacteriologically confirmed TB disease: ☐ Yes ☐ No -> in which year:

Direct contact with TB patients inside work- ☐ Yes ☐ No -> ☐ daily:  
place:  
in last 6 months -> ☐ weekly  
-> ☐ monthly  
-> ☐ less than monthly

Direct contact with TB patients outside workplace: ☐ Yes ☐ No -> ☐ in own household  
in last 6 months -> ☐ outside household

Use of N95 / FFP2 respirators: ☐ No  
☐ Yes, during specific duties only  
☐ Yes, always

--- also fill out other side ---

Date of latest HIV test: / /20

Latest HIV test result:

If never tested or negative: offer voluntary counselling and testing

Date of HIV test: / /

HIV test result: ☐ Negative ☐ Positive

If positive:

Date of latest CD4-count: / /20

CD4 count result: / /20

Current ART use: ☐ Yes ☐ No

BCG vaccination status ☐ Yes ☐ No ☐ Unknown

If yes, visible scar observed: ☐ Yes ☐ No

Date of TST testing: / /20

Date of TST reading: / /20

TST test result (in mm):

If initial TST and negative result (0-9 mm), 2nd TST 1-2 weeks later in the opposite forearm:

Date of 2nd TST testing: / /20

Date of 2nd TST reading: / /20

TST test result (in mm):

For Operational Research Protocol 1 Only(See page 130):

Date of blood drawing for IGRA: / /20

IGRA test results quantitative: .....

IGRA test result qualitative: ☐ Positive ☐ Negative

## **OR Appendix 2: Protocol and Questionnaire for Surveillance of Active TB disease** (modify for specific study setting as needed).

**The questionnaire below can be utilized for operational research protocols 2-4. For each protocol utilizing this questionnaire, the following standard procedures and definitions are recommended:**

### **Procedures**

**Enrollment procedure:** If a periodic TB disease screening program is already ongoing, then HCWs can be enrolled via the occupational health and safety (or employee health clinic) program. If not, then special arrangements will have to be made to recruit HCWs. Clinical decisions about treatment of active TB disease should be made in consideration of national TB guidelines. All positive TSTs, dependent on the study specific study protocol, will be referred for a full screening for active TB disease (including symptom screening, sputum collection and testing).

**Consent:** Written informed consent will be required from all HCWs before screening for TB disease.

**Database:** If not available, a database should be set up to record results of (bi-)annual screening of health workers for TB disease and the questionnaire information.

### **Definitions**

**TB disease:** should be defined utilizing standard WHO definitions.

### **Questionnaire administration**

Each participant will have a questionnaire completed by an appointed healthcare provider or data manager on demographics (age, sex, race, education, etc.), medical history (e.g. diabetes, HIV, immunosuppressive conditions), treatment for previous LTBI/disease, non occupational (e.g. household contact) and occupational TB exposure (e.g. work location, job title, year of training, duration of employment, contact with TB patients). HIV testing is at the discretion of participants and their healthcare providers (VCT and confidentiality must be ensured and HIV+ patients will need to be referred for evaluation).

### **Potential additional resources**

**Administrative records** can be utilized from facility on all HCWs, their hire dates, if they left the organization or died, transferred to another department, changed positions.

**National TB register** (individualized) can be utilized to match against for employees during the study period who may not have revealed their TB disease status to the health facility.

**Quarterly surveillance data on new smear positive TB cases for study catchment area:** this could be utilized to measure potential fluctuations in TB transmission rates in communities during the study period which can be controlled for.

----- *To be filled once* -----



## Staff Member Details

Name: ..... Written informed consent: ☐ Yes ☐ No  
 Date of birth:     /     /19     Personal unique number (e.g. staff number):  
 Gender:                                Male     Female  
 Job title:                                ☐ Medical Doctor     ☐ Nurse     ☐ Other, namely:  
 Total number of years of formal education:  
 Of which total number of years of formal medical training:  
 Employed in this facility since:     /     /19  
 Total number of years working in any healthcare facility, including employment at this facility:  
 Type of employment: ☐ administrative     ☐ custodial     ☐ laboratory     ☐ patient-care  
 Current work location(s): .....  
 (if more than one, which is the main location: .....)

----- to be filled every follow-up appointment and compiled with previously filled forms -----

<b>Date:</b>			
<b>Personal Unique Number:</b>			
<b>Name:</b>			
Change in work location within facility:	<input type="checkbox"/> Yes	<input type="checkbox"/> No	If yes, current location(s):..... .....
Date of employment termination at this health facility (if applicable):     /     /20			
<b>Medical History</b>			
Diabetes:	<input type="checkbox"/> Yes <input type="checkbox"/> No		
Other immunosuppressive condition:	<input type="checkbox"/> Yes <input type="checkbox"/> No	-> which condition: ..... .....	
History of TB prophylaxis: <input type="checkbox"/> Yes <input type="checkbox"/> No	-> in which year:		
History of bacteriologically confirmed TB disease: <input type="checkbox"/> Yes <input type="checkbox"/> No	-> in which year:		
Direct contact with TB patients inside work-place:	<input type="checkbox"/> Yes <input type="checkbox"/> No	-> <input type="checkbox"/> daily:	
		-> <input type="checkbox"/> weekly:	
		-> <input type="checkbox"/> monthly:	
		-> <input type="checkbox"/> less than monthly:	

Direct contact with TB patients outside workplace:	-> <input type="checkbox"/> in own household:
in last 6 months	-> <input type="checkbox"/> outside household
Use of N95 / FFP2 respirators:	<input type="checkbox"/> No
	<input type="checkbox"/> Yes, during specific duties only
	<input type="checkbox"/> Yes, always

--- also fill out other side ---

Date of latest HIV test:
--------------------------

Latest HIV test result:				
		If never tested or negative: offer voluntary counselling and testing		
		Date of HIV test:     /     /		
		HIV test result:	<input type="checkbox"/> Negative	<input type="checkbox"/> Positive
		If positive:		
		Date of latest CD4-count:     /     /20		
		CD4 count result:     /     /20		
		Current ART use:	<input type="checkbox"/> Yes	<input type="checkbox"/> No
Date of TB disease evaluation:		/     /20		
Sputum smear positive:	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Unknown	
Date of sputum collection:		/     /20		
Culture positive:	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Unknown	<input type="checkbox"/> Not Done
Date of specimen collection for culture:		/     /20		
Source of culture specimen:		<input type="checkbox"/> Sputum	<input type="checkbox"/> Blood	<input type="checkbox"/> Other: specify
Date of chest radiograph:		/     /20		
Result:	<input type="checkbox"/> Normal	<input type="checkbox"/> Cavitary	<input type="checkbox"/> Infiltrate	<input type="checkbox"/> Other <input type="checkbox"/> Not done
Does the employee have active TB disease:		<input type="checkbox"/> No	<input type="checkbox"/> No	If Yes, answer questions below
Site of active TB disease (choose 1):		<input type="checkbox"/> PULMONARY only		
		<input type="checkbox"/> Extra-pulmonary only		
		<input type="checkbox"/> Both pulmonary and extra-pulmonary		
Does the employee have bacteriologically confirmed MDR-TB?:		<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Unknown

### OR Appendix 3: TB infection control assessment on minimum requirements and supplementary measures.

Health Facility:	Date: / /20
Date of most recent Previous Assessment:	Date: / /20
Minimum requirements for the purpose of the study	
1. Infection control committee with a health facility TB-IC plan?	<input type="checkbox"/> Yes <input type="checkbox"/> No
2. Implementation of outpatient triage for cough?	<input type="checkbox"/> Yes <input type="checkbox"/> No
3. Collection of sputum outdoors or in separate, sufficiently ventilated rooms?	<input type="checkbox"/> Yes <input type="checkbox"/> No
4. Adequate ventilation in other consultation/examination areas, waiting areas and TB wards?	<input type="checkbox"/> Yes <input type="checkbox"/> No
5. Are smear-positive TB patients physically separated from non-infectious patients?	<input type="checkbox"/> Yes <input type="checkbox"/> No
Some countries may already have additional measures in place and may want to measure their effect as well. The following questions are examples of additional questions that can be tailored to a country's specific circumstances.	
Supplementary beyond the minimum infection control package as potentially defined by a specific study protocol in a specific setting	
6. Is there a designated focal point for TB-IC at the health facility?	<input type="checkbox"/> Yes <input type="checkbox"/> No
7. Is there evidence of TB-IC information, education and communication at the facility for cough etiquette i.e. posters and videos?	<input type="checkbox"/> Yes <input type="checkbox"/> No
8. Are patients routinely directed to utilize outdoor waiting areas and spaces?	<input type="checkbox"/> Yes <input type="checkbox"/> No

### OR Appendix 4: Assessment Tool: Assessing risk levels for HCWs by physical and functional areas in a healthcare facility

This risk assessment classification should be used as a conceptual guideline for each facility TB-IC focal point, team and/or study coordinator to distinguish between low and very high risk settings and procedures. This list is not exhaustive of all physical functional areas (such as housekeeping or physiotherapy) and procedures in a health facility, but the main risk areas and procedures of most health facilities are likely included here. If a particular facility TB-IC focal point or team has evidence that this general framework of risk classification does not fit their functional area or procedure, they should consult with the study coordinator to address this in the study design. This tool, for the purposes of the study, disregards potential risk to vulnerable patients and visitors e.g. infants, young children and immune-compromised persons.

#### ***Physical functional areas and procedures***

Assuming limited existing TB-IC controls are in place, risk of active transmission of TB infection and disease in a particular setting within a health facility is defined by the following factors: the likelihood of TB suspects or TB patients producing infectious TB droplet nuclei e.g., smear-positivity, in this particular setting or with this particular procedure, the potential duration of exposure, the potential number of TB suspects and TB cases in this area, and the potential for multi-drug resistant TB (MDR-TB) or extensively drug resistant TB (XDR-TB) exposure. TB exposure can happen anywhere in a health facility or in a community; however, some settings have higher risks because of the aforementioned factors. Administrative controls will be effective to reduce TB transmission in the whole facility. Due to limited human and financial resources, it is more efficient and cost-effective to strategically target areas of higher risk in a health facility with environmental controls and respiratory protection. Based on these assumptions and factors, the risk for infectious TB exposure within a facility has been classified as low, medium, high and very high risk as follows:

- **Low risk area or procedure:**  
An area or procedure within the health facility which has a limited likelihood of exposing staff to TB suspects or patients or to TB droplet nuclei from infectious TB patients or TB specimens. The primary risk in this area is a rare exposure to a staff, patient or visitor with TB.
- **Medium Risk Area or Procedure:**  
An area or procedure in the health facility which has a moderate likelihood of exposing staff, patients and visitors to TB suspects or patients or to TB droplet nuclei from infectious TB patients or TB specimens. TB cases or medium risk procedures may be present in these settings but for short durations or with few such incidents likely.
- **High Risk Area or Procedure:**  
An area or procedure within the health facility which has a high likelihood of exposing staff to TB suspects or patients or to TB droplet nuclei from infectious TB patients or TB specimens. High risk areas settings and procedures are where many infectious TB suspects (undetected) or many known infectious TB patients may be present or subject to high risk procedures. These settings may also have high concentrated numbers of MDR-TB suspects or patients.
- **Very High Risk Area or Procedure:**  
An area or procedure within the health facility which has a very high likelihood of exposing staff TB suspects or patients or to TB droplet nuclei from infectious TB patients or TB specimens. Very high risk areas and procedures are where many infectious TB suspects (undetected) or many known infectious TB patients may be present or subject to high risk procedures. These settings may also have high concentrated numbers of XDR-TB suspects or patients.

Location at Health Facilities	Low Risk	Medium Risk	High Risk	Very High Risk
<b>Administrative Areas (with no patient or suspect contact e.g., separate building than patients)</b>				
<b>Administrative areas (with limited patient or suspect contact or air exchange from patients)</b>				
<b>Maternity and Pediatric Wards</b>				
<b>ARV Outpatient Clinic</b>				
<b>Outpatients Department (waiting room and consultation room)</b>				
<b>Emergency Rooms</b>				
<b>Intensive Care and Internal Medicine Wards (inpatients)</b>				
<b>TB Outpatient (DOT) Clinics</b>				
<b>TB Inpatient Wards</b>				
<b>MDR-TB Wards</b>				
<b>XDR-TB Wards</b>				



**Administrative Areas:**

The risk of TB infection in these areas is generally considered low. However, the risk for this area is generally considered medium risk if TB patients and suspects infrequently visit these administrative areas. If the administrative area were in the same air space as infectious TB patients e.g. on a TB ward, then the risk would be considered high; however, this situation is generally unlikely for most health facilities. Further, it is important to note that the administrative employees who frequently visit high risk areas in the facility, without proper TB-IC measures, are at higher risk of TB infection or disease but this is not attributable to the administrative area but to the high risk areas that they visit. Further, if a staff sitting in these administrative areas develops infectious TB and exposes other staff in this area then the risk of TB in this area, due to that exposure, would be higher than normal.

**Maternity and Pediatric Wards:**

The risk of TB infection in these areas is generally considered medium to HCWs. The maternity wards generally include very short stays and pediatric patients (unless they are over 14 years old) are unlikely to have infectious TB. However, pregnant women may develop active and potentially infectious TB as a result of immunosuppression from pregnancy, if they are already infected with TB. Further, visitors with infectious TB in the maternity and pediatric wards could potentially infect others.

**ARV Clinics (outpatient):**

Outpatient ARV clinics are generally considered medium risk to HCWs. The duration of exposure is generally short in these outpatient settings. However, while many people co-infected with HIV and TB develop non-infectious TB disease, some will develop infectious TB disease and potentially expose others. Possibly poor ventilation and lack of cough etiquette practices, if there is an infectious TB patient there who has not been screened, pose higher risk for others exposed in these settings including staff. Visitors accompanying the persons seeking ARVs may have infectious TB (undetected or detected) and expose staff in these areas.

**Outpatients Department (waiting rooms and consultation rooms):**

Outpatient departments are generally considered medium risk as the duration of exposure is short. However, there are several factors which may make them higher risk. First, long waiting times and poor ventilation in waiting areas and consultation rooms pose high risk if undetected infectious cases of TB or known infectious TB cases visit them without proper screening, ventilation or cough etiquette. Second, persons with infectious TB are likely to visit these waiting areas and consultation rooms because they are increasingly more ill and seeking medical attention. Third, people living with HIV are likely to also have other non-TB illnesses for which they seek medical attention in these settings. Fourth, visitors accompanying the persons seeking medical advice may themselves have infectious TB (undetected or detected) and expose others in these areas.

**Emergency Rooms:**

Emergency rooms are generally considered medium risk as the duration of exposure is short. However, there are several factors which may make them higher risk. First, long waiting times and poor ventilation in waiting areas and consultation rooms pose high risk if undetected infectious cases of TB or known infectious TB cases visit them without proper screening, ventilation or cough etiquette. Second, persons with infectious TB are likely to visit these waiting areas and consultation rooms because they are increasingly more ill and seeking medical attention. Third, visitors accompanying the persons seeking medical advice may themselves have infectious TB (undetected or detected) and expose others in these areas.

**Intensive Care and Internal Medicine Wards (inpatients):**

Inpatient internal medicine and intensive care wards are generally considered high risk. First, the duration of exposure is generally longer than in outpatient settings. Second, lack of TB screening of patients upon admission may result in unknown infectious TB exposures to others for days or even weeks resulting in infection of others. Infectious TB patients are likely to be admitted as they can be very ill and be hospitalized for this reason. Third, potentially poor ventilation and lack of cough etiquette practices, if there is an infectious TB patient there, pose higher risk for health staff. Fourth, visitors accompanying the persons seeking medical advice may themselves have infectious TB (undetected or detected) and expose others in these areas for prolonged periods.

### **TB Outpatient (DOT) Clinics:**

TB outpatient (DOT) clinics are considered high risk. First, while the duration of exposure is generally short in these outpatient settings, the patients have active TB and some of them are infectious. Second, if the area is not properly ventilated, workers may be infected or re-infected by the infectious TB patients. Third, it is possible that the TB patients, even if on appropriate 1st line treatment, may have infectious MDR-TB or even XDR-TB that has not yet been detected.

### **TB inpatient wards:**

TB inpatient wards are considered high risk. First, there is a concentration of potentially infectious TB cases in this setting. Second, the duration of exposure from infectious TB could be prolonged, from several days to many weeks. Third, if appropriate TB infection control measures are not in place, workers may be at high risk to be infected or re-infected by the infectious TB patients. If smear-negative patients and smear-positive TB patients are not separated, the risk for staff infection increases because the wards will be bigger and require more staff. It is possible that a TB patient, even if on appropriate 1st line treatment, may have infectious MDR-TB or even XDR-TB that has not yet been detected. MDR-TB and XDR-TB cases are very difficult to treat, require prolonged treatment with injectable drugs and other drugs which have many side effects, are expensive to treat, and have poor cure rates compared to non-MDR and non-XDR-TB.

### **MDR-TB wards:**

MDR-TB inpatient wards are considered high to very high risk. First, there is a concentration of potentially infectious MDR-TB cases in this setting. Second, the duration of exposure from infectious MDR-TB could be prolonged, often several months, before their 2nd line drugs render them non-infectious. Third, if the area does not have appropriate infection control measures in place, will be at higher risk of being infected or re-infected by the infectious MDR-TB patients. Fourth, if smear-negative TB patients and smear-positive MDR-TB patients are not separated, the staff exposed to the infectious TB increases because the wards will be bigger and require more staff. MDR-TB cases are very difficult to treat, require prolonged treatment with injectable drugs and other drugs which have many side effects, are expensive to treat, and have poor cure rates compared to non-MDR and non-XDR-TB. It is possible that the MDR-TB patients, even if on appropriate 2nd line treatment, may have infectious XDR-TB that has not yet been detected.

### **XDR-TB wards:**

XDR-TB inpatient wards are considered very high risk. First, there is a concentration of potentially infectious XDR-TB cases in this setting. Second, the duration of exposure from infectious XDR-TB is likely to be prolonged, often many months, before the 2nd line drugs render them non-infectious. Third, if appropriate infection control measure are not in place, workers will be at a higher risk of being infected or re-infected by the infectious XDR-TB patients. Fourth, HIV infected staff in this setting may rapidly develop XDR-TB. Fifth, if smear-negative XDR-TB patients and smear-positive XDR-TB patients are not separated, the persons exposed to the infectious XDR-TB increases because the wards will be bigger, the wards will require more staff. Sixth, XDR-TB cases are very difficult to treat, require prolonged treatment with injectable drugs and other drugs which have many side effects, are expensive to treat, and have poor cure rates compared to non-MDR and non-XDR MDR-TB. Seventh, in some cases, XDR-TB may be considered untreatable.

<b>Procedure at health facilities</b>	Low Risk	Medium Risk	High Risk	Very High Risk
<b>Smear-microscopy</b>				
<b>Surgery</b> <b>(unless performing chest surgery on a TB patient or suspect)</b>				
<b>X-ray services</b>				

<b>Respiratory therapy e.g., spirometry</b>				
<b>Intubation</b>				
<b>Bronchoscopy services</b>				
<b>Culture and DST procedures of TB specimens</b>				
<b>Molecular testing with live M. Tuberculosis specimen processing</b>				
<b>Sputum collection</b>				
<b>Sputum induction</b>				

#### **Surgery (unless performing chest surgery on a TB patient or suspect):**

Surgery is usually considered to be a low risk procedure unless the operation is on an infectious TB patient. If the operation is on an infectious TB patient, the surgery would be considered moderate to high risk either due to exposure to the TB patients infectious cough or by potentially aerosolizing M. Tuberculosis bacilli from the surgery, particularly surgery involving the lungs or other infected organs.

#### **X-ray Services:**

X-ray technicians and others visiting the x-ray services may be at moderate to high risk of TB infection. While the duration of exposure is short, infectious TB patients (undetected or detected) usually have lung abnormalities and often receive diagnostic chest X-rays.

#### **Respiratory Therapy:**

If a patient is receiving such therapy to measure their lung capacity e.g. Spirometry and they have active infectious TB (detected or undetected), the procedure may put workers, visitors and other patients at high risk for exposure to infectious TB.

#### **Intubation:**

This procedure may induce cough in an infectious TB patient (undetected or detected) and expose workers, visitors and other patients to infectious TB.

#### **Bronchoscopy Services:**

This procedure may induce cough in an infectious TB patient (undetected or detected) and, without proper TB-IC controls in place, expose workers, visitors and other patients to infectious TB. [It is also theoretically possible to infect patients with the tubes by placing non-sterilized contaminated tubes into the next patients' lungs].

#### **Culture and DST procedures of live Mtb specimens:**

These procedures, without proper laboratory infection controls in place, are high risk for TB infection. However, the specimens may also be handled by HIV infected workers and potentially be MDR-TB or XDR-TB specimens, and therefore can be very high risk.

#### **Molecular testing with live Mtb specimen processing:**

These procedures, without proper laboratory infection controls in place, are high risk for TB infection. However, the specimens may also be handled by HIV infected workers and potentially be MDR-TB or XDR-TB specimens. Therefore, this procedure can be very high risk.

**Sputum Collection:**

This procedure, without proper ventilation, is high risk for TB infection. Further, if the specimen is collected in an enclosed area without proper ventilation, the next persons (including people living with HIV) who enter the enclosed area could be infected. The specimens may also be collected in the presence of HIV infected workers and potentially be MDR-TB or XDR-TB patients (detected and undetected). Therefore, this procedure can be very high risk.

**Sputum induction:** This procedure, without proper ventilation and respiratory protection, is high risk for TB infection. Further, if the specimen is collected in an enclosed area without proper ventilation, the next persons (including people living with HIV) who enter the enclosed area could be infected. The specimens may also be collected in the presence of HIV infected workers and potentially be MDR-TB or XDR-TB patients (detected and undetected). Therefore, this procedure can be very high risk.

**Other Procedures:** autopsies of TB patients are considered high risk procedures as the Mtb bacilli may still be alive and be aerosolized by the procedure, particularly from infected lungs or other organs, even though the patient has passed away.



