REVIEW ARTICLE

Transmission of *Mycobacterium Tuberculosis*

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Abstract

Introduction: Tuberculosis (TB) has been a leading killer of mankind since time immemorial. There are four key components in the TB elimination approach. They are known as "Detect–Treat–Prevent–Build". Under the preventive strategy, scaling up of airborne infection control measures is an important step in controlling the global disease burden.

Methods: This is a narrative review for which we used online databases such as PubMed, Embase, and CINAHL from inception to July 2024. The search terms used include TB, transmission, aerosols, cough, droplet nuclei, Wells–Riley equation, and ultraviolet germicidal irradiation (UVGI). All types of articles were selected.

Results: The primary mechanism of transmission of *Mycobacterium tuberculosis* (*M. tb*) is the inhalation of small infected droplet nuclei (1–5 µm in diameter) consisting of a few mycobacteria that have the capacity to reach the alveoli. The transmission dynamics of TB can be influenced by various human, environmental, and pathogenic factors. Several mechanisms such as coughing, sneezing, talking, laughing, singing, and normal tidal breathing can produce droplet nuclei.

Conclusion: It is crucial to thoroughly understand the mechanisms of TB transmission for a better understanding of TB dynamics. TB is mainly transmitted by droplet nuclei, and preventive strategies should incorporate this mechanism.

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Introduction

The term "tuberculosis (TB) transmission" indicates spread of TB bacilli from one person to another. The transmission of TB occurs through the airborne route by inhalation of droplet nuclei. Droplet nuclei are the infectious particles of TB of sizes ranging from 1 to 5 µm. They are produced by numerous aerosol-generating activities such as coughing, sneezing, talking, laughing, singing, and normal tidal breathing. The droplet nuclei are usually produced in patients with laryngeal or pulmonary TB disease.[1,2] The number of droplets produced by one cough episode is 500, and a treatment-naïve pulmonary TB patient generates on average 75,000 droplets per day. This number drops to 25 infectious droplets per day after 2 weeks of appropriate treatment.[2,3] Singing produces a higher percentage of droplet nuclei of up to 2.9 µm diameter than coughing (34.1 vs 26%). Tidal breathing is also an equally important maneuver in TB transmission.[4] In a modeling study, tidal breathing was responsible for almost 90% of the daily aerosolized *Mycobacterium tuberculosis* (*M. tb*) among symptomatic TB patients.[4] Patterson and Wood[5] suggested that the aerosols are produced in the larynx, bronchi, and bronchioles. However, bronchi and bronchiolar aerosols are primarily responsible for TB transmission. Moreover, singing, talking, coughing, and less commonly tidal breathing all produce bronchiolar aerosols. Tidal breathing exclusively produces bronchiolar aerosols. Therefore, TB can be spread even in the absence of coughing.

Wells in 1934 suggested that the small droplet, after emanating from the mouth, fell on the surface and that the rate of fall of the droplet is proportional to its surface area or diameter.[6] If the diameter of the droplets is larger than 1 mm, particles will fall to the surface in 0–6 seconds, but smaller droplets of <0.001 mm will take approximately 16.6 hours. The droplet nuclei in the environment undergo evaporation and become smaller in size, and the rate of this evaporation is proportional to the square of the diameter. These tiny droplets may remain airborne for a longer period and are infectious as they carry *M. tb*.[7] The average half-life of aerosolized TB bacilli is approximately 6 hours. The layer of respiratory secretions protects the droplet nuclei from natural irradiation, oxygen injury, dehydration, and other environmental stresses.[7] These nuclei, on inhalation by contact, can enter the lungs' periphery, establishing infection if they float in the air for a sufficient amount of time. The droplet nuclei on the surface are difficult to reaerosolize, as the viable bacilli are coupled to relatively big, nonrespirable particles that typically impact the relatively resistant upper airways.[8,9] Loudon et al.[3] documented that at 6 hours, 55.8% of the aerosols of *M. tb* (H37Rv) and 13.1–37.5% of the nontubercular mycobacteria survived. Children are usually less infectious due to the paucibacillary nature of the disease, less sputum production, and often have hilar or mediastinal lymphadenopathy, bronchial obstruction, and atelectasis.[10]

Brief History of Transmission of Tuberculosis

The concept of airborne transmission is not unexplored. Aristotle in 384–322 BC initially recognized the infectious nature of TB and its transmission *via* pernicious air.[11] Hippocrates (470–410 BC) asserted that "consumptives beget consumptives," supporting the idea that TB is inherited.[12] Galen (129–216 AD) stated, "When many sicken and die at once, we must look to a single common cause, the air we breathe."[13] In a seminal research in 1861, Louis Pasteur demonstrated that air was inhabited by microorganisms.[14] All of their statements support the concept of airborne TB transmission. A French military surgeon named Jean-Antoine Villemin (1827–1892) was the first person to demonstrate the transmissibility of TB from patient to animal.[15] In 1882, Koch showed that animals exposed to tubercle bacilli in the air developed a chronic form of TB and those animals exposed to massive doses died shortly.[16] Although Koch did not confirm it experimentally, he suspected the airborne transmission as well, assuming the majority of the cases occurred in the respiratory tracts; the bacilli are usually inhaled with air.[16] In 1899, German bacteriologist and hygienist Flügge laid down the concept of droplet transmission of TB. Moreover, his work led to the recognition of the use of surgical masks to prevent spread of infection by transmissible aerosols.[17] However, the scientific basis of

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droplet nuclei–mediated transmission of TB was based on Wells' research,[18] which showed that not all aerosols fell within a short distance from the source.[19] Flügge's theory did not highlight the role of evaporation. They believed that the size of the aerosols was constant. Loudon and Roberts in the 1960s reported the mechanisms of aerosolization by talking, singing, coughing, and sneezing.[2,20] Riley et al. were credited to first confirm the airborne transmission of TB experimentally in the human-to–guinea pig transmission study where the only contact between them was shared air.[21] They conducted the study on a six-bed TB ward at the Veterans Hospital in Baltimore. These rooms were sealed off from the rest of the hospital. The ward had a precisely calibrated and controlled closed-circuit ventilation system and a sizable animal exposure chamber situated in the system's exhaust duct. Guinea pigs were exposed to air vented from the pilot ward occupied by TB patients. The air in the exposure chamber and the ward that housed the TB patients had the same infectivity, according to earlier research by the same investigators.[22,23] The investigators performed tuberculin tests every month on the entire 150 guinea pigs. An autopsy and a histopathological examination were conducted on the animals showing positive tuberculin conversion. The presence of tubercles depicted through the examination was considered as the basis of the TB diagnosis. Over a period of 2 years, 71 guinea pigs became infected with TB, and over a period of 4 years, 134 guinea pigs contracted TB. The average number of infections contracted in a single month was approximately three (0–10). This study confirmed that transmission of TB infection occurred *via* airborne infection. Additionally, there was a noticeable variation in transmission of infection from TB patients. The author also demonstrated how guinea pigs were shielded from infection by ultraviolet germicidal irradiation (UVGI). The majority of infections were caused by three patients, indicating variability of aerial infectivity of TB patients.[24] Escombe et al.[25] subsequently reproduced the result by Riley. They used the *in vivo* air sampling model to study the airborne transmission of TB in human immunodeficiency virus (HIV)–TB coinfected patients. An animal facility that housed on average 92 guinea pigs was built above a mechanically ventilated HIV–TB ward in Lima, Peru. About 97 patients with pulmonary TB were admitted with a median duration of hospitalization of 11 days, and 42% had positive sputum microscopy results. There was a wide variability in the rate of TB infection as monthly rates of positive tuberculin skin test (TST) among the guinea pigs were 0–53%. The mean number of airborne infectious units or quanta was 8.3 per hour compared to 1.25 quanta per hour in Riley's cohort.

Subclinical TB also contributes to TB transmission. Nguyen et al.[26] conducted a multivariate analysis of data from TB prevalence and TB survey data in Vietnam. The adjusted risk ratio of TST positivity in children living with patients of subclinical TB was 2.26 (95% CI: 1.03–4.96) after adjusting for index smear status. Children aged 6–10 who lived with patients of smear-positive TB (both clinical and subclinical) had a similar elevated risk of TST positivity compared to those living with individuals without TB. Emery et al.[27] estimated the infectiousness of subclinical TB in relation to clinical TB at 1.93 (0.62–6.18, 95% prediction interval). Modeling analysis suggests that subclinical TB can cause 68% of global transmission of TB. Therefore, early diagnosis and treatment should be ensured.

Factors Related to Transmission of Tuberculosis

Factors related to TB transmission include characteristics of index patients and contacts, characteristics of the bacillus, and environment. Factors related to the index patients include the site of disease, bacillary load, presence of cough, lack of cough etiquette, and anti-TB therapy. Although both pulmonary and laryngeal TB are infectious, patients with laryngeal TB are more contagious compared to patients with pulmonary TB.[28] Patients with cavitary disease on a chest radiograph are at higher risk of transmitting infection, as a 2 cm cavity can contain 10^8 TB bacilli.[29] The minimum number to become smear-positive is 10,000 bacilli per mL of sputum,[30] whereas culture positivity requires approximately 10–100 live bacilli. Patients with smear-positive pulmonary TB are more susceptible to infection than smear-negative patients, as approximately 10^6–10^7 acid-fast bacilli per mL of sputum are expectorated by smear-positive individuals daily, whereas sputum from smear-negative individuals contains fewer than 10^3 bacilli per mL.[31,32] van Geuns et al.[31] estimated that among smear- and culture-positive patients, TST reactivity among household contacts (HHCs) and casual contacts was 20.2 and 3.7%, respectively. Among smear-negative and culture-positive patients, the corresponding figures among HHCs and casual contacts were only 1.1 and 0.2%, respectively. Although smear-negative individuals are less contagious, they also contribute to TB transmission.[33] Persistent cough (either spontaneous or induced) may also help in the transmission of TB bacilli. Amount and severity of cough in the source patient are also important, particularly when the patient is not following cough etiquette. Early initiation of effective chemotherapy rapidly makes the person noninfectious.[3,34] According to Styblo's estimation,[35] one untreated smear-positive case leads to approximately 10 secondary infections annually. Unsuspected TB patients in the ward are particularly common in high-TB-burden countries. They may fuel TB transmission in a busy hospital ward. Bates et al.[36] reported unsuspected TB among 13.4% of TB cases in Zambia. In a different study, 13 unsuspected TB patients were admitted, and 46% of them were diagnosed as MDR-TB.[37] In nations with high TB burdens, proactive TB screening must be performed on all inpatients.

Contacts

The risk factors of infection include closeness, frequency, and duration of exposure. HIV, other T-cell defects, structural lung disease, uncontrolled diabetes, and younger age may increase the risk of infection among the contacts. Among HHCs of smear-positive cases, the TST reactivity rates are 30–50% higher than among age-matched controls. On the contrary, the tuberculin reactivity rate is 5% higher than the community controls in culture-positive and smear-negative cases.[38] Paradkar et al.[39] from India observed that HHCs of adult pulmonary TB (PTB) patients had a higher rate of TB infection. Approximately 71% of 997 HHCs had baseline TST ≥5 mm or interferon-gamma release assay (IGRA) ≥0.35 IU/mL. Certain cough-inducing procedures such as bronchoscopy, endotracheal intubation, sputum induction, and cardiopulmonary resuscitation may also help in TB transmission. Loudon and Spohn[40] recorded the radiological extent, bacteriological status, and cough counts in patients with newly diagnosed and untreated pulmonary TB. The prevalence of tuberculin sensitivity among contacts of index TB patients with far advanced radiological disease was significantly higher compared to contacts of index patients with moderate or mild disease. When the index pulmonary TB patients were positive on microscopy and culture, culture-positive and smear-negative, and both smear and culture-negative, the corresponding prevalence of tuberculin reactivity among HHCs was 44.3, 21.4, and 14.3%, respectively. When the index pulmonary TB patients had mean cough counts of <12, 12–47.9, and >48, the corresponding prevalence of tuberculin reactivity among HHCs was 27.5, 31.8, and

43.9%, respectively. Grzybowski et al.[41] estimated the prevalence of infection among contacts of pulmonary TB patients. The prevalence was variable depending on the bacillary load. An increased risk of infection with increasing age was reported when compared to the general population. The prevalence of infection among smear-positive contacts, culture-positive pulmonary TB in the 0–4 years and ≥40 years age-groups was 29.1 and 61.1%, respectively.

Environmental Factors

The risk of transmission is determined by the exposure site and ventilation. If contacts are exposed to an infectious TB patient in an enclosed and small space with no cross-ventilation, there will be an increased chance of transmission. A well-ventilated room with a sufficient amount of air change per hour lowers the risk of transmission. Environmental factors, by increasing the concentration of droplet nuclei, may enhance the risk of transmission. The factors that might increase the concentration of droplet nuclei and the enhanced risk of transmission include exposure within a small enclosed space, inadequate ventilation, recirculation of air containing infectious aerosols, and improper sample handling within the laboratory.[42] This explains why TB outbreaks occur in enclosed places such as nursing homes, prisons, urban homeless shelters, aircraft, schools, and bars. Furthermore, several aerosol-generating procedures, such as open abscess irrigation, endotracheal intubation and suctioning, bronchoscopy, and autopsy, have the potential to transmit TB nosocomially.[43–46] Almost, all TB transmission occurs indoors. It has been reported among marijuana and cocaine users also.[47–49] The "shotgunning" drugs, where a person inhales smoke and then exhales into someone else's mouth, have the potential to effectively spread respiratory infections.[50]

Characteristics of the Bacilli

Various strains of TB bacilli have different transmission potential. Some strains are super-spreaders also. A large outbreak was reported by Valway et al.[51] in a small, rural community with a low-risk population in the USA. In five patients, active TB developed following a brief and casual exposure. The strain in this study differs from other strains in its growth characteristics. Mice administered the Erdman strain of *M. tb* showed approximately 1,000 and 10,000 bacilli per lung after 10 and 20 days, respectively, while mice infected with the virulent strains had approximately 10,000 and 10 million bacilli per lung, respectively.

Effective Chemotherapy

Effective chemotherapy for TB reduced the risk of transmission of infection markedly. After 2 weeks of appropriate chemotherapy, the number of infectious droplets drops to 25 per day.[52] Brooks et al.[34] demonstrated the efficacy of chemotherapy in 21 patients with pulmonary TB. They discharged the patients after 2 weeks of chemotherapy and measured the risk of new infection among 72 HHCs. The majority of patients were smear and culture-positive (19 patients) and had cavitary disease (16 patients). None of the 72 HHCs who were TST-negative on initial testing converted. There was a rapid drop in bacillary number postchemotherapy. Riley et al. also assessed the impact of drug therapy of index patients on the risk of transmission. In the case of drug-susceptible TB, untreated patients transmitted infection to 29 guinea pigs with 100% infectiousness. However, in the drug therapy group, only one guinea pig contracted infection, indicating a drastic reduction of infectivity by 98%. Similarly, with drug-resistant organisms, treatment reduced infectivity by 23%.[53]

Nosocomial Transmission of Tuberculosis

The fact that healthcare facilities, particularly in developing countries, have been known to be important locations for TB transmission since time immemorial. There are many examples of institutional outbreaks of drug-susceptible and drug-resistant TB.[54–56] Immunocompromised individuals, such as HIV-positive persons, are particularly vulnerable to contracting TB infection. In developing countries, data on the institutional spread of TB is often lacking due to the nonavailability of molecular epidemiological tools. The crowded indoors, outpatients, lack of triaging facilities, and respiratory isolation are good recipes for nosocomial transmission of TB. Moreover, TB infection prevention and control (IPC) program often remains neglected in resource-poor countries.[57] Using TST and IGRA, a cross-sectional study was conducted on 726 healthcare workers in India who had no prior history of TB. About 50% of the healthcare workers were positive for either of the two tests.[58] The follow-up survey among 216 medical and nursing students revealed the annual risk of infection of 5%, which is higher than the community average, suggesting potential nosocomial transmission.[59] The spread of extensively drug-resistant TB (XDR-TB) in Tugela Ferry, KwaZulu-Natal Province, South Africa, underscores the significance of infection control in preventing the nosocomial spread of TB.[60] There are two important aspects of this incident. The majority of patients had a primary transmission of TB as they are treatment-naïve. If the patient had been hospitalized in the preceding 2 years, hospitalization was a significant risk factor for XDR-TB, with an odds ratio of 3.7.[61] Among 53 XDR-TB patients, 67% had been hospitalized recently. There was a similar strain in 85% of patients. About 71% of XDR-TB cases reported by Gandhi et al.[62] had been exposed to at least one infectious XDR patient while in the hospital. The Tugela Ferry incident had also raised questions about the theory of loss of fitness of resistant strain.

Mathematical Models of Transmission

A mathematical model of TB transmission was proposed by Riley, who modified the Wells' use of the soper mass balance equation, assuming that the risk of TB from casual contact was much lower than that of measles.[23,63] This equation is known as the Wells–Riley equation.

Equation 1:

$$C = S\,(1 - e^{-Iqpt/Q})$$

Where,

C = Number of new cases.

S = Number of susceptible exposed.

e = Natural logarithm.

I = Number of infectious sources.

q = Number of quanta (infectious doses) generated per unit minute.

p = Human ventilation rate (L/minute).

t = Exposure duration.

Q = Infection-free ventilation (L/second) When air from the space is exchanged with uncontaminated air.

The Wells–Riley equation suggests that infectious cases, degree of infectivity, susceptible hosts who are exposed, exposure duration, and ventilation rate are important parameters during transmission of TB infection. A uniform virulence of organisms was assumed, as well as susceptibility of the individuals exposed to infection, which further made the base of the equation. So, it was only used in steady-state conditions. The resource-intensive measurement of room ventilation was an additional limitation. The problem of estimating a room's ventilation was solved by Rudnick and Milton, who suggested the use of human-generated indoor carbon dioxide (CO_2) levels as a natural tracer gas.[64] This equation can be used in both a steady state and a nonsteady state.

Variability of Infection

It is a fact that infectiousness is variable. Some individuals are more contagious than others, and the variability may occur over a

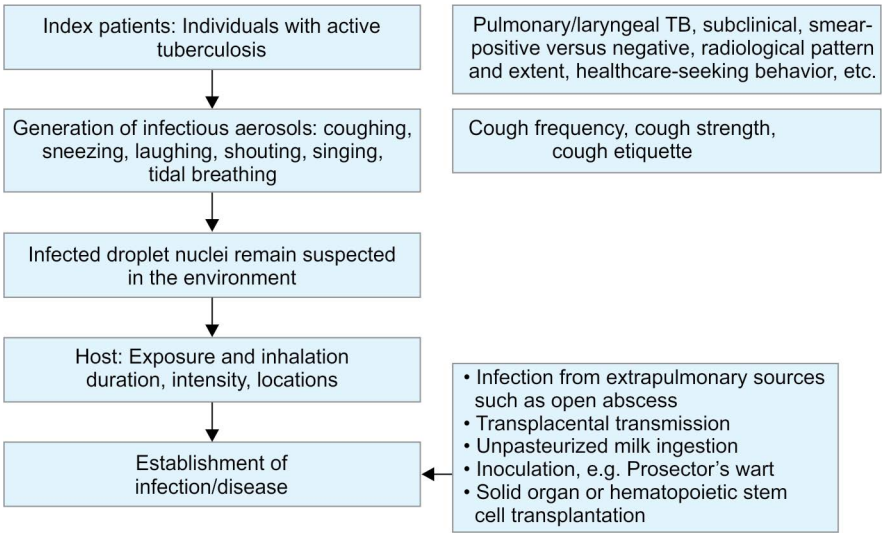

Fig. 1: The mode of transmission of TB

period in a patient.[62] The term "quanta" was used by Riley et al. to define the number of infectious airborne particles required to infect a contact. Even one or more airborne particles can establish the infection.[63] In an animal experiment, 63.2% of highly susceptible guinea pigs were exposed to tubercle bacilli available at a concentration that would allow each animal to inhale no more than an average one droplet nucleus. Therefore, the dose that causes 63.2% of exposed subjects to get infected is known as the quantum of infection.[65] The generation of infectious quanta is variable. In one study from the University of California, San Diego Medical Center, the risk of contracting TB infection was high in hospital employees when exposed in a bronchoscopy suite, as 77% of exposed were converted. During bronchoscopy and intubation of the index case, 249 infectious units per hour were generated.[43] The rate of infection aerosols formation was 1.25 quanta per hour in Riley's experiment, clearly suggesting a variability in infectiousness.[53] Melsew et al.[66] reported 9.9% super-spreading events from Victoria, Australia. Radiological extent of pulmonary diseases, bacteriological status, and mean 8-hour overnight cough counts determine the variability in TB transmission. The prevalence of TST sensitivity among contacts of index TB patients with far advanced radiological diseases was significantly higher compared to children who were contacts of index patients with moderate or mild disease radiologically.[40] Similarly, a higher prevalence of reactivity was observed among HHCs when index TB patients had microscopy positivity. When the index pulmonary TB patients were smear and culture-positive, smear-negative culture-positive, and both smear and culture-negative, the corresponding prevalence of TST reactivity among HHCs were 44.3, 21.4, and 14.3%, respectively.

Other Modes of Transmission

- Congenital *via* transplantation route.
- Inoculation, for example, Prosector's wart.
- Gastrointestinal—bovine TB, heavy inoculums, not due to contamination of foods.
- Other aerosols—laboratory and wound debridement.

Figure 1 shows various modalities of transmission of TB.

Newer Tool to Detect Infectiousness

Fennelly et al.[67] designed the "cough box" experiment to measure the infectious aerosols released while coughing by TB patients. He was the first to culture *M. tb* using droplet nuclei derived from 38 patients with infectious TB in Kampala, Uganda. In 27.7% of patients with culture-confirmed TB, *M. tb* could be cultured from cough aerosols. After coughing for 10 minutes, a median aerosol colony-forming unit (CFU) (range, 1–701) of 16 was generated. About 96.4% of cultivable particles were in the range of 0.65–4.7 µm in size. Small droplets are therefore the most culturable. Furthermore, small droplets can still form in the absence of evaporation. This study demonstrated a feasible technique for gathering cough aerosols in an environment with limited resources. It also demonstrated that not all patients with infectious TB are transmissible. In patients with pulmonary TB, Jones-López et al.[68] demonstrated that in 45% of cases, smear positivity was associated with aerosol production. Additionally, they found that the only risk associated with a new TB infection was high aerosol production (>10 CFU) (adjusted odds ratio, 4.81; 95% CI: 1.20–19.23). Therefore, among contacts, cough aerosols with high culture positivity are the main predictor of new infection. In future, a widely available, simple, better design, and cost-effective method to measure cough aerosols is required. Cough aerosol sampling measures the patient's aerosol production capacity and is a new study tool that has been proven to correlate better with household transmission. Facemask sampling provides an attractive, sensitive, and noninvasive way of stratifying the most infected individuals.

Role of Exhaled Breath Carbon Dioxide

Exhaled breath CO_2 level can be used as a surrogate for exhaled breath. Exhaled breath by an infected pulmonary TB patient releases infectious particles in the room occupied by the index patient. The only source of CO_2 in the room is the exhaled breath, as its CO_2 is over 40,000 parts per million, while outside air has about 350 parts per million CO_2 content. The vulnerable in the room may develop infection upon inhaling the infected exhaled breath. The "rebreathed air fraction" is defined as the inhaled air that was previously exhaled by someone inside the building. The ambient CO_2 concentration depends on the effect of occupancy and ventilation and is a good surrogate for the risk of airborne infection. Richardson et al.[69] used the Rudnick–Milton equation and found that for a classroom of 180 m^3, an indoor CO_2 concentration of 1,000 parts per million or 12 air changes per hour (ACH) corresponded with a critical rebreathed CO_2 fraction of 1.6%. A higher level of median CO_2 indicates inadequate ventilation and/or overcrowding, as well as being linked to an increased risk of TB transmission. Nathavitharana et al.[70] reported that the IGRA converters had higher median CO_2 levels compared to IGRA nonconverters (p <0.01). Every 100 parts per million rise in median CO_2 levels increased the repeat quantitative IGRA result by an odds of 1.81 (p = 0.01).

Conclusion

A thorough plan is necessary for the two hallmarks of the End TB Strategy, prevention and control of TB infections, while accounting for available resources, cost, and geographical constraints. Understanding the transmission mechanisms and the variables that can impact it would help in taking better infection prevention and maintaining control practices

in the hospital. Healthcare workers should be consistently educated and trained on control and prevention of TB infection, while active TB patients should be properly educated on respiratory hygiene and cough etiquette. Ultimately, a timely and rigorous adoption of prevention and control of TB infection, while accounting for the available resources, should be positively addressed at every level of the health facility.

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