Preventing Transmission of *Mycobacterium Tuberculosis*—A Refocused Approach

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KEYWORDS

• TB transmission • TB infection control • TB prevention • Respiratory isolation • Screening • Ultraviolet • Ventilation • Respirators

KEY POINTS

- Traditional tuberculosis (TB) infection control focuses on known patients with tuberculosis already on therapy, whereas most transmission is from patients with unsuspected TB or unsuspected drug resistance, not on effective therapy.
- For high-burden settings, a refocused, intensified, administrative control strategy, FAST (Find cases Actively, Separate temporarily, and Treat effectively based on molecular diagnostics), attempts to shorten the time from entry to a health care facility and the start of effective treatment.
- For low-burden settings, unsuspected TB also poses the greatest transmission risk, but this is better addressed by increased awareness through education.
- Because not every infectious case will be detected and promptly treated, air disinfection is important in high-risk settings. Environmental controls such as ventilation and germicidal air disinfection reduce risk. Increasing use of air conditioning in warming climates require air supplemental disinfection as windows are closed.
- Germicidal ultraviolet air disinfection is underused, but after natural ventilation, it is the most cost-effective and sustainable technology.

INTRODUCTION

Awareness of how *Mycobacterium tuberculosis* (*Mtb*) is spread, and precautions to prevent it, came long after Robert Koch's 1882 discovery of the causative bacillus.[1] In Thomas Mann's 1924 novel set in prewar Europe, for example, Hans Castorp visits his cousin, a tuberculosis patient in an alpine tuberculosis sanatorium, completely oblivious of any risk from sharing a room with his cousin for weeks and taking every meal in a dining hall filled with untreated, coughing patients with TB.[2] Little did he know that he already had the disease. Sanitoria were a form of treatment in the prechemotherapy era, not isolation facilities. Although long suspected as airborne, and the subject of numerous earlier transmission experiments, it was not until mid-twentieth century that Riley and colleagues[3] unequivocally proved the point by demonstrating human-to-guinea pig transmission when the only contact was shared air.[4] Further, Riley showed that all transmission stopped if the ward exhaust air was disinfected with ultraviolet light, and

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most importantly, transmission stopped almost immediately with the start of effective treatment, as shown in Table 1.[4]

THE RAPID IMPACT ON TRANSMISSION OF EFFECTIVE *M TUBERCULOSIS* TREATMENT

Table 1 shows the results of Riley's second, 2-year experiment, where patients with sputum smear- and culture-positive TB were admitted to the 6-bed Baltimore Veterans' Administration Hospital ward and either treated immediately or had their treatment delayed so that the impact of treatment could be quantified.[3] Treated patients, based on comparable person-time on the ward, were 98% less infectious that untreated patients. This was at a time when the only drugs available for treating TB were isoniazid (INH), para-aminosalicylic acid, and streptomycin, a relatively weak regimen by today's standards. Patients whose *Mtb* isolates were drug resistant, most often to INH, also became less infectious when treated with the remaining drugs, but the numbers were too few to be sure, according to Riley. An often-overlooked finding of this study was the rapidity of the impact of treatment on transmission. Patients began treatment at the same time that they entered the ward, not 2 weeks or even 2 days earlier. The powerful impact of effective chemotherapy on transmission was essentially *immediate* or as long as it took to reach therapeutic levels in tissues. So important and underappreciated is this observation that it deserves to be expressed in Riley's own words:[4]

> *The treated patients were admitted to the ward at the time treatment was initiated and were generally removed before the sputum became completely negative. Hence the decrease in infectiousness preceded the elimination of the organisms from the sputum, indicating that the effect was prompt as well as striking. …Drug therapy appeared to be effective in reducing the infectivity of patients with drug resistant organisms, but the data do not permit detailed analysis of the problem.*[4]

Independent of these landmark human-to-guinea pig experimental results, the rapid impact of effective treatment was also studied epidemiologically in the 1960s and 70s with several household contact investigations summarized by a review paper by Rouillion and colleagues.[5] Beginning with a controlled trial of ambulatory and hospital treatment in Madras, India, several observational studies in the United Studies showed that household contacts of newly diagnosed pulmonary TB cases that were tuberculin skin test (TST) negative after the index case started treatment were no more likely to convert their TST than noncontacts in the general population.[5,6] These studies were used as evidence in favor of the ambulatory treatment of TB, suggesting that patients on therapy rapidly became noninfectious, well before sputum smear and culture conversion, which occurs, on average, at about 2 months into treatment. But exactly how much therapy was needed was not discernible from epidemiologic observations, and Riley's human-to-animal data appear not to have been considered in formulating transmission control policies at that time. Instead, by consensus, Rouillion and colleagues[5] made first reference to "*less than 2 weeks*" as the amount of treatment that renders patients noninfectious, regardless of sputum smear or culture status, assuming a clinical

Table 1
Outcome of human-to-guinea pig *Mycobacterium tuberculosis* transmission studies, showing the rapid impact of effective treatment on transmission among drug-susceptible and drug-resistant patients

Patients with Susceptible *Mtb*	Numbers of GPs Infected	Relative Infectiousness[a]
Untreated	29	100%
Treated	1	2%
Patients with drug-resistant *Mtb*		
Untreated	14	28%
Treated	6	5%

Note that the only available drugs at the time were isoniazid (INH), streptomycin, and para-aminosalicylic acid, so drug-resistant patients, usually INH resistant at least, had very few treatment options.[4]

Abbreviation: GP, guinea pig.

[a] All smear-positive patients, relative to the amount of time spent on the ward.

From Riley RL, Mills CC, O'grady F, et al. Infectiousness of air from a tuberculosis ward. Ultraviolet irradiation of infected air: comparative infectiousness of different patients. Am Rev Respir Dis 1962;85:511–25; with permission.

response to treatment evident by decreasing cough, an increasing sense of well-being, and usually, less positive sputum smears.

> *There is an ever-increasing amount of evidence in support of the idea that abolition of the patient's infectiousness – a different matter from 'cure,' which takes months, and from negative results of bacteriological examinations, direct and culture, which may take weeks – is very probably obtained after less than 2 weeks of treatment….These facts seem to indicate very rapid and powerful action by the drugs on infectivity…*[5]

Although the *"2-week rule"* and the epidemiologic evidence on which it was based have been criticized as potentially biased, it has never been rigorously tested clinically.[7] Such a trial would be challenging to design and conduct in high- or low-risk settings. Instead, in recent years it is still common to see the assertion that patients responding to effective therapy who remain sputum smear- or culture-positive on effective treatment should be considered still infectious.[8] Because sputum smear positivity in untreated patients is appropriately used as one of several indicators of probable infectiousness, the grounds for confusion are clear. But as a result of this confusion, sputum smear conversion is still commonly used as a criterion for ending TB isolation or discharge from hospitals in low-prevalence settings despite the acceptance of entirely ambulatory TB treatment for more than 50 years. Another factor is that hospital infection control polices tend to be conservative at the expense of overisolation of patients rather than risking exposing health care workers or other patients. Finally, during the 1985 to 1992 resurgence of multidrug-resistant (MDR) TB in the United States and other countries, patients with *unsuspected* MDR-TB remained infectious after 2 weeks of what turned out to be *ineffective* therapy, but nevertheless tarnishing the dogma that patients could no longer transmit after 2 weeks treatment.[9] In an era of rapid molecular drug susceptibly testing, unsuspected drug-resistant TB is less likely in many parts of the world, but not everywhere.

THE IMPACT OF EFFECTIVE TREATMENT ON DRUG-RESISTANT TUBERCULOSIS TRANSMISSION

As noted, Riley's human-to-guinea pig studies, conducted in an era before MDR-TB and extensively drug-resistant (XDR) TB, left the issue of the impact of effective treatment for drug-resistant TB unresolved.[4] Given the 1985 to 1992 experience of MDR-TB transmission on treatment, albeit *infective* treatment, and the higher morbidity, mortality, and difficulty treating MDR-TB, health departments and hospitals adopted more rigorous transmission isolation policies, largely based on sputum smear, and sometimes culture conversion. Those policies largely remain in place today. Although conversion times have shortened with some of the newer treatment regimens for highly resistant TB, they are still measurable in months. But because it has been long known that transmission ceases well before sputum smear and culture conversion, it can be safely assumed that isolation under such policies is unnecessarily long but an understandable caution in the absence of transmission data for MDR-TB on treatment. Two other revivals of the Riley human-to-guinea pig transmission experimental model are relevant to the impact of treatment on transmission.[10–12]

In 2008, Escombe and colleagues[10,11] reported results from the first human-to-guinea pig (H-GP) transmission experiments since Riley's 50 years earlier. Escombe exposed 292 guinea pigs to the exhaust air from a TB-human immunodeficiency virus (HIV) ward in Peru. Over 505 days, 97 patients with HIV-TB infected 125 general practitioners (GPs), 98% were due to 9 patients with unsuspected MDR-TB, being treated for drug-susceptible (DS) TB. Three DS patients infected 1 GP each, but 2 of the patients had delayed treatment and 1 had had treatment stopped. This study confirmed Riley's earlier findings that effective treatment of DS *Mtb* nearly completely suppresses transmission, with transmission predominantly from unsuspected patients with MDR-TB not being effectively treated.[11] But what of MDR-TB treatment?

In 2005, Nardell and colleagues[12] also established an H-GP transmission facility in South Africa (Airborne Infection Research Facility [AIR]), specifically to study MDR-TB transmission, in part because DS patients on therapy do not infect GPs. The purpose was to study the dynamics of transmission and to test transmission interventions, such as germicidal ultraviolet air disinfection and masks on patients (to be discussed later), and also to examine the impact of treatment.[8,13,14] The assumption was that patients with MDR-TB just started on therapy would remain infectious long enough to infect guinea pigs. In the authors' first (pilot) study 26 DR patients infected 74% of 362 exposed GPs.[12] But in the next 4 experiments, a total of 109 patients selected by the same criteria (mostly sputum smear positive, cavitary chest x-ray, coughing, and just started on MDR-TB therapy) had highly variable results, in order, infecting 10% over 3 months, 53% over 2 months, 1% over

3 months, and 77% over 3 months exposure. The reason for this variability was not apparent until fingerprinting results of *Mtb* isolates from GPs infected in the pilot study came back, showing 8 different spoligotypes, but only 2 that transmitted to GPs, both associated with cases of unsuspected XDR-TB. XDR-TB existed but had not yet been described at the time of the AIR pilot study.[8] Although the standard South African MDR treatment regimen rapidly stopped MDR-transmission, it did not stop the transmission from unsuspected XDR-TB. In the fourth H-GP study, importantly, 27 patients with DR-TB exposed 90 GPs over 3 months, but only 1 GP was infected. Fortuitously, none of the 27 patients had XDR by conventional drug susceptibility testing or line probe assay. Effective MDR-TB treatment promptly suppressed all but one instance of MDR-TB H-GP transmission over 3 months.[8] But does specific XDR-TB treatment suppress XDR-TB transmission?

Recently, 2 as yet unpublished studies from the AIR facility address that question. Five patients with MDR-TB failing standard treatment were eligible to receive both bedaquiline and linezolid under South African policy. The patients entered the AIR facility and were studied for 8 days before (exhaust air to 90 GPs in chamber A) and for 11 days after starting therapy (exhaust air from the last 8 days to GPs in chamber B).[15] For the first 72 hours of treatment exhaust air did not expose GPs, to allow some time for drugs to act. There was no difference in the GP infection rate before and after the onset of drugs to which their *Mtb* was susceptible. Using a similar protocol, the highly curative "NIX-TB" regimen (bedaquiline, high-dose linezolid, and pretomanid) was then tested for its ability to rapidly suppress transmission to GPs. Patient-day exposure time of GPs before and after the start of treatment was the same and was the same as for the first study. Again, 72 hours treatment time was excluded to allow the drugs to reach tissues. This regimen completely suppressed transmission of patients with XDR/MDR-TB who qualified for the regimen.[16]

In summary, effective treatment of DS and MDR-TB seems to rapidly stop transmission, but for more highly resistant *Mtb*, the effect on transmission may depend on the specific drugs used, their pharmacokinetics/pharmacodynamics, and their effects on as yet unknown microbial mechanisms required for airborne transport and reestablishing infection in a new host. More research in this area in needed, including drugs delivered via the airways that might have selective effect on transmission.

UNSUSPECTED TUBERCULOSIS AND UNSUSPECTED DRUG RESISTANCE—THE PRINCIPAL SOURCES OF *M TUBERCULOSIS* TRANSMISSION

TB transmission control as currently practiced is *wrongly focused on patients with TB* and needs to be refocused. This seems to be true in both high- and low-burden setting, but for different reasons. If it is true that effective treatment renders patients with TB rapidly noninfectious, the logical corollary is that the greater risk in health care and other congregate settings is from persons with pulmonary TB not on effective therapy either because they are unsuspected and undiagnosed or because they have unsuspected drug resistance. There have been remarkably few studies quantifying the rate of undiagnosed TB in congregate settings where the most effective transmission is likely to occur.[17,18] **Fig. 1** conceptualizes risk of transmission as progressing slowly from

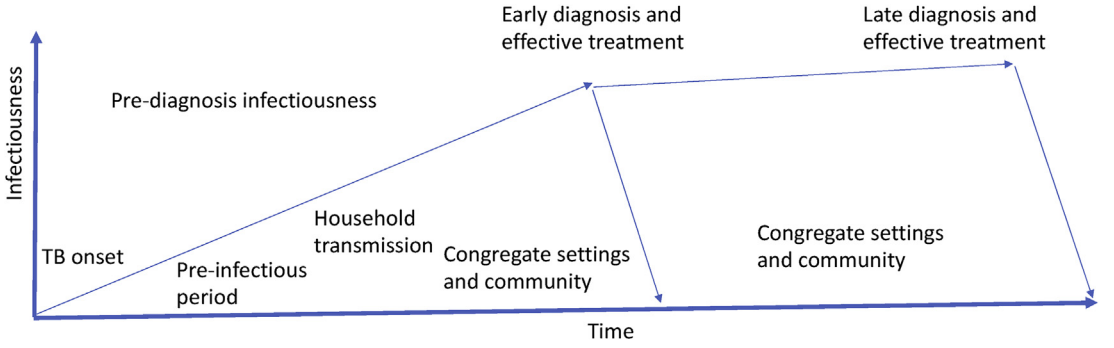

Fig. 1. Progressive TB infectiousness until diagnosis and effective treatment. *Reprinted* with permission of the American Thoracic Society. Copyright © 2019 American Thoracic Society. Riley RL, Mills CC, O'Grady F, et al. Infectiousness of air from a tuberculosis ward. Ultraviolet irradiation of infected air: comparative infectiousness of different patients. Am Rev Respir Dis 1962;85:511-25. The American Journal of Respiratory and Critical Care Medicine is an official journal of the American Thoracic Society.

the time of clinical onset, increasing with the cough, lung cavitation, and sputum smear positivity, to first infect household members sharing common air. But compared with congregate settings and the community, the number of susceptible persons in the household is limited and decreases as the most vulnerable are infected.[19] Despite less individual contact time in the community and nonresidential indoor congregate settings, increasing infectiousness and number of susceptible contacts results in greater spread outside of households, according to some analyses.[19] But as previously emphasized, transmission stops almost immediately with diagnosis and effective treatment of the index case. Active case finding and prompt effective treatment is increasingly recognized as the principal goal for controlling transmission-driven epidemics in high-burden settings. In low-burden settings where reactivation of latent infection predominates, not suspecting TB becomes the norm, and unsuspected cases continue to be the cause of focal outbreaks, for example, in intensive care units, dialysis units, and other clinical settings, as well as homeless shelters, and occasional nursing homes.

FIND CASES ACTIVELY, SEPARATE TEMPORARILY, AND TREAT EFFECTIVELY: A REFOCUSED, INTENSIFIED, ADMINISTRATIVE APPROACH TO TUBERCULOSIS TRANSMISSION CONTROL IN HIGH-BURDEN SETTINGS

If effective treatment renders most cases of TB quickly noninfectious, and most transmission in high-burden settings occurs from patients with unsuspected TB, or unsuspected drug resistance, not on effective treatment, it follows that one administrative approach to transmission control might be active case finding followed by rapid diagnosis and prompt effective treatment based on rapid molecular drug susceptibility testing.[20] This approach, packaged as F-A-S-T (Find cases Actively, Separate temporarily, and Treat effectively), has been piloted in many countries, and some early reports have been published.[21] So far, results indicate that liberally applying rapid molecular diagnostics in a chest hospital in Bangladesh, for example, resulted in the detection of many patients with otherwise unsuspected TB, especially among patients with a past history of TB. Most remarkably, so far, are results from a study of 2 TB hospitals in Russia.[22]

In Voronezh and Petrozavodsk, Russia, for example, investigators implemented a targeted form of F-A-S-T in 2 TBs hospitals to reduce transmission from patients with unsuspected MDR-TB. Hospitalization was prolonged before and after implementation—an average of 20.7 weeks before and 20.0 weeks after implementation.[22] Universal Xpert testing was initiated on all admissions to both the 800-bed and 120-bed facilities, followed by prompt (less than 48 hours) Xpert-directed treatment of DS and rifampin-resistant TB. Before implementation of universal Xpert testing it took an average of 76.5 days before MDR-TB was diagnosed and patients started on effective treatment. They compared the subsequent rate of MDR-TB generation associated with hospitalization to the baseline rate, pre-FAST. Of a total of 450 patients HR sensitive on admission before implementation, 12.2% were diagnosed with MDR-TB within 12 months of finishing treatment. Of the 259 patients isonizid and rifampin (HR) sensitive after implementation of universal molecular testing and prompt, effective treatment, only 3.1% were subsequently diagnosed with MDR-TB within 12 months of finishing treatment—a 78% odds reduction in MDR acquisition through the interruption of transmission by prompt, effective treatment of MDR-TB case in hospital.[22]

However, F-A-S-T is not applicable to all settings, for example, where the prevalence of TB is too low or too high. Where TB is an uncommon cause of cough, cough surveillance is sure to be a cost-ineffective screening strategy, as might any other screening test. Most positive results would likely be false positives under low-prevalence conditions. But in a crowded ambulatory clinic in Mumbai, for example, where transmission from unsuspected cases is occurring in waiting rooms and corridors, there is currently no inexpensive point-of-care test for TB disease that is sensitive, specific, and fast enough to allow routine detection, triage, and prompt treatment. At this time, an achievable strategy might be applying F-A-S-T for all hospital admission in selected high-burden settings, with a goal of promptly detecting and effectively treating otherwise unsuspected TB, and unsuspected drug resistance, thereby eliminating the likely sources of transmission. Measures of success include greater case detection among hospital admissions and a shorter time from entry until the start of effective treatment based on a molecular DST.[20] But even in such settings, questions remain. Asking patients about to be admitted about any cough, or cough for 2 weeks, may be an insensitive and nonspecific screening question in some populations or times of year. A screening chest radiograph with computer-assisted interpretation might detect most transmissible TB in low-HIV settings, such as Peru, but is it affordable and worth the radiation exposure?

OTHER TUBERCULOSIS TRANSMISSION FACTORS AND INTERVENTIONS

TB transmission is complex, involving characteristic of not only the infectious source case but also the organism, the environment, and the host, all of which are important in preventing transmission. **Fig. 2** depicts transmission broadly, listing key variables in each category, and possible interventions that impact transmission.

Source strength. Not all patients with pulmonary TB infect others. Epidemiologic studies have suggested that perhaps only 1 in 3 patients with pulmonary TB infect any contacts. Likewise, Sultan and colleagues[23] found great patient-to-patient variability in infectiousness even when patients were selected for having positive sputum smears and cultures. Likewise, Fennelly was able to detect culturable aerosol in about one-third of smear-positive patients.[24] Sputum smear positivity, cough frequency and strength, sputum viscosity, and ability to generate aerosol have long been considered source strength factors. As discussed, prompt detection and effective treatment (FAST) may be the best way to limit source strength. *Cough hygiene* and its equivalent, wearing *surgical masks*, stops large respiratory droplets from becoming airborne droplet nuclei. Simple surgical face masks worn by patients most of the day reduced transmission to guinea pigs by 56%.[14]

Organisms. Mtb strain virulence is likely a transmission factor but not one that affects transmission control efforts. Organism number and viability are controllable by air disinfection strategies: dilution, extraction, directional airflow, filtration, precipitation, and killing. Although a variety of chemical disinfectants, such as glycol vapors, have been tried in the past, by far the most effective and cost-effective approach to killing airborne pathogens is upper-room germicidal ultraviolet irradiation (GUV), as detailed later.[25,26] Natural ventilation is the most important means of air disinfection, globally, with mechanical ventilation used in more affluent countries.[27,28]

Host resistance. Resistance to TB infection and disease varies by individual innate and adaptive immunity, and through epigenetic influences, but protection is usually incomplete. Exposure to related environmental mycobacteria and leprosy increases resistance. Heavily exposed populations pass on resistance genetically, and possibly epigenetically, so called learned immunity.[29,30] From a transmission control perspective, BCG and a newer vaccine have been shown to convey resistance to infection as well as disease progression, although incomplete.[31] Diabetes, HIV-AIDS, and other illnesses and drugs lower resistance. The growing use of TNF inhibitors is the fastest growing category of therapeutics that often increase risk to TB infection or disease. Of potential practical importance, several host-directed therapies, notably metformin and the statins, may well prevent *Mtb* infection and progression to disease, and these or similar drugs may serve a protective role in the

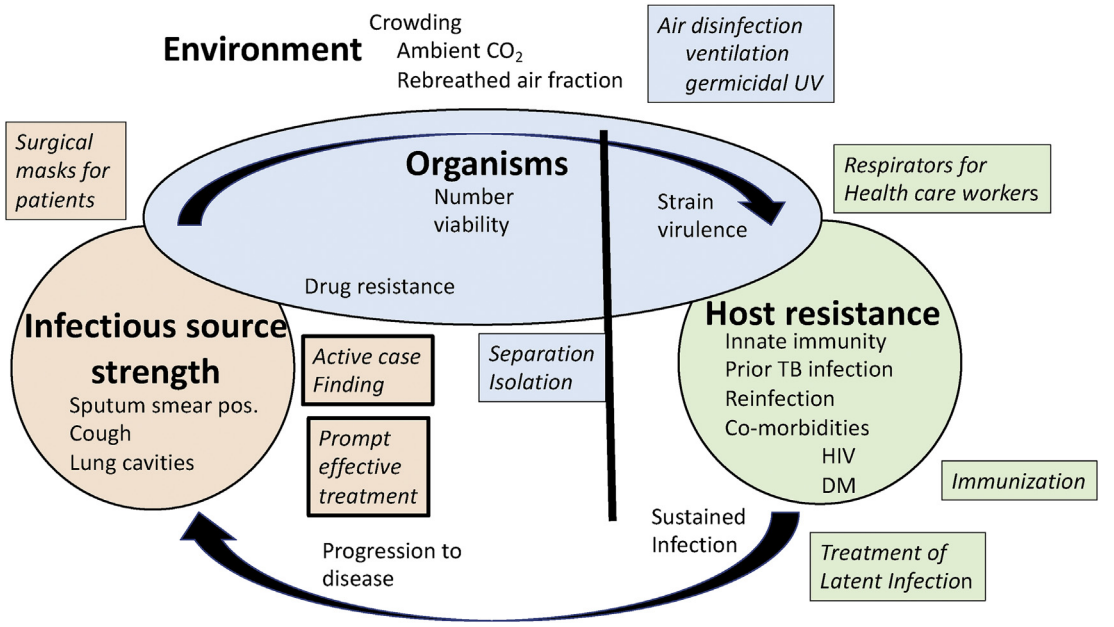

Fig. 2. Transmission factors and potential sites for intervention.

future.[32–34] Treatment of latent infection can prevent progression from infection to disease, but does it reduce the beneficial immunity of infection? There is no direct data, but analogy with BCG immunization suggests that, as hypersensitivity, the estimated 70% protection of previous infection persists long after viable organisms remain.[35]

REDUCING TUBERCULOSIS EXPOSURE FROM UNSUSPECTED SOURCES: THE ROLE OF ENVIRONMENTAL INTERVENTIONS AND RESPIRATORY PROTECTION

As emphasized, persons with infectious pulmonary tuberculosis remain infectious until diagnosed and started on effective therapy. But there are many settings where patients with undiagnosed TB can be anticipated and are not likely to all be promptly diagnosed and started on effective therapy, such as busy emergency rooms and crowded ambulatory waiting areas and corridors. Environmental controls are important in these and other areas.

Natural ventilation. In much of the world where TB is common, natural ventilation is the main form of air disinfection and can be highly effective, but there are many caveats, and there is the new threat of climate change—closed windows because more and more clinical areas are air conditioned and also to keep out polluted air.[36] With a building designed for cross-ventilation, in a warm or temperate climate, and with favorable outside conditions, it is hard to beat the effectiveness, low cost, and sustainability of natural ventilation (**Fig. 3**). Where climate permits, outdoor waiting areas are ideal and largely independent of building design. But many buildings are poorly designed for natural ventilation, with deep interior spaces where air exchange is limited. A common scenario in ambulatory setting are doctor's offices on both sides of a corridor, windows only in the offices, with cross-ventilation that depends on open transom windows above doors when doors are closed, while the corridors themselves becoming crowded waiting areas, as shown in **Fig. 4**. Windows are often closed because of cool night air or for security. Natural ventilation has long been limited to air infiltration in very cold climates, together with prolonged hospitalization and delayed diagnosis, accounting for the hypertransmission of MDR-TB in recent decades in Eastern Europe, Russia, FSU countries, and Central Asia. With global warming, however, similar conditions are becoming commonplace in hot countries, as windows are closed to allow for effective and efficient cooling with ductless air conditioners.[37] In an office occupied by 5 people in South Africa we recently demonstrated the effect of closing an open window and turning on a ductless air conditioner (AC) unit. Within an hour of closing the window ambient CO_2 measurements increased 4-fold with no plateau in sight, indicating comparable increase in risk of an airborne infection, given an infectious source in the room.[38] What are the options when natural ventilation is limited by building design or outside conditions?

In theory, there are 3 alternatives to natural ventilation. *Mechanical ventilation systems* are the norm in most resource rich countries, especially in large

Fig. 3. Crowded waiting area typical of ambulatory clinics in high-burden settings.

Fig. 4. MDR-TB Clinic, Karachi, Pakistan; Tariq Alexander Qaiser, architect. Note the wind scoop design in the main building and a covered outdoor waiting area, both taking full advantage of natural ventilation.

buildings such as hospitals. In poor countries where TB is prevalent, mechanical ventilation is uncommon in public buildings. It is expensive to install in new construction, difficult to retrofit, and expensive to operate and maintain, especially when outdoor air must be heated or cooled. Unless specifically designed for airborne infection control, and maintained, air exchange rates of outdoor air rarely reach the recommended 6-12 room air changes per hour (ACH). When operating optimally, however, mechanical ventilation assures that indoor conditions remain predictable day and night, season to season, independent of outside conditions.[39] Basic mechanical ventilation technology is well understood by trained mechanical engineers, despite often poor maintenance in practice due to administrative neglect.

An alternative air disinfection approach, heavily marketed around the world, is *room air cleaner technology*. Room air cleaners move room air through a filter or alternative germicidal technology (ultraviolet, plasma, etc) designed to remove or kill pathogens.[40] Sales presentations commonly show data proving that contaminated air is nearly completely disinfected when it exits in the device, thanks to their unique technology. What they rarely mention is the actual clean air delivery rate—the flow rate of decontaminated air produced by the device—and how many equivalent ACH that equates to in a given room. Moreover, there is a tendency for room air cleaners, with intake and outlet located near each other, to recapture just decontaminated air (short-circuiting), reducing the *effective* equivalent ACH produced. These devices vary greatly from one to another, but many produce no more than 1 to 2 equivalent ACH in average size rooms. It is a difficult engineering task to move all room air through a single device without unacceptable noise and drafts. In theory, room air cleaners should work, but in practice they tend to be suitable for small rooms where alternative technologies cannot be used.

Another air disinfection technology, highly effective but underused for more than 70 years, is GUV (**Fig. 5**). There are now 2 controlled studies showing 70% to 80% efficacy in reducing *Mtb* transmission under real hospital conditions.[41,42] Application guidelines are now scientifically based, and the technology is recommended in the new WHO TB Infection Control Guidelines.[43] Compared with room air cleaners that try to move room air through a disinfecting device, upper-room GUV disinfects large volumes of room air continuously, relying on air mixing between the upper and lower room to protect room occupants.[44,45] Air mixing can be assured by commonly available low-velocity mixing fans,

Fig. 5. Upper-room GUV fixture in use in a Russian hospital.

rated to produce at least 20 ACH between the upper and lower room. Properly used, GUV technology is safe. Fixtures are designed to deliver GUV to the upper room, blocking spill and reflection into the lower room. The major risk is eye irritation, almost always the result of poor installation, poor fixtures, or accidental direct exposure of workers to GUV in the upper room, such as painting or cleaning.

A major GUV application development is the requirement that fixture manufacturers have their devices independently tested in a lighting laboratory for total GUV output.[42,46] This is required to allow design engineers to dose rooms at approximately 12 mW/m^3 total volume, based on the published and subsequent experiments preventing transmission in a South African hospital. A disadvantage of GUV, compared with mechanical ventilation systems, is that engineers have generally not been trained in its use. Maintenance is not difficult but is necessary to assure sustained function. A manual on GUV maintenance is available in the literature and online in English, Spanish, and Russian: (http://www.stoptb.org/wg/ett/assets/documents/MaintenanceManual.pdf).

GUV is highly cost-effective compared with mechanical ventilation and room air cleaners. Volchenkov and Jensen used a bacterial aerosol to test the air disinfection effectiveness of

mechanical ventilation, 3 different room air cleaners, and GUV in a hospital in Vladimir, Russia, finding that GUV was more than 9 times more cost-effective compared with mechanical ventilation or room air cleaners per equivalent air change.[47] Barriers to the more effective use of GUV as the logical alternative to natural ventilation in high-burden settings include lack of familiarity with the technology, fear (unfounded) of radiation injury, lack of technical expertise to plan installations, lack of locally made high-quality fixtures, unreliable electrical power, and cost of installation and maintenance. A plan for sustainable implementation has been developed for India using an international service company that may solve many of these logistical barriers.[48,49] The rapid development of LED GUV, although years from commercial availability, will enable the use of solar power and battery back-up, addressing the power issue. As global warming leads to greater use of highly efficient cooling through ductless AC, the pairing of upper-room GUV fixtures and wall AC units that also provide excellent air mixing may further stimulate the development of high-quality, lower-cost GUV products.

RESPIRATORY ISOLATION

Respiratory isolation, as defined by the CDC, refers to a combination of administrative policies and environmental controls designed to prevent the spread of infectious droplet nuclei from patient known or suspected to have symptomatic, infectious pulmonary or extrapulmonary TB. Respiratory isolation is expensive to achieve in modern mechanically ventilated buildings because it means controlling and monitoring the pressure differences between rooms and corridors that drive directional airflow, assuring that flow is always entering the isolation room. For that reason, several respiratory isolation rooms are routinely found in hospitals in resource-rich settings, where they are used for a variety of potentially contagious respiratory infections, including patients thought to have TB. Respiratory isolation rooms are rarely found in resource-poor settings not only because of cost and technical limitations but also because of the number of patients who would require isolation if it were available. Instead, cohorting of like patients is the norm in many high-risk settings. For example, in Haiti, a naturally ventilated ward is used for sputum smear-positive patients assumed to have drug-susceptible TB for the initial days or weeks of treatment. For relapse patients in whom MDR-TB is more likely, a simple single-bed room is used, with doors and windows closed and an exhaust fan producing negative pressure (resulting in airflow into the room under the door). Air disinfection is enhanced by an upper-room GUV fixture and mixing fan. With the growing availability of rapid diagnostics and DST, the use of respiratory isolation in hospitals can and should be limited to just a few days as effective treatment is initiated and patients respond clinically.

In low-risk settings for TB, *hospital isolation is often overused*. Because TB has become uncommon and unfamiliar to health care workers and public health departments, it generates greater fear and fear of liability. Low-risk persons with upper lobe infiltrates are often isolated, but if they have no sputum, they remain in isolation based on strict smear-based discharge criteria. Because TB patients need *not* be admitted to hospital to start treatment, and household members have already been exposed, the threshold for discharge home for patients with DS TB once therapy starts should usually be low and not dependent on sputum smear conversion, as emphasized earlier. Smear-positive patients on effective therapy who are responding to therapy can and should be sent home after a few days, if hospitalized at all. Household members will be tested and started on preventive treatment if indicated. Homeless patients and other special situations require individualized treatment and isolation plans. Likewise, public health home quarantine guidelines need to be revised. Although patients with TB responding to effective therapy ought not immediately return to work in day care or a neonatal unit, for example, a few days of treatment is adequate, if they are responding to treatment, coughing less, and feeling better to return to most jobs based on available evidence. TB is a serious infection with systemic symptoms that often justifies time off for recovery but not for transmission control per se.

RESPIRATORS AND SURGICAL MASKS

Air disinfection only works in specific areas where it is applied and is not applied in every high-risk situation, transporting an unsuspected or untreated patient in an elevator or in the back of an ambulance, for example, Respiratory protection is considered the last category of interventions to prevent *Mtb* transmission because they only work when applied, which assumes awareness of risk.[50] Ironically, for that reason, they are most often used by health care workers in the presence of patients on effective therapy who are incorrectly assumed to be still infectious. They are more appropriate for health care workers in the emergency room or ambulatory setting seeing new patients with undiagnosed respiratory symptoms who may be at risk of pulmonary TB. They are

especially important for workers present at cough-generating procedures such as bronchoscopy and sputum induction in both high- and low-burden settings.

The distinction between *respirators* and *surgical masks* is important.[50] *Respirators* are designed to protect the wearer by excluding airborne particles, whereas *surgical masks* are designed to protect a surgical field or others in the room by reducing the production of airborne particles by the wearer. When recommended as an influenza precaution, surgical masks primarily serve as a barrier to touching contaminated surfaces and then touching your own nose or mouth. Although surgical masks block some (probably fewer than 50% depending on the mask) inhaled airborne particles, they are not a substitute for a "fit-tested" disposable or reusable N95 or equivalent respiratory, the filtration material that excludes virtually all airborne particles, allowing particles only around the imperfect face seal.[51] Face seal leak from most disposable respirators ranges from 10% to 20% and much lower if respirators have been qualitatively fit tested and a selection of sizes and models to fit a variety of face shapes is available. Beards make proper fit of ordinary respirators impossible. Persons with facial hair need to use a positive-pressure air-purifying respirator where fit testing is unnecessary, as all leakage is out. Such respirators offer maximum respiratory protection for a variety of applications, including exposure to known highly drug-resistant patients or their laboratory specimens or cultures.

Surgical masks are sometimes used temporarily on patients with known or suspected TB as a form of cough hygiene. Surgical masks are stigmatizing and should be used selectively for short periods *before*, but *not after* effective treatment starts. In human-to-guinea pig transmission experiments, simple over-the-ear surgical masks were 56% effective in preventing transmission when worn most of the day—that is, removed for eating, teeth brushing, etc.[14] Appropriate short-term use of surgical masks includes coughing patients in a waiting room or during transport before diagnosis and treatment or longer if drug resistance is suspected while awaiting laboratory results. Discharging patients on effective therapy with a box of face masks to be worn at home or at work is unnecessary and stigmatizing.

TESTING AND TREATING HEALTH CARE WORKERS FOR TUBERCULOSIS INFECTION AND DISEASE

The details of latent TB infection (LTBI) testing and treatment are discussed elsewhere in this issue. Its relevance to transmission control is mentioned here.

In low-burden settings, testing and treating health care workers for latent infection had long been the norm based on studies of nurses and doctors showing risks 2 or more times that of the general population. But just before the 1985 resurgence of TB, the necessity of ongoing screening was questioned, as conversion rates approached that of the community. With the 1985 to 1992 TB resurgence, worker testing was again emphasized, although Centers for Disease Control published criteria for institutions where testing is not required.[50] Now again, as TB rates in this country are far lower than 1985 rates, the value of ongoing testing for many workers should be reassessed. It is well known that under low-risk conditions, many positive results, TST or Interferon Gamma Release Assay (IGRA), will be false positives. Many 10 mm TST reactions and borderline positive IGRA tests are unlikely to represent TB infection, much less a risk of reactivation. Most "convertors" from just less than to just greater than the positive threshold under low-risk conditions are unlikely to have been recently TB infected—an event that normally cause a much greater immunologic response in an otherwise healthy host. Testing often results in unnecessary radiographs and treatment. Stopping testing, of course, risks missing some true health care worker infections, sometimes the only clue to recent exposure to a patient with unsuspected, untreated TB.

In high-burden settings, testing and treating LTBI, even among health care workers, is rarely done for a variety of reasons: limited resources for testing and treatment, stigma, and a different understanding of TB infection risk among them. Confounding by BCG vaccination makes tuberculin testing difficult to interpret. Although IGRA testing was developed to avoid BCG cross-reactivity, the high cost of IGRA testing and the difficulty of interpreting variable responses, likely representing ongoing exposure, combined with reluctance to accept treatment, has limited implementation. Still, as the ultrasound and other low-burden settings decades ago, health care workers are being exposed, infected, and becoming sick with TB at rates well greater than the general population. The prevention strategies outlined in this article should be implemented. In addition, efforts to develop targeted IGRA testing programs for high-risk workers, evidence-based interpretation algorithms, and practical treatment strategies accompanied by worker education still seem justified. New preventative treatments for drug-resistant infection are needed, possibly including host-directed therapies in the near future.

MORE COMPREHENSIVE, WORLD HEALTH ORGANIZATION EVIDENCE-BASED GUIDELINES

A revised WHO TB transmission control policy has recently been issued, and an accompanying implementation guide is being developed.[43] The policy document is limited by recommendations based on (scarce) hard evidence supplemented by expert opinion, whereas the implementation guide is less constrained, based on experience, with additional practical application advice.

SUMMARY

The focus of traditional TB transmission control needs to change from the patient known to have TB who is believed to be on effective therapy and who is responding to treatment, to interventions to prevent transmission from patients unsuspected of having TB or of having drug-resistant TB, who are not on effective treatment. In high-burden settings, by definition, any patient with new or prolonged cough, or other TB symptoms, should be rapidly "ruled out" for TB. How best to cost-effectively rule out TB with currently available diagnostics is unclear at this time. WHO has defined the properties of an effective "rule-out" test for TB, which is different (highly sensitive, but less specific) than a confirmatory "rule-in" test for the disease. For HIV, rapid tests have served both functions for years. In low-burden settings, most patients with typical but nonspecific TB symptoms will not have the disease, so the challenge for sensitive, but reasonably specific rule-out tests is even greater. The newest molecular diagnostics discussed elsewhere in this issue are both highly sensitive and highly specific, also providing rapid drug susceptibility results to guide initial therapy—but require a sputum specimen—a barrier at the TB screening stage.

As emphasized, effective treatment rapidly stops transmission of drug susceptible and MDR-TB. The "NIX-TB" oral regimen, still at the investigative stage" seem to also rapidly stop XDR-TB transmission in preliminary, as yet unpublished H-GP studies. Once on effective therapy, with evidence of a clinical response, further transmission control interventions are probably not needed, although warranted in settings (hospitals, congregate settings) where vulnerable populations could be exposed, should treatment prove ineffective.

Environmental controls, ventilation and GUV, are an important intervention where unsuspected, untreated, or inadequately treated TB poses a risk. Natural ventilation is the main mode of air disinfection where climate permits, but even in warm countries, its effectiveness is threatened by increasing use of air conditioning, requiring closed windows. The most effective, affordable, and sustainable companion technology (or substitute where natural ventilation is not possible) is GUV, properly planned, installed (using high-quality fixtures and air mixing), commissioned, and maintained according to readily available guidelines. Finally, respiratory protection should refocus limited use of quality, fit-tested respiratory protection for encounters with symptomatic persons at risk for pulmonary TB who are not likely on effective treatment. Surgical masks should be reserved for short-term use before effective treatment starts.

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