Published in final edited form as:

Curr HIV/AIDS Rep. 2013 September ; 10(3): . doi:10.1007/s11904-013-0164-x.

Transmission of Tuberculosis in Resource-Limited Settings

Tejaswi Kompala,

Boston University School of Medicine, 72 E. Concord Street, Boston, MA 02118, USA,
tkompala@gmail.com, Philanjalo Care Centre, Tugela Ferry, South Africa

Sheela V. Shenoi, and

Yale University School of Medicine, 135 College Street, AIDS Suite 323, New Haven, CT, USA,
sheela.shenoi@yale.edu

Gerald Friedland

Yale University School of Medicine, 135 College Street, AIDS Suite 323, New Haven, CT, USA

Abstract

Unrecognized transmission is a major contributor to ongoing TB epidemics in high-burden, resource-constrained settings. Limitations in diagnosis, treatment, and infection control in health-care and community settings allow for continued transmission of drug-sensitive and drug-resistant TB, particularly in regions of high HIV prevalence. Health-care facilities are common sites of TB transmission. Improved implementation of infection control practices appropriate for the local setting and in combination, has been associated with reduced transmission. Community settings account for the majority of TB transmission and deserve increased focus. Strengthening and intensifying existing high-yield strategies, including household contact tracing, can reduce onward TB transmission. Recent studies documenting high transmission risk community sites and strategies for community-based intensive case finding hold promise for feasible, effective transmission reduction. Infection control in community settings has been neglected and requires urgent attention. Developing and implementing improved strategies for decreasing transmission to children, within prisons and of drug-resistant TB are needed.

Keywords

Tuberculosis; Transmission; Resource-limited setting; South Africa; Infection control; Nosocomial; MDR/XDR TB; Ventilation; UV light; Household contact investigation; Health care workers; Intensive case finding; Community; HIV/TB co-infection

Introduction

Tuberculosis (TB) remains a major global health problem, in both HIV-positive and negative populations. The 2012 Global Tuberculosis Report by the WHO estimates 8.7 million new cases of TB during 2011 and 1.4 million deaths from TB. Of these, 430,000

© Springer Science+Business Media New York 2013

gerald.friedland@yale.edu.

Conflict of Interest The authors do not declare any conflicts of interest.

Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent

This article contains reference to studies with human subjects conducted by the authors. Informed consent was obtained from study subjects and the studies were approved by the University of KwaZuluNatal and Yale University.

deaths occurred disproportionately among HIV-positive people [1]. Among the HIV infected population, TB causes 1 in 5 deaths [2].

Globally, TB incidence rates are decreasing in line with the Millennium Development Goal (MDG) of reversing the overall rates and numbers of TB by 2015. However these rates mask the limited progress in some regions [1]. Twentytwo low-income and middle-income, high burden countries account for over 80 % of the world's TB cases [3]. India and China together constitute nearly 40 % of the global TB case burden. The African region holds 24 % of the world's cases, but has the highest incidence rates and mortality per capita worldwide [1].

TB remains a disease of over-burdened, under-resourced populations. Effective treatment regimens for drug sensitive TB have been available for decades, but obstacles in diagnosis, treatment, and infection control allow for ongoing transmission. In sub-Saharan Africa, especially, the HIV epidemic has fueled TB transmission and resulted in the largest TB/HIV co-infected population worldwide as 80 % of TB cases in this region occur in people living with HIV [1]. Further complicating global TB control is increasing numbers and rates of drug resistant TB, the majority of which are now believed to be the result of primary transmission and not necessarily treatment failure [4].

In this review, we consider studies of TB transmission from resource-limited settings worldwide. Our own work is based in South Africa, where TB transmission occurs in the context of widespread HIVinfection. We also consider studies in Asia, the Americas and Europe, where TB transmission is largely independent of HIV infection [1]. Throughout, we promote the common themes of early identification and strong infection control as 2 critical pillars that can limit the transmission of TB.

Infectious airborne droplets are responsible for TB transmission, as had been confirmed in the 1950's with Riley's classic guinea pig studies and repeated more recently by Escombe et al. [5–7]. Transmission is directly related to duration of exposure to airborne infectious particles [8, 9]. Five minutes of talking, or 1 cough, produce equivalent numbers of infectious particles, which can remain airborne for 30 minutes [10•]. When inhaled infectious droplets with *M. tuberculosis* (*M.Tb*) reach the alveoli, infection is established resulting in latent TB infection (LTBI), which is estimated to affect one third of the world's population [3]. Only a small proportion of those latently infected will ever develop active TB [3], become infectious and continue the transmission cycle. This risk of active TB is greatest in specific social and environmental contexts.

Health Care Based Transmission

Health care settings have long been recognized as critically important sites for transmission of *M. Tb*. This was recently and dramatically illustrated in Tugela Ferry in KwaZulu Natal province of South Africa, a poor, rural area of 180,000 traditional Zulu people with high prevalence of HIVand TB. As in many resource-limited settings, the local government hospital inpatient services are large and congested congregate wards. Crowding and poor ventilation are characteristic in inpatient and outpatient settings. Tugela Ferry became the site of recognition, in 2005, of a disastrous epidemic of extensively drug resistant (XDR) TB [11]. Primary transmission within the hospital was strongly suggested, as the majority of patients had not previously been treated for TB; yet most had been hospitalized within the previous 2 years, and cases also occurred among health care workers (HCW). Genotypic analysis revealed similar drug resistant strains in 90 % of the isolates, and an epidemiologic study found that 71 % of the XDR-TB cases had been exposed to at least 1 infectious XDR patient during their hospitalization [12•]. The timing and relationship among hospitalized cases over multiple years indicated many generations of transmission over time [12•].

Growing numbers of cases of drug-resistant TB have been recognized at this site, throughout KwaZulu Natal and other South African provinces, neighboring sub-Saharan African countries and worldwide [13]. Current evidence indicates that multi-drug resistant (MDR) and XDR-TB cases occurring worldwide are largely the result of primary transmission, occurring in both health care and community settings. [4, 14].

Although most attention has been directed towards nosocomial transmission in inpatient wards, risk of TB transmission is present throughout the health care system. A 2010 Peruvian study of an emergency department (ED) in a high burden TB setting highlighted the often overwhelming presence of undiagnosed, untreated, highly infectious patients in waiting rooms and triage areas where minimal infection control procedures are in place [15•]. ED staff had thousands of hours of unrecognized TB exposure; their rates of TB infection were more than 10 times greater than the general population [15•]. Similarly, more than 100 unsuspected, undiagnosed individuals in an outpatient waiting room in Tugela Ferry were found to have smear and culture positive TB over a 2 year period, that would have gone without recognition or action [16]. Hospitals throughout the developing world are over-burdened with potentially infectious patients. Without rapid diagnostics or infection control policies in place, every health care facility has the potential to contribute to the local and global TB epidemic.

Infection Control in the Healthcare Setting

Infection control plays a critical and often underappreciated and poorly implemented role in limiting transmission. Unrecognized TB and poor ventilation of patient areas are major determinants of TB transmission within health care facilities. While resource-limited settings face challenges due to high disease burden and limited funding, infection control recommendations can be modified accordingly and implemented (see Table 1 for summary of recommendations). The Centers for Disease Control and the WHO have established updated infection control guidelines for both resource-rich and resource-poor settings, to emphasize the critical responsibility of health care systems in limiting TB transmission. The guidelines recommend an approach to improving infection control at multiple levels: administrative, environmental, and personal [17]. The infection control strategies discussed here should be used together in synergistic combination to reduce health care associated transmission, and require ongoing monitoring. Although not all available in resource-limited settings, and not fully evaluated to demonstrate efficacy, an array of combined strategies can still be assembled and usefully employed to reduce airborne transmission even in such settings [18].

Administrative—Stronger infection control policies need to be implemented at national and facility levels, with common and transparent goals. At the facility level, designation of trained TB infection control teams is essential, with responsibility for promoting, implementing and enforcing infection control policies with consistent monitoring and evaluation. Example policies are noted (Table 1), and include cough hygiene education for all patients. Of note, a recent study in South Africa evaluated the use of simple surgical masks on MDR-TB patients, and found a 56 % decreased risk of TB transmission during their use, supporting this as a simple, low cost, and available intervention to reduce transmission [19•]. Other responsibilities include patient triage, separation of suspects, provision of care, and referral of TB suspects to TB programs, promoting shortened hospital stays, and shifts to outpatient treatment when possible [20]. Administrative strategies further include reducing diagnostic delays by demanding and implementing more efficient lab testing and result notification, and establishing and monitoring policies and practice for supporting HCW [21•].

Environmental—Effective ventilation is necessary for infection control but resource-limited settings face challenges due to facility limitations and budget constraints. The recommended 12 air changes per hour (ACH) can be achieved through both natural and mechanical ventilation [17, 22]. Prohibitive installation and maintenance costs, however, limit mechanical ventilation use in resource-limited settings [23]. Even when in use, mechanical ventilation often provides insufficient ACH [17, 24, 25]. For hospitals in which reliable mechanical ventilation and respiratory isolation are not an option, natural ventilation is a low-cost, highly effective alternative in temperate and tropical climates, home to most of the high burden TB countries. Escombe et al. evaluated differences in ventilation and TB risk in Peruvian hospitals that were either naturally or mechanically ventilated [23]. Naturally ventilated rooms had more than double the ACH than rooms mechanically ventilated, and had 18 times more ACH than rooms without ventilation. The potential TB transmission risk was significantly lower in naturally ventilated settings than in mechanically ventilated rooms [23]. A similar study of hospitals in Thailand demonstrated inadequate ventilation from the mechanical system, and significantly improved airflow with natural ventilation [24]. In the public hospital of Tugela Ferry, opening doors and windows significantly improved ventilation of the TB ward compared with mechanical ventilation [26].

Another low-cost, high-yield intervention to limit transmission is ultraviolet germicidal irradiation (UVGI). UV light fixtures that disinfect a patient space have long been considered an infection control tool. Especially in cold climates where natural ventilation may be less feasible, UV light irradiation presents an opportunity to sanitize sizeable air volumes, with large potential benefit for little cost [20]. Recent studies in South America and South Africa have demonstrated reductions in TB transmission by 70-80 % [21•, 27]. Upper room UVGI is especially well suited for neglected patient spaces—waiting areas and emergency departments—where infectious particles can be removed safely and at rates equivalent to mechanical ventilation [21•]. To successfully implement UV light systems, experts need to further develop and promote high quality, low cost fixtures that can be used in resource-limited settings.

Personal—Routine use of personal protection is recommended in addition to administrative and environmental infection controls. Personal protection includes regular use of respirators, with proper fit testing and a facility-wide monitoring system that encourages routine use. Though there is limited evidence, the WHO supports use of the personal N95 respirator as the best available method to prevent inhalation of infectious TB droplets [17]. Resource-limited settings face challenges in the regular use of disposable respirators. Frequently in high TB burden locations where they are most valuable, respirators are prohibitively expensive, ranging from US\$1 to \$2 each. An innovative TB program in Lesotho has piloted a non-disposable respirator that lasts indefinitely and requires minimal maintenance as a cost-effective alternative [21•]. A further major challenge is to ensure regular staff use of respirators, particularly in already uncomfortable climates. The use of simple surgical masks worn by patients in conjunction with respirators worn by staff may limit transmission in the health care setting. Additionally, all HCW should participate in mandatory, regular screening for TB and be encouraged to seek care for symptoms. Confidential HIV testing should be offered to all staff; those who are positive should have immediate and facilitated access to treatment, and placement in clinical areas with lower TB risk [17, 20, 21•].

Health Care Workers (HCW)

Studies of health care related transmission often focus on HCWs as a reflection of TB transmission rates occurring in health care facilities. Studies worldwide have conclusively

demonstrated that HCWs experience higher rates of TB infection [28-30]; the risk is greatest in low and middle-income countries that experience the largest burden of TB disease [29]. South African HCWs have been found to have higher rates of drug susceptible, MDR, and XDR-TB disease than the non-HCW population [31•, 32]. In one study of KwaZulu-Natal Province South Africa, HCW were 6 times more likely to be hospitalized with MDR-TB, and 7 times more likely to be hospitalized with XDR-TB, than the non-HCW population [31•]. This risk must be addressed with work place infection control measures designed to protect the health of both patients and those entrusted with their care [33]. HCWs have the worrisome potential to transmit TB to patients when not aware or afraid to disclose their disease because of stigma and employment concerns [34]. Though they experience greater transmission risk because of long cumulative periods of exposure, HCWs also represent a population of special concern because highly trained nurses and clinical staff are often in short supply in the developing world; the limited workforce is further threatened by both TB and fear of acquiring TB [19•, 35].

Community Based Transmission

TB transmission extends beyond health care settings and frequently occurs in community settings [18]. While often overshadowed by fears of health facility related transmission, unsuspected and undiagnosed TB is routinely transmitted in the home and other community arenas, particularly in high prevalence settings [36, 37•, 38•, 39••]. Documentation of community TB transmission and development, implementation, and monitoring of infection control policies in congregate community settings are critically important in TB infection control, though remain poorly developed [17]. Several studies of community based case finding and treatment have demonstrated that a focus on community transmission can be both clinically and cost effective [39••, 40•, 41], and should serve as models for needed community-based programs.

Impact of Social and Economic Living Conditions on TB Transmission

Recent studies in the urbanized townships of Cape Town, South Africa, have examined indoor daily interactions and their role in transmission risk. Four indoor locations – household, crèche/school, workplace, and public transport – accounted for 97 % of time spent indoors in this study population (Fig. 1) [10•, 37•]. Among these, transport and household settings were identified as 2 transmission “hotspots” [37•, 42]. In these locations the presence of multiple inter-generational contacts, often in crowded and poorly ventilated conditions, may allow for the mixing and exposure that are necessary for sustained community transmission of TB to occur. Some parallels have also been found between age and rates of TB disease. Youth are increasingly exposed to social contacts as they progress into adolescence and young adulthood [37•, 43]. Youths aged 10–19 were found to have the highest number of non-household close contacts; youth interacted with 40 % more contacts in the township population than similar age groups in industrialized European countries [10•]. The increased social interaction in the adolescent age group parallels increased rates of TB infection, suggesting that quantifiable exposure to infectious adults plays a role in transmission [10•].

In impoverished rural areas of South Africa, where transport, work places, and other congregate settings are more limited, traditional huts and homes have recently been shown to have extremely poor ventilation and corresponding high transmission risk when an infectious individual is present in the household (Table 2) [44]. Not surprisingly, in the recent epidemic of XDR-TB in rural South Africa, the majority of patients lived in typical, poorly ventilated dwellings, shared with susceptible household contacts [38, 44].

Household Transmission and Screening

Household contacts of an active TB case are at high risk for TB transmission due to long periods of exposure. Household contact tracing is an effective and efficient strategy for case finding, allowing for diagnosis and treatment of large numbers of high-risk populations at an earlier stage of disease, thereby reducing morbidity, mortality, and ongoing transmission.

A household case detection program in South Africa revealed culture confirmed TB prevalence rates that were nearly 15 times greater among household contacts of newly diagnosed TB patients than non-contact households [39••]. Similar household risk has been demonstrated in primary transmission of drug resistant strains. In rural Tugela Ferry, rates of MDR, and XDR-TB were 30–40 fold higher in household contacts than the general population [38•]. In Peru, household contacts of MDR and XDR-TB patients were also found to have higher incidence rates of TB disease [45, 46]. As HIV prevalence in Peru is significantly lower than in sub-Saharan Africa, these results demonstrate that, as with drug sensitive TB, MDR, and XDR-TB can be spread through primary transmission in household settings in both HIV-positive and negative populations. These studies highlight the importance of strong household case detection programs, regardless of regional HIV, or drug resistant TB prevalence. Since transmission may occur concurrently with index case diagnosis, thorough, *early* household contact investigation can identify many cases of transmitted disease and represents an effective public health strategy to limit further transmission [38•].

Community Transmission and Intensive Case Finding

Apart from household contact tracing, case finding at other community sites is valuable but not well developed. Intensive case finding strategies are being employed in community settings with mixed or only preliminary results. In one community randomized study in urban Harare, Zimbabwe, a mobile van strategy detected significantly more active TB cases than door-to-door visiting, resulting in a significant decrease in community prevalence of TB [40•]. A similar community based enhanced case finding trial in Zambia and South Africa, however, was less effective as an active case finding strategy and in reducing incidence of TB infection in children [47, 48]. A study being carried out in a remote rural area of KwaZulu-Natal, South Africa, employs a mobile team to identify difficult to reach populations by providing integrated TB and HIV screening at congregate settings such as pension pay points, municipality meetings, and taxi ranks. The strategy has identified substantial numbers of community residents with previously undiagnosed drug resistant and susceptible TB. Impact on clinical outcomes and TB prevalence is ongoing but not yet known [49]. Wide implementation of intensive case finding in community settings could have rapid effects on TB transmission and disease, but additional data about effectiveness is needed.

Special Populations

Children

In areas with high TB burden, children suffer major morbidity and mortality but are often under recognized and under reported, in part because of difficulties in diagnosis of childhood TB. While adults may have active disease from reactivation of latent infection *or* recent transmission, TB in children is generally a reflection of infection within the past year [50]. Children with TB, therefore, serve as a marker for recent transmission of TB within a community. The duration of exposure to infectious adults dictates children's transmission risk [51]. Because during the early years most indoortime is spent within the household, childhood transmission has been assumed to be almost exclusively from adults in the household [52]. Studies using genotypic analysis, however, have shown that children may

become infected by strains beyond the household [52]. Frequently, households are composed of an array of adults, many of whom are only present transiently and may not be identified as index cases or household members. Early diagnosis and treatment of infectious adults shortens the period of infectivity and benefits children by reducing exposure [51]. It is important to note as well, although not generally appreciated, that TB may be transmitted among children in health care facilities. A recent example of such transmission of XDR-TB in Tugela Ferry emphasizes the need for infection control within pediatric units in high prevalence TB areas [53].

Prisons

Prisoners and prison staff suffer from extremely high burdens of TB worldwide. Prison conditions, especially in the developing world, create a breeding ground for both drug-susceptible and drug-resistant TB [54]. Sick and healthy prisoners cohabit and compete for the same resources, with limited ventilation, minimal concern for their well-being and limited or no access to health care [55]. Rates of active TB disease are astonishingly high; 22.7 % of Zambian prisoners had active TB, and 42.1 % of Tanzanian prisoners within the first 2 years of incarceration. In Botswana, the point prevalence was 3797/100,000 among prisoners and in Malawi the prevalence was 5142/100,000 [54]. One study of a South African prison predicted an annual TB transmission risk of 90 % [56]. Unpublished data from Tugela Ferry reveals TB case notification rates of >2600/100,000 in local prisons. The WHO has made recommendations regarding the appropriate screening and health care of prisoners, but these are not implemented in the majority of developing world prisons [54]. Prisoners and prison staff interact with the general population; infection control deficiencies that allow rampant transmission of TB within the prison also result in spread once outside of the prison environment and increase TB prevalence in the surrounding community [54]. Models predict that active case finding [56] and annual sputum and PCR testing for active TB would be effective strategies for reducing TB among the prison population [55], but serious improvements in prison conditions and attention to political and human rights neglect are necessary to achieve international standards and reduce TB transmission [54].

Multi-Drug Resistant Tuberculosis

XDR-TB has emerged as a global challenge; cases have now been reported from 84 countries worldwide [4]. In South Africa and globally, MDR-TB is even more prominent, with more than 8000 cases estimated to occur annually in South Africa [4] and, most recently, more than 600,000 cases globally [57].

MDR-TB, including XDR, is most heavily concentrated in 27 high burden countries. China and India together produce almost 50 % of the world's MDR-TB case burden; the remainder of cases is concentrated in Eastern Europe, Central Asia and sub-Saharan Africa [4]. The present MDR-TB epidemic is being fueled largely by ongoing unrecognized primary transmission, now estimated to be responsible for 80 % of cases [4]. The WHO 2010 MDR-TB update reports only 7 % of the then estimated 440,000 MDR-TB cases globally were diagnosed and reported, and less than 3 % of those were enrolled in treatment [4], leaving inexcusably high numbers of undiagnosed and untreated MDR-TB patients to perpetuate transmission.

MDR and XDR-TB can be generated in environments throughout the world by TB treatment failure with subsequent transmission of resistant organisms beyond national borders. Globalization and international travel contribute to widespread dissemination of resistant organisms. Poor airborne infection control and delayed TB diagnosis in any region can present an international health challenge. A single disquieting example illustrates this point.

A South African born nurse with employment history in Tugela Ferry subsequently worked in the UK as a nurse for years, before presenting to a regional hospital and after substantial delay, was ultimately found to have MDR-TB [34]. Genotypic analysis of the patient's organism indicated likely acquisition in Tugela Ferry [34].

At present, high burden countries often rely on symptom-based or smear-based diagnoses alone. Culture results, and therefore drug sensitivity testing (DST), are unavailable for the majority of MDR cases [13, 58], resulting in inappropriate and ineffective treatment and ongoing primary transmission. Even for those who are correctly diagnosed, treatment poses a major challenge; the most effective treatment delivery programs achieve cure rates of only 60 % [21]. Overall cost of care for MDR treatment is at least 10 times greater than that for drug susceptible TB and drugs alone are 50–200 times more expensive [4]. The WHO estimates that the cost to treat an estimated 1.3 million MDR-TB cases in 2015 will be 16.2 billion US dollars [4].

The present MDR-TB challenge demands improvements in diagnosis and treatment [21]. Rapid diagnosis and recognition of drug resistance is required to initiate correct treatment and reduce transmission; culture with drug sensitivity testing should be performed routinely, with aid and uptake of new rapid technologies like GenXpert. Treatment programs should shift from hospital-based to community based [41] to limit nosocomial transmission, especially in areas of high HIV prevalence where contacts may be increasingly vulnerable to infection. A novel community based MDR-TB treatment program in South Africa, limiting inpatient stay and utilizing community health workers to provide treatment in patients' homes, has been shown to be an effective strategy with high treatment success and reduced lost to follow-up, likely reducing transmission in the hospital and community [41]. High rates of MDR-TB and XDR-TB in household contacts of known cases [38, 45, 46] make contact tracing and diagnosis of unsuspected disease a high-priority strategy.

Conclusions

Airborne transmission is the only mode of acquisition of MTB infection worldwide. Concerted efforts to limit transmission through early diagnosis, effective treatment, and implementation of strong infection control programs may reduce health care-based and community transmission. Airborne infection control is critically important in health care settings and can be implemented and achieved even in resource-limited settings. Increased attention and implementation is needed to protect both patients and HCW. In addition to health care facility elimination of TB transmission, increased emphasis should be placed on demonstrating effectiveness and widely implementing community screening and treatment strategies, particularly in high prevalence resource-limited settings. Successful early case finding and treatment in the community setting can prevent further spread of disease. While awaiting widespread availability of new and promising diagnostic tools and treatment, resources enabling enhanced use of existing strategies can reduce the transmission of drug-susceptible and drug-resistant TB and the associated morbidity and mortality in the most vulnerable populations, including children and prisoners.

Acknowledgments

The authors wish to thank the Doris Duke Charitable Foundation International Clinical Research Fellowship (ICRF) Program (TK) and the NIAID K23 Career Development Award Program (SS)

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

1. World Health Organization. Global Tuberculosis Report. World Health Organization; Geneva, Switzerland: 2012.
2. World Health Organization. World Health Organization HIV/TB Facts. World Health Organization; Geneva, Switzerland: 2011.
3. Lawn SD, Zumla AI. Tuberculosis. *The Lancet*. 2011; 378:57–72.
4. World Health Organization. Multidrug and extensively drugresistant tuberculosis (M/XDR-TB): 2010 global report on surveillance and response. WHO; Geneva, Switzerland: 2010.
5. Riley R. Aerial dissemination of pulmonary tuberculosis. *Am Rev Tuberc*. 1957; 76:931–41. [PubMed: 13488004]
6. Riley R, Mills C, 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. [PubMed: 14492300]
7. Escombe AR, Moore DA, Gilman RH, et al. The infectiousness of tuberculosis patients coinfecting with HIV. *PLoS medicine*. 2008; 5:188.
8. Wells, W. Airborne contagion and air hygiene. Harvard University Press; 1955.
9. Riley RL, Wells WF, Mills CC. Air hygiene in tuberculosis: quantitative studies of infectivity and control in a pilot ward. *Am Rev Tuberc*. 1957; 75:420–31. [PubMed: 13403171]
10. Johnstone-Robertson SP, Mark D, Morrow C, et al. Social mixing patterns within a South African township community: implications for respiratory disease transmission and control. *Am J Epidemiol*. 2011; 174:1246–55. [PubMed: 22071585] This study examines social interactions among township contacts, varying by physical proximity and location, and the potential relationship with respiratory spread of disease.
11. Gandhi N, Moll A, Sturm AW. Extensively drug-resistant tuberculosis (XDR-TB) as a cause of death among TB/HIV co-infected patients in a rural area in South Africa. *Lancet*. 2006; 368:1575–80. [PubMed: 17084757]
12. Gandhi NR, Weissman D, Moodley P, et al. Nosocomial transmission of extensively drug-resistant tuberculosis in a rural hospital in South Africa. *J Infect Dis*. 2013; 207:9–17. [PubMed: 23166374] This study confirms nosocomial transmission in the XDR TB outbreak in Tugela Ferry based on genotypic and epidemiologic analysis.
13. Moodley P, Shah NS, Tayob N, et al. Spread of extensively drugresistant tuberculosis in KwaZulu-Natal Province, South Africa. *PLoS medicine*. 2011; 6
14. Zhao Y, Xu S, Wang L, et al. National survey of drug-resistant tuberculosis in China. *N Engl J Med*. 2012; 366:2161–70. [PubMed: 22670902]
15. Escombe AR, Huaroto L, Ticona E, et al. Tuberculosis transmission risk and infection control in a hospital emergency department in Lima, Peru. *Int J Tuberc Lung Dis*. 2010; 14:1120–6. This study highlights the presence of unrecognized TB transmission in traditionally neglected patient spaces, including emergency departments.
16. Sheno SV, Brooks RP, Catterick K, Moll AP, Friedland GH. 'Cough officer' nurses in a general medical clinic successfully detect drug-susceptible and resistant tuberculosis. *Pub Health Act*. 2013; 3(1):46–50.
17. World Health Organization. WHO Policy on TB infection control in health-care facilities, congregate settings and house-holds. World Health Organization; Geneva: 2009. Available at: http://whqlibdoc.who.int/publications/2009/9789241598323_eng.pdf. [Accessed April 2013]
18. Basu S, Friedland G, Medlock J, et al. Averting epidemics of extensively drug-resistant tuberculosis. *Proc Natl Acad Sci USA*. 2009; 106:7672–7. [PubMed: 19365076]
19. Dharmadhikari AS, Mphahlele M, Stoltz A, et al. Surgical face masks worn by patients with multidrug-resistant tuberculosis: impact on infectivity of air on a hospital ward. *Am J Respir Crit Care Med*. 2012; 185:1104–9. [PubMed: 22323300] This study demonstrated that the simple intervention of surgical masks on hospitalized MDR-TB patients can reduce transmission risk by 56%

20. Sheno SV, Escombe AR, Friedland G. Transmission of drug-susceptible and drug-resistant tuberculosis and the critical importance of airborne infection control in the era of HIV infection and highly active antiretroviral therapy rollouts. *Clin Infect Dis*. 2010; 50(Suppl 3):S231–7. [PubMed: 20397953]
21. Nardell E, Dharmadhikari A. Turning off the spigot: reducing drug-resistant tuberculosis transmission in resource-limited settings. *Int J Tuberc Lung Dis*. 2010; 54:1233–43. [PubMed: 20843413] This review provides a summary of the challenges in controlling transmission of drug-resistant TB, and offers strategies to limit transmission
22. Jensen P, Lambert L, Iademarco M, Ridzon R. Guidelines for preventing the transmission of *Mycobacterium tuberculosis* in health-care settings. *Morb Mortal Wkly Rep*. 2005; 54:1–141.
23. Escombe AR, Oeser CC, Gilman RH, et al. Natural ventilation for the prevention of airborne contagion. *PLoS medicine*. 2007; 4:e68. [PubMed: 17326709]
24. Jiamjarasrangsi W, Bualert S, Chongthaleong A, et al. Inadequate ventilation for nosocomial tuberculosis prevention in public hospitals in Central Thailand. *Int J Tuberc Lung Dis*. 2009; 13:454–9. [PubMed: 19335950]
25. Menzies D, Fanning A, Yuan L, et al. Hospital ventilation and risk for tuberculous infection in Canadian health care workers. *Ann Intern Med*. 2000; 133:779–89. [PubMed: 11085840]
26. Friedland, G.; Moll, A.; Sheno SV., et al. Extensively and multidrug resistant tuberculosis (XDR/MDR TB) in Tugela Ferry, South Africa: five years later; 43rd Union World Conference on Lung Health: 2012; Kuala Lumpur, Malaysia. 2012;
27. Escombe AR, Moore DA, Gilman RH, et al. Upper-room ultraviolet light and negative air ionization to prevent tuberculosis transmission. *PLoS Med*. 2009; 6:e43. [PubMed: 19296717]
28. Joshi R, Reingold AL, Menzies D, Pai M. Tuberculosis among health-care workers in low- and middle-income countries: a systematic review. *PLoS medicine*. 2006; 3:e494. [PubMed: 17194191]
29. Menzies D, Joshi R, Pai M. Risk of tuberculosis infection and disease associated with work in health care settings. *Int J Tuberc Lung Dis*. 2007; 11:593–605. [PubMed: 17519089]
30. Sotgui G, Arbore AS, Cojocariu V, et al. High risk of tuberculosis in health care workers in Romania. *Int J Tuberc Lung Dis*. 2008; 12:606–11. [PubMed: 18492325]
31. O'Donnell MR, Jarand J, Loveday M, et al. High incidence of hospital admissions with multidrug-resistant and extensively drug-resistant tuberculosis among South African health care workers. *Ann Intern Med*. 2010; 153:516–22. [PubMed: 20956708] This study demonstrates the overwhelming TB risk to South African health care workers, with a 6-fold increase in MDR-TB and 7-fold increase in XDR-TB compared with the general population.
32. Kranzer K, Bekker LG, van Schaik N, et al. Community health care workers in South Africa are at increased risk for tuberculosis. *S Afr Med J*. 2010; 100:224–6. [PubMed: 20459967]
33. Friedland G. Protecting Health care workers; the critical role of airborne infection control, Editorial. *Int J Tuberc Lung Dis*. 2008; 12:585. [PubMed: 18492321]
34. Cooke GS, Beaton RK, Lessells RJ, et al. International spread of MDR TB from Tugela Ferry, South Africa. *Emerg Infect Diseases*. 2011; 17:2035–7. [PubMed: 22099091]
35. Kanjee Z, Amico KR, Li F, et al. Tuberculosis infection control in a high drug-resistance setting in rural South Africa: information, motivation, and behavioral skills. *J Infect Public Health*. 2012; 5:67–81. [PubMed: 22341846]
36. Basu S, Andrews JR, Poolman EM, et al. Prevention of nosocomial transmission of extensively drug-resistant tuberculosis in rural South African district hospitals: an epidemiological modelling study. *Lancet*. 2007; 370:1500–7. [PubMed: 17964351]
37. Wood R, Racow K, Bekker LG, et al. Indoor social networks in a South African township: potential contribution of location to tuberculosis transmission. *PloS One*. 2012; 7:e39246. [PubMed: 22768066] This study examines the nature and amount of time spent within indoor locations in an urban Africa setting; a few hotspots – households, school/creche, work, transport – contribute the majority of indoor time and may drive TB transmission in the community.
38. Vella V, Racialbuto V, Guerra R, et al. Household contact investigation of multidrug-resistant and extensively drug-resistant tuberculosis in a high HIV prevalence setting. *Int J Tuberc Lung Dis*. 2011; 15:1170–5. [PubMed: 21943840] This study identified high rates of primary transmission

of drug-resistant TB to household contacts of index cases, emphasizing the importance of early, thorough contact tracing to limit transmission.

- 39•. Shapiro AE, Variava E, Rakgokong MH, et al. Community-based targeted case finding for tuberculosis and HIV in household contacts of patients with tuberculosis in South Africa. *Am J Respir Crit Care Med*. 2012; 185:1110–6. [PubMed: 22427532] This study found increased rates of TB in household contacts of index patients, but emphasizes that sensitive diagnostic tools are necessary, as many cases would not have been identified through AFB smear alone.
- 40•. Corbett EL, Bandason T, Duong T, et al. Comparison of two active case-finding strategies for community-based diagnosis of symptomatic smear-positive tuberculosis and control of infectious tuberculosis in Harare, Zimbabwe (DETECTB): a cluster-randomized trial. *The Lancet*. 2010; 376:1244–53. This study found an active case finding strategy employing mobile vans in an urban African community to be effective at identifying TB cases and reducing TB prevalence rates over time.
41. Brust JC, Shah NS, Scott M, et al. Integrated, home-based treatment for MDR-TB and HIV in rural South Africa: an alternate model of care. *Int J Tuberc Lung Dis*. 2012; 16:998–1004. [PubMed: 22668560]
42. Andrews JR, Morrow C, Wood R. Modeling the role of public transportation in sustaining tuberculosis transmission in South Africa. *Am J Epidemiol*. 2013; 177:556–61. [PubMed: 23423215]
43. Middelkoop K, Bekker LG, Liang H, et al. Force of tuberculosis infection among adolescents in a high HIV and TB prevalence community: a cross-sectional observation study. *BMC Infect Dis*. 2011; 11:156. [PubMed: 21631918]
44. Lygizos M, Shenoi SV, Brooks R, et al. Natural ventilation reduces high TB transmission risk in traditional homes in rural KwaZulu-Natal, South Africa. *BMC Infect Dis*. 2013; 13:300. [PubMed: 23815441]
45. Becerra MC, Appleton SC, Franke MF, et al. Tuberculosis burden in households of patients with multidrug-resistant and extensively drug-resistant tuberculosis: a retrospective cohort study. *Lancet*. 2010; 377:147–52. [PubMed: 21145581]
46. Grandjean L, Crossa A, Gilman RH, et al. Tuberculosis in house-hold contacts of multidrug-resistant tuberculosis patients. *Int J Tuberc Lung Dis*. 2011; 15:1164–9. i. [PubMed: 21943839]
47. Ayles, H.; Godfrey-Faucet, P.; Byers, N., et al. The ZAMSTAR Study – Community and household interventions to reduce tuberculosis in Zambian and South African communities; 42nd Union World Conference on Lung Health: 2011; Lille, France. 2011;
48. Claassens M, van Schalkwyk C, den Haan L, et al. High prevalence of tuberculosis and insufficient case detection in two communities in the Western Cape, South Africa *PLoS Med*. 2013; 8:e58689.
49. Shenoi, SV.; Moll, AP.; Mntambo, AQ., et al. High yield from community-based intensive case finding (CBICF) for TB-HIV in rural South Africa; International Union Against TB and Lung Disease: November 2012; Kuala Lumpur. November 2012;
50. Wallgren A. The time-table of tuberculosis. *Tubercle*. 1948; 29:245–51. [PubMed: 18101320]
51. Wood R, Johnstone-Robertson S, Uys P, et al. Tuberculosis transmission to young children in a South African community: modeling household and community infection risks. *Clin Infect Dis*. 2010; 51:401–8. [PubMed: 20604716]
52. Schaaf HS, Michaelis IA, Richardson M, et al. Adult-to-child transmission of tuberculosis: household or community contact? *Int J Tuberc Lung Dis*. 2003; 7:426–31. [PubMed: 12757042]
53. Thomas TA, Shenoi SV, Heysell SK, et al. Extensively drug-resistant tuberculosis in children with human immunodeficiency virus in rural South Africa. *Int J Tuberc Lung Dis*. 2010; 14:1244–51. [PubMed: 20843414]
54. O'Grady J, Hoelscher M, Atun R, et al. Tuberculosis in prisons in sub-Saharan Africa-the need for improved health services, surveillance and control. *Tuberculosis*. 2011; 91:173–8. [PubMed: 21251881]
55. Winetsky DE, Negoescu DM, DeMarchis EH, et al. Screening and rapid molecular diagnosis of tuberculosis in prisons in Russia and Eastern Europe: a cost-effectiveness analysis. *PLoS medicine*. 2012; 9:e1001348. [PubMed: 23209384]

56. Johnstone-Robertson S, Lawn SD, Welte A, et al. Tuberculosis in a South African prison – a transmission modelling analysis. *S Afr Med J*. 2011; 101:809–13. [PubMed: 22272961]
57. World Health Organization. World Health Organization; Geneva, Switzerland: 2013. What is multidrug-resistant tuberculosis and how do we control it?. Available at <http://www.who.int/features/qa/79/en/index.html> [Accessed April 2013]
58. Li X, Zhang Y, Shen X, et al. Transmission of drug-resistant tuberculosis among treated patients in Shanghai, China. *J Infect Dis*. 2007; 195:864–9. [PubMed: 17299717]

Fig. 1.

Number of total contacts and time spent in 11 indoor locations in a South African township. Adapted from: Wood R, Racow K, Bekker LG, et al. Indoor social networks in a South African township: potential contribution of location to tuberculosis transmission. PloS one. 2012;7:e39246. Available at <http://www.plosone.org/static/license;jsessionid=B3710233547C96F1E8CE5018429405CA> Accessed April 2013

Table 1**Airborne infection control recommendations in resource-limited-settings**

Health Care Facilities	
Administrative	• Designate TB infection control team to promote control policies and monitor implementation within health care facilities and health system
Environmental	• Implement and emphasize use of combinations of strategies
Personal	• Optimize existing space and advise new constructions and renovations
	• Implement organized patient screening, triage, separation of infectious patients, and provision of care
	• Limit possibilities for transmission by instructing cough hygiene, shortening hospital stays, shifting to outpatient treatment when possible
	• Reduce diagnostic delays by improving lab efficiency and using new diagnostic technology
	• Support health care workers by providing regular screening and treatment for HIV and TB
	• Utilize natural ventilation when possible, in patient wards, clinics, and waiting areas
	• Design new or renovate facilities that improve patient flow and ventilation
	• Use ultraviolet germicidal irradiation fixtures, especially when adequate ventilation cannot be achieved
	• Expand and encourage use of personal respirators
	• Use simple surgical masks for patients entering the health care facility
Community Settings	
Administrative	• Engage in screening for HIV and TB (including prisons, homeless shelters, households)
Environmental	• Increase awareness of TB control policies among policy-makers beyond health care settings
Personal	• Include congregate settings in nation-wide case finding and surveillance activities
	• Encourage congregate events to take place outdoors with good ventilation when possible
	• Encourage ventilation on public transport
	• Educate on cough etiquette and respiratory hygiene
	• Implement household level contact tracing programs
	• In long-term stay facilities (prisons), screen individuals for TB and appropriately refer to TB care
	• Implement Isoniazid preventive therapy to HIV+ individuals without TB symptoms and to children 5 y who are contacts of individuals with drug susceptible TB
	• Comply with national guidelines for ventilation in public buildings, and with specific recommendations for prisons
	• Optimize ventilation by opening windows and doors
	• Isolate patient's living space when possible (e.g., own bedroom or hut)
	• Use ultraviolet germicidal irradiation fixtures in spaces where adequate ventilation cannot be achieved
	• Use masks and respirators when possible
	• Maximize time in open-air environments (e.g., socialize outside)
	• Organize rapid diagnostics and appropriate referral when TB is suspected
	• Refrain from close contact with children
	• Avoid or limit prolonged public transportation exposure
	• Encourage and provide opportunities for HIV testing and facilitate ART initiation

Table 2

ACH and estimated TB risk in Zulu huts in rural KwaZulu natal province, South Africa

Condition	Closed	Windows open	Windows & door open	P value
Mean (SD)				
ACH	3 (2.9)	9(7.1)	20 (13.1)	$P<0.0001$
TB risk	55.4 (27.8)	21.5 (14.1)	9.6 (4.7)	$P<0.0001$

* *ACH* air changes/h; TB risk is calculated with the Wells-Riley equation using 10 hour exposure. Adapted from [44]