HHS Public Access

Author manuscript

Int J Tuberc Lung Dis. Author manuscript; available in PMC 2015 December 28.

Published in final edited form as:

Int J Tuberc Lung Dis. 2014 September ; 18(9): 1019–1025. doi:10.5588/ijtld.13.0834.

Rapid Impact of Effective Treatment on Transmission of Multidrug Resistant Tuberculosis

Ashwin S. Dharmadhikari[1,2], **Matsie Mphahlele**[3], **Kobus Venter**[3], **Anton Stoltz**[4], **Rirhandzu Mathebula**[3], **Thabiso Masotla**[3], **Martie van der Walt**[3], **Marcello Pagano**[5], **Paul Jensen**[6], and **Edward Nardell**[1,2]

[1]Division of Pulmonary and Critical Care Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA

[2]Division of Global Health Equity, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA

[3]South African Medical Research Council, Pretoria, South Africa

[4]University of Pretoria, Pretoria, South Africa

[5]Department of Biostatistics, Harvard School of Public Health

[6]Centers for Disease Control and Prevention, Atlanta, Georgia, USA

Summary

Rationale—Effective treatment for drug susceptible tuberculosis rapidly renders patients non-infectious – long before sputum acid-fast smear or culture conversion to negative. Multidrug-resistant tuberculosis (MDR-TB) patients on treatment are currently assumed to remain infectious for months. While the resources required for prolonged hospitalization are a barrier to MDR-TB treatment scale-up, the safety of community treatment is clear.

Objectives—To estimate the impact of effect treatment on MDR-TB patient infectiousness.

Methods—A series of five human-to-guinea pig tuberculosis transmission studies tested various infection control interventions. Exhaust air from a hospital ward occupied by mostly sputum smear and culture positive MDR-TB patients exposed guinea pigs in adjacent chambers. Guinea pigs were tuberculin skin tested for infection. Only the control groups of guinea pigs from each study (no interventions used) provide the data for this analysis.

Measurements—The number of guinea pigs infected in each study is reported and correlated with *M. tuberculosis* drug susceptibility relative to treatment.

Name and Address of Corresponding Author: Ashwin S. Dharmadhikari, 641 Huntington Avenue, Suite 3A03, Boston, MA 02115, Tel: 617-432-2079, Fax: 617-432-2565, adharmadhikari@partners.org.

Author Contributions: A. Dharmadhikari played a major role in analyzing the data and writing and editing the manuscript; M. Mphahlele managed most of the experiments and was chief microbiologist; K. Venter managed the animal work and oversaw the function of the facility; A. Stoltz provided medical oversight and was on-site PI of several of the experiments; R. Mathebula was the study nurse for several of the experiments; T. Masotla was the mycobacteriology technician for most of the experiments; M. van der Walt was acting director of the MRC Pretoria Unit during these experiments and edited the manuscript; M. Pagano was the biostatistician for all experiments; P. Jensen was the chief engineer on the study; and E. Nardell was PI of all studies and wrote the first draft of the manuscript.

Main Results—Despite exposure to presumably infectious MDR-TB patients, guinea pig infection percentages ranged from 1 to 77% among the 5 experiments. In one experiment, in which 27 MDR-TB patients newly started on effective treatment exposed guinea pigs for 3 months, there was minimal transmission. In 4 other experiments with greater transmission, guinea pigs had been exposed to patients with unsuspected extensively drug resistant tuberculosis (XDR-TB) - not on effective treatment.

Conclusions—In this model, effective treatment appears to render MDR-TB patients rapidly non-infectious. Further prospective studies on this subject are needed.

Keywords

multidrug resistant tuberculosis; impact of treatment; transmission; extensively drug resistant tuberculosis

Introduction

WHO estimates that up to five hundred thousand new multidrug resistant tuberculosis (MDR-TB) cases occur each year. More than half occur in previously untreated persons—the result of transmission—and in many cases, re-infection[1]. There is considerable evidence that a substantial portion of tuberculosis transmission occurs in hospitals and other congregate settings[2–4]. Globally, most MDR-TB cases are treated in hospitals for at least the first 6 months while receiving injectable drugs[5,6]. They remain hospitalized until smear or culture conversion, the benchmark by which MDR-TB patients are generally considered non-infectious. However, in many high burden settings for MDR-TB, such as South Africa, there is a growing gap between the need for MDR-TB treatment and the availability of hospital beds, resulting in waiting periods for patients to begin therapy[7]. Moreover, the gap is increasing with the implementation of rapid molecular diagnostics testing for drug resistance[8]. In response, South Africa is implementing community-based treatment, as already practiced in many sites around the world[7,9]. Globally, however, enthusiasm for community-based treatment is dampened by concern about potential transmission before sputum smear and culture conversion[10,11].

Exactly how long MDR-TB patients remain infectious after the initiation of effective therapy is unclear. A 2008 task force of the US CDC Advisory Committee for the Elimination of Tuberculosis (ACET) reviewed the medical and public health literature and found little or no evidence in support of any particular policy[12]. For drug susceptible TB, however, policies from 5 public health sources indicated that isolation can be discontinued after two weeks of effective treatment, some specifying *with* and some *without sputum smear or culture conversion*. During the 1985–1992 resurgence of TB in the United States, nosocomial transmission of MDR-TB to other patients and health care workers was attributed largely to patients who were released from respiratory isolation after two weeks of ineffective therapy for *presumed* drug susceptible TB[13]. In response to what was at that time considered a critical policy failure, the *two week rule* was dismissed as not applicable to drug resistant TB[14]. Lacking specific data on the impact of *effective* treatment on MDR-TB, programs have commonly recommended respiratory isolation and/or separation of MDR-TB

patients on treatment until smear or culture conversion, which usually occurs after 2 to 6 months.

Here we present preliminary observations – obtained retrospectively from a series of 5 experiments conducted for other purposes – and discuss how our data, like previously published epidemiological and experimental observations for drug susceptible TB, show that MDR-TB transmission is rapidly reduced following the initiation of *effective* treatment – well before sputum smear and conversion.

Methods

This report consists of a descriptive re-analysis of the tuberculin skin test (TST) conversions among guinea pigs exposed in 5 separate human-to-guinea pig transmission experiments conducted to test infection control interventions. However, only conversions for animals in the control (non-intervention) chambers are used for this analysis.

The 5 experiments were conducted at the Airborne Infections Research (AIR) Facility in Mpumalanga Province, South Africa. The AIR facility consists of three, 2-bed patient rooms, corridor, common room, and ablution facilities, most of the air from which is exhausted through two large guinea pig exposure chambers in a separate, adjacent part of the building. Patients with documented MDR-TB admitted to the adjacent Mpumalanga Provincial MDR-TB Treatment Center to begin or continue standardized treatment were recruited, with informed consent, to participate in the study as human sources of contagion for the guinea pigs. The South African Ministry of Health standardized MDR-TB treatment regimen consisted of levofloxacin, kanamycin, ethionamide and either ethambutol or prothionamide, depending on in vitro susceptibility to ethambutol. Consent included agreement to spend at least 20 hours per day inside the AIR facility. AIR facility patients received exactly the same treatment as patients on the main MDR-TB wards from which they were recruited.

The AIR facility was designed to test airborne infection control interventions, such as germicidal ultraviolet air disinfection, surgical masks on patients, and mechanical room air (filtration) cleaners[15]. In those experiments, air from the patient rooms and corridor was exhausted to one guinea pig exposure chamber on odd calendar days when the intervention was in use and to identical control guinea pig exposure chambers on even calendar days when no intervention was in use. The difference in guinea pig infections was a direct measure of the efficacy of the interventions tested. Importantly, the guinea pig infections included in this current analysis are from the control guinea pig exposure chambers only. TB transmission to the control guinea pigs was therefore not influenced by the interventions being tested. In the pilot study only, organs/tissues from guinea pigs that developed active TB were frozen and subsequently cultured for *M. tuberculosis* using solid agar culture methods. *M. tuberculosis* isolates from the guinea pig tissues were further characterized by drug susceptibility testing (DST) in liquid media and by spoligotyping for linkage with human source case isolates on the ward at the time. (15) In the four other experiments, culturing of guinea pigs was not performed. The details of animal care, tuberculin skin testing, microbiology, and genetic fingerprinting have been published[15].

In all 5 experiments, enrolled subjects served primarily as sources of infectious droplet nuclei. Inclusion criteria were: 1) newly diagnosed MDR-TB referred to the provincial treatment center to begin or continue chemotherapy, 2) sputum smear positive status, 3) chronic cough, and 4) lung cavitation on chest radiograph. Not all inclusion criteria were required or present for each subject. Exclusion criteria included clinical conditions judged by the hospital physician to be pre-terminal or too poor for study participation. New subjects were recruited to replace existing subjects approximately every two to three weeks. In some experiments chronic patients on therapy who remained smear positive and coughing were admitted to the AIR facility to populate the ward with subjects likely to be infectious.

Patient bacteriology

Referrals to the MDR treatment center are based on South African National Reference Laboratory reports of MDR-TB from referring clinics or general hospitals, usually within the preceding 2 months. Following admission to the AIR facility, sputum samples were obtained three times per week for AFB smear, liquid culture, and DST by MGIT liquid culture. All *M. tuberculosis* isolates recovered after study entry were frozen for possible future analyses, including second-line DST and genotyping – procedures not included in our transmission intervention testing protocols. Second-line DST was performed using the MGIT and line-probe methodologies by the Medical Research Council[16], which is a supra-national reference laboratory for TB.

The human studies protocols were approved by the ethics committees of the South African Medical Research Council, CDC, Harvard School of Public Health, and Brigham and Women's Hospital. Animal use committees approved the protocols from the South African Medical Research Council, CDC, and Harvard Medical School.

Results

Subject characteristics

Demographic and clinical characteristics of subjects occupying the AIR facility in each study are shown in Table 1. All patients enrolled in the studies had chronic cough, and the large majority of patients in all study (exact proportion not shown) were smear positive at entry. Studies were conducted from 2005 to 2010.

Treatment initiation

Patients were routinely started on MDR-TB therapy after a brief initial evaluation, including the collection of sputum for culture and DST. In practice, treatment usually began either on the day of admission or the next day. On average, 76% percent of the MDR-TB patients admitted to the AIR facility had less than 24 hours of treatment (Table 1). As previously noted, occasional patients admitted to the AIR facility had been on therapy for weeks or months, but had remained smear positive and coughing. These patients greatly skew the mean and median duration of therapy and, in retrospect, some had XDR TB isolates, an important finding in this analysis.

Microbiology results

Although bacteriological evidence of MDR-TB is required for referral of patients to the Mpumalanga MDR-TB Treatment Center, repeat cultures in the hospital were sometimes negative. This phenomenon, along with contamination of stored specimens, accounts for incomplete patient microbiological data for some patients in several experiments.

Table 4 indicates the prevalence of XDR-TB among patient isolates available for full DST. Experiment 3 had the highest number of isolates available for drug susceptible testing. No XDR isolates were identified in that patient cohort, and this was subsequently confirmed by line probe assay.

Transmission

Despite consistent recruitment of presumably highly infectious patients into the AIR facility, there was marked experiment to experiment variation in the proportion of TST conversions among the exposed (control chamber only) guinea pigs (Table 2). In experiment 3, only 1 guinea pig infection occurred after 3 months exposure to 27 patients. All other experiments had 2 to 5 patients with XDR-TB and were associated with greater transmission.

Discussion

We performed a secondary analysis of guinea pigs exposed to patients with MDR-TB in experimental studies designed to investigate interventions to reduce airborne transmission. Our preliminary data suggest that the standard MDR treatment regimen in South Africa rapidly and effectively inhibited transmission. Our observations are consistent with the epidemiological and experimental evidence gathered over 60 years for drug susceptible TB showing that effective treatment is the dominant factor determining transmission cessation.

Epidemiological studies

The duration of infectiousness of tuberculosis patients started on therapy became a critical question soon after the introduction of effective drug regimens in the 1950s. As early as 1962, Crofton, reflecting on the prospective, randomized clinical trial of ambulatory treatment in Madras (now Chennai), India, suggested that hospitalization was probably not necessary for the prevention of further transmission[17,18]. In that study, home treatment from the beginning (with only INH and PAS) resulted in no more household infections or cases among household contacts than the same treatment given entirely in the hospital for an entire year[17].

Several other studies conducted in the United States support the consistent observation that patients on effective therapy were not infectious for previously uninfected household contacts regardless of positive sputum smear and culture status. In 1973, Brooks and colleagues reported the absence of TST conversions among 107 TST negative household contacts of 21 patients with tuberculosis sent home after up to 23 days hospitalization[19]. Nineteen of those 21 patients were still sputum smear positive when they were sent home, and some did not convert their sputum smear to negative until after 5 months treatment. In 1974, Gunnels and colleagues reported the infection rate among 500 household contacts of

155 TB patients sent home after 1 month of treatment[20]. There was no difference in the infection rate among 284 household contacts of 86 culture positive cases (52 of them smear and culture positive) compared to 216 household contacts of 69 culture negative cases.

In a comprehensive 1976 analysis of tuberculosis transmission factors and the impact of chemotherapy, Rouillon and colleagues reviewed these and other epidemiological studies of TST conversions among the household contacts and concluded:

> "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"[21].

This appears to be the first reference to what has become the *"two week rule"*. Its wide adoption in most infection control guidelines implicitly acknowledges the discordance of sputum smear and culture status and infectiousness of patients on therapy. Despite the rapid bactericidal effects of INH and rifampin-containing regimens, sputum smear and culture conversion uncommonly occurs by two weeks. The mean number of days before the first of three consecutive negative sputum smears has been reported as 33 days, and the median, 23 days[22].

In a critical review of the impact of chemotherapy on transmission, Menzies urged caution in accepting the conclusions of the Madras study, the only prospective, randomized clinical trial data, because of high rates of transmission in the community that could have obscured a difference in household transmission between home and hospital treatment[23]. Because the other household contact observations were not randomized trials, he pointed out the potential for bias if less sick and less infectious patients were sent home on treatment. He did not comment on the Gunnels study where both sputum smear and culture positive and negative patients were sent home. He further argued that uninfected household contacts at the time of diagnosis of the index case may represent individuals with greater innate or adaptive immunity to TB infection, and that most uninfected household contacts and health care workers today in low-burden settings are likely to be more vulnerable to infection than in the past. Implicit in his review of the literature is the common assumption that sputum smear or culture positive patients on therapy remain infectious. The same assumption is the basis for a recent report from Peru showing that 10% of successfully treated drug susceptible patients on chemotherapy remained culture positive at 60 days and, according to the authors, should be considered still infectious[24]. Menzies concluded that there was no credible evidence that sputum culture positive TB patients on therapy are not infectious[23]. While Riley's natural human-to-guinea pig studies (see below for further discussion of these) were cited in both the Menzies and Fitzwater papers, there was no mention that the profound impact on transmission was due to treatment started on *the same day* that the patients entered the experimental ward, long before sputum smear or culture conversion[23–25].

Experimental studies

In their first two year human-to-guinea pig transmission study, for the initial several months, Riley and colleagues observed 3 to 4 guinea pig infections per month from exposure to smear positive, chronic, previously *treated* TB patients[26]. However, for the following 4 month period, despite continued admission of smear positive patients, guinea pig infections stopped completely. This dramatic change in transmission corresponded to a change to recruiting new, previously *untreated* subjects. When chronic, previously *treated* TB patients were again admitted to the ward, transmission to guinea pigs resumed at previous rates, suggesting that effective treatment, started on the day of admission, had rapidly and profoundly interrupted transmission[26].

Recognizing the powerful impact of treatment on transmission, during his second 2-year study Riley exposed guinea pigs for periods to untreated as well as treated patients[25]. The result was a direct comparison of the relative effects of treatment on the infectiousness of patients with drug susceptible and drug resistant TB (Table 3). Note that there was no MDR-TB at that time since this was many years before the introduction of rifampin. The rapid effect of treatment on transmission was accomplished with just INH, PAS, and streptomycin[25]. As in the first study, treated patients were started *on the same day that they were admitted to the ward* – not two weeks or even two days before admission. The 98% reduction in infectiousness reported represented very little treatment with drug regimens far less effective than those used today. Some drug resistant cases also responded to treatment with the remaining effective drugs, but the numbers of such human subjects and guinea pig infections was too small for firm conclusions[25]. Riley concluded: “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.” Regarding drug resistant TB, he was more cautious because of the smaller numbers, concluding only that *“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”*[23].

In another similar, more recent study of the infectivity of TB/HIV patients using the human-to-guinea pig natural transmission model in Lima, Peru, Escombe observed that virtually all transmission was from inadequately treated drug resistant strains[27]. In that study, 97 HIV+ pulmonary TB patients exposed 292 guinea pigs over 505 days. Of these patients, 66 were culture positive and 35 were sputum smear positive. Of 125 infected guinea pigs, 122 (98%) were infected with strains genetically linked to 9 MDR patients who were inadequately treated or where treatment was delayed. Three drug susceptible patients infected one guinea pig each – two had had delayed treatment and one had had treatment stopped for side effects. These data are consistent with both Riley’s results and ours, suggesting transmission almost exclusively from patients on *ineffective* treatment. In Escombe’s study approximately 66% of patients with drug susceptible strains had been on 2 weeks or more of treatment at the time of admission (personal communication, R. Escombe, 2013). However, the 34% of drug susceptible TB patients treated less than 2 weeks, representing patients more likely to be infectious, failed to transmit their infection on treatment, except as noted above.

In our studies, in response to the surprising drop in infection rate observed between our pilot study and Experiment 1 (74% to 10%), we examined all available chest radiographs and concluded that the patients appeared to have similar disease severity and cavitation. Sputum smear score averaged 1.5 to 3 out of 3 in all 5 experiments. The same Hartley strain of guinea pigs had been obtained from the same breeder, and the skin testing reagents and procedures were identical. A probable explanation for the variable infection rates became apparent only retrospectively when the results were available for the drug susceptibility tests and spoligotypes from the stored pilot study isolates from both patients and guinea pigs. As we noted in the published report of our pilot study[28], all 13 available guinea pig isolates matched two strains from patients, which we retrospectively identified as XDR-TB. Subsequently, available isolates from the remaining experiments were sent for second-line DST, revealing that 4 of the 5 experiments with substantial transmission to guinea pigs had patients with unsuspected XDR-TB. Experiment 3, in which only 1 guinea pig was infected by 27 patients over 3 months, failed to have XDR-TB in any of 21 patient isolates available for second line DST.

Our preliminary data suggest that the standard MDR treatment regimen in South Africa rapidly and effectively inhibited transmission. Our observations are consistent with the epidemiological and experimental evidence gathered over 60 years for drug susceptible TB showing that effective treatment is the dominant factor determining transmission. The epidemiological literature suggests that only 1 in 3 smear positive tuberculosis patients, on average, infect their close contacts[29,30]. In cough aerosol sampling studies, *Mtb* was cultured from only approximately 1 in 3 smear positive patients[31]. Both human sources and mycobacterial strains vary in infectiousness[32]. Strikingly, however, the absence of XDR-TB isolates in Experiment 3 was associated with the near absence of transmission to guinea pigs, despite 3 months exposure to 27 sputum positive MDR-TB patients selected for probable infectiousness.

The mechanism by which effective chemotherapy rapidly reduces TB transmission is unknown. Loudon and colleagues theorized that as respiratory droplets evaporate into droplet nuclei, drug concentrations surrounding airborne organisms must increase dramatically, possibly inactivating organisms and blocking successful implantation in hosts[33]. However, experiments with aerosolized *M. tuberculosis* exposed to sub-lethal concentrations of INH still grew on settling plates and failed to support that argument, at least as far as culture was concerned[33]. However, in considering the discordance of aerosol infectivity and sputum culturability it should be noted that organisms in culture do not undergo the stresses of aerosolization or drug exposure, and that growth is supported under optimal culture conditions, whereas inhaled organisms face innate and adaptive host defenses. More intriguing are recent observations that *M. tuberculosis* can rapidly undergo massive transcriptional responses to moderate stresses without an effect on growth or survival[34]. It is plausible that rapid transcriptional responses to antimycobacterial drugs could impact virulence or tolerance to aerosolization without impacting growth in culture.

Study limitations

This is a retrospective re-analysis of data collected for transmission intervention studies. Clinical and microbiological data are incomplete, and we lacked second line drug susceptibility information on all patients entering the AIR Facility. Only recently has second-line DST become routinely available for MDR-TB patients failing the standard South African treatment regimen. Therefore, the diagnosis of extensively drug resistant TB (XDR-TB) was not available at the time of patient recruitment into our studies and could not have influenced their treatment during their stays in the AIR facility. Recovery of isolates from the guinea pigs was also limited. Nevertheless, we present observations that suggest that transmission occurred largely from patient cohorts that included unsuspected XDR-TB patients receiving standardized MDR-TB treatment, and that in the single cohort (experiment 3) in which we identified no XDR, there was nearly no transmission. We recognize that TB cases are inherently variable in infectiousness and that chance could account for these results, but our results are consistent with a large number of epidemiological and two other guinea pig studies that clearly demonstrate the predominant impact of treatment on transmission.

Conclusion

Airborne transmission may be the weak link in TB propagation, and it is likely that very little *effective* treatment may tip the balance against transmission. This has been recognized for drug susceptible TB, and our data suggest the same for MDR-TB. Although further studies are needed to fully understand the mechanism for this remarkable effect, the implications of these observations are profound. Although many programs already treat tuberculosis in the community from the beginning, these data should reinforce the safety of that policy – as long as effective treatment can be assured by rapid molecular testing and treatment delivery assured by directly observed therapy. These data also suggest a refocused approach to TB transmission control in institutions and in the community, with an emphasis on active case finding by cough surveillance, rapid molecular diagnosis, and the prompt institution of fully supervised effective treatment, based on molecular DST. However, caution is warranted in putting these findings into practice. *Effective, fully supervised* treatment cannot be overemphasized, especially in areas where drug resistance is common. It would be a serious mistake to assume that treatment without rapid molecular confirmation of drug susceptibility or effective delivery is appropriate. Finally, it is likely that the current treatment of XDR-TB is often ineffective in rapidly interrupting transmission. Fortunately, one or more of the novel agents on the horizon may accomplish that goal.

Acknowledgments

Sources of Support/Funding: NIOSH R01OH009050

We thank Elsabe de Kock of Retrasol, Inc. for her role as a regulatory consultant and data manager on the mask study and Willem Lubbe for engineering support on these studies at the AIR Facility.

References

1. Organziation WH. Multidrug and extensively drug-resistant TB (M/XDR-TB): 2010 Global Report on Surveillance and Response. Geneva: WHO; 2012.

2. WHO. WHO Policy on TB Infection Control in Health-Care Facilities, Congregate Settings and Households. Geneva: WHO; 2009.
3. Gelmanova IY, Keshavejee S, Golubchikova VT, Berezina V, Strellis AK, VYG, et al. Non-adherence, default, and the acquisition of multidrug resistance in a tuberculosis treatment program in Tomsk, Siberia. submitted for publication - to be resolved or listed as personal communication before publication.
4. Gandhi NR, Moll A, Sturm AW, Pawinski R, Govender T, Lalloo U, et al. Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. Lancet. 2006; 368(9547):1575–80. [PubMed: 17084757]
5. Fitzpatrick FK. A Systematic Review of the Cost and Cost Effectivenes of Treatment for Multidrug-Resistant Tuberculosis. Pharmacoeconomics. 2012
6. Mukherjee JS, Rich ML, Socci AR, Joseph JK, Viru FA, Shin SS, et al. Programmes and principles in treatment of multidrug-resistant tuberculosis. Lancet. 2004; 363(9407):474–81. [PubMed: 14962530]
7. Norbert Ndjeka, M, Director. Drug Resistance and TB and HIV, MOH, South Africa. In: Nardell, E., editor. Shortage of MDR-TB beds in South Africa. Durban: 2010.
8. Carvalho AC, Migliori GB, Cirillo DM. Tuberculosis in Europe: a problem of drug resistance or much more? Expert Rev Respir Med. 2010; 4(2):189–200. [PubMed: 20406085]
9. Loveday M, Wallengren K, Voce A, Margot B, Reddy T, Master I, et al. Comparing early treatment outcomes of MDR-TB in decentralised and centralised settings in KwaZulu-Natal, South Africa. Int J Tuberc Lung Dis. 2012; 16(2):209–15. [PubMed: 22236922]
10. Nardell E, Dharmadhikari A. Turning off the spigot: reducing drug-resistant tuberculosis transmission in resource-limited settings. Int J Tuberc Lung Dis. 2010; 14(10):1233–43. [PubMed: 20843413]
11. Kanjee Z, Catterick K, Moll AP, Amico KR, Friedland GH. Tuberculosis infection control in rural South Africa: survey of knowledge, attitude and practice in hospital staff. J Hosp Infect. 2011; 79(4):333–8. [PubMed: 21978608]
12. Mase S, Seaworth B, Nardell E, Flood J, Thomas J. Developing Guidelines for Discontinuation of Isolation for Patients with Multidrug-Resistant Tuberculosis. ACET presentation. 2009 In press.
13. Frieden TR, Fujiwara PI, Washko RM, Hamburg MA. Tuberculosis in New York City--turning the tide. N Engl J Med. 1995; 333(4):229–33. [PubMed: 7791840]
14. Jensen PA, Lambert LA, Iademarco MF, Ridzon R. Guidelines for preventing the transmission of Mycobacterium tuberculosis in health-care settings, 2005. MMWR Recomm Rep. 2005; 54(17):1–141. [PubMed: 16382216]
15. Dharmadhikari AS, Basaraba RJ, Van Der Walt ML, Weyer K, Mphahlele M, Venter K, et al. Natural infection of guinea pigs exposed to patients with highly drug-resistant tuberculosis. Tuberculosis (Edinb). 2011
16. Rusch-Gerdes S, Pfyffer GE, Casal M, Chadwick M, Siddiqi S. Multicenter laboratory validation of the BACTEC MGIT 960 technique for testing susceptibilities of Mycobacterium tuberculosis to classical second-line drugs and newer antimicrobials. J Clin Microbiol. 2006; 44(3):688–92. [PubMed: 16517840]
17. Andrews RHDS, Fox W, Radhakrishna S, Ramakrishnan CV, Velu S. Prevalence of tuberculosis among close family contacts of tuberculosis patients in south India and influence of segregation of the patient on the early attack rate. Bull Wld Hlth Org. :23.
18. Crofton J. The contribution of treatment to the prevention of tuberculosis. Bull Int Union Tuberc. 1962; 32:643–53.
19. Brooks SMLN, Young E. A Pilot Study Concerning the Infection Risk of Sputum Positive with Tuberculosis Patients on Chemotherapy. Am Rev Respir Dis. 1973; 108(4):799–804. [PubMed: 4741874]
20. Gunnels J, Bates J, Swindoll H. Infectivity of sputum positive tuberculosis patients on chemotherapy. Am Rev Resp Dis. 1974; 109:323. [PubMed: 4205432]
21. Rouillion APS, Parrot R. Transmission of tubercle bacilli: the effects of chemotherapy. Tubercle. 57:275–99.

22. Telzak EE, Fazal BA, Pollard CL, Turett GS, Justman JE, Blum S. Factors influencing time to sputum conversion among patients with smear- positive pulmonary tuberculosis [see comments]. Clin Infect Dis. 1997; 25(3):666–70. [PubMed: 9314458]
23. Menzies D. Effect of treatment on contagiousness of patients with active pulmonary tuberculosis. Infect Control Hosp Epidemiol. 1997; 18(8):582–6. [PubMed: 9276242]
24. Fitzwater SP, Caviedes L, Gilman RH, Coronel J, LaChira D, Salazar C, et al. Prolonged infectiousness of tuberculosis patients in a directly observed therapy short-course program with standardized therapy. Clin Infect Dis. 2010; 51(4):371–8. [PubMed: 20624064]
25. RILEY RL, MILLS CC, O'GRADY F, SULTAN LU, WITTSTADT F, SHIVPURI DN. 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]
26. Riley RLMC, Nyka W, et al. Aerial dissemination of pulmonary tuberculosis: a two-year study of contagion in a tuberculosis ward: 1959. Am J Epidemiol. 1995; 142:3–14. [PubMed: 7785671]
27. Escombe AR, Moore DA, Gilman RH, Pan W, Navincopa M, Ticona E, et al. The infectiousness of tuberculosis patients coinfected with HIV. PLoS Med. 2008; 5(9):e188. [PubMed: 18798687]
28. Dharmadhikari AS, Basaraba RJ, Van Der Walt ML, Weyer K, Mphahlele M, Venter K, et al. Natural infection of guinea pigs exposed to patients with highly drug-resistant tuberculosis. Tuberculosis (Edinb). 2011
29. Fennelly KP, Jones-Lopez EC, Ayakaka I, Kim S, Menyha H, Kirenga B, et al. Variability of infectious aerosols produced during coughing by patients with pulmonary tuberculosis. American journal of respiratory and critical care medicine. 2012; 186(5):450–7. [PubMed: 22798319]
30. van Geuns HA, Meijer J, Styblo K. Results of contact examination in Rotterdam, 1967–1969. Bull Int Union Tuberc. 1975; 50(1):107–21. [PubMed: 1218286]
31. Fennelly KP. Variability of airborne transmission of Mycobacterium tuberculosis: implications for control of tuberculosis in the HIV era. Clin Infect Dis. 2007; 44(10):1358–60. [PubMed: 17443475]
32. Glynn JR, Whiteley J, Bifani PJ, Kremer K, van Soolingen D. Worldwide occurrence of Beijing/W strains of Mycobacterium tuberculosis: a systematic review. Emerg Infect Dis. 2002; 8(8):843–9. [PubMed: 12141971]
33. Loudon RGBL, Coffman GK. Isoniazid and the survival of tubercle bacilli in airborne droplet nuclei. Am Rev Respir Dis. 1969; 100:172–6. [PubMed: 4979743]
34. Voskuil MI, Bartek IL, Visconti K, Schoolnik GK. The response of mycobacterium tuberculosis to reactive oxygen and nitrogen species. Front Microbiol. 2011; 2:105. [PubMed: 21734908]

Table 1

Demographic and clinical characteristics of patients in the 5 human-to-guinea pig transmission experiments

Study	Total Number of Patients	Patient Age, mean (range) in years	% female	% HIV infected (of n tested)	AFB Smear grade at study entry* (median, [IQR])	Duration of Treatment Prior to AIR Facility Entry (median) in days
Pilot	26	34 (18 – 68)	42%	63% (22)	2 [1–3]*	24.5
Experiment 1	24	38 (25 – 60)	33%	80% (20)	1.5 [0 – 3]	0
Experiment 2	15	40 (26 – 64)	46%	80% (15)	3 [3 – 3]	0
Experiment 3	27	34 (18 – 56)	42%	86% (21)	3 [3 – 3]	0
Experiment 4	17	37 (23 – 59)	53%	65% (17)	2 [1 – 3]	0

* for the pilot study, smear grade represents smear grade at exit from AIR facility

Int J Tuberc Lung Dis. Author manuscript; available in PMC 2015 December 28.

Table 2

Guinea pig infection rates in the five human-to-guinea pigs transmission studies. GP = guinea pig.

Experiment	Number of patients	Number of GPs Exposed	Duration of GP exposure (months)	Proportion (and number) of infected GPs (control chamber only)
Pilot	26	360	4	74% (266)
Experiment 1	24	90	3	10% (9)
Experiment 2	15	90	2	54% (49)
Experiment 3	27	90	3	1% (1)
Experiment 4	17	90	3	77% (69)

Table 3

Relative infectiousness of treated and untreated patients on Riley's experimental ward, drug resistant and drug susceptible, relative to time spend on the ward (insert reference)

TB Patients	Guinea Pigs Infected	Relative Risk (adjusted for time on the ward)
Susceptible		
61 Untreated	29	100%
29 Treated	1	2
Drug resistant		
6 Untreated	14	28
11 Treated	6	5

Table 4

Drug sensitivity of isolates from patients in the five human to guinea pig transmission experiments

Experiment	Isolates with full DST (number of subjects)	XDR isolates	Transmission to Guinea Pigs (Proportion Infected)
Pilot	11 (26)	3 (MGIT)	74%
Experiment 1	10 (24)	5 (MGIT)	10%
Experiment 2	11 (15)	2 (MGIT)	54%
Experiment 3	21 (27)	0 (MGIT)	1%
Experiment 4	10 (17)	2 (MGIT)	77%