INT J TUBERC LUNG DIS 18(9):1019–1025

http://dx.doi.org/10.5588/ijtld.13.0834

Rapid impact of effective treatment on transmission of multidrug-resistant tuberculosis

A. S. Dharmadhikari,*† M. Mphahlele,‡ K. Venter,‡ A. Stoltz,§ R. Mathebula,‡ T. Masotla,‡ M. van der Walt,‡ M. Pagano,¶ P. Jensen,# E. Nardell*†

*Division of Pulmonary and Critical Care Medicine, Brigham and Women's Hospital, and †Division of Global Health Equity, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA; ‡South African Medical Research Council, Pretoria, §University of Pretoria, Pretoria, South Africa; ¶Department of Biostatistics, Harvard School of Public Health, Boston, Massachusetts, #Centers for Disease Control and Prevention, Atlanta, Georgia, USA

SUMMARY

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

OBJECTIVES: To estimate the impact of treatment on infectiousness among MDR-TB patients.

METHODS: A series of five human-to-guinea pig TB transmission studies was conducted to test various interventions for infection control. Guinea pigs in adjacent chambers were exposed to exhaust air from a hospital ward occupied by mostly sputum smear- and culture-positive MDR-TB patients. The guinea pigs then underwent tuberculin skin testing for infection. Only the control groups of guinea pigs from each study (no interventions used) provide the data for this analysis. The number of guinea pigs infected in each study is reported and correlated with *Mycobacterium tuberculosis* drug susceptibility relative to treatment.

RESULTS: Despite exposure to presumably infectious MDR-TB patients, infection percentages among guinea pigs ranged from 1% to 77% in the five experiments conducted. In one experiment in which guinea pigs were exposed to 27 MDR-TB patients newly started on effective treatment for 3 months, there was minimal transmission. In four other experiments with greater transmission, guinea pigs had been exposed to patients with unsuspected extensively drug-resistant tuberculosis who were 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.

KEY WORDS: multidrug-resistant tuberculosis; impact of treatment; transmission; extensively drug-resistant tuberculosis

THE WORLD HEALTH ORGANIZATION (WHO) estimates that up to 500 000 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 to suggest that a substantial portion of TB 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] These patients remain hospitalized until smear or culture conversion, the benchmark by which MDR-TB patients are generally considered non-infectious. However, in many high MDR-TB burden settings, such as South Africa, there is a growing gap between the need for MDR-TB treatment and the availability of hospital beds, resulting in long waiting periods for patients to begin treatment.[7] The gap is now increasing with the implementation of rapid molecular diagnostic testing for drug resistance.[8] In response, South Africa is implementing community-based treatment, as is already practiced in many sites around the world.[7,9] Globally, however, enthusiasm for community-based treatment is dampened by concerns about potential transmission before sputum smear and culture conversion.[10,11]

Exactly how long MDR-TB patients remain infectious after the initiation of effective treatment

Correspondence to: Ashwin S Dharmadhikari, Brigham and Women's Hospital, Harvard Medical School, 641 Huntington Avenue, Suite 3A03, Boston, MA 02115, USA. Tel: (+1) 617 432 2079. Fax: (+1) 617 432 2565. e-mail: adharmadhikari@partners.org

Article submitted 25 November 2013. Final version accepted 3 April 2014.

[A version in French of this article is available from the Editorial Office in Paris and from the Union website www.theunion.org]

is unclear. A 2008 task force of the United States Centers for Disease Control and Prevention (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 (Julian Thomas, personal communication). For drug-susceptible TB, however, policies from five public health sources indicated that isolation can be discontinued after 2 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 2 weeks of ineffective therapy for presumed drug-susceptible TB.[12] In response to what was at that time considered a critical policy failure, the 2-week rule was dismissed as not applicable to drug-resistant TB.[13] 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 2–6 months.

Here we present preliminary observations obtained retrospectively from a series of five 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 culture conversion.

METHODS

This report is a descriptive re-analysis of tuberculin skin test (TST) conversions among guinea pigs exposed in five 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 five experiments were conducted at the Airborne Infections Research (AIR) Facility in Witbank, Mpumalanga Province, South Africa. The AIR facility consists of three two-bed patient rooms, a corridor, a 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, after providing 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 (EMB) or prothionamide, depending on the patient's in vitro susceptibility to EMB. Consent included agreement to spend at least 20 h 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 these 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 *Mycobacterium 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.[14] In the four other experiments, culture of guinea pig samples was not performed. The details of animal care, TST, microbiology and genetic fingerprinting have been published elsewhere.[14]

In all five experiments, enrolled subjects served primarily as sources of infectious droplet nuclei. Inclusion criteria were 1) newly diagnosed MDR-TB case 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 (CXR). Not all inclusion criteria were required or present for each subject. Exclusion criteria included clinical conditions judged by the hospital physician to be preterminal or too poor for study participation. New subjects were recruited to replace existing subjects approximately every 2–3 weeks. In some experiments, chronic patients on therapy who remained smear-positive and had cough were admitted to the AIR facility to populate the ward with subjects likely to be infectious.

Patient bacteriology

Referrals to the MDR-TB 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 acid-fast bacilli (AFB) smear, liquid culture and DST using MGIT™ liquid culture (BD, Sparks, MD, USA). 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,[15] 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, Pretoria, South Africa; the CDC, Atlanta, GA, USA; Harvard School of Public Health, Boston, MA, USA; and Brigham and Women's Hospital, Boston, MA, USA. Animal use committees approved the protocols from the South African Medical Research Council, the 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 studies (exact proportions not shown) were smear-positive at entry. Studies were conducted from 2005 to 2010.

Treatment initiation

Patients were routinely started on MDR-TB treatment 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 on the next day. On average, 76% of the MDR-TB patients admitted to the AIR facility had less than 24 h of treatment (Table 1). As previously noted, occasional patients admitted to the AIR facility had been on treatment for weeks or months, but had remained smear-positive and still had cough. These patients greatly skew the mean and median duration of treatment and, in retrospect, some had extensively drug-resistant TB (XDR-TB) isolates, an important finding in this analysis.

Microbiology results

Although bacteriological evidence for MDR-TB is required for referring 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 the incomplete patient microbiological data for some patients in several experiments.

Table 2 indicates the prevalence of XDR-TB among patient isolates available for full DST. Experiment 3 had the highest number of isolates available for DST. No XDR-TB isolates were identified in this patient cohort, which 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 3). In experiment 3, only one guinea pig infection occurred after 3 months' exposure to 27 patients. All other experiments had 2–5 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-TB 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 TB patients started on treatment became a critical question soon after the

Table 1 Demographic and clinical characteristics of patients in the five human-to-guinea pig transmission experiments

Study	Total patients *n*	Patient age, years, mean (range)	Female %	HIV-infected % (of *n* tested)	AFB smear grade at study entry* median [IQR]	Duration of treatment prior to AIR facility entry, days, median
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.
HIV = human immunodeficiency virus; AFB = acid-fast bacilli; IQR = interquartile range; AIR = Airborne Infections Research.

Table 2 DST of isolates from patients in the five human-to-guinea pig transmission experiments

Experiment	Isolates with full DST (number of subjects)	XDR-TB 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

DST = drug susceptibility testing; XDR-TB = extensively drug-resistant tuberculosis; MGIT = Mycobacteria Growth Indicator Tube.

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,[16] suggested that hospitalization was probably not necessary for the prevention of further transmission.[17] In that study, home treatment from the beginning (with only isoniazid [INH] and para-aminosalicylic acid [PAS]) resulted in no more household infections or cases among household contacts than when the same treatment was given entirely in the hospital for an entire year.[16]

Several other studies conducted in the United States support the consistent observation that patients on effective treatment were not infectious for previously uninfected household contacts, regardless of positive sputum smear and culture status. In 1973, Brooks et al. reported the absence of TST conversions among 107 TST-negative household contacts of 21 patients with TB sent home after up to 23 days' hospitalization.[18] Of the 21 patients, 19 were still sputum smear-positive when they were sent home, and some did not convert their sputum smear to negative until after 5 months of treatment. In 1974, Gunnels et al. reported the infection rate among 500 household contacts of 155 TB patients sent home after 1 month of treatment.[19] 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 TB transmission factors and the impact of chemotherapy, Rouillon et al. 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.[20]

This appears to be the first reference to what has become the '2-week rule'. Its wide adoption in most infection control guidelines implicitly acknowledges the discordance of sputum smear and culture status and the infectiousness of patients on treatment. Despite the rapid bactericidal effects of INH and rifampin (RMP) containing regimens, sputum smear and culture conversion rarely occurs by 2 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.[21]

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.[22] 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 household contacts who were uninfected at the time of diagnosis of the index case may represent individuals with greater innate or adaptive immunity to tuberculous 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 treatment 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

Table 3 Guinea pig infection rates in the five human-to-guinea pig transmission studies

Experiment	Patients *n*	Guinea pigs exposed *n*	Duration of guinea pig exposure months	Infected guinea pigs (control chamber only) *n* (%)
Pilot	26	360	4	266 (74)
Experiment 1	24	90	3	9 (10)
Experiment 2	15	90	2	49 (54)
Experiment 3	27	90	3	1 (1)
Experiment 4	17	90	3	69 (77)

Table 4 Relative infectiousness of treated and untreated patients on Riley's experimental ward, drug-resistant and drug-susceptible patients, relative to time spent on the ward[24]

TB patients	Guinea pigs infected *n*	Relative risk (adjusted for time on the ward)
Drug-susceptible		
Untreated ($n = 61$)	29	100
Treated ($n = 29$)	1	2
Drug-resistant		
Untreated ($n = 6$)	14	28
Treated ($n = 11$)	6	5

TB = tuberculosis.

to the authors, should be considered still infectious.[23] Menzies concluded that there was no credible evidence that sputum culture-positive TB patients on treatment are not infectious.[22] While Riley's natural human-to-guinea pig studies (see below for further discussion of these) were cited in both the Menzies and the Fitzwater et al. papers, there was no mention that the profound impact on transmission was due to treatment started on *the same day* the patients entered the experimental ward, long before sputum smear or culture conversion.[22–24]

Experimental studies

In their first 2-year human-to-guinea pig transmission study, for the initial several months, Riley et al. observed 3–4 guinea pig infections per month from exposure to smear-positive, chronic, previously treated TB patients.[25] However, over the following 4-month period, despite continued admission of smear-positive patients, the 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 the previous rates, suggesting that effective treatment, started on the day of admission, had rapidly and profoundly interrupted transmission.[25]

Recognizing the powerful impact of treatment on transmission, during their second 2-year study, Riley et al. 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 4). Note that there was no MDR-TB at that time, as this was many years before the introduction of RMP. The rapid effect of treatment on transmission was accomplished with just INH, PAS and streptomycin.[24] As in the first study, treated patients were started on the same day that they were admitted to the ward — not 2 weeks or even 2 days before admission. The reported 98% reduction in infectiousness represented very little treatment with drug regimens that are 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 to be drawn.[24] Riley et al. 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, they were 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'.[24]

In another similar, more recent study of the infectivity of patients with TB and human immunodeficiency virus (HIV) using the natural human-to-guinea pig transmission model in Lima, Peru, Escombe et al. observed that virtually all transmission was from inadequately treated drug-resistant strains.[26] In that study, 97 HIV-positive 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 nine MDR-TB patients who were inadequately treated or in whom treatment was delayed. Three drug-susceptible patients infected one guinea pig each: two had had delayed treatment and one had had treatment stopped due to side effects. These data are consistent with both Riley et al.'s results and ours, suggesting transmission almost exclusively from patients on ineffective treatment. In Escombe et al.'s study, approximately 66% of patients with drug-susceptible strains had been on $\geqslant 2$ weeks of treatment at the time of admission (personal communication, R Escombe, 2013). However, the 34% of drug-susceptible TB patients treated for <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 (from 74% to 10%), we examined all available CXRs and concluded that the patients appeared to have similar disease severity and cavitation. Sputum smear scores averaged 1.5–3 out of 3 in all five experiments. The same Hartley strain of guinea pigs had been obtained from the same breeder, and the TST reagents and procedures were identical. A probable explanation for the variable infection rates became apparent only retrospectively, when the

results were available for DST 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,[14] 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 four of the five experiments with substantial transmission to guinea pigs had patients with unsuspected XDR-TB. Experiment 3, in which only one guinea pig was infected by 27 patients over 3 months, failed to identify XDR-TB in any of the 21 patient isolates available for second-line DST.

Our preliminary data suggest that the standard MDR-TB 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. Epidemiological literature suggests that only 1/3 smear-positive TB patients, on average, infect their close contacts.[27,28] In cough aerosol sampling studies, *M. tuberculosis* was cultured from only approximately 1/3 smear-positive patients.[29] Both human sources and mycobacterial strains vary in infectiousness.[30] 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 et al. 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 the hosts.[31] However, experiments with aerosolized *M. tuberculosis* exposed to sublethal concentrations of INH still grew on settling plates and failed to support that argument, at least as far as culture was concerned.[31] However, considering the discordance of aerosol infectivity and sputum culturability, it should be noted that organisms in culture do not undergo the stress 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.[32] It is plausible that rapid transcriptional responses to anti-mycobacterial 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 information on second-line DST on all patients entering the AIR facility. Second-line DST has only recently become routinely available for MDR-TB patients failing the standard South African treatment regimen; the diagnosis of XDR-TB was therefore 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 patients with unsuspected XDR-TB receiving standardized MDR-TB treatment, and that in the single cohort (experiment 3) in which we identified no XDR-TB, 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 studies 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 that the same is applicable to 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 TB 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 is assured by directly observed therapy. These data also suggest that the approach to TB transmission control in institutions and in the community should be refocused, 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. The need for effective, fully supervised treatment cannot be overemphasized, particularly 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.

Acknowledgements

The authors thank E de Kock of Retrasol Inc. for her role as a regulatory consultant and data manager on the mask study and W Lubbe for engineering support on these studies at the AIR facility.

Sources of support/funding: NIOSH R01OH009050.

Conflict of interest: none declared.

References

1 World Health Organization. Multidrug and extensively drug-resistant TB (M/XDR-TB): 2010 global report on surveillance and response. WHO/HTM/TB/2010.3. Geneva, Switzerland: WHO, 2012.
2 World Health Organization. WHO policy on TB infection control in health care facilities, congregate settings and households. Geneva, Switzerland: WHO, 2009.
3 Gelmanova I Y, Keshavejee S, Golubchikova V T, et al. Barriers to successful tuberculosis treatment in Tomsk, Russian Federation: non-adherence, default and the acquisition of multidrug resistance. Bull World Health Organ 2007; 85: 703–711.
4 Gandhi N R, Moll A, Sturm A W, 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: 1575–1580.
5 Fitzpatrick F K, Floyd K. A systematic review of the cost and cost-effectivenes of treatment for multidrug-resistant tuberculosis. Pharmacoeconomics 2012; 30: 63–80.
6 Mukherjee J S, Rich M L, Socci A R, et al. Programmes and principles in treatment of multidrug-resistant tuberculosis. Lancet 2004; 363: 474–481.
7 Directorate for Drug-resistant Tuberculosis, TB & HIV, Chief Directorate for TB Control and Management. Multidrug-resistant tuberculosis. A policy framework on decentralised and deinstitutionalised management for South Africa. Durban, South Africa: Department of Health, 2010.
8 Carvalho A C, Migliori G B, Cirillo D M. Tuberculosis in Europe: a problem of drug resistance or much more? Expert Rev Respir Med 2010; 4: 189–200.
9 Loveday M, Wallengren K, Voce A, 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: 209–215.
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: 1233–1243.
11 Kanjee Z, Catterick K, Moll A P, Amico K R, Friedland G H. Tuberculosis infection control in rural South Africa: survey of knowledge, attitude and practice in hospital staff. J Hosp Infect 2011; 79: 333–338.
12 Frieden T R, Fujiwara P I, Washko R M, Hamburg M A. Tuberculosis in New York City—turning the tide. N Engl J Med 1995; 333: 229–233.
13 Jensen P A, Lambert L A, Iademarco M F, Ridzon R. Guidelines for preventing the transmission of *Mycobacterium tuberculosis* in health care settings, 2005. MMWR Recomm Rep 2005; 54: 1–141.
14 Dharmadhikari A S, Basaraba R J, Van Der Walt M L, et al. Natural infection of guinea pigs exposed to patients with highly drug-resistant tuberculosis. Tuberculosis (Edinb) 2011; 91: 329–338.
15 Rüsch-Gerdes S, Pfyffer G E, 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: 688–692.
16 Andrews R H, Devadatta S, Fox W, Radhakrishna S, Ramakrishnan C V, 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 World Health Organ 1960; 23: 463–510.
17 Crofton J. The contribution of treatment to the prevention of tuberculosis. Bull Int Union Tuberc 1962; 32 (2): 643–653.
18 Brooks S M, Lassiter N L, Young E. A pilot study concerning the infection risk of sputum positive with tuberculosis patients on chemotherapy. Am Rev Respir Dis 1973; 108: 799–804.
19 Gunnels J, Bates J, Swindoll H. Infectivity of sputum positive tuberculosis patients on chemotherapy. Am Rev Respir Dis 1974; 109: 323.
20 Rouillon A, Perdrizet S, Parrot R. Transmission of tubercle bacilli: the effects of chemotherapy. Tubercle 1976; 57: 275–299.
21 Telzak E E, Fazal B A, Pollard C L, Turett G S, Justman J E, Blum S. Factors influencing time to sputum conversion among patients with smear-positive pulmonary tuberculosis [see Comments]. Clin Infect Dis 1997; 25: 666–670.
22 Menzies D. Effect of treatment on contagiousness of patients with active pulmonary tuberculosis. Infect Control Hosp Epidemiol 1997; 18: 582–586.
23 Fitzwater S P, Caviedes L, Gilman R H, et al. Prolonged infectiousness of tuberculosis patients in a directly observed therapy short-course program with standardized therapy. Clin Infect Dis 2010; 51: 371–378.
24 Riley R L, Mills C C, O'Grady F, Sultan L U, Wittstadt F, Shivpuri D N. Infectiousness of air from a tuberculosis ward. Ultraviolet irradiation of infected air: comparative infectiousness of different patients. Am Rev Respir Dis 1962; 85: 511–525.
25 Riley R L Mills C C, 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.
26 Escombe A R, Moore D A, Gilman R H, et al. The infectiousness of tuberculosis patients coinfected with HIV. PLOS MED 2008; 5: e188.
27 Fennelly K P, Jones-Lopez E C, Ayakaka I, et al. Variability of infectious aerosols produced during coughing by patients with pulmonary tuberculosis. Am J Respir Crit Care Med 2012; 186: 450–457.
28 van Geuns H A, Meijer J, Styblo K. Results of contact examination in Rotterdam, 1967–1969. Bull Int Union Tuberc 1975; 50 (1): 107–121.
29 Fennelly K P. Variability of airborne transmission of *Mycobacterium tuberculosis*: implications for control of tuberculosis in the HIV era. Clin Infect Dis 2007; 44: 1358–1360.
30 Glynn J R, Whiteley J, Bifani P J, Kremer K, van Soolingen D. Worldwide occurrence of Beijing/W strains of *Mycobacterium tuberculosis*: a systematic review. Emerg Infect Dis 2002; 8: 843–849.
31 Loudon R G, Bumgarner L R, Coffman G K. Isoniazid and the survival of tubercle bacilli in airborne droplet nuclei. Am Rev Respir Dis 1969; 100: 172–176.
32 Voskuil M I, Bartek I L, Visconti K, Schoolnik G K. The response of mycobacterium tuberculosis to reactive oxygen and nitrogen species. Front Microbiol 2011; 2: 105.

RESUME

CADRE : Un traitement efficace de la tuberculose (TB) sensible aux médicaments rend rapidement les patients non infectants, bien avant que les frottis de crachats ou la culture ne se négativent. Les patients atteints de TB multirésistante (TB-MDR) en cours de traitement sont jusqu'ici censés rester contagieux pendant des mois. Comme les ressources nécessaires à une hospitalisation prolongée sont un obstacle à l'expansion du traitement de la TB-MDR, la fiabilité du traitement communautaire est claire.

OBJECTIFS : Estimer l'impact d'un traitement efficace sur le caractère contagieux des patients ayant une TB-MDR.

MÉTHODES : Une série de cinq études de transmission de la TB de l'homme au cobaye a testé plusieurs interventions de lutte contre la transmission de l'infection. Des cobayes ont été exposés dans des espaces contigus à l'air évacué d'un service hospitalier occupé surtout par des patients TB-MDR à frottis et culture positifs. Un test cutané à la tuberculine a été pratiqué chez les cobayes. Seul le groupe témoin de cobayes de chaque étude (sans intervention) fournit des données pour cette analyse. Le nombre de cobayes infectés dans chaque étude est rapporté et corrélé avec la sensibilité aux médicaments de *Mycobacterium tuberculosis* relative au traitement.

RÉSULTATS : En dépit d'une exposition à des patients TB-MDR présumés contagieux, le pourcentage d'infection des cobayes allait de 1% à 77% lors des cinq expériences. Dans l'une d'elles, où les cobayes étaient exposés à 27 patients TB-MDR pendant 3 mois, la transmission est restée minimale. Dans les quatre autres expériences, où la transmission était plus importante, les cobayes avaient été exposés à des patients porteurs d'une TB ultra-résistante et non reconnue qui n'étaient pas encore traités efficacement.

CONCLUSIONS : Dans ce modèle, un traitement efficace semble rendre les patients TB-MDR rapidement non contagieux. Il est cependant nécessaire de réaliser d'autres études prospectives dans ce domaine.

RESUMEN

MARCO DE REFERENCIA: El tratamiento eficaz de la tuberculosis (TB) normosensible suprime rápidamente la contagiosidad de los pacientes mucho tiempo antes de haber obtenido la conversión de la baciloscopia o del cultivo. Se piensa que los pacientes con diagnóstico de TB multidrogorresistente (TB-MDR) que reciben tratamiento siguen siendo contagiosos durante varios meses. Los recursos que exige una hospitalización prolongada constituyen un obstáculo a la ampliación de escala del tratamiento de la TB-MDR y al mismo tiempo es evidente la seguridad del tratamiento en medio comunitario.

OBJETIVOS: Evaluar el efecto del tratamiento de la TB-MDR sobre la contagiosidad.

MÉTODOS: En una serie de cinco estudios sobre la transmisión de la TB del ser humano al conejillo de Indias, se evaluaron varias intervenciones encaminadas a controlar la infección. Se expuso a los conejillos de Indias, en una cámara adyacente, al aire proveniente de una sección ocupada en su mayoría por pacientes con TB-MDR con baciloscopia y cultivo positivos. A fin de detectar la infección, se practicó la prueba tuberculínica a los conejillos. En este análisis solo se usaron los datos de los grupos testigo de conejillos de Indias en cada estudio (en los cuales no se ejecutó ninguna intervención). Se registró el número de conejillos de Indias infectados en cada estudio y se correlacionó con la sensibilidad de las cepas de *Mycobacterium tuberculosis* al tratamiento.

RESULTADOS: Pese a su exposición a pacientes con TB-MDR, supuestamente contagiosos, el porcentaje de infección en los conejillos de Indias osciló entre 1% y 77% en los cinco experimentos. En un estudio, en el cual se expusieron los conejillos durante 3 meses a 27 pacientes con diagnóstico de TB-MDR que acababan de comenzar un tratamiento eficaz, se observó un grado mínimo de transmisión. En los otros cuatro experimentos, con una mayor transmisión, los conejillos se habían expuesto a pacientes que presentaban TB extremadamente drogorresistente insospechada y cuyo tratamiento no era eficaz.

CONCLUSIÓN: En el modelo estudiado, el tratamiento eficaz parece suprimir rápidamente la contagiosidad de los pacientes con TB-MDR. Se precisan nuevos estudios prospectivos sobre este tema.