# Original Research

# **Annals of Internal Medicine**

# High Incidence of Hospital Admissions With Multidrug-Resistant and Extensively Drug-Resistant Tuberculosis Among South African Health Care Workers

Max R. O'Donnell, MD, MPH; Julie Jarand, BSc, MD; Marian Loveday, BSc, MPhil; Nesri Padayatchi, BSc, MBChB, DCH, DTM+H, DHSM, DPH, MS(Epi); Jennifer Zelnick, MSW, ScD; Lise Werner, MSc; Kasavan Naidoo, MSc, BSc; Iqbal Master, MBChB; Garth Osburn, MBChB; Charlotte Kvasnovsky, MD, MPH; Karen Shean, MSc; Madhukar Pai, MD, PhD; Martie Van der Walt, PhD; Charles R. Horsburgh, MD, MUS; and Keertan Dheda, MBBCh, PhD

**Background:** Nosocomial transmission has been described in extensively drug-resistant tuberculosis (XDR-TB) and HIV co-infected patients in South Africa. However, little is known about the rates of drug-resistant tuberculosis among health care workers in countries with high tuberculosis and HIV burden.

**Objective:** To estimate rates of multidrug-resistant tuberculosis (MDR-TB) and XDR-TB hospitalizations among health care workers in KwaZulu-Natal, South Africa.

**Design:** Retrospective study of patients with drug-resistant tuberculosis who were admitted from 2003 to 2008 for the initiation of drug-resistant tuberculosis therapy.

Setting: A public tuberculosis referral hospital in KwaZulu-Natal, South Africa.

Participants: 231 health care workers and 4151 non-health care workers admitted for initiation of MDR-TB or XDR-TB treatment.

Measurements: Hospital admission rates and hospital admission incidence rate ratios.

**Results:** Estimated incidence of MDR-TB hospitalization was 64.8 per 100 000 health care workers versus 11.9 per 100 000 non-health care workers (incidence rate ratio, 5.46 [95% CI, 4.75 to

6.28]). Estimated incidence of XDR-TB hospitalizations was 7.2 per 100 000 health care workers versus 1.1 per 100 000 non-health care workers (incidence rate ratio, 6.69 [CI, 4.38 to 10.20]). A higher percentage of health care workers than non-health care workers with MDR-TB or XDR-TB were women (78% vs. 47%; P < 0.001), and health care workers were less likely to report previous tuberculosis treatment (41% vs. 92%; P < 0.001). HIV infection did not differ between health care workers and non-health care workers (55% vs. 57%); however, among HIV-infected patients, a higher percentage of health care workers were receiving antiretroviral medications (63% vs. 47%; P < 0.001).

**Limitation:** The study had an observational retrospective design, is subject to referral bias, and had no information on type of health care work or duration of occupational exposure to tuberculosis.

**Conclusion:** Health care workers in this HIV-endemic area were substantially more likely to be hospitalized with either MDR-TB or XDR-TB than were non-health care workers. The increased risk may be explained by occupational exposure, underlining the urgent need for tuberculosis infection-control programs.

comprehensive infection-control policies. In South Africa,

www.annals.org

#### Primary Funding Source: None.

Ann Intern Med. 2010;153:516-522. For author affiliations, see end of text.

Mycobacterium tuberculosis (MTB) is among the leading causes of global mortality by an infectious agent (1). Health care workers, including those in developing countries, are at increased risk for occupational exposure to tuberculosis (2–4). In developed countries, outbreaks of drug-resistant tuberculosis among health care workers have been described in hospitals and settings in which patients with HIV/AIDS receive treatment (5, 6). These multidrugresistant tuberculosis (MDR-TB) outbreaks in industrialized countries were controlled after the implementation of

| See also:  |
|--|
| PrintEditors' Notes517Summary for Patients1-62                           |
| <b>Web-Only</b><br>Appendix Tables<br>Conversion of graphics into slides |

however, drug-resistant tuberculosis among health care workers has not been well characterized, even as endemic HIV has contributed to the nosocomial spread of drugresistant tuberculosis (3, 7). KwaZulu-Natal province, the epicenter of the South African HIV/AIDS epidemic (8) has high rates of

African HIV/AIDS epidemic (8), has high rates of MDR-TB and extensively drug-resistant tuberculosis (XDR-TB) (9). Recent studies indicate that nosocomial transmission is a potentially important factor in the spread of both MDR-TB and XDR-TB in KwaZulu-Natal (7, 10). A systematic review of occupational risk for drugsusceptible tuberculous infection and disease among health care workers in low- and middle-income countries found that tuberculosis rates among health care workers were substantially higher than that among the general population (4). Reports of an XDR-TB outbreak (9) and an XDR-TB treatment cohort in KwaZulu-Natal (11) included relatively high percentages of health care workers (5%). In KwaZulu-Natal, those who work in health care settings face occupational risks because of the high incidence of tuberculosis (3); the increased susceptibility to tuberculosis

due to HIV infection (12); and more recently, the emergence of drug-resistant strains of MTB (13).

We conducted a retrospective chart review at a public tuberculosis referral hospital in KwaZulu-Natal, South Africa, to identify cases of MDR-TB and XDR-TB among health care workers. We sought to address the following questions: Was the incidence of hospitalization for MDR-TB and XDR-TB higher among health care workers than among non-health care workers in KwaZulu-Natal? Was increased risk for MDR-TB and XDR-TB among health care workers associated with HIV infection? Were health care workers more likely than non-health care workers to have been previously treated for tuberculosis?

## **METHODS**

### Design

Our study was a retrospective chart review of patients hospitalized for initiation of treatment of MDR-TB or XDR-TB at King George V Hospital, a public tuberculosis referral hospital in KwaZulu-Natal. During the study, King George V Hospital was the only public hospital in the province that was authorized to initiate therapy for MDR-TB or XDR-TB, and all therapy for MDR-TB and XDR-TB was initiated on an inpatient basis. All patients hospitalized at King George V Hospital with either MDR-TB or XDR-TB from 1 January 2003 to 31 December 2008 for initial therapy for drug-resistant tuberculosis were included in this study.

All participants had culture-confirmed tuberculosis with MTB drug-susceptibility testing. Drug susceptibility to isoniazid, rifampin, ethambutol, streptomycin, ethionamide, ofloxacin, and kanamycin or amikacin was determined by using the modified proportional growth method on 7H11 agar according to standard techniques (14, 15). Multidrug-resistant tuberculosis was defined as resistance to isoniazid and rifampicin. Extensively drug-resistant tuberculosis was defined as resistance to isoniazid; rifampicin; any fluoroquinolone; and 1 of 3 injectable second-line antituberculosis agents: capreomycin, kanamycin, and amikacin (16).

All MDR-TB and XDR-TB admissions during the time period were identified by using a hospital-based database. This database has been maintained by the MDR-TB service at King George V Hospital since 1998. We reviewed the charts on all MDR-TB and XDR-TB health care workers in detail. Data were cleaned by removing patients who did not meet the case definition for MDR-TB or XDR-TB based on drug-susceptibility test results. For patients with repeated admissions to King George V Hospital, subsequent admissions were excluded. The admitting physician asked participants to self-identify as health care workers at the time of hospitalization as part of an occupational history. On the basis of this self-reported health care worker status, patients with MDR-TB and XDR-TB were classified as health care workers or non-health care

#### Context

The risks for multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) among health care workers are unknown in South Africa, where the rates of MDR-TB and XDR-TB in the general population are high.

### Contribution

This retrospective study estimated the rate of hospital admissions for the initiation of treatment of MDR-TB and XDR-TB in a single South African province during a period when all treatments occurred at a single referral hospital. Health care workers had 5 and 6 times the rates of admission for MDR-TB and XDR-TB treatment, respectively, as non-health care workers

#### Implication

Nosocomial transmission of MDR-TB and XDR-TB may be a major problem for health care workers in South Africa.

#### —The Editors

workers. These participants served as the numerators for incident hospitalization rate calculations.

To estimate denominators for incident hospitalization rates, we assumed that the population base for health care workers was all health care workers in KwaZulu-Natal and the general adult population in KwaZulu-Natal (excluding health care workers) was non-health care workers during the study period. We obtained data on the annual KwaZulu-Natal provincial adult population from the 2001 South African national census and 2007 population estimates from a national community survey (17, 18). Number of health care workers in the province was estimated by using enrollment in registering bodies for professional health care workers and number of filled posts in the provincial public health system for nonprofessional health care workers for each study year (19). We restricted analysis to participants' age ( $\geq 20$  years) because a health care worker position is an adult occupation and comparison with nonadults may have skewed estimated rate ratios. The estimate of the proportion of the population 20 years or older was from the KwaZulu-Natal 2001 census data. We calculated incidence rates by dividing the number of cases of tuberculosis in the group of interest by the population of that group. Further information on these estimates is included in Appendix Tables 1 and 2 (available at www.annals.org).

#### Statistical Analysis

We compared health care workers with MDR-TB and XDR-TB with non-health care workers by using a chisquare test for categorical variables, and medians were compared for continuous variables by using the Mann-Whitney U test. We calculated incidence rate ratios and 95% CIs by using Poisson regression analysis. Statistical analysis was done with SAS software, version 9.1 (SAS Institute, Cary, North Carolina). The Biomedical Research Ethics Committee of the University of KwaZulu-Natal, the Research Ethics Committee of the University of Cape Town, and the Institutional Review Board at Boston University Medical Center approved the study protocol.

#### Role of the Funding Source

No funding was received for this study.

#### RESULTS

From 2003 to 2008, 4941 persons were hospitalized for MDR-TB or XDR-TB at King George V Hospital. Approximately 5% of these self-identified as a health care worker. When patients younger than 20 years (n = 448)and repeated hospitalizations were excluded (n = 111), there were 231 health care workers and 4151 adult members of the general population (non-health care workers) hospitalized at King George V Hospital for initiation of treatment of MDR-TB (n = 4015) or XDR-TB (n =367). A total of 261 of 4382 (6%) patients with MDR-TB or XDR-TB were missing data on health care worker status. We categorized these 261 patients as non-health care workers for the purpose of analysis. Dates of treatment initiation for MDR-TB or XDR-TB were available for 67% (2771 of 4151) of non-health care workers and 98% (227 of 231) of health care workers. These dates confirmed that treatment was initiated for all patients with available data during their King George V Hospital admission (Figure).

During the study, 231 patients who self-identified as health care workers were hospitalized at King George V Hospital with either MDR-TB (n = 208) or XDR-TB (n = 23). Health care workers with MDR-TB or XDR-TB were mostly women (78%) and were young (median age, 35 years), with a high percentage of HIV infection among those tested (67%) (Table 1).



HCW = health care worker; KGW = King George V Hospital; MDR-TB = multidrug-resistant tuberculosis; TB = tuberculosis; XDR-TB = extensively drug-resistant tuberculosis.

\* Includes 261 patients in whom HCW status was missing.

518 19 October 2010 Annals of Internal Medicine Volume 153 • Number 8

Health care workers were referred from a mix of public (138 of 231 [60%]), private (31 of 231 [13%]), and public hospitals specializing in tuberculosis (56 of 231 [24%]). In some cases, this facility was the workplace of the health care worker; in other cases, it was a facility in which the health care worker was seen before referral to King George V Hospital. Specific health care worker occupation was not recorded in the medical record.

Health care workers hospitalized with drug-resistant tuberculosis were significantly less likely to report previous treatment of tuberculosis (95 of 231 [38%]) than were non-health care workers (3806 of 4151 [92%]; P <0.001). However, a substantial number of health care workers were missing data on previous treatment (116 of 231 [50%]). Among health care workers, those hospitalized with MDR-TB were significantly less likely to report previous treatment of tuberculosis (80 of 208 [38%]) than were health care workers hospitalized with XDR-TB (15 of 23 [65%]; P = 0.02). Data were not available regarding the previous tuberculosis diagnoses, drug-susceptibility patterns, or treatment courses. During the current treatment course, tuberculosis cultures converted to negative in 65% of health care workers with MDR-TB compared with 13% of health care workers with XDR-TB (P < 0.001). Hospital mortality was similar among health care workers infected with MDR-TB and XDR-TB (32% vs. 30%); sufficient follow-up data are not available to characterize overall survival or cure rates.

Non-health care workers with MDR-TB or XDR-TB and health care workers with MDR-TB or XDR-TB were similar in median age, HIV prevalence, tuberculosis type (pulmonary vs. extrapulmonary), and proportions of XDR-TB cases. A higher percentage of health care workers were women (78% vs. 47%; P < 0.001). HIV status was more likely to be known for health care workers (83%) than for non-health care workers (79%); similar proportions were known to have HIV infection (55% vs. 57%), but health care workers were more likely to be HIVnegative than non-health care workers (28% vs. 22%; P =0.04). Among patients known to be HIV-positive, a higher proportion of health care workers than non-health care workers were receiving antiretroviral medications at the time of hospital admission (63% vs. 47%; P < 0.001).

By using cases of health care workers and non-health care workers hospitalized at King George V Hospital as the numerator and age-adjusted total numbers of health care workers and provincial population as the denominator, we found an annual estimated incidence of hospital admissions for MDR-TB of 64.8 per 100 000 health care workers compared with an annual incidence of MDR-TB hospital admissions of 11.9 per 100 000 persons in the adult general population (incidence rate ratio, 5.46 [95% CI, 4.75 to 6.28]). Average annual incidence of XDR-TB hospital admissions was 7.2 per 100 000 health care workers and 1.1 per 100 000 persons in the adult general population (incidence rate ratio, 6.69 [CI, 4.38 to 10.20]) (Table 2).

# Table 1. Demographic and Treatment Characteristics of Health Care Workers and Non-Health Care Workers With MDR-TB and XDR-TB Hospitalized at King George V Hospital, 2003 to 2008\*

| Characteristic  | Health Car               | Health Care Workers |                   | Care Workers     |
|---|--------------------------|---------------------|-------------------|------------------|
|   | MDR-TB ( <i>n</i> = 208) | XDR-TB ( $n = 23$ ) | MDR-TB (n = 3807) | XDR-TB (n = 344) |
| Admission year. n (%)                                       |                          |                     |                   |                  |
| 2003  | 24 (11.5)                | 1 (4.4)             | 416 (10.9)        | 5 (1.5)          |
| 2004  | 19 (9.1)                 | 0 (0.0)             | 388 (10.2)        | 5 (1.5)          |
| 2005  | 22 (10.6)                | 2 (8.7)             | 482 (12.7)        | 34 (9.9)         |
| 2006  | 33 (15.9)                | 3 (13.0)            | 578 (15.2)        | 72 (20.9)        |
| 2007  | 67 (32.2)                | 5 (21.7)            | 958 (25.2)        | 126 (36.6)       |
| 2008  | 43 (20.7)                | 12 (52.2)           | 985 (25.9)        | 102 (29.7)       |
| Women, n (%)  | 162 (77.9)               | 18 (78.3)           | 1754 (46.1)       | 196 (57.0)       |
| Men, n (%)  | 46 (22.1)                | 5 (21.7)            | 2053 (53.9)       | 148 (43.0)       |
| Median age (IQR), y   | 35 (31–42)               | 38 (28–43)          | 34 (28–42)        | 35 (30–42)       |
| HIV status, n (%)   | 442 (54.2)               | 45 (65 2)           |                   | 240 (50 0)       |
| Positive  | FR (27.0)                | 15 (65.2)           | 2112 (55.5)       | 240 (69.8)       |
| Inegative   | 28 (27.9)<br>27 (17.9)   | 6 (26.1)            | 845 (22.2)        | 00 (19.2)        |
| HIV-positive and receiving antiretroviral drugs, n (%)      | 57 (17.6)                | 2 (6.7)             | 650 (22.5)        | 56(11.1)         |
| Yes   | 69 (61.1)                | 12 (80.0)           | 971 (46.0)        | 135 (56.3)       |
| No  | 44 (38.9)                | 3 (20.0)            | 1141 (54.0)       | 105 (43.8)       |
| Previous treatment of tuberculosis, $n(\%)$                 |                          |                     |                   |                  |
| Yes   | 80 (38.5)                | 15 (65.2)           | 3565 (93.6)       | 336 (97.7)       |
| No  | 20 (9.6)                 | 0 (0.0)             | 185 (4.9)         | 7 (2.0)          |
| Unknown   | 108 (51.9)               | 8 (34.8)            | 57 (1.5)          | 1 (0.3)          |
| Median drugs resistant to tuberculosis at baseline (IQR), n | 3 (2–7)                  | 6 (5–8)             | NA†               | NA†              |
| Median drugs in initial treatment regimen (IQR), n          | 6 (3–7)                  | 6 (4–7)             | NA†               | NA†              |
| Type of health care facility, n (%)                         |                          |                     |                   |                  |
| Private   | 30 (14.4)                | 1 (4.3)             | NA†               | NA†              |
| Public  | 125 (60.1)               | 13 (56.5)           | -                 | -                |
| Tuberculosis specialist                                     | 53 (25.5)                | 3 (13.0)            | -                 | -                |
| Unknown   | -                        | 6 (26.1)            | -                 | -                |
| Type of tuberculosis, n (%)‡                                |                          |                     |                   |                  |
| Pulmonary   | 97 (58.8)                | / (63.6)            | 1494 (52.9)       | 141 (58.3)       |
| Extrapulmonary  | 62 (37.6)                | 4 (36.4)            | 1265 (43.8)       | 101 (41.7)       |
| Nussing   | 6 (3.6)                  | 0 (0.0)             | 123 (4.4)         | 0 (0.0)          |

IQR = interquartile range; MDR-TB = multidrug-resistant tuberculosis; NA = not available; XDR-TB = extensively drug-resistant tuberculosis.

\* Percentage totals may sum to greater than 100% because of rounding.

+ These data were not available for non-health care workers.

‡ Data from 2003 to 2007.

#### DISCUSSION

The most striking finding in our study is the high incidence of hospital admission for drug-resistant tuberculosis among health care workers in KwaZulu-Natal, South Africa. Health care workers were found to have a 5- to 6-fold increased rate of hospital admission with MDR-TB or XDR-TB compared with non-health care workers. This burden of disease is particularly concerning because health care workers are also front-line care providers for patients with tuberculosis and HIV in the province.

The higher rate of hospitalization for drug-resistant tuberculosis among health care workers in our study most likely represents increased exposure to resistant MTB due to transmission within health care settings (20). The high rate of hospital admission for drug-resistant tuberculosis among health care workers is not likely explained by HIV infection because we did not find a difference in the percentage of health care workers and non-health care workers known to be HIV-positive. Health care workers did not report higher proportions of previous treatment of tuberculosis compared with non-health care workers. Therefore, previous treatment of tuberculosis does explain increased drug-resistant tuberculosis hospitalization rates for health care workers. Most health care workers in our study with MDR-TB or XDR-TB were young and female and had significant burden of HIV infection, which reflects the *Table 2.* Average Annual Incidence of Hospitalization for Treatment of Drug-Resistant Tuberculosis Among Health Care Workers and General Population Patients Hospitalized at King George V Hospital for Drug-Resistant Tuberculosis, 2003 to 2008\*

| Variable                   | Incidence in<br>Health Care<br>Workers<br>(per 100 000) | Incidence in<br>General<br>Population<br>Patients<br>(per 100 000) | Hospital<br>Admission<br>Incidence Rate<br>Ratio (95% CI)† |
|----------------------------|---|--|--|
| MDR or XDR-TB<br>incidence | 71.9  | 12.9   | 5.56 (4.87–6.35)   |
| MDR-TB incidence           | 64.8  | 11.9   | 5.46 (4.75–6.28)   |
| XDR-TB incidence           | 7.2   | 1.1  | 6.69 (4.38–10.20)  |

MDR-TB = multidrug-resistant tuberculosis; XDR-TB = extensively drug-resistant tuberculosis.

\* Restricted to persons aged  $\geq 20$  y.

+ P < 0.001 for all.

epidemiology of the HIV epidemic in KwaZulu-Natal (21). Female nurses are known to be a high-risk group for nosocomial tuberculosis (4) because of their close and prolonged risk of contact with patients with tuberculosis, and it is plausible that many young women in our cohort of health care workers were nurses or nursing trainees.

In South Africa, mortality associated with XDR-TB and HIV co-infection was highlighted by the wellpublicized 2006 outbreak at Tugela Ferry, KwaZulu-Natal (10). The authors suggested that because the XDR-TB outbreak was nosocomial, South African health care workers could be at high risk for primary acquisition of XDR-TB (20). Although we lack molecular epidemiologic data on tuberculosis isolates, we assume that many of the drug-resistant tuberculosis cases among health care workers reported in our study represent primary drug-resistant tuberculosis. This assumption is supported by the fact that health care workers in our study were less likely to report previous tuberculosis treatment than were non-health care workers and is consistent with other studies of risk for drug-susceptible tuberculosis among health care workers in Africa (3, 4, 22).

Drug-resistant tuberculosis among health care workers in the developing world has been underreported to date. To our knowledge, 1 case report has been published of a single health care worker infected with nosocomial XDR-TB in India (23). In the 1990s, case series from the United States reported nosocomial MDR-TB transmission to health care workers in a hospital (5), a dental clinic (24), and HIV/AIDS hospital wards (6). The increased risk for XDR-TB and MDR-TB hospitalization that we report is similar in magnitude to the estimated increased risk for drug-susceptible tuberculosis among health care workers in a hospital-based study (25) and in a systematic review of tuberculosis risk among health care workers in low-income countries (26). The elevated risk for XDR-TB among health care workers is a critical public health concern because of low cure rates, increased mortality, and potential nosocomial transmission to patients and other health care workers (25–28). The high proportion of HIV co-infection that we observed in health care workers admitted for initiation of tuberculosis therapy is particularly alarming, because in 2 recent studies, approximately 40% of patients co-infected with HIV and XDR-TB died within 12 months of therapy, and only 18% to 20% achieved culture conversion (11, 29).

Our study has several limitations owing to the challenges of collecting retrospective data in resourceconstrained settings. First, stigma may have prevented persons from seeking or accepting HIV testing (30); therefore, some HIV status may be misclassified, may be underreported, or both. Second, we lacked specific details about health care workers' occupational classifications, so we could not identify degree or duration of occupational exposures to MDR-TB and XDR-TB. Third, health care workers with drug-resistant tuberculosis may have been more likely to obtain microbiologic diagnosis, seek specialized referral, or access treatment at King George V Hospital compared with non-health care workers, leading to referral bias and an overestimate of MDR-TB or XDR-TB hospitalization incidence. For example, health care workers (who were more likely to be receiving antiretroviral drugs) may have been more likely to develop symptomatic tuberculosis (or immune reconstitution inflammatory syndrome) leading to increased tuberculosis diagnosis. On the other hand, health care workers are potentially less likely to seek care in a public health facility or self-identify as health care workers, leading to an underestimate of MDR-TB or XDR-TB hospitalization incidence. Fourth, the number of health care workers in KwaZulu-Natal was estimated by using professional registering bodies for professional workers and filled posts in the public health sector for nonprofessional workers (19). This undercounted the private sector of nonprofessional health care workers and could lead to an overestimate of hospitalization rates for drug-resistant tuberculosis among health care workers. On the other hand, the estimate may inflate the numbers of professional health care workers because registering bodies include health care workers who have retired, emigrated, or died or who no longer work in the health care sector, thus leading to an underestimate of rates (19). Fifth, patients may have come to King George V Hospital from other South African provinces or countries (for example, Leostho or Swaziland) resulting in an overestimation of our population-based rate estimates. The large distances between treatment centers and known health-seeking patterns in the region, however, make this an unlikely source of substantial error. Finally, our estimates of the incidence of drug-resistant tuberculosis are based on admission to a tuberculosis referral hospital rather than all diagnosed cases of MDR-TB and XDR-TB in KwaZulu-Natal. A recently published community-based study of MDR-TB and XDR-TB in KwaZulu-Natal reported nearly 50% 30-day mortality after collection of

sputum and before admission for appropriate second-line tuberculosis treatment. This suggests that our study of hospital admissions underestimates the incidence of MDR-TB and XDR-TB in KwaZulu-Natal (31) in both health care workers and non-health care workers.

From an infection-control standpoint, it is important to note that most health care workers with MDR-TB and XDR-TB were referred from, and may have worked at, non-tuberculosis specialist facilities. This implies that focusing infection-control efforts at specialist tuberculosis hospitals in South Africa to prevent nosocomial transmission is not enough. Although interventions for infection control and reduction of occupational risk in health care workers are well established in the developed world, they are not widely practiced in resource-poor settings (26). Targeted interventions, including administrative measures, environmental controls, and personal protection measures, have been recently reviewed (4, 26). Although some of these measures are out of reach in resource-poor settings, many are inexpensive and are potentially implementable, even in underresourced health care systems (26). Future research directions include identifying specific practices and occupational classifications that place health care workers at risk for drug-resistant tuberculosis. We are developing studies to identify obstacles to the implementation of best practices in infection control in KwaZulu-Natal health care institutions.

This study has implications for policymaking and the organization of health services in countries with endemic drug-resistant tuberculosis. Health care workers have a statistically significant higher risk for drug-resistant tuberculosis compared with the general population, and this should be addressed in policies for occupational risk reduction and infection control. Barriers, such as stigma around HIV status, are important to understand in order to construct effective occupational health and safety policies (30). A recently updated, evidence-based guideline on tuberculosis infection control for health care workers in hospitals and congregate settings published in 2009 by the World Health Organization (26) recommends prioritizing tuberculosis control on the national level. The guideline includes developing national infection-control policies in member states, implementing administrative and environmental controls, implementing ongoing surveillance for tuberculosis disease among health care workers, monitoring and evaluating infection-control measures, and conducting operational research. As our study suggests, policy measures that prioritize health care worker protection and risk may be critical for tuberculosis control in resource-constrained countries with endemic drug-resistant tuberculosis.

From Boston University School of Medicine and School of Public Health, Boston, Massachusetts; Centre for AIDS Programme of Research in South Africa, University of KwaZulu-Natal, Durban, South Africa; University of Calgary, Calgary, Alberta, Canada; Medical Research Council, Cape Town, South Africa; Salem State College School of Social Work, Salem, Massachusetts; King George V Hospital, Sydenham, South Africa; Emory University School of Medicine and Rollins School of Public Health, Atlanta, Georgia; University College London, London, United Kingdom; and McGill University, Montreal, Quebec, Canada.

Note: Drs. O'Donnell and Jarand contributed equally to this manuscript.

**Grant Support:** Dr. O'Donnell was supported by the National Institutes of Health (T32 AI52074; National Institutes of Allergy and Infectious Diseases) and an American Thoracic Society Career Development Award. In addition, Drs. O'Donnell and Padayatchi were supported by the Centre for AIDS Programme of Research. The National Institutes of Health and the U.S. Department of Health and Human Services funds the Centre for AIDS Programme of Research (A1069469). Dr. Padayatchi was also supported by Columbia University–Southern African Fogarty AIDS International Training and Research Programme funded by the Fogarty International Center, National Institutes of Health (D43TW00231). Dr. Pai is supported by a New Investigator Award from the Canadian Institutes of Health Research. These funding sources played no role in the study design or data analysis.

**Potential Conflicts of Interest:** Disclosures can also be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M10 -0897.

Reproducible Research Statement: Study protocol and statistical code: Available from Dr. O'Donnell (e-mail, max.odonnell@einstein.yu.edu). Data set: Not available.

Requests for Single Reprints: Max R. O'Donnell, MD, MPH, Division of Pulmonary Medicine, Albert Einstein College of Medicine, 1301 Morris Park Avenue, Bronx, NY 10461; e-mail, max.odonnell@einstein .yu.edu.

Current author addresses and author contributions are available at www .annals.org.

### References

1. World Health Organization. Global Tuberculosis Control: Surveillance, Planning, Financing. Geneva: World Health Organization; 2008.

2. 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. [PMID: 17519089]

3. Naidoo S, Jinabhai CC. TB in health care workers in KwaZulu-Natal, South Africa. Int J Tuberc Lung Dis. 2006;10:676-82. [PMID: 16776456]

 Joshi R, Reingold AL, Menzies D, Pai M. Tuberculosis among health-care workers in low- and middle-income countries: a systematic review. PLoS Med. 2006;3:e494. [PMID: 17194191]

5. Pearson ML, Jereb JA, Frieden TR, Crawford JT, Davis BJ, Dooley SW, et al. Nosocomial transmission of multidrug-resistant *Mycobacterium tuberculosis*. A risk to patients and health care workers. Ann Intern Med. 1992;117:191-6. [PMID: 1352093]

6. Dooley SW, Villarino ME, Lawrence M, Salinas L, Amil S, Rullan JV, et al. Nosocomial transmission of tuberculosis in a hospital unit for HIV-infected patients. JAMA. 1992;267:2632-4. [PMID: 1573751]

7. Basu S, Andrews JR, Poolman EM, Gandhi NR, Shah NS, Moll A, 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. [PMID: 17964351]

8. Abdool-Karim Q, Abdool-Karim SS. The evolving HIV epidemic in South Africa. Int J Epidemiol. 2002;31:37-40. [PMID: 11914290]

9. Buthelezi S. Situational analysis of TB drug resistance in KwaZulu-Natal Province, Republic of South Africa. In: Program and Abstracts of the 2nd Global

19 October 2010 Annals of Internal Medicine Volume 153 • Number 8 521

## ORIGINAL RESEARCH | South African Health Care Workers With Drug-Resistant Tuberculosis

XDR-TB Task Force Meeting, 9-10 April 2008, Geneva, Switzerland.

10. 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: 1575-80. [PMID: 17084757]

11. O'Donnell MR, Padayatchi N, Master I, Osburn G, Horsburgh CR. Improved early results for patients with extensively drug-resistant tuberculosis and HIV in South Africa. Int J Tuberc Lung Dis. 2009;13:855-61. [PMID: 19555535]

12. Wells CD, Cegielski JP, Nelson LJ, Laserson KF, Holtz TH, Finlay A, et al. HIV infection and multidrug-resistant tuberculosis: the perfect storm. J Infect Dis. 2007;196 Suppl 1:S86-107. [PMID: 17624830]

13. Raviglione MC, Smith IM. XDR tuberculosis—implications for global public health. N Engl J Med. 2007;356:656-9. [PMID: 17301295]

14. Reisner BS, Gatson AM, Woods GL. Evaluation of mycobacteria growth indicator tubes for susceptibility testing of *Mycobacterium tuberculosis* to isoniazid and rifampin. Diagn Microbiol Infect Dis. 1995;22:325-9. [PMID: 8582137]

15. Rüsch-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;44:688-92. [PMID: 16517840]

 Centers for Disease Control. Notice to Readers: Revised Definition of Extensively Drug-Resistant Tuberculosis MMWR. MMWR Morb Mortal Wkly Rep. 2006;55:1176.

17. Statistics South Africa. South African National Population Census 2001. Accessed at www.statssa.gov.za/census01/html/default.asp on 23 August 2010.

18. Statistics South Africa. South African Community Survey 2007. Accessed at www.statssa.gov.za/community\_new/content.asp on 23 August 2010.

19. Health Systems Trust. South African Health Review 2007. Accessed at www. hst.org.za/publications/711 on 23 August 2010.

20. Basu S, Galvani AP. The transmission and control of XDR TB in South Africa: an operations research and mathematical modelling approach. Epidemiol Infect. 2008;136:1585-98. [PMID: 18606028]

21. Abdool Karim SS, Churchyard GJ, Abdool Karim Q, Lawn SD. HIV infection and tuberculosis in South Africa: an urgent need to escalate the public health response. Lancet. 2009;374:921-33. [PMID: 19709731]

22. Galgalo T, Dalal S, Cain KP, Oeltmann J, Tetteh C, Kamau JG, et al. Tuberculosis risk among staff of a large public hospital in Kenya. Int J Tuberc Lung Dis. 2008;12:949-54. [PMID: 18647456]

23. James P, Christopher DJ, Balamugesh T, Gupta R. Death of a health care worker with nosocomial extensively drug-resistant tuberculosis in India [Letter]. Int J Tuberc Lung Dis. 2009;13:795-6. [PMID: 19460260]

24. Cleveland JL, Kent J, Gooch BF, Valway SE, Marianos DW, Butler WR, et al. Multidrug-resistant *Mycobacterium tuberculosis* in an HIV dental clinic. Infect Control Hosp Epidemiol. 1995;16:7-11. [PMID: 7897177]

25. Sotgiu G, Arbore AS, Cojocariu V, Piana A, Ferrara G, Cirillo DM, et al. High risk of tuberculosis in health care workers in Romania. Int J Tuberc Lung Dis. 2008;12:606-11. [PMID: 18492325]

26. World Health Organization. WHO policy on TB infection control in health-care facilities, congregate settings and households. Geneva: World Health Organization; 2009.

27. Askew GL, Finelli L, Hutton M, Laraque F, Porterfield D, Shilkret K, et al. *Mycobacterium tuberculosis* transmission from a pediatrician to patients. Pediatrics. 1997;100:19-23. [PMID: 9200355]

28. Dimitrova B, Hutchings A, Atun R, Drobniewski F, Marchenko G, Zakharova S, et al. Increased risk of tuberculosis among health care workers in Samara Oblast, Russia: analysis of notification data. Int J Tuberc Lung Dis. 2005;9:43-8. [PMID: 15675549]

29. Dheda K, Shean K, Zumla A, Badri M, Streicher EM, Page-Shipp L, et al. Early treatment outcomes and HIV status of patients with extensively drugresistant tuberculosis in South Africa: a retrospective cohort study. Lancet. 2010; 375:1798-807. [PMID: 20488525]

30. Zelnick J, O'Donnell M. The impact of the HIV/AIDS epidemic on hospital nurses in KwaZulu Natal, South Africa: nurses' perspectives and implications for health policy. J Public Health Policy. 2005;26:163-85. [PMID: 16022210]

31. Gandhi NR, Shah NS, Andrews JR, Vella V, Moll AP, Scott M, et al; Tugela Ferry Care and Research (TF CARES) Collaboration. HIV coinfection in multidrug- and extensively drug-resistant tuberculosis results in high early mortality. Am J Respir Crit Care Med. 2010;181:80-6. [PMID: 19833824]tional studies. J Clin Epidemiol. 2008;61:344-9. [PMID: 18313558] a randomized trial. JAMA. 2006;296:2927-38. [PMID: 17190893]

#### **ETOC**S

Register to receive the table of contents via e-mail at www.annals.org /site/misc/alerts.xhtml. You may choose to receive any or all of the following:

Notification that a new issue of *Annals of Internal Medicine* is online Complete table of contents for new issues Special announcements from ACP and *Annals* CME courses

Early-release articles

# **Annals of Internal Medicine**

Current Author Addresses: Dr. O'Donnell: Division of Pulmonary Medicine, Albert Einstein College of Medicine, 1301 Morris Park Avenue, Bronx, NY 10461.

Dr. Jarand: University of Calgary, 3500 26th Avenue Northwest, Calgary, Alberta T1Y 6J4, Canada.

Ms. Loveday: Medical Research Council of South Africa, Health Systems Research Unit, Francie van Zijl Drive, Parow Valley, Cape Town, South Africa.

Dr. Padayatchi, Ms. Werner, and Mr. Naidoo: Centre for the AIDS Programme of Research in South Africa (CAPRISA), Doris Duke Medical Research Institute (2nd Floor), University of KwaZulu-Natal, 719 Umbilo Road, Private Bag X7, Congella, 4013, Durban, South Africa.

Dr. Zelnick: Salem State College School of Social Work, 352 Lafayette Street, Salem, MA 01970.

Drs. Master and Osburn: 34 Holmleigh Road, Reservoir Hills, Durban, South Africa 4091.

Dr. Kvasnovsky: University of Maryland School of Medicine, 827 Saint Paul Street, Baltimore, MD 21202.

Ms. Shean and Dr. Dheda: Lung Infection and Immunity Unit, Division of Pulmonology & Clinical Immunology, University of Cape Town, Department of Medicine, H Floor, Old Main Building, Groote Schuur Hospital Observatory, Cape Town 7925, South Africa.

Dr. Pai: Department of Epidemiology & Biostatistics, 1020 Pine Avenue West, Montreal QC H3A 1A2, Canada.

Dr. Van der Walt: Tuberculosis Epidemiology and Intervention Research Unit, Private Bag X385, 0001 Pretoria, South Africa.

Dr. Horsburgh: Department of Epidemiology, Boston University School of Public Health, 72 East Newton Street, Boston, MA 02118.

Author Contributions: Conception and design: M.R. O'Donnell, M. Loveday, N. Padayatchi, I. Master, G. Osburn, M. Van der Walt, C.R. Horsburgh, K. Dheda.

Analysis and interpretation of the data: M.R. O'Donnell, J. Jarand, M. Loveday, N. Padayatchi, L. Werner, C. Kvasnovsky, M. Pai, M. Van der Walt, C.R. Horsburgh, K. Dheda.

Drafting of the article: M.R. O'Donnell, J. Jarand, N. Padayatchi, J. Zelnick, L. Werner, K. Naidoo, M. Van der Walt, K. Dheda.

Critical revision of the article for important intellectual content: M.R. O'Donnell, J. Jarand, M. Loveday, N. Padayatchi, C. Kvasnovsky, K. Shean, M. Pai, C.R. Horsburgh, K. Dheda.

| Appendix Table 2. | Estimates of | Adult Non-   | Health Care |
|-------------------|--------------|--------------|-------------|
| Worker Population | n in KwaZulu | -Natal, Sout | h Africa*   |

| Year  | Population in<br>KwaZulu-Natal, <i>n</i> | Population Aged<br>≥20 y, %† | Population in<br>KwaZulu-Natal<br>Aged ≥20 y, <i>n</i> |
|-------|--|------------------------------|--|
| 2001‡ | 9 426 017                                | 53.3                         | 5 024 068  |
| 2002  | 9 564 885                                | -                            | 5 098 084  |
| 2003  | 9 703 753                                | -                            | 5 172 100  |
| 2004  | 9 842 621                                | -                            | 5 246 117  |
| 2005  | 9 981 489                                | -                            | 5 320 134  |
| 2006  | 10 120 357                               | -                            | 5 394 150  |
| 2007§ | 10 259 230                               | -                            | 5 437 392  |
| 2008  | 10 400 009                               | -                            | 5 543 205  |

\* Data from references 17 and 18. National census data were obtained in 2001; a national community survey was done in 2007. Population estimates for the years in between were extrapolated. The percentage of the population aged  $\geq 20$  y (adult) is based on percentages from the 2001 national census.

<sup>+</sup> The percentage of the population aged  $\geq$ 20 y was assumed to be 53.3% from 2003 to 2008 because actual data were not available.

Population numbers and age structure are from the 2001 national census data.
Population numbers are from the 2007 community survey data.

Final approval of the artide: M.R. O'Donnell, J. Jarand, M. Loveday, N. Padayatchi, L. Werner, C. Kvasnovsky, M. Pai, M. Van der Walt, C.R. Horsburgh, K. Dheda.

Provision of study materials or patients: M. Loveday, N. Padayatchi, I. Master, G. Osburn, C. Kvasnovsky.

Statistical expertise: L. Werner, C.R. Horsburgh.

Obtaining of funding: C. Kvasnovsky, K. Shean.

Administrative, technical, or logistic support: M. Loveday, K. Shean, K. Dheda.

Collection and assembly of data: M.R. O'Donnell, J. Jarand, M. Loveday, C.R. Horsburgh.

#### Appendix Table 1. Estimates of Health Care Workers in Kwazulu-Natal, South Africa, by Year\*

| Occupational Classification+   | Year   |        |        |        |        | Total  |         |
|--|--------|--------|--------|--------|--------|--------|---------|
|  | 2003‡  | 2004   | 2005   | 2006   | 2007   | 2008   |         |
| Dental practitioners (includes all subclassifications)                 | 803    | 803    | 803    | 803    | 803    | 803    | 4818    |
| Enrolled nurses  | 12 404 | 12 404 | 12 404 | 13 936 | 13 936 | 13 936 | 79 020  |
| Professional nurses  | 20 202 | 20 202 | 20 202 | 20 202 | 20 202 | 20 202 | 121 212 |
| Student nurses   | 2051   | 2051   | 2051§  | 2232§  | 2175§  | 2175§  | 12 735  |
| Physicians (includes all subclassifications)                           | 6265   | 6265   | 6265   | 6265   | 6265   | 6265   | 37 590  |
| Nurses' assistants   | 5871   | 5871   | 5871§  | 6116§  | 6056§  | 6056§  | 35 841  |
| Environmental therapists, occupational therapists, or physiotherapists | 1643   | 1643   | 1643   | 1643   | 1643   | 1643   | 9858    |
| Radiographers  | 980    | 980    | 980    | 980    | 980    | 980    | 5880    |
| Pharmacists  | 1593   | 1593   | 1593   | 1666   | 1738   | 1738   | 9921    |
| Psychologists  | 697    | 697    | 697    | 697    | 697    | 697    | 4182    |
| Total  | 52 509 | 52 509 | 52 509 | 54 540 | 54 495 | 54 495 | 321 057 |

\* All values are numbers. Data from reference 19.

+ Registered with appropriate health services council (except nurses' assistants). May include health care workers who are abroad, retired, or nonpracticing; in the private sector; or in the public sector.

**‡** Estimates from years in which data were missing are based on known numbers of health care workers.

§ Filled posts in the public sector. These are positions for which registering boards do not exist and exclude private sector workers for whom data were not available.