

Knowledge of tuberculosis treatment prescription of health workers: A systematic review

Marieke J. van der Werf^{1,2}, Miranda W. Langendam³, Emma Huitric⁴, Davide Manissero⁴

¹ KNCV Tuberculosis Foundation, The Hague, The Netherlands

² Center for Infection and Immunity Amsterdam (CINIMA), Academic Medical Center, University of Amsterdam, The Netherlands

³ Dutch Cochrane Centre, Academic Medical Center, University of Amsterdam, The Netherlands

⁴ European Centre for Disease Prevention and Control (ECDC), Stockholm, Sweden

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Corresponding author:

Marieke J. van der Werf

KNCV Tuberculosis Foundation

P.O. Box 146

2501 CC The Hague

The Netherlands

Phone: + 31 70 427 0961

Fax: + 31 70 358 4004

Email: vanderwerfm@kncvtbc.nl

Abstract

Treating tuberculosis (TB) patients with inappropriate treatment regimens can lead to treatment failure, and thus uncured patients, and/or to the development of (multi)-drug resistance. A systematic review was performed to assess the knowledge of appropriate TB drug regimens among all categories of health care workers (HCW).

MEDLINE, EMBASE and other databases were searched for relevant articles in January, 2011. Observational studies published as of year 2000, which assessed HCW-knowledge of TB-treatment, were selected. A treatment regimen, drug dosage or treatment duration was considered inappropriate if it was not recommended by national guidelines or by the WHO.

Of 1,896 studies, 31 were included from 14 different countries. No study was performed in Europe. In all studies, HCWs with inappropriate knowledge of treatment regimens (8% to 100%) or treatment duration (5% to 99%) were observed. The few studies providing detailed data showed that HCWs mainly reported giving treatment regimens with too many drugs and for too long. Knowledge of appropriate doses was also insufficient in most studies.

The available studies show that there is a lack of knowledge of national or international TB treatment guidelines and recommendations. Generalization of the findings to other settings and countries should be done with caution.

Introduction

Treating tuberculosis (TB) patients with inappropriate TB treatment regimens, i.e. regimens that are not according to the World Health Organization (WHO) treatment guidelines (1-4), can result in the development of multi-drug resistance (MDR-TB) (5). A systematic review published as part of this series in the European Respiratory Journal assessed the percentage of TB patients that received an inappropriate treatment regimen (6). Thirty-seven studies were included. The studies were from 22 countries, and one study was from multiple countries. Almost all continents were represented. In 67% of the studies inappropriate treatment regimens were prescribed. The percentage of patients receiving inappropriate regimens ranged between 0.4% and 100%. In 19 studies detailed information on the treatment regimen was missing.

The prescription of adequate TB treatment (regimen, dosage, and duration) requires knowledge of existing treatment recommendations. Since 1993, the WHO has published and updated international Tuberculosis Treatment Guidelines (1-4), aiming to provide national TB programmes (NTPs) and the medical profession evidence-based, practical guidance on effective TB case-management. Many countries have considered and included these recommendations in their own national TB guidelines. Studies, often described as knowledge, attitude and practice (KAP) studies, assessing whether these recommendations are known to individual health care workers (HCWs) have been performed. These studies commonly measure either the extent of knowledge on TB treatment among HCWs, or the HCWs' intended behaviour ("What treatment would you prescribe for a TB patient?").

To add to the evidence obtained in the systematic review on TB treatment regimens prescribed to TB patients (6), and investigate a possible cause for inappropriate treatment, we conducted a systematic review of the literature to specifically assess the knowledge of appropriate TB drug regimens among health care workers (i.e. "do health care workers know what type of drugs, dosage, and duration of treatment are recommended by national guidelines or the WHO treatment guidelines?"). For the purpose of this study, health care workers are here-defined as individuals working in public and/or private health care facilities, and those undergoing medical training (medical students and interns).

Methods

We followed the Cochrane Handbook for Systematic Reviews and the PRISMA statement (7).

Search strategy

To identify relevant studies we conducted a literature search in the bibliographic databases MEDLINE and EMBASE on January 6, 2011. We also searched for guidelines in the National Guideline Clearinghouse and other guideline databases. Abstracts of conference proceedings were sought in BIOSIS. Reviews and guidelines were searched for in the TRIP data base (January/February 2011).

Keywords used in the search were determined in collaboration with the clinical librarian of the Dutch Cochrane Centre and included "Tuberculosis" OR "TB" OR "Mycobacterium" AND for TB treatment "Prescriptions" OR "Treatment regimen" OR "Combination treatment" OR "Treatment strategy /-ies" OR "Drug supply" OR "Standard treatment / standard regimen" OR "Inappropriate use, appropriate use, rational use, irrational use, misuse". The search was limited to the publication years 2000-2010 as we were interested in 'current' knowledge of treatment guidelines. We did not limit the search to a geographical area or countries. Also, we did not use any language restriction. If an English language abstract was available that provided the necessary information the article was included. We excluded case reports. The search strategy was supplemented by hand searching reference lists of included articles and identified relevant review articles.

Selection of studies

We included observational studies among HCW assessing knowledge of TB treatment (regimen, dosage, duration) or intended prescription practices ("What treatment would you prescribe?"). For both knowledge and intended prescription practices we will use the term 'knowledge' in this paper. We excluded studies that did not report knowledge of the treatment regimens, dosage, or treatment duration in sufficient detail to make a judgment on the appropriateness and in which the authors did not make a statement about appropriateness. Studies identified by the search strategy were reviewed for eligibility based on title and abstract by one investigator (MvdW). Full manuscripts of the references selected based on title/abstract were assessed by one investigator (MvdW). For both steps a 10% random sample was assessed by a second investigator (ML) and compared with the assessment of the first reviewer. Inconsistencies in assessment were discussed and disagreements resolved by consensus. A complete double selection was planned if the 10% random sample revealed relevant inconsistencies. There were no relevant inconsistencies.

Data extraction

One reviewer (MvdW) extracted all relevant data-items from the included studies using a data-extraction form. This included the following items: year of publication; country where study was performed; study-setting; aim of the study; period of data collection; type of HCW; selection method (of respondents); method of data collection; number of respondents selected/invited; number of respondents participating; any information on non-respondents; characteristics of included HCW (gender, age, education, etc); number of TB cases seen by each HCW ("experience"); intended or observed TB treatment; type of TB patient for which treatment is reported; TB treatment regimen; TB treatment dose; TB treatment duration;

prevalence of inappropriate regimen according to authors. A second reviewer (ML) checked the extracted results. Inconsistencies were discussed to obtain consensus.

Data analysis and synthesis of results

The results were summarized qualitatively. For studies describing treatment regimens reported by HCWs, but without indicating whether they were appropriate according to national or WHO guidelines, the reported regimens were assessed and assigned to the appropriate or inappropriate category by the authors using the WHO treatment guidelines as reference (1-3). Table 1 lists the applicable WHO treatment guideline for different periods. One reviewer assessed the regimens (MvdW) and the other reviewer (ML) cross-checked the assessment. The adequacy of knowledge of HCWs on regimen, dose, and duration of TB treatment is summarized. We present results for health care workers in private settings and health care workers in public settings.

Results

Study selection

The search in MEDLINE and EMBASE resulted in 1,896 unique references. A total of 21 papers were considered relevant (Figure 1). The National Guideline Clearinghouse, NICE, SIGN and TRIP data bases did not provide aggregated evidence of knowledge of TB treatment by HCWs. In BIOSIS, 583 references were identified using the keywords 'tuberculosis AND treatment' on May 20, 2011. Assessment of these references did not provide new references.

Checking the reference lists of the included papers revealed 10 relevant studies. Thus in total, 31 articles were included in the review. For two studies only abstracts were available (8;9).

Description of included studies

The objective of 29 of the 31 included studies was either to assess knowledge of TB treatment and/or intended practices on TB treatment, or to assess HCW compliance with the treatment guidelines. One study's objective was 'To identify the factors preventing a better understanding of TB as a social and medical problem' (10) and one study, of which only an abstract was available, did not specify the objective (9).

The median sample size of the included studies was 114 HCW (range 22-1355). The studies were performed in 14 different countries (Table 2), of which fourteen (45.2%) were in India or Pakistan. Almost all continents were represented: South Asia (n=15 studies), East and South East Asia (n=5 studies), South West Asia (n=4 studies), Africa (n=5 studies), America (n=2 studies). There were no studies from Europe.

A self-administered questionnaire was used in 12 (38.7%) studies (8;11-21), and in 13 (41.9%), participants were interviewed using a questionnaire (10;22-32). Four (12.9%) used a questionnaire but did not specify whether it was performed by interview or was a self-administered questionnaire (33-36). Two studies did not report how the data were collected (9;37).

Eleven studies (35.5%) selected HCWs using random selection methods (8;10;13;19;20;26-29;34;35), and 10 (32.3%) included all eligible individuals (11;14-17;21;22;24;31;36). Six (19.4%) studies used convenience- or purposeful-sampling, or included HCWs who wanted to participate (12;18;23;30;32;38), and four (12.9%) studies did not specify the selection method (9;25;33;37).

Sixteen (51.6%) studies were performed among HCW practising in a private setting (12-15;18-20;22-24;26-28;30;35;36), three (9.7%) among both HCW practicing in a private setting and in a public setting (21;29;31), three (9.7%) among medical students or interns (8;9;17), and nine (29.0%) studies did not specify whether the HCWs were practicing in a private or public setting (10;11;16;25;32-34;37;38) (Table 3).

Prevalence of inappropriate knowledge of TB treatment

The percentage of HCWs with inappropriate knowledge of TB regimens in the studies among private providers ranged between 20% and 100% (median 74%; Table 3); in one study the level was reported as higher than 41% (12). The level of inappropriate knowledge of treatment regimens ranged between 8% and 93% (median 73%) among HCWs practicing in settings other than uniquely private. Three studies did not provide the data to assess the

percentage (10;21;33), in one study it was less than 25% (37) and in another study more than 55% (17).

Fifteen studies provided information on HCWs experience in treating TB patients (12-16;22;24;29-36). In the 10 studies where at least 80% of the HCWs managed TB cases, or where the average number of TB cases managed per HCW was at least 5 per month, 8% to 100% had inappropriate knowledge of the recommended treatment regimen (median 61.5) (13-16;22;29;32;34-36).

Six studies provided data that allowed assessing whether HCWs' knowledge on the number of different drugs required in a TB treatment regimen was adequate, or whether they would prescribe too many or too few drugs. Three studies specifically reported about HCW practicing in a private setting. Auer et al. (2006) reported that 9 of 45 (20%) private practitioners would prescribe less than 4 drugs in the intensive phase for far-advanced TB (22); this is 22% of all inappropriate answers reported in the study. Khan et al. (2003) reported that 10 of 120 private physicians would prescribe less than 4 drugs in the intensive phase for pulmonary TB (15), i.e. 63% of all reported inappropriate treatment in the intensive phase. In another study, 2% of private practitioners would prescribe 3 drugs for sputum-positive pulmonary TB (36), whereas 18% would prescribe an inappropriate regimen of 4 or 5 drugs.

Three studies among health care workers for which the setting was not specified provided information about prescription of more or less than 4 drugs during the intensive phase. Cirit et al. (2003) reported that 98 of 162 (60%) physicians prescribed less than 4 drugs for newly diagnosed TB (25). Of 84 family physicians with an interpretable answer in the study by Rizvi et al. (2001), 20 (25%) would prescribe a 1-, 2- or 3-drug regimen for newly diagnosed pulmonary TB and 6 (8%) an inappropriate regimen of more than 4 drugs (34). Yu et al. (2002) reported that all health care workers reporting inappropriate prescription (8%) would prescribe a 3-drug regimen for pulmonary TB (32).

Six studies reported on the knowledge of TB drug-dose in regimens (11;15;20-22;37), Table 3. One study reported all mentioned doses as adequate (11). Two studies reported that 46% (20), and 50% (37) of the HCW would prescribe an incorrect dose (too low or too high). Three studies reported on knowledge of dose by individual drug (15;21;22), Table 4. In two studies, high doses were more frequently mentioned (15;22) than low doses for most drugs, and in one study, participants would more frequently prescribe low doses of isoniazid, pyrazinamide, and ethambutol (21). For rifampicin, the participants would more frequently prescribe high doses.

Knowledge of the duration of treatment regimens was reported in 13 studies (10;14;16;17;20;21;25;26;32-36). Between 1% and 95% of the HCWs knew the correct duration of treatment. Overall, only few health care providers would prescribe a regimen that was too short (<6 months): 3% (14), 8% (36), 11% (17), 52% (25), 4% (10), and none in the studies reported by Rizvi et al. (2001) (34) and Yu et al. (2002) (32).

Discussion

The studies included in this systematic review show that a large proportion of HCWs do not know or do not prescribe regimens that follow the recommended national or international guidelines.

Treatment with too few drugs, for a too short duration, has been shown to result in ineffective treatment outcomes of patients. Specifically, patients treated with regimens in which rifampicin is only given for the first one- to two-months; i.e. only used in the intensive treatment phase, have significantly worse treatment outcomes compared to regimens with rifampicin throughout therapy. These patients further have an increased risk of acquiring rifampicin-resistance (39). It has also been shown that treatment with fewer than four drugs in the intensive phase results in higher percentages of relapse cases (40). It is on this basis that WHO guidelines recommend for new pulmonary TB patients a regimen containing isoniazid, rifampicin, pyrazinamide and ethambutol in the 2-month intensive treatment phase, and isoniazid and rifampicin in the 4-month continuation treatment phase (4). The studies observed in this review, in which HCW reported prescribing too few drugs are therefore of concern, both for the treatment outcome of patients as well as for the risk for resistance-development. Three studies, without specified setting (private or public), reported a higher frequency of treatment with less than four drugs compared to treatment with more than four drugs (25; 32; 34).

A known cause for treatment default is the burden of drug side-effects to patients (41; 42). Three studies among HCWs practicing in a private setting reported a higher frequency of treatment with too many drugs among this group of HCWs (15; 22; 36). Whilst it is essential to treat TB with the recommended number of drugs and for the correct duration, due to the side effects caused by several drugs (especially in HIV-infected TB patients), the use of too many drugs should be avoided (43-45). This is further supported by the knowledge that treatment with an increased number of drugs, such as the treatment of MDR-TB; is known to cause a higher frequency of side effects (46) and is a known cause for default from treatment (41; 42). Based on this, prescribing more drugs than what is officially recommended should be discouraged so as to reduce development of side effects and thus default from treatment.

For most drugs, the occurrence of side effects is dose-dependent (47) and thus prescribing a higher dose will give a higher chance of side effects. In the three studies providing information on intended prescription of high doses (15; 21; 22), there was no clear tendency that excessive doses were more frequently prescribed than insufficient doses.

It should be noted that the included study populations in the identified studies might not be representative of all public and private health care workers. For example, none of the 31 included studies were from Europe. Also, India and Pakistan were highly over-represented, with almost half of the 31 studies set in these two countries alone. On the other hand, most of the studies used random selection, or included the complete target population, indicating that the participating health care workers should be representative of the target population.

In a separate study published in this series of the European Respiratory Journal we assessed the prevalence of inappropriate TB treatment in populations of TB patients (6) and observed that in 67% of the included studies, inappropriate regimens were prescribed. In this current review, all the included studies reported on HCWs' knowledge of TB regimens, and all showed a lack of knowledge among the different groups of HCW. Even among the 10 studies on HCWs with experience in managing TB patients, knowledge was insufficient (13-16; 22; 29; 32; 34-36). Although the HCW study population in the current study does not link specifically to the settings in our assessment of prevalence of inappropriate treatment (6), the lack of knowledge among HCW is a suggestive cause for the prevalence of inappropriate treatment regimens. In

other words, if knowledge of appropriate TB regimens is insufficient, the actual prescription is most likely also insufficient. Indeed, a previous study assessing which TB-treatment was actually prescribed by primary doctors, showed that 75% made prescription errors with respect to one or more aspects of treatment. This included errors in treatment regimen (45.2%), treatment duration (64.5%) and drug dosages (30%) (48). In another study, in which a simulation patient was used, only 2 (3.7%) prescriptions out of 53 met the required standards for TB patients as defined by the national TB program (49). These two studies measuring the actual practices are in line with the studies assessing HCW knowledge.

TB treatment consists of different treatment modalities: regimen, dose, frequency and duration. Most of the 31 included studies provided information on treatment regimen (91%, n=30), only a few studies provided information on dose (19%, n=6), or duration of the treatment regimen (42%, n=13), and none of the studies provided information on the frequency of treatment (i.e. daily, thrice weekly, twice weekly etc). The adequacy of the knowledge of TB treatment could therefore only be assessed to a limited extent.

Unpublished studies cannot be found with a systematic review search strategy and were thus not included in our search strategies. It is possible that studies recording mainly adequate knowledge of treatment regimens are less often published than studies that measure and report on inadequate knowledge. If this is the case, overall knowledge of health care workers on TB treatment might be better, compared to what we report in this systematic review.

Ten of the 31 studies included in our systematic review were identified by reviewing the references of included studies. These ten studies did not contain the keywords that we used in our search strategy with regard to the title, abstract or key words section. They did however contain the words "treatment" or "therapy" in the title or abstract. Since the words "treatment" or "therapy" are not specific and would result in a very large number of records we did not include them in our search strategy. With our search strategy and careful examination of the included studies' references, we believe that the majority of relevant published manuscripts on health care workers' knowledge of treatment were identified.

Conclusion

The available studies in this systematic review show that there is a lack of knowledge of the national or international guidelines and recommendations for TB treatment. Generalization of the findings to other settings and countries should be done with caution.

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Figure 1: Summary of literature search and study selection.

Note to figure: References excluded based on evaluation of full manuscript: treatment regimen insufficient detail (50-53); patient level data (54-56); pharmacy dispensing information (57;58); not measuring knowledge (48;49)

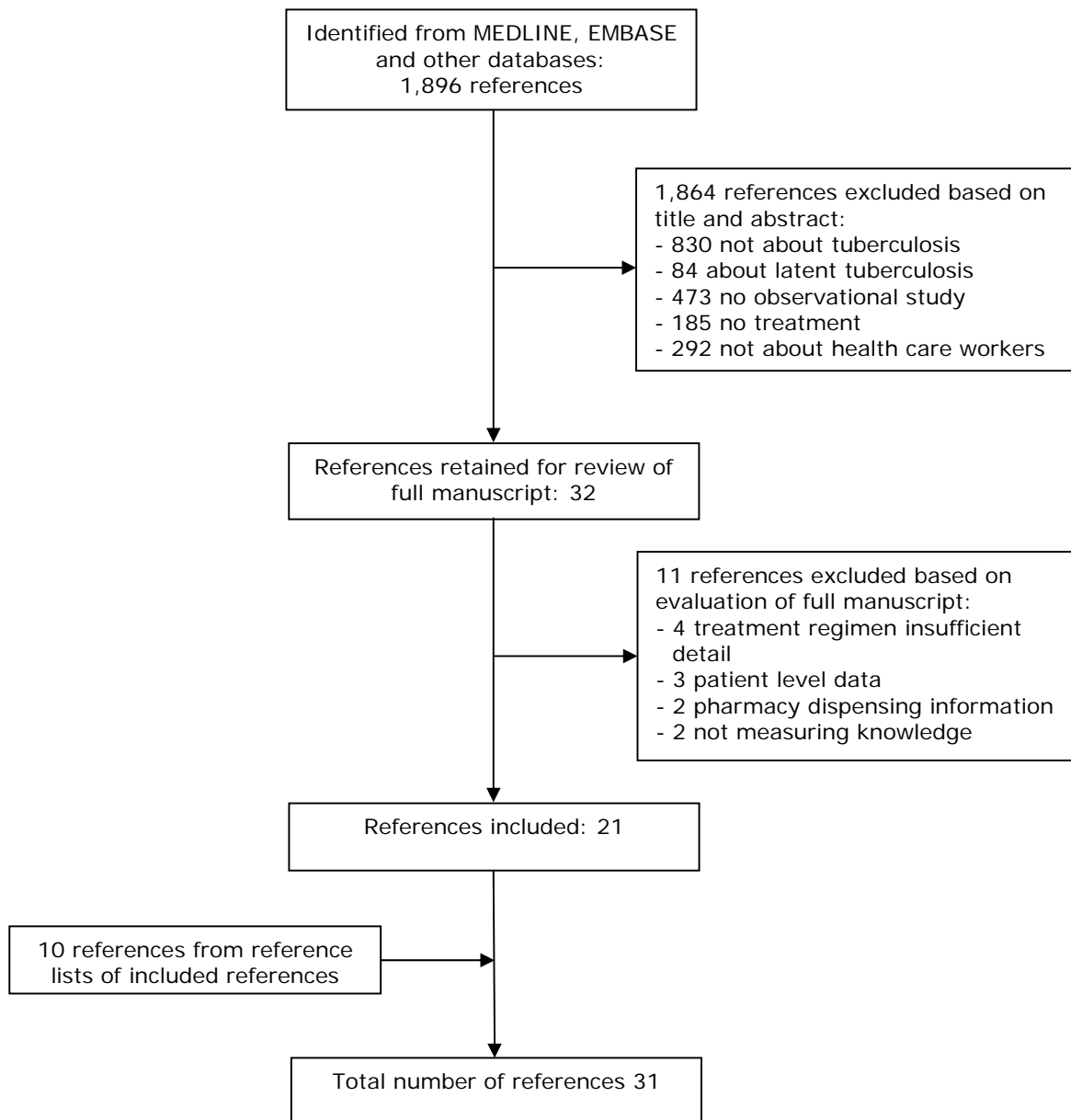


Table 1 Applicability of the different WHO treatment of tuberculosis guidelines

Years of data-collection	WHO guideline
1995-1999	First edition: 1993 (1)
1999-2004	Second edition: 1997 (2)
2005-2010	Third edition: 2003 (3)

Table 2: Characteristics of the included studies and prevalence of inappropriate regimens

Author	Country	Setting (of the study)	Period of data collection	Type of health care worker	Sample size
South Asia					
Agarwal 2009 (11)	India	Conference	2006	National and international orthopedic faculty and infectious disease experts	52
Roy 2005 (18)	India	Municipal area	Not reported	Qualified private medical practitioners	55
Udwadia 2010 (36)	India	Slum	Not reported	Private medical practitioners	106
Bhalla 2001 (37)	India	Medical institute	Not reported	Residents and faculty members from various departments	40
Rajpal 2007 (17)	India	Medical schools	2002	Interns that had gone through their training in various disciplines of medicine	287
Greaves 2007 (27)	India	City and surrounding area	2006	Private practitioners	45
Vandan 2008 (21)	India	District	2007	Medical physicians (public and private)	141
Datta 2010 (13)	India	District	2008	Private allopathic physicians	260
Hurtig 2000 (14)	Nepal	Municipality	1998	Licensed allopathic for profit private practitioners which were assumed to see tuberculosis patients	43
Shah 2003 (35)	Pakistan	Large cities	Not reported	Formally qualified medical graduates who were practicing medicine outside the government sector and who had managed at least one pulmonary tuberculosis patient during the previous year	245
Rizvi 2001 (34)	Pakistan	City	Not reported	Family physicians that had no postgraduate qualification and were treating at least 7-10 tuberculosis patients per months	150
Khan 2005 (9)	Pakistan	Teaching hospitals	Not reported	Interns	440
Khan 2003 (15)	Pakistan	City	2002	Qualified private practitioners	120
Shehzadi 2005 (38)	Pakistan	Regions	2003	General practitioners	88

Ahmed 2009 (12)	Pakistan	Rural district	2007	Private practitioners with basic medical degree and doing private practice for at least one year	22
<i>East and South East Asia</i>					
Bai 2003 (8)	China	Medical schools	Not reported	Final-year medical students	439
Mahendradhata 2007 (28)	Indonesia	City	2004	Private practitioners	164
Yu 2002 (32)	Philippines	Tertiary care hospital	Not reported	Specialist physicians who dealt with pulmonary tuberculosis patients	38
Auer 2006 (22)	Philippines	Urban district (Metro Manilla)	1999-2000	Private for-profit practitioners who treat tuberculosis	45
Portero 2003 (30)	Philippines	Country	2001	Private physicians	1355
<i>South West Asia</i>					
Shirzadi 2003 (20)	Iran	Large cities	2001-2002	Private sector physicians	732
Hashim 2003 (10)	Iraq	Public Health Centers in the country	2001-2002	Health care workers	500
Deveci 2003 (33)	Turkey	City	Not reported	Practicing physicians who provide first line treatment	66
Cirit 2003 (25)	Turkey	City	2001	Physicians	208
<i>Africa</i>					
Shimeles 2006 (19)	Ethiopia	City	2003	Private, for-profit medical doctors	120
Ayaya 2003 (23)	Kenya	Cosmopolitan town	Not reported	Medical doctors practicing privately	53
Chakaya 2005 (24)	Kenya	Slum	2001	Private health care providers	75
Suleiman 2003 (31)	Somalia	Part of country	2001	Qualified medical practitioners (public and private sector)	53
Nshuti 2001 (29)	Uganda	Urban district	1999	Doctor or medical assistant from public and private clinics	114

America					
Dato 2009 (26)	Argentina	City	2007	Private doctors: general practitioners, infectious disease specialists, and pulmonologists	61
LoBue 2001 (16)	United States of America	County	Not reported	Physicians who reported a tuberculosis suspect or case to the San Diego County Tuberculosis Control for the years 1995-1997	150

Table 3: Prevalence of inappropriate tuberculosis regimens, incorrect dose, and incorrect duration of tuberculosis treatment in different types of health care workers.

Reference to study	Prevalence of		
	Inappropriate regimen (%)	Incorrect dose (%)	Incorrect duration (%)
<i>Health care workers in private setting</i>			
Ahmed 2009 (12)	>41		
Auer 2006 (22)	91	Rifampicin 9 Isoniazid 84 Pyrazinamide 88 Ethambutol 57	
Ayaya 2003 (23)	77		
Chakaya 2005 (24)	92		
Dato 2009 (26)	22		33
Datta 2010 (13)	79		
Greaves 2007 (27)	58		
Hurtig 2000 (14)	49		31
Khan 2003 (15)	74	Rifampicin 24 Isoniazid 17 Pyrazinamide 48 Ethambutol 49	Rifampicin 50 Isoniazid 48 Pyrazinamide 39 Ethambutol 47
Mahendradhata 2007 (28)	73		
Portero 2003 (30)	89		
Roy 2005 (18)	70		
Shah 2003 (35)	100		99
Shimeles 2006 (19)	90		
Shirzadi 2003 (20)	66	46	50
Udwadia 2010 (36)	20		64
<i>Health care workers in public and private setting</i>			
Nshuti 2001 (29)	76		
Suleiman 2003 (31)	93		
Vandan 2008 (21)	No data	Rifampicin 22 Isoniazid 78 Pyrazinamide 47 Ethambutol 72	16
<i>Medical students or interns</i>			
Bai 2003 (8)	83		
Khan 2005 (9)	48		
Rajpal 2007 (17)	>55		70
<i>Health care workers setting not specified</i>			
Agarwal 2009 (11)	81	0	
Bhalla 2001 (37)	<25	50	
Cirit 2003 (25)	81		65
Deveci 2003 (33)	No data		52
Hashim 2003 (10)	No data		13
LoBue 2001 (16)	11		26
Rizvi 2001 (34)	33		87
Shehzadi 2005 (38)	70		
Yu 2002 (32)	8		5

Table 4: Percentage of health care providers that reported an inadequate dose for the four first line drugs rifampicin, isoniazid, pyrazinamide, and ethambutol in three studies providing information.

Drug	Percentage reporting an incorrect dose (%)					
	Auer 2006 (22)		Khan 2003 (15)		Vandan 2008 (21)	
	Too low	To high	Too low	To high	Too low	To high
Rifampicin	1 (2)	3 (7)	20 (20)	5 (4)	0 (0)	28 (22)
Isoniazid	2 (4)	36 (80)	6 (6)	13 (11)	98 (75)	3 (2)
Pyrazinamide	2 (5)*	35 (83)*	15 (15)	40 (33)	43 (33)	18 (14)
Ethambutol	10 (33)#	7 (23)#	10 (10)	47 (39)	83 (64)	11 (8)

* Data of 42 instead of 45 participants

Data of 30 instead of 45 participants