

## SERIES “RATIONAL USE OF ANTI-TUBERCULOSIS DRUGS”

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# Knowledge of tuberculosis-treatment prescription of health workers: a systematic review

Marieke J. van der Werf<sup>\*,#</sup>, Miranda W. Langendam<sup>†</sup>,  
Emma Huitric<sup>+</sup> and Davide Manissero<sup>+</sup>

**ABSTRACT:** Treating tuberculosis (TB) patients with inappropriate treatment regimens can lead to treatment failure and, thus, patients who have not been cured 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 healthcare workers (HCWs).

In January 2011, MEDLINE, EMBASE and other databases were searched for relevant articles. Observational studies published as of the year 2000 that 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 World Health Organization (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 (8–100%) or treatment duration (5–99%) 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. Generalisation of the findings to other settings and countries should be done with caution.

**KEYWORDS:** Healthcare workers, inappropriate, regimen, treatment, tuberculosis

Treating tuberculosis (TB) patients with inappropriate TB treatment regimens, *i.e.* regimens that are not in accordance with the World Health Organization (WHO) treatment guidelines [1–4], can result in the development of multidrug-resistant (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]. 37 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 TB treatment guidelines [1–4], aiming to provide national TB programmes (NTPs) and the medical profession with 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 studies, assessing whether these recommendations are known to individual healthcare workers (HCWs) have been performed. These studies commonly measure either the extent of knowledge about TB treatment among HCWs, or the HCWs' intended behaviour (“What treatment would you prescribe for a TB patient?”).

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### AFFILIATIONS

\*KNCV Tuberculosis Foundation, The Hague,

#Center for Infection and Immunity Amsterdam (CINIMA),

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

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

### CORRESPONDENCE

M.J. van der Werf  
European Centre for Disease Prevention and Control (ECDC)  
SE-171 83 Stockholm  
Sweden  
E-mail: marieke.vanderwerf@ecdc.europa.eu

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To add to the evidence obtained in the systematic review on TB treatment regimens prescribed to TB patients [6] and to 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 HCWs (*i.e.* “do HCWs 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, HCWs are defined as individuals working in public and/or private healthcare facilities, and those undergoing medical training (medical students and interns).

## METHODS

We followed the *Cochrane Handbook for Systematic Reviews* [7] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [8].

### 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 identifying relevant review articles.

### Selection of studies

We included observational studies among HCWs 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 regimen, 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 (M.J. van der Werf). Full manuscripts of the references selected based on title/abstract were assessed by one investigator (M.J. van der Werf). For both steps, a 10% random sample was assessed by a second investigator (M.W. Langendam) 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 (M.J. van der Werf) 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 nonrespondents; characteristics of included HCWs (sex, 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; and prevalence of inappropriate regimen according to authors. A second reviewer (M.W. Langendam) checked the extracted results. Inconsistencies were discussed to obtain consensus.

### Data analysis and synthesis of results

The results were summarised 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 guideline for different periods. One reviewer assessed the regimens (M.J. van der Werf) and the other reviewer (M.W. Langendam) cross-checked the assessment. The adequacy of knowledge of HCWs on regimen, dose and duration of TB treatment is summarised. We present results for HCWs in private settings and in public settings.

## RESULTS

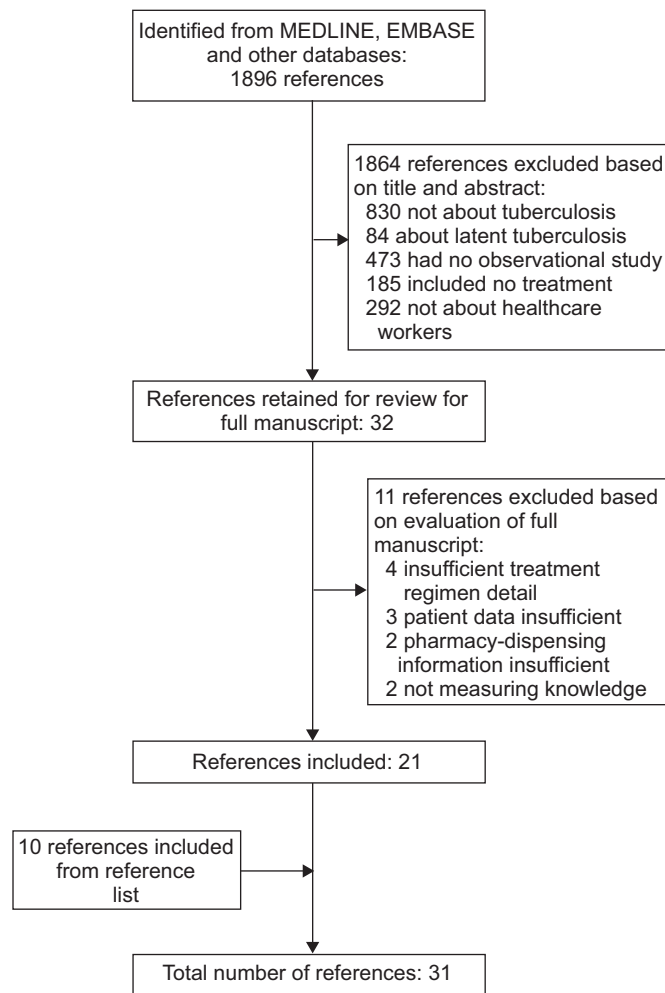
### Study selection

The search in MEDLINE and EMBASE resulted in 1,896 unique references. A total of 21 papers were considered relevant (fig. 1). The National Guideline Clearinghouse, National Institute for Health and Clinical Excellence (NICE), Scottish Intercollegiate Guidelines Network (SIGN) and TRIP databases 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 [20, 21].

**TABLE 1** Applicability of the different World Health Organization (WHO) treatment of tuberculosis guidelines

Period of data collection	WHO guidelines	[Ref.]
1995–1999	First edition: 1993	[1]
1999–2004	Second edition: 1997	[2]
2005–2010	Third edition: 2003	[3]



**FIGURE 1.** Summary of literature search and study selection. References were excluded based on evaluation of the full manuscript according to: treatment regimen given in insufficient detail [9–12]; level of patient data insufficient [13–15]; insufficient pharmacy dispensing information [16, 17]; and not measuring knowledge [18, 19].

**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” [22] and one study, of which only an abstract was available, did not specify the objective [21].

The median sample size of the included studies was 114 HCW (range 22–1,355). The studies were performed in 14 different countries (table 2), of which 14 (45.2%) were in either India or Pakistan. Almost all continents were represented: South Asia (15 studies), East and South East Asia (five studies), South West Asia (four studies), Africa (five studies), the Americas (two studies). There were no studies from Europe.

A self-administered questionnaire was used in 12 (38.7%) studies [20, 23, 24, 27, 29–31, 34, 36, 41, 44, 50] and, in 13 (41.9%) studies, participants were interviewed using a questionnaire [19, 22, 28,

37–40, 43, 45, 46–49]. Four (12.9%) used a questionnaire but did not specify whether it was performed by interview or was a self-administered questionnaire [25, 32, 33, 42]. Two studies did not report how the data were collected [21, 26].

11 (35.5%) studies selected HCWs using random selection methods [20, 22, 28, 30, 32, 33, 37, 41, 44, 48, 49] and 10 (32.3%) included all eligible individuals [23, 25, 27, 29, 31, 34, 39, 46, 47, 50]. Six (19.4%) studies used convenience- or purposeful-sampling, or included HCWs who wanted to participate [24, 35, 36, 38, 40, 45] and four (12.9%) studies did not specify the selection method [21, 26, 42, 43].

16 (51.6%) studies were performed among HCWs practising in a private setting [24, 25, 28, 30, 31, 32, 34, 36, 37, 39–41, 44–46, 49], three (9.7%) among both HCWs practising in a private setting and in a public setting [29, 47, 48], three (9.7%) among medical students or interns [20, 21, 27], and nine (29.0%) studies did not specify whether the HCWs were practising in a private or public setting [22, 23, 26, 33, 35, 38, 42, 43, 50] (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 >41% [39]. The level of inappropriate knowledge of treatment regimens ranged between 8% and 93% (median 73%) among HCWs practising in settings other than uniquely private. Three studies did not provide the data to assess the percentage [22, 29, 42], in one study it was <25% [26] and in another study >55% [27].

15 studies provided information on HCWs experience in treating TB patients [25, 30, 31–34, 36, 38–40, 42, 46–48, 50]. In the 10 studies where ≥80% of the HCWs managed TB cases, or where the average number of TB cases managed per HCW was at least five per month, 8% to 100% had inappropriate knowledge of the recommended treatment regimen (median 61.5) [25, 30–34, 38, 39, 48, 50].

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 on HCWs practising in a private setting. AUER *et al.* [39] reported that nine (20%) out of 45 private practitioners would prescribe fewer than four drugs in the intensive phase for far-advanced TB; this is 22% of all inappropriate answers reported in the study. KHAN *et al.* [34] reported that 10 out of 120 private physicians would prescribe fewer than four drugs in the intensive phase for pulmonary TB, *i.e.* 63% of all reported inappropriate treatment in the intensive phase. In another study, 2% of private practitioners would prescribe three drugs for sputum-positive pulmonary TB [25], whereas 18% would prescribe an inappropriate regimen of four or five drugs.

Three studies among HCWs for which the setting was not specified provided information about prescription of more or less than four drugs during the intensive phase. CIRIT *et al.* [43] reported that 98 (60%) out of 162 physicians prescribed fewer than four drugs for newly diagnosed TB. Of 84 family physicians with an interpretable answer in the study by RIZVI *et al.* [33], 20 (25%) would prescribe a one-, two- or three-drug regimen for

**TABLE 2** Characteristics of the included studies and prevalence of inappropriate regimens

First author [ref.]	Country	Study setting	Period of data collection	Type of HCW	Sample size n
<b>South Asia</b>					
AGARWAL [23]	India	Conference	2006	National and international orthopaedic faculty and infectious disease experts	52
ROY [24]	India	Municipal area	NR	Qualified private medical practitioners	55
UDWADIA [25]	India	Slum	NR	Private medical practitioners	106
BHALLA [26]	India	Medical institute	NR	Residents and faculty members from various departments	40
RAJPAL [27]	India	Medical schools	2002	Interns that had gone through their training in various disciplines of medicine	287
GREAVES [28]	India	City and surrounding area	2006	Private practitioners	45
VANDAN [29]	India	District	2007	Medical physicians (public and private)	141
DATTA [30]	India	District	2008	Private allopathic physicians	260
HURTIG [31]	Nepal	Municipality	1998	Licensed allopathic for profit private practitioners which were assumed to see TB patients	43
SHAH [32]	Pakistan	Large cities	NR	Formally qualified medical graduates who were practising medicine outside the government sector and who had managed at least one pulmonary TB patient during the previous year	245
RIZVI [33]	Pakistan	City	NR	Family physicians that had no postgraduate qualification and were treating at least 7–10 TB patients per month	150
KHAN [21]	Pakistan	Teaching hospitals	NR	Interns	440
KHAN [34]	Pakistan	City	2002	Qualified private practitioners	120
SHEHZADI [35]	Pakistan	Regions	2003	General practitioners	88
AHMED [36]	Pakistan	Rural district	2007	Private practitioners with basic medical degree and doing private practice for $\geq 1$ yr	22
<b>East and South East Asia</b>					
BAI [20]	China	Medical schools	NR	Final year medical students	439
MAHENDRADHATA [37]	Indonesia	City	2004	Private practitioners	164
YU [38]	Philippines	Tertiary care hospital	NR	Specialist physicians who dealt with pulmonary TB patients	38
AUER [39]	Philippines	Urban district (Metro Manila)	1999–2000	Private for-profit practitioners who treat TB	45
PORTERO [40]	Philippines	Country	2001	Private physicians	1355
<b>South West Asia</b>					
SHIRZADI [41]	Iran	Large cities	2001–2002	Private sector physicians	732
HASHIM [22]	Iraq	Public health centres in the country	2001–2002	HCWs	500
DEVECI [42]	Turkey	City	NR	Practising physicians who provide first-line treatment	66
CIRIT [43]	Turkey	City	2001	Physicians	208
<b>Africa</b>					
SHIMELES [44]	Ethiopia	City	2003	Private, for-profit medical doctors	120
AYAYA [45]	Kenya	Cosmopolitan town	NR	Medical doctors practising privately	53
CHAKAYA [46]	Kenya	Slum	2001	Private HCWs	75
SULEIMAN [47]	Somalia	Part of country	2001	Qualified medical practitioners (public and private sector)	53
NSHUTI [48]	Uganda	Urban district	1999	Doctor or medical assistant from public and private clinics	114
<b>Americas</b>					
DATO [49]	Argentina	City	2007	Private doctors: general practitioners, infectious disease specialists and pulmonologists	61
LoBUE [50]	USA	County	NR	Physicians who reported a TB suspect or case to the San Diego County Tuberculosis Control for the years 1995–1997	150

HCW: healthcare worker; NR: not reported; TB: tuberculosis.

**TABLE 3** Prevalence of inappropriate tuberculosis (TB) regimens, incorrect dose and incorrect duration of TB treatment in different types of healthcare workers (HCWs)

First author [ref.]	Prevalence %		
	Inappropriate regimen	Incorrect dose	Incorrect duration
<b>HCWs in private setting</b>			
AHMED [36]	>41		
AUER [39]	91	Rifampicin 9, isoniazid 84, pyrazinamide 88, ethambutol 57	
AYAYA [45]	77		
CHAKAYA [46]	92		
DATO [47]	22		33
DATTA [30]	79		
GREAVES [28]	58		
HURTIG [31]	49		31
KHAN [34]	74	Rifampicin 24, isoniazid 17, pyrazinamide 48, ethambutol 49	Rifampicin 50, isoniazid 48, pyrazinamide 39, ethambutol 47
MAHENDRADHATA [37]	73		
PORTERO [40]	89		
ROY [24]	70		
SHAH [32]	100		99
SHIMELES [44]	90		
SHIRZADI [41]	66	46	50
UDWADIA [25]	20		64
<b>HCWs in public and private setting</b>			
NSHUTI [48]	76		
SULEIMAN [47]	93		
VANDAN [29]	No data	Rifampicin 22, isoniazid 78, pyrazinamide 47, ethambutol 72	16
<b>Medical students or interns</b>			
BAI [20]	83		
KHAN [21]	48		
RAJPAL [27]	>55		70
<b>HCWs setting not specified</b>			
AGARWAL [23]	81	0	
BHALLA [26]	<25	50	
CIRIT [43]	81		65
DEVECI [42]	No data		52
HASHIM [22]	No data		13
LoBUE [50]	11		26
RIZVI [33]	33		87
SHEHZADI [35]	70		
YU [38]	8		5

newly diagnosed pulmonary TB and six (8%) an inappropriate regimen of more than four drugs. YU *et al.* [38] reported that all HCWs reporting an inappropriate prescription (8%) would prescribe a three-drug regimen for pulmonary TB [38].

Six studies reported on the knowledge of TB drug-dose in regimens (table 3) [23, 26, 29, 34, 39, 41]. One study reported all mentioned doses as adequate [23]. Two studies reported that 46% [41] and 50% [26] of the HCWs would prescribe an incorrect dose (either too low or too high). Three studies reported on knowledge of dose by individual drug (table 4) [29, 34, 39]. In two studies, high doses were more frequently mentioned [34, 39] than low doses for most drugs and, in one study, participants would more frequently prescribe low doses of isoniazid, pyrazinamide and

ethambutol [29]. For rifampicin, the participants would more frequently prescribe high doses.

Knowledge of the duration of treatment regimens was reported in 13 studies [22, 25, 27, 29, 31–33, 38, 41–43, 49, 50]. Between 1% and 95% of the HCWs knew the correct duration of treatment. Overall, only a few HCWs would prescribe a regimen that was too short (<6 months): 3% [31]; 8% [25]; 11% [27]; 52% [43]; 4% [22]; and none in the studies reported by RIZVI *et al.* [33] and YU *et al.* [38].

**DISCUSSION**

The studies included in this systematic review show that a large proportion of HCWs do not know or do not intend to

**TABLE 4** Percentage of healthcare workers that reported an inadequate dose for the four first-line drugs in three studies providing information

Drug	AUER [39]		KHAN [34]		VANDAN [29]	
	Too low	Too high	Too low	Too high	Too low	Too 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) <sup>#</sup>	35 (83) <sup>#</sup>	15 (15)	40 (33)	43 (33)	18 (14)
Ethambutol	10 (33) <sup>‡</sup>	7 (23) <sup>‡</sup>	10 (10)	47 (39)	83 (64)	11 (8)

Data are presented as n (%). <sup>#</sup>: 42 instead of 45 participants; <sup>‡</sup>: 30 instead of 45 participants.

prescribe regimens that follow the recommended national or international guidelines.

Treatment with too few drugs and 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 1 to 2 months, *i.e.* only used in the intensive treatment phase, have significantly worse treatment outcomes compared with regimens with rifampicin throughout therapy. Furthermore, these patients have an increased risk of acquiring rifampicin resistance [51]. It has also been shown that treatment with fewer than four drugs in the intensive phase results in higher percentages of relapse cases [52]. It is on this basis that, for new pulmonary TB patients, WHO guidelines recommend 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 HCWs reported prescribing too few drugs, are therefore of concern, both for the treatment outcome of patients and for the risk of resistance development. Three studies, without a specified setting (private or public), reported a higher frequency of treatment with fewer than four drugs compared with treatment with more than four drugs [33, 38, 43].

A known cause of treatment default is the burden of drug side-effects to patients [53, 54]. Three studies among HCWs practising in a private setting reported a higher frequency of treatment with too many drugs among this group of HCWs [34, 39, 25]. While 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 [55–57]. 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 [58] and is a known cause of default from treatment [53, 54]. Based on this, prescribing more drugs than 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 [59] 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 [29, 34, 39], there was no clear

tendency for excessive doses to be 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 HCWs. 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. Conversely, most of the studies either used random selection or included the complete target population, indicating that the participating HCWs 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 the current article, all the included studies reported on HCWs' knowledge of TB regimens, and all showed a lack of knowledge among the different groups of HCWs. Even among the 10 studies on HCWs with experience in managing TB patients, knowledge was insufficient [25, 30–34, 38, 39, 48, 50]. 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 HCWs 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 to also be 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%) [18]. In another study, in which a simulation patient was used, only two (3.7%) prescriptions out of 53 met the required standards for TB patients as defined by the NTP [19]. 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 frequently published than studies that measure and report on inadequate knowledge. If this is the case, overall knowledge of HCWs on TB treatment might be better compared to what we report herein.

10 out of the 31 studies included in our systematic review were identified by reviewing the references of included studies. These 10 studies did not contain the keywords that we used in our search strategy with regard to the title, abstract or keywords section. They did, however, contain the words "treatment" or "therapy" in the title or abstract. As 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 HCWs' 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. Generalisation of the findings to other settings and countries should be done with caution.

**STATEMENT OF INTEREST**

None declared.

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