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Prevalence of inappropriate tuberculosis treatment regimens: A systematic review

Miranda W. Langendam[1], Marieke J. van der Werf[2,3], Emma Huitric[4], Davide Manissero[4]

[1] Dutch Cochrane Centre, Academic Medical Center, University of Amsterdam, The Netherlands
[2] KNCV Tuberculosis Foundation, The Hague, The Netherlands
[3] Center for Infection and Immunity Amsterdam (CINIMA), Academic Medical Center, University of Amsterdam, The Netherlands
[4] European Centre for Disease Prevention and Control (ECDC), Stockholm, Sweden

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

Running Head: Inappropriate tuberculosis treatment regimens

Abstract

A potential threat to success of new tuberculosis (TB) drugs is the development of resistance. Using drugs in appropriate regimens such as recommended in the World Health Organization (WHO) treatment guidelines prevents the development of resistance. A systematic review was performed to assess the prevalence of inappropriate prescription of TB drugs for treatment of TB.

MEDLINE, EMBASE and other databases were searched for relevant articles in January 2011. Observational studies published from 2000 that included TB patients receiving treatment were selected. A treatment regimen was considered inappropriate if the regimen was not a WHO-recommended regimen.

Thirty-seven studies were included. In 67% of the studies inappropriate treatment regimens were prescribed. The percentage patients receiving inappropriate regimens varied between 0.4% and 100%. In 19 studies the quality of treatment regimen-reporting was low.

Despite the fact that assessment of inappropriate treatment was hampered by low quality of reporting, our data indicate a reasonable amount of inappropriate prescription of TB treatment regimens. Thus, there is a risk that new drugs will be used in inappropriate treatment regimens, even with WHO guidelines in place, introducing the risk of resistance development. This review highlights the need to improve implementation of the WHO treatment of tuberculosis guidelines.

Keywords: tuberculosis, treatment, regimen, inappropriate

Introduction

The tuberculosis (TB) drugs currently used date from more than 50 years ago. Soon after their introduction the emergence of drug resistance was observed.[1] This led to the use of a double drug-combination to prevent the emergence of drug resistance, and later to triple drug-combinations. Four drug short-course regimens were first tested in 1972 and showed good results.[2] A four drug short-course regimen is currently recommended by the World Health Organization (WHO).[3]

Recently, ten compounds have progressed to the clinical development pipeline for the treatment of tuberculosis (TB).[4] These new compounds, if properly managed, have the potential to become part of a future regimen that could greatly impact the global tuberculosis control effort. A potential threat to the success of the new compounds is the development of resistance caused by an inappropriate use of these drugs.[5] For these new drugs to remain effective it is essential they be used in regimens that prevent the development of resistance to the drugs. The WHO has developed guidelines on appropriate (standardized) TB treatment regimens that will cure patients and prevent the development of resistance. The first guideline were published in 1993; updates followed in 1997, 2003 and 2009.[3;6-8]

Implementation of global tuberculosis treatment guidelines requires the uptake of the recommendations in national tuberculosis treatment guidelines and the use of national treatment guidelines by all health workers. Initially, 83 (48%) of 174 countries reporting to WHO did not accept the WHO TB control strategy.[9] Ten years later, most countries were implementing the DOTS strategy, including four drug short-course regimens. Although countries have implemented the DOTS strategy, individual health care workers might not be aware of the strategy or might not be willing to implement the recommended regimens. Studies among health care workers show indeed that not all health care workers have been exposed to the national tuberculosis treatment guidelines and many are not prescribing recommended regimens.[10-12]

In intermediate-to-low TB incidence settings, a further challenge is that health care workers, due to the few cases of TB presenting, might not be aware of the global guidelines on TB treatment, and thus do not follow these. The EU is a heterogeneous setting, with countries and settings ranging from low-TB incidence to high incidence.[13] The challenge in low-incidence settings is to maintain the knowledge of TB and thus awareness of treatment regimens and guidelines.

To assess the future risk of new compounds being used in inappropriate TB regimens, a systematic review was conducted to assess the prevalence of inappropriate TB drug prescriptions (type, dose, frequency of dosing, and combination) for the treatment of TB. Appropriate treatment was defined according to the WHO guidelines.

Methods

Search strategy

To identify relevant studies we conducted a literature search in the bibliographic databases MEDLINE and EMBASE in January 2011. We searched for guidelines in the National Guideline Clearinghouse, and the NICE and SIGN databases. Abstracts of conference proceedings were sought in BIOSIS. Reviews and guidelines were searched for in the TRIP database. Key words 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 "Inappropiate use, appropriate use, rational use, irrational use, misuse". The search was limited to publication years 2000-2010 as we were interested in recent prescription behaviour. We excluded case reports. The search strategy was supplemented by hand searching reference lists of identified articles and relevant review articles.

Selection of studies

We included observational studies investigating the prescription of TB treatment regimens in a TB patient population; these can include cross-sectional studies and cohort studies, both prospective and retrospective. Only studies in which treatment regimen was measured as an outcome were included. We therefore excluded studies in which prescription of a treatment regimen was only described in the methods section. Furthermore, we excluded studies that provided information about the prescribed drugs but not about the prescribed treatment regimens, and studies that did not report the treatment regimens in sufficient detail to make a judgment on the appropriateness of the regimen. This also included studies with multidrug resistant TB (MDR-TB) patients that reported providing individualized treatment and did report the individual drug resistance patterns. We searched for publications from the year 2000 onwards. Papers with start of data-collection before 1995 were excluded because the first WHO treatment guideline was published in 1993. Assuming a two year implementation period, this guideline would only be expected to be followed from 1995 onwards. There was no language restriction.

Studies identified by the search strategy were reviewed for eligibility based on title and abstract by one investigator (MvdW). Full manuscripts of the records kept 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.

Data extraction

One reviewer (ML) extracted all relevant data-items from the included studies using a data-extraction form. A second reviewer (MvdW) independently extracted the main results of the included studies and checked the other extracted results for a subsample of the articles. Inconsistencies were discussed to obtain consensus.

Data analysis and synthesis of results

The results were summarized qualitatively. For studies that described treatment regimens without indicating whether they were appropriate according to WHO guidelines, the regimen was assessed and assigned to the appropriate or inappropriate category using the WHO guidelines as reference. Table 1 presents the applicable WHO guideline for different periods of data-collection in the individual studies. In the WHO TB treatment guidelines editions 1993 and 2003 there are specific

treatment guidelines for children. In 1997, there were no specific guidelines for children. We also noted if the authors of the manuscripts themselves considered the regimens appropriate or inappropriate. If the data allowed we assessed the adequacy of dosing frequency, dosage, and duration of TB treatment. We aimed to assess the prevalence of inappropriate TB regimen prescription for different patient populations and different geographical areas.

The quality of reporting of study characteristics and treatment regimens was assessed using a quality checklist developed for this review based on the STROBE statement (http://www.strobe-statement.org/index.php?id=strobe-home) (Box).

Results

Study selection

The search in MEDLINE and EMBASE resulted in 1,896 unique records. A total of 293 papers were considered potentially relevant based on title/abstract assessment (Figure 1). After full text assessment, 37 papers fulfilled the inclusion criteria. BIOSIS did not provide any additional records. Checking the reference lists of the included papers revealed no additional papers that fulfilled the inclusion criteria. The National Guideline Clearinghouse, NICE, SIGN, and TRIP data base did not provide aggregated evidence on the prevalence of inappropriate use of TB regimens.

Description of the included studies

Thirty-seven papers were included. Of these, 26 studies investigated treatment prescription in the general population (including 3 studies in children), and 11 studies were in special groups (4 in extrapulmonary TB, 1 in patients with isoniazid-resistant TB, and 6 in special patient groups). The 37 studies were from 22 countries, and one study was from multiple countries (this study is presented both in Table 2a and 2b). Almost all continents were represented: Africa (n=6), South-America (n=2), Europe (n=9) and Asia (n=20).

The included studies did not provide sufficient information to assess adequacy of dosing frequency, dose, and duration of TB treatment.

<u>General population, including children</u>
Of the 26 studies performed in the general population, 13 (50%) were performed in a hospital setting, 12 (46%) were based on TB registers and one study was performed in hospitals, a prison and welfare centres (Table 2a, b, and c). The sample sizes ranged between 32 and 24,760 TB patients.

Fourteen studies had a low quality treatment regimen reporting and ten of these also had low quality of reporting of the study and population characteristics. For the treatment regimens, this means that the regimens were not specified, or that the described regimens applied to an undefined mix of patients (new and retreatment cases, pulmonary TB and extrapulmonary TB cases and/or smear-negative and –positive cases) in which case it was not possible to categorize the treatment as appropriate or inappropriate. According to the author statements in these 14 studies, in two studies, all patients received appropriate regimens.[14;15] In eight studies, inappropriate regimens had been prescribed according to the authors; the percentage of patients on inappropriate regimens ranged from 0.4% to 45%.[16-23] For two studies we determined the prevalence of inappropriate treatment; this was 26% in the study from India and ≥10% in the study with children in Benin.[24;25] Two studies did not provide information on treatment regimens but reported on inadequate numbers of tablets and/or inadequate dosage.[26;27]

Six studies provided moderate quality information on the observed treatment regimens.[28-33] In all six studies, the prevalence of inappropriate treatment regimens could be calculated from the different treatment regimens or derived from a table in the paper, under the assumption that all cases were smear-positives (this could not be derived from the papers). For smear-negative cases, a non-Isoniazid, Rifampicin, Pyrazinamide, Ethambutol (HRZE) regimen might be appropriate in which case the prevalence of inappropriate treatment would be overestimated in our calculations.[8] The percentage of prescription of inappropriate TB treatment regimens ranged between 7% and 100%.

For six studies, high quality information on the observed treatment regimens was available.[34-39] In one study, among new TB cases, inappropriate regimens were prescribed to 26% of smear-positive pulmonary TB patients, 4% smear-negative pulmonary TB cases and 29% extrapulmonary TB cases.[35] In the study of Satayanarayana et al. less than 0.5% received a regimen without rifampicin and thus received inappropriate treatment.[39] There was no inappropriate treatment regimen prescription in the other studies.

Special groups

Of the 11 studies in special groups, four studies were performed in TB patients with extrapulmonary TB, Table 3.[40-43] The WHO recommends Category 1 treatment (HRZE or HRZS) for new cases with severe forms of extrapulmonary TB and Category 3 treatment for less severe forms (HRZ in 1993 and 1997, HRZE in 2003).[6-8] In two studies, all patients were treated as recommended by the WHO; these studies had very small sample size.[41;42] In the other two studies, the percentage of inappropriate treatment was 5% and 18%.[40;43]

One study investigated TB treatment of isoniazid-resistant patients in 2001-2005.[44] The WHO had no recommendations on appropriate treatment for isoniazid-resistant patients until 2009; therefore we could not assess the percentage of patients with inappropriate treatment.

Six studies reported on special populations such as pregnant women or AIDS patients. All studies had relatively small sample sizes, 9 to 52 TB patients. Two studies that provided sufficient information, 0% received inappropriate treatment [45;46], for two other studies 33 and 67% received inappropriate treatment [47;48], and for two studies insufficient information was provided.[49;50]

Discussion

In this review we assessed the prevalence of inappropriate prescription of TB drugs (type, dose, frequency of dosing, and combination) for treatment of TB. Appropriate treatment was defined according to the WHO guidelines. In total, 37 studies on TB treatment regimens were included. Only eight of these studies (6 in the general population and 2 in special groups) reported all information that was necessary to make an adequate assessment of the prevalence of the inappropriate treatment prescription. The main challenge with the data reporting was that the treatment regimens were often not provided separately for new and retreatment cases, smear-positives and smear-negatives and pulmonary TB and extrapulmonary TB (e.g. studies stated "all patients started on HRZE"). These patient characteristics are important to consider as the WHO recommends different treatment regimens for each of these categories.

We took a broad search and selection strategy to include as many studies as possible with data on prescription of TB treatment regimens. For 13 (35%) of the 37 included studies, evaluation of the prescribed treatment was one of the objectives (i.e., being specifically mentioned in the objective or aim of the study).[15;20-22;24-26;30;34;35;38;39;44] One would expect that these studies score 'moderate' or 'high quality' on treatment regimen reporting, but this was only the case for six of the 12 studies.

In 67% of the studies, inappropriate treatment regimens were prescribed and the percentage of patients on inappropriate treatment regimens varied widely, between 0.4% and 100%. The data suggest that the prevalence of inappropriate treatment was lower in the more recent years. These findings have to be interpreted with caution however, as the prevalence could often only be estimated and the quality of reporting was low.

It appears that many of the included studies are from settings that are, or should be, informed on WHO treatment guidelines. Few studies are from private health care settings and none of the studies examined patients of individual private doctors. These are two groups of health care workers in which familiarity with international TB guidelines might be lower and thus have a higher level of inappropriate treatment prescription. Studies examining what TB treatment regimens private practitioners would prescribe show that often national or international guidelines are not followed.[51-53]

Three studies were based in EU Member States with intermediate-to-low TB incidence (France, Germany and Spain)[16;18;22] and in all three studies, inappropriate treatment of cases was reported. Although the number of studies is limited and the quality of reporting ranged from low to high, these findings show that in the EU, inappropriate TB treatment is prescribed. As stated in the European Action Plan to Fight TB in the EU and the Follow-up of the Action Plan,[54;55] it is essential that all TB patients be diagnosed and provided optimal TB treatment; without such efforts, TB transmission cannot be prevented and TB elimination achieved. Furthermore, the risk for resistance-development remains. Regardless of TB incidence in a setting, providing accurate treatment is essential to prevent transmission as well as prevent development of drug-resistance.

In 17 (46%) of the 37 included studies the definition of TB diagnosis was not specified. Inspection of the data revealed that the availability of a TB case definition was not related to the quality of reporting of the treatment regimens or prevalence of inappropriate treatment regimens.

Ten studies (27%) had a data collection period that included two or more WHO guideline periods, for example 1993 and 1997. There are differences between the guidelines, the most important being the inclusion of streptomycin in Category 1 treatment. In 1993 and 1997 this was recommended in the guidelines, but not in 2003. In these cases, we considered both HRZE and HRZS as appropriate treatment.

TB treatment consists of different treatment modalities: regimen, dose, frequency and duration. Other important aspects necessary for a successful treatment outcome are treatment compliance and quality of the drugs. The WHO guidelines recommend treatment regimens with an intensive and continuation phase (e.g. HRZE for intensive phase, HR for continuation) and with a certain

frequency (3 days per week or daily), duration (e.g. 6 months) and dosage (e.g. 4-6 mg/kg INH daily). In this review we could only assess treatment regimen as there was insufficient information on dose, frequency and duration of treatment.

Defining any regimen that is in line with WHO Guidelines as “appropriate” and all others as "inappropriate" is a rough distinction between right and wrong. Treatment against TB may be inappropriate because; 1) the treatment duration is too short or the regimen contains too few drugs, has insufficient dose, or drugs in a wrong combination or, 2) the duration of treatment is too long, with excessive dose or number of drugs. The first error may cause drug-resistance, while the second error increases the risk of side-effects and consequently low treatment compliance and thus increased treatment failure. Unfortunately, in most included studies the treatment regimens were not reported in sufficient detail to make a distinction between these two forms of inappropriate treatment.

Conclusion

Despite the fact that assessment of the prevalence of inappropriate TB treatment regimens was hampered by low quality of reporting, our data indicate a reasonable amount of inappropriate prescription of TB treatment regimens, as this was observed in the majority of the included studies. Thus, there is a risk that new drugs will be used in inappropriate treatment regimens, even with official WHO guidelines in place, introducing the subsequent risk of resistance development to these new drugs. This review highlights the need to ensure optimal implementation of the WHO treatment of tuberculosis guidelines in all settings.

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Box: Quality of reporting checklist

Quality level	**Assessment**
Setting and population (S)	
High quality (***)	Adequate description of: 1. population demographics: at least age and gender 2. population TB: new/retreatment, type of TB and smear-positives/negatives 3. setting (where did the patients come from, e.g. private or public hospital, evaluation of TB control programme) 4. time period of data collection 5. sample size 6. TB diagnosis
Moderate quality (**)	Adequate description of population, setting, time period of data collection and sample size, but no information on TB diagnosis
Low quality (*)	No information on population, setting, time period of data collection and sample size
TB treatment regimens (TR)	
High (***)	All observed treatment regimens are reported, separately for new and retreatment cases, for PTB and EPTB and smear-positive and smear-negative cases
Moderate (**)	Treatment regimens are partly or fully specified, but information is missing. Assumptions are necessary for assessment of inappropriateness, and/or assessment is imprecise (e.g. >10%)
Low quality (*)	Treatment regimens are not specified in sufficient detail, but authors make statement

Figure 1: Summary of literature search and study selection.

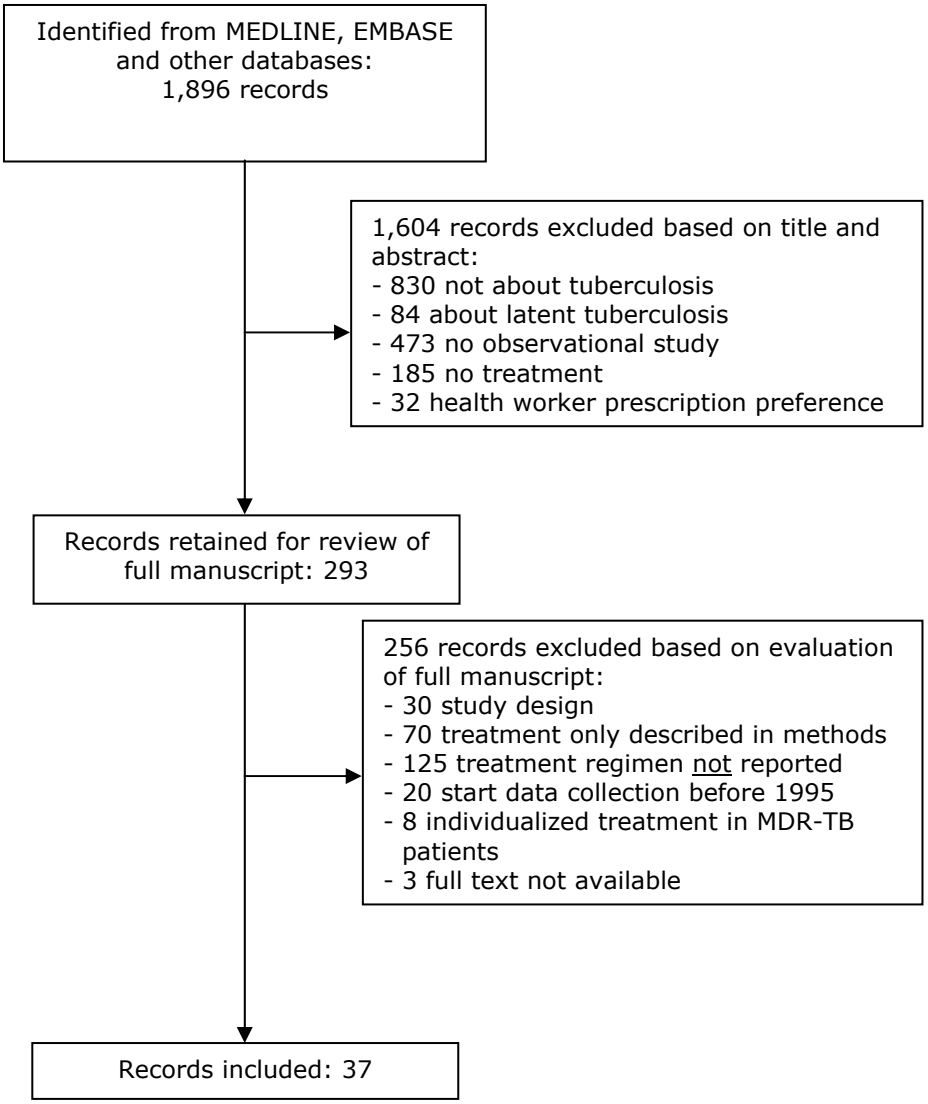

Table 1 Applicability of the different WHO guidelines

Years of data-collection	**WHO guideline**
1995-1999	First edition: 1993
1999-2004	Second edition: 1997
2005-2010	Third edition: 2003

Table 2a: Inappropriate TB treatment regimens in Asia: general population including children.

Study reference	Country	Setting	Period of data collection	Sample size	Inappropriate TB treatment regimens	Data quality	
						S	TR
Ishikawa 2003	Japan	Treatment program (not further specified)	Not reported	Not reported	Authors: 45% of smear-positive cases no standard treatment (HREZ[S]/HR[E])	*	*
Maseeh 2004	India	Tertiary care hospital	Not reported	n=118	Assessed from figure: 26% no HRZE (other 4-drug combination or more than 4 drugs)[1]	*	*
Thongraung 2008	Thailand	Hospitals (random sample of all Thai hospitals)	Not reported	n=383	Authors: 0% "All initial prescription had adhered to guideline" 43% had inappropriate dosage	*	*
Diop 2002[2]	Nepal	National TB programs	1996	n=1,163	Authors: "No nationally recommended treatment regimen for 0.4% of the cases."	*	*
Khan 2003	Pakistan	Outpatient clinics private hospital	1998	n=362	Assessed: 21% (new pulmonary TB cases)[1]	**	**
Quy 2006	Vietnam	TB Surveillance	1998-2000	n=1,834	Assessed: 0% (new smear-positives)	***	***
Ohkado 2006	Philippines	Patient survey in urban setting	2000	n=380	Assessed: 0% ("All new cases and previously treated cases were treated with standard regimens, 2HRZE/4HR and 2HRZES/1HRZE/5HRE respectively.")[1]	**[3]	***
Koh 2003	South Korea	Private hospital	2000-2001	n=232	Authors: 69% no HRZE for new pulmonary TB cases[1]	**[3]	**
Chamla 2004	China	Governmental TB hospital	2001	n=417	Assessed: New cases: up to 36% (other regimens appropriate)[1] Retreatment cases: 100%	***	**

Table 2a continued

Study reference	Country	Setting	Period of data collection	Sample size	Inappropriate TB treatment regimens	Data quality	
Quy 2003	Vietnam	Public-private mix project in hospitals	2001	n=400	Assessed (from table): New cases: 99% no NTP regimen (mostly overtreatment in number of drugs and duration) Retreatment cases: 84% no NTP regimen (different reasons) NTP regimen = Category 1 or 3, WHO 1997 "36 different intended treatment regimens were recorded on the 400 treatment cards; 4 were correct according to National TB Program guidelines"	**	**
Chiang 2010	Taiwan	Patients reported to Taiwan CDC	2003	n=1,716	Regimen: insufficient information Assessed (from table): inadequate dosage: 2-FDC: 26%, 3-FDC: 24%, RMP: 36% and INH: 12%	**	*
Datta 2010	India	Hospital	2003-2007	n=910	Authors: 0% "Appropriate treatment until 2006, and subsequently using DOTS strategy with standardized regimens (Revised National TB Control Program)"	*	*
Chengsorn 2009	Thailand	Public and private hospitals	2004-2006	n=7,526	Assessed (from table): Overall, 7% no HRZE (Category 1 WHO); 20% in private facilities, 6% in small public facilities and 4% in large public facilities.[1]	***	**
Liu 2010	China	Patient survey in TB dispensaries	2007	n=163	Assessed: New cases: 15%[1] Retreatment: 31%	*[4]	**

Table 2a continued

Study reference	Country	Setting	Period of data collection	Sample size	Inappropriate TB treatment regimens	Data quality	
Satyanara-yana 2010	India	National TB programme, study in children	2008	n=1,074	Assessed: <0.5% (WHO) 27% low dosage	***	***
TB Surveillance Centre 2010	Japan	TB Surveillance	2008	n=24,760	Authors: "21% did not use recommended treatment combination (Japanese Society for TB)."	*	*

* = low quality; ** = moderate quality; *** = high quality

S = Study characteristics; TR= Treatment regimens; TB= Tuberculosis; CDC= Center for Disease Control; NTP= National TB Program; H= Isoniazid; R= Rifampicin; E= Ethambutol; Z= Pyrazinamide; S= Streptomycin; WHO= World Health Organization

[1] For patients that did receive HRZE but were smear-negative or had less severe extrapulmonary TB, HRZE is overtreatment and therefore not appropriate

[2] This study is reported in Table 2a, results from Nepal and Table 2b, results from Kenya and Senegal

[3] Information on age and gender distribution is missing; all other variables reported

[4] Information on smear-negative/positive is missing; all other variables reported

Table 2b: Inappropriate TB treatment regimens in Africa: general population including children.

Study	Country	Setting	Period of data collection	Sample size	Inappropriate TB treatment regimens	Data quality	
						S	TR
Diop 2002[1]	Kenya, Senegal	National TB programs	1996	n=11,183	Authors: "No nationally recommended treatment regimen for 6.2% of the cases in Kenya, and 1.0% in Senegal."	*	*
Van Zyl 2006	South Africa	Community health clinic, study in children	1996-2003	n=99	Authors: 4% (national guidelines) Assessed: ≥77% (WHO)	*	*
Salaniponi 2003	Malawi	Non-private for profit hospitals	1999-2000	n=1,523	Assessed: 0% ("All patients [with recurrent TB] were treated with a re-treatment regimen [2HRZES/1HRZE/5HRE].")	**[5]	***
Harries 2004	Malawi	Public hospitals	2001	n=1,211	Assessed: new smear-positive pulmonary TB: 0% inappropriate regimen 7% wrong number of tablets	**	***
Elmahalli 2007	Egypt	Public hospital	2003	n=249	Authors: "Type and number of prescribed drugs not conforming to DOTS recommendations: 14% in initial phase and 5% in continuation phase."	**	*
Lalya 2010	Benin	Hospital, study in children	2003-2007	n=32	Assessed: ≥10% (thioacetazone regimens) Duration too long for most children (8 months)	*	*

* = low quality; ** = moderate quality; *** = high quality

S = Study characteristics; TR= Treatment regimens; TB= Tuberculosis; H= Isoniazid; R= Rifampicin; E= Ethambutol; Z= Pyrazinamide; S= Streptomycin; WHO= World Health Organization

[1] This study is reported in Table 2a, results from Nepal and Table 2b, results from Kenya and Senegal

Table 2c: Inappropriate TB treatment regimens in Europe and America: general population including children.

Study	Country	Setting	Period of data collection	Sample size	Inappropriate TB treatment regimens	Data quality	
Richardson 2000	USA	TB Control database	1995-1998	n=770	Authors: "Of the 770 cases, 28.7% did not receive the CDC-ATS recommended drug regimen (HRZE[S])."	*	*
Grupo del Trabajo del PMIT 2001	Spain	TB register	1996-1997	n=10,053	Authors: "More than 76% of the subjects were treated in agreement with Spanish guidelines."	*	*
Diel 2003	Germany	Public Health bureaus register	1997-1999	n=515	Authors: "As the survey shows, preferred tuberculosis treatment in Hamburg was a three-drug regimen (86.7%), with an average duration of about 9 months. This deviates from the WHO's recommended standard of a four-drug regimen, and also exceeds the recommended short-term treatment period of 6 months."	***	*
Valin 2008	France	Tertiary care hospitals, prison and welfare centres	2004	n=629	Authors: 14% no HRZE in intensive phase[1,2] "Duration of TB treatment was not applied as recommended in more than 33% of cases."	***	*
Hasker 2009	Uzbekistan	TB control program	2006	n=180	Assessed (from table): Pulmonary TB, new smear-positive: 26% Pulmonary TB, new smear-negative: 4% New extrapulmonary TB: 31%	**	***

* = low quality; ** = moderate quality; *** = high quality

S = Study characteristics; TR= Treatment regimens; TB= Tuberculosis; USA= United States of America; CDC-ATS= Center for Disease Control and American Thoracic Society; H= Isoniazid; R= Rifampicin; E= Ethambutol; Z= Pyrazinamide; S= Streptomycin; WHO= World Health Organization

[1] For patients that did receive HRZE but were smear-negative or had less severe extrapulmonary TB, HRZE is overtreatment and therefore not appropriate

[2] Non-HRZE regimens not specified. These regimens might be appropriate for smear-negatives and less severe forms of extrapulmonary TB.

Table 3: Inappropriate TB treatment regimens in special groups

Study	Country	Setting	Period of data collection	Type + sample size	Inappropriate TB treatment	Data quality	
						S	TR
Wei 2008	Taiwan	In- and outpatients, via tertiary care centre	1995-2004	Peripheral lymph-adenitis n=97	Assessed: 18%	*	*
Llewelyn 2000	United Kingdom	General hospital	1995-1998	Pregnant women n=13	Assessed: 0% (all HRZE; although mix of patients)	*	**
O'Donnel 2002	Brazil	Hospital	1997-1999	AIDS patients n=9	Assessed: At least 33%	*	**
Kuzucu 2004	Turkey	Hospital	1997-2002	Chest wall n=6	Assessed: 0%	***	***
Fennira 2006	Tunesia	Hospital	1997-2003	Vertebral n=5	Assessed: 0%	*	*
Cormican 2006	United Kingdom	TB clinic	1999-2004	Spinal n=22	Assessed: 5% (n=1, no isoniazid)	*	*
Fonseca 2006	Portugal	Hospital	1999-2005	TNA-α treated patients n=13	Assessed: 0% (all HRZE; although mix of patients)	*	**
Chang 2008	China	Governmental clinic	2001	Hepatotoxicity n=47	Assessed: Insufficient information	**	*
Kim 2008	South Korea	Hospital	2001-2005	Isoniazid resistant n=39	Assessed: No guidelines for isoniazid resistant TB available in 2001-2005	**	***
Godreuil 2009	France	Clinical mycobacterial laboratories	2002-2007	*M. microti* n=6	Assessed: 67%	***	**
Kawasaki 2009	Japan	Hospital	2005-2007	Patients who died from TB n=52	Assessed: Insufficient information	*	*

* = low quality; ** = moderate quality; *** = high quality

S = Study characteristics; TR= Treatment regimens; TB= Tuberculosis; H= Isoniazid; R= Rifampicin; E= Ethambutol; Z= Pyrazinamide; TNA-α= tumor necrosis factor-α

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