Lack of evidence to support policy development for management of contacts of multidrug-resistant tuberculosis patients: two systematic reviews

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_____ S U M M A R Y

BACKGROUND: Existing international guidelines provide different recommendations for the management of contacts of multidrug-resistant tuberculosis (MDR-TB) patients.

OBJECTIVE: To conduct two systematic reviews with the aim of identifying chemoprophylactic approaches that are effective in contacts of MDR-TB patients to assist in policy making.

DESIGN: We systematically searched the Medline, Embase, Central, LILACS, TRIP and BIOSIS Preview databases for studies on the effectiveness of anti-tuberculosis drugs in preventing active TB in persons at risk of developing MDR-TB. This was done as an update of a systematic review from 2006 using the same methodology. In addition, we searched for studies including persons at risk of developing TB after exposure to non-MDR-TB patients who were treated with anti-tuberculosis drugs other than isoniazid or rifampicin.

RESULTS: Of 1195 references assessed in the update, one additional study could be included. As the initial review included two studies, the total number of included studies equals three. One study reported no contacts who developed TB, whether or not they received prophylaxis. The other two studies showed non-significant risk differences of 4% (95%CI −3 to 12), and 5% (95%CI −2 to 11), both in favour of chemoprophylaxis. For the additional review, 2480 references were assessed, but none could be included.

CONCLUSION: The attention given to MDR-TB in recent years has not resulted in publications on preventive treatment for contacts of MDR-TB patients. The available evidence is not sufficient to support or reject preventive treatment. Furthermore, the combined available evidence is of very low quality.

KEY WORDS: prevention; multidrug resistance; latent TB

PREVENTIVE TREATMENT for contacts of tuberculosis (TB) patients is highly effective in both non-human immunodeficiency virus (HIV) infected and HIV-infected persons.[1,2] It is included in guidelines for TB control of, for example, the Centers for Disease Control and Prevention (CDC)/American Thoracic Society (ATS),[3] and the National Institute for Health and Clinical Excellence.[4] The evidence for this is mainly for isoniazid (INH) preventive treatment in drug-susceptible TB. In contrast, preventive treatment for contacts of INH and rifampicin (RMP) resistant, i.e., multidrug-resistant TB (MDR-TB), patients is controversial. In some guidelines, treatment with pyrazinamide (PZA) and ethambutol (EMB) or PZA and a quinolone (i.e., levofloxacin or ofloxacin) for 6–12 months is recommended for persons who are likely to be infected with MDR-TB and who are at high risk for developing active TB.[3] Other guidelines recommend that close contacts of MDR-TB patients should not be prescribed chemoprophylaxis but should receive careful clinical follow-up for a period of at least 2 years.[4,5]

An explanation for the difference in recommendations is that there is little evidence on the effectiveness of preventive treatment for contacts of MDR-TB patients: in other words, the guideline recommendations are not supported by sound and clear evidence. A systematic review by Fraser et al. concluded that evidence of the effects of treatment of latent tuberculosis infection (LTBI) in people exposed to MDR-TB is extremely limited in both quantity and quality.[6] Also, there are no randomised controlled trials comparing anti-tuberculosis drug regimens with an alternative anti-tuberculosis drug regimen, placebo or no intervention given to people exposed to MDR-TB to prevent active TB.[7]

The World Health Organization (WHO) estimates that 440 000 cases of MDR-TB occurred in 2008.[8] Of these, only 7% were identified and reported to the WHO, and of the reported cases only a fifth were

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

treated according to WHO standards.[8] Thus, countries seem to be responding slowly to the threat posed by MDR-TB. In April 2009, the WHO convened a ministerial meeting of countries with a high burden of MDR-TB in Beijing, China.[9] This paved the way for the 62nd World Health Assembly to adopt resolution WHA62.15 on the prevention and control of MDR-TB and extensively drug-resistant TB (XDR-TB). The resolution urges Member States to take action on multiple fronts towards achieving universal access to diagnosis and treatment of M/XDR-TB by 2015.

Although much attention is currently being given to M/XDR-TB control, preventive treatment for contacts of MDR-TB patients is not mentioned in the World Health Assembly resolution. A prioritised research agenda for MDR-TB published in 2008 calls for clinical trials or well-designed cohort studies of the efficacy of several individual drugs and drug combinations in preventive treatment of those persons presumably infected with drug-resistant TB.[10]

The attention currently being given to MDR-TB and the call for studies on preventive treatment for contacts of MDR-TB patients might have resulted in new studies since the systematic review performed by Fraser et al. 6 years ago.[6] We therefore conducted a systematic review on the effectiveness of anti-tuberculosis drugs for preventing active TB in persons at risk for developing M/XDR-TB, to collect and assess the evidence for policy making. Because drugs other than INH and RMP that are effective in preventing active TB in persons at risk for developing susceptible, mono- or poly-resistant TB might be effective in preventing active TB in persons at risk of developing M/XDR-TB. We therefore conducted a second systematic review in which we evaluated the effectiveness of drugs other than INH and RMP to prevent active TB in persons at risk of developing susceptible, mono- or polyresistant TB.

METHODS

Our main goal was to evaluate the effectiveness of anti-tuberculosis drugs in preventing active TB in persons at risk for developing MDR-TB. Persons at risk of developing active TB are persons exposed to TB infection by being in close contact with a patient with active TB, referred to as 'contacts'. Contacts can be infected with TB (i.e., diagnosed with LTBI), non-infected (negative test for LTBI) or with unknown infection status. We were also interested in the effectiveness of drugs other than INH and RMP in preventing active TB in contacts of non-MDR-TB patients, as this may provide indirect evidence for the effectiveness of these drugs to prevent active TB in contacts of M/XDR-TB patients. We conducted the two systematic reviews following the guidelines of the Cochrane Handbook for Systematic Reviews and the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.[11]

Search methods for identification of studies

For the main goal, the approach taken was to update the existing systematic review by Fraser et al.[6] We assessed the quality of the review using the AMSTAR tool.[12] As the search strategy was extensive and rigorous methods of data extraction were used, we decided to use the same methods and search strategy for data extraction. We took 1 year overlap with Fraser et al.:[6] as their search ended December 2004, we searched the databases from January 2004 to 19 April 2011. The search strategy used is given in Appendix A.*

For our second review on the effectiveness of drugs other than INH and RMP in preventing active TB in persons at risk of developing susceptible, mono- or poly-resistant TB, we included a list of anti-tuberculosis drugs other than INH and RMP in the search strategy. The list contained all drugs mentioned in the guidelines for the programmatic management of drug-resistant TB.[5] In addition, the following key words were used: 'tuberculosis' AND ('latent' OR 'contact' OR 'contact tracing [MeSH]' OR 'antibiotic prophylaxis [MeSH]' OR 'chemoprevention [MeSH]' OR 'prevent*' OR 'prophyla*'). The search strategy used can be found in Appendix B. There was no limit on calendar year or language. We included both published and unpublished studies.

For both reviews, we searched the same bibliographic databases as Fraser et al.: CENTRAL, Medline, LILACS and Embase.[6] In addition, we searched the TRIP database (systematic reviews and guidelines; search date 12 May 2011) and BIOSIS Preview (conference abstracts; search date 2 May 2011). The reference lists of identified articles and relevant review articles were checked for additional studies and ongoing controlled trials were searched via the WHO International Clinical Trials Registry Platform (ICTRP; search date 2 May 2011).

Selection of studies

The titles/abstracts of the records identified in the search were independently assessed by two reviewers. References selected by either of the reviewers were included. We evaluated whether the objective of the study was pharmacological treatment/chemotherapy of contacts of (MDR-)TB patients or whether it included information on a cohort of contacts of (MDR-)TB patients who received pharmacological treatment and that reported the outcomes, i.e., whether or not they developed TB. For the review on the effectiveness of other drugs, we evaluated whether the pharmacological treatment of contacts of TB patients was with drugs other than INH or RMP.

In the first phase, we included all publication types, i.e., reviews, letters and comments, as well as all types of primary studies and all languages. The reviews,

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* Appendices A and B are available in the online version of this article at http://www.ingentaconnect.com/content/iuatld/ijtld/2012/00000016/00000003/art00003

letters and comments were used for background information and to find additional primary studies. The full texts of potentially relevant studies were reviewed for further eligibility with regard to study design, patients, treatment and outcomes (active pulmonary TB, death from any cause, extra-pulmonary TB, adverse effects). The selection process was performed independently by two reviewers. Consensus was reached by discussion.

Data extraction and analysis

One reviewer (ML) extracted all relevant data items from the included studies, and this was carefully checked by a second reviewer (MvdW). Inconsistencies were discussed to obtain consensus.

The risk of bias of the individual studies was assessed by two reviewers independently. We used the Newcastle Ottawa Scale (NOS) for cohort studies.[13] We planned to do a meta-analysis for studies that were clinically and methodologically homogeneous. However, this was not possible as the studies were clinically and methodologically heterogeneous. The studies were summarised qualitatively. The quality of the evidence was assessed using the GRADE approach.[14]

RESULTS

1 Update of the review of Fraser et al. on the effectiveness of anti-tuberculosis drugs for preventing active TB in contacts of patients with MDR-TB

Study selection

Of the 1195 results from the January 2004–April 2011 search of CENTRAL, MEDLINE, Embase and LILACS, 19 references were considered potentially relevant (Figure 1). We also identified 30 reviews and assessed these for relevant references. After applying the eligibility criteria to the 19 full-text articles, one study was included. A list with the excluded studies and the reason for exclusion is provided in Table 1.[15–32] Fraser et al. selected two studies from the search up to December 2004;[6] the total number of included studies was therefore three.

A search of the BIOSIS database resulted in 392 records. The full-text manuscripts of two of these references were retrieved; neither met the eligibility criteria. The TRIP database revealed no additional relevant reviews or guidelines. There were no trials registered in the WHO International Clinical Trials Registry Platform on pharmacological treatment for contacts of active TB patients. We searched the reference lists of the included studies, relevant reviews and (inter)national guidelines, but found no other eligible studies.

Characteristics of the included studies

The characteristics of the included studies are presented in Table 2.[33–35] Attamna et al. described the incidence of MDR-TB disease in people who were in
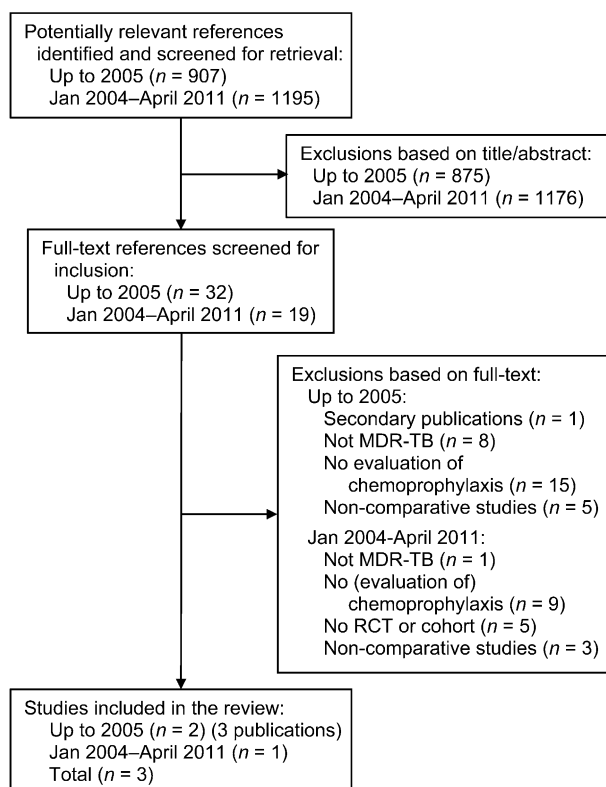

Figure 1 Search results of update of Fraser et al.[6]: effectiveness of anti-tuberculosis drugs in preventing active TB in contacts of patients with MDR-TB. The search results up to 2005 were copied from the review of Fraser et al.[6] MDR-TB = multidrug-resistant TB; RCT = randomised control trial; TB = tuberculosis.

close contact with pulmonary MDR-TB patients, and compared the incidence in persons who were offered prophylaxis with those who were not.[35] The study was performed between 1998 and 2006 in Israel, where there were no guidelines for prophylaxis in close contacts of MDR-TB patients. The decision was at the discretion of the treating physician. The duration of follow-up was at least 3 years, with a maximum of 6 years. A total number of 476 close contacts of 78 index patients were identified.

Kritski et al. studied close contacts of retreated MDR-TB patients between 1988 and 1992 in Brazil.[33] In this retrospective study, exposure time was defined

Table 1 Studies excluded at full reference screening and the reason for exclusion in the update of Fraser et al.:[6] effectiveness of anti-tuberculosis drugs for preventing active TB in contacts of MDR-TB patients

Reason for exclusion	n	Excluded studies Reference
Not MDR-TB	1	15
No evaluation of chemoprophylaxis	9	16–24
No randomised controlled trial or cohort study	5	25–29
Non-comparative study	3	30–32

TB = tuberculosis; MDR-TB = multidrug-resistant TB.

Table 2 Characteristics of included studies

Study description	Definition of index case	Definition of contact	Characteristics of contacts	Intervention and control	Follow-up	Outcomes
Kritski, 1996[33] Retrospective cohort based on patient records, 1988–1992, Brazil (n = 218)	M. tuberculosis isolated in sputum after 6 months of retreatment. MDR-TB defined as resistance to two or more anti-tuberculosis drugs; 92% MDR-TB. First person in household diagnosed with active disease	Contact: persons living in same household as the index case during the entire 5 previous years	Mean age 24.1; 84 children (38%) ≤15 years of age	INH (duration of treatment not reported) or no treatment	Exposure period was defined as time from first time of diagnosis of index case to time of identification of contact; 10604 person-months	New culture-confirmed TB cases
Schaaf, 2002[34] Prospective study in children aged ≤5 years, based on patient records, April 1994–January 2000, South Africa (n = 105)	Individual aged >15 years with sputum culture positive for M. tuberculosis, which was resistant to INH and RMP	Children aged ≤5 years, living and sleeping in the same house or group of clustered houses/shacks on the same residential site as the index case for at least 1 month	Male: 46%, median age 28 months (range 1–60)*	Individualised treatment. High dose INH 15–20 mg/kg/d, PZA 25–35 mg/kg/d, ETH 10–15 mg/kg/d and/or EMB 15–20 mg/kg/d and/or OFX 15 mg/kg/d for 6 months, the latter 2 drugs depending on the susceptibility pattern of the strain isolated from the index case Children who had received previous TB treatment or chemoprophylaxis with INH with or without RMP/PZA were not routinely prescribed another course of chemo-prophylaxis except when it was preferred by the parent rather than follow-up only Analysis: appropriate prophylaxis vs. no appropriate prophylaxis	4 months, 6 months, and every 6 months after until 30 months	TB disease (confirmed† and probable‡)
Attamna 2009[35] Prospective study based on patient records of TB centres, 1998–2006, Israel (n = 476)	Newly diagnosed patients with pulmonary MDR-TB	Close contact to patient with MDR-TB	Median age 29 years (range 2–87) Median tuberculin skin test value 10 mm (range 0–36)	Tailored regimen (mainly ciprofloxacin and PZA), INH, other treatment (duration of treatment not reported) or no treatment The decision on treatment was at the discretion of the physician	Median follow up 6 years (range 3–8); 2666 person-years	Incidence of MDR-TB

* All contacts, including contacts with active TB at initial interview (=14/125).
† Well-defined hilar or mediastinal adenopathy, miliary or endobronchial TB on chest radiograph; or adenopathy compressing airways identified by bronchoscopy and culture-positive for *M. tuberculosis* or acid-fast bacilli on microscopy.
‡ Well-defined hilar or mediastinal adenopathy, miliary or endobronchial TB on chest radiograph; or adenopathy compressing airways identified by bronchoscopy.
MDR-TB = multidrug resistant TB; INH = isoniazid; RMP = rifampicin; PZA = pyrazinamide; ETH = ethionamide; EMB = ethambutol; OFX = ofloxacin; TB = tuberculosis.

as the time from the first TB diagnosis of the index patient to time of identification of the contact case. Total duration of exposure was 10 406 person-months. The incidence of new TB cases was calculated within this time frame. Contacts could receive INH prophylaxis; however, the decision about and the timing of treatment were not clear from the paper. The definition of MDR-TB used in this study was resistance to two or more anti-tuberculosis drugs, not necessarily INH and RMP. A total of 218 contacts of 64 index patients agreed to participate; 92% of the index cases had an MDR pattern, i.e., resistance to at least INH and RMP.

The study by Schaaf et al. (1994–2000) was a prospective cohort study in young South African children in household contact with an adult with pulmonary MDR-TB.[34] All infected children and all children aged <2 years who had received no previous treatment or chemoprophylaxis of any kind for TB were offered chemoprophylaxis, classified by the authors as appropriate or inappropriate. Duration of follow-up was 30 months. In total, 125 contacts of 73 index patients were identified, of whom 14 (11%) were diagnosed with TB. There were 66 infected and 45 non-infected children; 6 children did not return for follow-up and were excluded from the analysis.

Risk of bias assessment

Table 3 presents a summary of the risk of bias assessment using the NOS Star template.[13] A study could be awarded a maximum of four stars for Selection, one star for Comparability and three stars for Outcome. The Selection items refer to representativeness of the exposed cohort, selection of the non-exposed, measurement of exposure and demonstration that the outcome of interest (active TB) was not present at

Table 3 Summary of the risk of bias assessment of the three included studies using the Newcastle Ottawa Scale Star Template*

Study identification	Selection	Comparability	Outcome
Attamna, 2009[35]	★ ★ ★		★ ★ ★
Kritski, 1996[33]	★ ★ ★		★ ★
Schaaf, 2002[34]	★ ★ ★		★ ★ ★

*A study could be awarded a maximum of one star for each numbered item within the Selection and Outcome categories and a maximum of two stars can be given for Comparability. For the Selection category, a star was awarded if the exposed cohort was representative, if the non-exposed cohort was drawn from the same community as the exposed cohort, if exposure was ascertained by secure record or by a structured interview, and if it was demonstrated that the outcome of interest was not present at start of study. For Comparability, one star was awarded if the study controlled for the most important factor, another star could be awarded if the study controlled for any additional factor. For Outcome, a star was awarded if the assessment of the outcome was an independent blind assessment or by record linkage, if there was a long enough follow-up for the outcomes to occur, and if there was complete follow-up or if the fact that subjects were lost to follow-up was unlikely to introduce bias.

the start of the study. Comparability refers to comparability of exposed and non-exposed, and Outcome to measurement of the outcome, duration of follow-up and completeness of follow-up.

In all studies, the untreated contacts were a selected group, because they had received previous TB treatment or chemoprophylaxis,[34] because the decision of treatment was at the discretion of the physician[35] or because the decision of whether or not to treat was not reported and thus unclear.[33] The results of the studies were not adjusted for confounders, which puts them also at high risk of bias.

Effects of the interventions

In one study, there were no TB events in the treated or the untreated group[35] (Table 4). As a relative risk could thus not be calculated for this study, we decided to

Table 4 Results of the update of the systematic review of Fraser et al.[6]

Study	Sample size *n*	Active TB disease *n* (%) Prophylaxis	Active TB disease *n* (%) No prophylaxis	Risk difference (95%CI)	Odds ratio (95%CI)
Kritski, 1996[33] Contacts*	218	2/45 (4.4) 1.2/1000 person-months	15/173 (8.7) 1.7/1000 person-months	−0.04 (−0.12 to 0.03)	0.49 (0.11 to 2.23)
Kritski, 1996[33] Infected contacts[†]	188	2/45 (4.4)	13/145 (9.0)	−0.05 (−0.12 to 0.03)	0.46 (0.07 to 2.32)
Schaaf, 2002[34] Contacts	61 infected;[‡] 44 non–infected[§]	Confirmed TB[¶] 0/41 (0)	Confirmed TB 3/64 (4.7)	Confirmed TB −0.05 (−0.11 to 0.02)	0.21 (0.01 to 4.21)
		Confirmed+probable TB[#] 2/41 (4.9)	Confirmed+probable TB 13/64 (20.3)	Confirmed+probable TB −0.15 (−0.27 to −0.04)	0.20 (0.04 to 0.94)
Attamna, 2009[35] Contacts	476	0/89 (0)	0/387 (0)	0.00 (−0.02 to 0.02)	—

*Persons living in the same household as the index case during the entire 5 previous years.
[†] Persons living in the same household as the index case during the entire 5 previous years with a tuberculin skin test result ≥10 mm.
[‡] Mantoux test ≥15 mm, a symptomatic, normal CXR or only calcifications in the lung parenchyma of regional lymph nodes on CXR.
[§] Asymptomatic, non-significant (<15 mm induration) Mantoux test, normal CXR and negative cultures for *M. tuberculosis.*
[¶] Well-defined hilar or mediastinal adenopathy, miliary or endobronchial TB on CXR; or adenopathy compressing airways identified by bronchoscopy and culture-positive for *M. tuberculosis* or acid-fast bacilli on microscopy.
[#] Well-defined hilar or mediastinal adenopathy, miliary or endobronchial TB on CXR; or adenopathy compressing airways identified by bronchoscopy.
TB = tuberculosis; CI = confidence interval; CXR = chest radiograph.

present the risk difference. In the two other studies, the risk of developing active TB disease was lower in the treated group, but the risk difference was not significant, i.e., 4% (95% confidence interval [CI] −3 to 12),[33] and 5% (95%CI −2 to 11),[34] both in favour of chemoprophylaxis. Schaaf et al. did find a significant risk difference between treated and untreated when assessing confirmed and probable TB, i.e., 15% (95%CI −27 to −4). Because of the low number of events the CIs were wide. Our other pre-defined outcomes —death, extra-pulmonary TB and adverse effects— were not measured in the included studies.

Quality of the evidence

We assessed whether we could upgrade the level of evidence in the GRADE profile. As there were limitations in study design, inconsistencies and imprecisions among the results, the quality of the evidence could not be upgraded. The quality of the evidence for the effectiveness of chemoprophylaxis to prevent active MDR-TB is thus assessed to be very low.

2 Review on the effectiveness of anti-tuberculosis drugs other than INH and RMP for preventing active TB in infected contacts of patients with non-MDR-TB

Study selection

Of the 2480 identified records, 238 references were considered potentially relevant (Figure 2). In a second round of title/abstract selection to identify primary studies, 48 references were identified as primary
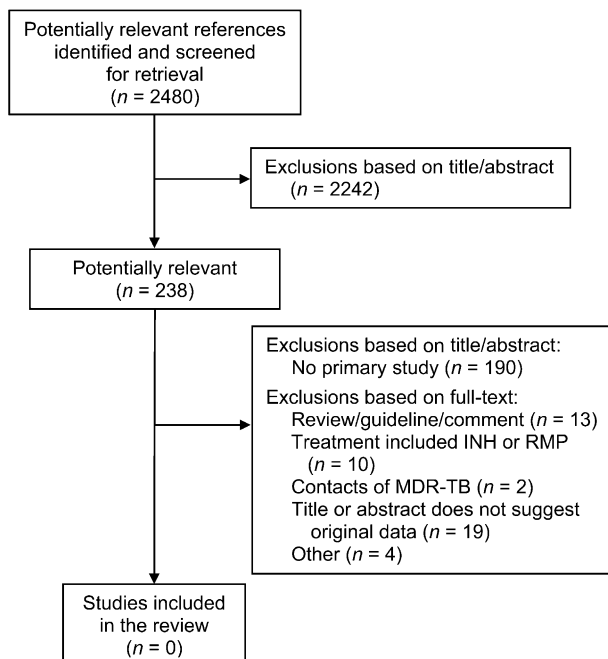

Figure 2   Search results of review on the effectiveness of anti-tuberculosis drugs other than INH and RMP for preventing active TB in infected contacts of patients with non-MDR-TB. INH = isoniazid; RMP = rifampicin; MDR-TB = multidrug-resistant TB; TB = tuberculosis.

Table 5   Studies excluded at full reference screening and the reason for exclusion from the review on the effectiveness of anti-tuberculosis drugs, other than INH and RMP, for preventing active TB in infected contacts of patients with non-MDR-TB

Reason for exclusion	Excluded studies	
	n	Reference
Regimen contains RMP or INH	11	36–46
Review or comment (no original data)	14	47–60
Included patients are contacts of MDR-TB patients	3	61–63*
No outcome reported of prophylactic treatment	1	64
Article could not be retrieved. General title of manuscript does suggest that it does not contain original data	19	65–83

* Published before 2004 and therefore not identified in the search for the update of the review of Fraser et al. (2006).[6] Two studies did not measure the outcome active TB[61,63] and the other study was non-comparative.[62]
INH = isoniazid; RMP = rifampicin; MDR-TB = multidrug-resistant tuberculosis.

studies, or the study type was unknown (based on title and/or abstract). After applying the eligibility criteria to the 48 full-text articles, none could be included (Figure 2, Table 5).[36–83]

A search of the BIOSIS database resulted in 392 records. The full-text manuscripts of two of these references were retrieved; neither met the eligibility criteria. The TRIP database was searched and revealed no additional relevant reviews or guidelines.

There were no registered trials on pharmacological treatment for contacts of active TB patients in the WHO International Clinical Trials Registry Platform. A search of the reference lists of relevant reviews and (inter)national guidelines provided no eligible studies.

DISCUSSION

Despite the attention given to MDR- and XDR-TB in recent years, few new publications have dealt with preventive treatment for contacts of MDR-TB patients. Only one additional cohort study has been published since the systematic review of Fraser et al. in 2006.[6] The combined quality of the evidence provided by the three included studies was assessed as very low, which means that any estimate of effect is very uncertain. In this case, it was not even possible to make an estimate of the effect, as the studies were clinically and methodologically too heterogeneous. The risk difference for the prevention of culture-confirmed TB calculated from the three included studies did not show a significant effect of preventive treatment. The absence of an effect needs to be interpreted with caution, as the sample sizes and number of events were low and the CIs wide.

As discussed in the introduction, the absence of clear evidence to support the prescription of preventive treatment for contacts of MDR-TB patients has resulted in different recommendations being proposed. The ATS and CDC guidelines recommend the administration of preventive treatment,[3] whereas

the WHO and the National Collaborating Centre for Chronic Conditions and the Centre for Clinical Practice strongly oppose chemoprophylaxis and recommend careful clinical follow-up for a period of at least 2 years.[4,5] This systematic review found no evidence to support one or the other recommendation.

As information from effectiveness studies provides insufficient clear evidence for the development of recommendations for management of contacts of MDR-TB patients, information on the side effects of preventive treatment might be useful. In most studies reporting on adverse effects during preventive treatment for contacts of MDR-TB patients with alternative regimens, side effects were very common.[25,61–63,84] Many contacts discontinued preventive treatment —14/16 (87.5%),[61] 13/22 (59.1%),[62] 35/48 (72.9%),[63] 17/17 (100%),[84] and 7/12 (58.3%)[25]—frequently due to the elevation of liver enzymes. No study reported a death due to preventive treatment.

Given the high prevalence of adverse effects[25,61–63,84] and the low quality of the evidence of the effect of preventive treatment, it would be interesting to know how many contacts develop TB with the same resistance and/or DNA profile as the index MDR-TB patient. This will of course depend on the likelihood that an infected contact has indeed been infected by the identified index case. In high TB prevalence areas, this is likely to be lower than in low TB prevalence areas. A study in Peru, a high-burden country, showed that of 142 contacts of MDR-TB patients who developed active TB, 129 (90.9%) had MDR-TB but only 77 (59.7%) had the same drug susceptibility testing (DST) results (to both EMB and streptomycin) as their respective index patients.[16] In contrast, in a study in Brazil, five (83%) of six contacts of MDR-TB cases who developed TB, for whom DST results were available, had the same bacterial susceptibility profiles as their index cases.[16,85] The study of Kritski et al., which is included in this systematic review, reports that, of the 13 isolates of contacts that developed TB, only 6 (46%) had a resistance pattern identical to those of their index case isolate.[33] Four of the 13 isolates (31%) were drug-resistant, but the DST pattern was different from that of the index case, and only three (23%) contacts had isolates susceptible to all drugs.[33] Thus, not every contact who develops TB will have received it from the putative index case. If a contact is actually infected with drug-susceptible TB, preventive treatment with a regimen suitable for contacts of MDR-TB patients would be overtreatment, and would expose the contact to the elevated risk of serious adverse effects. If preventive treatment is guided by the DST pattern of the presumed MDR-TB index case, whereas the contact has been infected by a different MDR-TB index patient, the selected preventive treatment may not be effective.

In conclusion, evidence on the effect of preventive treatment for contacts of MDR-TB patients is limited. The available evidence is not sufficient to support or reject preventive treatment, and is of very low quality. Evidence-based guideline development for preventive treatment of contacts of MDR-TB patients requires considerably more research, and preferably clinical trials.

References

1 Smieja M J, Marchetti C A, Cook D J, et al. Isoniazid for preventing tuberculosis in non-HIV-infected persons. Cochrane Database Syst Rev 2000; CD001363.
2 Akolo C, Adetifa I, Shepperd S, et al. Treatment of latent tuberculosis infection in HIV infected persons. Cochrane Database Syst Rev 2010; CD000171.
3 Targeted tuberculin testing and treatment of latent tuberculosis infection. Am J Respir Crit Care Med 2000; 161 (4 Pt 2): S221–S247.
4 National Collaborating Centre for Chronic Conditions and the Centre for Clinical Practice at NICE. NICE Clinical Guideline 117: clinical diagnosis and management of tuberculosis, and measures for its prevention and control. London, UK: NICE, 2011.
5 World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis. Emergency update 2008. WHO/HTM/TB/2008.402. Geneva, Switzerland: WHO, 2008.
6 Fraser A, Paul M, Attamna A, Leibovici L. Treatment of latent tuberculosis in persons at risk for multidrug-resistant tuberculosis: systematic review. Int J Tuberc Lung Dis 2006; 10: 19–23.
7 Fraser A, Paul M, Attamna A, et al. Drugs for preventing tuberculosis in people at risk of multiple-drug-resistant pulmonary tuberculosis. Cochrane Database Syst Rev 2006; CD005435.
8 Gandhi N R, Nunn P, Dheda K, et al. Multidrug-resistant and extensively drug-resistant tuberculosis: a threat to global control of tuberculosis. Lancet 2010; 375: 1830–1843.
9 A ministerial meeting of high M/XDR-TB burden countries. Beijing, China, 1–3 April 2009. http://www.who.int/tb_beijing meeting/en/index.html Accessed November 2011.
10 Cobelens F G, Heldal E, Kimerling M E, et al. Scaling up programmatic management of drug-resistant tuberculosis: a prioritized research agenda. PLoS Med 2008; 5: e150.
11 Higgins J P T, Green S. Cochrane handbook for systematic reviews of interventions. Oxford, UK: The Cochrane Collaboration, 2011.
12 Shea B J, Grimshaw J M, Wells G A, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol 2007; 7: 10.
13 Wells G A, Shea B J, O'Connell D, et al. The Newcastle Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis. http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm Accessed November 2011.
14 Guyatt G H, Oxman A D, Vist G E, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008; 336: 924–926.
15 Lardizabal A, Passannante M, Kojakali F, et al. Enhancement of treatment completion for latent tuberculosis infection with 4 months of rifampin. Chest 2006; 130: 1712–1717.
16 Becerra M C, Appleton S C, Franke M F, et al. Tuberculosis burden in households of patients with multidrug-resistant and

extensively drug-resistant tuberculosis: a retrospective cohort study. Lancet 2011; 377: 147–152.

17 Chemardin J, Paty M C, Renard-Dubois S, et al. Contact tracing of passengers exposed to an extensively drug-resistant tuberculosis case during an air flight from Beirut to Paris, October 2006. Euro Surveill 2007; 12: E071206.

18 de Vries G, van Altena R, van Soolingen D, et al. [An outbreak of multiresistant tuberculosis from Eastern Europe in the Netherlands]. Ned Tijdschr Geneeskd 2005; 149: 1921–1924. [Dutch]

19 Huang Y-W, Shen G-H, Lee J-J, Yang W-T. Latent tuberculosis infection among close contacts of multidrug-resistant tuberculosis patients in central Taiwan. Int J Tuberc Lung Dis 2010; 14: 1430–1435.

20 Llacer R L, Gonong J R, Balanag V, et al. Contact tracing of MDR-TB patients at the lung center of the Philippines. Respirology (2010) 15 (Suppl. 2), 26–54. [Oral Presentation Abstract OS-06-06]

21 Miramontes R, Lambert L, Haddad M B, et al. Public health response to a multidrug-resistant tuberculosis outbreak among Guatemalans in Tennessee, 2007. South Med J 2010; 103: 882–886.

22 Palmero D, Ritacco V, Ruano S, et al. Multidrug-resistant tuberculosis outbreak among transvestite sex workers, Buenos Aires, Argentina. Int J Tuberc Lung Dis 2005; 9: 1168–1170.

23 Pankhania B, Thompson C, Nash K, et al. Tuberculosis contact tracing at a school in a low-incidence area. Thorax 2009; Conference: A127.

24 Pineiro Perez R, Mellado Pena M J, Mendez Echevarria A, et al. [Exposure to multiresistant tuberculosis: study and follow-up of nine children]. An Pediatr (Barc) 2008; 68: 490–495. [Spanish]

25 Younossian A B, Rochat T, Ketterer J P, et al. High hepatotoxicity of pyrazinamide and ethambutol for treatment of latent tuberculosis. Eur Respir J 2005; 26: 462–464.

26 Cain K P, Nelson L J, Cegielski J P. Global policies and practices for managing persons exposed to multidrug-resistant tuberculosis. Int J Tuberc Lung Dis 2010; 14: 269–274.

27 Finnell S M, Christenson J C, Downs S M. Latent tuberculosis infection in children: a call for revised treatment guidelines. Pediatrics 2009; 123: 816–822.

28 Sneag D B, Schaaf H S, Cotton M F, et al. Failure of chemoprophylaxis with standard antituberculosis agents in child contacts of multidrug-resistant tuberculosis cases. Pediatr Infect Dis J 2007; 26: 1142–1146.

29 Takashima T, Kawabe Y. Strategies against multidrug-resistant tuberculosis. Kekkaku 2004; 79: 669–687. [Japanese]

30 Feja K, McNelley E, Tran C S, et al. Management of pediatric multidrug-resistant tuberculosis and latent tuberculosis infections in New York City from 1995 to 2003. Pediatr Infect Dis J 2008; 27: 907–912.

31 Sasaki Y, Yamagishi F, Yagi T. [Current situation of contacts examination and chemoprophylaxis for persons exposed to multi-drug resistant tuberculosis in ordinance-designated cities in Japan]. Kekkaku 2005; 80: 637–642. [Japanese]

32 Tochon M, Bosdure E, Salles M, et al. Management of young children in contact with an adult with drug-resistant tuberculosis, France, 2004–2008. Int J Tuberc Lung Dis 2011; 15: 326–330.

33 Kritski A L, Marques M J, Rabahi M F, et al. Transmission of tuberculosis to close contacts of patients with multidrug-resistant tuberculosis. Am J Respir Crit Care Med 1996; 153: 331–335.

34 Schaaf H S, Gie R P, Kennedy M, et al. Evaluation of young children in contact with adult multidrug-resistant pulmonary tuberculosis: a 30-month follow-up. Pediatrics 2002; 109: 765–771.

35 Attamna A, Chemtob D, Attamna S, et al. Risk of tuberculosis in close contacts of patients with multidrug resistant tuberculosis: a nationwide cohort. Thorax 2009; 64: 271.

36 Balague M, Sanchez F, Fernandez S, et al. [Difficulties to enroll patients in non-remunerated clinical trials. Results from a clinical trial comparing two treatment options for latent tuberculosis infection]. Medicina Clinica 2004; 122: 115. [Spanish]

37 Brown J M, Boparai N, Brown M, et al. Chemoprophylaxis following an outbreak of isoniazid-resistant tuberculosis in a community school: compliance and tolerance in an adolescent population to a regime of rifampicin and ethambutol. Thorax 2009; 64 (Suppl VI): A123.

38 Cayla J, Sanchez F, Martinez L, et al. [Treatment of tuberculous infection (antituberculous chemoprophylaxis)]. Enfermedades Emergentes 2001; 3: 90–91. [Spanish]

39 De Pinho A M F, Santoro-Lopes G, Harrison L H, et al. Chemoprophylaxis for tuberculosis and survival of HIV-infected patients in Brazil. AIDS 2001; 15: 2129–2135.

40 Gordin F. Short-term tuberculosis prophylaxis is effective in persons with HIV. Am Fam Physician 1998; 58: 948.

41 Higgins R M, Cahn A P, Porter D, et al. Mycobacterial infections after renal transplantation. Q J Med 1991; 78: 145–153.

42 LaMar J E II, Malakooti M A. Tuberculosis outbreak investigation of a US Navy amphibious ship crew and the marine expeditionary unit aboard, 1998. Mil Med 2003; 168: 523–527.

43 Macintyre C R, Ansari M Z, Carnie J, et al. No evidence for multiple-drug prophylaxis for tuberculosis compared with isoniazid alone in Southeast Asian refugees and migrants: completion and compliance are major determinants of effectiveness. Prev Med 2000; 30: 425–432.

44 Pang S C, Harrison R H, Brearley J, et al. Preventive therapy for tuberculosis in Western Australia. Int J Tuberc Lung Dis 1998; 2: 984–988.

45 Stein-Zamir C, Volovik I, Rishpon S, et al. Tuberculosis outbreak among students in a boarding school. Eur Respir J 2006; 28: 986–991.

46 Torres G. A short two-drug regimen prevents active TB. GMHC Treat Issues 1998; 12: 12.

47 Centers for Disease Control and Prevention. Use of short-course tuberculosis preventive therapy regimens in HIV- sero-negative persons. JAMA 1998; 280: 1736.

48 Amoudru C, Michot R, Azencott A, et al. [Prevention of tuberculosis in mining areas. The experience of the Nord and the Pas-de-Calais basin]. Acta Tuberculosea et Pneumologica Belgica 1975; 66: 128–137. [French]

49 Barton L L, Lepage P, De Rosa F G, et al. Treatment of latent tuberculosis infection (multiple letters). N Engl J Med 2003; 348: 1292–1294.

50 Geiter L J, O'Brien R J. From the Centers for Disease Control. Conference on new approaches for tuberculosis preventive therapy. J Infect Dis 1987; 156: 536–537.

51 Houston S, Long R, Hoeppner V, et al. Latent tuberculosis treatment (multiple letters). Can Med Assoc J 2002; 167: 452–454.

52 Johnston B L, Conly J M. Re-examining treatment of latent tuberculosis infection. Can J Infect Dis 2001; 12: 211–214.

53 Kirkland L R. Preventive therapy for multidrug-resistant tuberculosis. JAMA 1996; 276: 27–28.

54 Kritski A L. Tuberculosis preventive therapy for HIV-infected persons in less developed countries. Int J Tuberc Lung Dis 2000; 4 (Suppl 1): S76–S81.

55 Mitchison D A. Pyrazinamide in the chemoprophylaxis of tuberculosis. Am Rev Respir Dis 1990; 142: 1467.

56 Sane S V, Sane N S, Thakker S V, et al. Alternatives to INH chemoprophylaxis. Indian Pediatr 1995; 32: 935–937.

57 Sanklecha M U, Raghavan K, Mehta M N. Is INH alone enough for prophylaxis? Indian Pediatr 1995; 32: 105.

58 Shingadia D V, Baumer J H. Tuberculosis: diagnosis, management and prevention. Arch Dis Child Educ Pract Ed 2007; 92: ep27–ep29.

59 Singh N. Inching closer towards optimization of treatment for latent tuberculosis in liver transplant recipients. Transplantation 2007; 83: 1536–1537.

60 Yun J S, Lazarus A A, Gilbert R. Latent tuberculous infection. Disease-A-Month 2006; 52: 441–445.

61 Horn D L, Hewlett D Jr, Alfalla C, et al. Limited tolerance of ofloxacin and pyrazinamide prophylaxis against tuberculosis. N Engl J Med 1994; 330: 1241.

62 Ridzon R, Meador J, Maxwell R, et al. Asymptomatic hepatitis in persons who received alternative preventive therapy with pyrazinamide and ofloxacin. Clin Infect Dis 1997; 24: 1264–1265.

63 Lou H X, Shullo M A, McKaveney T P. Limited tolerability of levofloxacin and pyrazinamide for multidrug-resistant tuberculosis prophylaxis in a solid organ transplant population. Pharmacotherapy 2002; 22: 701–704.

64 Bay M R, Gonzalez G, Pedrini M, et al. Evaluation of the therapeutic fulfilment in the treatment or profilaxis of tuberculosis. Latin American Journal of Pharmacy 2007; 26: 609–613. [Spanish]

65 Balague M, Sanchez F, Martin V, et al. Treatment of latent tuberculosis infection in HIV-positive persons. Enfermedades Emergentes 2002; 4: 209–212. [Spanish]

66 Cohn D L, Iseman M D. Treatment and prevention of multidrug-resistant tuberculosis. Res Microbiol 1993; 144: 150–158.

67 Conen D. Preventive chemotherapy for tuberculosis. Ars Medici 1985; 5: 299 (Table 5). [German]

68 Grosset J. Present and new drug regimens in chemotherapy and chemoprophylaxis of tuberculosis. Bull Int Union Tuberc Lung Dis 1990; 65 (2–3): 86–91.

69 Krebs A, Steinbrueck P, Renger F, et al. Perspective of tuberculosis control: role of preventive chemotherapy. Zeitschrift fur Erkrankungen der Atmungsorgane 1979; 153: 60–65. [German]

70 Laylavoix F. [Treatment in cases of tuberculin reaction conversion]. Bordeaux Medical 1980; 13: 329–330. [French]

71 Mlczoch F. [Preventive treatment of tuberculosis]. Wiener Medizinische Wochenschrift 1972; 122: 773–777. [German]

72 Moorman J P, Mandell G L. Prophylactic TB therapy: what options when INH toxicity develops? J Respir Dis 1998; 19: 933.

73 Nakhosteen J A. Prophylaxis and therapy of pulmonary tuberculosis. Atemwegs- und Lungenkrankheiten 1990; 16: 123–125. [German]

74 Press P. Prophylaxis, detection and treatment of pulmonary tuberculosis. Revue Medicale de la Suisse Romande 1982; 102: 249–255. [French]

75 Prignot J. [Tuberculosis: chemoprophylaxis and chemotherapy in 1992]. Louvain Medical 1992; 111: 9–16. [French]

76 Rey D R. Prophylaxis and treatment in associated infection of tuberculosis and HIV. Archivos de Bronconeumologia 1992; 28: 51–54. [Spanish]

77 Rodriguez F G, Bernal Bermudez J A, Egido A G. [Clinical management of latent tuberculosis]. Medicina Clinica 2001; 117: 111–114. [Spanish]

78 Rojas-Pache C, Cerruti F. [*Mycobacterium tuberculosis* infection and HIV. Approach, treatment and prophylaxis]. Medecine et Hygiene 1991; 49: 1569–1576. [French]

79 Schonian U, Schmidt M, Ringelmann R. [Preventive chemotherapy in tuberculosis]. Immunitat und Infektion 1986; 14: 208–209. [German]

80 Simon K. [Prophylactic and preventive measures in the fight against tuberculosis]. Beitrage zur Klinik und Erforschung der Tuberkulose und der Lungenkrankheiten 1968; 137: 151–158. [German]

81 Solsona P J, Jimenez Fuentes M A, Mila A C, et al. [Clinical management of latent tuberculosis]. Med Clin (Barc) 2002; 118: 636–638.

82 Van Deutekom H. Chemoprophylaxis and chemotherapy of tuberculosis in HIV infected patients. Bull Int Union Tuberc Lung Dis 1990; 65 (2–3): 84–85.

83 Zierski M, Mokrzycki M. [Antibiotics in preventive therapy of pulmonary tuberculosis]. Gruzlica 1951; 19: 459–478. [Polish]

84 Papastavros T, Dolovich L R, Holbrook A, et al. Adverse events associated with pyrazinamide and levofloxacin in the treatment of latent multidrug-resistant tuberculosis. CMAJ 2002; 167: 131–136.

85 Teixeira L, Perkins M D, Johnson J L, et al. Infection and disease among household contacts of patients with multidrug-resistant tuberculosis. Int J Tuberc Lung Dis 2001; 5: 321–328.

APPENDIX A

Search strategy for the systematic review with the aim of evaluating the effectiveness of anti-tuberculosis drugs for preventing active TB in persons at risk of developing MDR-TB.

PubMed (MEDLINE)
Platform: NCBI PubMed
Database: PubMed
Date: 19 April 2011
Limits: data range: 1 January 2004 till 19 April 2011

1 tb[ALL]
2 tuberculosis[ALL]
3 Tuberculosis[MeSH]
4 #1 OR #2 OR #3
5 Drug Resistance, Multiple, Bacterial[MeSH]
6 MDR[ALL]
7 multidrug-resistant*[ALL]
8 Tuberculosis, Multidrug-Resistant[MeSH]
9 #5 OR #6 OR #7 OR #8
10 latent[ALL]
11 contact*[ALL]
12 contact tracing[MeSH]
13 Antibiotic Prophylaxis[MeSH]
14 chemoprevention[MeSH]
15 prevent*[ALL]
16 prophyla*[ALL]
17 #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16
18 #4 AND #9 AND #17

Embase
Platform: OvidSP
Database: Embase 1980–present
Date: 19 April 2011
Limits: publication year: 2004 to Present
Methodological filters: no filters used

1 tuberculosis.mp.
2 tb.mp.
3 exp tuberculosis/
4 or/1–3
5 exp multidrug resistance/
6 MDR.mp.
7 multidrug-resistant*.mp.
8 or/5–7
9 latent.mp.
10 contact*.mp.
11 exp contact examination/
12 exp antibiotic prophylaxis/
13 exp chemoprophylaxis/
14 prevent*.mp.
15 prophyla*.mp.
16 or/9–15
17 4 AND 8 AND 16

LILACS
We searched the LILACS database with the search string 'multirresistente AND tuberculosis' (Spanish

terms for multiresistant and tuberculosis) on 4 May 2011.

Cochrane Library (CENTRAL)
Platform: Wiley
Database: Cochrane database of systematic reviews, clinical trials, economic evaluations database
Date: 14 April 2011
Limits: no limits
Methodological filters: no filters used

1 (tb):ti,ab,kw
2 tuberculosis:ti,ab,kw
3 MeSH descriptor Tuberculosis explode all trees
4 (#1 OR #2 OR #3)
5 MeSH descriptor Drug Resistance, Multiple, Bacterial explode all trees
6 MDR:ti,ab,kw
7 multidrug-resistant*:ti,ab,kw
8 MeSH descriptor Tuberculosis, Multidrug-Resistant explode all trees
9 (#5 OR #6 OR #7)
10 latent:ti,ab,kw
11 contact*:ti,ab,kw
12 MeSH descriptor Contact Tracing explode all trees
13 MeSH descriptor Antibiotic Prophylaxis explode all trees
14 MeSH descriptor Chemoprevention explode all trees
15 prevent*:ti,ab,kw
16 prophyla*:ti,ab,kw
17 (#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16)
18 (#4 AND #9 AND #17)

APPENDIX B

Search strategy for the systematic review with the aim of assessing the effectiveness of drugs other than isoniazid and rifampicin to prevent active TB in contacts of non-MDR-TB patients.

MEDLINE
Platform: OvidSP
Database: Ovid MEDLINE® In-Process & Other Non-Indexed Citations and Ovid MEDLINE® 1948 to Present
Date: 19 April 2011
Limits: no limits were used
Methodological filters: no filters used

1 (tuberculo* OR TB OR scrofuloderma).ti,ab.
2 exp Tuberculosis/
3 1 OR 2
4 latent.mp.
5 contact*.mp.
6 exp Contact Tracing/
7 exp Antibiotic Prophylaxis/
8 exp Chemoprevention/

 9 prevent*.mp.
10 prophyla*.mp.
11 or/4–10
12 exp Ethambutol/
13 ethambutol.ti,ab.
14 pyrazinamide.mp. OR exp Pyrazinamide/
15 streptomycin.mp. OR exp Streptomycin/
16 amikacin.mp. OR exp Amikacin/
17 kanamycin.mp. OR exp Kanamycin/
18 capreomycin.mp. OR exp Capreomycin/
19 viomycin.mp. OR exp Viomycin/
20 enviomycin.mp. OR exp Enviomycin/
21 fluoroquinolones.mp. OR exp Fluoroquinolones/
22 levofloxacin.mp. OR exp Ofloxacin/
23 moxifloxacin.mp.
24 ofloxacin.mp.
25 ciprofloxacin.mp. OR exp Ciprofloxacin/
26 sparfloxacin.mp.
27 thioamides.mp. OR exp Thioamides/
28 cycloserine.mp. OR exp Cycloserine/
29 opc-67683.mp.
30 PA-824.mp.
31 thiacetazone.mp. OR exp Thioacetazone/
32 p-aminosalicylic acid.mp. OR exp Aminosalicylic Acid/
33 para-aminosalicyclic acid.mp.
34 PAS.mp.
35 ethionamide.mp. OR exp Ethionamide/
36 clofazimine.mp. OR exp Clofazimine/
37 rifabutin.mp. OR exp Rifabutin/
38 rifapentine.mp.
39 clarithromycin.mp. OR exp Clarithromycin/
40 linezolid.mp.
41 thioacetazone.mp. OR exp Thioacetazone/
42 thiocetazone.mp.
43 thioridazine.mp. OR exp Thioridazine/
44 exp Arginine/OR arginine.mp.
45 exp Vitamin D/OR vitamin d.mp.
46 r207910.mp.
47 exp Amoxicillin-Potassium Clavulanate Combination/
48 (amoxicillin AND (clavulanate OR clavulanic acid)).mp.
49 terizidone.mp.
50 protionamide.mp. OR exp Prothionamide/
51 imipenem.mp. OR exp Imipenem/
52 cilastatin.mp. OR exp Cilastatin/
53 TMC207.mp.
54 gatifloxacin.mp.
55 prothionamide.mp.
56 or/12–55
57 3 AND 11 AND 56

Embase
Platform: OvidSP
Database: Embase 1980–present
Date: 19 April 2011
Limits: publication year: no limits were used
Methodological filters: no filters used

 1 exp ETHAMBUTOL/OR ethambutol.mp.
 2 pyrazinamide.mp. OR exp PYRAZINAMIDE/
 3 streptomycin.mp. OR exp STREPTOMYCIN/
 4 amikacin.mp. OR exp AMIKACIN/
 5 kanamycin.mp. OR exp KANAMYCIN/
 6 capreomycin.mp. OR exp CAPREOMYCIN/
 7 viomycin.mp. OR exp VIOMYCIN/
 8 enviomycin.mp. OR exp ENVIOMYCIN/
 9 fluoroquinolones.mp. OR exp quinolone derivative/
10 levofloxacin.mp. OR exp LEVOFLOXACIN/
11 moxifloxacin.mp. OR exp MOXIFLOXACIN/
12 ofloxacin.mp. OR exp OFLOXACIN/
13 exp CIPROFLOXACIN/OR ciprofloxacin.mp.
14 sparfloxacin.mp. OR exp SPARFLOXACIN/
15 thioamides.mp. OR exp thioamide/
16 cycloserine.mp. OR exp CYCLOSERINE/
17 opc-67683.mp. OR exp "2,3 dihydro 2 methyl 6 nitro 2 [4 [4 (4 trifluoromethoxyphenoxy) 1 pipe ridinyl]phenoxymethyl]imidazo[2,1 b]oxazole"/
18 PA-824.mp. OR exp "6,7 dihydro 2 nitro 6 (4 trifluoromethoxybenzyloxy) 5h imidazo [2,1 b][1,3]oxazine"/
19 thiacetazone.mp. OR exp thioacetazone/
20 p-aminosalicylic acid.mp. OR exp aminosalicylic acid/
21 para-aminosalicyclic acid.mp.
22 PAS.mp.
23 ethionamide.mp. OR exp ETHIONAMIDE/
24 exp CLOFAZIMINE/OR clofazimine.mp.
25 rifabutin.mp. OR exp RIFABUTIN/
26 rifapentine.mp. OR exp RIFAPENTINE/
27 exp CLARITHROMYCIN/OR clarithromycin.mp.
28 linezolid.mp. OR exp LINEZOLID/
29 thioacetazone.mp. OR exp THIOACETAZONE/
30 thiocetazone.mp.
31 thioridazine.mp. OR exp THIORIDAZINE/
32 arginine.mp. OR exp ARGININE/
33 Vitamin D.mp. OR exp vitamin D/
34 r207910.mp. OR exp "1 (6 bromo 2 methoxy 3 quinolinyl) 4 dimethylamino 2 (1 naphthyl) 1 phenyl 2 butanol"/
35 exp amoxicillin plus clavulanic acid/
36 (amoxicillin AND (clavulanate OR clavulanic acid)).mp.
37 terizidone.mp. OR exp TERIZIDONE/
38 protionamide.mp. OR exp PROTIONAMIDE/
39 exp IMIPENEM/OR imipenem.mp.
40 exp CILASTATIN/OR cilastatin.mp.
41 TMC207.mp. OR exp "1 (6 bromo 2 methoxy 3 quinolinyl) 4 dimethylamino 2 (1 naphthyl) 1 phenyl 2 butanol"/
42 gatifloxacin.mp. OR exp GATIFLOXACIN/
43 prothionamide.mp. OR exp protionamide/
44 or/1–43
45 (latent OR prevent* OR prophyla*).mp. adj5 (tuberculosis.mp. OR tubercula.ti,ab. OR scrofuluderma.ti,ab.)

46 exp tuberculosis/
47 exp contact examination/
48 exp antibiotic prophylaxis/
49 exp chemoprophylaxis/
50 or/47–49
51 46 AND 50
52 51 OR 45
53 52 AND 44
54 animal/not human/
55 case report/
56 or/54–55
57 53 not 56

LILACS

We searched the LILACS database with the search strings 'latente AND tuberculosis' and 'contacto AND tuberculosis' (Spanish terms for latent, contact and tuberculosis) on May 4, 2011.

Cochrane Library
Platform: Wiley
Database: The Cochrane Library
Date: 19 April 2011
Limits: no limits were used
Methodological filters: no filters used

 1 (tuberculo* OR TB OR scrofuloderma):ti,ab
 2 MeSH descriptor Tuberculosis explode all trees
 3 (#1 OR #2)
 4 latent:ti,ab,kw
 5 contact*:ti,ab,kw
 6 prevent*:ti,ab,kw
 7 prophyla*:ti,ab,kw
 8 MeSH descriptor Contact Tracing explode all Trees
 9 MeSH descriptor Antibiotic Prophylaxis explode all trees
10 MeSH descriptor Chemoprevention explode all trees
11 (#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10)
12 (#3 AND #11)
13 MeSH descriptor Ethambutol explode all trees
14 MeSH descriptor Pyrazinamide explode all trees
15 MeSH descriptor Streptomycin explode all trees
16 MeSH descriptor Amikacin explode all trees
17 MeSH descriptor Kanamycin explode all trees
18 MeSH descriptor Capreomycin explode all trees
19 MeSH descriptor Viomycin explode all trees
20 MeSH descriptor Enviomycin explode all trees
21 MeSH descriptor Enviomycin explode all trees
22 MeSH descriptor Fluoroquinolones explode all trees
23 MeSH descriptor Ofloxacin explode all trees
24 MeSH descriptor Ciprofloxacin explode all trees
25 MeSH descriptor Thioamides explode all trees
26 MeSH descriptor Cycloserine explode all trees
27 MeSH descriptor Thioacetazone explode all trees
28 MeSH descriptor Aminosalicylic Acid explode all trees
29 MeSH descriptor Ethionamide explode all trees
30 MeSH descriptor Clofazimine explode all trees
31 MeSH descriptor Rifabutin explode all trees
32 MeSH descriptor Clarithromycin explode all trees
33 MeSH descriptor Thioacetazone explode all trees
34 MeSH descriptor Thioridazine explode all trees
35 MeSH descriptor Arginine explode all trees
36 MeSH descriptor Vitamin D explode all trees
37 MeSH descriptor Amoxicillin-Potassium Clavulanate Combination explode all trees
38 MeSH descriptor Prothionamide explode all trees
39 MeSH descriptor Imipenem explode all trees
40 MeSH descriptor Cilastatin explode all trees
41 ethambutol:ti,ab,kw OR pyrazinamide:ti,ab,kw OR streptomycin:ti,ab,kw OR amikacin:ti,ab,kw OR kanamycin:ti,ab,kw OR capreomycin: ti,ab,kw OR viomycin:ti,ab,kw OR enviomycin: ti,ab,kw OR fluoroquinolones:ti,ab,kw OR levo floxacin:ti,ab,kw OR moxifloxacin:ti,ab,kw OR ofloxacin:ti,ab,kw OR ciprofloxacin:ti,ab,kw OR sparfloxacin:ti,ab,kw OR thioamides: ti,ab,kw OR cycloserine:ti,ab,kw OR opc-67683:ti,ab,kw OR PA-824:ti,ab,kw OR thiacetazone:ti,ab,kw OR p-aminosalicylic acid ti,ab,kw OR para-aminosalicyclic acid:ti,ab,kw OR PAS:ti,ab,kw OR ethionamide:ti,ab,kw OR clofazimine:ti,ab,kw OR rifabutin:ti,ab,kw OR rifapentine:ti,ab,kw OR clarithromycin:ti,ab, kw OR linezolid:ti,ab,kw OR thioacetazone: ti,ab,kw OR thiocetazone:ti,ab,kw OR thioridazine:ti,ab,kw OR arginine:ti,ab,kw OR vitamin d:ti,ab,kw OR r207910:ti,ab,kw OR (amoxicillin and (clavulanate OR clavulanic acid)):ti,ab,kw OR terizidone:ti,ab,kw OR protionamide:ti,ab,kw OR imipenem:ti,ab,kw OR cilastatin:ti,ab,kw OR TMC207:ti,ab,kw OR gatifloxacin:ti,ab,kw OR prothionamide: ti,ab,kw
42 (#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #38 OR #40 OR #41)
43 (#12 AND #42)

RÉSUMÉ

OBJECTIF : Les recommandations existantes dans les directives internationales pour la prise en charge des sujets-contact des patients atteints de tuberculose à germes multirésistants (TB-MDR) sont diverses. Afin d'aider à la détermination d'une politique, nous avons mené deux revues systématiques ayant pour objectif d'identifier les approches chimioprophylactiques qui seraient efficientes chez les contacts de patients atteints de TB-MDR.

SCHÉMA : Nous avons recherché de manière systématique dans les bases de données Medline, Embase, CENTRAL, LILACS, TRIP et BIOSIS Preview les études sur l'efficience des médicaments antituberculeux pour la prévention d'une TB active chez les sujets à risque de développer une TB-MDR. Ceci constitue la mise à jour d'une revue systématique de 2006 au moyen de la même méthodologie. En outre, nous avons recherché les études incluant des personnes à risque de développer une TB après exposition à des patients non TB-MDR et qui avaient été traités par des médicaments antituberculeux autres que l'isoniazide ou la rifampicine.

RÉSULTATS : Sur les 1.195 références évaluées lors de la 2ème mise à jour, on n'a pu inclure qu'une seule étude supplémentaire. Comme la revue initiale avait comporté deux études, le nombre total d'études incluses est de trois. Dans une étude, aucun sujet-contact n'a développé la TB parmi ceux bénéficiant ou non de la prophylaxie. Dans les deux autres études, les différences de risque sont non significatives de 4% (IC95% –3 à 12) et de 5% (IC95% –2 à 11), toutes deux toutefois en faveur de la chimioprophylaxie. Dans la révision additionnelle, on a évalué 2.480 références dont aucune n'a pu être incluse.

CONCLUSION : L'attention retenue par la TB-MDR au cours des dernières années n'a pas entrainé de publications concernant le traitement préventif des sujets-contact de patients TB-MDR. Les évidences disponibles sont insuffisantes pour l'adoption ou le rejet d'un traitement préventif. De plus, les évidences combinées disponibles sont de qualité très médiocre.

RESUMEN

OBJETIVO: Las normas internacionales vigentes proponen diferentes recomendaciones sobre el manejo de los contactos de los pacientes con tuberculosis multidrogorresistente (TB-MDR). Con el propósito de contribuir a la formulación de las políticas, se llevaron a cabo dos reseñas bibliográficas a fin de definir las estrategias quimioprofilácticas eficaces dirigidas a los contactos de pacientes con TB-MDR.

MÉTODO: Se realizó una búsqueda sistemática en las bases de datos Medline, Embase, CENTRAL, LILACS, TRIP y BIOSIS Previews, sobre los estudios de eficacia de los medicamentos antituberculosos en la prevención de la TB activa en las personas con riesgo de contraer la TB-MDR. Esta búsqueda consistió en una actualización de la reseña sistemática llevada a cabo en el 2006, con un método equivalente. Se buscaron además estudios que incluyeran personas con riesgo de presentar TB tras una exposición a pacientes con TB sin MDR y que recibieron tratamiento con medicamentos antituberculosos diferentes a isoniazida o rifampicina.

RESULTADOS: De las 1195 referencias evaluadas en la actualización, se pudo incluir un estudio adicional. Dado que la reseña inicial incluyó dos estudios, se examinó un total de tres estudios. En un estudio, ninguno de los contactos contrajo la TB, ya sea que hubiesen recibido o no la profilaxis. En los dos estudios restantes, se observaron diferencias no significativas del riesgo de enfermedad activa: 4% (IC95% –3 a 12) y 5% (IC95% –2 a 11), ambos a favor de la quimioprofilaxis. En la nueva reseña se evaluaron 2480 referencias, pero no se pudo incluir ninguna.

CONCLUSIÓN: La atención que se ha prestado a la TB-MDR en los últimos años no ha dado lugar a publicaciones sobre el tratamiento preventivo de los contactos de pacientes con este tipo de TB. Los datos científicos existentes no son suficientes a fin de respaldar o rechazar la administración del tratamiento preventivo. Además, los datos acumulados en los estudios evaluados presentan una calidad deficiente.