Cochrane Library

Cochrane Database of Systematic Reviews

Shortened treatment regimens versus the standard regimen for drug-sensitive pulmonary tuberculosis (Protocol)

Grace AG, Mittal A, Jain S, Tripathy JP, Satyanarayana S, Tharyan P, Kirubakaran R

Grace AG, Mittal A, Jain S, Tripathy JP, Satyanarayana S, Tharyan P, Kirubakaran R.
Shortened treatment regimens versus the standard regimen for drug-sensitive pulmonary tuberculosis.
Cochrane Database of Systematic Reviews 2018, Issue 1. Art. No.: CD012918.
DOI: 10.1002/14651858.CD012918.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Protocol]

Shortened treatment regimens versus the standard regimen for drug-sensitive pulmonary tuberculosis

Angeline G Grace[1], Abhenil Mittal[2], Siddharth Jain[2], Jaya P Tripathy[3], Srinath Satyanarayana[3], Prathap Tharyan[4], Richard Kirubakaran[4]

[1]Department of Clinical Research, National Institute for Research in Tuberculosis, Chennai, India. [2]Department of Internal Medicine, All India Institute of Medical Sciences, New Delhi, India. [3]International Union Against Tuberculosis and Lung Disease (The Union), South-East Asia Regional Office, New Delhi, India. [4]Cochrane South Asia, Prof. BV Moses Center for Evidence-Informed Health Care and Health Policy, Christian Medical College, Vellore, India

Contact address: Angeline G Grace, Department of Clinical Research, National Institute for Research in Tuberculosis, No 1 Mayor Sathyamoorthy Road, Chetpet, Chennai, 600031, India. christoangeline@yahoo.com, angeline.g@nirt.res.in.

Editorial group: Cochrane Infectious Diseases Group.
Publication status and date: New, published in Issue 1, 2018.

Citation: Grace AG, Mittal A, Jain S, Tripathy JP, Satyanarayana S, Tharyan P, Kirubakaran R. Shortened treatment regimens versus the standard regimen for drug-sensitive pulmonary tuberculosis. *Cochrane Database of Systematic Reviews* 2018, Issue 1. Art. No.: CD012918. DOI: 10.1002/14651858.CD012918.

ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To evaluate the efficacy and safety of shortened treatment regimens, versus the standard six-month treatment regimen, in individuals with drug-sensitive pulmonary tuberculosis.

BACKGROUND

Description of the condition

Tuberculosis, a chronic infectious disease caused by air-borne transmission of aerosolized droplets of *Mycobacterium tuberculosis,* is a major global public health problem (WHO 2017b). There were an estimated 10.4 million new cases of tuberculosis and 1.7 million tuberculosis-related deaths in 2016, making tuberculosis one of the top 10 leading causes of death worldwide (WHO 2017a). Among the new cases identified, 90% were adults, 65% were men, 10% were children, and 10% had HIV co-infection (WHO 2017a). Among communicable diseases, tuberculosis is a major cause of mortality in the economically productive age group (15 to 49 years) (WHO 2017c). The top seven countries in the world identified as having a high tuberculosis burden are India, Indonesia, China, the Philippines, Nigeria, Pakistan, and South Africa (WHO 2017a). Although tuberculosis-related mortality fell by 37% between 2000 and 2016 worldwide, gaps in diagnosis and treatment persist (WHO 2017a). To add to the existing burden, 490,000 new cases of multidrug resistant (MDR)-tuberculosis and 110,000 cases of rifampicin-resistant tuberculosis were diagnosed in 2016, with India, China, and the Russian Federation contributing to 47% of the global estimates (WHO 2017a).

The World Health Organization (WHO)'s 'End TB [tuberculosis] Strategy' was approved by the World Health Assembly in May 2014 with the aim of accelerating the fight against the disease. The aim of the 'End TB Strategy' is to achieve a 95% reduction in the

mortality due to tuberculosis and a 90% reduction in the occurrence of new cases by the year 2035 compared with 2015 estimates (WHO 2015). This can be accomplished through a substantial decline in the numbers of tuberculosis cases and deaths in the years to come. However, the rate of decline in the incidence of tuberculosis was 1.9% from 2015 to 2016; to reach the targets of the 'End TB Strategy', this rate of decline has to increase to 4% to 5% yearly by 2020. Using the current standard WHO-approved treatment regimen, the treatment success rate for individuals with new and relapsed cases of drug-susceptible tuberculosis, as reported for the 2015 cohort, was 83% (WHO 2017a). Though this success rate is high when compared with that for individuals with multidrug-resistant tuberculosis (success rate of 54%), poor outcomes, such as failure to respond, death, and losses to follow-up, are of great concern given that one of the targets of the WHO's sustainable development goals for 2030 is to end the global tuberculosis epidemic (WHO 2015; WHO 2017a).

The current standard WHO-approved regimen is isoniazid, rifampicin, pyrazinamide, and ethambutol (HRZE) for two months (intensive phase) followed by isoniazid and rifampicin (with (HRE) or without (HR) ethambutol in areas of high resistance) for four months (continuation phase) (WHO 2010). This six-month treatment duration can adversely impact patient adherence to therapy (Zumla 2014). Poor adherence leads to the development of drug resistance and enhances the chances of relapse in such individuals (Ginsberg 2010; Ma 2010). Hence, new drug combinations are needed in order to shorten the course of treatment while maintaining high success rates and low relapse rates. Shortening the duration of treatment for individuals with either drug-sensitive or drug-resistant tuberculosis is a global research priority and will certainly be of great benefit to both patients and healthcare professionals. New tuberculosis drugs have begun to emerge from the clinical development pipeline, and shorter-duration regimens containing new compounds could improve adherence to therapy, and hence also promote infection control and better disease management (Ma 2010).

Description of the intervention

The need for combination therapy for tuberculosis is a result of the distinctive cellular structure of *M. tuberculosis* (a complex array of lipids, proteins, and glycolipids) and the tendency of the bacilli to develop resistance to monotherapy (Kerantzas 2017). Combinations of drugs are required to treat *M. tuberculosis*: combining drugs with both bactericidal activity and sterilising activity can help target the various bacterial subpopulations (actively dividing, slow growing, and dormant bacilli) present (Mitchison 1985). The bactericidal activity of a drug refers to its ability to kill metabolically active bacilli. An effective bactericidal drug prevents the transmission of the bacilli and the development of resistance to other drugs given as part of the regimen. The sterilising activity of a drug refers to its ability to kill all viable bacilli, including the micro-organisms tolerant to treatment with drugs. Drugs with good sterilising capacity have the potential to shorten the duration of tuberculosis treatment (Ma 2010). There are currently 10 compounds in clinical development for the treatment of tuberculosis, six have been specifically developed and four existing drugs have been repurposed. In recent years, various drugs have been tried in differing combinations to shorten the standard six-month treatment regimen and have shown promising preliminary results (Conde 2009; Rustomjee 2008).

Some of the desired characteristics of new antituberculosis drug compounds are as follows (Ma 2010).

- Effectiveness against both replicating and dormant tuberculosis bacilli.
- Novel mechanism of action.
- Improved safety profile (versus the standard treatment regimen).
- Good oral bioavailability.
- Low resistance development barrier.
- Minimal interaction with cytochrome p450 enzymes.
- Low cost.

The drugs at the forefront of this quest are the fluoroquinolones (moxifloxacin, levofloxacin, and gatifloxacin), rifamycins (rifabutin and rifapentine), nitroimidazoles, diarylquinolines, oxazolidinediones, and ethylenediamines. These drugs have been investigated in clinical trials in combination with, or as substitutes for, one of the standard first-line antituberculosis drugs with the aim of shortening the duration of treatment (Lienhardt 2010). Other second-line antituberculosis drugs, including amoxicillin clavulanate, linezolid, carbapenems, and clofazamine, are also potential candidates for a shorter duration antituberculosis regimen, along with other first-line drugs (D'Ambrosio 2015).

How the intervention might work

Fluoroquinolones

Fluoroquinolones possess good in vivo and in vitro bactericidal activity against *M. tuberculosis (*Moadebi 2007). This class of drugs acts on the enzyme DNA gyrase, thereby preventing bacterial DNA synthesis (Lienhardt 2010). This mechanism of action is distinct from that of other antituberculosis drugs, raising the possibility of synergistic activity. Overall the quinolones are well tolerated with minimal side effects on long-term administration (Schluger 2013). Fluoroquinolones, when added to an antituberculosis treatment regimen, can enhance the sterilizing and bactericidal effect of combination therapy and increase drug penetration into chronic tuberculosis lesions. Fluoroquinolones are also better tolerated than the standard first-line drugs and can shorten treatment duration, hence improving patient adherence to treatment (Ginsburg 2003). Although a trial of moxifloxacin-based regimens

given for four months in individuals with drug-sensitive tuberculosis did not demonstrate non-inferiority compared with the standard treatment regimen, it did find moxifloxacin-based regimens to be associated with a more rapid decrease in the mycobacterial load (Gillespie 2014). Gatifloxacin-based drug combinations have also been tested in which gatifloxacin replaced or was given in addition to ethambutol in the intensive and continuation phases of therapy (Jawahar 2013; Merle 2014).

The main concern with the quinolones is that they can prolong the QT interval, which may cause ventricular arrhythmias and sudden cardiac arrest (Schluger 2013). The frequency of torsades de pointes, the type of arrhythmia induced by fluoroquinolones, has been reported to be 1 per million with ciprofloxacin or levofloxacin, 3.8 per million with grepafloxacin, and 14.5 per million with sparfloxacin. The chance of arrhythmia is greater in individuals who have associated metabolic disorders, such as hypokalaemia or cardiac disease, or who are taking other drugs that can prolong the QT interval (Rubinstein 2002). However, a pooled analysis of data from phase II, III, and IV clinical trials comparing moxifloxacin with other antibiotics reported that there were no clinically relevant differences in cardiac adverse effects between moxifloxacin and comparators (Haverkamp 2012).

Rifamycins

Rifapentine is a new-generation rifamycin that acts by inhibiting the DNA-dependent RNA polymerase of *M. tuberculosis*. Like other rifamycins, rifapentine can cause (rarely) drug-induced hepatitis and thrombocytopenia (Munsiff 2006). What makes rifapentine a good candidate for tuberculosis therapy shortening and dosage simplification is its long half-life (10 to 15 hours for rifapentine versus two to three hours for rifampicin) and potency against *M. tuberculosis (*Temple 1999). The RIFAQUIN trial (high dose RIFApentine and a QUINolone in the treatment of pulmonary tuberculosis) team have assessed whether shorter tuberculosis regimens containing high-dose rifapentine and moxifloxacin are non-inferior to the standard treatment regimen (Jindani 2014).

Nitroimidazoles

Nitroimidazoles act against both multiplying and dormant bacilli, and thereby may be suitable for potentially shortening the duration of tuberculosis therapy (Ma 2010). Two imidazoles are currently being investigated in clinical trials for the treatment of individuals with tuberculosis: pretomanid and delamanid. Both are equally active against drug-sensitive and drug-resistant tuberculosis. They act on the bacilli through bioreduction of the nitroimidazole pharmacophore, the generation of reactive oxygen species, and the inhibition of mycolic acid synthesis (Matsumoto 2006). In phase II trials, QT prolongation was frequently seen in MDR-TB patients who received delamanid (Gler 2012). The bactericidal activity of a novel drug combination of pyrazinamide, moxifloxacin, clofazimine, and pretomanid has been compared with that of the standard treatment regimen in individuals with drug-sensitive and drug-resistant tuberculosis. This new regimen was well-tolerated and showed greater bactericidal activity than the standard regimen (Dawson 2015).

Diarylquinolines

One member of this class of drugs, bedaquiline, is approved as an antituberculosis drug by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) (Lessem 2015). Bedaquiline disrupts bacterial metabolism by affecting the synthesis of adenosine triphosphate (ATP) (Andries 2005). The drug is currently used for the treatment of MDR-tuberculosis, following the findings of a phase II trial that demonstrated the rapid culture conversion of sputum and low rates of acquired resistance to co-administered drugs (Diacon 2014). Like the quinolones, bedaquiline also can cause QT prolongation (Diacon 2012). The bactericidal activity of bedaquiline in animal studies was found to be superior to that of the top first-line drugs, rifampicin and isoniazid (Andries 2005); hence, the drug is being explored as a potential option for shortening the duration of treatment in individuals with drug-sensitive tuberculosis.

Oxazolidinediones

Linezolid and sutezolid inhibit the initiation of bacterial protein synthesis by acting on the 50S ribosomal subunit. Linezolid, a repurposed drug, is effective in the management of drug-resistant tuberculosis, but adverse effects, such as myelosuppression and peripheral neuropathy, restrict its long-term use (Sotgiu 2012). A newer addition to this class, sutezolid, is gaining attention as it has demonstrated greater potency as an antituberculosis drug than linezolid in murine models (Williams 2009). Phase I studies in humans found sutezolid to be safe and well-tolerated (Wallis 2010).

Ethylenediamines

The ethylenediamine, SQ109, inhibits protein synthesis by targeting the membrane transporter, MmpL3, in *M. tuberculosis,* and is effective against drug-susceptible and drug-resistant tuberculosis. In vitro studies showed favourable interactions and a synergistic action between sutezolid and bedaquiline (D'Ambrosio 2015; Sacksteder 2012).

Why it is important to do this review

Novel drug regimens are needed to address the challenges associated with patient adherence to the current standard six-month treatment regimen for tuberculosis (Ma 2010). Recent clinical trials have investigated the efficacy of newer regimens administered

for less than six months for the treatment of individuals with drug-sensitive tuberculosis. A systematic review of these trials will help guide the understanding of the efficacy and safety of these shorter regimens among individuals with drug-sensitive pulmonary tuberculosis. A previous Cochrane Review by Gelband 1999 concluded that longer periods of treatment (at least six months) resulted in higher success rates in individuals with active tuberculosis, but the improvement compared with regimens administered for less than six months was small. Another Cochrane Review on the use of fluoroquinolones in the treatment of tuberculosis, published in 2013, concluded that there was insufficient evidence to draw conclusions, but that larger trials investigating short-course fluoroquinolone-based regimens were in progress (Ziganshina 2013). First-line treatment with novel drug combinations administered for a shorter duration than the current standard six-month treatment regimen will improve treatment outcomes and thereby reduce the chances of disease transmission and burden in the population.

OBJECTIVES

To evaluate the efficacy and safety of shortened treatment regimens, versus the standard six-month treatment regimen, in individuals with drug-sensitive pulmonary tuberculosis.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomized controlled trials (RCTs) and quasi-RCTs.

Types of participants

Newly diagnosed individuals with pulmonary tuberculosis, as defined by sputum culture positivity, with presumed or proven drug-sensitive tuberculosis, of all ages. We will also include studies that included participants diagnosed with tuberculosis using the Xpert MTB/Rif, a rapid diagnostic test approved by WHO, rather than by culture. We will include participants irrespective of their HIV status. We will include studies reporting outcomes in extrapulmonary cases if the proportion of such cases is less than 10% of the entire cohort, or if disaggregated data are available.

Types of interventions

Intervention

Treatment regimens of less than six months' duration including any antituberculosis drug(s) or combinations thereof (new drugs or standard antituberculosis drugs at higher than recommended doses).

Control

The standard first-line therapy for pulmonary tuberculosis, defined as a regimen comprising two months of HRZE and four months of HR or HRE.

Types of outcome measures

Primary outcomes

- Relapse of tuberculosis, defined as clinical or bacteriological recurrence within two years of completion of antituberculosis therapy.

Secondary outcomes

- Death from any cause during antituberculosis therapy or within one year of treatment completion.
- Rates of discontinuation of therapy at any time point during treatment.
- Sputum culture/smear positivity at eight weeks, defined as the proportion of participants who remain smear or culture positive at the end of eight weeks of therapy.
- Development of secondary drug resistance to antituberculosis drugs, identified by drug susceptibility testing.
- Treatment failure, defined as persistent or recurrent positive sputum cultures at the time of treatment completion.

Adverse events

- Serious adverse events, defined as fatal or life-threatening, or requiring hospitalization or a change in treatment regimen.
- Other adverse events reported by the trial authors, such as hepatitis, prolongation of the QT interval, hypersensitivity reactions, thrombocytopenia, peripheral neuropathy, ocular toxicity, and arthralgia.

Search methods for identification of studies

We will attempt to identify all relevant trials regardless of language or publication status (published, unpublished, in press, and in progress).

Electronic searches

We will search the following databases using the search terms and strategy described in Appendix 1: Cochrane Infectious Diseases Group Specialized Register; Central Register of Controlled Trials (CENTRAL), published in The Cochrane Library; MEDLINE (PubMed); Embase OVID; LILACS (Latin American and Caribbean Health Science Information database); and Science Citation Index-Expanded (Web of Science). We will also search the website of the Indian Medlars Center (indmed.nic.in) and the South Asian Database of Controlled Clinical Trials (cochrane-sadcct.org). We will search the WHO International Clinical Trials Registry Platform (who.int/ictrp/en/), ClinicalTrials.gov (clinicaltrials.gov/ct2/home), the Clinical Trials Unit of the International Union against Tuberculosis and Lung Disease (theunion.org/what-we-do/research/clinical-trials), the UK Medical Research Council Clinical Trials Unit (ctu.mrc.ac.uk/), and the Clinical Trials Registry India (ctri.nic.in/) for trials in progress, using 'tuberculosis', 'regimen', 'shortened', and 'short' as search terms.

Searching other resources

We will search the following conference proceedings for abstracts of relevant trials: World Congress on TB, World Lung Conferences of the International Union Against Tuberculosis Lung Disease, American Thoracic Society Meeting Proceedings, and the British Society for Antimicrobial Therapy. We will contact relevant organizations, including the Global Partnership to Stop TB and the WHO, for ongoing or completed but unpublished trials. We will contact researchers and experts in the field of clinical trials to identify any additional eligible studies. We will also check the references of all included studies to identify additional relevant trials.

Data collection and analysis

Selection of studies

Two review authors (AG and AM) will independently screen all citations and abstracts identified by the search terms and strategy to decide on potentially eligible studies. We will obtain full-text articles of all the potentially eligible studies. We will scrutinize each report of each trial to ensure that multiple publications from the same trial are included only once. Based on the inclusion criteria, two review authors (AG and AM) will assess the articles for inclusion in the review. If eligibility is not clear or if there are discrepancies, we will resolve them through discussion or by consulting other review authors (SJ and JT), or by contacting the trial authors (if needed). We will list the studies we exclude with the reasons for their exclusion. We will present the study selection process in a PRISMA flow diagram.

Data extraction and management

Two review authors (AG and AM) will independently extract data using a pretested data extraction form. We will resolve discrepancies in the extracted data through discussion and by referring to the original articles. If needed, we will contact the corresponding author of the publication for further details when the data given in the article are not clear.

We will extract the following data from the included studies.

- Trial details: publication year, country where the trial was undertaken, authors, year in which the study was done, study design, number of participants recruited, inclusion criteria, exclusion criteria, recruitment sites.
- Baseline characteristics of participants: age, gender, nutritional status, socioeconomic data, comorbid illnesses, sputum smear grading, clinical presentation, disease severity, chest X-ray.
- Intervention and control arms: description of the drugs used in the trial, drug dosage, route and frequency of administration, duration of treatment in the intensive and continuation phases.
- Outcomes: we will extract the data for the primary and secondary outcomes as defined above.

For each outcome, we will extract information on the number of participants randomized. For dichotomous outcomes, we will extract the number of participants who experienced the event.

Assessment of risk of bias in included studies

Two review authors (AG and AM) will independently assess the risk of bias in the trials included in the review using Cochrane's 'Risk of bias' tool in Review Manager 5 (RevMan 5) (RevMan 2014). We will assess each of the included trials for risk of bias in seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other potential biases. We will attempt to contact the trial authors if data are unclear or if any relevant details are missing. We will resolve disagreements through discussion with a third review author (JT, SS or PT). For each domain in the 'Risk of bias' assessment, we will judge the risk of bias as low, high, or unclear. We will record our judgements and the support for these judgements in 'Risk of bias' tables accompanying the characteristics of each included study, and will summarize the findings in a 'Risk of bias' summary and graph.

Measures of treatment effect

We will compare dichotomous outcomes using risk ratios as the primary measure of effect. We will present the measures with 95% confidence intervals.

Unit of analysis issues

When a multiarm study contributes multiple comparisons to a particular meta-analysis, for dichotomous data we will split the 'shared' group data appropriately to avoid double counting.

Dealing with missing data

We will contact the trial authors to obtain missing or when data are insufficient. We will aim to carry out a complete case analysis where data are missing. We will explore the potential effects of missing data through a series of sensitivity analyses. As a sensitivity analysis, we will carry out a best-worst case analysis (the 'best-case' scenario is that all participants with missing outcomes in the experimental intervention group had good outcomes, and all those with missing outcomes in the control intervention group had poor outcomes; the 'worst-case' scenario is the converse).

Assessment of heterogeneity

We will assess heterogeneity among the trials by inspecting forest plots for inconsistency in the magnitude or direction of the effect estimates, with non-overlapping confidence intervals. We will apply the Chi^2 test with a 10% level of statistical significance to detect inconsistencies in study results that exceed chance, and also use the I^2 statistic with a value of 50% or greater denoting significant heterogeneity in the results (intertrial variability that exceeds random error). However, if an opposite direction of effect estimates and gross non-overlapping of confidence intervals of individual trials are observed, we may lower the acceptable level of heterogeneity to an I^2 statistic of 30%.

Assessment of reporting biases

If 10 or more trials are included in a meta-analysis, we will evaluate the possibility of publication bias by constructing funnel plots.

Data synthesis

We will analyse the data using RevMan 5 (RevMan 2014) and will group the trials according to comparisons. We will perform meta-analysis if there are more than two trials in any comparison. We will use a fixed-effect model to combine the data unless significant heterogeneity (I^2 statistic $\geq$ 50%) is present, in which case, if appropriate, we will use a random-effects model. If meta-analysis is not appropriate, we will present the data in the text and in tables, and provide narrative summaries. We will assess the quality of the evidence for the outcomes that are important for clinical decision making (treatment failure, relapse, death from any cause, adverse events, and the development of drug resistance at any point after the initiation of anti-tuberculosis therapy) using GRADE principles. We will construct 'Summary of findings' tables using the GRADEpro Guideline Development Tool to guide our interpretation of results and conclusions (GRADEpro GDT).

Subgroup analysis and investigation of heterogeneity

If we identify significant heterogeneity, we will explore potential sources by carrying out the following subgroup analyses for the primary outcome measures: age (children and adults), HIV status (positive and negative), and category of shortened treatment regimen (fluoroquinolone-based and non-fluoroquinolone-based).

Sensitivity analysis

We will perform sensitivity analyses if there are sufficient data (that is, at least 10 trials are available). We will conduct sensitivity analyses to examine the impact of 'Risk of bias' components on the results.

ACKNOWLEDGEMENTS

We thank Vittoria Lutje, the Information Specialist of the Cochrane Infectious Diseases Group (CIDG), for her guidance with the literature search strategy. We are grateful to Paul Garner, CIDG Coordinating Editor, for his comments and support.

RK is supported by the Effective Health Care Research Consortium. This Consortium and the CIDG editorial base is funded by UK aid from the UK Government for the benefit of developing countries (Grant: 5242). The views expressed in this review do not necessarily reflect UK government policy.

This protocol was undertaken as a part of the training course aimed to build capacity on undertaking Systematic Reviews within India, especially in the context of tuberculosis. The training project was conceived and implemented by the South East Asia office of the International Union against Tuberculosis and Lung Diseases (The Union) in collaboration with Central TB Division, Ministry of Health and Family Welfare, Government of India, and Cochrane South Asia. The training was generously supported by the U.S. Agency for International Development (USAID). We also thank the Department for International Development (DFID), UK, for funding the Global Operational Research Fellowship Programme at The Union, Paris, France in which JT and SS work as Senior Operational Research Fellows.

REFERENCES

Additional references

Andries 2005

Andries K, Verhasselt P, Guillemont J, Göhlmann HW, Neefs JM, Winkler H, et al. A diarylquinoline drug active on the ATP synthase of Mycobacterium tuberculosis. *Science* 2005;**307**(5707):223–7.

Conde 2009

Conde MB, Efron A, Loredo C, De Souza GR, Graça NP, Cezar MC, et al. Moxifloxacin versus ethambutol in the initial treatment of tuberculosis: a double-blind, randomised, controlled phase II trial. *Lancet* 2009;**373** (9670):1183–9.

D'Ambrosio 2015

D'Ambrosio L, Centis R, Sotgiu G, Pontali E, Spanevello A, Migliori GB. New anti-tuberculosis drugs and regimens: 2015 update. *ERJ Open Research* 2015;**1**(1):00010–2015.

Dawson 2015

Dawson R, Diacon AH, Everitt D, van Niekerk C, Donald PR, Burger DA, et al. Efficiency and safety of the combination of moxifloxacin, pretomanid (PA-824), and pyrazinamide during the first 8 weeks of antituberculosis treatment: a phase 2b, open-label, partly randomised trial in patients with drug-susceptible or drug-resistant pulmonary tuberculosis. *Lancet* 2015;**385**(9979):1738–47.

Diacon 2012

Diacon AH, Donald PR, Pym A, Grobusch M, Patientia RF, Mahanyele R, et al. Randomized pilot trial of eight weeks of bedaquiline (TMC207) treatment for multidrug-resistant tuberculosis: long-term outcome, tolerability, and effect on emergence of drug resistance. *Antimicrobial Agents and Chemotherapy* 2012;**56**(6):3271–6.

Diacon 2014

Diacon AH, Pym A, Grobusch MP, de los Rios JM, Gotuzzo E, Vasilyeva I, et al. Multidrug-resistant tuberculosis and culture conversion with bedaquiline. *New England Journal of Medicine* 2014;**371**(8):723–32.

Gelband 1999

Gelband H. Regimens of less than six months for treating tuberculosis. *Cochrane Database of Systematic Reviews* 1999, Issue 4. [DOI: 10.1002/14651858.CD001362

Gillespie 2014

Gillespie SH, Crook AM, McHugh TD, Mendel CM, Meredith SK, Murray SR, et al. Four-month moxifloxacin-based regimens for drug-sensitive tuberculosis. *New England Journal of Medicine* 2014;**371**(17):1577–87.

Ginsberg 2010

Ginsberg AM. Tuberculosis drug development: progress, challenges, and the road ahead. *Tuberculosis (Edinburgh, Scotland)* 2010;**90**(3):162–7.

Ginsburg 2003

Ginsburg AS, Grosset JH, Bishai WR. Fluoroquinolones, tuberculosis, and resistance. *Lancet. Infectious Diseases* 2003;**3**(7):432–42.

Gler 2012

Gler MT, Skripconoka V, Sanchez-Garavito E, Xiao H, Cabrera-Rivero JL, Vargas-Vasquez DE, et al. Delamanid for multidrug-resistant pulmonary tuberculosis. *New England Journal of Medicine* 2012;**366**(23):2151–60.

GRADEpro GDT [Computer program]

McMaster University (developed by Evidence Prime). GRADEpro GDT. Version accessed 12 November 2017. Hamilton (ON): McMaster University (developed by Evidence Prime), 2015.

Haverkamp 2012

Haverkamp W, Kruesmann F, Fritsch A, van Veenhuyzen D, Arvis P. Update on the cardiac safety of moxifloxacin. *Current Drug Safety* 2012;**7**(2):149–63. [PUBMED: 22873499]

Jawahar 2013

Jawahar MS, Banurekha VV, Paramasivan CN, Rahman F, Ramachandran R, Venkatesan P, et al. Randomized clinical trial of thrice-weekly 4-month moxifloxacin or gatifloxacin containing regimens in the treatment of new sputum positive pulmonary tuberculosis patients. *PLoS One* 2013;**8** (7):e67030.

Jindani 2014

Jindani A, Harrison TS, Nunn AJ, Phillips PPJ, Churchyard GJ, Charalambous S, et al. High-dose rifapentine with moxifloxacin for pulmonary tuberculosis. *New England Journal of Medicine* 2014;**371**(17):1599–608.

Kerantzas 2017

Kerantzas CA, Jacobs WR. Origins of combination therapy for tuberculosis: lessons for future antimicrobial development and application. *mBio* 2017;**8**(2):e01586–16.

Lefebvre 2011

Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Lessem 2015

Lessem E, Cox H, Daniels C, Furin J, McKenna L, Mitnick CD, et al. Access to new medications for the treatment of drug-resistant tuberculosis: patient, provider and community perspectives. *International Journal of Infectious Diseases* 2015;**32**:56–60.

Lienhardt 2010

Lienhardt C, Vernon A, Raviglione MC. New drugs and new regimens for the treatment of tuberculosis: review of the drug development pipeline and implications for national programmes. *Current Opinion in Pulmonary Medicine* 2010; **16**(3):186–93.

Ma 2010

Ma Z, Lienhardt C, McIlleron H, Nunn AJ, Wang X. Global tuberculosis drug development pipeline: the need and the reality. *Lancet* 2010;**375**(9731):2100–9.

Matsumoto 2006
Matsumoto M, Hashizume H, Tomishige T, Kawasaki M, Tsubouchi H, Sasaki H, et al. OPC-67683, a nitro-dihydro-imidazooxazole derivative with promising action against tuberculosis in vitro and in mice. *PLoS Medicine* 2006;**3**(11):e466.

Merle 2014
Merle CS, Fielding K, Sow OB, Gninafon M, Lo MB, Mthiyane T, et al. A four-month gatifloxacin-containing regimen for treating tuberculosis. *New England Journal of Medicine* 2014;**371**(17):1588–98.

Mitchison 1985
Mitchison DA. The action of antituberculosis drugs in short-course chemotherapy. *Tubercle* 1985;**66**(3):219–25.

Moadebi 2007
Moadebi S, Harder CK, Fitzgerald MJ, Elwood KR, Marra F. Fluoroquinolones for the treatment of pulmonary tuberculosis. *Drugs* 2007;**67**(14):2077–99.

Munsiff 2006
Munsiff SS, Kambili C, Ahuja SD. Rifapentine for the treatment of pulmonary tuberculosis. *Clinical Infectious Diseases* 2006;**43**(11):1468–75.

RevMan 2014 [Computer program]
Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Rubinstein 2002
Rubinstein E, Camm J. Cardiotoxicity of fluoroquinolones. *Journal of Antimicrobial Chemotherapy* 2002;**49**(4):593–6.

Rustomjee 2008
Rustomjee R, Lienhardt C, Kanyok T, Davies GR, Levin J, Mthiyane T, et al. A phase II study of the sterilising activities of ofloxacin, gatifloxacin and moxifloxacin in pulmonary tuberculosis. *International Journal of Tuberculosis and Lung Disease* 2008;**12**(2):128–38.

Sacksteder 2012
Sacksteder KA, Protopopova M, Barry CE, Andries K, Nacy CA. Discovery and development of SQ109: a new antitubercular drug with a novel mechanism of action. *Future Microbiology* 2012;**7**(7):823–37.

Schluger 2013
Schluger NW. Fluoroquinolones in the treatment of tuberculosis: which is best?. *American Journal of Respiratory and Critical Care Medicine* 2013;**188**(7):768–9.

Sotgiu 2012
Sotgiu G, Centis R, D'Ambrosio L, Alffenaar JWC, Anger HA, Caminero JA, et al. Efficacy, safety and tolerability of linezolid containing regimens in treating MDR-TB and XDR-TB: systematic review and meta-analysis. *European Respiratory Journal* 2012;**40**(6):1430–42.

Temple 1999
Temple ME, Nahata MC. Rifapentine: its role in the treatment of tuberculosis. *Annals of Pharmacotherapy* 1999; **33**(11):1203–10.

Wallis 2010
Wallis RS, Jakubiec WM, Kumar V, Silvia AM, Paige D, Dimitrova D, et al. Pharmacokinetics and whole-blood bactericidal activity against Mycobacterium tuberculosis of single doses of PNU-100480 in healthy volunteers. *Journal of Infectious Diseases* 2010;**202**(5):745–51.

WHO 2010
World Health Organization. Guidelines for treatment of tuberculosis. 4th edition. 2010. WHO/HTM/TB/2009.420. www.who.int/tb/publications/2010/9789241547833/en/ (accessed 1 July 2017).

WHO 2015
World Health Organization. The End TB Strategy. Global strategy and targets for tuberculosis prevention, care and control after 2015. WHO/HTM/TB/2015.19. www.who.int/tb/post2015_strategy/en/ (accessed 1 August 2017).

WHO 2017a
World Health Organization. Global Tuberculosis Report 2017. www.who.int/tb/publications/global_report/en/ (accessed 12 November 2017).

WHO 2017b
World Health Organization. Fact sheet on tuberculosis. October 2017. www.who.int/mediacentre/factsheets/fs104/en/ (accessed 12 November 2017).

WHO 2017c
World Health Organization. Bending the curve - ending TB: annual report 2017. apps.who.int/iris/bitstream/10665/254762/1/978929022584-eng.pdf. WHO Regional Office for South–East Asia, (accessed 12 July 2017).

Williams 2009
Williams KN, Stover CK, Zhu T, Tasneen R, Tyagi S, Grosset JH, et al. Promising antituberculosis activity of the oxazolidinone PNU-100480 relative to that of linezolid in a murine model. *Antimicrobial Agents and Chemotherapy* 2009;**53**(4):1314–9.

Ziganshina 2013
Ziganshina LE, Titarenko AF, Davies GR. Fluoroquinolones for treating tuberculosis (presumed drug-sensitive). *Cochrane Database of Systematic Reviews* 2013, Issue 6. [DOI: 10.1002/14651858.CD004795.pub4

Zumla 2014
Zumla AI, Gillespie SH, Hoelscher M, Philips PPJ, Cole ST, Abubakar I, et al. New antituberculosis drugs, regimens, and adjunct therapies: needs, advances, and future prospects. *Lancet. Infectious Diseases* 2014;**14**(4):327–40.

* *Indicates the major publication for the study*

APPENDICES

Appendix 1. MEDLINE (OVID) search strategy

Search set	MEDLINE (OVID)[1]
1	tuberculosis or TB.mp
2	Tuberculosis [Mesh]
3	1 or 2
4	moxifloxacin or levofloxacin or gatifloxacin or rifamycins or rifabutin or rifapentineor bedaquiline or delamanid or pretomanid. mp
5	"Antitubercular Agents"[Mesh] OR "Diarylquinolines"[Mesh] OR "Antibiotics, Antitubercular"[Mesh] or "Fluoroquinolones"[Mesh]
6	diarylquinolin* or TMC 207-BDQ or nitroimidazol* or PA 824- pretomanid or oxazolidinon* or LZD or ethylenediamin* or SQ 109.mp
7	4 or 5 or 6
8	regimen* OR short OR shortened OR months OR dose OR dosing OR schedule* [Title/abstract]
9	"Drug Administration Schedule"[Mesh]
10	"Medication Therapy Management"[Mesh]
11	"Time Factors"[Mesh]
12	8 OR 9 OR 10 OR 11
13	3 AND 7 AND 12^

[1]We will use search terms in combination with the search strategy for retrieving trials developed by the Cochrane Collaboration (Lefebvre 2011).

This is the preliminary search strategy for MEDLINE (OVID). We will adapt it for use with other electronic databases. We will report all search strategies in full in the final version of the review.

CONTRIBUTIONS OF AUTHORS

AG, AM, SJ, and JPT wrote the protocol. SS, PT, and RK provided advice on the content. All authors agreed with the final draft of the protocol.

DECLARATIONS OF INTEREST

AG has no known conflicts of interest.

AM has no known conflicts of interest.

SJ has no known conflicts of interest.

JT has no known conflicts of interest.

SS has no known conflicts of interest.

PT is a programme partner of the Effective Health Care Research Consortium and a recipient of a grant under this project. He was also contracted by Cochrane to help build capacity in authors from India and the region to undertake systematic reviews.

RK has no known conflicts of interest.

SOURCES OF SUPPORT

Internal sources

- National Institute for Research in Tuberculosis, Indian Council of Medical Research, India.

Employment for Angeline G Grace

- All India Institute of Medical Sciences, New Delhi, India.

Employment for Abhenil Mittal and Siddharth Jain

- International Union Against Tuberculosis and Lung Disease (The Union), South-East Asia Regional Office, India.

Employment for Jaya P Tripathy and Srinath Sathyanarayana

- Christian Medical College, Vellore, India.

Employment for Prathap Tharyan and logistic support for the Prof BV Moses Center for Evidence-Informed Health Care and Health Policy that hosts the Cochrane South Asia

- Liverpool School of Tropical Medicine, UK.

External sources

- Department for International Development (DFID), UK.

Grant: 5242. Project funding for the Effective Health Care Research Consortium; salary for Richard Kirubakaran and support for the Prof BV Moses Center for Evidence-Informed Health Care and Health Policy that hosts Cochrane South Asia