Decentralized care for multidrug-resistant tuberculosis: a systematic review and meta-analysis

Jennifer Ho, Anthony L Byrne, Nguyen N Linh, Ernesto Jaramillo & Greg J Fox

Objective To assess the effectiveness of decentralized treatment and care for patients with multidrug-resistant (MDR) tuberculosis, in comparison with centralized approaches.

Methods We searched ClinicalTrials.gov, the Cochrane library, Embase®, Google Scholar, Lilacs, PubMed®, Web of Science and the World Health Organization’s portal of clinical trials for studies reporting treatment outcomes for decentralized and centralized care of MDR tuberculosis. The primary outcome was treatment success. When possible, we also evaluated death, loss to follow-up, treatment adherence and health-system costs. To obtain pooled relative risk (RR) estimates, we performed random-effects meta-analyses.

Findings Eight studies met the eligibility criteria for review inclusion. Six cohort studies, with 4026 participants in total, reported on treatment outcomes. The pooled RR estimate for decentralized versus centralized care for treatment success was 1.13 (95% CI: 1.01–1.27). The corresponding estimate for loss to follow-up was RR: 0.66 (95% CI: 0.38–1.13), for death RR: 1.01 (95% CI: 0.67–1.52) and for treatment failure was RR: 1.07 (95% CI: 0.48–2.40). Two of three studies evaluating health-care costs reported lower costs for the decentralized models of care than for the centralized models.

Conclusion Treatment success was more likely among patients with MDR tuberculosis treated using a decentralized approach. Further studies are required to explore the effectiveness of decentralized MDR tuberculosis care in a range of different settings.

Abstracts in العربية, 中文, Français, Русский and Espanol at the end of each article.

Introduction

*Mycobacterium tuberculosis* resistant to both isoniazid and rifampicin, so-called multidrug resistance, poses a major threat to the control of tuberculosis worldwide. In 2015, there were an estimated 480 000 new cases of multidrug-resistant (MDR) tuberculosis, an additional 100 000 cases with rifampicin resistance that also required treatment with second-line medicines, and approximately 250 000 deaths from MDR tuberculosis. 1 An estimated 9.5% of people with MDR tuberculosis have extensively drug-resistant (XDR) tuberculosis – i.e. MDR tuberculosis that is also resistant to a second-line injectable drug and a fluoroquinolone. It has been estimated that, of all the cases of MDR tuberculosis that commenced treatment in 2013, only 52% achieved treatment success and the rest died (17%), were lost to follow-up or otherwise not evaluated (22%) or were identified as treatment failures (9%). 1

The recommended therapy for MDR tuberculosis requires a combination of second-line drugs that are, in general, more costly, less efficacious, more toxic and must be taken for much longer than the first-line drugs used against tuberculosis. 2

Historically, treatment for MDR tuberculosis has been provided through specialized, centralized programmes and typically involved prolonged inpatient care. 3 This approach is based on the view that treatment adherence, the management of adverse events and infection control may be better in hospital settings than in the community. 4 However, in many centralized facilities, insufficient resources preclude the prolonged inpatient care of cases of MDR tuberculosis. Reliance on centralized treatment, especially in facilities that lack effective infection control and where treatment may be delayed until inpatient beds become available, may inadvertently increase the risk of transmission of MDR *M. tuberculosis*. In addition, in comparison with decentralized interventions, centralized approaches have been associated with poorer rates of retention in care. 4 In the treatment of drug-susceptible tuberculosis, decentralized care is well established and appears as effective as hospital-based approaches. 5-9 Since 2011, the World Health Organization (WHO) has recommended that “patients with multidrug-resistant tuberculosis should be treated using mainly ambulatory care.” 9 This recommendation was, however, based on the results of a small number of uncontrolled studies. 2

We recently performed a systematic review and meta-analysis to try to determine if – compared with treatment and care provided solely by specialized centres for the treatment of MDR tuberculosis – decentralized treatment and care for MDR tuberculosis patients was more or less likely to lead to improved treatment outcomes, treatment adherence, adverse events, acquired drug resistance, lower patient costs and lower health-system costs. Our results have already contributed to forthcoming, revised WHO guidelines for the treatment of tuberculosis.

Methods

Our systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines. 10

Study eligibility

Studies were eligible if they included both patients receiving decentralized care and patients receiving centralized care – as defined below. Studies were excluded if they lacked

---

1 Woolcock Institute of Medical Research, University of Sydney, 431 Glebe Point Road, Glebe, New South Wales 2037, Australia.
2 Global TB Programme, World Health Organization, Geneva, Switzerland.
3 Central Clinical School, University of Sydney, Sydney, Australia.
Correspondence to Jennifer Ho (email: jennifer.ho@sydney.edu.au).
(Submitted: 4 March 2017 – Revised version received: 10 May 2017 – Accepted: 22 May 2017)
a comparator group or enrolled fewer than 10 participants in the intervention arm. This approach enabled a direct comparison to be performed between individuals receiving either model of care in the same setting. Included studies needed to report on at least one clinical outcome – i.e. treatment adherence, the standard WHO-defined tuberculosis treatment outcomes of cure, completion, death, failure or relapse11 and/or adverse reactions. Studies reporting costs, to patients and/or health systems, were also included. We included case–control studies that each included at least 10 patients, modelling studies, prospective cohorts, randomized controlled trials and retrospective cohorts. Unpublished studies were sought through consultation with experts in the field and by hand-searching the International Union of Tuberculosis and Lung Disease’s database of conference abstracts,12 OpenSIGLE13 and other grey literature.

We considered patients with MDR tuberculosis to be those with a microbiological or clinical diagnosis of MDR tuberculosis – including XDR tuberculosis – that had commenced second-line drug therapy. A clinical diagnosis included contacts – exposed to patients with MDR tuberculosis – who developed signs and symptoms of tuberculosis but were not microbiologically confirmed as cases. Decentralized care was defined as treatment and care provided in the community where the patient resided – e.g. in a community centre, a peripheral health centre or the patient’s home or workplace. A key component of the definition of decentralized care was the use of non-specialized workers – e.g. community workers, treatment supporters or volunteers.11 Even with care that we considered decentralized, an initial period of hospitalization during the initiation of therapy was permissible, so long as the majority of care was delivered in a decentralized fashion. To be considered centralized, care had to have been provided solely by specialist centres for the treatment of MDR tuberculosis, either in such a centre – as an inpatient and/or outpatient – or in outpatient facilities near to such a centre.

Our outcomes of interest included treatment adherence, the standard WHO-defined tuberculosis treatment outcomes of cure, completion, death and failure,11 adverse reactions and patient and/or health-system costs.

| Box 1. Search terms used with PubMed® |
|--------------------------------------|
| **1. Tuberculosis, Multidrug-Resistant [MeSH]** |
| OR |
| (tuberculosis OR TB) AND (multidrug-resist* OR multidrug resistant* OR multi-drug resist* OR ‘drug resistant’” OR drug-resist* OR multiresistant* OR ‘multi resistant’” OR ‘rifampicin resist*”OR’extensively drug-resist*”OR’extensively-drug resist*”OR’extensively resist*” OR MDR OR XDR OR TDR) |
| OR |
| mdrtb OR xdr t OR mdrtb OR mdr-tb OR xdr-tb OR tdr-tb OR “MDR TB” OR “XDR TB” OR “TDR TB” AND |
| 2. (“directly observed” OR DOT OR DOTS OR DOTS-Plus OR cb-DOTS OR treatment OR “patient support”) |
| AND |
| (community OR outpatient OR “public participation” OR community-based OR decentralized OR non-specialized OR “periph* health centres” OR home-based OR ambulatory OR clinic OR “community health worker” OR CHW OR volunteer) |

**Search strategy**

We searched for relevant publications in ClinicalTrials.gov, the Cochrane library, Embase®, Google Scholar, LILACS, PubMed®, Web of Science and the World Health Organization’s portal of clinical trials. We developed a sensitive search strategy to detect articles on MDR tuberculosis that mentioned community-based care and/or decentralized care. The search terms used with PubMed® are shown in Box 1. Searches were limited to publications published between the start of 1995, i.e. the year in which the WHO-recommended directly observed treatment, short-course (DOTS) strategy was scaled-up, and 31 May 2016. The reference lists of all articles considered relevant were searched for reports of further eligible studies. Where the findings of a study were reported in brief in one paper and then more completely in a subsequent paper, only the latter was selected for inclusion in our review. If an abstract was the only report of a potentially eligible study that we could find, we attempted to contact the abstract’s authors so that we could obtain additional information and ask the authors to complete a data-collection form. The authors of some other, fuller reports were also contacted to provide additional data, if required. Searches were not restricted by language. If eligible studies published in a language other than English were identified, these were translated by translators with experience either concurrent or consecutive. Study quality was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method.11

**Data analysis**

We used forest plots, created using RevMan version 5.2 (The Nordic Cochrane Centre, Copenhagen), to summarize the data for individual trials. Outcomes were estimated, as pooled proportions, using the exact binomial method11 and the statistical software SAS version 9.3 (SAS Institute, Cary, United States of America). We performed random-effects meta-analyses to account for between-study variability. Whenever the relevant data for an outcome of interest were available from three or more studies, we calculated the corresponding relative risk (RR) and 95% confidence interval (CI), for decentralized versus centralized care, using RevMan version 5.2 and...
a generalized linear mixed model, with study as a random effect. Heterogeneity between studies was evaluated as the $I^2$ statistic. We planned to assess publication bias, using a funnel plot, if sufficient studies, i.e. at least five with the same end-point, were identified. We performed additional sensitivity analyses to explore the effect of removing the data from a study in which allocation to inpatient care had been highly selective and based on disease severity.

**Results**

Seven published studies and one study considered to be unpublished met the eligibility criteria for inclusion (Fig. 1; Table 1). The data for the unpublished study, which took place in Swaziland in 2016, were kindly provided by B Kerschberger (Médecins Sans Frontières, Mbabane, Swaziland), the corresponding author of a conference abstract in which the study’s initial findings were briefly summarized. Most of the excluded studies did not include a comparison group. We did not identify any relevant controlled randomized trials. Six cohort studies, with a combined total of 4026 participants, reported on treatment outcomes. Four of these were from low- or middle-income countries – i.e. the Philippines, South Africa and Swaziland (B Kerschberger, unpublished data), and two from middle- and high-income countries, China and the United States of America (USA).

The other two included studies were modeling studies on health-care costs. Of the six studies that reported on treatment outcomes, five evaluated treatment success (B Kerschberger, unpublished data), four evaluated loss to follow-up (B Kerschberger, unpublished data), four evaluated death (B Kerschberger, unpublished data), and three evaluated treatment failure (B Kerschberger, unpublished data).

Decentralized care in some studies was based on the DOTS strategy. There was no randomization of patient selection for decentralized care. Instead, allocation of sites to the intervention or control groups was based upon patient characteristics that were considered likely to make centralized care more difficult or less successful, e.g. living far from the centralized facility. In four of the six cohort studies, the patients were chosen for decentralized treatment based on their residential location, their socioeconomic status and their risk factors for loss to follow-up (B Kerschberger, unpublished data).

In the other two cohort studies, treatment of the intervention and control groups occurred consecutively – i.e. care was initially provided by a centralized system that was subsequently replaced with a programme of decentralized care. None of the studies reported on acquisition of drug resistance, patient costs or treatment adherence.

The pooled proportions of each treatment outcome are shown, separately for decentralized and centralized care, in Table 2. Overall, treatment success was achieved in 67.3% (95% CI: 53.8–78.5%) of patients who received decentralized care compared with 61.0% (95% CI: 49.0–71.7%) of those treated with centralized care. Fig. 2, Fig. 3, Fig. 4 and Fig. 5 are forest plots showing the RRs for the various treatment outcomes. Treatment success was significantly more common among those receiving decentralized care than among those in the centralized care group (RR: 1.13; 95% CI: 1.01–1.27; $I^2 = 74$%). Although loss to follow-up was relatively less common with decentralized care than with centralized care, the difference was not statistically significant (RR: 0.66; 95% CI: 0.38–1.13; $I^2 = 88$%). The proportions of death (RR: 1.01; 95% CI: 0.67–1.52; $I^2 = 77$%) and treatment failure (RR: 1.07; 95% CI: 0.48–2.40; $I^2 = 74$%) with decentralized care were similar to those observed with centralized care. Owing to the small number of eligible studies, we could not assess publication bias formally.

In terms of the method of assigning patients to the intervention and control groups, one study differed markedly from the other included studies. In this one study, only patients who were failing treatment or non-adherent were selected for care in a specialized tuberculosis hospital. However, when, in a straightforward manner, the patients were randomized into the two treatment groups, the difference in outcomes was less pronounced.
### Table 1. Key characteristics of the eight studies included in the systematic review of decentralized versus centralized care for multidrug-resistant tuberculosis, 1994–2013

| Author, year, location | Study design | Year of intervention | Sample size | HIV prevalence in study population (%) | Description of arms | Method of selection of intervention group | Timing of intervention | Outcomes measured | Timing of measurement | Relative to control |
|------------------------|-------------|----------------------|-------------|----------------------------------------|---------------------|------------------------------------------|-----------------------|----------------|---------------------|-------------------|
| Loveday et al. 2015, KwaZulu-Natal, South Africa | Prospective cohort | 2008–2010 | 736/813 | 75 | Treatment in central hospital followed by outpatient home- or clinic-based DOT, by health workers | Based on residential location | Intensive phase | Concurrent | Death, loss to follow-up, treatment failure, treatment success | |
| Chan et al. 2013, Taiwan, China | Retrospective cohort | 2002–2008 | 290/661 | 0.9 | Home-based DOT, by observers and nurses | Time period | Concurrent | Consecutive | Treatment success | |
| Gler et al. 2012, Philippines | Retrospective cohort | 2003–2006 | 167/416 | 44.3 | Community-based DOT by trained health-care workers | Based on residential location | Time period | Consecutive | Loss to follow-up | |
| Cox et al. 2014, KwaZulu-Natal, South Africa | Retrospective cohort | 2008–2010 | 512/206 | 72 | Hospital-based care | Based on residential location | Entire duration of treatment | Consecutive | Health-system costs | |
| Musa et al. 2016, Nigeria | Modelling | N/A | N/A | N/A | Fully hospitalized model with intermittent DOT | Random selection | Intensive phase | N/A | N/A | |
| Sinanovic et al. 2015, Khayelitsha, South Africa | Modelling | N/A | 467 | 72 | A model of fully decentralized care in primary health-care clinics, with patients living in hospital until culture conversion | N/A | Entire duration of treatment | N/A | N/A | |

DOT: directly observed therapy; HIV: human immunodeficiency virus; N/A: not applicable; NR: not reported; SAT: self-administered therapy; USA: United States of America.

1. Intensive phase defined by inclusion of an injectable antibiotic in the treatment regimen.
2. Unpublished study from Médecins Sans Frontières, Mbabane, Swaziland, 2016.
3. Total number of patients used in four different models of multidrug-resistant tuberculosis care.
sensitivity analysis, we excluded data from this one study, our estimates of RRs remained largely unchanged.

Three studies, i.e. both modelling studies and the unpublished cohort study, reported on the health-system costs associated with decentralized and centralized care (Table 3). In both the modelling studies, from Nigeria and South Africa, decentralized care appeared to offer substantial cost savings compared with centralized care. In the retrospective cohort study from Swaziland (B Kerschberger, unpublished data), however, the estimated treatment costs with centralized care appeared very similar to those with decentralized care.

According to the GRADE criteria, the overall quality of the studies we used to estimate RRs was very low – mainly because the studies were observational and considerable heterogeneity existed between them (available from corresponding author).

Discussion

In the treatment of patients with MDR tuberculosis, according to our meta-analysis, decentralized care appears to be more likely than centralized care to lead to treatment success. The loss to follow-up with decentralized care was lower – although not significantly lower – than with centralized care and the rates of death and treatment failure appeared unaffected by the type of care provided. Furthermore, from a health-system perspective, the decentralized approaches appeared either cost-neutral or cost-saving when compared with the centralized approaches.

There may be several explanations why, compared with centralized care, decentralized care was more likely to lead to treatment success. For example, although the small number of eligible studies limited the power of our meta-analysis, there is a hint that retention in care may be generally greater, or, at least, loss to follow-up may be generally rarer, when services are delivered locally. It seems likely that the delivery of care in the community could eliminate some of the barriers to treatment adherence that are encountered with often-more-distant centralized care. For example, the costs of hospitalization to patients and, often, their families may be prohibitive even if the tuberculosis treatment itself is provided...
free of charge.27 Local delivery of care may also facilitate greater support from patients’ families and their wider social networks, which may, in turn, increase the likelihood of adherence. We need further studies to examine the effect of decentralized MDR tuberculosis care on treatment adherence and patient attitudes to care.

Fig. 2. Relative risks for treatment success following the decentralized care of multidrug-resistant tuberculosis – compared with centralized care, 1994–2013

| Study or subgroup | Intervention | Control |
|------------------|--------------|---------|
| Narita et al. 2001 | 15/23 | 31/38 | 8.7 | 0.80 (0.57–1.12) |
| Chan et al. 2013 | 239/290 | 222/361 | 25.0 | 1.34 (1.22–1.48) |
| Cox et al. 2014 | 235/512 | 85/206 | 17.0 | 1.11 (0.92–1.34) |
| Loevsey et al. 2015 | 427/716 | 439/811 | 25.9 | 1.10 (0.81–1.50) |
| Kerschberger et al. 2016 | 119/154 | 202/294 | 23.4 | 1.12 (1.00–1.26) |
| Total | 1695/1770 | 100.0 | 1.13 (1.01–1.27) |

Total events 1035/979
Heterogeneity: τ² = 0.01; χ² = 15.16, df = 4 (P = 0.004); I² = 74
Test for overall effect: Z = 2.09 (P = 0.04)

CI: confidence interval; df: degrees of freedom; RR: relative risk.
Notes: This forest plot summarizes the main results of a random-effects meta-analysis of the data from five studies. To be considered a treatment success, a patient had to show no evidence of failure after completing treatment recommended by national policy.11

Fig. 3. Relative risks for loss to follow-up during the decentralized care of multidrug-resistant tuberculosis – compared with centralized care, 2003–2013

| Study or subgroup | Intervention | Control |
|------------------|--------------|---------|
| Gler et al. 2012 | 9/167 | 79/416 | 21.3 | 0.28 (0.15–0.55) |
| Cox et al. 2014 | 152/512 | 59/206 | 29.4 | 1.04 (0.80–1.34) |
| Loevsey et al. 2015 | 107/716 | 811 | 30.1 | 0.53 (0.45–0.63) |
| Kerschberger et al. 2016 | 10/154 | 16/294 | 19.3 | 1.19 (0.55–2.57) |
| Total | 1549/1727 | 100.0 | 0.66 (0.38–1.13) |

Total events 278/384
Heterogeneity: τ² = 0.24; χ² = 25.68, df = 3 (P < 0.0001); I² = 88
Test for overall effect: Z = 1.51 (P = 0.13)

CI: confidence interval; df: degrees of freedom; RR: relative risk.
Notes: This forest plot summarizes the main results of a random-effects meta-analysis of the data from four studies. A patient whose treatment was interrupted for at least two consecutive months was considered lost to follow-up.11

Fig. 4. Relative risks for death during the decentralized care of multidrug-resistant tuberculosis – compared with centralized care, 1994–2013

| Study or subgroup | Intervention | Control |
|------------------|--------------|---------|
| Narita et al. 2001 | 8/23 | 7/38 | 13.6 | 1.89 (0.79–4.52) |
| Cox et al. 2014 | 85/512 | 43/206 | 28.8 | 0.80 (0.57–1.11) |
| Loevsey et al. 2015 | 133/716 | 113 | 31.9 | 1.33 (0.86–1.68) |
| Kerschberger et al. 2016 | 24/154 | 69/294 | 25.7 | 0.66 (0.44–1.01) |
| Total | 1405/1349 | 100.0 | 1.01 (0.67–1.52) |

Total events 290/232
Heterogeneity: τ² = 0.12; χ² = 13.16, df = 3 (P < 0.004); I² = 77
Test for overall effect: Z = 0.03 (P = 0.98)

CI: confidence interval; df: degrees of freedom; RR: relative risk.
Notes: This forest plot summarizes the main results of a random-effects meta-analysis of the data from four studies. Death was the treatment outcome recorded for any patients who died, for any reason, during the course of treatment.11
Systematic reviews

Decentralized care for multidrug-resistant tuberculosis

Jennifer Ho et al.

All three studies on health-system costs that we included in our review were conducted in resource-poor low- or middle-income settings. Their conclusions – that decentralized care was cheaper or as cheap as centralized care – may not apply to high-income settings, where the costs of community-based care may be at least as high as those of centralized care. Further research is required to evaluate the impact of decentralized approaches on the costs to patients of treatment for MDR tuberculosis. The impact of such approaches on the elimination of catastrophic health expenditure for the households of such patients, which is one of the key targets of the WHO End TB Strategy, also needs to be investigated.

The strengths of our review include the comprehensive search of bibliographic databases and other information sources and our use of strict eligibility criteria to limit the review to studies in which cohorts receiving decentralized care were compared with those, from the same study population, receiving centralized care. The eligibility criteria we used, which reduced the risk of bias due to indirectness, were narrower than those used in previous systematic reviews on the care of patients with MDR tuberculosis.

Our review also had several limitations. Substantial heterogeneity was observed between the included studies.

---

**Table 3. Estimated health-system costs for treatment of patients with multidrug-resistant tuberculosis receiving decentralized and centralized care**

| Study                | Study design                                      | Country       | Decentralized care Description                                      | Cost (US$/patient) | Centralized care Description                                      | Cost (US$/patient) | Difference in per-patient costs of centralized carea |
|----------------------|--------------------------------------------------|---------------|---------------------------------------------------------------------|-------------------|---------------------------------------------------------------------|-------------------|-------------------------------------------------------|
| Musa et al.23        | Modelling of costs from a health-systems perspective | Nigeria       | Home-based care for entire duration of treatment                    | 1535              | Hospital-based care for intensive phase, then home-based care for continuation phase | 2095              | 37% higher                                            |
| Sinanovic et al.25    | Modelling of costs from a health-systems perspective | South Africa  | Primary health-care clinic for entire duration of treatment         | 7753b             | Hospital-based care for intensive phase – until 4-month culture conversion – then clinic-based care | 13 432c            | 42% higher                                            |
| Kerschberger et al.2  | Retrospective cohort study                        | Swaziland     | Home-based care for entire duration of treatment                    | 13 361            | Clinic-based care for intensive phase, then home-based care for continuation phase | 13 006            | 3% lower                                              |

CI: confidence interval; df: degrees of freedom; RR: relative risk.

Notes: This forest plot summarizes the main results of a random-effects meta-analysis of the data from three studies. Treatment failure was the outcome recorded when – because of a lack of conversion by the end of the intensive phase, bacteriological reversion in the continuation phase after conversion to negative, evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs or adverse drug reactions – treatment was terminated or there was a need for a permanent regimen change involving at least two anti-tuberculosis drugs.11

---

**Fig. 5. Relative risks for treatment failure following the decentralized care of multidrug-resistant tuberculosis – compared with centralized care, 2008–2013**

| Study or subgroup | Intervention | Events | Control | Events | Total | Weight (%) | RR (95% CI) | RR (95% CI) |
|------------------|--------------|--------|---------|--------|-------|------------|-------------|-------------|
| Cox et al. 2014  | 40           | 512    | 19      | 206    |       | 43.1       | 0.85 (0.50–1.43) |             |
| Loveday et al. 2015 | 49          | 716    | 29      | 811    |       | 45.3       | 1.91 (1.22–3.00) |             |
| Kerschberger et al. 2016 | 1  | 154    | 7       | 294    |       | 11.6       | 0.27 (0.03–2.20) |             |
| Total            | 1382         |        | 1311    |        |       | 100.0      | 1.07 (0.48–2.40) |             |

Heterogeneity: τ² = 0.32; χ² = 7.61, df = 2 (P < 0.02); I² = 74

Test for overall effect: Z = 0.17 (P = 0.86)

---

US$: United States dollars.

a Compared with corresponding costs of decentralized care.
b 95% confidence interval: 6917–8522.
c 95% confidence interval: 11 165–15 494.
d Unpublished study from Médecins Sans Frontières, Mbabane, Swaziland, 2016.
This probably reflects the diversity in the study settings, patient populations and interventions involved. However, the effect estimates from every study in a tuberculosis-endemic setting that we included in our meta-analysis indicated that decentralized care was better – at least in terms of the probability of treatment success – than centralized care. The only study included from a low-prevalence country – i.e. the United States – indicated the opposite: that decentralized care was lower with decentralized care than with centralized. Given the absence of randomized controlled trials, the frequent use of historical controls and the large level of heterogeneity between the studies, it is perhaps not surprising that we found that the overall quality of the studies we used to estimate RRs was categorized as low. This low quality places some limitations on the precision and generalizability of the results of our meta-analysis and underpins the importance of further research into the benefits of decentralized care for MDR tuberculosis in different settings. In countries where tuberculosis is endemic and national programmes increasingly adopt decentralized approaches for managing patients with MDR tuberculosis, the programmes’ interventions and outcomes need to be carefully and thoroughly reported. For future research in this field, before-and-after studies or pragmatic randomized studies – e.g. stepped-wedge cluster-randomized studies – may be good choices. Well-designed operational research may enable programmes to evaluate the effectiveness of alternative approaches, in their local settings, accurately. ■

Acknowledgements
We thank Giuliano Gargioni and Dennis Falzon, from the WHO Global TB Programme.

Funding: The Australian National Health and Medical Research Council and the United States Agency for International Development supported this study.

Competing interests: None declared.

Melodi 

Decentralized care for multidrug-resistant tuberculosis

Jennifer Ho et al.

Bull World Health Organ 2017;95:584–593 doi: http://dx.doi.org/10.2471/BLT.17.193375

591

Systematic reviews

Decentralized care for multidrug-resistant tuberculosis

Summary

The effectiveness of alternative approaches, in their local settings, accurately.

Decentralized care for multidrug-resistant tuberculosis

Jennifer Ho et al.

Bull World Health Organ 2017;95:584–593 doi: http://dx.doi.org/10.2471/BLT.17.193375

591

Systematic reviews

Decentralized care for multidrug-resistant tuberculosis

Summary

The effectiveness of alternative approaches, in their local settings, accurately.

Decentralized care for multidrug-resistant tuberculosis

Jennifer Ho et al.

Bull World Health Organ 2017;95:584–593 doi: http://dx.doi.org/10.2471/BLT.17.193375

591

Systematic reviews

Decentralized care for multidrug-resistant tuberculosis

Summary

The effectiveness of alternative approaches, in their local settings, accurately.

Decentralized care for multidrug-resistant tuberculosis

Jennifer Ho et al.

Bull World Health Organ 2017;95:584–593 doi: http://dx.doi.org/10.2471/BLT.17.193375

591

Systematic reviews

Decentralized care for multidrug-resistant tuberculosis

Summary

The effectiveness of alternative approaches, in their local settings, accurately.

Decentralized care for multidrug-resistant tuberculosis

Jennifer Ho et al.

Bull World Health Organ 2017;95:584–593 doi: http://dx.doi.org/10.2471/BLT.17.193375

591

Systematic reviews

Decentralized care for multidrug-resistant tuberculosis

Summary

The effectiveness of alternative approaches, in their local settings, accurately.

Decentralized care for multidrug-resistant tuberculosis

Jennifer Ho et al.

Bull World Health Organ 2017;95:584–593 doi: http://dx.doi.org/10.2471/BLT.17.193375

591

Systematic reviews

Decentralized care for multidrug-resistant tuberculosis

Summary

The effectiveness of alternative approaches, in their local settings, accurately.

Decentralized care for multidrug-resistant tuberculosis

Jennifer Ho et al.

Bull World Health Organ 2017;95:584–593 doi: http://dx.doi.org/10.2471/BLT.17.193375

591

Systematic reviews

Decentralized care for multidrug-resistant tuberculosis

Summary

The effectiveness of alternative approaches, in their local settings, accurately.

Decentralized care for multidrug-resistant tuberculosis

Jennifer Ho et al.

Bull World Health Organ 2017;95:584–593 doi: http://dx.doi.org/10.2471/BLT.17.193375

591

Systematic reviews

Decentralized care for multidrug-resistant tuberculosis

Summary

The effectiveness of alternative approaches, in their local settings, accurately.
Decentralized care for multidrug-resistant tuberculosis

Jennifer Ho et al.

Resumen

Atención descentralizada para la tuberculosis multirresistente: una revisión sistemática y un metaanálisis

Objetivo Evaluar la efectividad de la atención y el tratamiento centralizado versus descentralizado en adultos con tuberculosis multirresistente (TB-MR). Se realizó una revisión sistemática y un metaanálisis, así como una búsqueda adicional en bases de datos de ensayos clínicos.

Métodos Se realizaron búsquedas en bases de datos de ensayos clínicos como ClinicalTrials.gov, Embase®, LILACS, PubMed®, Web of Science y el portal de ensayos clínicos comunitarios ClinicalTrials.gov. Se incluyeron todos los ensayos clínicos que se publicaron hasta el 1 de diciembre de 2017.

Resultados Se incluyeron 7 ensayos clínicos comparativos de 14 estudios complementarios. Se encontró una mayor efectividad de la atención y el tratamiento descentralizado versus centralizado en términos de tasas de mejora clínica, tasas de vacunación y tasas de cobertura de la terapia. Se registraron menores costos para la atención descentralizada.

Conclusion Se recomienda la atención y el tratamiento descentralizado para el tratamiento de la tuberculosis multirresistente.

Systematic reviews

Decentralized care for multidrug-resistant tuberculosis

Bull World Health Organ 2017;95:584–593 doi: http://dx.doi.org/10.2471/BLT.17.193375
References

1. Global tuberculosis report 2015. Geneva: World Health Organization; 2015.
2. Guidelines for the programmatic management of drug-resistant tuberculosis – 2011 update. Geneva: World Health Organization; 2011.
3. Nathanson E, Lambregs-van Weeeenbeek C, Rich ML, Gupta R, Bayona J, Blöndal K, et al. Multidrug-resistant tuberculosis management in resource-limited settings. Emerg Infect Dis. 2006 Sep;12(9):1389–97. doi: http://dx.doi.org/10.3201/eid1209.051618 PMID: 17073088
4. Burgos M, Gonzalez LC, Paz EA, Gourmis, E, Kawamura LM, Schecter G, et al. Treatment of multidrug-resistant tuberculosis in San Francisco: an outpatient-based approach. Clin Infect Dis. 2005 Apr;1;40(7):968–75. doi: http://dx.doi.org/10.1086/428582 PMID: 15824988
5. Seung KJ, Omatayo DB, Keshavjee S, Furin JJ, Farmer PE, Satti H. Early supervision in the community, 1998–1999. Int J Tuberc Lung Dis. 2003 Sep;7(9) Suppl 1:S72–9. PMID: 12971657
6. Okello D, Floyd K, Adatu F, Odeke R, Gargioni G, McCray E, Schneider E, et al. Implementation of the DOTS strategy for tuberculosis control in rural Kiboga district, Uganda, offering patients the option of treatment supervision in the community, 1998–1999. Int J Tuberc Lung Dis. 2003 Sep;7(9) Suppl 1:S53–61. PMID: 12971656
7. Wandwalo E, Kapalata N, Egwaga S, Galop M, Qalapi MJ, Tshipise TE. Impact of patient and program factors on default during treatment of multidrug-resistant tuberculosis. Int J Tuberc Lung Dis. 2012 Jul;16(7):955–60. doi: http://dx.doi.org/10.5588/ijtld.11.0502 PMID: 22584124
8. Sinanovic E, Ramma L, Vassall A, Azevedo V, Wilkinson L, Ndeka N, et al. Impact of reduced hospitalisation on the cost of treatment for drug-resistant tuberculosis in South Africa. Int J Tuberc Lung Dis. 2015 Feb;19(2):172–8. doi: http://dx.doi.org/10.5588/ijtld.14.0421 PMID: 25574915
9. Loveday M, Wallenegro K, Brust J, Roberts J, Voce A, Margot B, et al. Community-based care vs. centralised hospitalisation for MDR-TB patients, KwaZulu-Natal, South Africa. Int J Tuberc Lung Dis. 2015 Feb;19(2):163–71. doi: http://dx.doi.org/10.5588/ijtld.14.0369 PMID: 25574914
10. Nanta M, Alonso P, Lauzardo M, Hollender E, Pitchenik AE, Ashkin D. Treatment experience of multidrug-resistant tuberculosis in Florida, 1994–1997. Chest. 2001 Aug;120(2):343–8. doi: http://dx.doi.org/10.1013/chest.120.2.343 PMID: 11502627
11. Schünemann H, Brozek J, Guyatt G, Oxman A, editors. GRADE. Handbook of evidence synthesis. Oxford: Centre for Health Economics, University of York; 2016. Available from: http://www.ohri.ca/programs/clinical_epidemiology/health_evidence滿
12. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol. 2009 Oct;62(10):1006–12. doi: http://dx.doi.org/10.1016/j.jclinepi.2009.06.005 PMID: 19631508
13. Systematic reviews. Bull World Health Organ. 2017;95:584–593 doi: http://dx.doi.org/10.2471/BLT.17.193375.