Is 6 Months of Antitubercular Chemotherapy as Effective as More Than 6 Months Regimen in Spinal Tuberculosis? A Systematic Review and Meta-analysis

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Historically, osteoarticular tuberculosis (TB), including spinal TB, was treated with prolonged course of antitubercular therapy (ATT). Due to various challenges, there has been reluctance to explore the use of short-course ATT in spinal TB. However, with the success of short-course ATT being demonstrated in other forms of extrapulmonary TB, the subject is open for debate again. Therefore, we systematically reviewed various published literature to determine whether short-course treatment regimen (6 months) of ATT provides equivalent results in terms of disease healing as long-course treatment regimen (≥ 9 months) in the management of spinal TB. Five electronic databases (PubMed, MEDLINE, EMBASE, CENTRAL, and Web of Science) and their reference lists were searched to identify relevant randomized controlled trials with at least 1 year of follow-up that compared short-course with standard-course ATT for treatment of spinal TB. The methodological quality of included studies was assessed, and their data were extracted. A meta-analysis was used to calculate pooled effect sizes and 95% confidence interval (CI). The outcome measure was healed status of the disease at the final follow-up. Of 331 publications identified through literature search, eight publications describing six randomized studies were included. Moreover, 375 of 414 patients (90.58%) who received 6 months of ATT had healed status at their final follow-up compared to 404 of 463 patients (87.26%) who received ≥ 9 months of ATT. Overall, the healed status of spinal TB was equivalent in patients in both groups (pooled relative risk, 0.98; 95% CI, 0.92–1.04; $p=0.439$). However, there was considerable heterogeneity among the trials ($I^2=40.8\%$, $p=0.149$). The results suggest that the use of short-course (6 months) chemotherapy may be considered for the treatment of spinal TB in view of the similarity in the healing response achieved compared to treatment regimens of longer duration.

Keywords: Spinal tuberculosis; Pott's disease; Antitubercular drugs; Meta-analysis; Short course

Introduction

Tuberculosis (TB) is a leading cause of morbidity and mortality among all age groups, especially in developing countries [1]. Extrapulmonary TB (EPTB) comprises

16.4% of the TB burden [2]. Skeletal TB is a major contributor to morbidity in children, adolescents, and young adults and consists of 10%–20% of the EPTB burden [3]. Spinal TB accounts for almost 50% of the total burden of skeletal TB [4]. According to the World Health Organiza-

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tion (WHO) database, the incidence of TB has increased in the last 4 decades to 10 million new cases annually in 2019 [1]. However, morbidity and mortality have decreased, which is attributable to the development and worldwide adoption of inexpensive and effective modern antitubercular therapy (ATT) [5]. Advances in imaging techniques and diagnostic tests have also led to an improvement in diagnosis, initiation, and optimization of treatment and follow-up of these patients.

Most existing resources for research, diagnosis, and treatment of TB have been aimed at pulmonary TB—as this is overwhelmingly the most commonly encountered form of TB and, due to its mechanism of transmission, has been considered more important for public health and TB control. The low incidence rates of spinal TB in developed countries and poor data reporting with lack of national-scale registries for spinal TB in developing countries have made it difficult to generate high-quality evidence to provide recommendations regarding appropriate treatment duration in spinal TB. This is augmented by the fact that it is difficult to conclusively document healing of spinal TB. The conventional practice of providing long-course treatment regimens for spinal TB has been based on the poor penetration of antitubercular drugs in the bone, possible blunting action in closed anoxic conditions due to acidic microenvironment found in spinal TB lesions and the potentially devastating course of disease if left partially treated [6-8]. Ideally, the only conclusive method of documenting healed disease would be vertebral biopsy—which is not feasible in a practical scenario considering that repeated biopsies may be needed and diagnostic yield of a biopsy may be poor. The paucibacillary nature of spinal TB makes it difficult to accurately label the disease as “healed”. A combination of various tests (clinical response, radiological response on plain radiography or magnetic resonance imaging [MRI], and inflammatory markers such as C-reactive protein [CRP]) may improve the accuracy of “healing criteria”. Therefore, in common practice, clinical and radiological resolution at the completion of ATT with no disease relapse at a 2-year follow-up is defined as healed status [9-13].

Considering the aforementioned challenges in spinal TB, to date, there has been reluctance to explore the use of short-course antitubercular chemotherapy in spinal TB. However, with the success of short-course ATT in other forms of EPTB [14,15] and recent evidence suggesting the same in spinal TB [16,17], the subject is open for

debate again. Reaching a global consensus on the ideal treatment duration in spinal TB is important. Longer duration of administration than necessary tends to prolong the exposure to side effects and places a burden on either the patient’s pockets or public health spending, depending on the healthcare system of each country. Conversely, shorter durations risk inadequate disease healing with its attendant complications, such as progression of deformity or development of neurological deficit, and would also contribute to drug resistance.

Therefore, we reviewed various published literature for the recommended duration of chemotherapy in spinal TB. This study aimed to determine whether a shorter course of chemotherapy (6 months) provide equivalent results in terms of healing of the disease as the standard duration of chemotherapy (≥ 9 months) in the treatment of spinal TB.

Materials and Methods

A protocol for conducting this review was registered in PROSPERO on August 24, 2020 (registration no., CRD42020200938) [18]. We followed the PRISMA (Pre-

Fig. 1. Flowchart outlining the systematic review process in accordance to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (2009).

ferred Reporting Items for Systematic Reviews and Meta-Analyses) 2009 guidelines, outlined in Fig. 1.

1. Eligibility criteria

We included studies that described adults or children with primary, drug-sensitive spinal TB (single level or multi-level) who received drug treatment with at least isoniazid and rifampicin for spinal TB and whose healing status was assessed at the endpoint of therapy or during the follow-up period. Only randomized controlled trials (RCTs) comparing short-course chemotherapy with standard-course (≥ 9 months) chemotherapy, with a follow-up period of at least 12 months after completion of chemotherapy, were included. Studies published between 1980 and 2019, in the English language originally and those available with English translation, were included. Studies on patients who had known multi-drug resistant (MDR) and extremely drug-resistant TB, who had received second-line ATT, and in whom healing/resolution of disease at the endpoint of therapy or during the specified follow-up period had not been reported were excluded. Moreover, nonrandomized prospective studies, retrospective studies, case reports, case series, and review articles were excluded. All unrelated studies, duplicated studies, abstract-only papers, and articles without available full text were excluded.

2. Search strategy

We performed a thorough search of the electronic databases to identify RCTs performed on humans on PubMed (1968–2020), MEDLINE (1968–2020), EMBASE (1954–2020), The Cochrane Central Register of Controlled Trials (CENTRAL) (1954–2020), and Web of Science (1956–2020). The last search date was August 25, 2020. Search strategies included a combination of various free-text terms and appropriate subject indexing (e.g., Medical Subject Headings [MeSH], such as tuberculosis spine, TB spine, Pott's disease, spinal tuberculosis, chemotherapy, antitubercular therapy, duration, course, short-course, and clinical trial).

3. Data abstraction and management

All records were collected into a reference manager library. After the removal of duplicates, two independent

reviewers (A.A. and S.S.) screened the titles and abstracts of all selected articles to decide which ones to include. Any disagreement regarding inclusion/exclusion of a study was resolved through discussion and consensus or by consultation with the senior author (B.G.). Moreover, the reference lists of key articles identified during the search were screened for additional relevant articles. The second round of screening was conducted by reviewing the full-text articles of selected studies. The list of excluded studies with the reasons for omission is presented in Table 1 [13,19–44].

4. Assessment of methodological quality

The risk of bias of each included RCT was assessed using the adapted GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach with the 11-point criteria as recommended by the Cochrane Back Review Group [45]. Only studies that adequately fulfilled 50% (6/11) or more of the validity criteria were considered to have low risk of bias (Table 2) [16,17,46–49]. The two authors resolved disagreements in the assessment of the risk of bias by consensus.

5. Data extraction, synthesis, and analysis

A data extraction form was created in Excel, and data were entered into the spreadsheets. Data collected on each study included basic information on the study, including research title, first author, publication year, study type, sample size, demographic characteristics, affected areas of the spine, chemotherapeutic regimen used, duration of administration, inclusion and exclusion criteria, criteria for healing, and healing rate. Various studies used a variable combination of outcome measures, such as symptomatic relief, neurological recovery, subsidence of abscesses/sinuses, normalization of erythrocyte sedimentation rate or CRP level, and radiographic and/or MRI changes suggestive of resolution with no signs of relapse on follow-up.

6. Statistical methods

The meta-analysis was conducted using Stata ver. 15.2 (Stata Corp., College Station, TX, USA). The random-effects model using the DerSimonian and Laird method was used to calculate pooled effect sizes and its 95% confidence interval (CI) limit with the help of the METAN

Table 1. Studied excluded from the systematic review after reviewing the full-text

Study	Reason for exclusion
Abbas et al. [19] (2013)	All patients received 12 months of ATT
Bakhsh [20] (2010)	Only discusses about the diagnosis of spinal tuberculosis
Batirel et al. [21] (2015)	No comparison between short vs standard course chemotherapy
Bodapati et al. [22] (2017)	Duration of ATT not clear, no comparative groups
Cao et al. [23] (2018)	All patients received 18 months of ATT
Guo et al. [24] (2010)	No comparison between short vs. standard course chemotherapy
Jain et al. [25] (2012)	No comparison between short vs. standard course chemotherapy
Jutte et al. [26] (2006)	No comparison between short vs. standard course chemotherapy
Karaeminogullari et al. [27] (2007)	No comparison between short vs. standard course chemotherapy
Kotil et al. [28] (2007)	All patients received 15–18 months of ATT
Mittal et al. [13] (2019)	No randomization; wide variability in the duration of chemotherapy
Moon et al. [29] (1987)	No comparison between short vs. standard course chemotherapy
MRC [30] (1998)	No details about the short vs. standard course RCTs. Mainly discusses about the other MRC trials (e.g., POP jacket, debridement, etc.)
Niu et al. [31] (2017)	No comparison between short vs. standard course chemotherapy
Parthasarathy et al. [32] (1999)	10-Year follow-up of MRC Madras study, with greater loss of follow-up
Patankar [33] (2016)	No comparison between short vs. standard course chemotherapy
Patil et al. [34] (2014)	All patients received 12 months of ATT
Qian et al. [35] (2016)	No comparison between short vs. standard course chemotherapy
Rajasekaran et al. [36] (1998)	Did not discuss the duration of ATT; Also, the sample overlaps with the MRC Madras study
Rajeswari et al. [37] (1997)	No comparison between short vs. standard course chemotherapy
Upadhyay et al. [38] (1996)	Data on healing/final outcome not clearly stated in results
Valsalan et al. [39] (2012)	No comparison between short vs. standard course chemotherapy
Wang et al. [40] (2007)	Excluded as this is a subset of the Wang et al. [41] (2013) study
Wang et al. [41] (2013)	Retrospective study; no comparison between short course and standard chemotherapy
Wardak et al. [42] (2014)	Duration of ATT not clear; no comparative groups
Wu [43] (1990)	No comparison between short vs. standard course chemotherapy
Zhang et al. [44] (2013)	No comparison between short vs. standard course chemotherapy

ATT, anti-tubercular therapy; RCT, randomized controlled trial; MRC, Medical Research Council; POP, plaster of Paris.

command [50,51]. Forest plots were generated, displaying the proportion of patients with resolution of the disease, with corresponding 95% CI. We examined the variation in the magnitude of effect and quantified the heterogeneity using I^2 statistic. No subgroup analysis was conducted.

Results

1. Study selection

The search yielded 323 articles, and additional eight relevant articles were identified by going through the references of these searched articles. After removing 128 dupli-

cations, the titles and abstracts of 195 articles were further screened for relevance based on the inclusion and exclusion criteria. A total of 35 full-text articles were assessed for eligibility, of which eight publications, discussing six trials (the other two were follow-up studies of two of these trials), were included in the systematic review [16,17,46-49,52,53]. The six randomized trials compared groups of patients receiving antitubercular chemotherapy at different durations. Five of these studies were RCTs, and one was described as a prospective randomized study. Three of the trials were part of the British Medical Research Council (MRC) Working Party on Tuberculosis of the Spine series (one of them in coordination with the Indian Council

Table 2. Assessment of methodological quality of the 6 trials on the basis of the Cochrane Back Review Group 11 points criteria

Variable	Study					
	MRC [46]	MRC [47]	MRC [48]	Wang et al. [16]	Banga et al. [49]	Nene et al. [17]
Year of publication	1986	1993	1989	2013	2018	2019
Criteria						
Was the randomization adequate?	Yes	Not sure	Yes	Yes	Not sure	Yes
Was the treatment allocation concealed?	Yes	Not sure	Yes	Yes	Not sure	Not sure
Were the groups similar at baseline regarding the most important prognostic indicators?	Yes	Yes	Yes	Yes	Not sure	Yes
Were the patients blinded?	Not sure	Not sure	Not sure	Not sure	No	No
Was the care provider blinded?	Not sure	Not sure	Not sure	Not sure	Not sure	No
Was the outcome assessor blinded?	Not sure	Not sure	Not sure	Not sure	Not sure	Not sure
Were cointerventions avoided or similar?	Yes	Yes	Yes	Yes	Yes	Yes
Was the compliance acceptable in all groups?	Yes	Yes	Yes	Yes	Yes	Yes
Was the drop-out rate described and acceptable?	Yes	Yes	Yes	Yes	Yes	Yes
Was the timing of the outcome assessment in all groups similar?	Yes	Yes	Yes	Yes	Yes	Yes
Did the analysis include an intention-to-treat analysis?	Yes	Yes	Yes	Yes	Yes	Yes
Total score	8	6	7	7	5	7

MRC, Medical Research Council.

of Medical Research). These studies were conducted in Hong Kong, Korea, and India in the 1970s and 1980s on patients with spinal TB and showed results at 3 years of follow-up [46-48]. Two additional publications (one was a 5-year follow-up report of all three aforementioned trials reported together, and the other was a 5-year follow-up report of the MRC 1989 trial) were reviewed [52,53]. The next one was a prospective randomized study, where patients were randomized by allowing them to extract envelopes that had random numbers [16]. The last two studies were recent RCTs from India [17,49]. The 5-year follow-up data for Korea (MRC 1993) reported in the MRC 1999 paper was not included in the analysis as there was a considerable dropout rate at 5 years; hence, only the 3-year follow-up data of this study are presented here [52].

2. Study characteristics

1) Inclusion, exclusion, diagnostic, and healing criteria
All studies included patients with clinical and radiological evidence of spinal TB. Since the MRC trials were conducted in the pre-MRI era, only plain radiographs of the spine were used in the diagnosis, in addition to the clinical features (n=723). However, the other three studies included MRI in making the diagnosis (n=315). The trial by Nene

et al. [17] routinely used computed tomography (CT)-guided biopsy in confirming the diagnosis of all patients included in their study (n=100).

The MRC trials included patients with TB affecting the first thoracic to first sacral vertebrae only. However, the other three studies did not restrict their inclusion criteria to the thoracolumbar region and included cases of cervical and sacral TB. The MRC trials excluded patients with serious extraspinal disease, which was likely to affect their management or response to treatment; patients who received ATT for ≥ 12 months, patients with severe paraplegia, and those who already underwent surgery for spinal TB. Wang et al. [16] excluded patients who had any contraindication to surgical intervention. Banga et al. [49] and Nene et al. [17] excluded patients with a history of ATT administration and those with MDR TB.

The MRC trials considered clinical and radiological resolution (on anteroposterior and lateral radiographs of the spine) as the criteria for healing. Clinical resolution was defined as resolution of patient's symptoms (decrease in pain, improvement in neurological status, absence of constitutional symptoms, weight and appetite gain, and healing of discharging sinuses, if any), and radiological resolution was defined as decrease in fuzziness of endplate or sclerosis, fusion of adjacent vertebrae, sharpening of

Table 3. Characteristics of studies included in the review

Study	Place of study	Study design	Inclusion criteria	Exclusion criteria	Diagnosis	Healing criteria
MRC [46] (1986), [52] (1999)	Hong Kong	RCT	1. Clinical and radiographic evidence of active spinal TB (from the first thoracic to the first sacral vertebrae).	1. Patients with serious extra-spinal disease which was likely to affect their management or response to treatment. 2. Patients who gave a history of antituberculous therapy for 12 months or more in the past.	Clinical examination, radiographs of spine and chest, Mantoux test, urine culture for TB bacilli, smear and culture of pus from sinus (if present), and sputum in any patient with radiographic evidence of pulmonary TB. (No MRI)	Clinical (symptoms, signs, abscesses, sinuses, deficit) and radiological resolution
MRC [47] (1993)	Korea	RCT	1. Clinical and radiographic evidence of active spinal TB (from the first thoracic to the first sacral vertebrae). 2. Patients who were likely to be available for observation for a period of 5 years.	1. Patients who had paralysis severe enough to prevent them from walking across a room unaided. 2. Patients with serious extra-spinal disease (tuberculous or non-tuberculous) and likely to affect the management or response to treatment. 3. Patients who gave a history of antituberculosis therapy for 12 months or more in the past, or 3 months or more immediately before admission. 4. Patients with a history of previous surgery for spinal TB.	Clinical examination, radiographs of spine and chest, Mantoux test, urine culture for TB bacilli, smear and culture of pus from sinus (if present) and sputum in any patient with radiographic evidence of pulmonary TB. (No MRI)	Clinical (symptoms, signs, abscesses, sinuses, deficit) and radiological resolution
MRC [48] (1989), [52] (1999), Reetha et al. [53] (1994)	India	RCT	1. Clinical and radiographic evidence of active spinal TB (from the first thoracic to the first sacral vertebrae).	1. Patients who had paralysis of the lower limbs severe enough to prevent them from walking across a room. 2. Patients with serious extra-spinal disease (tuberculous or non-tuberculous). 3. Patients who gave a history of antituberculous therapy for 12 months or more in the past. 4. Patients with a history of major surgery for their spinal TB.	1. Complete clinical (including neurological) examination 2. AP and lateral radiographs of whole spine and PA radiograph of the chest 3. Culture of two specimens of pus from any abscess or sinus (if present) and three sputum specimens from patients with radiographic evidence of pulmonary TB 4. Sensitivity tests to isoniazid and rifampicin on positive cultures of Mycobacterium tuberculosis. (No MRI)	Clinical (symptoms, signs, abscesses, sinuses, deficit) and radiological resolution
Wang et al. [16] (2013)	China	Prospective randomized study	1. Patients with spinal TB diagnosed according to clinical, radiological and etiological, and histopathological results. 2. Patients who were appropriate candidates for surgical debridement of tubercular focus (cases with compression of the spinal cord or cauda equina causing neurological dysfunction, cases with spinal instability, cases with serious or progressive kyphosis, patients having large abscesses, bone sequestration, cavitation, or sinus tract formation).	1. Any contraindication to surgical intervention.	Clinical examination, imaging, and etiological and histopathological results	Clinical examination, neurological examination, X-ray, CT, MRI, LFT, KFT, USG for abscesses

(Continued on next page)

Table 3. Continued

Study	Place of study	Study design	Inclusion criteria	Exclusion criteria	Diagnosis	Healing criteria
Banga et al. [49] (2018)	India	RCT	1. The new cases of spinal TB, diagnosed based on clinical examination, radiological assessment, ESR, biopsy, and without neurological deficit.	1. Patients with a history of antitubercular treatment in the past. 2. Patients with skip lesions of TB, TB meningitis, and HIV positive status.	1. Clinical examination 2. Radiological assessment 3 ESR 4. Biopsy	Radiological healing
Nene et al. [17] (2019)	India	RCT	1. Patients with clinico-radiological suspicion of spinal TB, who were then subjected to CT-guided biopsy to prove the diagnosis.	1. Patients who gave a history of antitubercular treatment in the past. 2. Patients with documented multidrug-resistant TB.	CT-guided biopsy (with positive histopathology or microbiology)	Composite clinical, laboratory (CBC and ESR), and radiological resolution

MRC, Medical Research Council; RCT, randomized controlled trial; TB, tuberculosis; MRI, magnetic resonance imaging; AP, anteroposterior; PA, posteroanterior; CT, computed tomography; LFT, liver function test; KFT, kidney function test; USG, ultrasound; ESR, erythrocyte sedimentation rate; HIV, human immunodeficiency virus; CBC, complete blood count.

cortical margins, remineralization, and revisualization of bony trabeculae. Wang et al. [16] and Nene et al. [17] considered composite clinical, laboratory, and radiological factors (plain radiography, CT, and MRI) in declaring the disease of a patient as healed. The signs of resolution on CT were similar to those on plain radiographs. The MRI criteria they used were decreased bone marrow edema, decreased soft tissue collections, decreased subligamentous spread, and fatty replacement of the marrow seen as hyperintensity on T1 and T2-weighted images and/or lack of contrast enhancement on post-gadolinium MRI. Banga et al. [49] only considered radiological resolution (plain radiography and MRI) in declaring a patient healed and did not discuss whether they also considered clinical improvement. The detailed criteria used in the individual studies are shown in Table 3 [16,17,46-49,52,53].

2) Characteristics of the participants

A total of 1,038 patients were enrolled in the six studies. Demographic and important clinical data of these six studies are summarized in Table 4 [16,17,46-49,52,53]. A total of 158 patients were excluded from the MRC studies during the analysis of healing at the final follow-up due to various reasons, such as change in the diagnosis during surgery due to growth of pyogenic organism on culture of operative specimen, absence of evidence of tuberculous lesion during surgery, healed spinal lesion during surgery, modification of chemotherapy due to toxicity, treatment default or loss of follow-up, and death due to mostly non-tuberculous causes. Three patients from the study by Banga et al. [49] were excluded due to loss of follow-up. All patients in the two remaining studies completed the required follow-up. The MRC studies did not specify the average age and sex distribution in their patients; however, almost half of patients included in these three MRC trials were aged <15 years. The age and sex distribution of the three remaining studies are demonstrated in Table 4.

Most patients had tuberculous lesion in the lumbar and lumbosacral spine (n=392), followed by those in the thoracic spine (n=288), thoracolumbar spine (n=162), cervical spine (n=17), cervicothoracic spine (n=10), multifocal (n=7), and sacral spine (n=1). In the MRC trials, no patient had severe paraplegia, but 53 patients had some neurological deficit at admission. Moreover, 54 patients in the trial by Wang et al. [16] and 27 patients in the trial by Nene et al. [17] had some form of neurological deficit. Although the presence of drug resistance was an exclu-

Table 4. Demographic and relevant clinical data of the six studies included in the review

Study	Sample size at enrolment	Age	Gender	Area of the spine affected	Neurologic deficit	Drug resistance
MRC [46] (1986), [52] (1999)	60	<15 yr (13); 15–54 yr (28); ≥55 yr (9)	Not specified	Thoracic (18), thoracolumbar (4), lumbar/lumbosacral (28)	3	6 of the 43 patients' operative samples tested were resistant for 1 drug
MRC [47] (1993)	359	0–4 yr (78); 5–14 yr (68); 15–34 yr (76); 35–54 yr (40); ≥55 yr (3)	Not specified	Thoracic (94), thoracolumbar (58), lumbar (78), lumbosacral (35)	33	Not mentioned
MRC [48] (1989), [52] (1999), Reetha et al. [53] (1994)	304	<15 yr (84); 15–54 yr (158); ≥55 yr (8)	Not specified	Thoracic (93), thoracolumbar (33), lumbar and lumbosacral (124)	17	Not mentioned
Wang et al. [16] (2013)	185	USCC group: 37.96±16.30 yr; StdCC group: 41.53±15.76 yr	USCC (M=54, F=42); StdCC (M=50, F=39)	Cervical (7), cervicothoracic (3), thoracic (38), thoracolumbar (42), lumbar (72), lumbosacral (23)	54 (30/96 and 24/89)	5 Cases of MDR TB
Banga et al. [49] (2018)	30	0–20 yr (3); 21–40 yr (14); >40 yr (10)	M (15), F (12)	Cervical (2), thoracic (14), thoracolumbar (3), lumbar (8)	None were included	None (excluded if known)
Nene et al. [17] (2019)	100	SCC group: 36.5 yr (range, 12–71 yr); StdCC group: 52 yr (range, 16–91 yr)	SCC (M=26, F=26); StdCC (M=23, F=25)	Cervical (8), cervicothoracic (7), thoracic (31), thoracolumbar (22), lumbar (21), lumbosacral (3), sacral (1), multifocal (7)	27/100	None (excluded if known)

MRC, Medical Research Council; USCC, ultra-short-course chemotherapy; StdCC, standard-course chemotherapy; M, male; F, female; MDR TB, multi-drug resistant tuberculosis; SCC, short-course chemotherapy.

sion criterion in all these studies, in the MRC 1986 trial in Hong Kong, the operative samples in six of 43 patients were resistant to one of the drugs, and five patients in the study by Wang et al. [16] were found to have MDR on samples obtained during surgery.

3) Results of individual studies

All six studies used different regimens of ATT, with at least isoniazid and rifampicin/ethambutol in all these regimens. The duration of ATT varied from as short as 4 to 18 months [16,47]. All drugs were administered orally, except streptomycin, which was administered via the intramuscular route. All cohorts received ATT dosage according to patients' weight. Intermittent regimen (thrice weekly) was administered in only one study in the intervention group (6-month directly observed therapy short course) [49]. All other studies provided daily regimen. The regimens used, duration in their respective cohorts, number of individuals in each group assessed at the final follow-up, and number of patients declared to have disease resolution at that time, with their follow-up duration, are presented in Table 5 [16,17,46-49,52,53]. Surgical intervention was conducted in all patients in the MRC 1986

trial (n=50) and trial by Wang et al. [16] (n=185) and in the Rad 6 group of the MRC 1989 trial (n=82); no patient underwent surgery in the MRC 1993 trial; and only those patients with surgical indications underwent surgery with or without spinal instrumentation in the studies by Banga et al. [49] (n=unspecified) and Nene et al. [17] (n=46). No patient in any of the six trials had disease relapse till their final follow-up. The mean follow-up duration varied from 15 to 87 months across the studies.

All cohorts in the six studies reported reasonable healing rates except one [47]. Only the results of MRC 1993 (specifically the 9H+P/E regimen) were clearly inferior compared to all other cohorts of the included studies. In the meta-analysis, cohorts receiving 6-month regimen in each trial were pooled into the “intervention” arm, and cohorts in all trials receiving ATT for 9–18 months were pooled into the “control” arm. The trial by Nene et al. [17] reported a 100% healing rate in both groups, that is, no unfavorable outcome (no events in both groups). Therefore, it had no (i.e., zero) weight in the pooled analysis and was excluded from the forest plot. The analysis was conducted based on the healing rate in patients assessed at the final follow-up. Moreover, 90.58% (375/414) of pa-

Table 5. ATT regimens used, duration of administration, number of people in each group at final follow-up, healing rate with the follow-up duration of the studies included in the review

Study	Regimen used	Duration of ATT	Surgery done	No. at completion	Healing status	Healing rate	Follow-up duration	Relapse rate on follow-up
MRC [46] (1986), [52] (1999)	6 HRS 6HR+3HR (with S twice weekly for 1st 6 mo)	6 mo 9 mo	All patients had modified Hong Kong operation (n=50)	24 26	23/24 25/26	95.8% 96.2%	5 yr	None
MRC [47] (1993)	6HR 9HR 9H+P/E 18H+P/E	6 mo 9 mo 9 mo 18 mo	None	65 71 62 67	53/65 53/71 45/62 18H+P/E=53/67	81.54% (53/65) 75.50% (151/200)	3 yr	None
MRC [48] (1989), [52] (1999), Reetha et al. [53] (1994)	Rad 6=6 HR+Hong Kong surgery Amb6=6HR Amb 9=9HR	6 mo 6 mo 9 mo	Hong Kong operation in Rad 6 group (n=82)	82 82 86	72/82 75/82 84/86	87.8% 91.5% 97.7%	5 yr	None
Wang et al. [16] (2013)	USCC=2SHRZ+HRZ (2-4; average 2.5 mo) StdCC=2SHRZ+7HRZ	4-6 mo (average, 4.5 mo) 9 mo	Radical debridement, bone grafting, and anterior or posterior instrumentation (n=185)	96 89	88/96 83/89	91.67% 93.26%	At least 5 yr (average, 69.1 mo; range, 61-87 mo)	Not specified
Banga et al. [49] (2018)	DOTS: 2HRZE+4HR 3 times a week Daily regimen: 3HRZE+9HR daily	6 mo 12 mo	Only those with progressive neurologic deficit or appearance of deficit after 3 weeks of antitubercular therapy were operated	13 14	12/13 13/14	92.31% 92.86%	15 mo	None
Nene et al. [17] (2019)	SCC: 2HRZE+4HR (E continued if sensitivity of H was unknown) StdCC: 2HRZE+10HR (E continued if sensitivity of H was unknown)	6 mo 12 mo	Only those patients with progressive neurologic deficit, severe mechanical back pain, and those with spine at risk signs, were operated on (18/52 vs. 28/48).	52 48	52 48	100% 100%	Minimum 2 yr (average, 52 mo; range, 26-78 mo)	None

ATT, anti-tubercular therapy; MRC, Medical Research Council; H, isoniazid; R, rifampicin; S, streptomycin; Z, pyrazinamide; P, PAS; E, ethambutol; USCC, ultra-short-course chemotherapy; StdCC, standard course chemotherapy; SCC, short-course chemotherapy.

Table 6. Healing status at final follow-up

No.	Study	Country	Short course chemotherapy			Conventional chemotherapy			Relative risk
			No.	Improved	Risk	No.	Improved	Risk	
1	MRC [52] (1999)	Hong Kong	24	23	0.96	26	25	0.96	1.00
2	MRC [47] (1993)	Korea	65	53	0.82	200	151	0.75	1.08
3	MRC [52] (1999), Reetha et al. [53] (1994)	India	164	147	0.90	86	84	0.98	0.92
4	Wang et al. [16] (2013)	China	96	88	0.92	89	83	0.93	0.98
5	Banga et al. [49] (2018)	India	13	12	0.92	14	13	0.93	0.99
6	Nene et al. [17] (2019)	India	52	52	1.00	48	48	1.00	1.00
Total			414	375	-	463	404	-	-

MRC, Medical Research Council.

Fig. 2. Forest plot of the relative risk (RR) of successful outcome with 6 months regimen and more than 6 months regimen. The center of the squares and the horizontal line represent estimated RR and 95% confidence interval (CI) of each included study respectively. The diamond represents the summary RR and 95% CI. Heterogeneity and overall effect are given on the left side of the summary statistics. Weights are from random effects analysis. I^2 =percentage of total variation across the studies that is the result of heterogeneity rather than chance.

Fig. 3. Funnel plot for outcomes among followed-up patients. RR, relative risk; SE, standard error.

tients who received 6 months of ATT had healed status at their final follow-up compared to 87.26% (404/463) of patients who received ≥ 9 months of ATT (Table 6) [16,17,47,49,52,53].

Overall, the healed status of spinal TB was equivalent among patients in both 6 months and >6 months group (pooled relative risk [RR], 0.98; 95% CI, 0.92–1.04; test of $RR=1$, $z=0.77$, $p=0.439$) (Figs. 2, 3) [16,17,47,49,52]. There was a considerable heterogeneity among the trials ($I^2=40.8\%$), which was not statistically significant (heterogeneity chi-square=6.76; degrees of freedom=4; $p=0.149$). The test of heterogeneity is poor at detecting true heterogeneity in meta-analyses such as this one, which includes a small number of studies. Therefore, the power of the test in such circumstances is low [54]. Because the test of heterogeneity, in this case, is poor in detecting true heterogeneity, a nonsignificant p -value should not be taken as evidence of homogeneity [55].

Discussion

Over the past few decades, antitubercular chemotherapy

has emerged as the cornerstone in the management of spinal TB. With successful outcomes being demonstrated by ambulatory chemotherapy, the indications for surgical intervention in spinal TB have decreased; for most surgeons, these indications include severe paraplegia at presentation, progressive neurological deficit while on treatment, progressive deformity, persistent back pain due to mechanical instability, and lack of clinical response to chemotherapy. Chemotherapy alone for the treatment of spinal TB has several advantages, including ambulatory treatment, avoidance of hospital stay, avoidance of morbidity related to surgery, and cost-effectiveness. The developed and developing countries are at dramatically different stages in their fight against TB, which has led to a difference in the priority given to TB as a public health problem by different countries. Due to this relative lack of large, multicenter studies, there is a lack of consensus about the appropriate duration of administration of ATT in spinal TB.

There is a wide variation in the duration of ATT advocated for spinal TB by the guidelines of various national and international societies. This ranges from 6 to 18 months. The British MRC guidelines suggest multi-drug combination chemotherapy for 6–9 months for the treatment of TB of the dorsolumbar spine [56]. The limitations of the research council's studies were the exclusion of patients with multiple vertebral involvement, TB of the cervical spine, and major neurologic deficit. The National Institute for Health and Care Excellence guidelines and the WHO recommend 6 months and 9 months of treatment, respectively, for spinal TB [57,58]. Similarly, the American and the Canadian Thoracic Societies recommend 6–9 months and 9–12 months of treatment, respectively [58,59]. While there is a certain amount of discrepancy even in these standard guidelines (range, 6 to 12 months), all these guidelines are from developed countries with low disease burden. In developing countries, there are still no national consensus guidelines that specifically mention the treatment duration for spinal TB. In addition to spine surgeons (orthopedicians or neurosurgeons), spinal TB in these high-burden countries is also commonly treated by physicians, infectious disease specialists, or pulmonologists. This results in great heterogeneity in treatment, leading to lack of standardization of treatment duration at the national and international levels. The common practice of continuing treatment until completion of radiological healing may be unnecessary—since radiological

healing has been believed to lag behind clinical response [60]. The long track record of short-course chemotherapy in pulmonary TB and its recently reported success in several forms of EPTB have led to the emergence of calls for short-course regimens to be investigated for spinal TB.

In a bid to compile the understanding that can be gleaned from existing evidence, we performed a meta-analysis of all prospective RCTs comparing short-course antitubercular chemotherapy with treatment regimens of longer durations, which met our well-defined inclusion criteria. Our meta-analysis shows that 6-month regimen of ATT is equivalent to the standard 9–18-month regimen in terms of clinical and radiological disease resolution, although there was considerable heterogeneity among the trials. In these studies, clinical and radiological resolution were used to determine the endpoint of treatment. There have been systematic reviews and meta-analyses in the literature that have compared chemotherapy alone to chemotherapy with surgical intervention in spinal TB [26,44]. Moreover, van Loenhout-Rooyackers et al. [61] performed a literature review in 2002 that evaluated whether 6 months of ATT was good enough to prevent relapse as effectively as more than 6 months of ATT in spinal TB. To the best of our knowledge, this is the first meta-analysis that compared the effectiveness of 6-month regimen of ATT with the standard 9–18-month regimen in spinal TB.

There are some limitations to this review. First, there was a paucity of literature comparing the shorter courses with the longer duration of ATT. Importantly, high-quality RCTs were lacking in this area. This was a reason that only six studies were included in our review. Second, the follow-up data reported in the MRC 1999 publication for the MRC 1993 (Korea) trial were inadequate. Third, MRC trials were performed nearly 4 decades ago. Therefore, the current clinical relevance of these trials is difficult to determine, given the advances in management with four-drug ATT and surgery for spinal TB. Fourth, there was considerable heterogeneity in the presentation of results across the studies, including a lack of reporting of sex distribution in the MRC trials. Lastly, there is a gap in the timeline between the selected studies: the MRC trials were conducted in the 1970s and 1980s, while the three remaining studies were conducted within the last decade. This led to a discrepancy in the healing criteria between these two different groups of studies, as the MRC trials were conducted in the pre-MRI era and thus the resolution of disease activity and relapses could not be assessed

by MRI in patients included in these trials, which form the majority of the sample size of our review. The co-interventions were dissimilar in some comparative groups as surgery was more commonly offered to patients receiving shorter duration of chemotherapy (317 of 414 patients in the 6-month course group were routinely offered radical debridement surgery), which may have been a confounding factor, leading to better results with shorter course of ATT as the reduction of disease burden during surgery for spinal TB is believed to promote early radiological fusion and quick relief of symptoms in patients. However, evidence suggests that routine surgery in addition to chemotherapy does not necessarily improve the prognosis of patients with spinal TB [26]. Nevertheless, we still divided the cohorts in the six studies into two groups and did a comparison in the healing rate between them.

Conclusions

The six trials comparing short-course treatment regimens (6 months) to longer regimens (≥ 9 months) show no significant difference in the healing or disease resolution. However, a considerable number of patients receiving 6-month regimen underwent routine surgery, which could be a major confounding factor. This study echoes the widely recognized principle of medical treatment being the first-line management for spinal TB. The existing evidence from the studies included in this meta-analysis—although not without its limitations—suggests that the use of short-course (6 months) chemotherapy may be considered for the treatment of spinal TB in view of the similarity in the healing response achieved compared to treatment regimens of longer duration. If a shorter course of antitubercular chemotherapy could be adopted in clinical practice for spinal TB, it would contribute to improved patient compliance, decrease the cost, and minimize the side effects of these medications. However, we emphasize the need to be watchful for disease relapse until definitive conclusions can be drawn based on more prospective RCTs recruiting a larger study population.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Author Contributions

Conception and design: AA, BG, NM, VG; intellectual content: AA, BG, NM; literature search: AA, BG, NM, SS; data acquisition: AA, SS; data analysis and interpretation: AA, NM, SS, VG; manuscript writing: AA; manuscript preparation: BG; manuscript editing and review: AA, BG, NM, SS, VG; statistical analysis: VG; and approval of final manuscript and agree to be accountable for all aspects of work: all authors.

References

1. World Health Organization. Global tuberculosis report 2019 [Internet]. Geneva: World Health Organization; 2019 [cited 2021 Jan 22]. Available from: <https://apps.who.int/iris/bitstream/handle/10665/329368/9789241565714-eng.pdf>.
2. World Health Organization, Regional Office for South-East Asia. Tuberculosis control in the South-East Asia region: annual report 2016 [Internet]. Geneva: World Health Organization; 2016 [cited 2021 Jan 22]. Available from: <https://apps.who.int/iris/handle/10665/205286>.
3. Teo HE, Peh WC. Skeletal tuberculosis in children. *Pediatr Radiol* 2004;34:853-60.
4. Polley P, Dunn R. Noncontiguous spinal tuberculosis: incidence and management. *Eur Spine J* 2009;18:1096-101.
5. Zumla A, Nahid P, Cole ST. Advances in the development of new tuberculosis drugs and treatment regimens. *Nat Rev Drug Discov* 2013;12:388-404.
6. Ge Z, Wang Z, Wei M. Measurement of the concentration of three antituberculosis drugs in the focus of spinal tuberculosis. *Eur Spine J* 2008;17:1482-7.
7. Novaes RD, Teixeira AL, de Miranda AS. Oxidative stress in microbial diseases: pathogen, host, and therapeutics. *Oxid Med Cell Longev* 2019;2019:8159562.
8. Tuli SM. Tuberculosis of the spine: a historical review. *Clin Orthop Relat Res* 2007;460:29-38.
9. Jain AK. Tuberculosis of the spine: a fresh look at an old disease. *J Bone Joint Surg Br* 2010;92:905-13.
10. Nene A, Bhojraj S. Results of nonsurgical treatment of thoracic spinal tuberculosis in adults. *Spine J* 2005;5:79-84.
11. Singh R, Magu NK, Rohilla RK. Clinicoradiologic profile of involvement and healing in tuberculosis of

- the spine. *Ann Med Health Sci Res* 2016;6:311-27.
12. Andronikou S, Jadwat S, Douis H. Patterns of disease on MRI in 53 children with tuberculous spondylitis and the role of gadolinium. *Pediatr Radiol* 2002;32:798-805.
 13. Mittal S, Jain AK, Chakraborti KL, Aggarwal AN, Upreti L, Bhayana H. Evaluation of healed status in tuberculosis of spine by fluorodeoxyglucose-positron emission tomography/computed tomography and contrast magnetic resonance imaging. *Indian J Orthop* 2019;53:160-8.
 14. Jullien S, Jain S, Ryan H, Ahuja V. Six-month therapy for abdominal tuberculosis. *Cochrane Database Syst Rev* 2016;11:CD012163.
 15. Jullien S, Ryan H, Modi M, Bhatia R. Six months therapy for tuberculous meningitis. *Cochrane Database Syst Rev* 2016;9:CD012091.
 16. Wang Z, Shi J, Geng G, Qiu H. Ultra-short-course chemotherapy for spinal tuberculosis: five years of observation. *Eur Spine J* 2013;22:274-81.
 17. Nene AM, Patil S, Kathare AP, Nagad P, Nene A, Kapadia F. Six versus 12 months of anti tubercular therapy in patients with biopsy proven spinal tuberculosis: a single center, open labeled, prospective randomized clinical trial-a pilot study. *Spine (Phila Pa 1976)* 2019;44:E1-6.
 18. Aryal A, Garg B. Duration of anti-tubercular chemotherapy in Pott's spine: a systematic review: PROSPERO 2020 CRD42020200938 [Internet]. London: National Institute for Health Research; 2020 [cited 2021 Jan 22]. Available from: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=200938.
 19. Abbas A, Rizvi SR, Mahesri M, Salahuddin HR. Conservative management of spinal tuberculosis: initial series from Pakistan. *Asian Spine J* 2013;7:73-80.
 20. Bakhsh A. Medical management of spinal tuberculosis: an experience from Pakistan. *Spine (Phila Pa 1976)* 2010;35:E787-91.
 21. Batirel A, Erdem H, Sengoz G, et al. The course of spinal tuberculosis (Pott disease): results of the multinational, multicentre Backbone-2 study. *Clin Microbiol Infect* 2015;21:P1008.
 22. Bodapati PC, Vemula RC, Mohammad AA, Mohan A. Outcome and management of spinal tuberculosis according to severity at a tertiary referral center. *Asian J Neurosurg* 2017;12:441-6.
 23. Cao G, Rao J, Cai Y, et al. Analysis of treatment and prognosis of 863 patients with spinal tuberculosis in Guizhou province. *Biomed Res Int* 2018;2018:3265735.
 24. Guo LX, Ma YZ, Chen X, Bao D, Luo XB. Clinical study of short-course chemotherapy combined with radical operation in retreating spinal tuberculosis. *Zhongguo Gu Shang* 2010;23:491-4.
 25. Jain AK, Srivastava A, Saini NS, Dhammi IK, Sreenivasan R, Kumar S. Efficacy of extended DOTS category I chemotherapy in spinal tuberculosis based on MRI-based healed status. *Indian J Orthop* 2012;46:633-9.
 26. Jutte PC, van Loenhout-Rooyackers JH. Routine surgery in addition to chemotherapy for treating spinal tuberculosis. *Cochrane Database Syst Rev* 2006;(1):CD004532.
 27. Karaeminogullari O, Aydinli U, Ozerdemoglu R, Ozturk C. Tuberculosis of the lumbar spine: outcomes after combined treatment of two-drug therapy and surgery. *Orthopedics* 2007;30:55-9.
 28. Kotil K, Alan MS, Bilge T. Medical management of Pott disease in the thoracic and lumbar spine: a prospective clinical study. *J Neurosurg Spine* 2007;6:222-8.
 29. Moon MS, Kim I, Woo YK, Park YO. Conservative treatment of tuberculosis of the thoracic and lumbar spine in adults and children. *Int Orthop* 1987;11:315-22.
 30. Walker AS. A 15-year assessment of controlled trials of the management of tuberculosis of the spine in Korea and Hong Kong: thirteenth report of the Medical Research Council Working Party on Tuberculosis of the Spine. *J Bone Joint Surg Br* 1998;80:456-62.
 31. Niu N, Wang Q, Shi J, et al. Clinical and genomic responses to ultra-short course chemotherapy in spinal tuberculosis. *Exp Ther Med* 2017;13:1681-8.
 32. Parthasarathy R, Sriram K, Santha T, Prabhakar R, Somasundaram PR, Sivasubramanian S. Short-course chemotherapy for tuberculosis of the spine: a comparison between ambulant treatment and radical surgery: ten-year report. *J Bone Joint Surg Br* 1999;81:464-71.
 33. Patankar AP. Tuberculosis of spine: an experience of 30 cases over two years. *Asian J Neurosurg* 2016;11:226-31.
 34. Patil SS, Mohite S, Varma R, Bhojraj SY, Nene AM. Non-surgical management of cord compression in tuberculosis: a series of surprises. *Asian Spine J* 2014;8:315-21.

35. Qian J, Rijiepu A, Zhu B, Tian D, Chen L, Jing J. Outcomes of radical debridement versus no debridement for the treatment of thoracic and lumbar spinal tuberculosis. *Int Orthop* 2016;40:2081-8.
36. Rajasekaran S, Shanmugasundaram TK, Prabhakar R, Dheenadhayalan J, Shetty AP, Shetty DK. Tuberculous lesions of the lumbosacral region: a 15-year follow-up of patients treated by ambulant chemotherapy. *Spine (Phila Pa 1976)* 1998;23:1163-7.
37. Rajeswari R, Balasubramanian R, Venkatesan P, et al. Short-course chemotherapy in the treatment of Pott's paraplegia: report on five year follow-up. *Int J Tuberc Lung Dis* 1997;1:152-8.
38. Upadhyay SS, Saji MJ, Yau AC. Duration of antituberculosis chemotherapy in conjunction with radical surgery in the management of spinal tuberculosis. *Spine (Phila Pa 1976)* 1996;21:1898-903.
39. Valsalan R, Purushothaman R, Raveendran M, Zacharia B, Surendran S. Efficacy of directly observed treatment short-course intermittent regimen in spinal tuberculosis. *Indian J Orthop* 2012;46:138-44.
40. Wang Z, Ge Z, Jin W, et al. Treatment of spinal tuberculosis with ultrashort-course chemotherapy in conjunction with partial excision of pathologic vertebrae. *Spine J* 2007;7:671-81.
41. Wang XY, Luo CK, Li WW, et al. A practical therapeutic protocol for cervical tuberculosis. *Eur J Trauma Emerg Surg* 2013;39:93-9.
42. Wardak GM, Panezai H, Kakar RM. Efficacy of conservative management with anti tuberculosis treatment in patients with spinal tuberculosis. *Pak J Neurol Surg* 2014;18:156-61.
43. Wu QQ. Preliminary report of short-course tuberculosis of the spine. *Zhonghua Jie He He Hu Xi Za Zhi* 1990;13:160-1,191.
44. Zhang X, Ji J, Liu B. Management of spinal tuberculosis: a systematic review and meta-analysis. *J Int Med Res* 2013;41:1395-407.
45. Van Tulder M, Furlan A, Bombardier C, Bouter L; Editorial Board of the Cochrane Collaboration Back Review Group. Updated method guidelines for systematic reviews in the Cochrane collaboration back review group. *Spine (Phila Pa 1976)* 2003;28:1290-9.
46. A controlled trial of six-month and nine-month regimens of chemotherapy in patients undergoing radical surgery for tuberculosis of the spine in Hong Kong: tenth report of the Medical Research Council Working Party on Tuberculosis of the Spine. *Tubercle* 1986;67:243-59.
47. Controlled trial of short-course regimens of chemotherapy in the ambulatory treatment of spinal tuberculosis: results at three years of a study in Korea: twelfth report of the Medical Research Council Working Party on Tuberculosis of the Spine. *J Bone Joint Surg Br* 1993;75:240-8.
48. Indian Council of Medical Research; British Medical Research Council Working Party. A controlled trial of short-course regimens of chemotherapy in patients receiving ambulatory treatment or undergoing radical surgery for tuberculosis of the spine. *Indian J Tuberc* 1989;36:1-21.
49. Banga RK, Singh J, Dahuja A, Garg RS. Spinal tuberculosis: directly observed treatment and short course or daily anti tubercular therapy: are we over treating? *Open Orthop J* 2018;12:380-8.
50. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177-88.
51. Harris RJ, Deeks JJ, Altman DG, Bradburn MJ, Harbord RM, Sterne JA. Metan: fixed-and random-effects meta-analysis. *Stata J* 2008;8:3-28.
52. MRC Working Party on Tuberculosis of the Spine, Darbyshire J. Five-year assessment of controlled trials of short-course chemotherapy regimens of 6, 9 or 18 months' duration for spinal tuberculosis in patients ambulatory from the start or undergoing radical surgery: fourteenth report of the Medical Research Council Working Party on Tuberculosis of the Spine. *Int Orthop* 1999;23:73-81.
53. Reetha AM, Sivasubramanian S, Parthasarathy R, Somasundaram PR, Prabhakar R. Five-year findings of a comparison of ambulatory short course chemotherapy with radical surgery plus chemotherapy for tuberculosis of the spine in Madras. *Indian J Orthop* 1994;28:7-13.
54. Higgins J, Thompson S, Deeks J, Altman D. Statistical heterogeneity in systematic reviews of clinical trials: a critical appraisal of guidelines and practice. *J Health Serv Res Policy* 2002;7:51-61.
55. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557-60.
56. Kumar K. Spinal tuberculosis, natural history of disease, classifications and principles of management with historical perspective. *Eur J Orthop Surg Trau-*

matol 2016;26:551-8.

57. National Institute for Health and Care Excellence. Tuberculosis: NICE guidance: recommendations [Internet]. London: National Institute for Health and Care Excellence; 2016 [cited 2021 Feb 5]. Available from: <https://www.nice.org.uk/guidance/ng33/chapter/recommendations>.
58. Saeed K, Esposito S, Ascione T, et al. Hot topics on vertebral osteomyelitis from the International Society of Antimicrobial Chemotherapy. *Int J Antimicrob Agents* 2019;54:125-33.
59. Fisher D, Elwood K. Nonrespiratory tuberculosis. In: Fisher D, Elwood K, editors. *Canadian tuberculosis standards 7th edition*: 2014 [Internet]. Ottawa: Canadian Thoracic Society, Canadian Lung Association, Public Health Agency of Canada; 2014 [cited 2021 Feb 5]. Available from: <https://www.canada.ca/en/public-health/services/infectious-diseases/canadian-tuberculosis-standards-7th-edition/edition-19.html>.
60. Tins BJ, Cassar-Pullicino VN, Lalam RK. Magnetic resonance imaging of spinal infection. *Top Magn Reson Imaging* 2007;18:213-22.
61. Van Loenhout-Rooyackers JH, Verbeek AL, Jutte PC. Chemotherapeutic treatment for spinal tuberculosis. *Int J Tuberc Lung Dis* 2002;6:259-65.