Treatment of tuberculosis and optimal dosing schedules

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ABSTRACT

Intermittent tuberculosis treatment regimens have been developed to facilitate treatment supervision. Their efficacy has been substantiated by clinical trials and tuberculosis control programmes, notwithstanding the lack of head-to-head comparison between daily and intermittent regimens. Recently, there has been opposing evidence from observational studies, pharmacokinetic-pharmacodynamic studies and animal models that intermittent treatment increases the risk of relapse, treatment failure or acquired rifamycin resistance, especially among HIV-infected patients. Systematic reviews have been conflicting. PubMed, Ovid MEDLINE and EMBASE were systematically searched for publications in English to evaluate the evidence about dosing schedules and treatment efficacy. Levels of evidence and grades of recommendation were assigned largely according to clinical evidence with reference to the Scottish Intercollegiate Guidelines Network guideline development handbook. A total of 32 articles were included after excluding 331 ineligible articles, 42 non-analytical studies, 22 narrative reviews or expert opinions and 44 articles embedded in systematic reviews. These included 9 systematic reviews, 8 controlled studies, 9 pharmacokinetic-pharmacodynamic studies, 5 mouse studies and 1 article about guinea pig experiments. Findings suggest high levels of evidence for using daily dosing schedules, especially during the initial phase in the presence of cavitation, isoniazid resistance and advanced HIV co-infection, to reduce the risk of treatment failure, recurrence and acquired drug resistance including acquired rifamycin resistance. This review justifies the use of daily schedules in standard tuberculosis treatment regimens (particularly in the initial phase), corroborates prevailing understanding of pharmacokinetics-pharmacodynamics and mycobacterial persisters, and supports exploration of rifapentine-containing regimens in higher dosages and frequency.

INTRODUCTION

Tuberculosis (TB) is an old infectious disease. Despite the availability of chemotherapy against the tubercle bacillus, our battle with this old human enemy is still far from over. With the rather unusual biological characteristics of this pathogen,[1] the disease shows a distinctive natural history[2 3] and a very slow response to existing chemotherapeutic agents.[1 4 5] Poor treatment adherence, acquired drug resistance, treatment failure and relapse have been encountered since the early days of chemotherapy.[6] A series of landmark trials in Madras (now Chennai),[7 8] Africa, Hong Kong and Singapore helped to establish the currently adopted 6-month standard regimens given under supervision.[9] These studies laid the foundation for the global comprehensive strategy for TB control known as directly observed treatment, short-course (DOTS), which was promulgated in 1993 by the World Health Organization (WHO) alongside a declaration of TB as a global emergency.[10] Despite some recent controversies over the exact role of the act of directly observed treatment (DOT),[11–13] no alternative method of drug administration has been conclusively shown to offer a similarly high rate of treatment success as that demonstrated by DOTS under functional programme settings.[14–16]

Intermittent drug delivery either throughout the entire 6-month course or only during the continuation phase in the last 4 months has been widely adopted to facilitate treatment supervision on an outpatient basis ever since the introduction of DOTS.[17] The lower number of treatment visits helps to reduce both operational and patient-related costs, especially if long travelling distances are involved. As intermittent treatment poses lesser interference on usual lifestyles, patients can carry on their regular daily activities and work. This helps to promote access to care and treatment adherence by patients, especially in resource-limited areas or for underprivileged segments of populations.

In vitro demonstration of the post-antibiotic effect (PAE) has provided the scientific basis for intermittent TB treatment in clinical settings by showing that exposure to drugs, especially isoniazid, for a few hours resulted in suppression of mycobacterial growth for several days.[18–21] For rifampicin and possibly other TB drugs, free peak drug concentration to minimum inhibitory concentration (MIC) ratio best correlates with the PAE and suppression of resistance.[21] The PAE has also been suggested by animal studies. A series of guinea pig experiments have shown that, when the same total drug amount is given as a single dose or fractionated into multiple doses of different sizes, better efficacy is observed with high doses given at long intervals, especially for rifampicin and ethambutol.[22] This suggests concentration-dependent activity in the tested drug. Higher doses in murine models also demonstrated longer PAEs with the exception of rifampicin.[23] PAEs of TB drugs in humans were first demonstrated in non-rifampicin regimens in a randomised controlled clinical trial that compared twice-weekly isoniazid plus streptomycin and daily isoniazid plus para-aminosalicylic acid in the treatment of pulmonary TB,[24] and later in clinical trials of 6-month rifampicin- and isoniazid-containing regimens in the 1970s and 1980s.

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Standard 6-month intermittent regimens have been widely used in TB control programmes with good results.[25 26] Although the exact mechanisms are not fully understood, the PAE is thought to be commonly mediated via suppression of bacterial RNA or protein synthesis.[27]

However, a number of recent studies have challenged the orthodoxy of intermittent treatment. In order to facilitate the development of new TB drugs and regimens for successful implementation in TB control programmes based on DOTS, we conducted a systematic review to examine the seemingly controversial evidence about dosing intermittency and treatment efficacy across different subpopulations of patients. Measures of treatment efficacy included relapse or recurrence, treatment failure, cure, drug resistance and acquired rifamycin resistance.

METHODS

PubMed, Ovid MEDLINE and EMBASE were systematically searched through 2 June 2010 for publications in English using a search algorithm that combined the following keywords in Medical Subject Headings, titles, abstracts, or journal titles, as appropriate, with the help of Boolean operators ('and', 'or') and wildcards (*): (i) tuberculosis; (ii) relapse or recurrence; (iii) treatment and failure; (iv) resistance, and rifamycin, rifampin, rifampicin, rifabutin or rifapentine; (v) intermittent, interruption, once-weekly, twice-weekly, biweekly, three-times-weekly, thrice-weekly, once a week, twice a week, thrice a week, dosing schedule, or dosing frequency; (vi) systematic review or meta-analysis; (vii) Cochrane Database Systematic Review or Clinical Evidence; (viii) therapy, chemotherapy, treatment, rifamycin, rifampin, rifampicin, rifabutin, or rifapentine; and (ix) pharmacokinetics and pharmacodynamics. The search algorithm in PubMed is shown in appendix 1 in the online supplement. The above literature search was supplemented by a WHO reference.[28]

The literature search included clinical studies, in vitro studies, animal experiments, narrative reviews or expert opinion, with focus on systematic reviews and controlled clinical studies. Only analytical clinical studies that evaluated the relationship between dosing schedules and treatment efficacy of rifamycin-based regimens or non-analytical clinical studies involving rifamycin-based regimens given for at least 6 months were included. Non-analytical studies, expert opinions and narrative reviews were subsequently excluded when a clinical question could be sufficiently addressed by systematic reviews or controlled clinical studies. Levels of evidence and grades of recommendation were assigned largely according to clinical evidence with reference to the Scottish Intercollegiate Guidelines Network guideline development handbook[29] (see appendix 2 in the online supplement). Studies rated as having high risk of bias were not used for making recommendations. The risk of bias was judged as high when major potential confounders were not adjusted, low in the absence of quality assessment in systematic reviews or blind assessment when outcome was assessed by objective data, and not applicable for non-conclusive findings.

Studies of non-rifampicin regimens, irrelevant articles and those with no specific information about the impact of dosing schedules on treatment efficacy were excluded. Articles already embedded in systematic reviews were also excluded to reduce materials to a manageable size without losing essential information. Data were extracted by the first author (KCC) and checked by the co-authors for accuracy and interpretation. Disagreement was resolved by consensus.

RESULTS

The search algorithm initially identified 469 articles. A total of 331 articles were excluded for the following reasons: irrelevance (n=295), effect of dosing schedule on treatment efficacy not evaluated (n=23), rifampicin given for less than 6 months (n=12) and update within the same year (n=1). After further excluding 42 non-analytical studies, 22 narrative reviews or expert opinions and 44 articles already included in systematic reviews, and adding two articles[22 30] from a WHO reference,[28] a total of 32 articles were included in the current review (figure 1). These publications included nine systematic reviews with or without meta-analysis, eight controlled studies, nine pharmacokinetic-pharmacodynamic (PK-PD) studies, five studies of TB mouse models and one publication about guinea pig experiments. Studies included in the current review can be grouped under five categories: HIV-related TB, HIV-negative TB, TB with isoniazid resistance, childhood TB, and in vitro studies and animal experiments.

HIV-related TB

Table 1 shows three studies regarding the impact of dosing intermittency on treatment efficacy in HIV-related TB: one systematic review with meta-analysis and two retrospective cohort analyses. All suggest that intermittent treatment, especially in the initial phase, reduces treatment efficacy as shown

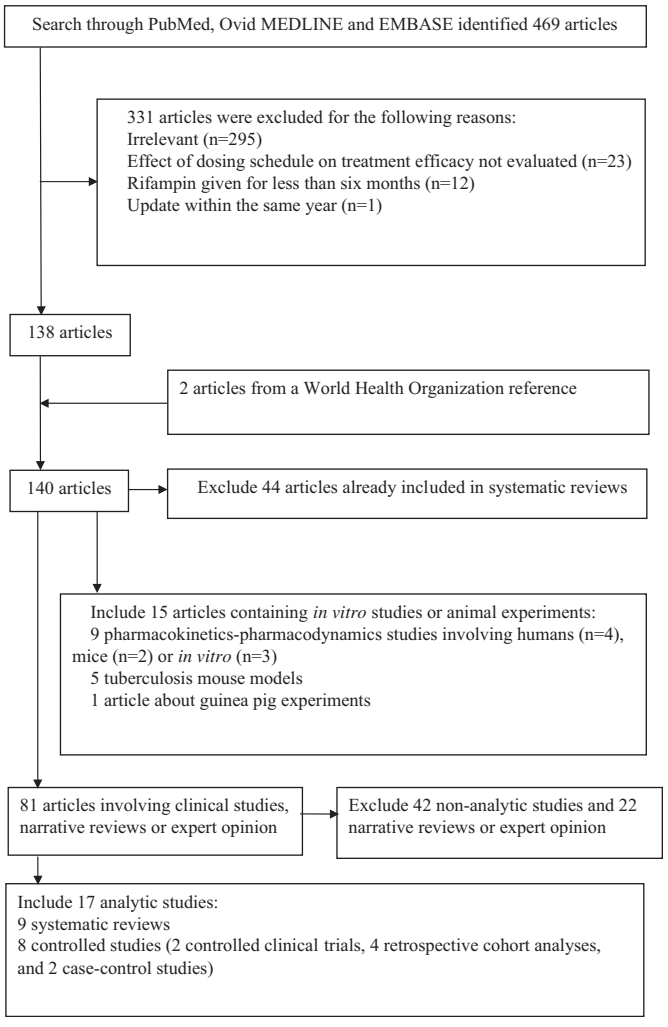

Figure 1 Flow diagram of reviewed articles.

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Table 1 Studies regarding impact of dosing intermittency on treatment efficacy in HIV-related tuberculosis

Authors, year of publication	Measures of treatment efficacy	Source of study materials	Study design	Main findings	Strengths	Weaknesses	Risk of bias
Khan *et al*, 2010[31]	Failure, relapse	Multiple countries	Systematic review and meta-analysis*	Compared with partially intermittent treatment with daily initial phase, thrice-weekly treatment throughout was associated with higher rates of failure (adjusted RR 4.0, 95% CI 1.5 to 10.4) and relapse (adjusted RR 4.8, 95% CI 1.8 to 12.8).	The study clearly addressed a focused question with good coverage on methodology and assessment of study quality. Literature search was sufficiently rigorous.	There was considerable heterogeneity across studies.	Low
Nahid *et al*, 2007[32]	Relapse	USA	Retrospective cohort analysis	Compared with daily treatment, intermittent treatment was associated with relapse (adjusted HR 4.12, 95% CI 1.09 to 15.6).	The study clearly addressed a focused question in a well-defined cohort with well-covered comparison between participants and those lost to follow-up. Outcomes were clearly defined with reliable assessment of exposure. Main potential confounders were considered. CIs were provided.	Assessment of outcome was not blind.	Low
Li *et al*, 2005[33]	Relapse, acquired rifamycin resistance	USA	Retrospective cohort analysis	Intermittent compared with daily treatment in the initial phase significantly increased the risk of relapse and acquired rifamycin resistance (HR for relapse 6.7, 95% CI 1.1 to 40.1; HR for acquired rifamycin resistance 6.4, 95% CI 1.1 to 38.4).	The study clearly addressed a focused question in a well-defined cohort. Outcomes were clearly defined, with reliable assessment of exposure. Main potential confounders were considered. CIs were provided.	Assessment of outcome was not blind. No comparison was made between participants and those lost to follow-up.	Low

*Articles identified by the literature search and included in systematic reviews identified by the current review are shown in appendix 3 in the online supplement.

by a higher risk of treatment failure, relapse or acquired rifamycin resistance. The level of evidence is 1+ and the grade of recommendation for avoiding dosing intermittency, especially in the initial phase in HIV-related TB, is A.

HIV-negative TB

Table 2 shows 11 studies regarding the impact of dosing intermittency on treatment efficacy in HIV-negative tuberculosis: six systematic reviews with or without meta-analysis, two controlled clinical trials, one retrospective cohort analysis and two case–control studies. The risk of bias was low for four, high for three and not applicable for four. Studies with a low risk of bias suggest that intermittent treatment reduces TB treatment efficacy as shown by a higher risk of relapse or treatment failure. The negative impact appears to be most prominent in the presence of initial cavitation.[34 35] A systematic review of standard 6-month regimens suggests no significant difference between daily treatment throughout and daily treatment in the initial phase.[35] Among studies with a high risk of bias, all except one suggest that dosing intermittency does not reduce treatment efficacy.

The level of evidence for a negative impact of dosing intermittency on TB treatment efficacy in HIV-negative TB is 1+ and the grade of recommendation for avoiding dosing intermittency, especially in the initial phase in the presence of cavitation, is A.

TB with isoniazid resistance

Table 3 shows two studies regarding the impact of dosing intermittency on treatment efficacy in TB with isoniazid resistance. Both suggest that dosing intermittency reduces TB treatment efficacy as shown by a higher risk of treatment failure, relapse or acquired drug resistance. The level of evidence is 1+ and the grade of recommendation for avoiding dosing intermittency, especially in the initial phase in the presence of isoniazid resistance, is A.

Childhood TB

Table 4 shows one study regarding the impact of dosing intermittency on treatment efficacy in childhood TB. It suggests that twice-weekly TB treatment may be less efficacious than daily treatment in achieving cure. The level of evidence is 1+ and the grade of recommendation for avoiding dosing intermittency in childhood TB is A.

In vitro studies and animal experiments

Table 5 shows 15 in vitro studies and animal experiments. All except two suggest that dosing intermittency may reduce treatment efficacy with internal consistency. PK-PD studies have substantiated the association between dosing intermittency and treatment efficacy by reaffirming that the classical pharmacodynamic parameter, which is the area under the concentration-time curve (AUC) to MIC ratio, best correlates with the bactericidal or sterilising effect of rifampicin[21 49] and pyrazinamide.[50] Such findings corroborate the significant association between AUC of rifabutin and failure or relapse in a clinical trial,[51] the treatment-shortening effect of rifapentine-based regimens in TB mouse models[52–54] and an increase in the risk of relapse[55] or treatment failure with acquired resistance to rifampicin or isoniazid following reduction in dosing frequency in TB mouse models.

DISCUSSION

The current review suggests high levels of evidence for using daily dosing schedules, especially in the initial phase, to reduce

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Table 2 Studies regarding impact of dosing intermittency on treatment efficacy in HIV-negative tuberculosis

Authors, year of publication	Measures of treatment efficacy	Source of study materials	Study design	Main findings†	Strengths	Weaknesses	Risk of bias
Chang *et al*, 2006[35]	Relapse	Multiple countries	Systematic review and meta-analysis*	A logistic risk model showed a significant dose-response relationship between dosing schedules and relapse, with the following odds (95% CI) of relapse relative to daily regimens: 1.6 (0.6 to 4.1) for daily initial phase (IP) + thrice-weekly continuation phase (CP), 2.8 (1.3 to 6.1) for daily IP + twice-weekly CP, 2.8 (1.4 to 5.7) for thrice-weekly, 5.0 (2.4 to 10.5) for daily IP + once-weekly rifapentine, and 7.1 (3.3 to 15.3) for thrice-weekly IP + once-weekly rifapentine. In the presence of cavitation, only 6 months daily or daily IP + thrice-weekly CP attained best estimated relapse risks below 5%.	The study clearly addressed a focused question with good coverage on methodology. Literature search was sufficiently rigorous. Studies were sufficiently similar to make combining them reasonable. Sensitivity analysis gave consistent findings.	Study quality was not addressed. A deterministic mathematical model was used for estimating treatment outcome in subgroups.	Low
Gao *et al*, 2009[36]	Relapse	USA, Canada, Hong Kong, China	Systematic review and meta-analysis*	Once- or twice-weekly rifapentine and daily rifampicin have similar efficacy for treating HIV-negative pulmonary TB. Once-weekly or less of rifapentine increases the risk of bacteriological relapse in comparison with twice- or thrice-weekly rifampicin (pooled relative risks were 2.44 (95% CI 1.15 to 5.18) and 1.71 (95% CI 1.13 to 2.58), respectively.	The study clearly addressed a focused question with good coverage on methodology and assessment of study quality. Literature search was sufficiently rigorous.	There was no evidence of heterogeneity by the chi square test of heterogeneity but degree of freedom was relatively small.	Low
Mwandumba *et al*, 2000, 2001[37 38]	Failure, relapse	Hong Kong	Systematic review*	With only one randomised controlled trial included, there were insufficient data for comparing treatment efficacy of fully intermittent and daily regimens.	A conventional approach was used.	Data were insufficient for drawing a conclusion.	NA
Cox *et al*, 2008[39]	Recurrence	Multiple countries	Systematic review*	Although several clinical trials may support the use of daily treatment regimens, studies reporting TB recurrence after intermittent regimens have been limited. Few studies under routine programmatic conditions have reported TB recurrence. Considerable heterogeneity across studies precluded attribution of TB recurrence to dosing schedules.	A conventional approach was used.	Data were insufficient for drawing a conclusion.	NA
Ziganshina *et al*, 2009[40]	Cure, relapse	Multiple countries	Systematic review*	It is uncertain whether intermittent treatment, taken 2 or 3 times a week, is more efficacious than daily treatment in enhancing cure rates or decreasing relapse rates of newly diagnosed TB.	A conventional approach was used.	Data were insufficient for drawing a conclusion.	NA
Menzies *et al*, 2009[41]	Failure, relapse	Multiple countries	Systematic review and meta-analysis*	Treatment outcomes (failure or relapse) for all intermittent schedules evaluated were similar to daily schedules, but there is insufficient evidence to support administration of treatment twice weekly throughout therapy.	The study clearly addressed a focused question with good coverage on methodology and assessment of study quality. Literature search was sufficiently rigorous.	Main potential confounders such as initial cavitation and 2-month culture status were not considered. Also, the inclusion of daily regimens with rifampicin given for <6 months might have introduced bias.	High

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Table 2 Continued

Authors, year of publication	Measures of treatment efficacy	Source of study materials	Study design	Main findings†	Strengths	Weaknesses	Risk of bias
Prasad *et al*, 2001[42]	Cure	India	Controlled clinical trial	Bacteriological response was comparable and favourable for 43 culture-proven TB patients allocated to 2HREZ/4HR (n=21) and $2HREZ_3/4HR_3$ (n=22) regardless of initial drug resistance (82.3% vs 100% without resistance, and both 100% with resistance).	The study clearly addressed a focused question.	Sample size was too small for drawing a conclusion.	NA
Alvarez *et al*, 2009[43]	Drug resistance	Brazil	Retrospective cohort analysis	No significant differences were found between partially intermittent treatment with daily initial phase (daily for one month, then thrice weekly) and daily treatment throughout among 5138 patients in terms of drug resistance rates.	The study clearly addressed a focused question in a well-defined cohort. Outcomes were clearly defined, with reliable assessment of exposure.	Main potential confounders were not considered. Assessment of outcome was not blind. CIs were not provided.	High
Chang *et al*, 2004[34]	Relapse	Hong Kong	Nested case–control study	Thrice-weekly treatment increased the risk of relapse in comparison with daily treatment (OR 3.92, 95% CI 1.78 to 8.63). For culture-proven pulmonary TB without cavitation, the 30 month relapse rate for standard thrice-weekly regimen was 1.1% (95% CI 0.6% to 2.0%). The corresponding rates in the presence of cavitation were 3.3% (95% CI 1.9% to 5.5%) for standard daily regimen, and 7.8% (95% CI 4.0% to 14.6%) for standard thrice-weekly regimen.	The study clearly addressed a focused question with cases and controls taken from the same cohort. Cases were clearly defined and differentiated from controls that were randomly selected from the cohort. Exposure status was ascertained in a standard way. Main potential confounders were considered. CIs were provided.	Assessment of outcome was not blind.	Low
Paramasivan *et al*, 1993[44]	Cure, acquired drug resistance	India	Non-randomised controlled clinical trial	Comparing $2HRZ_2+4HR_2$ versus $2HRZ+4HR_2$; culture-positive rates at the end of treatment were 19.6% and 8.1% overall, respectively, and 13.2% and 6.9% among initially drug-sensitive cases, respectively. The corresponding acquired drug resistance rates among initially drug-sensitive cases were 81.0% and 30.2%. All differences were statistically significant. Partially intermittent treatment with daily initial phase might be better than twice-weekly treatment throughout in terms of cure rate and acquired drug resistance rate.	The study clearly addressed a focused question.	Cases and controls might not be taken from comparable populations. Only 14.7% cases treated twice-weekly throughout and 41.2% treated daily in the initial phase were included in overall assessment, less for drug-sensitive cases. No comparison was made between participants and non-participants. Confounders were not considered. No CI was provided.	High
Singla *et al*, 2009[45]	Failure	India	Prospective case–control analysis	The number of treatment interruptions is an independent risk factor for treatment failure.	The study clearly addressed a focused question with cases and controls taken from comparable populations. Cases were clearly defined and differentiated from controls. Exposure status was ascertained in a standard way. Main potential confounders were considered. CIs were provided.	Acid-fast bacilli smear instead of culture was used to assess treatment outcome. Only 40% of those with positive smears at month 5 were culture-negative. It is uncertain whether factors associated with failure defined by smear are the same as those of failure defined by culture.	Low

*Articles identified by the literature search and included in systematic reviews identified by the current review are shown in appendix 3 in the online supplement.
†A number before and a suffix in subscript after a treatment regimen stands for the number of months and frequency per week, respectively.
H, isoniazid; NA, not applicable; R, rifampicin; TB, tuberculosis; Z, pyrazinamide.

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Table 3 Studies regarding impact of dosing intermittency on treatment efficacy in tuberculosis with isoniazid resistance

Authors, year of publication	Measures of treatment efficacy	Source of study materials	Study design	Main findings	Strengths	Weaknesses	Risk of bias
Menzies *et al*, 2009[46]	Failure, relapse, acquired drug resistance	Multiple countries	Systematic review and meta-analysis*	Among TB patients with initial mono-resistance to isoniazid, partially intermittent treatment with daily initial phase reduces the rates of failure, relapses and acquired drug resistance.	The study clearly addressed a focused question with good coverage on methodology and assessment of study quality. Literature search was sufficiently rigorous.	There was considerable heterogeneity across studies.	Low
Escalante *et al*, 2001[47]	Relapse	USA	Retrospective cohort analysis	Twice-weekly treatment was associated with relapse among subjects with resistance to isoniazid. Thrice-weekly and daily treatment showed similar efficacy.	The study clearly addressed a focused question in a well-defined cohort. Outcomes were clearly defined, with reliable assessment of exposure.	Assessment of outcome was not blind. No comparison was made between participants and non-participants. Main potential confounders were not considered. CIs were not provided.	High

*Articles identified by the literature search and included in systematic reviews identified by the current review are shown in appendix 3 in the online supplement.
TB, tuberculosis.

Table 4 Studies regarding impact of dosing intermittency on treatment efficacy in childhood tuberculosis

Authors, year of publication	Measures of treatment efficacy	Source of study materials	Study design	Main findings	Strengths	Weaknesses	Risk of bias
Menon *et al*, 2010[48]	Cure	India, South Africa, Turkey	Systematic review and meta-analysis*	By per protocol analysis, children treated intermittently were less likely to be cured than those treated daily (OR 0.27, 95% CI 0.14 to 0.51). By intention to treat analysis, findings were similar but statistically non-significant (OR 0.66, 95% CI 0.23 to 1.84). Twice-weekly TB treatment may be less efficacious than daily treatment in terms of cure rates for children.	The study clearly addressed a focused question with good coverage on methodology and assessment of study quality. Literature search was sufficiently rigorous. Statistical tests showed no evidence of significant heterogeneity.	Studies lacked uniformity in diagnosis and assessment of outcome.	Low

*Articles identified by the literature search and included in systematic reviews identified by the current review are shown in appendix 3 in the online supplement.
TB, tuberculosis.

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Table 5 In vitro or animal studies regarding impact of dosing intermittency on efficacy of tuberculosis treatment

Authors, year of publication	Measures of treatment efficacy	Source of study materials	Study design	Main findings	Likely impact of dosing intermittency on treatment efficacy of standard regimens
Weiner *et al*, 2005[51]	Acquired rifamycin resistance	USA	PK-PD study involving human subjects	Lower AUC (0—24) of rifabutin and perhaps AUC (0—12) of isoniazid were associated with failure or relapse with acquired rifamycin resistance in HIV-related TB treated with twice-weekly therapy.	Negative
Weiner *et al*, 2003[57]	Relapse	USA	PK study involving human subjects	Among HIV-negative patients given either H and R twice weekly or H and rifapentine once weekly in continuation phase, failure/relapse was associated with low H concentrations (AUC 0—12) rather than any rifamycin PK parameter. Dosing schedule of rifampicin appeared to be unrelated to relapse.	No
Goutelle *et al*, 2009[58]	Not applicable	France	Population PK model for rifampicin	Among 34 human volunteers given 600 mg rifampicin, the proportions of subjects achieving target values for C_{max}/MIC ratio and AUC (0—24)/MIC ratio in epithelial lining fluid were only 35.9% and 54.5%, respectively.	Negative
Gupta *et al*, 2008[59]	Not applicable	India	PK-PD studies in children	C_{max}, elimination half-life and clearance for pyrazinamide 15 and 25 mg/kg per day differed non-significantly. This might suggest a difference in AUC/MIC (and hence sterilizing activity) between daily and intermittent treatment regimens.	Negative with a caveat: the PAE of intermittent pyrazinamide may compensate for less sterilising activity due to lower AUC/MIC
Mitchison, 1979[22]	Not applicable	UK	Guinea pig experiments	When the same total drug amount is given as single dose or fractionated into multiple doses of different sizes, better efficacy is observed with high doses given at long intervals, especially for rifampicin and ethambutol.	Positive
Rosenthal *et al*, 2008[52]	Relapse	USA	TB mouse model	Mice with TB disease were treated daily or thrice-weekly with rifapentine, pyrazinamide, and either isoniazid or moxifloxacin. The duration of treatment necessary to achieve stable cure was 10 weeks for daily regimens and 12 weeks for thrice-weekly regimens, regardless of whether isoniazid or moxifloxacin was used. All mice receiving standard daily therapy with rifampicin, isoniazid, and pyrazinamide relapsed after 12 weeks of treatment.	Negative
Rosenthal *et al*, 2007[53]	Relapse	USA	TB mouse model	Replacing rifampicin with rifapentine and isoniazid with moxifloxacin dramatically increased the activity of the standard daily regimen. No relapse was observed after just 3 months of treatment with daily or thrice-weekly rifapentine- and moxifloxacin-containing regimens, whereas the standard daily regimen required 6 months to prevent relapse.	Negative
Rosenthal *et al*, 2006[54]	Relapse	USA	TB mouse model	Stable cure was achieved after 4 months of twice-weekly rifapentine (15 mg/kg or 20 mg/kg) plus isoniazid- or moxifloxacin-containing therapy, but only after 6 months of standard daily therapy (10 mg/kg). Twice-weekly rifapentine displayed more favourable pharmacodynamics than did daily rifampicin.	Negative

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Table 5 Continued

Authors, year of publication	Measures of treatment efficacy	Source of study materials	Study design	Main findings	Likely impact of dosing intermittency on treatment efficacy of standard regimens
Veziris *et al*, 2005[55]	Relapse	France	TB mouse model	Mice were treated with rifapentine, isoniazid and moxifloxacin given once a week during 5.5 months, preceded by 2 weeks of daily treatment with isoniazid, rifampicin, pyrazinamide, and moxifloxacin. When used at high dosages, such a regimen effectively achieved stable cure in mouse TB. The relapse rate increased from 0 to 11% when treatment was once-weekly throughout.	Negative
Daniel *et al*, 2000[56]	Treatment failure, acquired drug resistance	France	TB mouse model	Reducing dosing frequency in the initial phase from daily to twice-weekly increased the risk of treatment failure with emergence of resistance to rifampicin or isoniazid.	Negative
Jayaram *et al*, 2003[49]	Not applicable	India	PK-PD study in a murine aerosol infection model	Dose ranging and fractionation studies demonstrated that AUC (0—24)/MIC of rifampicin correlated best (r^2=0.95) with a reduction in bacterial counts, followed by C_{max}/MIC (r^2=0.86) and the time that the concentration remained above the MIC (r^2=0.44).	Negative
Jayaram *et al*, 2004[60]	Not applicable	India	PK-PD study in a murine aerosol infection model	Dose fractionation studies demonstrated that AUC (0—24)/MIC of isoniazid correlated best (r^2=0.83) with the bactericidal efficacy, followed by C_{max}/MIC (r^2=0.73).	Negative with a caveat: AUC/MIC of isoniazid is probably comparable for daily and intermittent regimens
Gumbo *et al*, 2009[50]		USA	In vitro PK-PD study	The sterilising effect of pyrazinamide was linked to AUC (0—24) to MIC ratio (r^2=0.80—0.90), with 90% of the maximal effect being achieved by a ratio of 209.08. Resistance suppression was associated with the percentage of time that the concentration persisted above the MIC (r^2=0.73—0.91).	Negative with a caveat: the PAE of intermittent pyrazinamide may compensate for less sterilising activity due to lower AUC/MIC
Gumbo *et al*, 2007[21]		USA	In vitro PK-PD model	The PAE of rifampicin lasted for at least 5.2 days and closely related to free C_{max} to MIC ratio (r^2=0.96). The microbial killing of rifampicin was linked to AUC (0—24) to MIC ratio, and suppression of resistance was associated with free C_{max} to MIC ratio.	Negative
Budha *et al*, 2009[61]	Not applicable	USA	In vitro PK-PD study	The time-kill data suggest that AUC (0—24)/MIC is the PK/PD index most explanatory of the antimicrobial effect of isoniazid.	Negative with a caveat: AUC/MIC of isoniazid is probably comparable for daily and intermittent regimens

AUC, area under the curve; C_{max}, peak serum concentration; H, isoniazid; MIC, minimum inhibitory concentration; PAE, post-antibiotic effect; PK-PD, pharmacokinetics-pharmacodynamics; R, rifampicin; TB, tuberculosis.

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the risk of treatment failure, recurrence and acquired drug resistance (including acquired rifamycin resistance, particularly in patients with advanced HIV infection). Compared with intermittent treatment throughout, daily treatment throughout significantly reduces the risk of relapse in the presence of initial cavitation[34 35] or HIV infection,[32] while daily treatment in the initial phase significantly reduces failure, relapse and acquired drug resistance rates among patients with HIV infection[31 33] or isoniazid-resistant strains.[46 47] Treatment with a daily initial phase followed by a thrice-weekly continuation phase is probably comparable to daily treatment throughout.[35] Inconclusive findings from systematic reviews[37–40] are largely due to insufficient head-to-head comparison of different schedules in controlled clinical trials, which has been provided by only one randomised controlled trial.[62 63] Negative findings from a systematic review and meta-analysis[41] may be partly attributable to lack of controlling for major confounders of relapse such as initial cavitation and 2-month sputum culture status,[34 64 65] and partly due to the inclusion of daily regimens containing no rifampicin in the continuation phase, such as isoniazid and ethambutol[66] or isoniazid and pyrazinamide.[67–69]

The available evidence suggests that the effect of dosing schedules on treatment efficacy is best harnessed in the initial phase rather than in the continuation phase. In fact, there has been in vitro evidence for a few decades that the more rapid the antibacterial effect, the less likely is the emergence of persisters and the lower is the risk of relapse.[70] It has been hypothesised that there are four subpopulations of tubercle bacilli: actively dividing bacteria, bacteria that divide slowly in an acidic microenvironment, semi-dormant persisters that are metabolically active in spurts, and dormant bacilli.[22] While rifampicin and pyrazinamide have appreciable sterilising activity,[71 72] rifampicin is the only first-line TB drug with putative activity against persisters, which are also characterised by phenotypic resistance to isoniazid. This hypothesis of mycobacterial subpopulations has been supplemented by a Yin-Yang model of reverters and persisters, which suggests a dynamic change between bacillary persisters and the other subpopulations during treatment of both TB disease and latent TB infection.[5] Thus, optimising bactericidal and sterilising effects of TB drugs in the initial phase can minimise the overall bacterial load from which persisters emerged. A smaller population of persisters, which are phenotypically resistant to isoniazid and virtually eradicated only by rifampicin, leads to a lower probability of selecting out rifampicin-resistant mutants (and hence acquired rifamycin resistance) that are inadequately contained by poor host immunity in advanced HIV infection.[73]

Several biological factors may explain why using daily dosing schedules of standard rifampicin regimens improves treatment efficacy. First, while it may be sufficient for drugs with prolonged PAEs to kill rapidly or slowly dividing bacteria that replicate periodically, intermittent treatment may be less efficacious against persisters with intermittent metabolic activity when dosing is asynchronous with the metabolic bursts. Increasing the frequency of dosing reduces the chance of asynchrony. Second, food–drug interaction with rifampicin may cause erratic absorption of rifampicin.[74] Lastly, protein binding may also reduce penetration of rifampicin into cavities, especially during the continuation phase when there is less inflammation and more fibrosis.[75] The maximum serum concentration of rifampicin is reduced to approximately 2 mg/l after food.[74] It has been shown that broth-determined MIC for rifampicin ranged from 0.06 to 0.25 mg/l.[76] Assuming that 80% of rifampicin in blood is bound to protein,[74] total plasma rifampicin levels of 0.3–1.25 mg/l can achieve broth-determined MIC. However, based on a peak serum rifampicin level of approximately 12 mg/l in patients treated with rifampicin 600 mg daily[74 77] and a peak sputum rifampicin level of approximately 6 mg/l at the same rifampicin dosage,[74 78] rifampicin levels in TB cavities may be about half of serum levels. More frequent dosing may compensate for less sterilising activity and shorter PAEs due to lower rifampicin levels in TB cavities.

It is perhaps important not to forget PAEs in the pursuit of optimal dosing schedules. Twice-weekly high-dose isoniazid is at least as efficacious as daily isoniazid.[24] Pyrazinamide 3 g thrice weekly, which is higher than the average dosage used in intermittent regimens, is more effective than 1.5 g once daily.[79] In a relatively small clinical trial involving thrice-weekly treatment of patients with predominantly isoniazid-resistant TB with rifampicin, ethambutol and pyrazinamide, the 2-year relapse rate was non-significantly lower among subjects given pyrazinamide 2.5–3 g thrice weekly than those given pyrazinamide 1.5–2 g thrice weekly (11.3% vs 16.3%).[80] If not for the higher risk of immune-mediated adverse events due to intermittent high-dose rifampicin[81–83] and unwarranted fear of hepatotoxicity due to intermittent high-dose pyrazinamide,[79 84 85] the observed difference between daily and intermittent treatment regimens might be reduced by increasing dosages of rifampicin and pyrazinamide in intermittent regimens. The much longer elimination half-life of rifapentine may allow intermittent treatment without compromising treatment efficacy,[52–54] and make it possible to harness PAEs to facilitate DOT and better suppress drug resistance.[21]

Optimising dosing schedules should not be the only approach for improving TB treatment. Lessons from the study of pyrazinamide, which has completely different mechanisms of sterilising activity from rifampicin, have suggested that shortening TB treatment necessitates development of new drugs that are able to eradicate persisters with different modes of action.[86] Unfortunately, the development of new drugs with good sterilising activity is difficult and in part hampered by the lack of good surrogate markers of relapse. Further studies for identifying better surrogates of relapse seem warranted.[87 88] In addition, timely initiation of effective antiretroviral treatment in HIV-related TB can restore CD4 counts and reduce the risk of recurrence[89] and possibly acquired rifamycin resistance.

In conclusion, the current review suggests high levels of evidence for using daily schedules in standard TB treatment regimens, especially during the initial phase in the presence of cavitation, isoniazid resistance and advanced HIV co-infection. It corroborates prevailing understanding of pharmacokinetics-pharmacodynamics and mycobacterial persisters and supports exploration of rifapentine-containing regimens in higher dosages and frequency.[34–45]

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