

1 **Quality of reporting of outcomes in phase III studies of pulmonary**
2 **tuberculosis: a systematic review**

3

4 **Corresponding Author**

5 Laura Jayne Bonnett PhD CStat FHEA

6 Department of Biostatistics,

7 Waterhouse Building, Block F,

8 1-5 Brownlow Street,

9 University of Liverpool,

10 Liverpool,

11 L69 3GL

12 L.J.Bonnett@liverpool.ac.uk

13

14 **Co-Authors**

15 Gie Ken-Dror PhD

16 Department of Biostatistics and Department of Clinical Infection, Microbiology & Immunology,

17 Waterhouse Building, Block F

18 1-5 Brownlow Street,

19 University of Liverpool,

20 Liverpool,

21 L69 3GL

22 gkendror@liverpool.ac.uk

23

24 Geraint Rhys Davies BM PhD FRCP DTM&H

25 Department of Clinical Infection, Microbiology, & Immunology,

26 Ronald Ross Building,

27 8 West Derby Street,

28 University of Liverpool,

29 Liverpool,

30 L69 7BE

31 gerrydavies@doctors.org.uk

32

33

34

35

1 **Abstract**

2 ***Background***

3 Despite more than sixty years of clinical trials, tuberculosis (TB) still causes a high global burden of
4 mortality and morbidity. Treatment currently requires multiple drugs in combination, taken over a
5 prolonged period. New drugs are needed to shorten treatment duration, prevent resistance and reduce
6 adverse events. However, to improve on current methodology in drug development, a more complete
7 understanding of the existing clinical evidence base is required.

8
9 ***Methods***

10 A systematic review was undertaken to summarise outcomes reported in Phase III trials of patients
11 with newly-diagnosed pulmonary TB. A systematic search of databases (PubMed, MEDLINE,
12 EMBASE, CENTRAL and LILACs) was conducted on 30th November 2017 to retrieve relevant peer
13 reviewed articles. Reference lists of included studies were also searched. This systematic review
14 considered all reported outcomes.

15
16 ***Results***

17 Of 248 included studies 229 considered “on-treatment” outcomes whilst 148 reported “off-treatment”
18 outcomes. There was wide variation and ambiguity in the definition of reported outcomes, including
19 their relationship to treatment and in the time points evaluated. Additional challenges were observed
20 regarding the analysis approach taken (per protocol versus intention to treat) and the varying durations
21 of “intensive” and “continuation” phases of treatment. Bacteriological outcomes were most frequently
22 reported but radiological and clinical data were often included as an implicit or explicit component of
23 the overall definition of outcome.

24
25 ***Conclusions***

26 Terminology used to define long-term outcomes in phase III trials is inconsistent, reflecting evolving
27 differences in protocols and practices. For successful future cumulative meta-analysis, the findings of

1 this review suggest that greater availability of individual patient data and the development of a core
2 outcome set would be desirable. In the meantime we propose a simple and logical approach which
3 should facilitate combination of key evidence and inform improvements in the methodology of TB
4 drug development and clinical trials.

5

6 **Keywords**

7 Tuberculosis, Systematic review, Outcomes, Phase III Clinical Trials

8

1 **Background**

2 Tuberculosis (TB) remains a major killer amongst infectious diseases with 10.4 million new cases and
3 1.8 million deaths worldwide in 2015.[1] Though TB incidence has fallen by an average of 1.5% per
4 year since 2000, this needs to accelerate to a 4-5% annual decline to reach the 2020 milestones of the
5 World Health Organisation’s End TB Strategy which include reducing TB deaths by 90% and cutting
6 new cases by 80% between 2015 and 2030.[2] Ending the TB epidemic by 2030 is also among the
7 health targets of the newly adopted Sustainable Development Goals.[3]

8 Current treatment for drug-sensitive tuberculosis, involves administration of four drugs for six
9 months, while for multi-drug resistant disease, up to seven drugs for nine to twenty-four months may
10 be required. New drugs and regimens are required to shorten treatment duration, reduce toxicity and
11 combat drug resistance but the optimal critical path for novel regimens is not well-defined. Currently,
12 clinical development of a single novel TB drug is expected to take not less than six years, while a
13 completely novel combination regimen developed sequentially would require around twenty years or
14 more.[4] Phase III trials aiming to shorten the duration of first-line TB therapy must be large and
15 follow-up prolonged because of the strength of the current comparator in assuring stable cure.[5]

16 Recent such trials have been costly and global capacity for supporting them is limited.[6]

17 Possible outcomes for phase III TB trials have a number of important dimensions. Studies may focus
18 on bacteriological, clinical and/or radiological outcomes, or some combination of the three and these
19 outcomes are typically followed on multiple occasions during and after treatment. The structure of
20 treatment regimens has varied historically with de-intensification after an initial “intensive” phase a
21 common feature and the necessary duration of follow-up post-treatment has not been defined.

22 Investigators commonly report apparently simple outcomes such as cure, relapse and death which
23 may have very different meanings in different studies. This diversity is problematic as without
24 comparability of outcomes across trials it is challenging to synthesize evidence effectively and draw
25 the methodological conclusions necessary to inform decision-making for public health and improve
26 the conduct of future trials. This issue has become pressing in light of recent prominent
27 disappointments in phase III studies and with the emerging need in the field to evaluate novel

1 combinations of drugs efficiently.[7] With this in mind, we systematically reviewed the literature of
2 phase III studies in pulmonary TB to determine how outcomes are currently defined, and how
3 commonly they are used in published studies to date.

4

5 **Methods**

6 The available literature was searched for randomised controlled trials, or quasi-randomised trials
7 meeting the following inclusion criteria: trials including patients with smear and culture positive
8 pulmonary tuberculosis, trials including patients receiving treatment for the first time or with known
9 isoniazid mono-resistant organisms on susceptibility testing, and including regimens containing any
10 combination of the following drugs. Historic first-line treatment regimens with existing clinical data
11 were included. Additionally, any drugs with an active phase II clinical development programme were
12 also included. In particular trials including regimens containing any combination of ethambutol (E),
13 gatifloxacin (G), isoniazid (H), bedaquiline (J), levofloxacin (L), moxifloxacin (M), ofloxacin (O),
14 para-aminosalicylic acid (P), PA-824 (Pa), rifampicin (R), rifabutin (Rb), rifapentine (Rp),
15 streptomycin (S), thiacetazone (T), and pyrazinamide (Z) were considered. There were no specific
16 exclusion criteria in order to keep the review as broad as possible.

17 PubMed, MEDLINE, EMBASE, CENTRAL and LILACs were searched on 30th November 2017
18 using a defined inclusive search strategy as follows, without language restrictions. No date
19 restrictions were applied

- 20 1. Tuberculosis and clinical trials
- 21 2. Rifampicin or isoniazid or pyrazinamide or ethambutol or thiacetazone or para-aminosalicylic
22 acid or streptomycin or rifabutin or rifapentine or levofloxacin or ofloxacin or gatifloxacin or
23 moxifloxacin or bedaquiline or PA-824
- 24 3. 1 & 2

25 Hand searching of reference lists of included studies and relevant reviews was also undertaken to
26 ensure all relevant studies were included. Two authors (LB and GK-D) assessed all studies evaluating
27 either monotherapy or combination regimens for inclusion. Phase III studies were identified on a case-

1 by-case basis according to whether the study reported primary end of treatment or post-treatment
2 outcomes at an appropriate sample size. Ambiguous cases and any disagreements were resolved by
3 discussion with the third author (GD). Two investigators (LB & GK-D) extracted the data using a
4 piloted data extraction form. Data were summarised using appropriate graphical and numerical
5 summaries in R (version 3.3.2). In the case of multiple publications relating to a single study the
6 publication with the largest number of reported outcomes was included as the main publication. The
7 associated manuscripts were also checked for additional outcomes which were additionally reported
8 as though they were part of the main publication. The protocol for this systematic review is available
9 on request. The review was not registered with PROSPERO.

10 As a sensitivity analysis, we considered Venn diagrams for the reported outcomes in trials published
11 before 1995 and from 1995 onwards. This cut-off was chosen as representing the start of the modern
12 era in TB clinical trials.

13

14 **Results**

15 **Characteristics of included studies**

16 Figure 1 illustrates the flow of studies through the review. The main reasons for exclusion were
17 failure to meet the inclusion criteria, and study design other than randomised controlled trial. In total,
18 248 relevant studies were identified and included. The included studies ranged in year of publication
19 from 1950 until 2016 (Figure 2). Only 45 (18%) of the included studies were published after 1995.

20 Hence the majority of included studies may not be expected to conform to the CONSORT guidelines
21 on reporting of items such as trial design, intervention, participants, and outcomes.[8] 39 studies were
22 reported in languages other than English. The most frequent alternative languages were Japanese (12
23 studies), German (8 studies) and French (7 studies) with alternatives including Chinese, Italian,
24 Danish, Russian, Dutch, Portuguese, Romanian and Polish.

25 Figure 3 summarises the duration of treatment across studies and the extent of follow-up. The most
26 frequent treatment durations were 6 and 12 months. Some studies only treated patients for 2
27 months[9-11] while others tested treatment plans lasting 36 months.[12, 13] Follow-up after treatment

1 was completed was most frequently undertaken at 6, 12, 18, and 24 months. The shortest duration of
2 follow-up was 4 months[14] with some studies opting for 60 months of follow-up (e.g.[15-17]).
3 During pilot data extraction, it was noted that definitions of treatment failure and relapse used in the
4 reports were often inconsistently related to stage of treatment. For this reason, for the purposes of the
5 review, outcomes were classified as “on-treatment” if treatment was continuing at the time of their
6 evaluation, “off-treatment” if treatment had already been completed and “end of treatment” if they
7 represented the final on-treatment evaluation.

8

9 **Definitions of outcomes**

10 There was wide variation in the definition and type of outcomes reported in the included studies.
11 Nearly all reported multiple outcomes without any clear distinction between primary and secondary
12 outcomes. Therefore all the outcomes included in each study were considered (n=1378), and are
13 summarised in Additional file 1. The most frequently reported outcomes were the proportion of
14 participants experiencing a “relapse” (positive bacteriological tests in the “off-treatment” phase) (136
15 out of 1378 reported outcomes, 10%), improvement or change in radiograph (n=100, 7%), and death
16 from all or unspecified causes (n=90, 7%). Adverse events were also frequently reported (n=179,
17 13%).

18 The reported outcomes can be broadly categorised into bacteriological (for example negative or
19 positive mycobacterial cultures on various media), radiological (for example number of cavities seen
20 on chest radiograph) and clinical (for example death), evaluated on or off treatment. A Venn diagram
21 summarising the number of trial reports including each of these categories of outcomes can be seen in
22 Additional file 2; 27 studies reported only off-treatment outcomes while 106 studies reported only on-
23 treatment outcomes. The sensitivity analysis considering the reported outcomes in trials published
24 before 1995 and from 1995 onwards can be seen in Additional file 3. It appears that in recent years
25 trials have been less reliant on radiological results.

26

27 **Bacteriological outcomes**

1 218 (82%) studies reported a bacteriological endpoint on treatment whilst 139 (52%) reported such an
2 endpoint off treatment. There was a lack of consistency in whether sputum smear results were
3 characterised as positive or negative and considerable variation in the time points at which relapse
4 was assessed. Cultures or smear status were more frequently reported as negative (102 of 1378
5 reported outcomes, 7%) than positive (24, 2%).

6 Some studies considered “relapse” on treatment [18], while others considered it at various time points
7 off treatment such as 12 [19], 18 [20], 24 [21], 36 [22], and 60 months.[17] The definition of relapse
8 also varied across studies, some considering relapse as defined by smear results [23], by both culture
9 and smear results [23], or according to radiographic confirmation alone.[24] In some modern trials,
10 relapse was adjusted for molecular typing methods.[25] Similar variability was observed among
11 definitions of treatment failure.[23] Among bacteriological outcomes, the number of cultures obtained
12 also varied from one culture at one time point (e.g. [26-28]) to multiple cultures at one time point,
13 sometimes within one study (e.g. [29, 30]). Some studies adopted an intention to treat approach to
14 analysis and included patients with missing or contaminated culture results, while others used a per
15 protocol approach and excluded these patients. Poor quality reporting and high risk of bias meant it
16 was mostly impossible to distinguish these situations.

17

18 **Death**

19 126 (51%) studies reported an outcome related to death (either on treatment, or off treatment). Death
20 was classified in multiple ways ranging from all causes [31], through non-TB [32], to TB [33],
21 assessed at a number of time points, and expressed as a variety of endpoints ranging from proportion
22 to time to event. 53 (21%) of studies attempted to attribute cause of death to TB.

23

24 **Composite endpoints**

25 A subset of the included studies considered an explicitly composite endpoint of “unfavourable” as
26 against “favourable”[34]. “Unfavourable” in modern trials characteristically included bacteriologically
27 or clinically defined treatment failure or relapse [35], death from all causes (with the possible exception
28 of trauma) while on treatment, death from TB in the off-treatment phase, failure to complete the

1 treatment regimen within a defined timeframe and/or withdrawal from the study before the end of
2 treatment.[14] However, there were often potentially significant differences in the exact definition and
3 implementation of the “unfavourable” outcome, even among the most recently conducted trials
4 evaluating very similar treatment regimens.

5

6 **Conclusions**

7 Our systematic review identified considerable and potentially important variation among reported
8 outcomes and their definitions among phase III trials of treatment for TB. These differences were
9 apparent across a number of key dimensions and details. While the review necessarily reflects the
10 evolution of clinical trials in TB over more than six decades, our findings have implications for the
11 design and conduct of such studies in the future.

12 It is possible that the definition of outcomes could be related to progress and trends within clinical
13 guidelines in the pulmonary TB area (e.g. [36]). Such guidelines may have contributed to some
14 changes in reported outcomes over time. However, the guidelines are focussed on programmatic
15 treatment strategies and diagnostic methods rather than outcomes to be reported within clinical trials.

16 Overall, studies were frequently hampered by the use of ambiguous or incompletely defined terms
17 such as “treatment failure” and “relapse” which often appeared to embody unstated clinical or
18 temporal assumptions. Over time, objective and usually blinded bacteriological assessments have
19 been increasingly prioritised by TB trialists, particularly during the on-treatment phase while off-
20 treatment outcomes, although similarly based on bacteriology, often also have a clinical and/or a
21 radiological dimension which is not always explicit. In addition, the historical concept of “relapse”
22 has been complicated by the recognition of reinfection enabled by novel molecular techniques. There
23 was inconsistency in selection of the time points at which the outcomes were considered, the precise
24 requirements for declaring bacteriological assessments negative or positive and in the total duration of
25 off-treatment follow-up. While on-treatment outcomes would logically be reported as conversion to
26 negative status and off-treatment outcomes as conversion to positive status, this distinction was not

1 consistently applied across trials. In addition few trials clearly defined or reported per-protocol or
2 intention-to-treat analysis populations or losses to follow-up.

3 To avoid some of these problems, trialists have increasingly wished to explicitly combine several
4 endpoints into a composite endpoint which better reflects the total performance of a treatment
5 regimen over the entire course of treatment and follow-up and avoids the conditional linkage between
6 on-treatment and off-treatment outcomes (absence of a poor on-treatment outcome being a
7 precondition for off-treatment follow-up). Historically, these composite endpoints have been
8 described as “favourable”/“unfavourable”. While this is a logical approach, in practice the scope of
9 this composite endpoint may vary significantly, even between recent trials and the importance of
10 some components can vary between trial settings, particularly mortality in study populations with a
11 high rate of HIV seropositivity. Without closer harmonisation of such composite endpoints, it will
12 remain important to continue to clearly report the disaggregated component outcomes as well as the
13 composite in order to facilitate appropriate meta-analysis.

14 In a prior systematic review of methodology in phase II studies in TB, we identified multiple
15 competing approaches and analysis methods, which may be equally valid in an exploratory
16 context.[37] Phase III outcomes however are confirmatory in nature and require broader consensus
17 from both trialists and regulators. This review suggests that simple measures could improve the
18 quality of reporting of phase III studies and also highlights the need to develop a core outcome set for
19 future pivotal trials in TB. This would provide a set of clearly defined outcomes to be reported in
20 each study,[38] but which would not be exhaustive giving trialists the freedom to report other
21 outcomes of specific interest. The Core Outcome Measures in Effectiveness Trials (COMET)
22 Initiative brings together people interested in the development and application of agreed standardised
23 sets of outcomes. Thus our work is relevant in a broader setting than just trials within tuberculosis.
24 Agreement on a meaningful core outcome set would make it easier for future trials to be compared,
25 contrasted and combined in systematic reviews, ultimately facilitating understanding and accelerating
26 improvement of treatment strategies for patients with TB. This work is currently ongoing for phase II
27 studies within TB following a recent systematic review of outcomes.[37] However, pending

1 development of, and agreement on, such a core outcome set, we suggest some interim
2 recommendations for reporting of future phase III trials:
3 Endpoints should be explicitly referred to in terms of their timing in relation to the end of treatment.
4 Rather than the traditional and sometimes ambiguous terms “treatment failure” and “relapse”,
5 bacteriological, clinical and/or radiological outcomes would be more clearly described as “on-
6 treatment” or “off-treatment”.
7 Composite primary endpoints, for example, “unfavourable” or “favourable” should be clearly defined
8 in trial reports and appropriately disaggregated into their components in relevant analyses.
9 Reporting of bacteriological outcomes should clearly specify the definition of bacteriological
10 conversion (whether negative or positive, including whether more than one time point is required and
11 whether samples are to be replicated at each time point) and report the reasons for missing cultures
12 (not obtained, contaminated). While for phase II it seems most logical to report outcomes as
13 conversion to culture negativity, for the purposes of reporting combined endpoints in phase III trials it
14 is most consistent to report the positive on- and off-treatment outcomes together to avoid
15 conditionality.
16 Finally, where these recommendations cannot be met, availability of individual patient data could
17 facilitate appropriate re-analysis and combination of similar outcomes wherever possible thus
18 enabling and reducing heterogeneity in future meta-analyses. Improving the quality and interpretation
19 of this evidence base will be critical in providing the best possible information on the equipoise and
20 design of future clinical trials in TB.

21

22 **List of Abbreviations**

23 E - Ethambutol

24 G – Gatifloxacin

25 H – Isoniazid

26 J – Bedaquiline

27 L – Levofloxacin

- 1 M - Moxifloxacin
- 2 O – Ofloxacin
- 3 P - Para-aminosalicylic acid
- 4 Pa - PA-824
- 5 R – Rifampicin
- 6 Rb – Rifabutin
- 7 Rp – Rifapentine
- 8 S – Streptomycin
- 9 T - Thiacetazone
- 10 TB – Tuberculosis
- 11 Z - Pyrazinamide

12

13 **Declarations**

14 **Ethics Approval and Consent to Participate**

15 Not applicable

16

17 **Consent for Publication**

18 Not applicable

19

20 **Availability of Data and Materials**

21 The dataset generated and analysed during the current study are not publically available due to legal
22 and ethical agreements. It is hoped that the data will be stored in a central repository in due course.

23

24 **Competing Interests**

25 LB, GK-D and GD declare that they have no competing interests.

26

27 **Funding**

1 The research leading to these results has received funding from the Innovative Medicines Initiative Joint
2 Undertaking under *grant agreement* n°115337, resources of which are composed of financial
3 contribution from the European Union’s Seventh Framework Programme (FP7/2007-2013) and EFPIA
4 companies’ in kind contribution.

5

6 **Authors’ Contributions**

7 GD, GK-D and LB identified all relevant studies for inclusion in the review. LB and GK-D extracted
8 and summarised all the relevant data, drafted and revised the manuscript. GD drafted and revised the
9 manuscript. All three authors read and approved the final manuscript.

10

11 **Acknowledgements**

12 The authors gratefully acknowledge the assistance of Vittoria Lutje, Information Retrieval Specialist
13 for the Cochrane Infectious Disease Group who provided assistance with the development of the
14 search strategy.

15

16 **References**

- 17 1. **Tuberculosis** [<http://www.who.int/mediacentre/factsheets/fs104/en/>]
- 18 2. World Health Organisation: **The End TB Strategy**. 2014.
- 19 3. United Nations: **Resolution adopted by the General Assembly on 25 September 2015**. 2015.
- 20 4. [<http://www.cptrinitiative.org/>]
- 21 5. Nunn AJ, Phillips PP, Gillespie SH: **Design issues in pivotal drug trials for drug sensitive**
22 **tuberculosis (TB)**. *Tuberculosis* 2008, **88**:S85-S92.
- 23 6. Van Niekerk C, Ginsberg A: **Assessment of global capacity to conduct tuberculosis drug**
24 **development trials: do we have what it takes?** *The International Journal of Tuberculosis and*
25 *Lung Disease* 2009, **13.11**:1367-1372.
- 26 7. Lienhardt C, Raviglione M, Spigelman M, Hafner R, Jaramillo E, Hoelscher M, Zumla A,
27 Gheuens J: **New Drugs for the Treatment of Tuberculosis: Needs, Challenges, Promise,**

- 1 **and Prospects for the Future.** *Journal of Infectious Diseases* 2012, **205**:S241-S249.
- 2 8. Begg C, Cho M, Eastwood S, et al.: **Improving the quality of reporting of randomized**
3 **controlled trials: The consort statement.** *JAMA* 1996, **276**:637-639.
- 4 9. **Sputum-smear-negative pulmonary tuberculosis: controlled trial of 3-month and 2-**
5 **month regimens of chemotherapy.** *Lancet* 1979, **313(8131)**:1361-1363.
- 6 10. **A controlled trial of a 2-month, 3-month, and 12-month regimens of chemotherapy for**
7 **sputum smear-negative pulmonary tuberculosis: the results at 30 months. Hong Kong**
8 **Chest Service/Tuberculosis Research Centre, Madras/British Medical Research Council.**
9 *Am Rev Respir Dis* 1981, **124(2)**:138-142.
- 10 11. **A controlled trial of 2-month, 3-month, and 12-month regimens of chemotherapy for**
11 **sputum-smear-negative pulmonary tuberculosis. Results at 60 months.** *Am Rev Respir Dis*
12 1984, **130(1)**:23-28.
- 13 12. Dawson J, Devadatta S, Fox W, Radhakrishna S, Ramakrishnan C, Somasundaram P, Stott H,
14 Tripathy S, Velu S: **A 5-year study of patients with pulmonary tuberculosis in a concurrent**
15 **comparison of home and sanatorium treatment for one year with isoniazid plus PAS.**
16 *Bulletin of the World Health Organization* 1966, **34(4)**:533-551.
- 17 13. Devadatta S, Andrews R, Angel J, Bhatia A, Fox W, Janardhanam B, Radhakrishna S,
18 Ramakrishnan C, Subbaiah T, Velu S: **Progress in the second and third years of patients**
19 **with quiescent pulmonary tuberculosis after a year of chemotherapy at home or in**
20 **sanatorium, and influence of further chemotherapy on the relapse rate.** *Bulletin of the*
21 *World Health Organization* 1961, **24**:149-175.
- 22 14. Jindani A, Harrison TS, Nunn AJ, Phillips PP, Churchyard GJ, Charalambous S, Hatherill M,
23 Geldenhuis H, McIlleron HM, Zvada SP: **High-dose rifapentine with moxifloxacin for**
24 **pulmonary tuberculosis.** *New England Journal of Medicine* 2014, **371**:1599-1608.
- 25 15. Engbaek H, Heckscher T, Højgaard C, Larsen S, Rasmussen K, Vergmann B: **Tuberculosis**
26 **treated with rifampicin, ethambutol and isoniazid: Danish tuberculosis trial 1972-1974.**
27 *European journal of respiratory diseases* 1982, **63(2)**:84-93.
- 28 16. Santha T, Rehman F, Mitchison D, Sarma G, Reetha A, Prabhaker R: **Split-drug regimens for**

- 1 **the treatment of patients with sputum smear-positive pulmonary tuberculosis--a unique**
2 **approach.** *Tropical medicine & international health: TM & IH* 2004, **9**:551-558.
- 3 17. Balasubramanian R SS, Vijayan VK, Ramachandran R, Jawahar MS, Paramasivan CN,
4 Selvakumar N, Somasundaram PR.: **Five year results of a 3-month and two 5-month**
5 **regimens for the treatment of sputum-positive pulmonary tuberculosis in south India.**
6 *Tubercle* 1990, **71**:253-258.
- 7 18. Paunescu E: **Preliminary results of a short-course antituberculosis regimen including**
8 **Sinerdol-EH and applied under operational conditions.** *Rev Ig Bacteriol Virusol Parazitol*
9 *Epidemiol Pneumoftiziol Pneumoftiziol* 1985, **34(2)**:149-155.
- 10 19. **Controlled Clinical Trial of Short-Course (6 month) Regimens of Chemotherapy for**
11 **Treatment of Pulmonary Tuberculosis.** *The Lancet*, **299**:1079-1085.
- 12 20. **Isoniazid with thiacetazone (thioacetazone) in the treatment of pulmonary tuberculosis in**
13 **East Africa. Third Report of Fifth Investigation. A co-operative study in East African**
14 **hospitals, clinics and laboratories with the collaboration of the East African and British**
15 **Medical Research Councils.** *Tubercle* 1973, **54**:169-179.
- 16 21. **Five-Year Follow-Up of a Controlled Trial of Five 6-Month Regimens of Chemotherapy**
17 **for Pulmonary Tuberculosis.** *American Review of Respiratory Disease* 1987, **136**:1339-1342.
- 18 22. **A controlled trial of 6-month and 12-month regimens after negative conversion of sputum**
19 **in the original treatment of pulmonary tuberculosis. Report of the 21st series of controlled**
20 **trials of chemotherapy. Cooperative Study Unit of Chemotherapy of Tuberculosis of**
21 **National Sanatoria in Japan (CSUCTNS).** *Kekkaku* 1984, **59(2)**:81-89.
- 22 23. Van Deun A, Aung KJM, Hamid Salim MA, Ali MA, Naha MS, Das PK, Hossain MA,
23 Declercq E: **Extension of the intensive phase reduces unfavourable outcomes with the 8-**
24 **month thioacetazone regimen.** *The International Journal of Tuberculosis and Lung Disease*
25 2006, **10(11)**:1255-1261.
- 26 24. Priimak AA SM, Sagalovich VIa, Tarasova EF, Goncharov AM, Glazkov PV, Makeenkova LI,
27 Ladniuk VM.: **Preliminary results of a study on shortening periods of treatment and**
28 **temporary disability of patients with tuberculosis of the respiratory organs.** *Problmy*

- 1 *Tuberkuleza* 1989, **10**:15-18.
- 2 25. Velu S, Andrews RH, Angel JH, Devadatta S, Fox W, Gangadharam PRJ, Narayana ASL,
3 Ramakrishnan CV, Selkon JB, Somasundaram PR: **Progress in the second year of patients**
4 **with quiescent pulmonary tuberculosis after a year of domiciliary chemotherapy, and**
5 **influence of further chemotherapy on the relapse rate.** *Bulletin of the World Health*
6 *Organization* 1961, **25(3)**:409-429.
- 7 26. Muschenheim C, McDermott W, McCune R, Deuschle K, ORMOND L, Tompsett R:
8 **Pyrazinamide-Isoniazid in Tuberculosis. II. Results in 58 Patients with Pulmonary**
9 **Lesions One Year after the Start of Therapy.** *American Review of Tuberculosis and*
10 *Pulmonary Diseases* 1954, **70(4)**:743-747.
- 11 27. Gravendeel JM, Asapa AS, Becx-Bleumink M, Vrakking HA: **Preliminary results of an**
12 **operational field study to compare side-effects, complaints and treatment results of a**
13 **single-drug short-course regimen with a four-drug fixed-dose combination (4FDC)**
14 **regimen in South Sulawesi, Republic of Indonesia.** *Tuberculosis* 2003, **83**:183-186.
- 15 28. Baba H, Shinkai A, Azuma Y: **Controlled Clinical Trial of Three 6 Month Regimens of**
16 **Chemotherapy for Pulmonary Tuberculosis (Preliminary Report).** *Kekkaku (Tuberculosis)*
17 1978, **53(5)**:287-294.
- 18 29. African E: **Isoniazid with Thiacetazone (Thioacetazone) in the Treatment of Pulmonary**
19 **Tuberculosis in East Africa-Third Investigation: The Effect of an Initial Streptomycin**
20 **Supplement. A Co-operative Study in East African Hospitals and Laboratories.** *Tubercle*
21 1966, **47**:1-32.
- 22 30. Jacob MC, Joseph MS, Venkataraman MP, Kailasam MS, Prema MK, Raghunathan MR,
23 Narayana MA: **A Controlled Comparison of a Twice-Weekly and Three Once-Weekly**
24 **Regimens in.** *Bull Org mond Sant* 1970, **43**:143-206.
- 25 31. Doster BM, FJ; Newman, R; Woolpert, SF: **Ethambutol in the initial treatment of**
26 **pulmonary tuberculosis. U.S. Public Health Service tuberculosis therapy trials.** *Am Rev*
27 *Respir Dis* 1973, **107(2)**:177-190.
- 28 32. Snider Jr D, Long M, Cross F, Farer L: **Six-months isoniazid-rifampin therapy for**

- 1 **pulmonary tuberculosis. Report of a United States Public Health Service Cooperative**
2 **Trial.** *The American review of respiratory disease* 1984, **129(4):573-579.**
- 3 33. Tam C, Chan S, Lam C, Leung C, Kam K, Morris J, Mitchison D: **Rifapentine and isoniazid**
4 **in the continuation phase of treating pulmonary tuberculosis: initial report.** *American*
5 *journal of respiratory and critical care medicine* 1998, **157:1726-1733.**
- 6 34. Lienhardt C, Cook SV, Burgos M, et al.: **Efficacy and safety of a 4-drug fixed-dose**
7 **combination regimen compared with separate drugs for treatment of pulmonary**
8 **tuberculosis: The study c randomized controlled trial.** *JAMA* 2011, **305:1415-1423.**
- 9 35. Gillespie SH, Crook AM, McHugh TD, Mendel CM, Meredith SK, Murray SR, Pappas F,
10 Phillips PPJ, Nunn AJ: **Four-Month Moxifloxacin-Based Regimens for Drug-Sensitive**
11 **Tuberculosis.** *The New England journal of medicine* 2014, **371:1577-1587.**
- 12 36. World Health Organisation: *Guidelines for treatment of tuberculosis.* Fourth Edition edn; 2009.
- 13 37. Bonnett LJ, Davies GR: **Quality of outcome reporting in phase II studies in pulmonary**
14 **tuberculosis.** *Trials* 2015, **16:518.**
- 15 38. Clarke M: **Standardising outcomes for clinical trials and systematic reviews.** *Trials* 2007,
16 **8:39.**

17

18 **Figure Legends**

19 Figure 1: Flow of studies in the review

20 Figure 2: Year of publication of included studies

21 Figure 3: Bar charts illustrating the number of included studies reporting each duration of treatment
22 (left: blue bars) and also the duration of follow-up (right: green bars)

23

24 **Additional File Titles and Legends**

25 Additional File 1: Reported outcomes

26 Additional File 2: Venn diagram summarising all reported outcomes.

- 1 Additional File 3: Venn diagrams summarising all reported outcomes according to the sensitivity
- 2 analysis (i.e. pre- and post-CONSORT).