# BMJ Open Respiratory Research

# Quantifying non-adherence to anti-tuberculosis treatment due to early discontinuation: a systematic literature review of timings to loss to follow-up

Elizabeth F Walker [iD],[1] Mary Flook,[2] Alison J Rodger,[3] Katherine L Fielding,[4,5] Helen R Stagg [iD] [4]

For numbered affiliations see end of article.

**Correspondence to**
Professor Helen R Stagg;
helen.stagg@lshtm.ac.uk

## ABSTRACT

**Background** The burden of non-adherence to anti-tuberculosis (TB) treatment is poorly understood. One type is early discontinuation, that is, stopping treatment early. Given the implications of early discontinuation for treatment outcomes, we undertook a systematic review to estimate its burden, using the timing of loss to follow-up (LFU) as a proxy measure.

**Methods** Web of Science, Embase and Medline were searched up to 14 January 2021 using terms covering LFU, TB and treatment. Studies of adults (≥ 18 years) on the standard regimen for drug-sensitive TB reporting the timing of LFU (WHO definition) were included. A narrative synthesis was conducted and quality assessment undertaken using an adapted version of Downs and Black. Papers were grouped by the percentage of those who were ultimately LFU who were LFU by 2 months. Three groups were created: <28.3% LFU by 2 months, ≥28.3–<38.3%, ≥38.3%). The percentage of dose-months missed due to early discontinuation among (1) those LFU, and (2) all patients was calculated.

**Results** We found 40 relevant studies from 21 countries. The timing of LFU was variable within and between countries. 36/40 papers (90.0%) reported the percentage of patients LFU by the end of 2 months. 31/36 studies (86.1%) reported a higher than or as expected percentage of patients becoming LFU by 2 months. The percentage of dose-months missed by patients who became LFU ranged between 37% and 77% (equivalent to 2.2–4.6 months). Among all patients, the percentage of dose-months missed ranged between 1% and 22% (equivalent to 0.1–1.3 months).

**Conclusions** A larger than expected percentage of patients became LFU within the first 2 months of treatment. These patients missed high percentages of dose months of treatment due to early discontinuation. Interventions to promote adherence and retain patients in care must not neglect the early months of treatment.

**PROSPERO registration number** CRD42021218636.

## WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ A previous systematic literature review by Kruk *et al* investigated the global timing of when patients become lost to follow-up (LFU), taking studies from 1998 up to 2006 from low-income and middle-income countries.

## WHAT THIS STUDY ADDS

⇒ This study updates and extends the previous systematic review and demonstrates a novel method of estimating the global burden of one form of non-adherence (early discontinuation) using the timing of LFU as a proxy. In our systematic review, 31/36 studies (86.1%) reported as expected or a larger than expected percentage of patients becoming LFU within the first 2 months of treatment (33.3% was expected for a given study, with an allowable range of ≥28.3–<38.3%). Patients becoming LFU within the first 2 months of treatment miss high percentages of dose months due to early discontinuation.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Interventions to promote adherence and retain patients in care must not neglect the early months of treatment.

## BACKGROUND

Tuberculosis (TB) is responsible for 1.3 million deaths a year globally, placing it in the top 10 causes of death.[1] An important obstacle to the elimination of TB lies in the issues surrounding non-adherence to anti-TB drug therapies.[2–5] In order to reduce levels of non-adherence, healthcare systems have invested heavily in digital and other technologies, but the evidence that these technologies lead to improved treated outcomes is limited.[6]

Non-adherence is when medication is not taken by the patient as agreed with the healthcare provider. It can be summarised into three main types: late initiation (without an associated date extension to the regimen), the sporadic missing of doses and early discontinuation.[7] The latter is when treatment ceases to be taken before the intended regimen duration has been completed. Early

discontinuation is an important form of non-adherence as it can result in a large percentage of doses being missed, especially if the discontinuation occurs early in the treatment course.

The currently most commonly used treatment for drug-sensitive TB consists of 2 months of daily isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E), followed by 4 months of daily H and R (2HRZE/4HR). Estimating the burden of non-adherence to TB treatment resulting from early discontinuation is important for improving the design of both TB treatment regimens and adherence-promoting interventions.[8] While this would ideally be undertaken using adherence data monitored daily, to date insufficient information is available globally. Thus, proxy measurements are required.

Loss to follow-up (LFU) to TB treatment is defined by the WHO as the interruption of treatment for two consecutive months or more.[9 10] If a patient returns to care after being LFU, treatment needs to be restarted from the beginning. The timing of LFU can thus be used as a proxy measurement for early discontinuation, enabling calculation of its burden using a standardised outcome within TB surveillance systems (LFU). For high TB burden countries in particular, the use of widely available proxy measures is important as standardised adherence measures are uncommon and rarely documented.

Our study aimed to estimate the burden of non-adherence due to early discontinuation among patients with TB treated with 2HRZE/4HR in different settings globally, using the timing of LFU as a proxy variable. First, we updated and extended a previous systematic review by Kruk *et al*.[4] Their review examined the timings of LFU across multiple anti-TB regimens in low-income and middle-income countries and was published in 2008. Second, we used these data to calculate the burden of early discontinuation in different settings.

In order to optimise adherence-promoting interventions, knowing the burden of early discontinuation is vital. Currently, the use of published data on the timing of patients becoming LFU is an economical and accessible method of achieving this.

## METHODS
### Data sources and search terms
We undertook a systematic literature review to identify studies that documented the timing of LFU for adults undergoing the standard 2HRZE/4HR regimen for drug-sensitive TB. Three online bibliographic databases were searched on 14 January 2021: (1) Embase, (2) Medline (R) and In-Process, In-Data-Review & Other Non-Indexed Citations (1946 to 14 January 2021) and (3) the Web of Science Core Collection. The first and second databases were searched through Ovid. The search strategy was designed around three groups of terms: TB, LFU and treatment. We used Medical Subject Headings (MeSH)/Embase Subject Headings (Emtree) terms (where applicable), and free text terms. The full

search is documented in online supplemental material A. Reference lists of included papers were also searched for additional relevant studies.

Our overall criteria for inclusion were observational and intervention studies; published after 1998; of adult patients (18 years or over), where the majority of patients were being treated with the 6-month 2HRZE/4HR regimen, dosed daily; where the protocol of the study required each patient to be followed up for the full 6-month duration of their treatment; where the WHO definition of LFU was used; and where reported LFUs did not occur after 6 months. Where studies did not explicitly state that they used that an alternative definition of LFU, and the balance of probabilities indicated that they used the correct definition, they were included. These studies were, however, excluded in a sensitivity analysis. We made the assumption that the majority of TB treated with 2HRZE/4HR was drug sensitive. Online supplemental material B compares this study's exclusion and inclusion criteria to the previous work of Kruk *et al*.[4] Broadly, we extended the search to 2021, removed the geographical restrictions and imposed criteria to restrict included papers to studies in adults, more precise definitions of LFU and use of 2HRZE/4HR.

We restricted to studies published after 1998 as per Kruk *et al* because the introduction of standardised WHO recommended reporting mechanisms and Directly Observed Treatment Short course meant that these studies were more likely to contain relevant data.

### Study screening
Papers were downloaded to EndNote and deduplicated prior to screening. All papers were screened by two reviewers (EFW and MF) in three stages: first screened by title, then by abstract and then by full text. The two reviewers compared their screening at each of the three stages. Discrepancies between the two reviewers were resolved by discussion, with a third reviewer (HRS) available to arbitrate, where necessary. Additionally, the bibliographies of papers chosen to be included in the review were searched.

### Data extraction
The main data extracted were the timing of when LFU occurred among people who were LFU by 6 months. It was expected that papers would report timings in a variety of ways; thus, accordingly, the data extraction tool allowed for flexible reporting. Two reviewers extracted all data in duplicate. Discrepancies in the data extractions were re-examined by both reviewers to determine the correct figures reported, with HRS available to arbitrate. A list of the full set of extracted fields is available in online supplemental material C.

To aid comparison to the Kruk *et al* review, WHO region was identified for each study,[11] together with the economic status of the country as classified by the World Bank: lower income country (LIC), lower middle income

country (LMIC), upper middle income country (UMIC) or high-income country.[12] Studies were attributed their World Bank Status according to the year or years that the study took place. Additionally, we classified all studies on the basis of their TB burden (high TB, high TB-HIV, high multidrug resistant (rifampicin resistant) (MDR (RR))-TB, not high burden) according to standardised definitions and again according to when the study took place (online supplemental material D). While classifying studies, we noted that some of the categories did not exist in the year that the study was conducted, and that countries often appeared in multiple lists.

## Data analysis

Due to extensive variability in the settings in which studies occurred and heterogeneity in the timings of when LFU occurred, a narrative synthesis was conducted. First, studies were grouped on the basis of when LFU occurred in their patient populations. We sought to determine if losses were even throughout treatment or uneven. If they were even, we would have expected a third of LFUs to have happened by the end of the second month of treatment, as 2 months is a third of the way through the 6-month treatment regimen. Thus, papers were categorised into three groups: (1) those for which roughly a third of LFUs occurred in the first two months (allowable range ≥28.3–<38.3%), (2) papers where more than a third occurred in the first 2 months (≥38.3%), and (3) papers where less than a third occurred in the first 2 months (<28.3%).

In addition, the proportion of dose-months missed due to early discontinuation (ie, the cessation of treatment before 6 months were completed) was calculated for each study among (a) all individuals who became LFU; and (b) all patients in the study, data permitting.

For the purpose of the dose-months missed calculations, a dose-month was considered as 28 days (4 weeks) as this is consistent with how anti-TB medication is prescribed. Calculations were performed using the percentage of patients LFU by 2 months into treatment (ie, during the intensive phase), as this was the most common measure reported among included studies. It was assumed that patients LFU in first 2 months of treatment (ie, during the intensive phase) missed 5 months of treatment (ie, the average time point of loss was halfway through the 2-month intensive phase, the end of treatment month one. Therefore, 6 months minus 1 month equals 5 months). It was also assumed that patients LFU during the continuation phase (ie, the last 4 months of treatment) missed 2 months of treatment (ie, the average time point of loss was halfway through the 4-month continuation phase—the end of treatment month four. Therefore, 6 months minus 4 months equals 2 months).

Thus, the proportion of dose-months missed of expected dose-months among those LFU, (a), is as follows:

$$\frac{(5n_i + 2n_c)}{6(n_i + n_c)}$$

where $n_i$ was the number LFU by the end of 2 months (intensive phase) and $n_c$ was the number LFU after 2 months (continuation phase).

To calculate (b), the proportion of dose-months missed due to LFU for all patients in the study, we used:

$$\frac{(5n_i + 2n_c)}{6n_t}$$

where $n_t$ was number of people in the study.

Where papers had data on the timing of LFU that was more granular than the percentage of patients LFU during the intensive versus continuation phase, these data were also extracted such that we could examine our use above of a time point of loss halfway through each phase. Only papers that contained data for both phases were extracted. Papers where patients were required to have been on treatment for a month to be included in the study were not extracted. Where data were given for timepoint zero but the paper did not state that it included pretreatment LFU in its definition of LFU, these data were included in the next lowest time category.

A sensitivity analysis was undertaken excluding studies where the percentage of individuals taking a regimen other than 2HRZE/4HR was documented or thought likely to be greater than 10% (eg, because the patients had MDR disease, or were retreatment patients). The precise regimen used for patients with drug-sensitive TB was not always defined within a study.

## Quality assessment

We used the Downs and Black quality assessment tool for this study (online supplemental material E).[13] We adjusted this tool for three reasons: (1) because our included studies were estimating a single proportion (rather than comparing two or more proportions), (2) so we could assess the precision of studies, as well as power, (3) in response to the guidance of Deeks *et al*.[14] We also adjusted the quality assessment questions slightly depending on whether the underlying study aimed to specifically measure the timing of LFU (online supplemental material E). This was in order to not unfairly penalise those that did not aim specifically to measure LFU timings.

A single-sample post-hoc power calculation was conducted per study as part of the quality assessment, as per Downs and Black.[13] We assessed each study's power to reject the null hypothesis that 33% of the individuals who became LFU did so by 2 months (as 2 months is a third of the way through treatment). For the power calculations, we used data on the number of individuals LFU and the actual percentage of individuals LFU by 2 months. We set our alpha to 5%. Study power was scored as follows: >95%–≤100%= score 1, >90%–≤95%= score 2, >85%–≤90%= score 3, 80%–≤85%= score 4, >70%–≤80%=score 5, ≤70% = score 6.

Additionally, precision was scored to assess if the sample size of each study allowed for a precise estimate of the percentage of individuals LFU by 2 months (online supplemental material F). We calculated the SE for this percentage for each study and assessed whether it was equivalent to ≤10% relative precision around the percentage LFU at 2 months (score 1), >10–≤35% (score 2), >35–≤60% (score 3), or >60% (score 4). These percentage thresholds were derived based on a pragmatic decision about what a 'meaningful' difference in certainty around the percentage of people LFU by 2 months would be.

Two reviewers conducted the quality assessment in duplicate, with disagreements resolved by HRS.

### Patient and public involvement

None.

### RESULTS

After deduplication, 6973 articles were available for screening (figure 1). Eight hundred thirty-eight articles were selected for full-text screening, of which 40 were found eligible for inclusion, including 1 additional paper of relevance recommended by an expert in the field. All included papers met our definition of LFU. Some stated that they included pretreatment LFU.[15 16] We excluded studies that focused on children. Some studies included both children and adults; several used 15 years of age as a cut-off for adulthood rather than 18 years. Thirteen studies stated or implied that they included children under 15 years of age. Where possible, we solely extracted data for adults.

Papers where dosing was not documented to be daily were excluded during full-text screening; one included some thrice weekly dosing but it was not possible to ascertain how many patients underwent this.[17] Where possible, the exact drugs included in the regimen were checked, but many papers did not report this information. Nine studies were earmarked for exclusion in the sensitivity analysis, that is, >10% of individuals in these studies were not taking the regimen 2HRZE/4HR.[18–26]

Seven papers were close to inclusion but did not quite meet the requirements of our review (online supplemental material G).

The 40 studies came from 21 countries across all 6 of the WHO regions, with the majority (14/40, 35.0%) from South-East Asia (table 1, figure 2A). Twelve studies came from LICs, 5 came from UMICs, 2 came from HICs and 25 from LMICs (numbers do not add to 40 as 3 studies spanned years when a country transferred between LIC and LMIC status, and 1 study spanned years when a country moved from being an LMIC to a UMIC). The size of studies varied widely; the smallest had 62 in the source population from which the number LFU was derived and the largest 158 668 (table 2). The percentage of patients in each study who became LFU across the studies ranged from 1.4% to 30.2% (table 2).
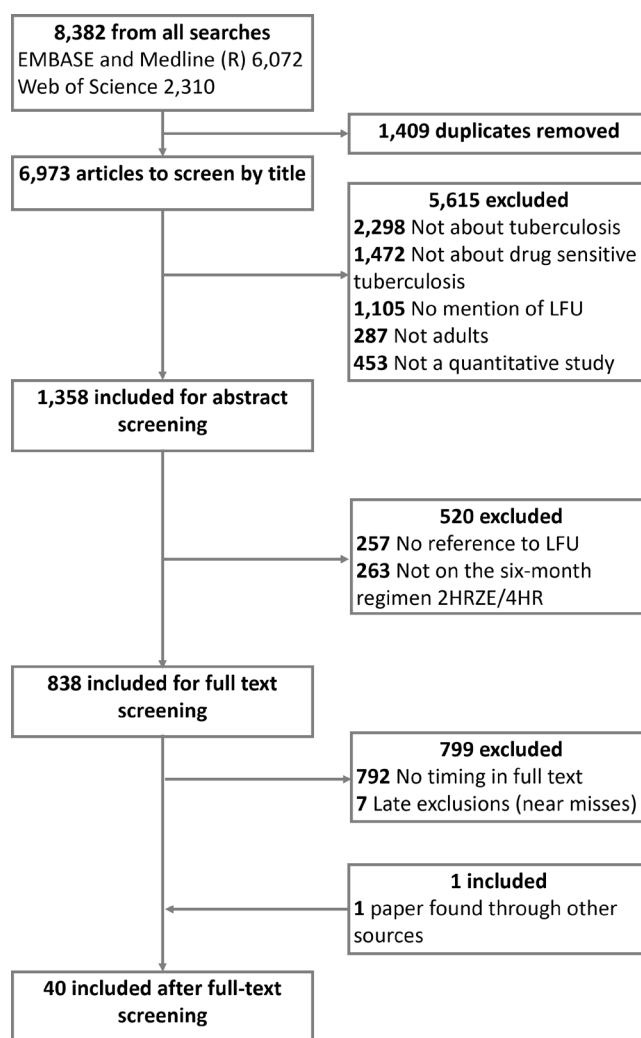


**Figure 1** Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram. PRISMA diagram depicting the flow of papers through the exclusion/inclusion process. 2HRZE/4HR—the 6-month anti-tuberculosis regimen consisting for 2 months of isoniazid (H), rifampicin (R), pyrazinamide (Z), and ethambutol (E) followed by 4 months of H and R; LFU, loss to follow-up.

### Quality assessment

Of the 40 papers, 10 (25.0%) aimed to measure the timing of LFU, that is, had the same aim as this review. Studies were generally reasonably powered for the outcome of interest (online supplemental table 1): 19 papers (47.5%) were assigned a score of 1. Fourteen (35.0%) achieved only the lowest score. Eleven papers (27.5%) achieved the highest score for precision. Five studies could not be scored for power or precision—four did not report the percentage of patients who became LFU by 2 months and, in one, no-one became LFU by 2 months.

**Table 1** Summary of included papers

| Country | WHO region | WHO classification of country burden | World Bank income level | Author, year | Year(s) of study | Population | Study design* |
|---|---|---|---|---|---|---|---|
| Cameroon | African Region | High TB-HIV | LMIC | Pefura Yone et al[33] 2011 | 2009 | Patients registered at the TB referral centre in the capital city | Cohort |
| | | High TB-HIV | LMIC | Pefura-Yone et al[27] 2016 | 2012–2013 | Patients treated at 18 diagnosis and treatment centres in the capital city | Cohort |
| China (including Hong Kong SAR) | Western Pacific Region | High TB | LMIC | Chang et al[20] 2004 | 1999 | Patients registered at government chest clinics | Cohort |
| | | High TB | LMIC | Chan-Yeung et al[19] 2003 | 1996 | Patients registered in the main chest service in Hong Kong | Cohort |
| | | High TB/high TB-HIV/ high MDR (RR)-TB | UMIC | Wei et al[25] 2012 | 2007–2008 | Migrants TB patients in Shanghai | Intervention study (control arm only) |
| Ethiopia | African Region | High TB/high TB-HIV/ high MDR (RR)-TB | LIC | Ambaw et al[45] 2018 | 2014–2016 | Patients registered at particular clinics with staff trained in the WHO's Mental Health Gap Action Programme in northern and south central Ethiopia. Patients had to be on treatment at least a month | Cohort |
| | | High TB/high TB-HIV | LIC | Munoz-Sellart et al[46] 2010 | 2002–2007 | Patients registered in seven health centres and one district hospital in southern Ethiopia who were on treatment for at least 4 weeks. Centres purposely selected to be accessible to researchers | Cohort |
| | | High TB/high TB-HIV/ high MDR (RR)-TB | LIC | Shaweno et al[23] 2020 | 2008–2015 | Patients registered in Sheka Zone of Ethiopia who were on treatment at least a month | Cohort |
| France | European region | Not a HBC | HIC | Tetart et al[24] 2020 | 1997–2016 | Patients registered in hospital in northern France that was the regional reference centre for infectious diseases | Cohort |
| Haiti | Region of the Americas | High TB-HIV | LIC | Schnaubelt et al[16] 2018 | 2012–2015 | National surveillance data | Cohort |
| India | South-East Asian Region | High TB/high TB-HIV/ high MDR (RR)-TB | LMIC | Chakrabartty et al[28] 2019 | 2011–2014 | Patients treated in West Bengal with random/stratified sampling of TB units | Cohort |
| | | High TB | LIC | Dandona et al[29] 2004 | 2002 | Patients registered at selected TB units in four states | Cohort |
| | | High TB | LMIC | Pardeshi[34] 2010 | 2004 | Patients registered for DOTS in one district in western India | Cohort |
| | | High TB/high TB-HIV/ high MDR (RR)-TB | LMIC | Parida et al[35] 2014 | 2010–2011 | Patients on self-administered treatment registered at one hospital in south western India | Cohort |

Continued

**Table 1** Continued

| Country | WHO region | WHO classification of country burden | World Bank income level | Author, year | Year(s) of study | Population | Study design* |
|---|---|---|---|---|---|---|---|
| | | High TB/high TB-HIV/ high MDR (RR)-TB | LMIC | Paunikar et al[22] 2019 | 2015 | Patients registered in one hospital in western India | Cohort |
| | | High TB/high TB-HIV/ high MDR (RR)-TB | LMIC | Rathee et al[30] 2016 | 2010–2011 | Patients registered at a specific DOTS centre | Cohort |
| | | High TB/high TB-HIV/ high MDR (RR)-TB | LMIC | Vasudevan et al[47] 2014 | 2011 | Patients registered at TB unit in Southern India who were on treatment at least a month | Cohort |
| | | High TB/high TB-HIV/ high MDR (RR)-TB | LMIC | Veeramani and Madhusudhan[48] 2015 | 2014 | Patients registered in DOTS centres in one TB unit in southern India | Cohort |
| | | High TB/high TB-HIV/ high MDR (RR)-TB | LMIC | Zhou et al[36] 2020 | 2014–2017 | Male patients registered at RNTCP clinics in two districts in southern India | Cohort |
| Indonesia | South-East Asian Region | High TB/high TB-HIV/ high MDR (RR)-TB | LMIC | Rutherford et al[49] 2013 | 2010–2012 | Patients registered at a community health clinic in West Java | Cohort |
| Kenya | African Region | High TB/high TB-HIV | LIC | Kizito et al[50] 2011 | 2006–2008 | Patients registered in three clinics in an informal settlement in Nairobi | Cohort |
| | | High TB/high TB-HIV | LIC/LMIC | Masini et al[15] 2016 | 2013–2014 | National surveillance data | Cohort |
| | | High TB/high TB-HIV | LIC | Muture et al[37] 2011 | 2005–2007 | Patients registered in 30 high-volume public health facilities in Nairobi | Case-control |
| | | High TB/high TB-HIV | LMIC | Sitienei et al[31] 2015 | 2012–2013 | National surveillance data | Cohort |
| Kuwait | Eastern Mediterranean Region | Not a HBC | HIC | Zhang et al[26] 2014 | 2010–2012 | Patients registered as inpatients or outpatients with pulmonary TB in two government facilities | Cohort |
| Malaysia | Western Pacific Region | Not a HBC | UMIC | Fun et al[51] 2013 | 2011 | Patients registered in public treatment centres in western district of Malaysia | Case control |
| Moldova | European Region | High MDR (RR)-TB | LMIC | Jenkins et al[38] 2013 | 2007–2010 | National surveillance data | Cohort |
| Myanmar | South-East Asian Region | High TB/high TB-HIV/ high MDR (RR)-TB | LIC/LMIC | Aung et al[52] 2019 | 2012–2016 | Patients registered at DOTS clinics across the country | Cohort |
| Nigeria | African Region | High TB/high TB-HIV/ high MDR (RR)-TB | LMIC | Alobu et al[39] 2014 | 2011–2012 | Patients registered in one public and one private hospital (both with high patient numbers) in a south western state of Nigeria | Cohort |
| | | High TB/high TB-HIV/ high MDR (RR)-TB | LIC/LMIC | Ukwaja[32] 2013 | 2006–2010 | Patients registered in a tertiary care hospital who were coinfected with HIV | Cohort |

Continued

**Table 1** Continued

| Country | WHO region | WHO classification of country burden | World Bank income level | Author, year | Year(s) of study | Population | Study design* |
|---|---|---|---|---|---|---|---|
| Peru | Region of the Americas | Not a HBC | UMIC | Lackey et al[53] 2015 | 2010–2011 | Patients registered with smear positive pulmonary TB in one district of north eastern Lima | Cohort |
| Russian Federation | European Region | High TB | LMIC | Jakubowiak et al[17] 2009 | 2003 | Patients with pulmonary TB registered in six Russian regions | Cohort |
| South Africa | African Region | High TB/high TB-HIV/high MDR (RR)-TB | UMIC | Berry et al[18] 2019 | 2010–2015 | National surveillance data but for two metropolitan municipalities | Cohort |
| | | High TB/high TB-HIV/high MDR (RR)-TB | LMIC/UMIC | Kigozi et al[21] 2017 | 2003–2012 | National surveillance data | Cohort |
| Sri Lanka | South East Asian Region | Not a HBC | LMIC | Pinidiyapathirage et al[54] 2008 | 2001–2002 | Patients registered in two districts presenting to a specific chest hospital | Cohort |
| Tajikistan | European Region | High MDR (RR)-TB | LIC | Wohlleben et al[55] 2017 | 2011–2012 | National surveillance data but restricted to districts with higher numbers of LFUs | Case control |
| Thailand | South-East Asian Region | High TB/high TB-HIV | LMIC | Anuwatnonthakate et al[56] 2008 | 2004–2006 | Patients registered for pulmonary TB treatment in the national infectious diseases hospital or any public or private hospital in four provinces | Cohort |
| | | High TB/high TB-HIV | LMIC | Kittikraisak et al[57] 2009 | 2005–2006 | HIV coinfected patients registered at the national infectious diseases referral hospital and in public treatment facilities in three other provinces who were on treatment for at least 4 weeks | Cohort |
| Uzbekistan | European Region | Not a HBC | LIC | Hasker et al[58] 2008 | 2005 | Patients registered in Tashkent city with pulmonary TB | Case control |
| Yemen | Eastern Mediterranean Region | Not a HBC | LMIC | Saleh Jaber et al[40] 2018 | 2013–2015 | Patients registered in two cities with the highest levels of TB and LFU who had undergone at least 4 weeks of treatment | Cohort |

Included papers presented ordered by the country in which they were conducted. If there were multiple papers per country, the papers are then arranged alphabetically by the first author's surname. Year(s) of study is defined as the years that patients were recruited.
*Note although the original study design may differ from that listed, the study design documented charts the effective design for the data we extracted.
DOTS, Directly Observed Treatment Short course; HBC, high burden country; HIC, high-income country; LFU, lost to follow-up; LIC, lower income country; LMIC, lower middle income country; MDR (RR), multidrug resistant (rifampicin resistant); RNTCP, Revised National Tuberculosis Control Programme; SAR, Special Administrative Region; TB, tuberculosis; UMIC, upper middle income country.
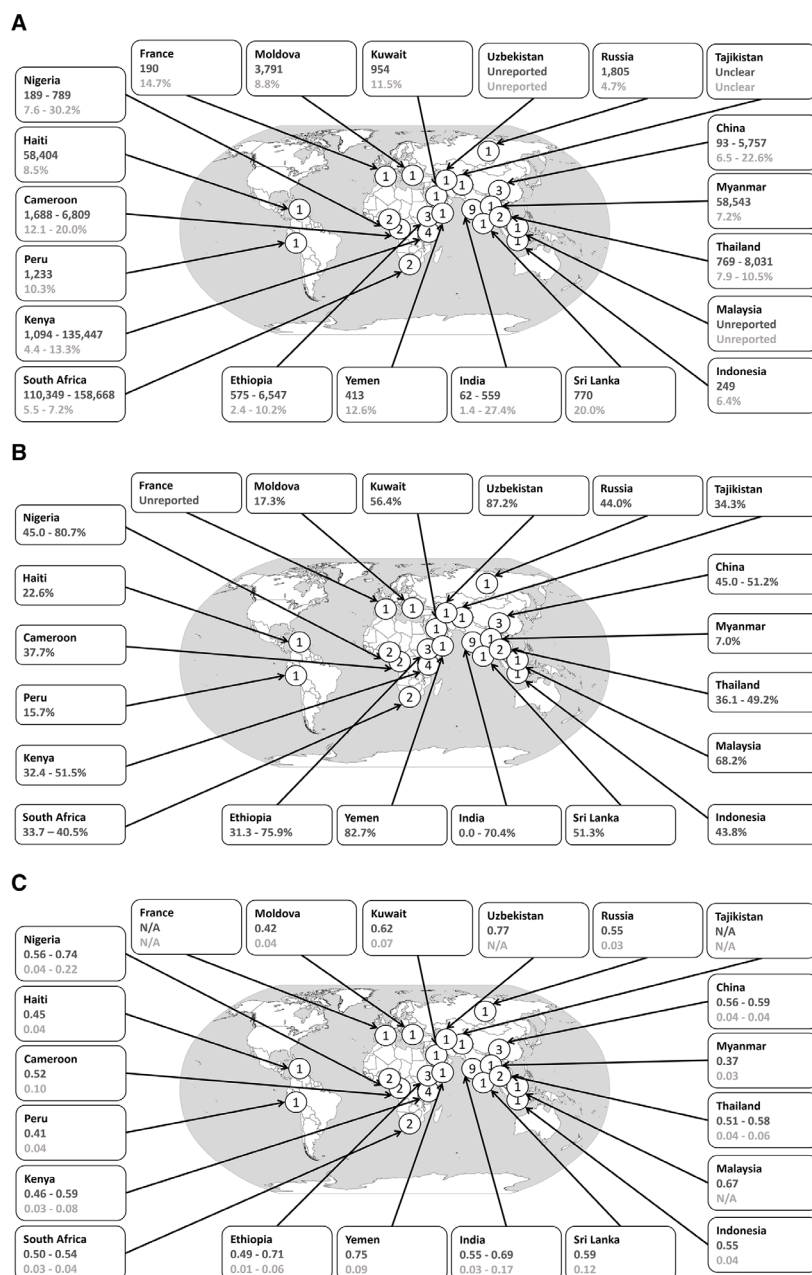
**A**

| Country | Dark grey | Light grey |
|---|---|---|
| France | 190 | 14.7% |
| Moldova | 3,791 | 8.8% |
| Kuwait | 954 | 11.5% |
| Uzbekistan | Unreported | Unreported |
| Russia | 1,805 | 4.7% |
| Tajikistan | Unclear | Unclear |
| Nigeria | 189 – 789 | 7.6 – 30.2% |
| Haiti | 58,404 | 8.5% |
| Cameroon | 1,688 – 6,809 | 12.1 – 20.0% |
| Peru | 1,233 | 10.3% |
| Kenya | 1,094 – 135,447 | 4.4 – 13.3% |
| South Africa | 110,349 – 158,668 | 5.5 – 7.2% |
| China | 93 – 5,757 | 6.5 – 22.6% |
| Myanmar | 58,543 | 7.2% |
| Thailand | 769 – 8,031 | 7.9 – 10.5% |
| Malaysia | Unreported | Unreported |
| Indonesia | 249 | 6.4% |
| Ethiopia | 575 – 6,547 | 2.4 – 10.2% |
| Yemen | 413 | 12.6% |
| India | 62 – 559 | 1.4 – 27.4% |
| Sri Lanka | 770 | 20.0% |

**B**

| Country | Value |
|---|---|
| France | Unreported |
| Moldova | 17.3% |
| Kuwait | 56.4% |
| Uzbekistan | 87.2% |
| Russia | 44.0% |
| Tajikistan | 34.3% |
| Nigeria | 45.0 – 80.7% |
| Haiti | 22.6% |
| Cameroon | 37.7% |
| Peru | 15.7% |
| Kenya | 32.4 – 51.5% |
| South Africa | 33.7 – 40.5% |
| China | 45.0 – 51.2% |
| Myanmar | 7.0% |
| Thailand | 36.1 – 49.2% |
| Malaysia | 68.2% |
| Indonesia | 43.8% |
| Ethiopia | 31.3 – 75.9% |
| Yemen | 82.7% |
| India | 0.0 – 70.4% |
| Sri Lanka | 51.3% |

**C**

| Country | Dark grey | Light grey |
|---|---|---|
| France | N/A | N/A |
| Moldova | 0.42 | 0.04 |
| Kuwait | 0.62 | 0.07 |
| Uzbekistan | 0.77 | N/A |
| Russia | 0.55 | 0.03 |
| Tajikistan | N/A | N/A |
| Nigeria | 0.56 – 0.74 | 0.04 – 0.22 |
| Haiti | 0.45 | 0.04 |
| Cameroon | 0.52 | 0.10 |
| Peru | 0.41 | 0.04 |
| Kenya | 0.46 – 0.59 | 0.03 – 0.08 |
| South Africa | 0.50 – 0.54 | 0.03 – 0.04 |
| China | 0.56 – 0.59 | 0.04 – 0.04 |
| Myanmar | 0.37 | 0.03 |
| Thailand | 0.51 – 0.58 | 0.04 – 0.06 |
| Malaysia | 0.67 | N/A |
| Indonesia | 0.55 | 0.04 |
| Ethiopia | 0.49 – 0.71 | 0.01 – 0.06 |
| Yemen | 0.75 | 0.09 |
| India | 0.55 – 0.69 | 0.03 – 0.17 |
| Sri Lanka | 0.59 | 0.12 |

**Figure 2** Global distribution of included studies, the timing of loss to follow-up, and the percentage of dose-months missed due to early discontinuation. Maps display the countries from which data emanated, with the number of studies per nation illustrated in each circle placed on the corresponding nation. Each map shows different findings from countries, as detailed in this paper. China includes Hong Kong Special Administrative Region. Russia=Russian Federation. Reported numbers are for the number of people included in our calculations, as opposed to the original numbers in the study. These numbers could differ, for example, due to not all patients in a study being treated with the eligible regimen, or having data available on the timing of LFU. Forty studies included in (A), of which 36 provide data in the balloons of (B and C). (A) Dark grey—number of participants in the study or studies, that is, the source population from which the number LFU was derived. Light grey—percentage of patients LFU or the range of percentages. (B) Dark grey—percentage LFU by 2 months, of those LFU. Range if more than one study from a country. (C) Dark grey—the proportion or range of proportions of dose-months missed due to early discontinuation among patients that were LFU. Light grey—the proportion or range of proportions of dose-months missed due to early discontinuation among all patients in the study. Where not all LFUs had timing data, the dose-month calculations were adjusted to reflect the entire population LFU. LFU, loss to follow-up.

Overall, study quality was good. Studies scored well for reporting their design and methods and gave clear definitions of their processes: only six papers (15.0%) had study designs that were not well reported. Eight studies (12.5%) did not clearly report their findings. Papers generally did not show signs of potential observer bias; data were usually extracted from health records. Seven studies (one of which aimed to

**Table 2** Timing of losses to follow-up and percentage of dose-months lost due to early discontinuation, by study

| Country | Author, year | Number patients in the study (source population from which the number LFU derived) | Number of patients LFU in the study | Percentage of patients LFU in the study | Number of patients who became LFU by 2 months | Percentage of patients LFU by 2 months among patients who became LFU | Proportion of dose-months missed due to early discontinuation among patients who became LFU | Proportion of dose-months missed due to early discontinuation among all patients in the study |
|---|---|---|---|---|---|---|---|---|
| Cameroon | Pefura Yone et al[33] 2011 | 1688 | 337 | 20.0% | 127 | 37.7% | 0.52 | 0.10 |
| | Pefura-Yone et al[27] 2016* | 6809 | 824 | 12.1% | N/A | N/A | N/A | N/A |
| China (including Hong Kong SAR) | Chang et al[20] 2004 | 1266 | 82 | 6.5% | 42 | 51.2% | 0.59 | 0.04 |
| | Chan-Yeung et al[19] 2003 | 5757 | 442 | 7.7% | 199 | 45.0% | 0.56 | 0.04 |
| | Wei et al[25] 2012* | 93 | 21 | 22.6% | N/A | N/A | N/A | N/A |
| Ethiopia | Ambaw et al[45] 2018 | 575 | 14 | 2.4% | 6 | 42.9% | 0.55 | 0.01 |
| | Munoz-Sellart et al[46] 2010 | 6547 | 667 | 10.2% | 209 | 31.3% | 0.49 | 0.05 |
| | Shaweno et al[23] 2020 | 1341 | 116 | 8.7% | 88 | 75.9% | 0.71 | 0.06 |
| France | Tetart et al[24] 2020* | 190 | 28 | 14.7% | N/A | N/A | N/A | N/A |
| Haiti | Schnaubelt et al[16] 2018 | 58404 | 4951 | 8.5% | 1117 | 22.6% | 0.45 | 0.04 |
| India | Chakrabartty et al[28] 2019* | (unreported) | 145 | N/A | N/A | N/A | N/A | N/A |
| | Dandona et al[29] 2004 | (unclear) | 744 | N/A | 371 | 49.9% | 0.58 | N/A |
| | Pardesh[34] 2010 | 275 | 14 | 5.1% | 9 | 64.3% | 0.65 | 0.03 |
| | Parida et al[35] 2014 | 62 | 17 | 27.4% | 10 | 58.8% | 0.63 | 0.17 |
| | Paunikar et al[22] 2019 | 365 | 5 | 1.4% | 0 | 0.0% | N/A† | N/A† |
| | Rathee et al[30] 2016 | 101 | 16 | 15.8% | 11 | 68.8% | 0.68 | 0.11 |
| | Vasudevan et al[47] 2014 | 527 | 28 | 5.3% | 14 | 50.0% | 0.58 | 0.03 |
| | Veeramani and Madhusudhan[48] 2015 | 282 | 27 | 9.6% | 19 | 70.4% | 0.69 | 0.07 |
| | Zhou et al[36] 2020 | 559 | 82 | 14.7% | 23 | 44.2% | 0.55 | 0.08 |
| Indonesia | Rutherford et al[49] 2013 | 249 | 16 | 6.4% | 7 | 43.8% | 0.55 | 0.04 |
| Kenya | Kizito et al[50] 2011 | 1094 | 146 | 13.3% | 36 | 32.4% | 0.46 | 0.08 |
| | Masini et al[15] 2016 | 81600 | 3568 | 4.4% | 1836 | 51.5% | 0.59 | 0.03 |
| | Muture et al[37] 2011 | (unreported) | 359 | N/A | 164 | 45.7% | 0.56 | N/A |
| | Sitienei et al[31] 2015 | 135447 | 6439 | 4.8% | 2962 | 46.0% | 0.56 | 0.03 |
| Kuwait | Zhang et al[26] 2014 | 954 | 110 | 11.5% | 62 | 56.4% | 0.62 | 0.07 |
| Malaysia | Fun et al[51] 2013 | (unreported) | 176 | N/A | 120 | 68.2% | 0.67 | N/A |
| Moldova | Jenkins et al[38] 2013 | 3791 | 335 | 8.8% | 58 | 17.3% | 0.42 | 0.04 |
| Myanmar | Aung et al[52] 2019 | 58543 | 4215 | 7.2% | 293 | 7.0% | 0.37 | 0.03 |
| Nigeria | Alobu et al[39] 2014 | 789 | 60 | 7.6% | 27 | 45.0% | 0.56 | 0.04 |

Continued

**Table 2** Continued

| Country | Author, year | Number patients in the study (source population from which the number LFU derived) | Number of patients LFU in the study | Percentage of patients LFU in the study | Number of patients who became LFU by 2 months | Percentage of patients LFU by 2 months among patients who became LFU | Proportion of dose-months missed due to early discontinuation among patients who became LFU | Proportion of dose-months missed due to early discontinuation among all patients in the study |
|---|---|---|---|---|---|---|---|---|
| | Ukwaja[32] 2013 | 189 | 57 | 30.2% | 46 | 80.7% | 0.74 | 0.22 |
| Peru | Lackey et al[53] 2015 | 1233 | 127 | 10.3% | 20 | 15.7% | 0.41 | 0.04 |
| Russian Federation | Jakubowiak et al[17] 2009 | 1805 | 84 | 4.7% | 37 | 44.0% | 0.55 | 0.03 |
| South Africa | Berry et al[18] 2019 | 158 668 | 8710 | 5.5% | 3524 | 40.5% | 0.54 | 0.03 |
| | Kigozi et al[21] 2017 | 110 349 | 7980 | 7.2% | 2690 | 33.7% | 0.50 | 0.04 |
| Sri Lanka | Pinidiyapathirage et al[54] 2008 | 770 | 154 | 20.0% | 79 | 51.3% | 0.59 | 0.12 |
| Tajikistan | Wohlleben et al[55] 2017 | (unclear) | 300 | N/A | 103 | 34.3% | N/A | N/A |
| Thailand | Anuwatnonthakate et al[56] 2008 | 8031 | 841 | 10.5% | 414 | 49.2% | 0.58 | 0.06 |
| | Kittikraisak et al[57] 2009 | 769 | 61 | 7.9% | 22 | 36.1% | 0.51 | 0.04 |
| Uzbekistan | Hasker et al[58] 2008 | (unreported) | 117 | N/A | 102 | 87.2% | 0.77 | N/A |
| Yemen | Jaber et al[40] 2018 | 413 | 52 | 12.6% | 43 | 82.7% | 0.75 | 0.09 |

LFU by 2 months and percentages of dose-months lost due to early discontinuation (see formulae in the methods) (1) among those LFU and (2) the entire study population. Papers with no data on the number LFU by 2 months reported other timing of LFU data; see main text. Papers ordered by country; if multiple papers per country papers are arranged alphabetically by first author's surname. Reported numbers are for the number of people included in our calculations. These numbers could differ from the original numbers in a study due to, for example, not all patients in a study being treated with the eligible regimen or having data available on the timing of LFU. Where not all LFUs had timing data, the dose-month calculations were adjusted to reflect the entire population LFU.
*The timing of LFU was reported in these papers but the number LFU by 2 months could not be extracted.
†0.0% LFU at 2 months and thus this figure not calculated.
LFU, loss to follow-up; N/A, not applicable as the study did not report all the figures necessary; SAR, Special Administrative Region.

| Studies where more than a third of patients were LFU by the end of the first two months of treatment | Studies in which roughly a third of patients became LFU by the end of the first two months of treatment | Studies where less than a third of patients were LFU by the end of the first two months of treatment |
|---|---|---|
| China- 2 (45.0%, 51.2%)<br>Ethiopia- 2 (42.9%, 75.9%)<br>India- 7 (44.2%, 49.9%, 50.0%, 58.8%, 64.3%, 68.8%, 70.4%)<br>Indonesia- 1 (43.8%)<br>Kenya- 3 (45.7%, 46.0%, 51.5%)<br>Kuwait- 1 (56.4%)<br>Malaysia- 1 (68.2%)<br>Nigeria- 2 (45.0%, 80.7%)<br>Russian Federation- 1 (44.0%)<br>Sri Lanka- 1 (51.3%)<br>South Africa- 1 (40.5%)<br>Thailand- 1 (49.2%)<br>Uzbekistan- 1 (87.2%)<br>Yemen- 1 (82.7%)<br><br>**Total: 25** | Cameroon- 1 (37.7%)<br>Ethiopia- 1 (31.3%)<br>Kenya- 1 (32.4%)<br>South Africa- 1 (33.7%)<br>Tajikistan- 1 (34.3%)<br>Thailand- 1 (36.1%)<br><br>**Total: 6** | Haiti- 1 (22.6%)<br>India- 1 (0.0%)<br>Moldova- 1 (17.3%)<br>Myanmar- 1 (7.0%)<br>Peru- 1 (15.7%)<br><br><br>**Total: 5** |

**Figure 3** Studies grouped by timing when loss to follow-up occurred. Papers grouped by the percentage of patients who became LFU by 2 months among those LFU and by the country in which they were undertaken. The number indicates the number of studies from each country that satisfy the timing definition for that column, the figure in brackets the percentage of patients who became LFU who were LFU by 2 months. If LFU occurred evenly, approximately one-third of patients would be expected to be LFU by 2 months (central column). Four studies did not report the percentage of patients who became LFU by 2 months. China includes Hong Kong Special Administrative Region. Total number of studies—36. LFU, loss to follow-up.

measure the timing of LFU) did not clearly define what LFU was, but also did not provide an alternative to the WHO definition.[25 27–32]

### Timing of LFU

Of the 40 papers, 36 (90.0%) presented the percentage of patients LFU by the end of 2 months, that is, at the end of the intensive phase (figure 2B). Alternative data were also reported, for example, Chakrabartty et al and Wei et al stated that 42.8% and 61.9% of participants were LFU by month one, respectively.[25 28] Pefura Yone et al (2011) and Pefura-Yone et al (2016) stated that the median time to LFU was 90 and 120 days, respectively.[27 33] Tetart et al reported a mean of 8 weeks and Ukwaja et al of 2.2 months.[24 32]

The percentage LFU by 2 months ranged from 0.0% to 87.2% (36 studies), varying substantially both between and within countries (eg, 31.3%–75.9% in Ethiopia). Grouping the papers by what percentage of patients became LFU by 2 months, we found that the vast majority (31/36, 86.1%) reported an expected or greater than expected percentage LFU during the intensive phase (figure 3). In the sensitivity analysis excluding papers where the percentage of individuals not taking the regimen 2HRZE/4HR was documented (or thought likely to be to be) greater than 10%, this figure remained static (25/29, 86.2%) (online supplemental material H,

figure 2). When we excluded papers where the definition of LFU was not completely clear (although, on balance, we felt it was likely to meet our criterion), we also had similar findings (27/32, 84.4%) (online supplemental material I, figure 2).

Thirteen papers reported the timing of LFU such that our choice to use a time point of loss halfway through the intensive and continuation phases could be examined (online supplemental material J).[15 16 18 19 22 26 33–39] For LFU that occurred during the intensive phase (online supplemental material J panel b), substantial variability in the percentage that occurred during the first month was seen (10/13 studies (90.9%) provided these data), with no obvious pattern by country. Of the 10, 4 (40.0%) studies had >40%–≤60% of their intensive phase LFU occurring during the first month, 5 (50.0%) ≤40%, and 1 (10.0%) >60%. Examining the continuation phase data (online supplemental material J panel c), again substantial variability was observed without an obvious pattern. All 13 studies (100.0%) had data for the fourth month, of which 5 (38.5%) had >40–≤60% of their continuation phase LFU occurring up to this point and 8 (61.5%) >60%.

### Proportion of doses missed due to early discontinuation

Next, we used the timing of LFU data to calculate the proportion of dose-months missed due to early

discontinuation. Figures ranged from 0.37 to 0.77 (Myanmar and Uzbekistan, respectively; equivalent to 2.2–4.6 months) among those who were LFU and from 0.01 to 0.22 (Ethiopia and Nigeria, respectively; equivalent to 0.1–1.3 months) among all patients within a study (figure 2C). Proportions varied between and within countries. For example, a study from Yemen reported a high proportion of missed dose-months among those LFU of 0.75 (4.5 months of treatment) and 0.09 missed among the whole patient population (0.5 months of treatment) as the study had a low proportion of patients LFU.[40] By comparison, in one study from Nigeria, we found the proportion of missed dose-months was 0.74 (4.4 months of treatment) among those LFU and 0.22 (1.3 months of treatment) across all patients, as the percentage of patients LFU was higher than in Yemen.[32] Findings were not dissimilar in the sensitivity analysis excluding papers where the percentage of individuals not taking the regimen 2HRZE/4HR was documented (or thought likely to be to be) greater than 10% (online supplemental material H figure 1c). This was also true when we excluded papers where the definition of LFU was not completely clear (although, on balance, we felt it was likely to meet our criterion) (online supplemental material H figure 1c). This did, however, lead to the loss of the Nigerian study with 0.22 dose-months missed across all patients.

## DISCUSSION

In this systematic review, we present the first estimates of the burden of non-adherence due to early discontinuation from the drug-sensitive anti-TB regimen 2HRZE/4HR. By using LFU as a proxy measure for early discontinuation, we were able to use published studies for our calculations and rely on a globally reported, standardised, measure. Forty relevant studies from all six WHO world regions were identified. Globally and within countries, studies displayed great variability regarding when patients became LFU. While timing of when patients became LFU varied considerably (from 0.0% to 87.2% of patients becoming LFU by 2 months), 31 out of 36 papers containing relevant information reported a higher than or as expected percentage of patients becoming LFU during the first 2 months of treatment. It is likely that the complexity of the regimen, potentially greater likelihood of side-effects, and other factors such as stigma contribute to this burden of discontinuation early in treatment.[28] Early discontinuation calculations reflected the varied results found in timing to LFU, demonstrating an estimated 2.2–4.6 dose-months missed among those LFU and 0.1–1.3 months across all patients.

This paper extended and updated Kruk et al's 2008 systematic review of the timing of LFU among patients with TB in low-income and middle-income countries.[4] Kruk et al's study spanned 10 countries and found highly heterogeneous figures that could not be statistically aggregated, which was consistent with our findings. Their data suggested, however, that the majority of patients who became LFU completed the intensive phase of treatment, that is, the first two months; thus, Kruk et al argued for the importance of regimen shortening in decreasing the likelihood of LFU. Contrary to Kruk et al's findings, our study found that LFU occurred disproportionately during the intensive phase. The likely source of this difference was the different inclusion criteria surrounding treatment regimens.

Looking beyond drug-sensitive TB, we are aware of one meta-analysis of the timing of LFU for MDR disease. The study undertook an individual patient data (IPD) meta-analysis among 4099 patients with MDR-TB from 22 countries.[41] It found that the median time to LFU was 7 months (IQR 3–11 months). The majority of studies in the IPD meta-analysis included patients on 20–24 month regimens for MDR-TB.

Our study sought to quantify the burden of early discontinuation using the timing of LFU as a proxy marker, as limited dose-by-dose adherence data have been available to date. We are aware of one study that has explicitly quantified the percentage of doses missed due to early discontinuation, using dose-by-dose data from patients with drug-sensitive TB in China.[42] In contrast to our findings, this study found that early discontinuation was more common after the first 2 months of treatment than before; however, any period of discontinuation (even of a single dose) was considered and thus the findings are not directly comparable. Additionally, the patients in this study were within a cluster-randomised trial of medication event monitor boxes and thus may have behaved differently to the patients in our review, where the majority of data were collected within observational studies and from clinical notes.

A key strength of our review is that it presents the first estimates of the burden of early discontinuation from the drug-sensitive anti-TB regimen 2HRZE/4HR, using routine data. Our review used the WHO's standardised definition of LFU,[9 10] and thus we will not have captured discontinuation of less than 2 months towards the end of treatment. Although the WHO definition of LFU technically covers both non-initiation of treatment and treatment stoppages of 2 months, we focused on the latter within this study in order to fulfil our aim of quantifying discontinuation. The use of a human filter during our search led to the initial exclusion of Pardeshi[34] and possibly other papers of which we are not aware. Our calculations of the percentage of dose-months lost due to early discontinuation would have been improved by the presence of more accurate data on either the timing of LFU (ie, monthly data) or, ideally, dose-by-dose adherence data.[8] Examination of 13 papers which provided more granular data on the timing of LFU indicated that intensive phase calculations could potentially have benefitted from the use of a timepoint of loss later than halfway, which would result in less dose-months being missed. The continuation phase calculations could potentially have benefitted from an earlier timepoint,

which would result in more dose-months being missed. In the absence of a meta-analysis (problematic, given heterogeneity) and even more detailed data (complex, when LFU is generally recorded at clinical appointments that is, monthly), suggesting exact alternatives to the use of a timepoint of loss halfway through each treatment phase is difficult. Additionally, data sparsity and heterogeneity made using monthly data on its own (ie, without trying to fit it into a framework of phase) impossible. Our approach means that, where studies documented a higher burden of LFU during the intensive phase, we are currently overestimating the dose-months missed among both the population LFU and study population. Where studies documented a lower burden of LFU during the intensive phase, we are underestimating the dose-months missed in both populations. We excluded studies from children and adolescents, but note the importance of studying adherence in both of these population groups, particularly adolescents, for whom further work is required. We performed sensitivity analysis to account for the fact that some included studies contained patients not treated with 2HRZE/4HR and where the definition of LFU was not completely clear.

The findings of our review have interesting implications for the development and refinement of adherence-promoting interventions. The reasons why patients discontinue from treatment at different times are likely to be multifactorial and should be part of intervention development. We were able to find only a single study (included in this systematic review) that reported on the reasons for early discontinuation at different time points, which explored stigma.[28] We found that the proportion of doses missed due to discontinuation varied substantially between countries. A single summary figure of the burden of early discontinuation globally is thus unlikely to be helpful for National TB Programmes. Instead, country-specific or even setting-specific data are required for informed decision-making. Settings where early discontinuation is common and occurs in the intensive phase may require different adherence-promoting interventions (or different components of interventions) versus those where early discontinuation is less common or occurs relatively late in treatment.

The advent of shortened regimens has the potential to remove much of the early discontinuation issue by reducing the time window in which it can occur,[43] and the economic, social and psychological pressure that longer regimens place on patients. Given our findings about the burden of early discontinuation during the intensive phase, however, roll-out of regimens such as that successfully trialled in Study 31 needs to be closely monitored to ascertain their real-world impact.[44]

## CONCLUSIONS

In conclusion, in our systematic review of the burden of early discontinuation from the drug-sensitive TB regimen 2HRZE/4HR, we found that the timing of LFU varied considerably both between and within countries. The majority of papers, however, reported high percentages of patients becoming LFU by the end of 2 months, which emphasises the need for interventions promoting healthcare engagement and adherence early on in treatment. The impact of shortened regimens on global patterns of discontinuation needs to be closely monitored.

**Author affiliations**
[1]Usher Institute, University of Edinburgh, Edinburgh, UK
[2]Faculty of Life and Health Sciences, University of Liverpool, Liverpool, UK
[3]Institute for Global Health, University College London, London, UK
[4]Department of Infectious Disease Epidemiology, London School of Hygiene & Tropical Medicine, London, UK
[5]School of Public Health, University of the Witwatersrand- Johannesburg, Johannesburg, South Africa

**Competing interests** HRS declares funding directly related to this study from the UK Medical Research Council (MRC) (MR/R008345/1) and the NIHR Health Technology Assessment Programme, UK (16/88/06). HRS also declares payments or honorarium from the Latvian Society Against Tuberculosis (event funded by Otsuka and Johnson and Johnson) outside of this work. MF declares funding directly related to this study from UK MRC (MR/R008345/1). EFW declares funding directly related to this study from the UK MRC (MR/N013166/1). AR and KLF have no competing interests to declare related to this study.

**Patient consent for publication** Not applicable.

**Ethics approval** Not applicable.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** All data relevant to the study are included in the article or uploaded as supplementary information.

**ORCID iDs**
Elizabeth F Walker http://orcid.org/0000-0003-4339-0574
Helen R Stagg http://orcid.org/0000-0003-4022-3447

## REFERENCES
1 World Health Organization. Global tuberculosis report 2023. 2023. Available: https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2023 [Accessed 08 Dec 2023].

2    DiStefano MJ, Schmidt H. mHealth for tuberculosis treatment adherence: a framework to guide ethical planning, implementation, and evaluation. *Glob Health Sci Pract* 2016;4:211–21.

3    Karat AS, Jones ASK, Abubakar I, *et al*. "You have to change your whole life": a qualitative study of the dynamics of treatment adherence among adults with tuberculosis in the United Kingdom. *J Clin Tuberc Other Mycobact Dis* 2021;23:100233.

4    Kruk ME, Schwalbe NR, Aguiar CA. Timing of default from tuberculosis treatment: a systematic review. *Trop Med Int Health* 2008;13:703–12.

5    Matteelli A, Rendon A, Tiberi S, *et al*. Tuberculosis elimination: where are we now. *Eur Respir Rev* 2018;27:148.

6    Ngwatu BK, Nsengiyumva NP, Oxlade O, *et al*. The impact of digital health technologies on tuberculosis treatment: a systematic review. *Eur Respir J* 2018;51:1701596.

7    Vrijens B, De Geest S, Hughes DA, *et al*. A new taxonomy for describing and defining adherence to medications. *Br J Clin Pharmacol* 2012;73:691–705.

8    Stagg HR, Flook M, Martinecz A, *et al*. All nonadherence is equal but is some more equal than others? Tuberculosis in the digital era. *ERJ Open Res* 2020;6:00315-2020.

9    Linh NN, Viney K, Gegia M, *et al*. World Health Organization treatment outcome definitions for tuberculosis: 2021 update. *Eur Respir J* 2021;58:2100804.

10   Definitions and reporting framework for tuberculosis – 2013 revision (WHO/HTM/TB/2013.2). Geneva World Health Organization; 2013. Available: https://apps.who.int/iris/handle/10665/79199 [Accessed 19 Jan 2022].

11   World Health Organization. World health organization regions by country 2021. Available: https://www.who.int/countries [Accessed 20 Jan 2021].

12   World Bank. World Bank country and lending groups. 2022. Available: https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups [Accessed 24 Jan 2023].

13   Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health* 1998;52:377–84.

14   Deeks J, Dinnes J, D'Amico R, *et al*. Evaluating non-randomised intervention studies. *Health Technol Assess* 2003;7:27.

15   Masini EO, Mansour O, Speer CE, *et al*. Using survival analysis to identify risk factors for treatment interruption among new and retreatment tuberculosis patients in Kenya. *PLoS ONE* 2016;11:e0164172.

16   Schnaubelt ER, Charles M, Richard M, *et al*. Loss to follow-up among patients receiving anti-tuberculosis treatment, Haiti, 2011-2015. *Public Health Action* 2018;8:154–61.

17   Jakubowiak W, Bogorodskaya E, Borisov S, *et al*. Treatment interruptions and duration associated with default among new patients with tuberculosis in six regions of Russia. *Int J Infect Dis* 2009;13:362–8.

18   Berry KM, Rodriguez CA, Berhanu RH, *et al*. Treatment outcomes among children, adolescents, and adults on treatment for tuberculosis in two metropolitan municipalities in Gauteng province, South Africa. *BMC Public Health* 2019;19:973.

19   Chan-Yeung M, Noertjojo K, Leung CC, *et al*. Prevalence and predictors of default from tuberculosis treatment in Hong Kong. *Hong Kong Med J* 2003;9:263–8.

20   Chang KC, Leung CC, Tam CM. Risk factors for defaulting from anti-tuberculosis treatment under directly observed treatment in Hong Kong. *Int J Tuberc Lung Dis* 2004;8:1492–8.

21   Kigozi G, Heunis C, Chikobvu P, *et al*. Factors influencing treatment default among tuberculosis patients in a high burden province of South Africa. *Int J Infect Dis* 2017;54:95–102.

22   Paunikar AP, Khadilkar HA, Doibale MK, *et al*. Survival analysis of treatment defaulters among tuberculosis patients in government medical college and hospital, Aurangabad. *Indian J Community Med* 2019;44:44–7.

23   Shaweno T, Getnet M, Fikru C. Does time to loss to follow-up differ among adult tuberculosis patients initiated on tuberculosis treatment and care between general hospital and health centers? A retrospective cohort study. *Trop Med Health* 2020;48:9.

24   Tetart M, Meybeck A, Assaf A, *et al*. Factors of loss to follow-up during tuberculosis treatment in a low-incidence region. *Med Mal Infect* 2020;50:28–35.

25   Wei X, Zou G, Yin J, *et al*. Providing financial incentives to rural-to-urban tuberculosis migrants in Shanghai: an intervention study. *Infect Dis Poverty* 2012;1.

26   Zhang Q, Gaafer M, El Bayoumy I. Determinants of default from pulmonary tuberculosis treatment in Kuwait. *Sci World J* 2014;2014:672825.

27   Pefura-Yone E, Enono-Edende P, Fatime-Abaicho H, *et al*. Health care system and patient determinants of loss to follow-up during tuberculosis treatment in capital city of Cameroon. *Am J Respir Crit Care Med* 2016;193.

28   Chakrabartty A, Basu P, Ali KM, *et al*. Tuberculosis related stigma attached to the adherence of directly observed treatment short course (DOTS) in West Bengal, India. *Indian J Tuberc* 2019;66:259–65.

29   Dandona R, Dandona L, Mishra A, *et al*. Utilization of and barriers to public sector tuberculosis services in India. *Natl Med J India* 2004;17:292–9.

30   Rathee D, Arora P, Meena M, *et al*. Comparative study of clinico-bacterio-radiological profile and treatment outcome of smokers and nonsmokers suffering from pulmonary tuberculosis. *Lung India* 2016;33:507–11.

31   Sitienei J, Kipruto H, Mansour O, *et al*. Correlates of default from anti-tuberculosis treatment: a case study using Kenya's electronic data system. *Int J Tuberc Lung Dis* 2015;19:1051–6.

32   Ukwaja KN. Tuberculosis treatment default among TB-HIV Co-infected patients in Nigeria. *Ann Trop Med Public Health* 2013;6:382.

33   Pefura Yone EW, Kengne AP, Kuaban C. Incidence, time and determinants of tuberculosis treatment default in Yaounde, Cameroon: a retrospective hospital register-based cohort study. *BMJ Open* 2011;1:e000289.

34   Pardeshi GS. Time of default in tuberculosis patients on directly observed treatment. *J Glob Infect Dis* 2010;2:226–30.

35   Parida A, Bairy KL, Chogtu B, *et al*. Comparison of directly observed treatment short course (DOTS) with self-administered therapy in pulmonary tuberculosis in Udupi District of South India. *J Clin Diagn Res* 2014;8:HC29–31.

36   Zhou TJ, Lakshminarayanan S, Sarkar S, *et al*. Predictors of loss to follow-up among men with tuberculosis in Puducherry and Tamil Nadu, India. *Am J Trop Med Hyg* 2020;103:1050–6.

37   Muture BN, Keraka MN, Kimuu PK, *et al*. Factors associated with default from treatment among tuberculosis patients in Nairobi province, Kenya: a case control study. *BMC Public Health* 2011;11:696.

38   Jenkins HE, Ciobanu A, Plesca V, *et al*. Risk factors and timing of default from treatment for non-multidrug-resistant tuberculosis in Moldova. *Int J Tuberc Lung Dis* 2013;17:373–80.

39   Alobu I, Oshi SN, Oshi DC, *et al*. Risk factors of treatment default and death among tuberculosis patients in a resource-limited setting. *Asian Pac J Trop Med* 2014;7:977–84.

40   Saleh Jaber AA, Khan AH, Syed Sulaiman SA. Evaluation of tuberculosis defaulters in yemen from the perspective of health care service. *J Pharm Health Serv Res* 2018;9:381–92.

41   Walker IF, Shi O, Hicks JP, *et al*. Analysis of loss to follow-up in 4099 multidrug-resistant pulmonary tuberculosis patients. *Eur Respir J* 2019;54:1800353.

42   Stagg HR, Lewis JJ, Liu X, *et al*. Temporal factors and missed doses of tuberculosis treatment. A causal associations approach to analyses of digital adherence data. *Ann Am Thorac Soc* 2020;17:438–49.

43   Papineni P, Phillips P, Lu Q, *et al*. TRUNCATE-TB: an innovative trial design for drug-sensitive tuberculosis. *Int J Infect Dis* 2016;45:404.

44   Dorman SE, Nahid P, Kurbatova EV, *et al*. Four-month rifapentine regimens with or without moxifloxacin for tuberculosis. *N Engl J Med* 2021;384:1705–18.

45   Ambaw F, Mayston R, Hanlon C, *et al*. Untreated depression and tuberculosis treatment outcomes, quality of life and disability, Ethiopia. *Bull World Health Organ* 2018;96:243–55.

46   Muñoz-Sellart M, Cuevas LE, Tumato M, *et al*. Factors associated with poor tuberculosis treatment outcome in the Southern region of Ethiopia. *Int J Tuberc Lung Dis* 2010;14:973–9.

47   Vasudevan K, Jayakumar N, Gnanasekaran D. Smear conversion, treatment outcomes and the time of default in registered tuberculosis patients on RNTCP DOTS in Puducherry, South India. *J Clin Diagn Res* 2014;8:JC05–8.

48   Veeramani G, Madhusudan S. Study on default among tuberculosis patients treated under directly observed treatment short course. *Der Pharmacia Lettre* 2015;7:163–8.

49   Rutherford ME, Hill PC, Maharani W, *et al*. Risk factors for treatment default among adult tuberculosis patients in Indonesia. *Int J Tuberc Lung Dis* 2013;17:1304–9.

50   Kizito KW, Dunkley S, Kingori M, *et al*. Lost to follow up from tuberculosis treatment in an urban informal settlement (Kibera),

Nairobi, Kenya: what are the rates and determinants? *Trans R Soc Trop Med Hyg* 2011;105:52–7.

51 Fun WH, Wu DBC, Cheong YM, *et al*. The health and economic effects on public health due to patients' default in tuberculosis treatment in Malaysia. *Value Health* 2013;16:A365.

52 Aung YK, Swe PP, Kyaw Z, *et al*. Differential loss to follow-up rates among adult tuberculosis patients - findings from the largest private sector tuberculosis clinic database in Myanmar. *PLoS One* 2019;14:e0218450.

53 Lackey B, Seas C, Van der Stuyft P, *et al*. Patient characteristics associated with tuberculosis treatment default: a cohort study in a high-incidence area of Lima, Peru. *PLoS ONE* 2015;10:e0128541.

54 Pinidiyapathirage J, Senaratne W, Wickremasinghe R. Prevalence and predictors of default with tuberculosis treatment in Sri Lanka. *Southeast Asian J Trop Med Public Health* 2008;39:1076–82.

55 Wohlleben J, Makhmudova M, Saidova F, *et al*. Risk factors associated with loss to follow-up from tuberculosis treatment in Tajikistan: a case-control study. *BMC Infect Dis* 2017;17:543.

56 Anuwatnonthakate A, Limsomboon P, Nateniyom S, *et al*. Directly observed therapy and improved tuberculosis treatment outcomes in Thailand. *PLoS ONE* 2008;3:e3089.

57 Kittikraisak W, Burapat C, Kaewsa-ard S, *et al*. Factors associated with tuberculosis treatment default among HIV-infected tuberculosis patients in Thailand. *Trans R Soc Trop Med Hyg* 2009;103:59–66.

58 Hasker E, Khodjikhanov M, Usarova S, *et al*. Default from tuberculosis treatment in Tashkent, Uzbekistan; who are these Defaulters and why do they default *BMC Infect Dis* 2008;8:97.

15

**Supplementary material**


# Quantifying nonadherence to anti-tuberculosis treatment due to early discontinuation: A systematic literature review of timings to loss to follow-up

1

Supplemental material

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

*BMJ Open Respir Res*

**Supplementary Material A- Search terms**

Medline, Embase (both through Ovid), and the Web of Science were searched on the 14th January 2021 using the following terms.

**Medline and Embase**

| | Term | Results |
|---|---|---|
| 1 | tuberculos*.mp. | 307,639 |
| 2 | TB.mp. | 122,769 |
| 3 | Tuberculosis/ or exp tuberculosis, pulmonary/ | 169,839 |
| 4 | "lost to follow up".mp. | 48,952 |
| 5 | "loss to follow up".mp. | 12,286 |
| 6 | "drop out".mp. | 12,399 |
| 7 | LTFU.mp. | 1,824 |
| 8 | LFU.mp. | 420 |
| 9 | Interruption.mp. | 48,578 |
| 10 | default*.mp. | 43,217 |
| 11 | discontinuation.mp. | 123,825 |
| 12 | treatment.mp. | 9,762,609 |
| 13 | therapy.mp. | 9,624,927 |
| 14 | "Directly Observed Therapy".mp. | 4,777 |
| 15 | DOT.mp. | 73,513 |
| 16 | 1 or 2 or 3 | 340,011 |
| 17 | 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 | 281,664 |
| 18 | 12 or 13 or 14 or 15 | 14,270,364 |
| 19 | 16 and 17 and 18 | 6,700 |
| 20 | limit 19 to human | 6,195 |
| 21 | limit 20 to yr="1998 -Current" | 6,072 |

**Web of Science**

| | Term | Results |
|---|---|---|
| 1 | TS=(tuberculo* or TB) | 177,034 |
| 2 | TI=(tuberculo* or TB) | 90,942 |
| 3 | AB=(tuberculo* or TB) | 122,072 |
| 4 | TI=("lost to follow up" or "loss to follow up" or drop*out or LTFU or LFU or interruption or defaul* or discontinuation) | 24,435 |
| 5 | TS=("lost to follow up" or "loss to follow up" or drop*out or LTFU or LFU or interruption or defaul* or discontinuation) | 170,482 |
| 6 | AB=("lost to follow up" or "loss to follow up" or drop*out or LTFU or LFU or interruption or defaul* or discontinuation) | 142,961 |
| 7 | TI=(treatment or therapy or "DOT" or "directly observed therapy") | 1,591,350 |
| 8 | AB=(treatment or therapy or "DOT" or "directly observed therapy") | 4,655,327 |
| 9 | TS=(treatment or therapy or "DOT" or "directly observed therapy") | 5,837,603 |
| 10 | 1 or 2 or 3 | 177,034 |
| 11 | 4 or 5 or 6 | 170,482 |
| 12 | 7 or 8 or 9 | 5,837,603 |
| 13 | 10 and 11 and 12 | 2,310 |

**Supplementary Material B- Comparison of our review to Kruk *et al.***

This work was an extension and update of a previous review by Kruk *et al.*[1] with different inclusion and exclusion criteria.

|  | Kruk inclusion criteria | Our inclusion criteria |
|---|---|---|
| **Population** | Studies limited to lower middle and low income countries, no limit to patient age, studies published between 1998-2006. | No restriction by country, adult patients over the age of 18, studies published between January 1998-January 2021. |
| **Exposure** | All drug therapies for drug sensitive TB. | Patients being treated with the six-month drug sensitive TB regimen 2HRZE/4HR, dosed daily. |
| **Outcome** | Definition of LFU not restricted to the WHO definition: 'A variety of criteria for defining TB default were accepted (e.g. noncompletion of treatment, an interruption of 2 or more months).' | LFU defined as per the WHO definition. Papers where an alternative definition of LFU was not stated, and it was thought likely that the WHO definition was used, were included. |

*2HRZE/4HR- two months of isoniazid (H), rifampicin (R), pyrazinamide (Z), and ethambutol (E) followed by four months of H and R; LFU- loss to follow-up; TB- tuberculosis; WHO- World Health Organization*

Supplemental material

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

*BMJ Open Respir Res*

**Supplementary Material C- Data extraction tool**

The following data extraction tool was used for the review.

| Items extracted | Study |
|---|---|
| Author | |
| Title | |
| Year of publication | |
| Journal | |
| Study population | |
| Study design | |
| Years under study | |
| Country of study | |
| Size of study population | |
| Percentage of the study population not on 2HRZE/4HR | |
| Number in study population LFU by 6 months | |
| Percentage of study population LFU by 6 months | |
| Timing of LFU | |
| Number in study population LFU by 2 months | |
| Percentage of study population LFU by 2 months | |
| Additional data on the timing of LFU | |

*2HRZE/4HR- two months of isoniazid (H), rifampicin (R), pyrazinamide (Z), and ethambutol (E) followed by four months of H and R; LFU- loss to follow-up*

4

Supplemental material

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

*BMJ Open Respir Res*

**Supplementary Material D- Classifying the burden of disease**

Studies were classified on the basis of the burden of disease in the country at the time of the study. There were four categories, all defined by the World Health Organization (WHO):

1) ***High tuberculosis (TB) burden countries***. For data from the years 1996-1998 'high-burden' was classified as the top 22 countries for estimated TB incidence.[2-4] For data from the year 1999,[5] this was increased to 23 countries. For data from the period 2000-2015, this was formalised as the countries ranked 1st to 22nd in terms of their estimated number of incident cases in 2000, with Mozambique replacing Peru in 2002.[6] For the period 2016-20 a set list of 30 countries was chosen: the 20 countries with the highest estimated numbers of incident TB cases, plus the top 10 countries with the highest estimated TB incidence rate not otherwise in the top 20 by absolute number.[6] For the period 2021-25 again a set list of 30 countries was chosen, determined as per 2016-20.[7]

2) ***High TB-HIV burden countries***. This list was established in 2005 as the 41 countries that accounted for 97% of the estimated global number of HIV-positive TB cases, and re-assessed yearly up until 2009.[6, 8] From the 2009 changes to 2015, it was a static list of 41 countries.[6] For the period 2016-20 a set list of 30 countries was chosen: the 20 with the highest estimated numbers of incident TB cases among people living with HIV, plus the top 10 countries with the highest estimated TB/HIV incidence rate that were not in the top 20 by absolute number.[6] For the period 2021-25 again a set list of 30 countries was chosen, determined as per 2016-20.[7]

3) ***High multidrug resistant (rifampicin resistant) (MDR (RR))-TB burden countries***. This list was established in 2008 as 27 countries estimated by WHO in that year to have had at least 4,000 MDR-TB cases occurring annually and/or at least 10% of newly registered TB cases with MDR-TB.[6] Between 2009 and 2015 the list of 27 countries was static.[6] For the period 2016-2020 it became a list of 30 countries, the 20 with the highest estimated numbers of incident MDR-TB cases, plus the top 10 countries with the highest estimated MDR-TB incidence rate that were not in the top 20 by absolute number.[6] For the period 2021-25 again a set list of 30 countries was chosen, determined as per 2016-20.[7] The inclusion of RR-TB reflected the WHO's recommendations around the use of GeneXpert in 2010.[9]

4) ***Not a high burden country***. Countries that do not fit into any of the categories above.

5

Supplemental material

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

*BMJ Open Respir Res*

**Supplementary Material E- Quality assessment tool**

Our study used an adapted version of Downs and Black to assess the quality of included papers.[10] We inserted questions 8, 13, 11, 16 as per the guidance of Deeks *et al.*[11]

Questions 1-6 and 17-19 were completed for all studies. Questions 7-11 were answered if the study did not specifically aim to measure the timing of loss to follow-up (LFU). Questions 12-16 were answered if the aim/one of the aims of the study was to measure the timing of LFU.

| | |
|---|---|
| 1 | Was the study design clearly reported? |
| 2 | Was the hypothesis/aim/objective of the study clearly described? |
| 3 | Were the characteristics of the patients included in the study clearly described? |
| 4 | Were the patients that were in the study at the point of measuring the timing of LFU representative of the population targeted in the aim? |
| 5 | Were the main findings of the study clearly described? |
| 6 | If any of the results of the study were based on 'data dredging', was this made clear? |
| 7 | Were the main outcomes to be measured clearly described in the introduction or methods section? |
| 8 | Was LFU measured using accurate (valid and reliable) information? |
| 9 | Was there potential for observer bias in ascertainment of LFU? |
| 10 | Did the study provide estimates of the random variability in the data for the main outcome(s)? |
| 11a | Were all reported LFUs within the first six months of treatment (if treatment was extended beyond six months)? |
| 11b | If answer to 11a was no, were the LFU numbers reported clearly enough to allow extraction of how many patients were LFU after the end of the six month treatment period? |
| 12 | Was the main outcome (i.e. LFU) to be measured clearly described in the introduction or methods section? |
| 13 | Was the main outcome (i.e. LFU) measured using accurate (valid and reliable) information? |
| 14 | Was there potential for observer bias in ascertainment of the outcome (i.e. LFU)? |
| 15 | Did the study provide estimates of the random variability in the data for the main outcome (i.e. LFU)? |
| 16a | Were all reported LFUs within the first six months of treatment (if treatment was extended beyond six months)? |
| 16b | If answer to 16a was no, were the LFU numbers reported clearly enough to allow extraction of how many patients were LFU after the end of the six month treatment period? |
| 17 | Were the study results appropriately interpreted e.g. in terms of the strength of the evidence, its application/implications, and causality? |
| 18 | Precision score |
| 19 | Power score |

*LFU- loss to follow-up.*

6

**Supplementary Material F- Relative precision**

The relative precision $(R)$ for a confidence interval for a proportion $(p = n/N)$ is given by:

$$p \pm (Rp)$$

For each study, we calculated $R$ based on a 95% confidence interval (CI), which is given by:

$$R = \frac{(1.96 SE)}{p}$$

where

$$SE = \sqrt{\frac{p(1-p)}{N}}$$

$R$ was given a score ranging from 1-4 based on the following (pragmatic) groups:

Relative precision score =1      $R$ ≤0.10 (10%)
Relative precision score =2      $R$ >0.10 and ≤0.35
Relative precision score =3      $R$ >0.35 and ≤0.60
Relative precision score =4      $R$ >0.60


Examples:
For the Dandona study,[12] the proportion of everyone who became LFU who was LFU by two months was $p$ =371/744=0.50
Therefore, $SE$ =0.0183, giving $R$ =7.2% and the precision score was 1.

For the Vasudevan study,[13] the proportion of everyone who became LFU who was LFU by two months was $p$ =14/28=0.50
Therefore, $SE$ =0.0945, giving $R$ =37.0% and the precision score was 3.

7

**Supplementary Material G- Late stage exclusion papers**

The following are papers that were excluded late in the full text screening process as they were close to inclusion but did not quite meet the requirements of our review.

| Paper | Reason for exclusion |
|---|---|
| Enane, 2019[14] | Study focussed on children, adolescents and young adults. Whilst it was possible to extract data for young adults separately, they would have been unrepresentative of the overall population with TB. |
| Kliimann, 2010[15] | Reported LFUs were across a very long time period and it was not possible to restrict the data extracted to those within six months of the start of treatment. |
| Hailemeskel, 2017[16] | Introduction of the paper suggested all patients received streptomycin. |
| Lepcha, 2017[17] | Discussion suggested regimen dosed thrice weekly. |
| Mundra, 2017[18] | Discussion suggested regimen dosed thrice weekly. |
| Secretary of Jan Swasthya Sahyog, 2018[19] | It was not possible to extract data from this paper due to concerns about the consistency of the stated denominators. |
| Sariem, 2020[20] | Timings were reported for 'defaulters', which included more individuals than just those who fulfilled the WHO definition of LFU. |

*LFU- Loss to follow-up; TB- tuberculosis; WHO- World Health Organization*

**Supplementary Material H- Sensitivity analyses (treatment regimen)**

**Supplementary Material H Figure 1 - Sensitivity analysis (treatment regimen): Global distribution of included studies, the timing of LFU, and the percentage of dose-months missed due to early discontinuation**

*This figure replicates figure 2 in the main manuscript, but additionally excludes studies where the percentage of individuals not taking the regimen two months of isoniazid, rifampicin, ethambutol and pyrazinamide followed by four months of isoniazid and rifampicin was documented (or thought likely to be to be) greater than 10%.*

*Maps display the countries from which data emanated, with the number of studies per nation illustrated with a circle placed on the relevant nation. China includes Hong Kong Special Administrative Region. Russia= Russian Federation. Reported numbers are for the number of people included in our calculations. These numbers could differ from the original numbers in a study due to e.g. not all patients in a study being treated with the eligible regimen or having data available on the timing of LFU. 31 studies included in panel a), of which 29 provide data in the balloons of panels b) and c).*

*a) Dark grey- number of participants in the study or studies i.e. the source population from which the number LFU was derived. Light grey- percentage of patients LFU or the range of percentages.*

*b) Dark grey- percentage LFU by two months, of those LFU. Range if more than one study from a country.*

*c) Dark grey- the proportion or range of proportions of dose-months missed due to early discontinuation among patients that were LFU. Light grey- the proportion or range of proportions of dose-months missed due to early discontinuation among all patients in the study. Where not all LFUs had timing data the dose-month calculations were adjusted to reflect the entire population LFU.*

*LFU- loss to follow-up.*

a)

Supplemental material

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

*BMJ Open Respir Res*

b)

Moldova
17.3%

Uzbekistan
87.2%

Russia
44.0%

Tajikistan
34.3%

Nigeria
45.0 - 80.7%

Haiti
22.6%

Cameroon
37.7%

Peru
15.7%

Kenya
32.4 - 51.5%

Myanmar
7.0%

Thailand
36.1 - 49.2%

Malaysia
68.2%

Ethiopia
31.3 - 42.9%

Yemen
82.7%

India
44.2 - 70.4%

Sri Lanka
51.3%

Indonesia
43.8%

c)

Moldova
0.42
0.04

Uzbekistan
0.77
N/A

Russia
0.55
0.03

Tajikistan
N/A
N/A

Nigeria
0.56 - 0.74
0.04 - 0.22

Haiti
0.45
0.04

Cameroon
0.52
0.10

Peru
0.41
0.04

Kenya
0.46 - 0.59
0.03 - 0.08

Myanmar
0.37
0.03

Thailand
0.51 - 0.58
0.04 - 0.06

Malaysia
0.67
N/A

Indonesia
0.55
0.04

Ethiopia
0.49 - 0.55
0.01 - 0.05

Yemen
0.75
0.09

India
0.55 - 0.69
0.03 - 0.17

Sri Lanka
0.59
0.12

10

**Supplementary Material H Figure 2 - Sensitivity analysis (treatment regimen): Studies grouped by timing of patients becoming LFU**

*This figure replicates figure 3 in the main manuscript, but additionally excludes studies where the percentage of individuals not taking the regimen two months of isoniazid, rifampicin, ethambutol and pyrazinamide followed by four months of isoniazid and rifampicin was documented (or thought likely to be to be) greater than 10%.*

*Papers grouped by the percentage of patients who became LFU by two months among those LFU and by the country in which they were undertaken. The number indicates the number of studies from each country that satisfy the timing definition for that column, the figure in brackets the percentage of patients who became LFU who were LFU by two months. If LFU occurred evenly, approximately one third of patients would be expected to be LFU by two months (central column). Four studies did not report the percentage of patients who became LFU by two months. Total number of studies- 29. LFU-loss to follow-up.*

| Studies where more than a third of patients were LFU by the end of the first two months of treatment | Studies in which roughly a third of patients became LFU by the end of the first two months of treatment | Studies where less than a third of patients were LFU by the end of the first two months of treatment |
| --- | --- | --- |
| Ethiopia- 1 (42.9%)<br>India- 7 (44.2%, 49.9%, 50.0%, 58.8%, 64.3%, 68.8%, 70.4%)<br>Indonesia- 1 (43.8%)<br>Kenya- 3 (45.7%, 46.0%, 51.5%)<br>Malaysia- 1 (68.2%)<br>Nigeria- 2 (45.0%, 80.7%)<br>Russian Federation- 1 (44.0%)<br>Sri Lanka- 1 (51.3%)<br>Thailand- 1 (49.2%)<br>Uzbekistan- 1 (87.2%)<br>Yemen- 1 (82.7%)<br><br>**Total: 20** | Cameroon- 1 (37.7%)<br>Ethiopia- 1 (31.3%)<br>Kenya- 1 (32.4%)<br>Tajikistan- 1 (34.3%)<br>Thailand- 1 (36.1%)<br><br>**Total: 5** | Haiti- 1 (22.6%)<br>Moldova- 1 (17.3%)<br>Myanmar- 1 (7.0%)<br>Peru- 1 (15.7%)<br><br>**Total: 4** |

11

**Supplementary Material I- Sensitivity analyses (LFU definition)**

**Supplementary Material I Figure 1 - Sensitivity analysis (LFU definition): Global distribution of included studies, the timing of LFU, and the percentage of dose-months missed due to early discontinuation**

*This figure replicates figure 2 in the main manuscript, but additionally excludes studies where the definition of LFU was not completely clear (although, on balance, we felt they were likely to meet our criterion).*

*Maps display the countries from which data emanated, with the number of studies per nation illustrated with a circle placed on the relevant nation. China includes Hong Kong Special Administrative Region. Russia= Russian Federation. Reported numbers are for the number of people included in our calculations. These numbers could differ from the original numbers in a study due to e.g. not all patients in a study being treated with the eligible regimen or having data available on the timing of LFU. 33 studies included in panel a), of which 32 provide data in the balloons of panels b) and c).*

*a) Dark grey- number of participants in the study or studies i.e. the source population from which the number LFU was derived. Light grey- percentage of patients LFU or the range of percentages.*

*b) Dark grey- percentage LFU by two months, of those LFU. Range if more than one study from a country.*

*c) Dark grey- the proportion or range of proportions of dose-months missed due to early discontinuation among patients that were LFU. Light grey- the proportion or range of proportions of dose-months missed due to early discontinuation among all patients in the study. Where not all LFUs had timing data the dose-month calculations were adjusted to reflect the entire population LFU.*

*LFU- loss to follow-up.*

a)

Supplemental material

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

*BMJ Open Respir Res*

b)



c)

Supplemental material

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

*BMJ Open Respir Res*

**Supplementary Material I Figure 2 - Sensitivity analysis (LFU definition): Studies grouped by timing of patients becoming LFU**

*This figure replicates figure 3 in the main manuscript, but additionally excludes studies where the definition of LFU was not completely clear (although, on balance, we felt they were likely to meet our criterion).*

*Papers grouped by the percentage of patients who became LFU by two months among those LFU and by the country in which they were undertaken. The number indicates the number of studies from each country that satisfy the timing definition for that column, the figure in brackets the percentage of patients who became LFU who were LFU by two months. If LFU occurred evenly, approximately one third of patients would be expected to be LFU by two months (central column). Total number of studies- 32. LFU- loss to follow-up.*

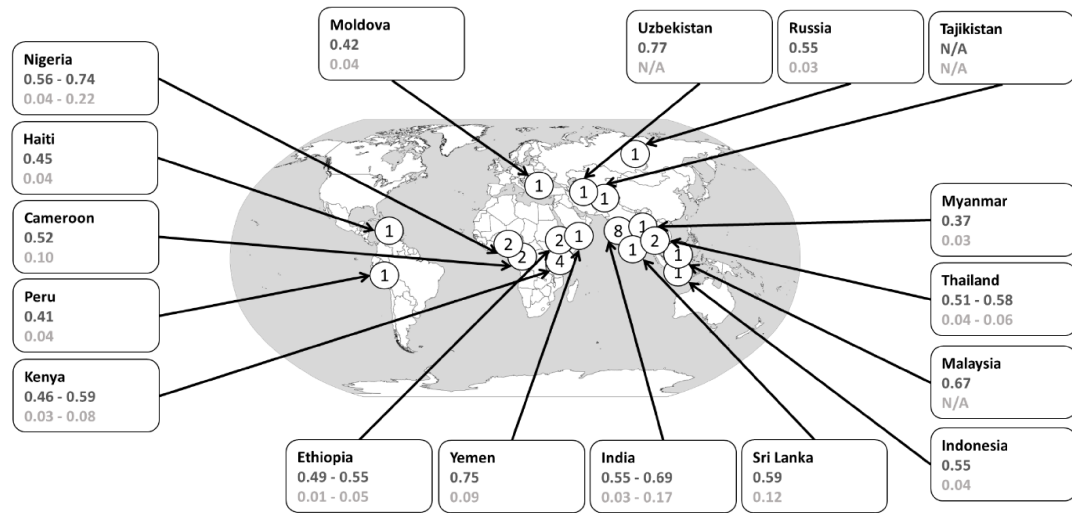| Studies where more than a third of patients were LFU by the end of the first two months of treatment | Studies in which roughly a third of patients became LFU by the end of the first two months of treatment | Studies where less than a third of patients were LFU by the end of the first two months of treatment |
|---|---|---|
| China- 2 (45.0%, 51.2%)<br>Ethiopia- 2 (42.9%, 75.9%)<br>India- 5 (44.2%, 50.0%, 58.8%, 64.3%, 70.4%)<br>Indonesia- 1 (43.8%)<br>Kenya- 2 (45.7%, 51.5%)<br>Kuwait- 1 (56.4%)<br>Malaysia- 1 (68.2%)<br>Nigeria- 1 (45.0%)<br>Russian Federation- 1 (44.0%)<br>Sri Lanka- 1 (51.3%)<br>South Africa- 1 (40.5%)<br>Thailand- 1 (49.2%)<br>Uzbekistan- 1 (87.2%)<br>Yemen- 1 (82.7%)<br><br>**Total: 21** | Cameroon- 1 (37.7%)<br>Ethiopia- 1 (31.3%)<br>Kenya- 1 (32.4%)<br>South Africa- 1 (33.7%)<br>Tajikistan- 1 (34.3%)<br>Thailand- 1 (36.1%)<br><br>**Total: 6** | Haiti- 1 (22.6%)<br>India- 1 (0.0%)<br>Moldova- 1 (17.3%)<br>Myanmar- 1 (7.0%)<br>Peru- 1 (15.7%)<br><br>**Total: 5** |

14

Supplemental material

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

*BMJ Open Respir Res*

**Supplementary Material J- Granular timing of LFU data**

*We plotted cumulative LFU for the thirteen studies with granular data on the timing of LFU. Panel a) contains data across the entire treatment period, b) only the intensive phase, and c) only the continuation phase. Cumulative LFU was calculated separately per phase for panels b) and c). Paunikar 2019 had no individuals LFU prior to the third month and thus does not have datapoints in panel b).*

a)



b)

Supplemental material

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

*BMJ Open Respir Res*

c)

Supplemental material

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

*BMJ Open Respir Res*

**References**

1.      Kruk ME, Schwalbe NR, Aguiar CA. Timing of default from tuberculosis treatment: a systematic review. Trop Med Int Health. 2008;13(5):703-12.

2.      World Health Organization. Global Tuberculosis Control: WHO report 1998. https://iris.who.int/bitstream/handle/10665/63835/WHO_TB_98.237.pdf?sequence=1. Accessed 05 October 2023.

3.      World Health Organization. Global Tuberculosis Control: WHO report 1999. https://iris.who.int/bitstream/handle/10665/63835/WHO_TB_99.259.pdf?sequence=3. Accessed 05 October 2023.

4.      World Health Organization. Global Tuberculosis Control: WHO report 2000. https://iris.who.int/bitstream/handle/10665/63835/WHO_TB_98.237.pdf?sequence=2. Accessed 05 October 2023.

5.      World Health Organization. Global Tuberculosis Control: WHO report 2001. https://iris.who.int/bitstream/handle/10665/63835/WHO_CDS_TB_2001.287.pdf?sequence=4. Accessed 05 October 2023.

6.      World Health Organization. Use of high burden country lists for TB by WHO in the post-2015 era. https://www.almendron.com/tribuna/wp-content/uploads/2018/04/high-tb-burdencountrylists2016-2020.pdf. Accessed 05 October 2023.

7.      World Health Organization. WHO global lists of high burden countries for tuberculosis (TB), TB/HIV and multidrug/rifampicin-resistant TB (MDR/RR-TB), 2021–2025. Background document. https://cdn.who.int/media/docs/default-source/hq-tuberculosis/who_globalhbcliststb_2021-2025_backgrounddocument.pdf?sfvrsn=f6b854c2_9. Accessed 05 October 2023.

8.      World Health Organization. WHO report 2005. Global Tuberculosis control. Surveillance, Planning, Financing. https://iris.who.int/bitstream/handle/10665/144569/9241562919_eng.pdf?sequence=1. Accessed 05 October 2023.

9.      World Health Organization. Xpert MTB/RIF implementation manual: technical and operational 'how-to'; practical considerations. https://www.who.int/publications/i/item/9789241506700. Accessed 05 October 2023.

10.     Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health. 1998;52(6):377-84.

11.     Deeks JJ, Dinnes J, D'Amico R, *et al.* Evaluating non-randomised intervention studies. Health Technol Assess. 2003;7(27):iii-x, 1-173.

12.     Dandona R, Dandona L, Mishra A, *et al.* Utilization of and barriers to public sector tuberculosis services in India. Natl Med J India. 2004;17(6):292-9.

13.     Vasudevan K, Jayakumar N, Gnanasekaran D. Smear Conversion, Treatment Outcomes and the Time of Default in Registered Tuberculosis Patients on RNTCP DOTS in Puducherry, Southern India. J Clin Diagn Res. 2014;8(10):JC05-8.

14.     Enane LA, Lowenthal ED, Arscott-Mills T, *et al.* Investigating Outcomes of Adolescents and Young Adults (10-24 Years of Age) Lost to Follow-up from Tuberculosis Treatment in Gaborone, Botswana. Pediatr Infect Dis J. 2019;38(10):e271-e4.

15.     Kliiman K, Altraja A. Predictors and mortality associated with treatment default in pulmonary tuberculosis. Int J Tuberc Lung Dis. 2010;14(4):454-63.

16.     Hailemeskel S, Mohammed OY, Ahmed AM. Retrospective assessment of the status and determinants of tuberculosis treatment outcome among patients treated in government hospitals in North Shoa Administrative Zone, Amhara Regional State, Ethiopia. Res Rep Trop Med. 2017;8:65-71.

17.     Lepcha LS, Jain AK, Nandy P. Sociodemographic profile and treatment outcome of tuberculosis patients registered under directly observed treatment short course in East Sikkim with reference to defaulters. JMS - Journal of Medical Society. 2017;31:147–51.

17

18.     Mundra A, Deshmukh PR, Dawale A. Magnitude and determinants of adverse treatment outcomes among tuberculosis patients registered under Revised National Tuberculosis Control Program in a Tuberculosis Unit, Wardha, Central India: A record-based cohort study. J Epidemiol Glob Health. 2017;7(2):111-8.

19.     Secretary Of Jan Swasthya S, Laux TS, Patil S. Predictors of tuberculosis treatment outcomes among a retrospective cohort in rural, Central India. J Clin Tuberc Other Mycobact Dis. 2018;12:41-7.

20.     Sariem CN, Odumosu P, Dapar MP, *et al.* Tuberculosis treatment outcomes: a fifteen-year retrospective study in Jos-North and Mangu, Plateau State, North - Central Nigeria. BMC Public Health. 2020;20(1):1224.

Supplemental material

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

*BMJ Open Respir Res*

## Online Supplemental Table 1 - Quality assessment of included studies

*Quality assessment of included studies, undertaken using an adapted version of Downs and Black.[13] Questions 1-6 and 17-19 were answered for all studies. Questions 7-11 were answered if the study did not specifically aim to measure the timing of LFU. Questions 12-16 were answered if the aim/one of the aims of the study was to measure the timing of LFU. Power scores >95-≤100%= score 1, >90-≤95%= score 2, >85-≤90%= score 3, >80-≤85%= score 4, >70-≤80%=score 5, ≤70% = score 6. Precision scores- ≤10% relative precision around the percentage LFU at two months in the study (score 1), >10 - ≤35% (score 2) or, >35 - ≤60% (score 3), or >60% (score 4). LFU- loss to follow-up; N- no; N/A- not applicable, question was unanswered as it was irrelevant for that paper; U- unsure; Y- yes.*

| | | Pefura Yone, 2011[33] | Pefura-Yone, 2016[27] | Chang, 2004[20] | Chan-Yeung 2003[19] | Wei, 2012[25] | Ambaw, 2018[45] | Munoz-Sellart, 2010[46] | Shaweno, 2020[23] | Tetart, 2020[24] | Schnaubelt, 2018[16] | Chakrabartty, 2019[28] | Dandona, 2004[29] | Pardeshi, 2010[34] | Parida, 2014[35] | Paunikar, 2019[22] | Rathee, 2016[30] | Vasudevan, 2014[47] | Veeramani and Madhusudhan, 2015[48] | Zhou, 2020[36] | Rutherford, 2013[49] | Kizito, 2011[50] | Masini, 2016[15] | Muture, 2011[37] | Sitienei, 2015[31] | Zhang, 2014[26] | Fun, 2013[51] | Jenkins, 2013[38] | Aung, 2019[52] | Alobu, 2014[39] | Ukwaja, 2013[32] | Lackey, 2015[53] | Jakubowiak, 2009[17] | Berry, 2019[18] | Kigozi, 2017[21] | Pinidiyapathirage, 2008[54] | Wohlleben, 2017[55] | Anuwatnonthakate, 2008[56] | Kittikraisak, 2009[57] | Hasker, 2008[58] | Saleh Jaber, 2018[40] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Study design clear | Y | Y | Y | Y | N | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | N | Y | Y | Y | Y | Y | Y | N | N | Y | Y | Y | Y | Y | Y | Y | N | Y | N | Y | Y | Y | Y | Y |
| 2 | Hypothesis/ aims/ objectives clear | Y | Y | Y | Y | N | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| 3 | Patient characteristics clear | Y | Y | Y | Y | N | Y | Y | Y | Y | Y | N | N | N | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| 4 | Selection bias | Y | Y | Y | N | N | Y | N | Y | Y | Y | U | U | U | N | Y | U | Y | Y | Y | N | Y | Y | N | N | Y | N | U | Y | N | N | N | Y | Y | Y | Y | N | Y | Y | U | N |
| 5 | Main findings | Y | Y | Y | Y | Y | Y | Y | Y | N | N | Y | N | Y | Y | N | Y | Y | Y | Y | Y | Y | Y | Y | N | N | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | N | Y | N | Y |
| 6 | Data dredging | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| 7 | Main outcomes clear | | N | Y | Y | N | Y | Y | | Y | Y | N | Y | | Y | | Y | | Y | Y | Y | Y | | N | Y | Y | | Y | Y | | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| 8 | Measurement of LFU accurate | | U | Y | Y | Y | Y | Y | | U | Y | Y | Y | | Y | | U | | Y | Y | Y | Y | | Y | Y | Y | | Y | Y | | Y | Y | Y | Y | N | Y | Y | Y | Y | | Y |
| 9 | Observer bias | | U | N | N | Y | Y | N | | U | N | N | Y | | N | | U | | Y | N | N | N | | N | N | N | | N | N | | N | N | N | N | Y | N | N | N | | N |
| 10 | Estimates of random variability | | Y | Y | Y | N | N | Y | | Y | Y | N | N | | N | | Y | | N | Y | Y | Y | | Y | Y | N | | Y | Y | | Y | Y | Y | Y | Y | Y | Y | N | Y | | Y |
| 11a | All reported LFUs within 6 months? | | U | N | U | U | Y | U | | U | Y | N | Y | | Y | | U | | Y | Y | Y | Y | | Y | N | U | | Y | Y | | N | Y | Y | U | N | U | Y | Y | | Y |
| 11b | If no, do reported LFU numbers reflect this? | | U | N | U | U | N/A | U | | U | N/A | N | N/A | | N/A | | U | | N/A | N/A | N/A | N/A | | N/A | N | U | | N/A | N/A | | N | N/A | N/A | U | Y | U | N/A | N/A | | N/A |

1

| | | Pefura Yone, 2011[33] | Pefura-Yone, 2016[27] | Chang, 2004[20] | Chan-Yeung 2003[19] | Wei, 2012[25] | Ambaw, 2018[45] | Munoz-Sellart, 2010[46] | Shaweno, 2020[23] | Tetart, 2020[24] | Schnaubelt, 2018[16] | Chakrabartty, 2019[28] | Dandona, 2004[29] | Pardeshi, 2010[34] | Parida, 2014[35] | Paunikar, 2019[22] | Rathee, 2016[30] | Vasudevan, 2014[47] | Veeramani and Madhusudhan, 2015[48] | Zhou, 2020[36] | Rutherford, 2013[49] | Kizito, 2011[50] | Masini, 2016[15] | Muture, 2011[37] | Sitienei, 2015[31] | Zhang, 2014[26] | Fun, 2013[51] | Jenkins, 2013[38] | Aung, 2019[52] | Alobu, 2014[39] | Ukwaja, 2013[32] | Lackey, 2015[53] | Jakubowiak, 2009[17] | Berry, 2019[18] | Kigozi, 2017[21] | Pinidiyapathirage, 2008[54] | Wohlleben, 2017[55] | Anuwatnonthakate, 2008[56] | Kittikraisak, 2009[57] | Hasker, 2008[58] | Saleh Jaber, 2018[40] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 12 | Main outcomes (LFU) clear | Y | | | | | | | Y | | | | | Y | Y | Y | | | | | | | Y | Y | | | | Y | | | N | | | | | | | | | Y | |
| 13 | Main outcome (LFU) measures accurate | Y | | | | | | | Y | | | | | Y | Y | Y | | | | | | | Y | Y | | | | Y | | | Y | | | | | | | | | Y | |
| 14 | Observer bias | N | | | | | | | N | | | | | N | N | N | | | | | | | N | N | | | | N | | | N | | | | | | | | | N | |
| 15 | Estimates of random variability | Y | | | | | | | Y | | | | | N | Y | N | | | | | | | Y | Y | | | | Y | | | Y | | | | | | | | | N | |
| 16a | All reported LFUs within six months? | Y | | | | | | | Y | | | | | N | N | N | | | | | | | N | Y | | | | Y | | | U | | | | | | | | | N | |
| 16b | If no, do reported LFU numbers reflect this? | N/A | | | | | | | N/A | | | | | Y | N | Y | | | | | | | Y | N/A | | | | N/A | | | U | | | | | | | | | N | |
| 17 | Interpretation | Y | Y | N | Y | N | Y | Y | Y | N | Y | N | Y | Y | N | N | N | Y | N | Y | Y | Y | Y | Y | N | Y | Y | Y | Y | N | Y | Y | Y | Y | Y | Y | Y | Y | Y | N | Y |
| 18 | Precision score | 2 | N/A | 2 | 1 | N/A | 3 | 2 | 1 | N/A | 1 | N/A | 1 | 3 | 3 | N/A | 2 | 3 | 2 | 2 | 3 | 2 | 1 | 2 | 1 | 2 | 1 | 2 | 2 | 2 | 2 | 3 | 2 | 1 | 1 | 2 | 2 | 1 | 2 | 1 | 2 |
| 19 | Power score | 6 | N/A | 3 | 1 | N/A | 6 | 6 | 1 | N/A | 1 | N/A | 1 | 6 | 6 | N/A | 5 | 6 | 1 | 6 | 6 | 6 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 6 | 1 | 1 | 6 | 1 | 6 | 1 | 6 | 1 | 6 | 1 | 1 |

2