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Impact of diagnostic strategies for tuberculosis using lateral flow urine lipoarabinomannan assay in people living with HIV (Review)

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[Intervention Review]

Impact of diagnostic strategies for tuberculosis using lateral flow urine lipoarabinomannan assay in people living with HIV

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ABSTRACT

Background

Tuberculosis is the primary cause of hospital admission in people living with HIV, and the likelihood of death in the hospital is unacceptably high. The Alere Determine TB LAM Ag test (AlereLAM) is a point-of-care test and the only lateral flow lipoarabinomannan assay (LF-LAM) assay currently commercially available and recommended by the World Health Organization (WHO). A 2019 Cochrane Review summarised the diagnostic accuracy of LF-LAM for tuberculosis in people living with HIV. This systematic review assesses the impact of the use of LF-LAM (AlereLAM) on mortality and other patient-important outcomes.

Objectives

To assess the impact of the use of LF-LAM (AlereLAM) on mortality in adults living with HIV in inpatient and outpatient settings.

To assess the impact of the use of LF-LAM (AlereLAM) on other patient-important outcomes in adults living with HIV, including time to diagnosis of tuberculosis, and time to initiation of tuberculosis treatment.

Search methods

We searched the Cochrane Infectious Diseases Group Specialized Register; the Cochrane Central Register of Controlled Trials (CENTRAL); MEDLINE (PubMed); Embase (Ovid); Science Citation Index Expanded (Web of Science), BIOSIS Previews, Scopus, LILACS; ProQuest Dissertations and Theses; ClinicalTrials.gov; and the WHO ICTRP up to 12 March 2021.

Selection criteria

Randomized controlled trials that compared a diagnostic intervention including LF-LAM with diagnostic strategies that used smear microscopy, mycobacterial culture, a nucleic acid amplification test such as Xpert MTB/RIF, or a combination of these tests. We included adults (≥ 15 years) living with HIV.

Data collection and analysis

Two review authors independently assessed trials for eligibility, extracted data, and analysed risk of bias using the Cochrane tool for assessing risk of bias in randomized studies. We contacted study authors for clarification as needed. We used risk ratio (RR) with 95% confidence intervals (CI). We used a fixed-effect model except in the presence of clinical or statistical heterogeneity, in which case we used a random-effects model. We assessed the certainty of the evidence using GRADE.

Main results

We included three trials, two in inpatient settings and one in outpatient settings. All trials were conducted in sub-Saharan Africa and assessed the impact of diagnostic strategies that included LF-LAM on mortality when the test was used in conjunction with other tuberculosis diagnostic tests or clinical assessment for clinical decision-making in adults living with HIV.

Inpatient settings

In inpatient settings, the use of LF-LAM testing as part of a tuberculosis diagnostic strategy likely reduces mortality in people living with HIV at eight weeks compared to routine tuberculosis diagnostic testing without LF-LAM (pooled RR 0.85, 95% CI 0.76 to 0.94; 5102 participants, 2 trials; moderate-certainty evidence). That is, people living with HIV who received LF-LAM had 15% lower risk of mortality. The absolute effect was 34 fewer deaths per 1000 (from 14 fewer to 55 fewer).

In inpatient settings, the use of LF-LAM testing as part of a tuberculosis diagnostic strategy probably results in a slight increase in the proportion of people living with HIV who were started on tuberculosis treatment compared to routine tuberculosis diagnostic testing without LF-LAM (pooled RR 1.26, 95% CI 0.94 to 1.69; 5102 participants, 2 trials; moderate-certainty evidence).

Outpatient settings

In outpatient settings, the use of LF-LAM testing as part of a tuberculosis diagnostic strategy may reduce mortality in people living with HIV at six months compared to routine tuberculosis diagnostic testing without LF-LAM (RR 0.89, 95% CI 0.71 to 1.11; 2972 participants, 1 trial; low-certainty evidence). Although this trial did not detect a difference in mortality, the direction of effect was towards a mortality reduction, and the effect size was similar to that in inpatient settings.

In outpatient settings, the use of LF-LAM testing as part of a tuberculosis diagnostic strategy may result in a large increase in the proportion of people living with HIV who were started on tuberculosis treatment compared to routine tuberculosis diagnostic testing without LF-LAM (RR 5.44, 95% CI 4.70 to 6.29, 3022 participants, 1 trial; low-certainty evidence).

Other patient-important outcomes

Assessment of other patient-important and implementation outcomes in the trials varied. The included trials demonstrated that a higher proportion of people living with HIV were able to produce urine compared to sputum for tuberculosis diagnostic testing; a higher proportion of people living with HIV were diagnosed with tuberculosis in the group that received LF-LAM; and the incremental diagnostic yield was higher for LF-LAM than for urine or sputum Xpert MTB/RIF.

Authors' conclusions

In inpatient settings, the use of LF-LAM as part of a tuberculosis diagnostic testing strategy likely reduces mortality and probably results in a slight increase in tuberculosis treatment initiation in people living with HIV. The reduction in mortality may be due to earlier diagnosis, which facilitates prompt treatment initiation. In outpatient settings, the use of LF-LAM testing as part of a tuberculosis diagnostic strategy may reduce mortality and may result in a large increase in tuberculosis treatment initiation in people living with HIV. Our results support the implementation of LF-LAM to be used in conjunction with other WHO-recommended tuberculosis diagnostic tests to assist in the rapid diagnosis of tuberculosis in people living with HIV.

PLAIN LANGUAGE SUMMARY

Impact of diagnostic strategies for tuberculosis using lateral flow urine lipoarabinomannan test in people living with HIV

What was the aim of this review?

Tuberculosis is the leading cause of death in people living with HIV. The disease is particularly difficult to diagnose in people living with HIV, in part because it is often challenging to produce sputum for diagnosis. The lateral flow urine lipoarabinomannan test (LF-LAM) is a World Health Organization (WHO)-recommended rapid test to assist in the detection of active tuberculosis in people living with HIV. This review is limited to studies that used the Alere Determine TB LAM Ag test (AlereLAM), which is the only LF-LAM test currently recommended by the WHO; thus LF-LAM refers only to AlereLAM in this review. Rapid and early tuberculosis diagnosis may allow for prompt treatment and prevent severe illness and death. The aim of this review was to determine whether the use of LF-LAM testing had an effect on death and other patient-important outcomes in people living with HIV.

Key messages

In inpatient settings, the use of LF-LAM as part of a tuberculosis diagnostic testing strategy likely reduces deaths and probably results in a slight increase in tuberculosis treatment initiation in people living with HIV.

In outpatient settings, the use of LF-LAM testing as part of a tuberculosis diagnostic strategy may reduce deaths and may result in a large increase in tuberculosis treatment initiation in people living with HIV.

What was studied in the review?

We searched for trials in adults (15 years and older) that evaluated the effect of a tuberculosis diagnostic strategy that included the LF-LAM test compared to standard care using other WHO-recommended diagnostic tests in adults living with HIV.

What were the main results of the review?

We identified three trials, two in inpatient settings and one in outpatient settings.

Inpatient settings

In inpatient settings, the use of LF-LAM testing as part of a tuberculosis diagnostic strategy likely reduces mortality in people living with HIV at eight weeks compared to routine tuberculosis diagnostic testing without LF-LAM (2 trials, 5102 participants, moderate-certainty evidence).

In inpatient settings, the use of LF-LAM testing as part of a tuberculosis diagnostic strategy probably results in a slight increase in the proportion of people living with HIV who were started on tuberculosis treatment compared to routine tuberculosis diagnostic testing without LF-LAM (2 trials, 5102 participants moderate-certainty evidence).

Outpatient settings

In outpatient settings, the use of LF-LAM testing as part of a tuberculosis diagnostic strategy may reduce mortality in people living with HIV at six months compared to routine tuberculosis diagnostic testing without LF-LAM (1 trial, 2972 participants, low-certainty evidence).

In outpatient settings, the use of LF-LAM testing as part of a tuberculosis diagnostic strategy may result in a large increase in the proportion of people living with HIV who were started on tuberculosis treatment compared to routine tuberculosis diagnostic testing without LF-LAM (1 trial, 3022 participants, low-certainty evidence).

Other patient-important outcomes

The included studies assessed other patient-important outcomes in different ways. The studies demonstrated that more people living with HIV were able to produce urine compared to sputum for tuberculosis diagnostic testing, and more people living with HIV were diagnosed with tuberculosis in the group that received LF-LAM.

How up-to-date is the review?

We searched for relevant trials up to 12 March 2021.

SUMMARY OF FINDINGS

Summary of findings 1. Effect of LF-LAM compared to no LF-LAM on mortality and tuberculosis treatment initiation in people living with HIV, inpatient settings

Patient or population: adults living with HIV
Setting: inpatients (Peter 2016 in 10 hospitals in South Africa, Tanzania, Zambia and Zimbabwe; Gupta-Wright 2018 in 2 hospitals in South Africa and Malawi)
Intervention: diagnostic strategy including LF-LAM
Comparison: standard of care (diagnostic strategy that did not include LF-LAM)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no LF-LAM	Risk with LF-LAM				
Mortality at 8 weeks	230 per 1000	196 per 1000 (175 to 216)	RR 0.85 (0.76 to 0.94)	5102 (2 RCTs)	⊕⊕⊕⊖ MODERATE[a,b]	In inpatient settings, the use of LF-LAM testing as part of a tuberculosis diagnostic strategy likely reduces mortality in people living with HIV at eight weeks compared to routine tuberculosis diagnostic testing without LF-LAM.
People started on tuberculosis treatment	305 per 1000	384 per 1000 (287 to 515)	RR 1.26 (0.94 to 1.69)	5102 (2 RCTs)	⊕⊕⊕⊖ MODERATE[a,b]	In inpatient settings, the use of LF-LAM testing as part of a tuberculosis diagnostic strategy probably results in a slight increase in the proportion of people living with HIV who were started on tuberculosis treatment compared to routine tuberculosis diagnostic testing without LF-LAM.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **LF-LAM:** lateral flow urine lipoarabinomannan assay; **RCT:** randomized controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]We did not downgrade. In Gupta-Wright 2018, investigators, all study staff (other than the laboratory technician and statistician), hospital-attending clinical teams, and participants were masked to the study group allocation. In Peter 2016, neither participants nor research nurses were masked to either allocation or test results. However, we doubt that the test results were biased in light of this.

[b]We downgraded one level for indirectness. The two trials were conducted in African countries. We do not have direct evidence of the applicability of the findings to other settings outside of Africa, although we note that Peter 2016 took place at 10 sites across four countries, and Gupta-Wright 2018 took place in two sites across two countries. In Gupta-Wright 2018, the test was conducted in the laboratory, not at the point of care. In addition, the intervention in Gupta-Wright 2018 was a combination of urine LAM and urine Xpert. In Peter 2016, the intervention was urine LAM plus a "nurse-informed" treatment decision. These additional considerations may not reflect how the test would be performed in routine practice.

Summary of findings 2. Effect of LF-LAM compared to no LF-LAM on mortality and tuberculosis treatment initiation in people living with HIV, outpatient settings

Patient or population: adults living with HIV

Settings: outpatients (Grant 2020 in 24 primary healthcare clinics in South Africa)

Intervention: diagnostic strategy including LF-LAM
Comparison: standard of care (diagnostic strategy that did not include LF-LAM)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with no LF-LAM	Risk with LF-LAM				
Mortality at 6 months	102 per 1000	90 per 1000 (72 to 113)	RR 0.89 (0.71 to 1.11)	2972 (1 RCT)	⊕⊕⊖⊖ LOW[a,b]	In outpatient settings, the use of LF-LAM testing as part of a tuberculosis diagnostic strategy may reduce mortality in people living with HIV at six months compared to routine tuberculosis diagnostic testing without LF-LAM.
People started on tuberculosis treatment	114 per 1000	618 per 1000 (534 to 714)	RR 5.44 (4.70 to 6.29	3022 (1 RCT)	⊕⊕⊖⊖ LOW[a,b]	In outpatient settings, the use of LF-LAM testing as part of a tuberculosis diagnostic strategy may result in a large increase in the proportion of people living with HIV who were started on tuberculosis treatment compared to routine tuberculosis diagnostic testing without LF-LAM.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **LF-LAM:** lateral flow urine lipoarabinomannan assay; **RCT:** randomized controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

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[a]We downgraded one level for indirectness. Only one trial was included, which was conducted in South Africa. We do not have direct evidence of the applicability of the findings to other settings.
[b]We downgraded one level for imprecision. The 95% CI crosses 1; nonetheless this point estimate is consistent with the effect seen in inpatients and we did not downgrade further.

BACKGROUND

The same or similar text appears in the Background section in several other Cochrane protocols and reviews on tests for diagnosing tuberculosis (Bjerrum 2019; Kay 2020; Kohli 2021; Shapiro 2021).

Description of the condition

Tuberculosis (TB) is an airborne infection caused by the bacterium *Mycobacterium tuberculosis*. Although pulmonary tuberculosis (infection in the lungs) is the most common form of the disease, tuberculosis can affect almost any other site in the body (extrapulmonary tuberculosis). Globally in 2019, 10 million people were estimated to become sick due to tuberculosis, of whom 1.4 million died (including 208,000 people living with HIV), making tuberculosis a leading cause of death due to an infectious disease in adults (WHO Global Tuberculosis Report 2020). Tuberculosis is the primary cause of hospital admission and death in people living with HIV, with cohort studies demonstrating an in-hospital attributable mortality of 25% in HIV-positive adults and 30% in HIV-positive children across regions (Ford 2016). A systematic review of health facility-based autopsy studies demonstrated that in-hospital mortality may be even higher, with tuberculosis accounting for approximately 40% of deaths in HIV-positive people (Gupta 2015). Furthermore, it is likely that current estimates of mortality that rely on verbal autopsies underestimate mortality due to HIV-associated tuberculosis (Karat 2017). Importantly, in almost half of those with tuberculosis, the disease remained undiagnosed at the time of death (Gupta 2015). Tuberculosis is a curable infection, and global policy emphasizes the importance of early diagnosis and initiation of effective treatment to improve individual outcomes and decrease transmission (Barrera 2015; WHO Global Tuberculosis Report 2020). The World Health Organization (WHO) estimates that, from 2000 to 2019, more than 60 million lives were saved by diagnosing and treating tuberculosis. The COVID-19 pandemic threatens to reverse the gains made in recent years. A modelling study by the WHO suggests that there could be between 200,000 and 400,000 additional tuberculosis deaths in 2020 if, over a period of three months, 25% to 50% fewer people were detected and treated with tuberculosis (WHO Global Tuberculosis Report 2020).

In 2019, there was a substantial gap (2.9 million) between the 10 million estimated cases of tuberculosis and the number of people newly diagnosed and reported to national programmes (WHO Global Tuberculosis Report 2020). Even those who are diagnosed often face extensive delays (Hanson 2017; Sreeramareddy 2014). The agreed-upon best reference standard for pulmonary tuberculosis is sputum culture (Lewinsohn 2017). However, culture is a relatively complex and slow procedure, and test results may not be available for two to eight weeks. Xpert MTB/RIF (Cepheid, Sunnyvale, USA), Xpert Ultra (Cepheid, Sunnyvale, USA), and Truenat (Molbio Diagnostics/Bigtec Labs, Goa/Bengaluru, India) are molecular diagnostic assays that use nucleic acid amplification to determine the presence of *M tuberculosis* and resistance to rifampicin (one of the core first-line antibiotics used to treat tuberculosis). They are recommended by the WHO as initial tests for any person being evaluated for tuberculosis (WHO Consolidated Guidelines (Module 3) 2020). Xpert MTB/RIF and Xpert Ultra can be used to test extrapulmonary specimens; however, for most non-respiratory specimens, the sensitivity is lower than for sputum specimens (Kohli 2021). Individuals with tuberculosis and HIV co-infection face particular challenges since they are often unable to produce sputum specimens and are more likely than HIV-negative individuals to have extrapulmonary disease, which is harder to diagnose (Pai 2016; Shivakoti 2017). The WHO recommends that people living with HIV be systematically screened for active tuberculosis at each visit to a health facility (WHO Compendium of WHO Guidelines 2018). Typically, screening consists of evaluation for four symptoms of tuberculosis: cough, fever, night sweats, and weight loss, followed, for those who screen positive, by microbiological testing, which should include a WHO-recommended rapid diagnostic test in all individuals being evaluated for tuberculosis (WHO Consolidated Guidelines (Module 3) 2020). However, increasing data from prevalence surveys demonstrate high rates of tuberculosis in asymptomatic individuals (WHO Global Tuberculosis Report 2020), highlighting the gap in current symptom-based screening approaches, which is particularly pertinent for those at higher risk of disease progression, such as people living with HIV.

There is an urgent need for a rapid non-sputum-based diagnostic test for tuberculosis (WHO Target Product Profile 2014). Such a biomarker-based diagnostic test should ideally be highly sensitive, enable a short time to diagnosis (less than one hour), have minimal maintenance and ideally no calibration, and be low cost (< USD 6) (WHO Target Product Profile 2014). There has been growing interest in the detection of mycobacterial antigens such as lipoarabinomannan (LAM) in urine, a specimen that is easy to collect and process without the infection control risks associated with the collection of sputum. Despite increasing interest in the development of biomarker-based tuberculosis diagnostics (MacLean 2019), only one biomarker-based test has been recommended by the WHO for tuberculosis diagnosis: the lateral flow lipoarabinomannan assay (LF-LAM) (WHO Consolidated Guidelines (Module 3) 2020).

Description of the intervention

The LF-LAM assay is a commercially available point-of-care test for active tuberculosis. This review is limited to studies that used the Alere Determine TB LAM Ag (AlereLAM) (Abbott, Palatine, IL, USA, previously Alere Inc, Waltham, MA, USA), which is the only LF-LAM test currently recommended by the WHO; thus in the context of this review, LF-LAM refers only to AlereLAM. LF-LAM is an immunocapture assay that detects LAM antigen in urine. LAM is a lipopolysaccharide present in mycobacterial cell walls (Brennan 2003), which is released from metabolically active or degenerating bacterial cells during tuberculosis disease (Briken 2004). LAM is detectable in the urine of people with active tuberculosis disease by enzyme-linked immunosorbent assay (ELISA) and the lateral flow testing platforms (Lawn 2012; Minion 2011; Shah 2016). LF-LAM is performed manually by applying 60 µL of urine to the test strip and incubating at room temperature for 25 minutes (Alere 2020). The strip is then inspected by eye. The intensity of any visible band on the test strip is graded by comparing it with the intensities of the bands on a manufacturer-supplied reference scale card. Of note, the reference scale was revised in January 2014. Prior to January 2014, the reference scale card included five bands (grade 1 representing a very low intensity band to grade 5 representing a high/dark intensity band). After January 2014, the manufacturer revised the reference scale card to have four reference bands, such that the band intensity for the new grade 1 corresponded to the band intensity for the previous grade 2). Under the current manufacturer recommendations (using the revised four

bands reference card), only bands that are grade 1 or higher are considered positive (Alere 2020; Bjerrum 2019). If there are no bands, or the bands present do not meet the degree of colour intensity of the reference card (a faint band in the patient window that is lighter than the first positive band on the reference card), the test should be considered negative (WHO Operational Handbook (Module 3) 2020).

The original Cochrane Review on the diagnostic accuracy of LF-LAM, Shah 2016, and a meta-analysis of an earlier generation of the LAM ELISA test, Minion 2011, both demonstrated increased sensitivity for tuberculosis amongst people living with HIV with advanced immunosuppression, compared to people living with HIV with higher CD4 counts. Several hypotheses may explain the higher sensitivity of urine LAM in people living with HIV including higher bacillary burden and antigen load (Shah 2010), greater likelihood of genitourinary tract tuberculosis, and greater glomerular permeability to allow increased antigen levels in urine (Lawn 2016; Minion 2011).

A Cochrane Review update on the diagnostic accuracy of LF-LAM for the detection of tuberculosis in HIV-positive adults found that LF-LAM has a sensitivity of 42% and specificity of 91% to diagnose tuberculosis in HIV-positive individuals with tuberculosis symptoms and sensitivity of 35% and specificity of 95% in HIV-positive individuals not assessed for tuberculosis symptoms. LF-LAM sensitivity is higher in inpatients compared to outpatients and those with lower CD4 cell counts compared to those with higher CD4 counts, whereas specificity is lower in both of these subgroups (Bjerrum 2019).

In 2015, informed by the original Cochrane Review (Shah 2016), the WHO made a conditional recommendation for using LF-LAM to assist with the diagnosis of tuberculosis in HIV-positive people with advanced disease, and a strong recommendation against using the test "as a screening test for tuberculosis" based on the data among unselected participants (WHO Consolidated Guidelines (Module 3) 2020). Based on evidence from randomized trials and an updated Cochrane Review (Bjerrum 2019), the WHO currently recommends that LF-LAM should be used to assist in the diagnosis of active tuberculosis in HIV-positive adults, adolescents, and children (WHO Consolidated Guidelines (Module 3) 2020). The key change from the WHO 2015 guidelines is a broadening of the indication for use of the LF-LAM assay among HIV-positive inpatients with signs and symptoms of active tuberculosis (pulmonary and extrapulmonary) irrespective of their CD4 count or inpatients with advanced HIV or who are seriously ill or irrespective of signs and symptoms of active tuberculosis if they have a CD4 count of less than 200 cells/µL. The updated guidelines recommend the use of LF-LAM in HIV-positive outpatients and children with signs and symptoms of tuberculosis (pulmonary or extrapulmonary tuberculosis, or both forms) or irrespective of signs and symptoms of active tuberculosis if they have a CD4 count of less than 100 cells/µL, based on the generalization of data from adult inpatients, whilst acknowledging the limitation of the available data. The WHO recommends that LF-LAM should not be used for general tuberculosis screening in people without HIV "owing to sub-optimal sensitivity". The guidelines further suggest that LF-LAM should be used in combination with existing tests, and not as a replacement test (to existing tests) (WHO Consolidated Guidelines (Module 3) 2020).

Fujifilm SILVAMP TB LAM (FujiLAM, co-developed by Foundation for Innovative New Diagnostics (FIND), Geneva, Switzerland and Fujifilm, Tokyo, Japan) is a new, urine-based, point-of-care test for tuberculosis diagnosis in people living with HIV. In an individual participant data meta-analysis that included five cohorts of people living with HIV, FujiLAM was found to have superior sensitivity, 70.7% (95% confidence interval (CI) 59.0% to 80.8%), compared to LF-LAM sensitivity of 42.3% (95% CI 31.7% to 51.8%), against a microbiological reference standard; FujiLAM had lower specificity, 90.9% (95% CI 87.2% to 93.7%), compared to LF-LAM specificity of 95.3% (95% CI 92.2% to 97.7%) (Broger 2020). A post hoc analysis of two cohort studies in which retrospective urine testing using FujiLAM was undertaken demonstrated that FujiLAM would have rapidly detected tuberculosis in up to 89% of patients who died within three months, and that a negative FujiLAM result in patients with tuberculosis was associated with between 86% and 97% probability of survival to three months (Sossen 2020). A cohort study from Ghana demonstrated that FujiLAM test positivity was associated with an increased cumulative risk of mortality at six months with a hazard ratio of 4.80 (95% CI 3.01 to 7.64) (Bjerrum 2020). At the time of this writing, additional prospective clinical trials of FujiLAM are ongoing to generate data for an updated WHO policy review. We are not aware of any published trials that have evaluated the effect of FujiLAM on patient outcomes.

How the intervention might work

LF-LAM has lower sensitivity to detect tuberculosis in adults living with HIV than the internationally suggested minimum target of 65% for non-sputum based tuberculosis tests, recommended for trained microscopy technicians (WHO Target Product Profile 2014). However, since it is a rapid point-of-care assay, it is expected that obtaining a positive LF-LAM result will enable the prompt initiation of tuberculosis therapy in people living with HIV who are more likely to have advanced tuberculosis disease and be at higher risk for adverse outcomes, including death. Additionally, since people living with HIV are less likely to be able to produce sputum, which is needed to perform other WHO-recommended rapid tests such as Xpert MTB/RIF, Xpert Ultra, and Truenat, the use of LF-LAM may increase the yield of microbiologically confirmed tuberculosis.

Why it is important to do this review

This review is important for several reasons. To our knowledge, evidence of the effects of diagnostic tests for tuberculosis on patient outcomes has often been inferred from diagnostic accuracy studies rather than randomized trials. An exception is the Xpert MTB/RIF assay, described below. The impact of a diagnostic test relies on the test results being used to guide clinical management (di Ruffano 2012). The best way to evaluate the effect of a test strategy is by using a test-and-treat randomized controlled trial design. In this design, researchers assign patients to an experimental versus a standard testing approach and measure the (test strategy) effect on mortality and other patient outcomes (di Ruffano 2012; Schünemann 2016).

Regarding the LF-LAM assay, a multisite randomized controlled trial published in 2016 demonstrated that bedside urine LAM-guided initiation of antituberculosis treatment in HIV-positive adult inpatients with presumptive tuberculosis was associated with decreased eight-week mortality (Peter 2016). A second large multisite randomized controlled trial has subsequently been published (Gupta-Wright 2018), which did not demonstrate

a significant decrease in mortality across the overall study population, but found a reduction in mortality in three predefined subgroups (participants with signs and symptoms of tuberculosis, participants with CD4 < 100 cells/μL, and participants with anaemia defined as haemoglobin < 8 g/dL). In addition, several observational cohort studies have suggested an association between urine LAM positivity and higher disease severity and mortality (Drain 2015; Drain 2017; LaCourse 2018; Lawn 2012; Lawn 2016). Despite the availability of WHO guidelines recommending the use of urine LF-LAM testing for tuberculosis diagnosis amongst people living with HIV (WHO Consolidated Guidelines (Module 3) 2020), urine LF-LAM testing has not been scaled up in high tuberculosis/HIV burden countries (Saran 2019). A systematic review will enable us to include a larger number of participants in the analysis and investigate factors that affect patient outcomes across study settings.

Trials that assess the effect of novel diagnostic tests on patient outcomes are challenging because of the many and varied steps in the test-treatment pathway (di Ruffano 2012; Schünemann 2016). Regarding Xpert MTB/RIF, we are aware of seven randomized trials (Calligaro 2015; Churchyard 2015; Cox 2014; Mupfumi 2014; Ngwira 2019; Theron 2014a; Trajman 2015), and an individual participant data meta-analysis that included five of these trials (Di Tanna 2019), which have examined the impact of the test on mortality in relation to smear microscopy or diagnostic algorithms reflective of usual practice. All seven aforementioned trials were conducted in routine healthcare settings. However, only two of these trials showed a statistically significant impact on mortality (Ngwira 2019; Trajman 2015). Several reasons have been proposed to explain the variable evidence for the impact of Xpert MTB/RIF on mortality, including high rates of empirical treatment, insufficient sample size, and health system weaknesses (Auld 2016; Schumacher 2016; Schumacher 2019; Theron 2014b). A recently published Cochrane Review highlights the challenges of determining the effect on all-cause mortality of using Xpert MTB/RIF rather than smear microscopy and found that Xpert MTB/RIF probably reduced mortality among people living with HIV and demonstrated a variable effect on other patient-important outcomes (Haraka 2021).

The aim of our systematic review is to determine the impact of the use of LF-LAM on mortality and other patient-important outcomes. This review, along with the Cochrane Review update on the diagnostic test accuracy of LF-LAM (Bjerrum 2019), will have important implications for the further scale-up of this diagnostic test and the use of other similar tests in high tuberculosis burden countries in the future. In addition, this review may contribute to implications for future research concerning the design of trials of new diagnostic tools.

OBJECTIVES

To assess the impact of the use of LF-LAM (AlereLAM) on mortality in adults living with HIV in inpatient and outpatient settings.

To assess the impact of the use of LF-LAM (AlereLAM) on other patient-important outcomes in adults living with HIV, including time to diagnosis of tuberculosis, and time to initiation of tuberculosis treatment.

METHODS

Criteria for considering studies for this review

Types of studies

We included only randomized controlled trials (RCTs) and cluster-RCTs. We excluded other study designs and data reported only in abstracts, reviews, comments, and editorial notes.

Types of participants

We included participants who were adults (15 years and older is considered 'adult' for purpose of tuberculosis surveillance) living with HIV.

We included studies in which there was a suspicion of tuberculosis amongst study participants based on the presence of signs and symptoms compatible with tuberculosis (studies with symptomatic participants), as well as studies that included participants who presented for medical care irrespective of signs and symptoms of tuberculosis (studies with unselected participants). Signs and symptoms of tuberculosis included cough, fever, weight loss, and night sweats.

Types of interventions

Intervention

Diagnostic strategies that used LF-LAM either alone or in combination with other tests.

Control

Diagnostic strategies that used smear microscopy, mycobacterial culture, or Xpert MTB/RIF, or a combination of these tests, which did not include LF-LAM.

Types of outcome measures

Primary outcomes

- All-cause mortality during study follow-up time.
- Tuberculosis-related mortality during study follow-up time.

Secondary outcomes

- Time to diagnosis of tuberculosis.
- Time to tuberculosis treatment initiation.
- Time from diagnosis to tuberculosis treatment initiation.
- Proportion of study participants who were diagnosed with tuberculosis.
- Proportion of study participants who were treated for tuberculosis.
- Proportion of study participants who were treated for tuberculosis but did not have tuberculosis.
- Proportion of study participants who were able to produce a specimen for diagnostic testing.
- Incremental diagnostic yield due to addition of LF-LAM to the diagnostic algorithm.
- Tuberculosis-related treatment outcomes (treatment success or failure, relapse or cure).

Search methods for identification of studies

Electronic searches

The search for this review was conducted in conjunction with the search for a Cochrane Review update on the diagnostic accuracy of AlereLAM (Bjerrum 2019). That literature search was conducted up to 11 May 2018. In addition, specifically for this intervention review, we conducted a search up to 12 March 2021 in the following databases, using the search terms reported in Appendix 1:

- Cochrane Infectious Diseases Group Specialized Register;
- Cochrane Central Register of Controlled Trials (CENTRAL) (2021, Issue 3);
- MEDLINE (PubMed, from 1966 to 12 March 2021);
- Embase (Ovid, from 1947 to 12 March 2021);
- Science Citation Index Expanded (SCI-EXPANDED, from 1900 to 12 March 2021), Conference Proceedings Citation Index - Science (CPCI-S, from 1900 to 12 March 2021), and BIOSIS Previews (from 1926 to 12 March 2021), all three using the Web of Science platform;
- LILACS (Latin American and Caribbean Health Science Information database) (BIREME, from 1982 to 12 March 2021);
- Scopus (from 1995 to 12 March 2021).

We also searched US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov/) and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP, apps.who.int/trialsearch/) to identify ongoing trials, and ProQuest Dissertations & Theses A&I (from 1861) to identify relevant dissertations (searches conducted up to 12 March 2021). We also included search results from the original Cochrane Review (Shah 2016). We performed the searches with no language restriction.

Searching other resources

We further examined reference lists of relevant reviews and studies and searched the WHO website.

Data collection and analysis

Selection of studies

We used Covidence systematic review software to manage the selection of studies (Covidence). The search for this review was conducted in parallel with the search for the Cochrane Review update on the diagnostic accuracy of LF-LAM for tuberculosis (Bjerrum 2019). Two review authors (MS and SB) working independently screened titles and abstracts (including those that were identified in the original Cochrane Review on the diagnostic accuracy of LF-LAM for tuberculosis (Shah 2016)) to identify citations that included data on health impact. We retrieved the article of any citation identified by either review author for full-text review. Then, two other review authors (RRN and PL) working independently assessed articles for inclusion using predefined inclusion and exclusion criteria. In the study selection process, we assessed the full-texts of the 15 studies included in the Cochrane Review update, as well as any studies excluded during the full-text screening (Bjerrum 2019). Any differences in opinion were resolved through discussion. We listed studies excluded after full-text assessment and their reasons for exclusion in a PRISMA flow diagram (Moher 2009).

Data extraction and management

We developed and piloted a standardized data extraction form. Subsequently, two review authors (RRN and PL) independently extracted data from each included study. Any disagreements were resolved through discussion or by consulting a third review author (KRS). We extracted data on the following:

- Author, publication year, study design, country(ies), clinical setting (outpatient or inpatient), number enrolled and analysed.
- Participants: age, HIV status and whether they are taking antiretroviral therapy, presence of symptoms (symptoms versus unselected).
- Mode of mortality assessment, type of mortality (all-cause versus tuberculosis-related), timing of mortality assessment.
- LF-LAM grade and use of old versus new reference card, timing of LF-LAM.
- Mortality analysis metrics used (risk ratio, absolute risk reduction, (adjusted) hazard ratio or Kaplan-Meier, (adjusted) odds ratio).
- Comparator groups analysed.
- Mortality in the intervention group, mortality in the control group.
- Mortality data stratified by CD4 count.
- Time to diagnosis; time to treatment initiation; time from diagnosis to treatment initiation.
- Proportion of study participants who were diagnosed with tuberculosis.
- Proportion of study participants who were treated for tuberculosis.
- Proportion of study participants who were treated for tuberculosis and did not have tuberculosis.
- Proportion of study participants who were able to produce a specimen for diagnostic testing.
- Other outcomes assessed in the study (e.g. incremental diagnostic yield due to addition of LF-LAM to the diagnostic algorithm).
- Other tuberculosis-related outcomes (e.g. treatment success or failure, relapse or cure).

We contacted study authors for clarification as needed.

Assessment of risk of bias in included studies

Two review authors (RRN and PL) independently assessed risk of bias using the Cochrane tool for assessing risk of bias in randomized studies (Higgins 2011), employing Review Manager 5 (Review Manager 2020). We contacted the corresponding study authors for clarification or more information if data were missing or unclear. Any discrepancies were resolved through discussion or by consulting a third review author (KRS) if required. We assessed the included studies for the method of allocation, sequence generation and allocation concealment, blinding, missing outcome data, outcome measurement and reporting, and selective reporting bias. We assessed the risk of bias as low, high, or unclear.

Measures of treatment effect

We presented our findings of the effect of the use of LF-LAM on dichotomous outcomes using risk ratios or hazard ratios (when

effect measure was time-to-event) with respective 95% confidence intervals.

Unit of analysis issues

We decided that if we identified cluster-RCTs, we would extract adjusted measures of effect where possible. If the study authors did not perform any adjustment for clustering, we would adjust the raw data using an intraclass correlation coefficient (ICC) value. If an ICC value was not reported in the study, we would contact the study authors for this information, obtain it from similar studies, or estimate the ICC. We would not present results from cluster-RCTs that were not adjusted for clustering. If we identified cluster-RCTs, we would estimate the ICC, and perform sensitivity analyses to investigate the robustness of our analyses. If we identified studies for inclusion that had multiple intervention arms, we would include data from these studies by either combining intervention arms, or by splitting the control group so that participants would only be included in the meta-analysis once.

Dealing with missing data

Before extracting data from the studies, we determined the reasons for missing data by attempting to contact the respective corresponding study author. We investigated whether the missingness of data may have introduced attrition bias. We would carry out an available-case analysis if we considered the missing data to be missing at random. If we suspected that missing data were not missing at random, we would perform sensitivity analyses in which we imputed the data using specific assumptions, such as assuming all missing participants experienced or did not experience the event.

Assessment of heterogeneity

We assessed the existence of clinical heterogeneity by examining differences in study characteristics and participant demographic factors in order to inform decisions regarding the appropriateness of pooling data from studies in meta-analysis. We assessed statistical heterogeneity by visually inspecting forest plots and using a Chi^2 test for heterogeneity (with a P value of 0.10 for significance), and the I^2 statistic as a measure of inconsistency across studies, with an I^2 value of 50% higher representing substantial heterogeneity (Deeks 2021).

Assessment of reporting biases

We planned to assess reporting biases if more than 10 studies were included in the meta-analysis by examining the funnel plots visually for symmetry or asymmetry and interpreting test results in the context of visual inspection of funnel plots. In the case of asymmetry, we would follow recommendations for interpretation as recommended by Sterne 2011.

Data synthesis

We conducted analyses using Review Manager 5 (Review Manager 2020). For dichotomous outcomes, we performed meta-analyses to estimate the pooled risk ratio (95% confidence interval). We used a fixed-effect model unless we identified clinical or statistical heterogeneity, in which case we used a random-effects model. For time-to-event outcomes, we would perform meta-analyses to estimate the pooled hazard ratio (95% confidence interval).

Subgroup analysis and investigation of heterogeneity

Based on data availability, we performed subgroup analyses in participants with varying CD4 levels, in particular, CD4 > 200 cells/µL versus CD4 ≤ 200 cells/µL, and CD4 > 100 cells/µL versus CD4 ≤ 100 cells/µL. The rationale for subgroup analyses stratified by CD4 count is because we hypothesized that the use of urine LAM would have a larger effect on mortality in participants with lower CD4 counts, since the diagnostic accuracy of urine LAM is higher with lower CD4 counts (Bjerrum 2019).

Sensitivity analysis

We planned to perform sensitivity analyses in the case of circumstances that we thought were likely to influence outcomes, including the following.

- Excluding studies with missing data that were likely to influence the outcome.
- Excluding studies with outliers that were suspected to influence the outcome.
- Excluding studies with high risk of bias that were likely to affect the outcome.

Outliers would have been identified on visual examination of forest plots as extreme values that we judged important to investigate the effect of excluding. None of the included studies had missing data, outliers, or a high risk of bias that was likely to influence the outcome. However, we performed sensitivity analyses in which we imputed the data using specific assumptions. Based on prior literature informing the expected tuberculosis mortality at eight weeks (Ford 2016; Nliwasa 2018), we varied the mortality event rate in missing participants between 0% and 25%.

Summary of findings and assessment of the certainty of the evidence

We summarized our findings in the summary of findings tables. We assessed the certainty of evidence using the GRADE approach (Hultcrantz 2017), employing GRADEpro GDT software (GRADEpro GDT). We rated each important outcome (primary outcomes) as described by Balshem 2011, as follows.

- High: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect.
- Low: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
- Very low: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Randomized controlled trials start as high-certainty evidence, but can be downgraded if there are valid concerns within the following five domains: risk of bias, imprecision, inconsistency, indirectness, and publication bias. Studies can also be upgraded if there is a large effect, a dose-response effect, and if all plausible residual confounding would reduce a demonstrated effect or would suggest a spurious effect if no effect was observed (Balshem 2011).

As recommended, we reported the findings in simple, standardized statements (Santesso 2020).

RESULTS

Description of studies

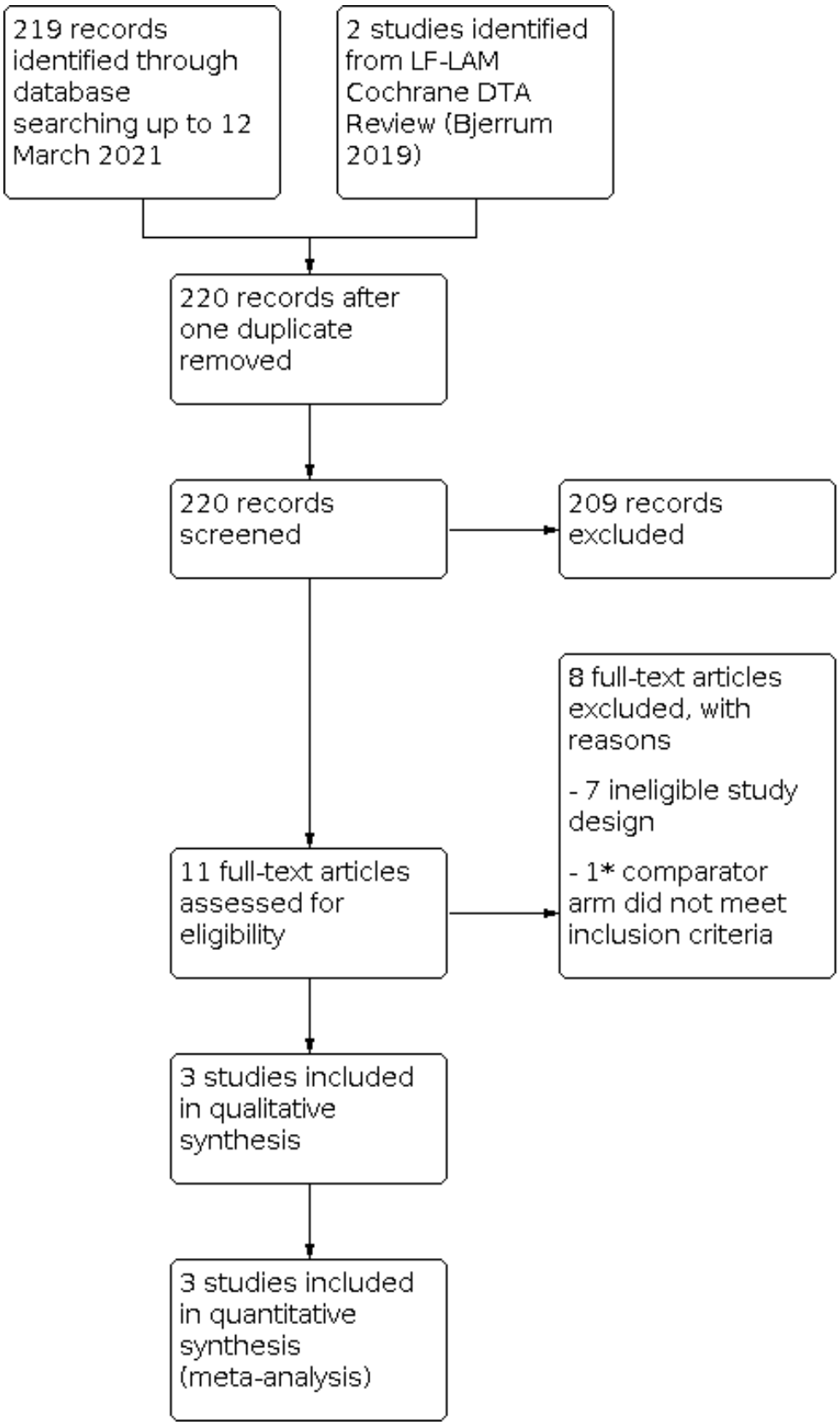
We provided descriptions of the included studies in the Characteristics of included studies and Table 1, 'Characteristics of studies that evaluated a diagnostic intervention that included LF-LAM in adults living with HIV'. We provided descriptions of the excluded studies in Characteristics of excluded studies.

Results of the search

The literature search for this review was conducted in conjunction with the search for a Cochrane Review update on the diagnostic accuracy of LF-LAM (Bjerrum 2019). Two studies that were included by Bjerrum 2019 were identified as meeting the inclusion criteria for this review (Gupta-Wright 2018; Peter 2016). Our updated searches identified a further 218 unique studies for title and abstract screening, two of which met the criteria for full-text review (Blanc 2020; Grant 2020), and one of which met our inclusion criteria to undergo data extraction (Grant 2020). A flow diagram of the study selection process is shown in Figure 1.

Figure 1. Study flow diagram. The literature search for this review was conducted in conjunction with the search for a Cochrane Review on the diagnostic accuracy of LF-LAM (AlereLAM) (Bjerrum 2019). We initially identified 189 studies for title and abstract screening, of which 41 were selected for full-text review. Fifteen studies were identified for Bjerrum 2019, and two studies were identified for this review. Updated literature searches on 12 November 2019 and 12 March 2021 identified one additional study. *In this study, the standard-of-care arm utilized a diagnostic strategy that did not include any of the tuberculosis tests described in our protocol as criteria for inclusion, and the

study was not used to guide clinical decision-making, precluding comparison of the impact of LF-LAM compared to other diagnostic strategies (Blanc 2020).



Included studies

We included three studies that assessed the impact of LF-LAM on mortality when the test was used for clinical decision-making; two of these took place in inpatient settings (Gupta-Wright 2018; Peter 2016), and one in outpatient settings (Grant 2020). Both inpatient studies were multisite RCTs conducted in sub-Saharan African countries that evaluated the impact of a diagnostic strategy that included LF-LAM as a tuberculosis diagnostic test to guide treatment initiation in HIV-positive adults, comparing all-cause mortality at 56 days (eight weeks) between the LF-LAM intervention arm and standard-of-care control arm (Gupta-Wright 2018; Peter 2016). The outpatient study was an open-label cluster-RCT conducted in South Africa that evaluated the impact of a diagnostic strategy that included LF-LAM as a tuberculosis diagnostic test to guide treatment initiation in people living with HIV, comparing all-cause mortality at six months between the LF-LAM intervention arm and standard-of-care control arm (Grant 2020). None of the trials reported the cause of death, including tuberculosis-related mortality.

Important differences between the trials evaluating the impact of LF-LAM on mortality

There were several differences between the trials. Although both of the trials in inpatient settings were multisite studies, Peter 2016 took place at 10 sites across four countries (South Africa, Tanzania, Zambia, Zimbabwe), whilst Gupta-Wright 2018 was conducted at two sites in two countries (South Africa and Malawi). Gupta-Wright 2018 screened patients admitted to medical wards, and Peter 2016 screened patients admitted to emergency units and short-stay wards, in addition to medical wards. In Peter 2016, a trained nurse conducted the LF-LAM testing at the bedside and reported the LF-LAM result to the clinical team along with a recommendation regarding treatment based on the results, whilst in Gupta-Wright 2018, all LF-LAM testing as well as Xpert MTB/RIF was conducted within the laboratory and reported as a combined tuberculosis screening result (i.e. positive, negative, not done (combined for all tuberculosis screening tests performed rather than only for the individual LF-LAM result)). The intervention in Gupta-Wright 2018 included LF-LAM and urine Xpert MTB/RIF, thus the impact of LF-LAM cannot be separated from urine Xpert MTB/RIF, although the authors note that of the patients with microbiologically confirmed tuberculosis, the diagnostic yield from LF-LAM was 75% (158/210) compared to 35% (74/210) for urine Xpert MTB/RIF and 40% (85/210) for sputum Xpert MTB/RIF. The median CD4 count was lower in Peter 2016 compared to Gupta-Wright 2018 (84 cells/µL versus 227 cells/µL). This, in addition to lower body mass index (BMI) and Karnofsky scores, suggests that the population evaluated in the Peter 2016 study may have been sicker. Overall severity of illness was higher in Peter 2016 (mortality 21% in LF-LAM and 25% in no LF-LAM arms) compared to Gupta-Wright 2018 (mortality 18% in LF-LAM and 21% in no LF-LAM arms). The percentage of participants on antiretroviral therapy was lower in Peter 2016 than in Gupta-Wright 2018 (48% versus 72%). A greater proportion of participants were started on tuberculosis treatment in Peter 2016 compared to Gupta-Wright 2018 (50% versus 17%), likely reflecting different inclusion criteria (clinical suspicion of tuberculosis in the former compared with an unselected population irrespective of symptoms in the latter) and a consequent difference in the severity of illness in the study populations between the two trials. Despite these differences, we considered the interventions implemented, target population, and study setting to be sufficiently similar in both inpatient trials to permit pooling in a meta-analysis.

The outpatient trial was conducted at 24 primary healthcare clinics in South Africa (Grant 2020). In Grant 2020, study nurses at intervention clinics assessed patients using a multifactorial assessment, consisting of tuberculosis symptoms, BMI, point-of-care haemoglobin concentrations, and urine LF-LAM results. A positive urine LF-LAM result was one of the high probability criteria defined in the study algorithm which categorized participants as high probability of tuberculosis, for which initiation of tuberculosis treatment was recommended immediately followed by antiretroviral treatment two weeks later, versus medium probability of tuberculosis, for which symptom-guided investigation was recommended, versus low probability of tuberculosis, for which initiation of antiretroviral treatment was recommended. Although this trial was conducted in outpatient settings, where participants are typically expected to be less sick than in inpatient settings, the eligibility criteria included having a CD4 count of 150 cells/µL or less, and the median CD4 count was lower than in the two inpatient trials (72 cells/µL). Most participants (69%) were symptomatic, although this was not part of the eligibility criteria. Individuals with clinical signs necessitating urgent referral to secondary care were excluded.

Excluded studies

We excluded eight full-text articles from the literature searches performed up to 12 March 2021. We excluded seven of these studies because they were not RCTs (Cummings 2019; Gupta-Wright 2019; Huerga 2019; Kubiak 2018; Mathabire Rucker 2019; Mthiyane 2019; Naidoo 2019). We excluded one study because the standard-of-care arm utilized a diagnostic strategy that did not include any of the tuberculosis tests that we described in our protocol criteria for inclusion, and was not used to guide clinical decision-making, precluding comparison of the impact of LF-LAM to other diagnostic strategies (Blanc 2020).

Risk of bias in included studies

The assessment of risk of bias in the included studies is shown in Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

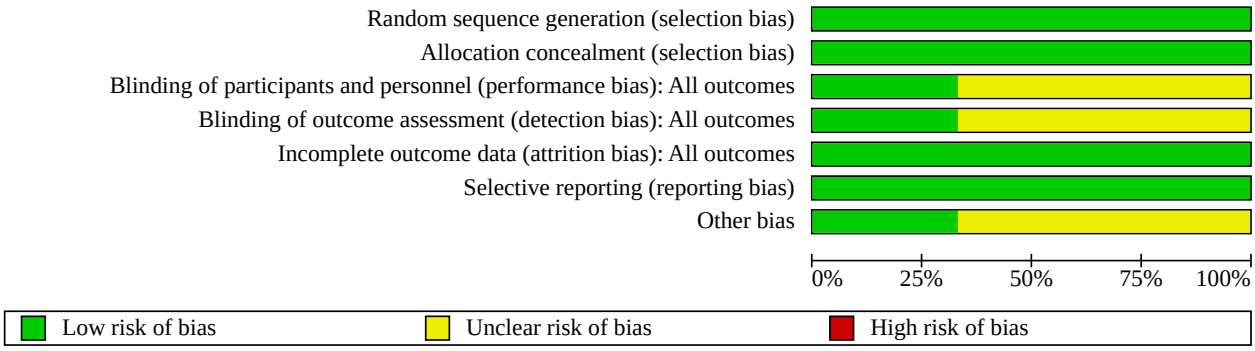
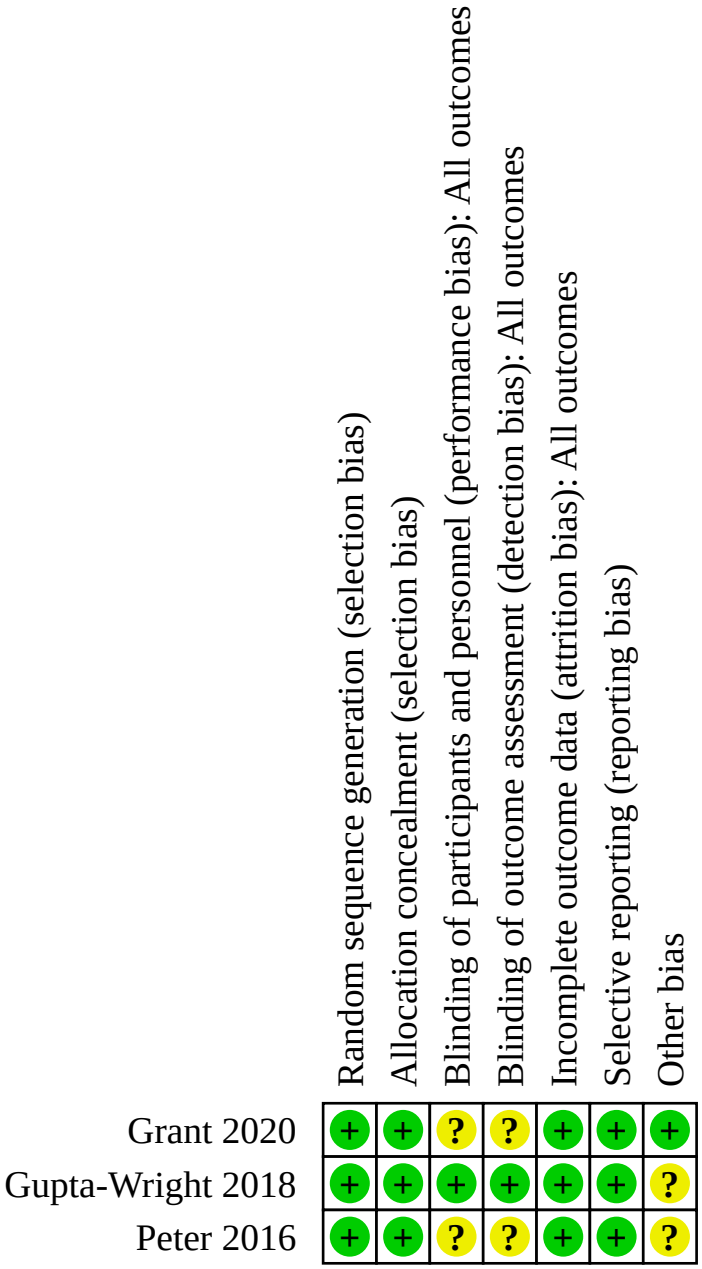


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias domain for each included study.



Allocation

Gupta-Wright 2018 and Peter 2016 used random sequence generation and were thus assessed as at low risk of selection bias in this domain, and were also judged to be at low risk of selection bias with respect to allocation concealment. In Peter 2016, participants were assigned to the intervention arm which included LF-LAM versus standard-of-care using computer-generated allocation lists. Research nurses who did not have access to these lists either contacted a data manager by telephone or used a text message system to assign each participant. In Gupta-Wright 2018, study nurses or clinicians took a consecutive sealed envelope which contained the unique patient identifier but did not reveal the study group, to which they remained masked. In Grant 2020, randomization at the clinic level was performed by a study

statistician to achieve reasonable balance, taking into account mean CD4 count, peri-urban versus rural clinic location, and total monthly antiretroviral therapy initiations.

Blinding

We judged two studies to have an unclear risk of both performance and detection bias because participants and research staff in Peter 2016 and Grant 2020, and clinic staff in Grant 2020, were not masked to either allocation or test results, and it is unclear how this lack of blinding may have affected clinical decision-making. Since investigators, all study staff (other than the laboratory technician and statistician), hospital attending clinical teams, and participants were masked to the study group allocation in Gupta-Wright 2018, we judged this trial to be at low risk of bias.

Incomplete outcome data

We judged all three studies to have a low risk of attrition bias due to incomplete outcome data, reporting a 5% loss to follow-up rate (Peter 2016); 1% loss to follow-up rate (Gupta-Wright 2018); and 0% loss to follow-up rate (Grant 2020), respectively.

Selective reporting

We judged all three studies to have a low risk of reporting bias, as they prespecified their primary and secondary outcome measures in clinical trial registries (ClinicalTrials.gov ID: NCT01770730 (Peter 2016), ISRCTN ID: ISRCTN71603869 (Gupta-Wright 2018), and ISRCTN ID: ISRCTN35344604 and number DOH-27-0812-3902 in the South African National Clinical Trials Register (Grant 2020)).

Other potential sources of bias

We judged the two studies in inpatient settings to have an unclear risk of other bias (Peter 2016; Gupta-Wright 2018). The informed consent requirements for both inpatient trials may have resulted in the exclusion of people who were critically ill, who would have been part of the target population for the intervention in real-world practice settings. Similarly, limiting enrolment to standard working hours and for less than 48 hours after admission may have also introduced other bias. Peter 2016 also noted a heterogeneous mortality effect across the four countries in which the study was conducted. We judged Grant 2020 to have a low risk of other bias because although there were some differences between the intervention and standard-of-care groups, notably presence of tuberculosis symptoms, prior receipt of isoniazid preventive therapy, and receipt of tuberculosis tests in the preceding six months, we did not think these differences were likely to introduce bias.

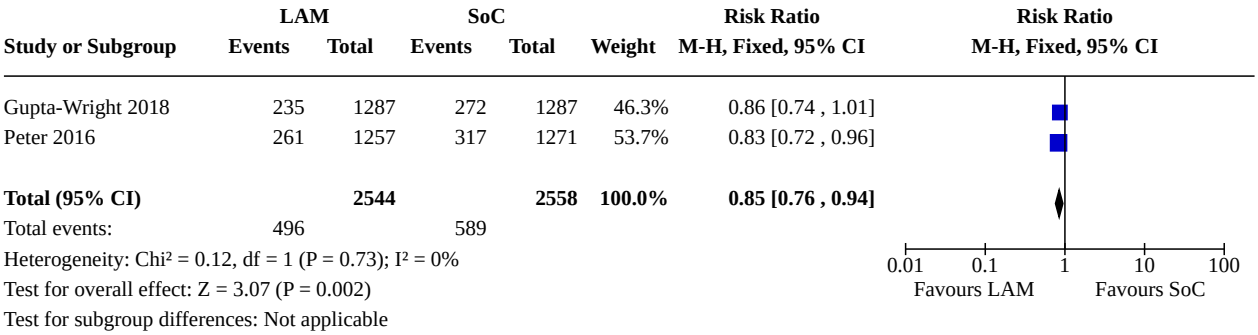
Effects of interventions

See: **Summary of findings 1** Effect of LF-LAM compared to no LF-LAM on mortality and tuberculosis treatment initiation in people living with HIV, inpatient settings; **Summary of findings 2** Effect of LF-LAM compared to no LF-LAM on mortality and tuberculosis treatment initiation in people living with HIV, outpatient settings

Impact of LF-LAM on mortality in inpatient settings

Both included trials assessed mortality at eight weeks. The pooled risk ratio (RR) was 0.85 (95% confidence interval (CI) 0.76 to 0.94; 5102 participants, 2 trials, Analysis 1.1, Figure 4). That is, people living with HIV who received LF-LAM had 15% lower risk of mortality. The absolute effect was 34 fewer deaths per 1000 (from 14 fewer to 55 fewer) (moderate-certainty evidence) (Summary of findings 1).

Figure 4. Forest plot comparing the risk ratios for mortality in participants in inpatient settings who received a diagnostic intervention including LAM compared to those who received standard of care (SoC). Mortality was assessed at eight weeks in Gupta-Wright 2018 and Peter 2016. Between brackets are the 95% confidence intervals (CI) for the risk ratios. The figure shows the estimated mortality risk ratio for each study (blue square) and its 95% CI (black horizontal line) and the pooled estimated mortality risk ratio combining results (black diamond).



Owing to a 5% loss to follow-up rate in Peter 2016 with the possibility of potentially unbalanced study arms, we performed sensitivity analyses to investigate the robustness of the available-case analyses. The pooled RR was 0.87 (95% CI 0.78 to 0.97) with a 25% mortality event rate in the intervention compared to 0% event rate in the standard-of-care group (Analysis 1.2, Figure 5), and 0.82 (95% CI 0.74 to 0.91) with a 0% mortality event rate in the intervention compared to 0% event rate in the standard-of-care group (Analysis 1.3, Figure 6). We thus found that the overall meta-analysis result remained statistically significant regardless of varying the hypothetical event rate amongst missing data, and we can therefore be confident in our overall finding.

Figure 5. Forest plot comparing the risk ratios for mortality at eight weeks in participants in inpatient settings who received a diagnostic intervention including LAM compared to those who received standard of care (SoC), sensitivity analysis with 25% mortality in missing participants receiving LAM and 0% mortality in missing participants receiving SoC. Between brackets are the 95% confidence intervals (CI) for the risk ratios. The figure shows the estimated mortality risk ratio for each study (blue square) and its 95% CI (black horizontal line) and the pooled estimated mortality risk ratio combining results from both studies (black diamond).

	LAM		SoC			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Gupta-Wright 2018	235	1287	272	1287	46.1%	0.86 [0.74 , 1.01]	
Peter 2016	281	1336	317	1323	53.9%	0.88 [0.76 , 1.01]	
Total (95% CI)		**2623**		**2610**	**100.0%**	**0.87 [0.78 , 0.97]**	
Total events:	516		589				

Heterogeneity: Chi² = 0.02, df = 1 (P = 0.88); I² = 0%
Test for overall effect: Z = 2.57 (P = 0.01)
Test for subgroup differences: Not applicable

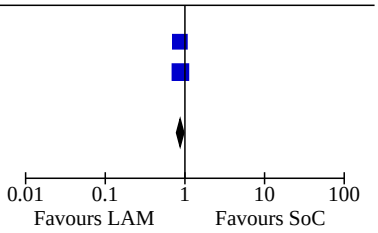
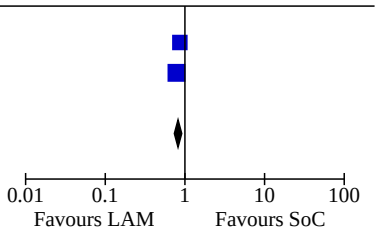


Figure 6. Forest plot comparing the risk ratios for mortality at eight weeks in participants in inpatient settings who received a diagnostic intervention including LAM compared to those who received standard of care (SoC), sensitivity analysis with 0% mortality in missing participants receiving LAM and 25% mortality in missing participants receiving SoC. Between brackets are the 95% confidence intervals (CI) for the risk ratios. The figure shows the estimated mortality risk ratio for each study (blue square) and its 95% CI (black horizontal line) and the pooled estimated mortality risk ratio combining results from both studies (black diamond).

	LAM		SoC			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Gupta-Wright 2018	235	1287	272	1287	45.1%	0.86 [0.74 , 1.01]	
Peter 2016	261	1336	330	1323	54.9%	0.78 [0.68 , 0.90]	
Total (95% CI)		**2623**		**2610**	**100.0%**	**0.82 [0.74 , 0.91]**	
Total events:	496		602				

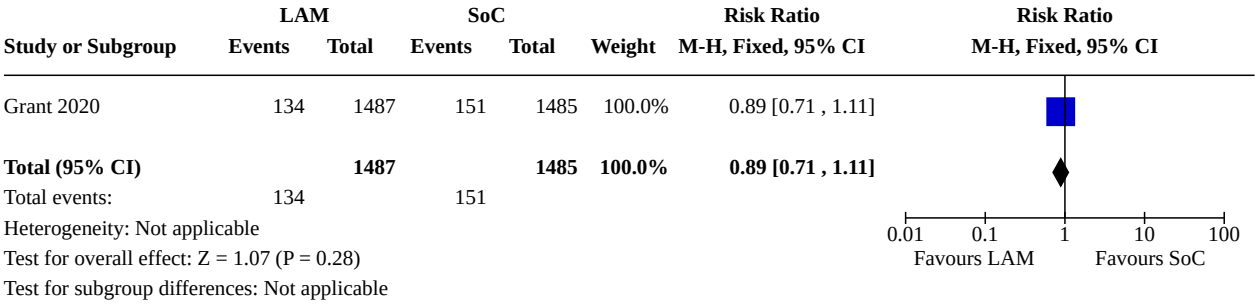
Heterogeneity: Chi² = 0.82, df = 1 (P = 0.36); I² = 0%
Test for overall effect: Z = 3.69 (P = 0.0002)
Test for subgroup differences: Not applicable



Impact of LF-LAM on mortality in outpatient settings

The one included trial assessed mortality at six months. The RR was 0.89 (95% CI 0.71 to 1.11; 2972 participants, 1 trial, Analysis 1.4, Figure 7; Summary of findings 2). Although this trial did not detect a difference in mortality at six months in people living with HIV who had received LF-LAM testing as part of a tuberculosis diagnostic strategy compared to routine tuberculosis diagnostic testing without LF-LAM, the direction of effect was towards a mortality reduction, and similar to the effect in people evaluated in inpatient settings.

Figure 7. Forest plot reporting the risk ratio for mortality at six months in participants in outpatient settings who received a diagnostic intervention including LAM compared to those who received standard of care (SoC). Between brackets are the 95% confidence intervals (CI) for the risk ratios. The figure shows the estimated mortality risk ratio for each study (blue square) and its 95% CI (black horizontal line) and the pooled estimated mortality risk ratio combining results (black diamond).

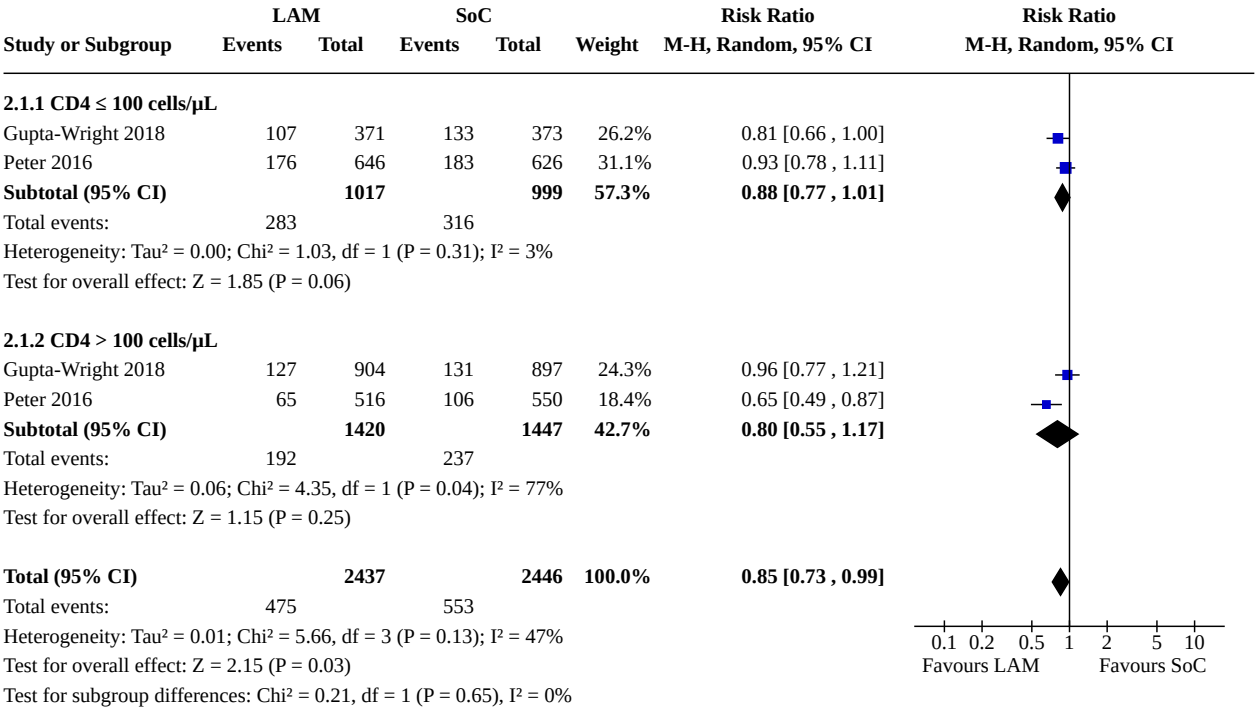


Impact of LF-LAM on mortality in inpatient settings with CD4 ≤ 100 cells/µL versus CD4 > 100 cells/µL

Analysis 2.1 examines the impact of LF-LAM on mortality in individuals in inpatient settings stratified by CD4 count with a threshold of 100 cells/µL. Table 2 demonstrates the heterogeneity in effect estimates across CD4 strata that were seen within and between the two included trials.

For individuals with a CD4 count of ≤ 100 cells/µL, the pooled RR was 0.88 (95% CI 0.77 to 1.01; 2016 participants, 2 trials, Analysis 2.1.1, subgroup 1, Figure 8).

Figure 8. Forest plot comparing the risk ratios for mortality in inpatients who received a diagnostic intervention including LAM compared to those who received standard of care (SoC), mortality at eight weeks, by CD4 strata ≤ 100 cells/µL versus > 100 cells/µL. Between brackets are the 95% confidence intervals (CI) for the risk ratios. The figure shows the estimated mortality risk ratio for each study (blue square) and its 95% CI (black horizontal line) and the pooled estimated mortality risk ratio combining results from both studies (black diamond).



For individuals with a CD4 count of > 100 cells/µL, the pooled RR was 0.80 (95% CI 0.55 to 1.17; 2867 participants, 2 trials, Analysis 2.1.2, subgroup 2, Figure 8).

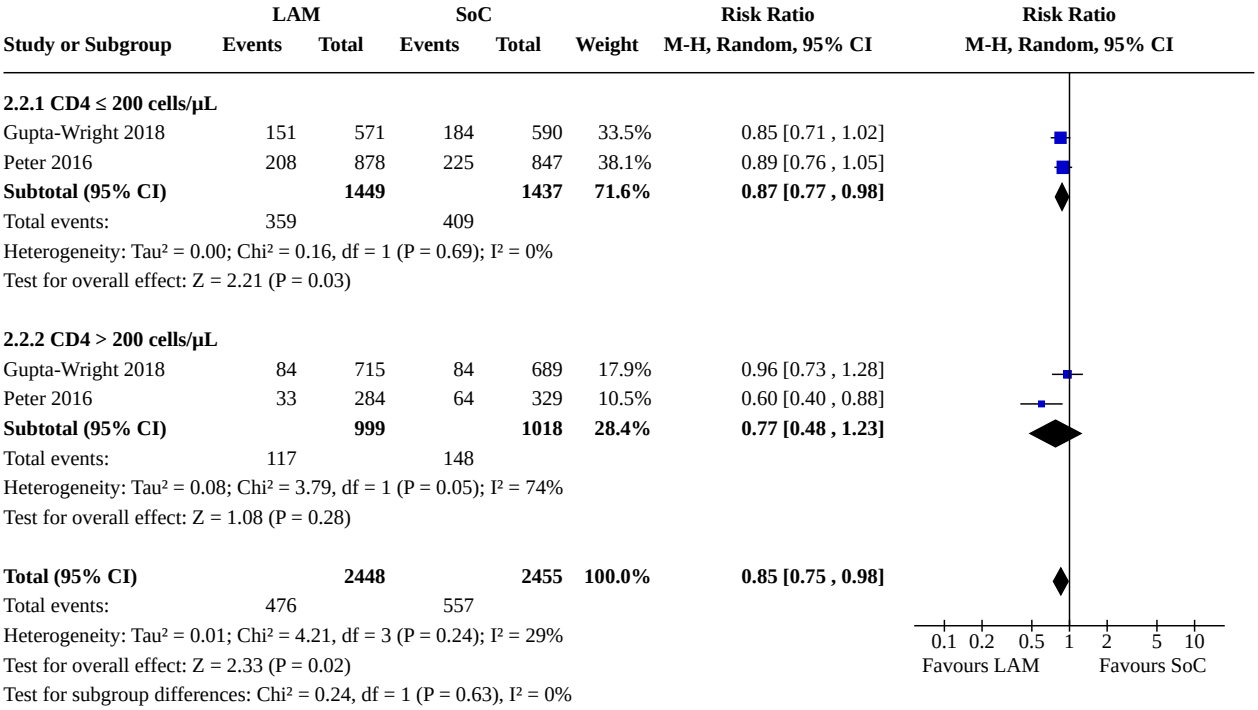
Given that the I^2 statistic for Analysis 2.1.2 demonstrated substantial heterogeneity, we used a random-effects model for these meta-analyses.

Impact of LF-LAM on mortality in inpatient settings with CD4 ≤ 200 cells/µL versus CD4 > 200 cells/µL

Analysis 2.2 examines the impact of LF-LAM on mortality in individuals in inpatient settings stratified by CD4 count with a threshold of 200 cells/µL. Table 2 demonstrates the heterogeneity in effect estimates across CD4 strata that were seen within and between the two included trials.

For individuals with a CD4 count of ≤ 200 cells/µL, the pooled RR was 0.87 (95% CI 0.77 to 0.98; 2886 participants, 2 trials, Analysis 2.2.1, subgroup 1, Figure 9).

Figure 9. Forest plot comparing the risk ratios for mortality in inpatients who received a diagnostic intervention including LAM compared to those who received standard of care (SoC), mortality at eight weeks, by CD4 strata ≤ 200 cells/µL versus > 200 cells/µL. Between brackets are the 95% confidence intervals (CI) for the risk ratios. The figure shows the estimated mortality risk ratio for each study (blue square) and its 95% CI (black horizontal line) and the pooled estimated mortality risk ratio combining results from both studies (black diamond).



For individuals with a CD4 count of > 200 cells/µL, the pooled RR was 0.77 (95% CI 0.48 to 1.23; 2017 participants, 2 trials, Analysis 2.2.2, subgroup 2, Figure 9).

Given that the I^2 statistic for Analysis 2.2.2 demonstrated substantial heterogeneity, we used a random-effects model for these meta-analyses.

Impact of LF-LAM on mortality in outpatient settings with CD4 < 50 cells/µL versus CD4 ≥ 50 cells/µL

Analysis 2.3 examines the impact of LF-LAM on mortality in outpatient settings stratified by CD4 count with a threshold of 50 cells/µL.

For individuals with a CD4 count of < 50 cells/µL, the RR was 1.01 (95% CI 0.78 to 1.31, 460 person-years, 1 trial, Analysis 2.3.1, subgroup 1), that is a detectable difference in mortality was not seen in study participants with a CD4 count of < 50 cells/µL who received a diagnostic assessment that included LF-LAM testing compared to those undergoing standard of care without LF-LAM.

For individuals with a CD4 count of ≥ 50 cells/µL, the RR was 0.76 (95% CI 0.55 to 1.05, 942 person-years, 1 trial, Analysis 2.3.2, subgroup 2), that is the direction of effect was towards a decrease in mortality in study participants with a CD4 count of ≥ 50 cells/µL who received a diagnostic assessment that included LF-LAM testing compared to those undergoing standard of care without LF-LAM.

Other patient-important and implementation outcomes

Although mortality was the primary patient-important outcome of interest, we also recorded data on other patient-important outcomes. However, data for our prespecified secondary outcomes were often not reported or were analysed variably between studies, which limited our ability to perform meta-analyses.

Time to diagnosis, time to tuberculosis treatment initiation, and time from diagnosis to tuberculosis treatment initiation

Gupta-Wright 2018 found that the time from randomization to diagnosis was marginally shorter in the LF-LAM intervention group compared to the standard-of-care group (median 0 days (interquartile range (IQR) 0 to 1)) versus 1 day (IQR 0 to 6), adjusted hazard ratio 1.55 (95% CI 1.29 to 1.87). Time from diagnosis to

treatment was short (median 1 day (IQR 0 to 1)) and did not differ between the group that received LF-LAM and the standard-of-care group (adjusted hazard ratio 0.83, 95% CI 0.69 to 1.01).

Peter 2016 reported that time-to-treatment initiation in the group that received LF-LAM was shorter than in the group that did not receive LF-LAM, with a higher proportion of those treated having antituberculosis treatment initiated by the end of days 1 to 4 of hospitalization (84% versus 76%, P < 0.001).

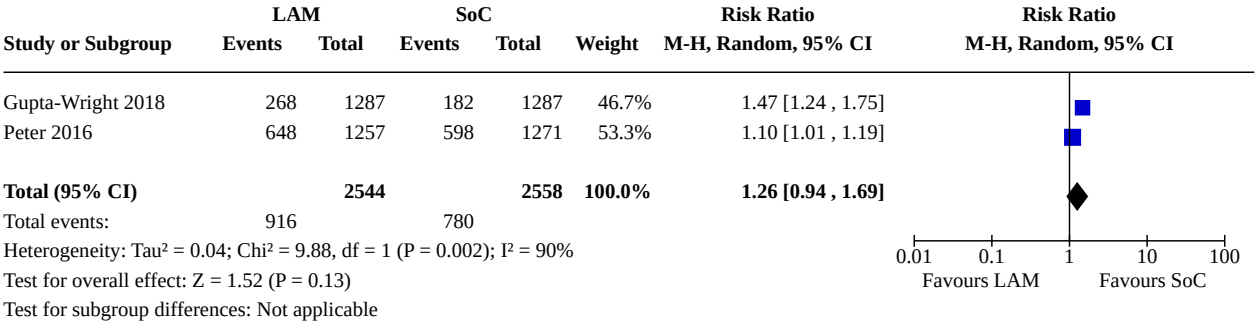
Proportion of study participants who were diagnosed with tuberculosis

Gupta-Wright 2018 reported that increases in tuberculosis diagnoses in the intervention group that received LF-LAM (22% of tuberculosis diagnoses) compared to the standard-of-care group (15% of tuberculosis diagnoses) were not confined to high-risk subgroups, with an overall adjusted absolute risk difference of 7.3% (95% CI 4.4 to 10.2). These results were adjusted for study sites; unadjusted data were not provided.

Proportion of study participants who were treated for tuberculosis

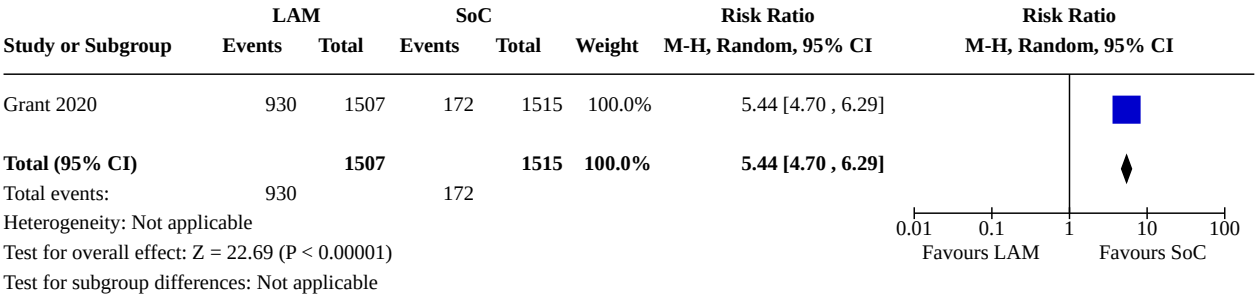
In inpatient settings, both included trials assessed tuberculosis treatment initiation. The pooled RR was 1.26 (95% CI 0.94 to 1.69; 5102 participants, 2 trials, Analysis 3.1, Figure 10). Of note the, I^2 statistic (90%) suggested substantial heterogeneity, thus we used random-effects meta-analysis. We hypothesize that this heterogeneity was due to the smaller difference between the proportion of participants initiated on treatment for the group that received the diagnostic intervention that included LF-LAM compared to the standard-of-care group that did not receive LF-LAM in Peter 2016 compared to Gupta-Wright 2018. This difference is likely reflective of the population in Peter 2016 being sicker, resulting in a higher likelihood of empiric treatment even in the standard-of-care group, compared to Gupta-Wright 2018, in which participants were enrolled irrespective of symptoms and signs of tuberculosis and were less sick (Table 1).

Figure 10. Forest plot comparing the risk ratios for proportion of participants in inpatient settings treated for tuberculosis who received a diagnostic intervention including LAM compared to those who received standard of care (SoC). Between brackets are the 95% confidence intervals (CI) for the risk ratios. The figure shows the proportion for each study (blue square) and its 95% CI (black horizontal line) and the pooled estimated mortality risk ratio combining results from both studies (black diamond).



In outpatient settings, the included trial assessed tuberculosis treatment initiation. The RR was 5.44 (95% CI 4.70 to 6.29, 3022 participants, 1 trial, Analysis 3.2, Figure 11).

Figure 11. Forest plot reporting the risk ratio for proportion of participants in outpatient settings treated for tuberculosis who received a diagnostic intervention including LAM compared to those who received standard of care (SoC). Between brackets are the 95% confidence intervals (CI) for the risk ratios. The figure shows the proportion for the study (blue square) and its 95% CI (black horizontal line).



Proportion of study participants who were treated for tuberculosis but did not have tuberculosis

None of the included trials evaluated the proportion of study participants who were treated for tuberculosis but did not have tuberculosis.

Proportion of participants who were able to produce a specimen for diagnostic testing

Both inpatient trials reported that a higher proportion of study participants were able to provide urine as a diagnostic specimen compared to sputum. Gupta-Wright 2018 reported that urine was provided by 99% (2548/2574) of participants, whereas only 57% (1464/2574) were able to produce sputum. Of note, the proportion of participants able to produce sputum in Malawi (39%, 518/1316) was lower than in South Africa (75%, 946/1258). Peter 2016 similarly reported that 99% (2507/2528) were able to produce a urine specimen; however, in this study 93% (2355/2528) were able to produce a sputum specimen for diagnosis. We believe that this heterogeneity between studies may reflect the enrolment of a population with a higher burden of pulmonary disease in Peter 2016, or study operational factors such as improved counselling regarding specimen collection or the availability and use of sputum induction for participants who were unable to produce sputum spontaneously in Peter 2016. In contrast, only a single spontaneous sputum specimen was collected in Gupta-Wright 2018.

Incremental diagnostic yield due to addition of LF-LAM to the diagnostic algorithm

Gupta-Wright 2018 reported that increases in tuberculosis diagnoses in the intervention group that received LF-LAM (22% of tuberculosis diagnoses) compared to the standard-of-care group (15% of tuberculosis diagnoses) were not confined to high-risk subgroups, with an overall adjusted absolute risk difference of 7.3% (95% CI 4.4 to 10.2). These results were adjusted for study sites; unadjusted data were not provided. Gupta-Wright 2018 reported that of participants with microbiologically confirmed tuberculosis who had only one positive LF-LAM test, LF-LAM had an incremental diagnostic yield of 41% (87/210), compared to 6% (13/210) for urine Xpert MTB/RIF and 14% (30/210) for sputum Xpert MTB/RIF.

Tuberculosis-related treatment outcomes (treatment success or failure, relapse or cure)

None of the included trials evaluated other tuberculosis-related treatment outcomes (treatment success or failure, relapse or cure).

DISCUSSION

Summary of main results

Two trials in inpatient settings and one trial in outpatient settings assessed the impact of diagnostic strategies that included LF-LAM on mortality when the test was used in conjunction with other tuberculosis diagnostic tests or clinical assessment for clinical decision-making in people living with HIV (see Summary of findings 1 and Summary of findings 2). In inpatient settings, the use of LF-LAM testing as part of a tuberculosis diagnostic strategy likely reduces mortality in people living with HIV at eight weeks compared to routine tuberculosis diagnostic testing without LF-LAM (moderate-certainty evidence). Although the certainty of the evidence is moderate, this finding represents a moderate effect on a patient important outcome (mortality) and in an important population (people living with HIV) that is aligned with the decision of the WHO Guideline Development Group, which issued a "strong recommendation for the intervention" in the inpatient context (WHO Consolidated Guidelines (Module 3) 2020). In outpatient settings, the use of LF-LAM testing as part of a tuberculosis diagnostic strategy may reduce mortality in people living with HIV at six months compared to routine tuberculosis diagnostic testing without LF-LAM (low-certainty evidence). Although this trial did not detect a difference in mortality, the direction of effect was towards a mortality reduction, and the effect size was similar to that in inpatient settings.

Assessment of other patient-important and implementation outcomes in the trials varied. In inpatient settings, the use of LF-LAM testing as part of a tuberculosis diagnostic strategy probably results in a slight increase in the proportion of people living with HIV who were started on tuberculosis treatment compared to routine tuberculosis diagnostic testing without LF-LAM. In outpatient settings, the use of LF-LAM testing as part of a tuberculosis diagnostic strategy may result in a large increase in the proportion of people living with HIV who were started on tuberculosis treatment compared to routine tuberculosis diagnostic testing without LF-LAM. The included trials demonstrated that a higher proportion of people living with HIV were able to produce urine compared to sputum for tuberculosis diagnostic testing; a higher proportion of people living with HIV were diagnosed with tuberculosis in the group that received LF-LAM; and the incremental diagnostic yield was higher for LF-LAM than for urine or sputum Xpert MTB/RIF.

Overall completeness and applicability of evidence

The three included trials were conducted in sub-Saharan Africa, thus we do not have direct evidence of the applicability of the findings to other settings outside of Africa. Although the majority of people with HIV-associated tuberculosis live in sub-Saharan Africa, caution is required with respect to inferences to policy from the limited number of trials conducted to date. Although the only outpatient trial, Grant 2020, was conducted at multiple clinics in one country (South Africa), both inpatient trials included more than one country, and Peter 2016 included four countries, which increases the applicability of the study findings to settings outside of South Africa, which is important because other countries in sub-Saharan Africa are more resource-constrained than South Africa.

We emphasize the importance of the finding that despite differences in study design, two large, multicentre trials demonstrated that the use of LF-LAM reduced mortality in inpatient settings, which increases generalizability. In Gupta-Wright 2018, the test was performed in the laboratory, not at the point of care. The intervention in Gupta-Wright 2018 was a combination of LF-LAM and urine Xpert MTB/RIF, which could impact generalizability, and introduces heterogeneity since it is not possible to assess the impact of LF-LAM alone in this study. In Peter 2016, the intervention was bedside LF-LAM plus a "nurse-informed" treatment decision. In Grant 2020, the intervention was a study nurse-led diagnostic evaluation that included assessment of tuberculosis symptoms, BMI, fingerprick haemoglobin testing, and point-of-care LF-LAM testing. There was heterogeneity in the inpatient trial populations in that Gupta-Wright 2018 screened patients admitted to medical wards, and Peter 2016 screened patients admitted to emergency units, short-stay wards, and medical wards. This may have biased the study populations to being sicker, particularly if this led to

an earlier time of enrolment in Peter 2016, although both trials only enrolled patients admitted for less than 48 hours. We note that the informed consent requirements for both inpatient trials likely resulted in the exclusion of patients who were critically ill, and that enrolment being limited to standard working hours and for less than 48 hours after admission may have affected the representativeness of the population studied. In Grant 2020, patients who met criteria for urgent referral to secondary care were excluded, as were patients with a higher risk of adverse events due to tuberculosis treatment, specifically those with chronic liver disease or high weekly alcohol intake.

These additional considerations may not reflect how the test will be performed in routine practice in other clinical settings. Important questions related to implementation remain, such as how diagnostic algorithms will be implemented to identify patients to undergo LF-LAM testing; what is the impact of LF-LAM being performed at the bedside by staff who may be less familiar with the challenges of interpreting the results based on the reference scale card versus in the laboratory by trained staff; and how will LF-LAM results be acted upon, particularly in the clinical scenario where the LF-LAM test is positive, and another test such as Xpert is negative. The relatively low accuracy of the current LF-LAM test may compromise its impact, depending upon how it is interpreted by the end-users of the test, for example if a negative LF-LAM test is interpreted as the absence of tuberculosis. We await studies that evaluate the impact of more accurate urine LAM tests, such as FujiLAM (Broger 2020), on mortality and patient-important outcomes.

The only trial evaluating the impact of LF-LAM in outpatient settings did not demonstrate an effect on mortality, although the direction of effect was towards a mortality reduction, and the effect size was similar to that in inpatient settings. However, we do not consider that inpatient status should necessarily be a limiting factor for test use. We note that people with HIV presenting in outpatient settings with tuberculosis may be very sick, which aligns with the WHO's conditional recommendation for the use of LF-LAM in this population. We also emphasize that mortality is not the only patient-important outcome to be considered. Results from all three trials included in this review demonstrated an increase or direction of effect towards an increase in tuberculosis treatment initiation amongst people who received a diagnostic strategy that included LF-LAM, which is an important implementation outcome as part of efforts to improve the quality of tuberculosis care.

Potential explanations for heterogeneity in effect estimates across CD4 strata

We hypothesized that effect estimates may vary between CD4 strata (summarized in Table 2 for the inpatient trials Gupta-Wright 2018 and Peter 2016) owing to factors that could lead to either a reduced or improved effect size for participants with CD4 ≤ 100 cells/µL or CD4 ≤ 200 cells/µL, compared to CD4 > 100 cells/µL or CD4 > 200 cells/µL, respectively. Similarly, the results for Grant 2020 summarized in Analysis 2.3 demonstrate that CD4 count may be associated with both LF-LAM positivity, and mortality (i.e. it can serve simultaneously as a covariate of interest and outcome). CD4 count could also be associated with antiretroviral therapy (ART) usage, and empiric tuberculosis treatment initiation. Consequently, these factors could impact the effect of any benefit from earlier diagnosis (e.g. through LF-LAM implementation) and lead to variable effects (of LF-LAM implementation). For example, if in both study arms participants with a lower CD4 were more likely to start tuberculosis treatment (which would be done empirically in the standard-of-care arm), then the benefit of confirmed diagnosis by LF-LAM could be blunted. Conversely, individuals with lower CD4 are more likely to have LF-LAM positivity leading to earlier treatment diagnosis and initiation. LF-LAM compared to standard of care could therefore have reduced mortality. LF-LAM positivity is also associated with mortality (Gupta-Wright 2016; Shah 2016). Consequently, earlier diagnosis through LF-LAM may not lead to a modifiable outcome, since having a lower CD4 count is associated with an increased risk of mortality (Kaplan 2018). LF-LAM positivity may also serve as a surrogate for a point-of-care CD4 test, thus LAM positivity could have stimulated earlier ART initiation (which may have a mortality benefit) if it is interpreted as a CD4 proxy. LF-LAM may also be a marker of bacterial load (Shah 2010), and treatment may thus have differential impact amongst people with tuberculosis who have a positive LF-LAM test compared to people with tuberculosis who have a negative LF-LAM test, but neither included study compared mortality in participants with a positive versus negative LF-LAM test.

Understanding whether the use of LF-LAM testing has a differential impact on mortality at lower CD4 counts is clinically relevant given the higher overall risk of tuberculosis-related mortality in these subgroups. Since the results from individual studies were heterogeneous within CD4 strata, and neither inpatient trial reported mortality rates by CD4 strata, evidence to explain how the effectiveness of the use of LF-LAM may vary according to CD4 count is uncertain. However, the subgroup analyses demonstrated that the direction of effect was towards decreased mortality for all CD4 strata examined, and that the effect did not vary significantly between different CD4 subgroups, aside from CD4 count < 50 cells/µL in the trial that was conducted in outpatient settings (Grant 2020).

Analysis of subgroup data, particularly those stratified by CD4 count, is limited, since the trials were not powered to detect changes at the subgroup level. Consequently, these results must be interpreted with caution when considering how the impact of the use of LF-LAM may vary according to CD4 count. Despite some differences in the pooled effect estimates across CD4 strata, these differences were not statistically significant, and the direction of the pooled effect estimates was towards a decrease in mortality for each CD4 stratum, aside from CD4 count < 50 cells/µL in Grant 2020. CD4 subgroup analysis results may not have reached statistical significance owing to the association of lower CD4 count with both LF-LAM positivity and mortality. LF-LAM positivity is also associated with increased mortality, thus LF-LAM-directed treatment may have been insufficient to avert the increased mortality associated with LF-LAM positivity. Understanding whether there is a difference in treatment outcomes amongst those who have a positive LF-LAM result compared to a negative LF-LAM result, adjusting for time of tuberculosis treatment, ART usage, and CD4 count may be important for future LAM implementation.

Secondary implementation outcomes

Analysis of secondary outcome data should also be interpreted with caution, given the substantial heterogeneity between the three trials. The differences in these secondary outcomes, including time to treatment initiation and likelihood of being able to produce a specimen for tuberculosis diagnostic testing, may reflect

the different severity of illness in the study populations. Peter 2016 included people with signs and symptoms of tuberculosis, whereas Gupta-Wright 2018 included people irrespective of signs and symptoms of tuberculosis. It is likely that enrolment of a sicker population in Peter 2016 resulted in more individuals in both arms being started on tuberculosis treatment. It may be that sicker individuals in Peter 2016 had a higher burden of respiratory disease that resulted in a higher proportion being able to produce a sputum specimen, or other operational factors such as potentially improved counselling related to specimen production may have increased the feasibility and yield of sputum-based testing. Similarly, although Grant 2020 was performed in outpatient settings, the median CD4 count was lower than for the two trials performed in inpatient settings, which likely resulted in more people being started on tuberculosis treatment.

Other implementation considerations

This review evaluated the impact of LF-LAM to guide treatment decisions in the context of clinical trials. Further implementation research is needed to assess the reach, effectiveness, costs, and other operational considerations during programmatic implementation.

Quality of the evidence

Details regarding the downgrading of the certainty of the evidence using the GRADE approach are included in the summary of findings tables. Our main reason for downgrading the certainty of the evidence for the analysis of trials in inpatient settings was indirectness, a concern about the generalizability to other settings due to heterogeneity in the diagnostic strategy used (aside from the use of LF-LAM) owing to the use of a pragmatic trial design. In both trials, patients who could not give informed consent were ineligible to participate, which may have biased the effect of the intervention towards the null if sicker patients were less likely to be able to give informed consent. Our reasons for downgrading the certainty of the evidence for the analysis of trials in outpatient settings were concerns about indirectness, given that only one trial, conducted in South Africa, was included, and imprecision, based on the wide 95% confidence interval that was reported.

Potential biases in the review process

We were careful to limit bias in the review process by strict adherence to Cochrane methods. Since policymakers, clinicians, and members of the wider tuberculosis community considered this review to be critical to decision-making, we included subgroup analyses by CD4 count, even though only three trials were identified for inclusion in the review, and we specified these analyses a priori in our protocol. We advise that results from these subgroup analyses be interpreted with caution given the small number of studies and residual heterogeneity between results of individual studies analysed according to CD4 count. However, the selection of CD4 count was also motivated by biological and clinical considerations, and we note that both inpatient trials contributed more than 2000 participants to each CD4 strata analysed.

Agreements and disagreements with other studies or reviews

We are not aware of other systematic reviews on this topic. A systematic review that sought to evaluate the prognostic value of LF-LAM to determine mortality risk demonstrated that the detection of LF-LAM in urine was independently associated with increased risk of mortality during treatment, after adjusting for other factors associated with mortality (Gupta-Wright 2016). Another recent study evaluating the implementation of LF-LAM (excluded from this review due its observational study design) found that LAM-positive patients not diagnosed through other tools and not treated for tuberculosis had a significantly higher risk of mortality compared to LAM-positive patients who received treatment (Huerga 2019). This is consistent with our explanation of the heterogeneity in effect estimates observed across CD4 strata, which we hypothesized may reflect the increased mortality associated with LF-LAM positivity, although the studies included in our review did not specifically evaluate mortality in patients who had a LF-LAM positive test compared to those who had a LF-LAM negative test. Our review is the only systematic review to assess the impact of using a diagnostic testing strategy that includes the use of LF-LAM to guide management decisions on mortality and other patient-important outcomes.

AUTHORS' CONCLUSIONS

Implications for practice

In inpatient settings, the use of LF-LAM as part of a tuberculosis diagnostic testing strategy likely reduces mortality and probably results in a slight increase in tuberculosis treatment initiation in people living with HIV. The reduction in mortality is likely due to earlier diagnosis, which facilitates prompt treatment initiation. In outpatient settings, the use of LF-LAM testing as part of a tuberculosis diagnostic strategy may reduce mortality and may result in a large increase in tuberculosis treatment initiation in people living with HIV. Our results support the implementation of LF-LAM to be used in conjunction with other WHO-recommended tuberculosis diagnostic tests to assist in the rapid diagnosis of tuberculosis in people living with HIV.

Implications for research

Given the limited number of trials on this topic, there is less certainty in the effect estimates for the subgroup analyses stratified by CD4 count, which reflects a patient population of clinical importance. Additional studies will help to understand the heterogeneity demonstrated in effect estimates across CD4 strata and to determine the impact of LF-LAM testing on mortality and patient-important outcomes in outpatient populations. There is also an urgent need for studies evaluating the effect of LF-LAM on patient-important outcomes in children. Further studies are needed to understand the impact of new, urine-based, point-of-care tests that detect urine LAM for tuberculosis diagnosis, such as the FujiLAM assay, on mortality and patient-important outcomes that inform the use of LAM assays on both diagnostic and treatment pathways. The use of implementation science research can strengthen the evidence base to inform the adoption of interventions such as LF-LAM by health systems.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Grant 2020

Study characteristics		
Methods	RCT	
Participants	3022 HIV-positive adults, outpatients	
Interventions	Composite clinical assessment including tuberculosis symptoms, BMI, haemoglobin concentration, and urine LAM result	
Outcomes	Mortality	
Notes	Mortality assessed at 6 months.	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "A statistician randomised primary health-care clinics (1:1), using computer-generated random numbers, to the intervention or standard of care (control)."
Allocation concealment (selection bias)	Low risk	Quote: "A statistician randomised primary health-care clinics (1:1), using computer-generated random numbers, to the intervention or standard of care (control), based on restriction to achieve reasonable balance, separately, for mean CD4 count, peri-urban versus rural clinic location, and total monthly ART initiations."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Due to the nature of the intervention being examined, participants, research staff, and clinic staff were aware of group allocation."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "To ascertain possible serious and severe adverse events... research nurses and research assistants enquired about symptoms and history suggesting possible adverse events at every study visit, including early study review visits for participants in the intervention group, and sought relevant data in case note reviews. Due to the pragmatic trial design, no equivalent early study visits were done for participants in the control group; thus we anticipat-

Grant 2020 *(Continued)*

		ed that adverse events would be more completely ascertained in the intervention group."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Vital status at 6 months was determined for 1487 (98.7%) of 1507 participants in the intervention group and 1485 (98.0%) of 1515 participants in the control group."
Selective reporting (reporting bias)	Low risk	Comment: the authors prespecified primary and secondary outcomes for analysis, which they reported.
Other bias	Low risk	Although there were some differences between the intervention and standard-of-care groups, notably the presence of tuberculosis symptoms, prior receipt of isoniazid preventive therapy, and receipt of tuberculosis tests in the preceding 6 months, we did not consider these differences to be likely to introduce bias.

Gupta-Wright 2018

Study characteristics		
Methods	RCT	
Participants	2574 HIV-positive adults, inpatients (unselected)	
Interventions	Urine LAM + urine Xpert + sputum Xpert versus standard of care (which included sputum Xpert)	
Outcomes	Mortality	
Notes	Mortality assessed at 56 days.	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "a randomisation list of unique patient identifiers was generated by the study statistician using a computer-generated random block size."
Allocation concealment (selection bias)	Low risk	Quote: "On enrolment, study nurses or clinicians took a consecutive sealed opaque envelope containing the unique patient identifier but not the study group, to which they remained masked. A paired set of sealed envelopes were kept in a locked cabinet in the study laboratory, labelled with the unique patient identifier and containing the study group allocation. These were opened by the laboratory technician on receipt of study tuberculosis screening specimens."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Investigators, all study staff (other than the laboratory technician and statistician), hospital attending clinical teams, and patients were masked to the study group allocation."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "tuberculosis screening results were reported to the attending clinical team as positive, negative, or not done to maintain masking, with neither study group nor individual test results communicated to attending clinical or study teams."

Gupta-Wright 2018 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "27 (1%) of 2574 patients were lost to follow-up at 56 days after hospital discharge"
Selective reporting (reporting bias)	Low risk	Comment: the authors prespecified primary and secondary outcomes for analysis, which they reported.
Other bias	Unclear risk	Comment: did not include a culture reference standard, used laboratory-based rather than bedside LAM, consent requirements may have biased study towards a less sick population

Peter 2016

Study characteristics	
Methods	RCT
Participants	2528 HIV-positive adults, inpatients (symptoms)
Interventions	Urine LAM plus TB diagnostic tests: smear, Xpert, and culture versus standard TB diagnostic tests: smear, Xpert, and culture
Outcomes	Mortality
Notes	Mortality assessed at 8 weeks.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "We randomly assigned eligible patients..using computer generated allocation lists." Comment: issue arose with duplicate randomization numbers, but this was resolved.
Allocation concealment (selection bias)	Low risk	Quote: "Once an eligible patient was identified, the research nurse at each site (who did not have access to these lists) either contacted a centrally located data manager by telephone to obtain assignment or used a text-message system, which automatically accessed the allocation list used to assign each patient."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Neither patients nor research nurses were masked to either allocation or test results."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Neither patients nor research nurses were masked to either allocation or test results."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "8-week outcome data were available for 2411 (95%) of 2528 patients in the modified Intention-to-treat analysis."

Peter 2016 *(Continued)*

Selective reporting (reporting bias)	Low risk	Comment: the authors prespecified primary and secondary outcomes for analysis, which they reported.
Other bias	Unclear risk	Heterogeneous mortality effect noted across the four countries in which the study was conducted. Variable use of tuberculosis diagnostics and treatment across the study sites. Variable illness severity across sites. Consent requirements may have biased study towards a less sick population.

BMI: body mass index
LAM: lipoarabinomannan
RCT: randomized controlled trial
TB: tuberculosis

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Blanc 2020	Standard-of-care arm utilized a diagnostic strategy that did not include any of the tuberculosis tests described in our protocol as criteria for inclusion, and study was not used to guide clinical decision-making, precluding comparison of the impact of LF-LAM compared to other diagnostic strategies.
Cummings 2019	Not an RCT
Gupta-Wright 2019	Not an RCT
Huerga 2019	Not an RCT
Kubiak 2018	Not an RCT
Mathabire Rucker 2019	Not an RCT
Mthiyane 2019	Not an RCT
Naidoo 2019	Not an RCT

LF-LAM: lateral flow urine lipoarabinomannan assay
RCT: randomized controlled trial

DATA AND ANALYSES

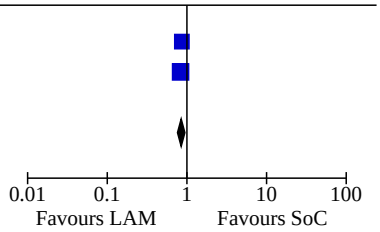
Comparison 1. Meta-analyses comparing mortality for LAM versus standard of care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Mortality at 8 weeks, inpatient settings	2	5102	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.76, 0.94]
1.2 Sensitivity analysis - 25% mortality in missing participants (LAM) and 0% in missing participants (standard of care)	2	5233	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.78, 0.97]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.3 Sensitivity analysis - 0% mortality in missing participants (LAM) and 25% in missing participants (standard of care)	2	5233	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.74, 0.91]
1.4 Mortality at 6 months, outpatient settings	1	2972	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.71, 1.11]

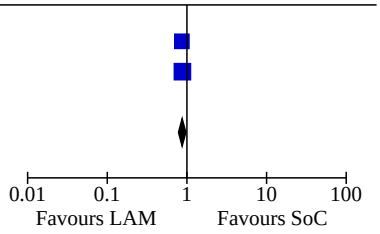
Analysis 1.1. Comparison 1: Meta-analyses comparing mortality for LAM versus standard of care, Outcome 1: Mortality at 8 weeks, inpatient settings

	LAM		SoC			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Gupta-Wright 2018	235	1287	272	1287	46.3%	0.86 [0.74 , 1.01]	
Peter 2016	261	1257	317	1271	53.7%	0.83 [0.72 , 0.96]	
Total (95% CI)		**2544**		**2558**	**100.0%**	**0.85 [0.76 , 0.94]**	
Total events:	496		589				
Heterogeneity: Chi² = 0.12, df = 1 (P = 0.73); I² = 0%							
Test for overall effect: Z = 3.07 (P = 0.002)							
Test for subgroup differences: Not applicable							



Analysis 1.2. Comparison 1: Meta-analyses comparing mortality for LAM versus standard of care, Outcome 2: Sensitivity analysis - 25% mortality in missing participants (LAM) and 0% in missing participants (standard of care)

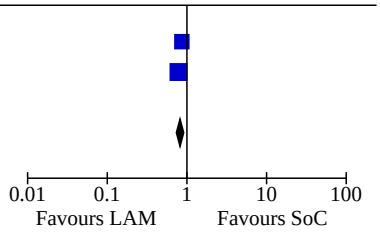
	LAM		SoC			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Gupta-Wright 2018	235	1287	272	1287	46.1%	0.86 [0.74 , 1.01]	
Peter 2016	281	1336	317	1323	53.9%	0.88 [0.76 , 1.01]	
Total (95% CI)		**2623**		**2610**	**100.0%**	**0.87 [0.78 , 0.97]**	
Total events:	516		589				
Heterogeneity: Chi² = 0.02, df = 1 (P = 0.88); I² = 0%							
Test for overall effect: Z = 2.57 (P = 0.01)							
Test for subgroup differences: Not applicable							



Analysis 1.3. Comparison 1: Meta-analyses comparing mortality for LAM versus standard of care, Outcome 3: Sensitivity analysis - 0% mortality in missing participants (LAM) and 25% in missing participants (standard of care)

Study or Subgroup	LAM Events	LAM Total	SoC Events	SoC Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gupta-Wright 2018	235	1287	272	1287	45.1%	0.86 [0.74 , 1.01]
Peter 2016	261	1336	330	1323	54.9%	0.78 [0.68 , 0.90]
Total (95% CI)		**2623**		**2610**	**100.0%**	**0.82 [0.74 , 0.91]**
Total events:	496		602			

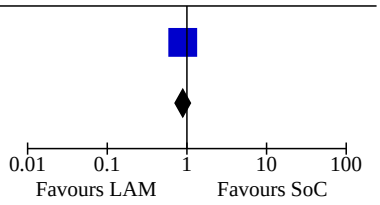
Heterogeneity: Chi² = 0.82, df = 1 (P = 0.36); I² = 0%
Test for overall effect: Z = 3.69 (P = 0.0002)
Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1: Meta-analyses comparing mortality for LAM versus standard of care, Outcome 4: Mortality at 6 months, outpatient settings

Study or Subgroup	LAM Events	LAM Total	SoC Events	SoC Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Grant 2020	134	1487	151	1485	100.0%	0.89 [0.71 , 1.11]
Total (95% CI)		**1487**		**1485**	**100.0%**	**0.89 [0.71 , 1.11]**
Total events:	134		151			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.07 (P = 0.28)
Test for subgroup differences: Not applicable



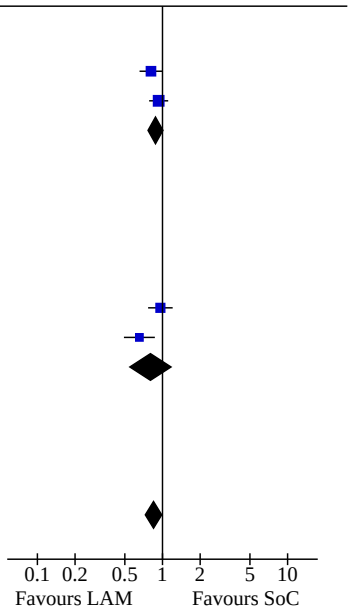
Comparison 2. Meta-analyses comparing mortality for LAM versus standard of care, stratified by CD4 strata

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Mortality at 8 weeks, inpatients - stratified by CD4 ≤ 100 versus > 100 cells/µL	2	4883	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.73, 0.99]
2.1.1 CD4 ≤ 100 cells/µL	2	2016	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.77, 1.01]
2.1.2 CD4 > 100 cells/µL	2	2867	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.55, 1.17]
2.2 Mortality at 8 weeks, inpatients - stratified by CD4 ≤ 200 versus > 200 cells/µL	2	4903	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.75, 0.98]
2.2.1 CD4 ≤ 200 cells/µL	2	2886	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.77, 0.98]
2.2.2 CD4 > 200 cells/µL	2	2017	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.48, 1.23]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.3 Mortality at 6 months, outpatients - stratified by CD4 count < 50 cells/µL versus ≥ 50 cells/µL	1	1402	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.73, 1.09]
2.3.1 CD4 < 50 cells/µL	1	460	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.78, 1.31]
2.3.2 CD4 ≥ 50 cells/µL	1	942	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.55, 1.05]

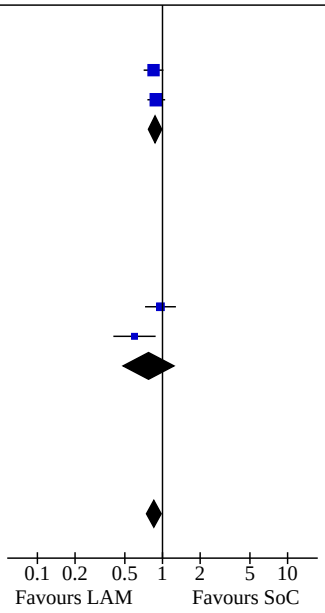
Analysis 2.1. Comparison 2: Meta-analyses comparing mortality for LAM versus standard of care, stratified by CD4 strata, Outcome 1: Mortality at 8 weeks, inpatients - stratified by CD4 ≤ 100 versus > 100 cells/µL

Study or Subgroup	LAM Events	LAM Total	SoC Events	SoC Total	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 CD4 ≤ 100 cells/µL						
Gupta-Wright 2018	107	371	133	373	26.2%	0.81 [0.66 , 1.00]
Peter 2016	176	646	183	626	31.1%	0.93 [0.78 , 1.11]
Subtotal (95% CI)		**1017**		**999**	**57.3%**	**0.88 [0.77 , 1.01]**
Total events:	283		316			
Heterogeneity: Tau² = 0.00; Chi² = 1.03, df = 1 (P = 0.31); I² = 3%						
Test for overall effect: Z = 1.85 (P = 0.06)						
2.1.2 CD4 > 100 cells/µL						
Gupta-Wright 2018	127	904	131	897	24.3%	0.96 [0.77 , 1.21]
Peter 2016	65	516	106	550	18.4%	0.65 [0.49 , 0.87]
Subtotal (95% CI)		**1420**		**1447**	**42.7%**	**0.80 [0.55 , 1.17]**
Total events:	192		237			
Heterogeneity: Tau² = 0.06; Chi² = 4.35, df = 1 (P = 0.04); I² = 77%						
Test for overall effect: Z = 1.15 (P = 0.25)						
Total (95% CI)		**2437**		**2446**	**100.0%**	**0.85 [0.73 , 0.99]**
Total events:	475		553			
Heterogeneity: Tau² = 0.01; Chi² = 5.66, df = 3 (P = 0.13); I² = 47%						
Test for overall effect: Z = 2.15 (P = 0.03)						
Test for subgroup differences: Chi² = 0.21, df = 1 (P = 0.65), I² = 0%						



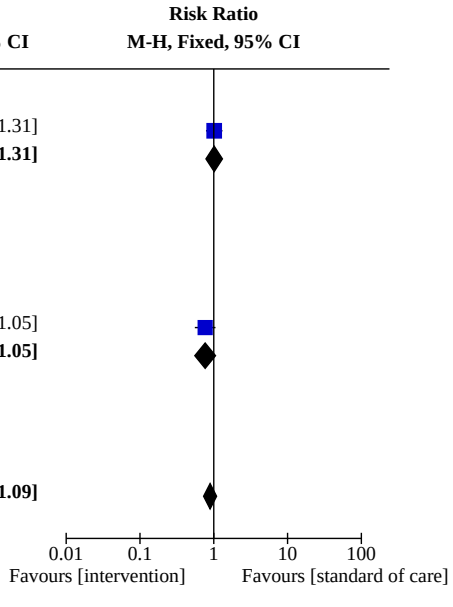
Analysis 2.2. Comparison 2: Meta-analyses comparing mortality for LAM versus standard of care, stratified by CD4 strata, Outcome 2: Mortality at 8 weeks, inpatients - stratified by CD4 ≤ 200 versus > 200 cells/µL

Study or Subgroup	LAM Events	LAM Total	SoC Events	SoC Total	Weight	Risk Ratio M-H, Random, 95% CI
2.2.1 CD4 ≤ 200 cells/µL						
Gupta-Wright 2018	151	571	184	590	33.5%	0.85 [0.71 , 1.02]
Peter 2016	208	878	225	847	38.1%	0.89 [0.76 , 1.05]
Subtotal (95% CI)		**1449**		**1437**	**71.6%**	**0.87 [0.77 , 0.98]**
Total events:	359		409			
Heterogeneity: Tau² = 0.00; Chi² = 0.16, df = 1 (P = 0.69); I² = 0%						
Test for overall effect: Z = 2.21 (P = 0.03)						
2.2.2 CD4 > 200 cells/µL						
Gupta-Wright 2018	84	715	84	689	17.9%	0.96 [0.73 , 1.28]
Peter 2016	33	284	64	329	10.5%	0.60 [0.40 , 0.88]
Subtotal (95% CI)		**999**		**1018**	**28.4%**	**0.77 [0.48 , 1.23]**
Total events:	117		148			
Heterogeneity: Tau² = 0.08; Chi² = 3.79, df = 1 (P = 0.05); I² = 74%						
Test for overall effect: Z = 1.08 (P = 0.28)						
Total (95% CI)		**2448**		**2455**	**100.0%**	**0.85 [0.75 , 0.98]**
Total events:	476		557			
Heterogeneity: Tau² = 0.01; Chi² = 4.21, df = 3 (P = 0.24); I² = 29%						
Test for overall effect: Z = 2.33 (P = 0.02)						
Test for subgroup differences: Chi² = 0.24, df = 1 (P = 0.63), I² = 0%						



Analysis 2.3. Comparison 2: Meta-analyses comparing mortality for LAM versus standard of care, stratified by CD4 strata, Outcome 3: Mortality at 6 months, outpatients - stratified by CD4 count < 50 cells/µL versus ≥ 50 cells/µL

Study or Subgroup	Intervention Events	Intervention Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.3.1 CD4 < 50 cells/µL						
Grant 2020	77	227	78	233	51.1%	1.01 [0.78 , 1.31]
Subtotal (95% CI)		**227**		**233**	**51.1%**	**1.01 [0.78 , 1.31]**
Total events:	77		78			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.10 (P = 0.92)						
2.3.2 CD4 ≥ 50 cells/µL						
Grant 2020	57	476	73	466	48.9%	0.76 [0.55 , 1.05]
Subtotal (95% CI)		**476**		**466**	**48.9%**	**0.76 [0.55 , 1.05]**
Total events:	57		73			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.64 (P = 0.10)						
Total (95% CI)		**703**		**699**	**100.0%**	**0.89 [0.73 , 1.09]**
Total events:	134		151			
Heterogeneity: Chi² = 1.83, df = 1 (P = 0.18); I² = 45%						
Test for overall effect: Z = 1.11 (P = 0.26)						
Test for subgroup differences: Chi² = 1.80, df = 1 (P = 0.18), I² = 44.5%						



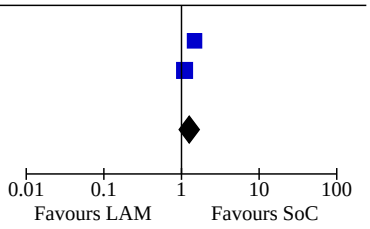
Comparison 3. Meta-analyses comparing proportion of participants treated for tuberculosis for LAM versus standard of care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Proportion of participants treated for tuberculosis, inpatient settings	2	5102	Risk Ratio (M-H, Random, 95% CI)	1.26 [0.94, 1.69]
3.2 Proportion of participants treated for tuberculosis, outpatient settings	1	3022	Risk Ratio (M-H, Random, 95% CI)	5.44 [4.70, 6.29]

Analysis 3.1. Comparison 3: Meta-analyses comparing proportion of participants treated for tuberculosis for LAM versus standard of care, Outcome 1: Proportion of participants treated for tuberculosis, inpatient settings

	LAM		SoC			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Gupta-Wright 2018	268	1287	182	1287	46.7%	1.47 [1.24 , 1.75]	
Peter 2016	648	1257	598	1271	53.3%	1.10 [1.01 , 1.19]	
Total (95% CI)		**2544**		**2558**	**100.0%**	**1.26 [0.94 , 1.69]**	
Total events:	916		780				

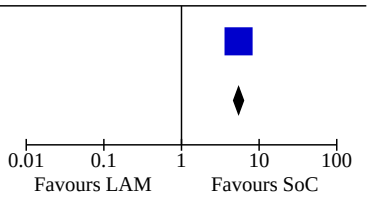
Heterogeneity: Tau² = 0.04; Chi² = 9.88, df = 1 (P = 0.002); I² = 90%
Test for overall effect: Z = 1.52 (P = 0.13)
Test for subgroup differences: Not applicable



Analysis 3.2. Comparison 3: Meta-analyses comparing proportion of participants treated for tuberculosis for LAM versus standard of care, Outcome 2: Proportion of participants treated for tuberculosis, outpatient settings

	LAM		SoC			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Grant 2020	930	1507	172	1515	100.0%	5.44 [4.70 , 6.29]	
Total (95% CI)		**1507**		**1515**	**100.0%**	**5.44 [4.70 , 6.29]**	
Total events:	930		172				

Heterogeneity: Not applicable
Test for overall effect: Z = 22.69 (P < 0.00001)
Test for subgroup differences: Not applicable



ADDITIONAL TABLES

Table 1. Characteristics of studies that evaluated a diagnostic intervention that included LF-LAM in adults living with HIV

Study	Population	Countries	Design	Intervention	Who performed LF-LAM, and how was it used?	Median CD4 count	Karnofsky score	BMI	Outcomes assessed
Gupta-Wright 2018	2574 adults living with HIV, inpatients (included irrespective of signs and symptoms of tuberculosis - unselected participants)	South Africa (1 site), Malawi (1 site)	RCT Duration: 2 years, from October 2015 to September 2017	Urine LAM (LF-LAM) + urine Xpert + sputum Xpert versus SoC (included sputum Xpert for all, with further option to send additional samples for routine investigations)	Testing, including LF-LAM, was performed by the study laboratory technician. TB screening results were reported to the attending clinical team as positive, negative, or not done (individual test results, including LF-LAM, were not reported).	227 cells/µL	60	21.7	Primary outcome: • Mortality at 56 days Secondary outcomes: • Proportion initiated on TB treatment • Proportion able to produce specimen for diagnosis • Incremental diagnostic yield • Time to diagnosis • Time to treatment initiation
Peter 2016	2528 adults living with HIV, inpatients (included if they had signs and symptoms of tuberculosis - symptomatic participants)	South Africa (4 sites), Zimbabwe (2 sites), Zambia (2 sites), Tanzania (2 sites)	RCT Duration 21 months, from January 2013 to October 2014	Urine LAM (LF-LAM) plus standard available TB diagnostic tests: smear, Xpert, and culture versus SoC: TB diagnostic tests: smear, Xpert, and culture	LF-LAM was performed by the study nurse at the bedside. Results were verbally reported to the attending clinician as LAM is positive (with grade) or negative, and if positive, that TB treatment was indicated.	84 cells/µL	50	18.8	Primary outcome: • Mortality at 8 weeks Secondary outcomes: • Proportion initiated on

Table 1. Characteristics of studies that evaluated a diagnostic intervention that included LF-LAM in adults living with HIV *(Continued)*

									TB treatment • Proportion able to produce specimen for diagnosis
Grant 2020	3022 adults living with HIV, outpatients (included if CD4 count <= 150 cells/μL, no history of ART in past 6 months or TB treatment in past 3 months, i.e. presence or absence of symptoms was not part of eligibility criteria)	South Africa (24 primary healthcare clinics)	RCT Duration: 2 years, from December 2012 to December 2014	Assessment of TB symptoms, BMI, point-of-care haemoglobin concentrations, and urine LAM (LF-LAM) results, which were combined in an algorithm and interpreted as high, medium, or low probability of TB, which was used to guide treatment decision-making versus SoC which did not specify the testing approach but did not include urine LAM	Study nurses performed LF-LAM testing in the intervention clinics and interpreted the results in conjunction with the other clinical assessment findings to determine the probability of TB, and issued treatment based on a study algorithm stratified by the probability of TB.	72 cells/μL	NR	21.4	Primary outcome: • Mortality at 6 months Secondary outcome: • Proportion initiated on TB treatment

Abbreviations: ART: antiretroviral treatment, BMI: body mass index, LF-LAM: lateral flow urine lipoarabinomannan assay, NR: not reported, RCT: randomized controlled trial, SoC: standard of care, TB: tuberculosis

Table 2. Summary of pooled meta-analysis data evaluating the effect of a diagnostic intervention that included LF-LAM on mortality in inpatient settings, stratified by CD4 count

CD4 strata	Studies	Participants	Pooled risk ratios (95% CI)
≤ 100 cells/μL	2	2016	0.88 (0.77 to 1.01)
> 100 cells/μL	2	2867	0.80 (0.55 to 1.17)
≤ 200 cells/μL	2	2886	0.87 (0.77 to 0.98)
> 200 cells/μL	2	2017	0.77 (0.48 to 1.23)

LF-LAM: lateral flow urine lipoarabinomannan assay; CI: confidence interval

APPENDICES

Appendix 1. Detailed search strategies

MEDLINE (PubMed) search history

#9	Search (#3) AND (#7) AND #8)
#8	Search test OR assay OR antigen OR Ag OR lateral flow assay*OR urine antigen OR point of care Field: Title/Abstract
#7	Search (#4) OR #5) OR #6
#6	Search LAM; Field: Title/Abstract
#5	Search "lipoarabinomannan" [Supplementary Concept]
#4	Search lipoarabinomannan ; Field: Title/Abstract
#3	Search (#1) OR #2)
#2	Search tuberculosis Or TB Field: Title/Abstract
#1	Search ("Tuberculosis"[Mesh]) OR "Mycobacterium tuberculosis"[Mesh]

Embase 1947-Present, updated daily

Search strategy:

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1 tuberculosis.mp. or tuberculosis/ or Mycobacterium tuberculosis/

2 lipoarabinomannan.mp. or lipoarabinomannan/

3 LAM.mp.

4 2 or 3

5 1 and 4

6 (test or assay or antigen or Ag or lateral flow assay* or urine antigen or point of care).mp.

7 4 and 6

Cochrane Central Register of Controlled Trials, issue 3 of 12, March 2021

#1 tuberculosis:ti,ab,kw (Word variations have been searched)

#2 TB:ti, ab, kw

#3 MeSH descriptor: [Mycobacterium tuberculosis] explode all trees

#4 MeSH descriptor: [Tuberculosis] explode all trees

#5 #1 or #2 or #3 or #4

#6 LAM:ti,ab,kw

#7 lipoarabinomannan:ti,ab,kw

#8 #6

Database: **LILACS**

Search on: tuberculosis or TB [Words] and lipoarabinomannan or LAM [Words]

Science Citation Index Expanded (SCI-EXPANDED), Conference Proceedings Citation Index- Science (CPCI-S), and BIOSIS Previews (all from Web of Science)

TOPIC: (tuberculosis or TB) AND TOPIC: (lipoarabinomannan or LAM) AND TITLE: (test OR assay OR antigen OR Ag OR lateral flow assay*OR urine antigen OR point of care)

Scopus

((TITLE-ABS-KEY (tuberculosis OR tb)) AND (lam OR lipoarabinomannan)) AND (TITLE (test OR assay OR antigen))

Proquest Dissertations & Theses

ab(tuberculosis) AND (lam OR lipoarabinomannan) AND ab((test OR assay OR antigen OR Ag OR lateral flow assay*OR urine antigen OR point of care))

ClinicalTrials.gov

LAM | Recruiting, Not yet recruiting, Active, not recruiting, Enrolling by invitation Studies | Tuberculosis

Also searched for Lipoarabinomannan

WHO ICTRP: LAM or Lipoarabinomannan and tuberculosis

CONTRIBUTIONS OF AUTHORS

RRN and KRS drafted the manuscript, with specific input from MC for the sections on data analysis. SB, PL, and MS provided critical revisions to the manuscript. All review authors read and approved the final manuscript draft.

DECLARATIONS OF INTEREST

RRN has no known conflicts of interest. She serves voluntarily as Chair of a tuberculosis advocacy organisation, TB Proof, based in South Africa. Although TB Proof has not directly led advocacy efforts related to urine LAM, the organisation has supported calls to improve access to urine LAM based on WHO guidance.

PL has no known conflicts of interest.

MC has no known conflicts of interest.

SB has no known conflicts of interest.

KRS has received financial support from Cochrane Infectious Diseases, UK; McGill University, Canada; and USAID, USA, administered by the World Health Organization Global TB Programme, Switzerland for the preparation of systematic reviews and educational materials. She has also received consultancy fees from Foundation for Innovative New Diagnostics (FIND), Switzerland (for the preparation of systematic reviews and GRADE tables); honoraria; and travel support to attend WHO guideline meetings.

MS has no known conflicts of interest.

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- Foreign, Commonwealth, and Development Office (FCDO), UK

  Project number: 300342-104

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We revised the review objective from the protocol (Steingart 2019), such that it is stratified by clinical setting (inpatient versus outpatient). Primary stratification by clinical setting is consistent with the clinical pathway suggested by the current World Health Organization guidelines (WHO Consolidated Guidelines (Module 3) 2020), since a priori there is likely to be clinical heterogeneity with respect to inpatient and outpatient participant groups. We were only able to perform meta-analyses for one of our prespecified secondary outcomes (proportion of participants started on tuberculosis treatment), since data on the other outcomes were either not reported or only reported in one of the three included studies.

INDEX TERMS

Medical Subject Headings (MeSH)

*Antibiotics, Antitubercular [therapeutic use]; *HIV Infections [complications] [drug therapy]; Lipopolysaccharides; *Mycobacterium tuberculosis; Rifampin; Sensitivity and Specificity; *Tuberculosis [diagnosis] [drug therapy]; *Tuberculosis, Pulmonary [drug therapy]

MeSH check words

Adult; Humans