Enhanced Diagnostic Workup for Patients About to Start Empiric Tuberculosis Treatment in Lusaka, Zambia

NCT-number: not yet assigned

Version: 8-12-2024

Background and justification: Tuberculosis remains a common disease worldwide, with an estimated 10 million new cases in 2020. It is one of the leading causes of death worldwide, causing an estimated 1,3 million deaths in 2020.[1] In Sub-Saharan Africa in particular, the combined burden of tuberculosis and human immunodeficiency virus (HIV) infection leads to increased tuberculosis prevalence and mortality. Tuberculosis is a treatable disease, and most, if not all, deaths could be prevented by timely diagnosis and appropriate treatment. Unfortunately, diagnosing tuberculosis can be challenging.[2] Several diagnostic strategies have been developed, but the most impactful development in recent years has been the widespread implementation of the GeneXpert MTB/RIF test. This is a cartridge-based nucleic acid amplification test, which can be used with minimal supporting laboratory structure, and has an estimated sensitivity and specificity for diagnosing pulmonary tuberculosis in adults of 85% and 98%, respectively.[1,3]

The GeneXpert MTB/RIF test replaced sputum smears for acid-fast bacilli as a first-line test, which had much lower sensitivity for diagnosing pulmonary tuberculosis. Historically, this lower sensitivity meant that clinicians also had to rely on clinical factors to determine whether to start tuberculosis treatment. Currently, the practice of giving empiric tuberculosis treatment to patients who had negative microbiology diagnostics is still widespread.[4–7] However, in the GeneXpert MTB/RIF era, this might no longer be appropriate.[8–11]

For example, in Zambia, there were an estimated 40000 new tuberculosis cases in 2020 (with 92% pulmonary tuberculosis), 100% of whom were tested with GeneXpert MTB/RIF (or other rapid molecular diagnostics). However, only 51% of all patients who were treated for pulmonary tuberculosis were bacteriologically confirmed.[1] This is not consistent with the supposed 85% sensitivity of the GeneXpert MTB/RIF test. This might mean that a significant proportion of patients, perhaps in the order of 30-40% of all patients, and 60-80% of all empirically treated patients, receives tuberculosis treatment inappropriately. Standard tuberculosis treatment can be burdensome, as the usual treatment duration is 6 months, and 5-10% of patients are estimated to experience serious side effects.[2] In some cases, a self-limiting condition such as a viral respiratory tract infection might be the underlying diagnosis, which would not need to be followed up for six months. More importantly, empiric tuberculosis treatment can delay the diagnosis of another severe underlying condition such as malignancy, pulmonary aspergillosis, or interstitial lung disease. It has been shown that mortality is higher in patients that are empirically treated for tuberculosis, and this may be in part to missed other diagnoses.[12]

Over the past years, the departments of pulmonology and radiology from St. Antonius Hospital have been holding bimonthly videoconferences with the department of pulmonology at University

Teaching Hospital in Lusaka, Zambia. We have mainly discussed patients with suspected interstitial lung disease. Our experience has taught us that interstitial lung diseases, which have barely been reported in Sub-Saharan Africa, can indeed be identified when you look well enough, and that these patients have oftentimes received inappropriate empiric tuberculosis treatment prior to the diagnosis of interstitial lung disease.[26,27]

In recent years, specialty services, such as a pulmonology clinic, as well as computed tomography (CT)-scanning and novel microbiological tests have become available in Zambia, as well as other developing countries. This, in combination with the widespread availability of the high-sensitivity GeneXpert MTB/RIF test, leads us to believe that common practice of giving empiric tuberculosis treatment after a negative initial microbiological test for tuberculosis is no longer appropriate. In this study we want to explore the feasibility of an enhanced diagnostic workup for patients about to start empiric tuberculosis treatment and the impact this has on patient diagnoses and outcomes. This workup will include discussing patients in international multidisciplinary videoconferences when needed.

Societal relevance: No specific societal relevance.

Economic relevance: Might be associated with cost savings if tuberculosis treatment can be avoided, if long follow-up is avoided for self-limiting conditions and if severe conditions are diagnosed and treated in a timelier manner.

Medical relevance: Appropriate diagnosis and treatment are the cornerstone of medicine. This is in accordance with the principles of beneficence and non-maleficence. If the enhanced diagnostic workup does indeed lead to more appropriate diagnosis and treatment, this likely impacts patient quality of life and might even impact patient survival.

Other relevance: If the study findings are positive, this will justify the further building of specialty services as an addition to program-based tuberculosis services in Zambia and other developing countries.

Statement of the problem:

Tuberculosis is often diagnosed on a clinical basis, even with the widespread availability of highly sensitive laboratory tests such as GeneXpert MTB/RIF. This might lead to overtreatment of tuberculosis, as well as misdiagnosis and incorrect or delayed treatment for other respiratory diseases.

Literature review: A recent systematic review found that over half of patients with presumed tuberculosis (i.e. patients in whom tuberculosis was considered as a diagnosis, but who did not necessarily receive empiric tuberculosis treatment) do not have a final diagnosis of active tuberculosis, but little is known about the healthcare needs of these patients.[13] A study from the United Kingdom found that the rate of misdiagnosis was 10.8%, and was higher in patients with pulmonary tuberculosis who had a negative sputum smear.[14] In a study from the Republic of Korea, the rate of misdiagnosis of TB was not reported in clinically diagnosed patients, but the main alternative diagnoses in patients that were misdiagnosed as pulmonary TB were infections with non-tuberculous mycobacteria, bacterial pneumonia, and malignancy.[15]

There are several previous studies into alternative diagnoses in patients who were empirically treated for tuberculosis, but high-quality evidence is lacking. The only prospective study was done in Tanzania, and included 36 patients. Of these patients, 23 completed all additional investigations, and only 2 of these patients (6%) were confirmed to have tuberculosis. The other patients were diagnosed with pneumonia, bronchiectasis, interstitial lung disease, non-tuberculous pleural disease, malignancy, and chronic pulmonary aspergillosis.[16] A retrospective study in Pakistan found that 45% of 61 patients who received empiric treatment later were found to have an alternative diagnosis, including malignancies, heart failure, chronic pulmonary aspergillosis, and bronchiectasis.[17] In another study by the same authors, it was found that over a third of patients with allergic bronchopulmonary aspergillosis in a Pakistani tertiary care hospital, had initially been misdiagnosed as tuberculosis.[18] In a study from Nigeria, it was found that a significant proportion of patients that were re-treated for tuberculosis, and had been classified as treatment failures, actually had chronic pulmonary aspergillosis.[19] What complicates matters, is that pulmonary aspergillosis is frequently seen as a late complication of cavitary tuberculosis, even if the latter has been adequately treated. [20]A recent systematic review highlighted 80 cases in which various types of pulmonary fungal infections were initially misdiagnosed as tuberculosis.[21] Furthermore, a study from South-Africa found that almost all patients who were treated for lymphoma at a tertiary level hospital, had received empiric tuberculosis treatment in the year prior.[22] A study from Uganda found a lower, but still significant rate of 30% misdiagnosis of tuberculosis in patients with HIV-associated lymphoma.[23] A study from Malawi in a general oncology department found a misdiagnosis as tuberculosis in 1% of all referred patients.[24]

Interestingly, in another study from Uganda, it was found that 88% of 162 patients who received a course of broad-spectrum antibiotics instead of empiric tuberculosis treatment, showed clinical improvement and 4% were treated for an alternative respiratory disease.[25]

Type of research: prospective intervention study

Research question: does an enhanced diagnostic workup for patients about to start empiric tuberculosis treatment in Lusaka, Zambia, lead to alternative diagnoses and improved patient outcomes after six months?

Primary objective: to determine in what proportion of patients who are about to start empiric tuberculosis treatment, an alternative diagnosis can be made through the use of a concise additional workup by an experienced pulmonary physician, including review of available data, as well as additional laboratory, functional, and imaging investigations

Secondary objectives: to determine whether establishing and treating alternative diagnoses in patients who were about to start empiric tuberculosis treatment leads to improved quality of life and survival after six months

In- and exclusion criteria: All adult patients who have a negative initial GeneXpert MTB/RIF test on sputum, but are about to start standard first-line treatment for suspected pulmonary tuberculosis on clinical grounds (i.e. empiric tuberculosis treatment), at four first-level Hospitals in Lusaka, Zambia. Patients will be excluded if they are inpatients (due to suspected tuberculosis).

Number of eligible patients per year: Estimated 410 eligible patients per year in Chawama (450 clinically diagnosed pulmonary tuberculosis patients at Chawama first-level hospital in 2023, including children). The total population at Chawama first-level hospital in 2023 included 5361 presumptive tuberculosis cases, of whom 5270 had GeneXpert MTB/RIF testing done, and of whom 426 had a positive result from GeneXpert MTB/RIF. There is a discrepancy with the number of bacteriologically confirmed tuberculosis cases, which is reported at 663 for the year. The reason for this is not entirely clear, but might be due to additional testing being performed at different facilities, and the use of other tests for diagnosing tuberculosis, such as lipoarabinomannan assay and acid-fast bacilli smear. Interestingly, the percentage of patients who had a tuberculosis relapse was higher in patients being treated empirically than in patients with bacteriologically confirmed tuberculosis (107 out of 450 (24%) versus 107 out of 663 (16%)).

Treatment outcomes for 2022 are as follows: 618 bacteriologically confirmed new cases of which 523 were cured (85%), 29 completed treatment, 36 died (6%), 3 failed treatment, 24 were lost to follow up, and 3 were not evaluated; 123 bacteriologically confirmed tuberculosis relapses of which 115 were

cured (93%), 5 died (4%), 2 were lost to follow up, and 1 was not evaluated; 352 clinically diagnosed new cases of which 308 completed treatment (88%), 35 died (10%), 1 failed treatment, 7 were lost to follow up, and 1 was not evaluated; 156 clinically diagnosed tuberculosis relapses of which 143 completed treatment (92%), 9 died (6%), and 3 were lost to follow up.

The other first-level hospitals had somewhat lower numbers of patients in 2023.

Intervention: All included patients will undergo the study intervention. Participants will be included from the tuberculosis clinic at first-level hospitals. They will be reviewed by one of the study physicians prior to initiating empiric tuberculosis treatment. A full history and physical examination will be taken and available results will be reviewed (laboratory results, sputum results, and chest X-ray). Depending on the results, appropriate measures will be taken there, including possible treatment with antibiotics or a wait-and-see approach for suspected viral infections. If further diagnostics are deemed to be indicated, a patient will be referred to the pulmonology clinic at University Teaching Hospital in Lusaka, Zambia. There, appropriate additional diagnostics will be requested, including additional blood tests (such as aspergillus serology), repeat chest X-ray, spirometry, CT-scan of the chest (if no other clear clinical diagnosis), bronchoscopy (if indicated based on CT-scan) and sputum and/or bronchial washing bacterial and mycobacterial cultures. The empiric treatment will be withheld initially if the study investigator thinks that an alternative diagnosis is more likely, while awaiting the additional investigations. If the study investigator thinks it is in the interest of the patient, then empiric tuberculosis treatment will be initiated while awaiting the results for the additional investigations. When a final diagnosis is made, appropriate treatment decisions will be made. If a clear diagnosis cannot be made locally, patients will be discussed in a multidisciplinary team meeting between St. Antonius Hospital and University Teaching Hospital.

Methods: Participants will be asked to participate in the study once the clinician at the first-level hospital has decided to start empiric tuberculosis treatment. If the patients provide written informed consent, they will be reviewed by the study physician on-site, and possibly referred for further investigations as described above. Quality of life will be assessed at baseline, as well as during follow up. Patients will be followed up for 6 months, at which time every patient file will be reviewed by a study investigator and the final diagnosis will be determined.

<u>Primary outcome:</u> diagnosis at 6 months (tuberculosis versus alternative diagnosis)

Secondary outcomes: quality of life at 6 months (EUROHIS-QOL), change in quality of life from baseline to 6 months (EUROHIS-QOL), survival at 6 months, number of patients that received tuberculosis treatment, number of patients that had side effects attributed to tuberculosis treatment,

Number of patients to include: 300

Sample size calculation: The power is set at 80% and α at 0.05. Assuming a 10% mortality in the historic control group (based on 2022 tuberculosis outcome data from Chawama first-level hospital), and a 5% mortality in the intervention group, 238 patients will have to be included. A safety margin of 20% of refusal to participate in the study and loss to follow up is assumed, so that approximately 300 patients will have to be included.

Statistical analysis: Descriptive statistics will be used to describe percentage of alternative diagnoses, as well as percentage of patients that has quality of life scores indicating they are not satisfied or very dissatisfied, the percentage of patients who received tuberculosis treatment and the percentage of patients that had side effects attributed to tuberculosis treatment. Paired analyses will be used to compare quality of life at baseline and during follow up. Multivariate regression analyses will be used to identify what factors associate with quality of life and survival. We will use per-protocol analysis methods for the primary analyses, with intention-to-treat analyses as a secondary tool. We will use a historic control group of patients who underwent empiric TB treatment at the study sites in the year prior to the study as a comparison for survival. Additionally, as data for the tuberculosis clinic are collected in a standard fashion, it will be able to compare the number of patients being referred to the clinic, the number of patients receiving treatment for bacteriologically confirmed tuberculosis, and the number of patients receiving empiric tuberculosis treatment, as well as treatment outcome data, between the study period and the period prior to and after the study.

Burden and risks for participants: The burden for the participants consists of having to travel to University Teaching Hospital (4.2 km – 10.6 km distance) for review and potential additional investigations that cannot be done on the same day (CT-scan and bronchoscopy). The additional investigations might necessitate venepuncture (slightly painful, low risk of hematoma or bleeding), chest X-ray (low dose radiation (0.1mSv)), spirometry (low risk of feeling uncomfortable), and

potentially CT-scan of the chest (medium dose radiation (6.1 mSv)), and bronchoscopy (discomfort for most patients, risk of serious complications (e.g. bleeding, pulmonary oedema, pneumothorax) ca. 1%). It needs to be emphasized that these investigations would be considered as the standard-of-care in a high-resource setting, and, in that sense, are not actually an additional burden at all.

Study duration: 16 months

Start date: 1/12/2024

Final inclusion: 31/12/2025

End date: 30/06/2026

Dissemination plan:

The results of this study will be written up as a scientific article after analyses. The article will be published in an international peer-reviewed scientific journal. The results will also be presented at a relevant scientific conference, such as the Pan African Thoracic Society conference. Furthermore, we will endeavour to share the results from our research with relevant stakeholders, such as the tuberculosis program manager of the Zambian Ministry of Health.

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