Pilot Summary Report

Revisiting the cost-effectiveness of Xpert MTB/RIF: lessons learned from South Africa

Background

In 2014, 1.5 million people died from tuberculosis (TB), 25% of whom had HIV, and 13% of whom had multi-drug resistant TB (MDR-TB). A central challenge to the reduction in deaths from TB is to correctly identify TB in a timely manner. The diagnosis of TB in most high TB burden settings is based on sputum smear microscopy (hereafter written as microscopy). Microscopy has a limited sensitivity, especially in people living with HIV/AIDS (PLWHA), and cannot distinguish MDR-TB. This poor performance, together with a lack of access to laboratory facilities in many low- and middle-income countries, contributes to low levels of TB case detection globally, particularly in countries with a high prevalence of HIV.

In 2010, a new test, Xpert MTB/RIF (Cepheid, Sunnyvale, California) (hereafter written as Xpert) received a guideline recommendation from the World Health Organization (WHO) for use as an initial diagnostic test for TB. Model-based economic evaluations preceding the WHO guideline recommendation in 2010 predicted that the introduction of Xpert would be cost-effective through reductions in TB-related mortality, and/or reductions in the over-treatment of TB. Recognising the importance of evaluation and its role as an ‘early adopter’ of Xpert, the National Department of Health, South Africa (NDoH) agreed to a pragmatic cluster-randomised trial, the XTEND study, to assess the impact and cost-effectiveness of Xpert introduction. The XTEND study found no evidence that the Xpert introduction reduced 6-month mortality risk among adult clinic attendees being investigated for TB. We present the results of the economic evaluation conducted alongside the XTEND study, using extensive primary data collection on both costs and health outcomes.

Methods

We were guided in our analytical approach by the reference case developed by the ‘Methods for Economic Evaluation Project’ (MEEP). Our general approach reflects the economic school of thought that, even when trial results find no significant evidence of an effect, a full cost-effectiveness analysis should be performed, presenting all uncertainty in
both costs and effects. We therefore performed both a comparative cost and cost-effectiveness analysis of Xpert versus the ‘standard of care’ of microscopy (hereafter referred to as the ‘microscopy arm’. From a societal perspective, we compared cost per person investigated for TB and the cost per DALY averted. The population studied was a cohort of persons being evaluated for TB attending primary health care clinics in South Africa.

The time frame for our economic analysis was ‘within trial’ from enrolment until the six-month follow-up interview. This may exclude three factors that potentially could influence cost-effectiveness post six months, and will not have been captured in the XTEND study. Firstly, by reducing time with TB, Xpert may have reduced the transmission of TB. However, XTEND found no evidence for differences in time to treatment, the factor most likely to impact transmission. Secondly, XTEND may improve outcomes by hastening the time to effective treatment in those with MDR-TB. XTEND was not powered to examine differences in time to MDR-TB treatment initiations. There is some evidence emerging that Xpert may reduce time to MDR-TB treatment from other studies, by around 3 weeks, but no corresponding evidence of improved health outcomes. Thirdly, increased diagnosis and survival from TB may increase ART costs. However, there was no increase in numbers of person initiating ART observed during XTEND, nor substantial changes in mortality.

Given the dearth of primary cost data available, we collected extensive primary data on outcomes and costs. We constructed a dataset containing individual patient-level costs and outcomes for each XTEND participant as the basis for our analysis. The details of our costing methods, prices and unit costs of each patient event are reported elsewhere. We estimated total costs for Xpert and the microscopy arm by multiplying unit or ‘per event’ costs by the number of health service use ‘events’ experienced by the XTEND study cohort. Data on patient events (outpatient visits, treatment regimens and diagnostic tests used) were collected from case note abstractions (from paper and electronic records) and by self-report from the XTEND participant follow-up interviews (conducted on all XTEND participants). Where discrepancies between data sources were observed, a set of decision rules were developed and applied based on plausibility and consistency between data. We estimate DALYs averted as our main measure of incremental outcome. We used deaths reported from the XTEND study (see Table S3) to estimate years of life lost (YLLs). Years lived with disability (YLDs) experienced by the XTEND participants were estimated using the number of days with
TB symptoms, assuming that symptoms either stopped two weeks into treatment start, continued to death, or stopped within two weeks of not returning to care. We applied disability weights used in the Global Burden of Disease 2010 \(^{13}\). For those with HIV on antiretroviral therapy (ART) for HIV we applied the TB only disability weight \(^{12}\). All DALYs averted were estimated using a 3% discount rate and no age weighting.

The cost and cost-effectiveness analysis considered the clustered design and baseline imbalance between study arms\(^{14}\). For both analyses we selected a two-stage cluster level analysis with bootstrapping. For the cost analysis, we applied a multiple ordinary least square (OLS) regression model with robust standard errors using 200 bootstrap replications and adjusting for HIV status, socio-economic status (SES), ethnicity, education, marital status, age group, sex, province, BMI group, and number of symptoms. We used this method to estimate and compare incremental costs, incremental health services cost, incremental patient-incurred diagnostic tests and incremental treatment costs per study participant between the two study arms. We present the uncertainty around our incremental cost-effectiveness ratios using cost effectiveness planes and acceptability curves and apply a one-way sensitivity analysis around a 0% and a 3% discount rate. All costs are presented in 2014 US dollars.

**Results**

We find that Xpert roll-out in South Africa neither decreased nor increased the provider- or patient-incurred costs of TB investigation, diagnosis and treatment in the period from symptoms to six months after initial investigation – and in this sense was ‘cost-neutral’. The additional cost of Xpert equipment and tests was mitigated by a reduction in costs elsewhere in the TB cascade of care. Combining cost neutrality with the lack of any significant mortality impact, we find that the introduction of Xpert did not improve the cost-effectiveness of drug-susceptible TB diagnosis in South Africa, during the early stages of Xpert roll-out.

This finding differs from modelled predictions of cost-effectiveness of Xpert introduction. Previous economic models assumed that for persons investigated for TB with Xpert who did not have an initial positive result, the follow-on pathway would either be: a) highly sensitive, but with low specificity (for example based on chest radiography), resulting in overtreatment; or b) be limited to a small proportion of patients, and highly specific – resulting in high levels of TB-related mortality\(^4\). Sensitivity and specificity were assumed to be negatively
correlated with one another. The models assumed that the clinical practice along this ‘negative’ pathway would be unaltered with Xpert introduction. The TB NEAT trial implemented the former case (a)) and demonstrated that, in settings where the standard of care comprised high coverage of empirical treatment (based on chest radiograph results), Xpert introduction may have no impact on mortality, observing that Xpert may replace, but not reduce, empirical treatment. TB-NEAT’s individual randomisation design may also have promoted empirical treatment in the Xpert arm by making providers more aware of the limitations of TB diagnostics generally. When the TB NEAT results were used to re-parameterise economic models, Xpert was found to be cost-effective, although cost-effectiveness was reduced by 60% from previous estimates by the same research group conducted prior to the WHO guidance.

In contrast, in a pragmatic setting, we found the latter case (b), that few people were followed-up and started on treatment following an Xpert negative result. In the context of ‘real world’ Xpert roll-out, this may be explained due to clinicians overly trusting Xpert results to rule out TB, influenced by the country-wide messages received aimed at changing diagnostic practices rapidly. As a result we find also that, even in a routine setting with low levels of empirical treatment, Xpert does not improve cost-effectiveness to the extent of previous predictions.

References


