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A Systematic Review of Reported Cost for Smear and Culture Tests during Multidrug-Resistant Tuberculosis Treatment

Chunling Lu1,2,*, Qing Liu3, Aartik Sarma4, Christopher Fitzpatrick5, Dennis Falzon5, Carole D. Mitnick2,9

1 Division of Global Equity, Department of Medicine, Brigham and Women’s Hospital, Boston, Massachusetts, United States of America, 2 Department of Global Health and Social Medicine, Harvard Medical School, Boston, Massachusetts, United States of America, 3 Department of Global Health and Population, Harvard School of Public Health, Boston, Massachusetts, United States of America, 4 Harvard Medical School, Boston, Massachusetts, Boston, Massachusetts, United States of America, 5 Stop TB Department, World Health Organization, Geneva, Switzerland

Abstract

Background: In 2011, World Health Organization revised its recommendation for microbiological monitoring during treatment for multidrug-resistant tuberculosis (MDR-TB) by increasing the frequency of culture examination from quarterly to monthly after culture conversion. Implementing the recommendation requires substantial additional investment in laboratory infrastructure. The objective of this review is to provide cost evidence that is needed for national TB programs to budget for optimal monitoring strategies.

Methods and Findings: We conducted the first systematic literature review on unit cost estimates of three monitoring strategies: 1) smear only; 2) culture only; 3) combined smear and culture. 26 peer-reviewed studies were selected by searching 10 databases in English and Chinese for literature published between 1995 and 2012. Cost estimates were converted into 2010 constant USD and international dollars. We assessed the quality of the estimates using a matrix with five essential elements and provided a cost projection for the combined smear and culture tests where the data were available. The 26 studies reported the cost estimates in 16 predominantly high- or middle-income countries from 1993 to 2009. The estimated unit cost for smear, culture, and combined tests ranges from $0.26 to $10.50, $1.63 to $62.01, and $26.73 to $39.57, respectively. The ratio of culture to smear costs varies from 1.35 to 11.98. The wide range of estimates is likely attributable to using different laboratory methods in different regions and years and differing practices in collecting and reporting cost data. Most studies did not report information critical for generalizing their conclusions.

Conclusion: The paucity and low quality of unit cost estimates for TB monitoring in resource-poor settings impose technical challenges in predicting the resources needed for strengthening microbiological monitoring. To improve the validity and comparability of the cost data, we strongly advocate the data collection, estimation, and reporting follow protocols proposed by WHO.

Introduction

Management of multidrug-resistant tuberculosis (MDR-TB) requires extensive monitoring of patients using bacteriologic testing. This is necessary to evaluate interim response to treatment; determine if patient isolation, regimen change, or adjunct therapy is required; and to classify patient treatment outcomes. In order to optimize the ability to detect non-response to treatment, recent changes to World Health Organization (WHO) Guidelines for the Programmatic Management of Drug-Resistant TB increased the frequency of sputum culture monitoring from quarterly to monthly after sputum culture conversion [1]. This recommendation was the result of a systematic analysis, which observed increased delays in detection of treatment failure with bi-monthly or quarterly culture screening, and with exclusive reliance on smear [1]. The available evidence, which was based on observational data and modeling, is considered to be of low quality [2], implying that new evidence would be very likely to change the recommendation.

* E-mail: Chunling.Lu@hms.harvard.edu
9 These authors contributed equally to this work.
One important consideration of implementing the recommendation is the increased cost required to assure monthly culture, in addition to smear. This will require substantial additional investment in laboratory infrastructure since current capacity of conventional laboratory is insufficient in many low-resource settings. In 2010, eight of the 22 high-burden countries (HBCs) that account for 80% of global TB cases did not meet the target of one microscopy center per 100,000 people. Among the 36 countries with the highest burden of TB and MDR-TB in the world, 20 had less than the recommended capacity of one laboratory to perform culture examination per 5 million people [3]. In order for national TB programs to budget for implementation of optimal monitoring, or to make decisions about the implementing alternative monitoring strategies, information on costs of these strategies is essential.

Although new molecular tests have been validated and approved by WHO for diagnostic purposes [4], to date, these tests have no role in monitoring treatment. Consequently, this study focuses exclusively on sputum smear microscopy and sputum culture for tuberculosis.

The purpose of this study is to provide cost estimates for the different MDR-TB monitoring strategies recommended by WHO. We conducted a systematic literature review of the published cost estimates for three strategies to monitor bacteriologic response of patients on MDR-TB treatment: 1) smear only; 2) culture only; 3) combined smear and culture. Our objectives are to (1) provide a comprehensive list of published cost estimates for the three testing strategies, (2) assess the quality and limitation of the published cost estimates, (3) project the cost of combined testing when data are available, and (4) compare costs across monitoring schedules and methods when data are available.

Methods

Literature Search Strategy

We searched the literature published in peer-reviewed journals from 1995 to 2012 in both English and Chinese through 10 databases: Pubmed, Embase, Web of Knowledge, Health Economic Evaluation and Database (HEED), Econlit, National Health Service Economic Evaluation Database (NHSEED), Cost-Effectiveness Analysis Registry (CEA), Research Papers in Economics (RePEc), European Network of Health Economic Evaluation Database (EURONHEED), China National Knowledge Infrastructure (CNKI), Google Scholar and WHO. We also searched grey literature from System for Information on Grey Literature in Europe (OpenSIGLE), Healthcare Management Information Consortium (HMIC) database, National Technical Information Service (NTIS), and Biological Abstracts (BIOSIS). We refined the search strategy in consultation with experts from Harvard Countway Library of Medicine and used a combination of three parts of keywords (e.g. “costs/economics/expenditure/price”, “Tuberculosis,” and “smear/culture/diagnosis/laboratory”) when searching through databases. The detailed key words used in the search can be found in Table S1. The search was conducted between 23 March and 25 April, 2012. Citations were collected and managed electronically using EndNote X5. A total of 475 citations were selected in the search. 107 duplicates were automatically identified by EndNote and removed. This left a total of 368 studies, which were screened in two phases (Figure 1). First, we excluded 296 articles that did not contain cost information on MDR-TB diagnosis strategies in their abstracts. In the second phase, the full texts of the 72 remaining articles were evaluated and 46 were excluded because they do not have specific cost information for testing strategies. Our final study includes 26 articles [5–30]. One study [26] reported unit cost estimates for three countries and we listed the estimates separately in results. No protocol exists for systematic review of this topic.

Quality Assessment

We constructed a matrix to assess the quality of collected cost estimates. In order for the cost estimates to be useful and comparable, we sought at least the following information from...
### Table 1. Summary of published studies by income group, as per World Bank classification [5–30].

| Country          | Author (publication year) | Testing type* | Data collection year | Level of estimates | Data sources                                                                                                                 | Included items in cost estimation                                                                 |
|------------------|---------------------------|---------------|----------------------|--------------------|----------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|
| **High-income countries** |                           |               |                      |                    |                                                                                                                            |                                                                                                   |
| Canada           | Menzies. et al. (2006) [5] | S; C: solid & liquid media, liquid media only; SC: smear & liquid media only | 2005–2006           | National           | Interim Federal Health Fee Schedule                                                                                         | Labor, equipment, supplies, and overhead                                                          |
| Estonia          | Floyd et al. (2012) [6]   | S; C          | 2001–2002            | National           | Sources of data included expenditure records, interviews with staff and patients, project records and databases, clinical records, the social insurance system | Not specified                                                                                     |
| Finland          | Rajalaihi et al. (2004) [7]| SC            | 2000                 | Local(Pirkanmaa and Varsinais-Suomi) | Pirkanmaa Hospital District                                             | Not specified                                                                                     |
| Italy            | Miglioli et al. (1999) [8]| S; C          | 1995                 | National           | Nationwide, 41 TB-reporting units self-selected into participating in the study                                            | Buildings, diagnostic facilities, salaries, overhead, and direct examination costs                 |
| UK               | Dinnes et al. (2007) [9]  | C: standard culture, rapid culture, culture and first-line sensitivity on solid media | Not available | National           | Price list from the Public Health Laboratory Mycobacterium Reference Unit                                                   | Not specified                                                                                     |
| USA              | Heymann et al. (1999) [10]| S; C          | 1995                 | National           | National Jewish Center for Immunology and Respiratory Medicine in Denver and Massachusetts state public health laboratory | Not specified                                                                                     |
| Wurtz et al. (1998) [11]| SC                     | 1993          | Local(Chicago)      | A public hospital ’s 1993 Medicare Schedule C charges and a state university hospital located in close proximity to the study hospital | Not specified                                                                                     |
| GA for TB Drug Development (2001) [12]| C                   | 2000          | National            | Medical Resource Based Relative Value Scale Reimbursement Schedule                                                  | Not specified                                                                                     |
| **Upper-middle-income countries** |                           |               |                      |                    |                                                                                                                            |                                                                                                   |
| Brazil           | Dowdy et al. (2008) [13]  | C; LJ, MGIT   | 2006–2008            | Local(Rio de Janeiro) | 29 municipal health clinics and hospitals randomly selected                                                                 | Culture tubes and media, decontamination reagents, cryovials for pellet storage, lab supplies and equipment and personnel; fixed costs: transportation, and automated MGIT 960 reader |
| Scherer et al. (2009) [14]| S; ZN; C; LJ; SC; ZN+LJ | 2003–2004    | Local(Porto Alegre City) | Public Reference Laboratory, Centro de Desenvolvimento Científico e Tecnológico and Fundação Estadual de Produção e Pesquisa em Saúde | Laboratory running costs and patient costs (including costs for travel, food and income loss)       |
| China            | Chen et al. (2011) [15]   | S; C          | Not available        | National           | Cited from the websites on health expenditure                                                                            | Not specified                                                                                     |
| Thailand         | Kamolratanakul et al. (2002) [16]| S; C                   | 1996–1997            | National           | Four referral centers were randomly selected from four geographical regions (Eastern, Southern, Northern and Northeastern) | Oversehead costs and materials costs                                                                 |
| Sohn et al. (2008) [17]| S; ZN, FM                | 2007–2008    | National            | National Tuberculosis Reference Laboratory                                                                                 | Capital assets(e.g., building space, equipment, staff, laboratory consumables and chemicals, and recurrent costs |
| Peru             | Suárez et al. (2002) [18]| S; ZN; C; LJ   | 1997–1999            | National           | MDR-TB unit in Lima                                                                                                       | Not specified                                                                                     |
| Russia           | Floyd et al. (2012) [18]  | S; C          | 2001–2002            | Local(Tomsk Oblast) | Sources of data included expenditure records, interviews with staff and patients, project records and databases, clinical records | Not specified                                                                                     |
| Country                     | Author (publication year) | Testing type* | Data collection year | Level of estimates                     | Data sources                                                                 | Included items in cost estimation                                                                 |
|-----------------------------|---------------------------|---------------|----------------------|----------------------------------------|-------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
|                            |                           |               |                      |                                        |                                                                               |                                                                                               |
| WHO Policy Brief            |                           | S; C          | 2003                 | Local (Vladimir Oblast)                | Clinical diagnostic laboratory of general health care; level II clinical diagnostic laboratory within primary health care services | Not specified                                                                                         |
|                             | Balabanova et al. (2009) | C: MGIT, LJ   | 2006–2008            | Local (Samara Oblast)                 | Cental TB laboratory of Samara Region                                           | Decontamination (including specimen transportation costs), prep LJ, overhead, building, equipment, staff, medical supplies |
| South Africa                | Sinanovic et al. (2003)  | S; C          | 1998–1999            | Local (Guguletu and Nyanga)           | Cape Town City Council, the South African Institute for Medical Research, the TB Care Association, local equipment suppliers, car dealers, staff interviews and patient survey, building, staff costs, medical supplies | Not specified                                                                                         |
|                             | Albert (2004)             | S: ZN; C: BACTEC 460TB | 2003                | Local (Cape Town)                     | National Health Laboratory Service (NHLS), Cape Town                            | Not specified                                                                                         |
|                             | Hausler et al. (2006)     | S; C          | Not available        | Local (Cape Town)                     | Three public primary health care facilities                                    | Not specified                                                                                         |
|                             | Vassall et al. (2011)     | S: LED; C: MGIT | Not available        | National                              | Urban or periurban primary care health centers in South Africa                 | Building, overhead, staff, equipment and consumables, quality control and maintenance, and calibration inputs |

**Lower-middle income countries**

| Country                     | Author (publication year) | Testing type* | Data collection year | Level of estimates                     | Data sources                                                                 | Included items in cost estimation                                                                 |
|-----------------------------|---------------------------|---------------|----------------------|----------------------------------------|-------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| India                       | Muniyandi et al. (2006)  | S             | 2002                 | Local (Tamil Nadu)                     | All the government health facilities, including subcenters situated in a TB unit of a rural district of Tamil Nadu | Staff salary, costs incurred for reagents, drugs, maintenance, stationery and fuel etc. |
|                             | Vassall et al. (2011)     | S: LED; C: LJ | Not available        | National                              | Urban or periurban primary care health centers in India                       | Building, overhead, staff, equipment and consumables, quality control and maintenance, and calibration inputs |
| Zambia                      | Mueller et al. (2008)     | C: HLJ, CLJ, MGGIT, AMGGIT | 2006                | National                              | Zambia National TB Reference Laboratory                                     | Overhead costs, running costs (rent of the building, utilities, vehicle running, staff management), culture-specific costs, equipment, consumables, staff costs |

**Low income countries**

| Country                     | Author (publication year) | Testing type* | Data collection year | Level of estimates                     | Data sources                                                                 | Included items in cost estimation                                                                 |
|-----------------------------|---------------------------|---------------|----------------------|----------------------------------------|-------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| Kenya                       | Kivihya-Ndugga et al. (2003) | S: FM, ZN   | 2000–2001            | Local (Nairobi)                       | Nairobi City Council Chest Clinic                                            | Labour costs, investment costs and running costs                                           |
| Uganda                      | Okello et al. (2003)      | S             | 1995–1999            | Local (Kiboga)                        | Kiboga district hospital and two Masindi district hospitals                 | Not specified                                                                                         |
each study: (1) the year of cost data being collected; (2) the level of estimates (national or regional), (3) the specific diagnostic methods and materials used; (4) the sources of data; and (5) the components included in cost estimation. We treated each category as binary and assigned values “0” or “1”. For instance, if a study reported the year of data being collected, “Data collection year” takes value of 1, 0 otherwise. In tables and figures, we used publication year as a proxy if the studies did not report information data collection year. If the estimate is national, “National estimate” takes value 1, 0 otherwise. If test methods (such as light-emitting diode [LED], Ziehl-Neelsen [ZN], etc) were reported in the paper, “Specification of test methods” takes value of 1, 0 otherwise. If cost data were directly collected from health facilities, “direct data sources” takes value of 1. If cost data were obtained from published price list, “direct data sources” takes value of 0. If the cost components included in estimating the unit cost of tests was reported by the paper, “specification of cost items” takes value of 1, 0 otherwise. We then summed the scores across the five categories for each estimate with 0 representing the weakest quality and 5 the best. When information was available, we also listed cost components in Table 1 so the readers could identify which cost components were included in cost estimation.

Projection of Unit Costs of Combined Smear and Culture Tests

When smear and culture costs were reported separately in the same study and the cost for combined tests was not available, we imputed the unit cost of the combined tests by adding the unit costs of the two testing strategies. The imputed value may serve as an upper bound estimate for the combined test. Total costs for combined tests may be lower than the imputed value due to a single set of procedures being performed for both tests (e.g., for sputum collection, transport, and processing). All cost estimates were converted into 2010 constant USD using an exchange rate and GDP deflator from International Monetary Fund [31]. To adequately represent the distinction of costs across different countries, the international dollar is preferable since it adjusts the distortion effect of non-traded goods compared to single US$ value [32]. When detailed cost information was available to identify the cost of traded and non-traded goods, we also converted the cost estimates to 2010 international dollars using purchasing power parity [33].

Analyzing Existing Data

When papers provided unit cost estimates for both the culture and smear tests, we calculated the cost ratio of culture to smear. For studies with the values of the cost components, we first classified the components into two categories, traded and non-traded goods, based on the definition from the WHO guideline for cost-effectiveness analysis. Traded goods (e.g. equipment, supplies and pharmaceuticals) are available on the international market and available to all countries at an international market price. Personnel, utilities, buildings and domestic transport are treated as non-traded goods [32]. We then calculated the share of the two types of goods in unit cost.

Results

Assessing Existing Studies

26 studies published between 1995 and 2012 reported cost estimates in 16 countries (Table 1). Of these, 22 studies were conducted in high-income or upper-middle income countries. Five studies reported unit cost estimates in four low and lower-middle income countries (India, Zambia, Kenya and Uganda) [26–30].
of the selected studies reported unit cost estimates for smear test alone. 19 studies reported unit cost estimates for culture test alone. Five studies reported cost estimates for combined smear and culture test in four middle-upper or high income countries.

The quality of reported data varied considerably among 26 studies. Five of them did not report which year the cost data were collected, 12 of them reported national estimates, 14 of them specified the methods used for test, 20 of them obtained data directly from health facilities, and 13 of them provided the cost components that were used to estimate of unit costs (Table 2). Components of cost estimates were not reported in a standardized way. Some studies only included costs for materials and overhead, while others included costs on building, equipment, or even patients' spending on travel, food and income loss due to sick leave. Using our quality scale, two studies scored 5 points, 11 studies scored 4, and 13 studies scored 3 or below (Table 2).

Table 2. Quality assessment of the studies (1 = yes; 0 = no).

| Author                      | 1) Data collection year | 2) National estimate | 3) Specification of test type | 4) Direct data source | 5) Specification of cost items | Sum |
|-----------------------------|-------------------------|----------------------|-------------------------------|-----------------------|--------------------------------|-----|
| Mueller et al. [28]         | 1                       | 1                    | 1                             | 1                     | 1                              | 5   |
| Sohn et al. [17]            | 1                       | 1                    | 1                             | 1                     | 1                              | 5   |
| Dowdy et al. [13]           | 1                       | 0                    | 1                             | 1                     | 1                              | 4   |
| Kamolratanakul et al. [16]  | 1                       | 1                    | 0                             | 1                     | 1                              | 4   |
| Balabanova et al. [20]      | 1                       | 0                    | 1                             | 1                     | 1                              | 4   |
| Menzies, et al. [5]         | 1                       | 1                    | 1                             | 0                     | 1                              | 4   |
| Sánchez et al. [18]         | 1                       | 1                    | 1                             | 1                     | 0                              | 4   |
| Vassall et al. (South Africa) [26] | 0               | 1                    | 1                             | 1                     | 1                              | 4   |
| Vassall et al. (India) [26] | 0                       | 1                    | 1                             | 1                     | 1                              | 4   |
| Vassall et al. (Uganda) [26] | 0                       | 1                    | 1                             | 1                     | 1                              | 4   |
| Whitelaw et al. [25]        | 1                       | 0                    | 1                             | 1                     | 1                              | 4   |
| Scherer et al. [14]         | 1                       | 0                    | 1                             | 1                     | 1                              | 4   |
| Chihota et al. [24]         | 1                       | 0                    | 1                             | 1                     | 1                              | 4   |
| Kivhaya-Ndugga et al. [29]  | 1                       | 0                    | 1                             | 1                     | 1                              | 4   |
| Migliori et al. [8]         | 1                       | 1                    | 0                             | 1                     | 1                              | 4   |
| Albert [22]                 | 1                       | 0                    | 1                             | 1                     | 1                              | 4   |
| Heymann et al. [10]         | 0                       | 1                    | 1                             | 1                     | 0                              | 3   |
| Musiyandi et al. [27]       | 1                       | 0                    | 1                             | 1                     | 1                              | 3   |
| Dinnes et al. [9]           | 0                       | 1                    | 1                             | 0                     | 0                              | 2   |
| WHO Policy Brief [19]       | 1                       | 0                    | 0                             | 1                     | 0                              | 2   |
| GA for TB Drug Development [12] | 1               | 1                    | 0                             | 0                     | 0                              | 2   |
| Rajalathi et al. [7]        | 1                       | 0                    | 0                             | 1                     | 0                              | 2   |
| Wurtz et al. [11]           | 1                       | 0                    | 0                             | 1                     | 0                              | 2   |
| Okello et al. [30]          | 1                       | 0                    | 0                             | 1                     | 0                              | 2   |
| Floyd et al. (Estonia) [6]  | 1                       | 1                    | 0                             | 0                     | 0                              | 2   |
| Hauser et al. [23]          | 0                       | 0                    | 0                             | 1                     | 0                              | 1   |
| Chen et al. [15]            | 0                       | 1                    | 0                             | 0                     | 0                              | 1   |
| Sinanovic et al. [21]       | 1                       | 0                    | 0                             | 0                     | 0                              | 1   |
| Floyd et al. (Tomsk Oblast) [6] | 1              | 0                    | 0                             | 0                     | 0                              | 1   |

Notes: We treat each category as binary and assign values “0” or “1”. 1) “data collection year”: whether or not the data collection year was provided in the study. If yes, “data collection year” = 1, 0 otherwise; 2) “national estimate”: whether or not the cost was estimated at national level. If yes, “national estimate” = 1, 0 otherwise; 3) “specification of test type”: whether or not the test was provided in the study, e.g. ZN/FM, MGIT/LJ. If yes, “specification of test type” = 1, 0 otherwise; 4) “direct data source”: whether or not the cost was directly collected from health facilities (e.g. hospital, clinic, laboratory etc.). If yes, “direct data source” = 1, 0 otherwise; 5) “specification of cost items”: whether or not the study described the components included in cost estimation. If yes, “specification of cost items” = 1, 0 otherwise. All the studies are ranked by the summation of five scores from highest to lowest.

Cost Estimates

Estimated costs of smear microscopy, presented in Figure 2 in constant 2010 USD, vary across countries from $0.26 in Tamil Nadu, India (2002) [27] to $10.50 in Thailand (1996–1997) [16]. Unsurprisingly, unit costs for sputum smear differed in a given country and year when different microscopy methods were used. For example, in Cape Town, South Africa, unit costs for smear with light-emitting diode (LED) microscopy and Ziehl-Neelsen (ZN) in 2009 were $1.64 and $2.11 respectively [25].

The estimated unit cost for mycobacterial culture is between $1.63 in Vladimir Oblast, Russia (2003) [19] and $62.01 in the United Kingdom (2007) [9] (Figure 3). Estimates in the same country and same year unsurprisingly vary when different media were used and follow-up tests were required. For example, in Brazil, unit costs of culture vary from $18.48 to $35.14 during the same period (2006–2008). The former value is the cost per
negative culture using solid media for eight patients per week; the latter value is the cost per positive culture using MGIT for eight patients per week [13].

Limited data were available for the cost of combined testing. Results have only been reported in four countries and the values ranged from $26.73 in Canada (2005–2006) [5] to $39.57 in USA (1997) [10] (Figure 4). The imputed unit cost of combined tests ranged from $1.16 in Vladimir Oblast, Russia (2003) [19] to $48.23 in Thailand (1996–1997) [16]. The majority of imputed estimates lies between $10 and $30.

The distribution of cost estimates for sputum smear is right-skewed, with a median of $1.67 (Figure 5). The cutoff points for the 25th and 75th percentiles are $1.21 and $2.54 respectively. The median of cost estimates for smear tests is $18.48 with $11.08 as the 25th percentile and $33.33 as the 75th percentile. For combined testing, the median cost is $16.82, the 25th percentile is $10.62 and the 75th percentile is $26.81.

12 studies reported cost estimates for both smear and culture tests performed separately. The ratio of estimated costs for culture to smear varies from 1.35 to 11.98 (Table 3); most are larger than 1.6, the ratio that has been used previously in the context of cost and cost-effectiveness studies for drug-susceptible TB [34]. The median ratio is 3.75. Notably, the ratio is available for only one low-income (Uganda, 2011) [26] and one lower-middle income country (India, 2011) [26]. Studies conducted between 1998 and 2011 in South Africa reported ratios from 2 to 11.98 [21,22,23,26].

Eight studies broke down estimated costs by traded inputs (i.e. supplies and equipment) and non-traded inputs (such as labor). A large variation is observed in the percentage of costs attributed to traded inputs (Table 4): for smear tests, it ranges from 0.95% [16] to 70.87% [17], and for culture test, it ranges from 21.16% [13] to 75.39% [20]. Unit cost estimates did not change significantly in 2010 international dollars ($): $1.34–19.24 for smear testing and $15.32–38.84 for culture testing.

Discussion

The existing unit cost estimates for smear, culture, and combined smear and culture tests are very limited, especially in low or lower-middle income countries. Nevertheless, a wide range of published unit cost estimates was observed. For smear alone, the estimated unit cost is between $0.26 and $10.5. For culture alone, the estimated unit cost is between $1.63 and $62.01. For combined
smear and culture testing, the estimated unit cost is between $2.27 and $48.23. Adjustment for purchasing power parity does not fully explain the wide range of unit cost estimates we observed. The wide variability of unit costs is partly due to using different materials and methods in testing, or conducting the study in different years or regions, partly due to non-standardized practice in unit cost defining, data collecting, and reporting. For example, for those with cost components available, the reported components vary greatly across studies, from only including material and overhead cost to covering the costs of building, equipment, and even the spending of patients. Cost data were obtained from different sources, including citing figures from a price list.
collecting data from a single health facility in a specific area of a country, and aggregating data from all regions in a country. Non-standardized cost estimates make it very difficult for cross-setting comparison and making meaningful inference.

The quality of the estimates is a concern. About one fifth of the selected studies did not even report the year in which cost data were collected. Half of the selected studies did not specify test methods (Migliori, or Kamolratanakul, or Qunfei, for example) used in reported smear or culture tests. Almost half of the studies did not report what components were included in cost estimation. Since we know these factors have a significant bearing on cost estimates, the lack of standardization—and low quality overall—in cost data collecting and reporting present major challenges for improving our knowledge of unit costs of various MDR-TB monitoring strategies.

The calculated unit cost ratio for culture tests to smear tests from existing studies is greater than the 1.6, a number which was previously generated from cost data collected from a government laboratory in South Africa [34]. The extent to which this ratio varies between countries will likely depend on the relative weight of non-traded inputs in the cost of each test. The cost of non-traded inputs such a labour is more sensitive than the cost of traded inputs to the income level of a given country. Therefore, if the share of non-traded inputs in total cost is smaller for cultures than it is for smears, we would expect the ratio to be higher in the lowest income countries and lower in the highest income countries.

The new recommended strategy of monthly—rather than minimum of quarterly—culture test after culture conversion, would cost more. If smear and culture were done quarterly, only 6 combined tests would be required (in addition to 14 monthly smears). According to the current recommendations of monthly smear and culture, 20 combined tests would be required. Smear and culture both have limited ability to predict poor treatment response [1,35]. Culture, however, is much more accurate than smear in detecting the presence of viable mycobacteria. Smear microscopy sensitivity estimates range from 40 to 76%, with lower sensitivity in children and HIV-coinfected patients [36–40]. As the Guidelines note, “high value was placed on outcomes such as preventing death, decreasing the transmission of MDR-TB that could result from its delayed diagnosis, and avoiding increased use of resources. [1]” Consequently, increased costs associated with more frequent culture test may be justified because of the

### Table: Unit cost in 2010 USD for combined smear and culture test

| Region   | Country                  | Year       | Cost (2010 USD) | Notes                                                                 |
|----------|--------------------------|------------|-----------------|----------------------------------------------------------------------|
| AMR      | Brazil                   | 2003-2004  | $26.81 (ZN + LJ) | (ZF + LJ)                                                              |
|          | Canada                   | National   | $26.73 (Smear + liquid culture media) |                                                                         |
|          | USA                      | Chicago    | $39.14 (AFB smear and culture) |                                                                         |
|          |                          | National   | $30.34 (Smear and conventional culture) |                                                                         |
|          |                          | National   | $39.57 (Smear and radiometric culture) |                                                                         |
| EUR      | Finland                  |            | $31.55          |                                                                         |
| AMR      | South Africa             | Cape Town  | $8.88           |                                                                         |
|          |                          | 2003       | $8.36 (ZN + BACTEC 460TB) |                                                                         |
|          |                          | 2003       | $13.62 (ZN + BACTEC 460TB + identification of MDR-TB) |                                                                         |
|          |                          | Guguletu, Nyanga | $10.62             |                                                                         |
|          |                          | National   | $16.82 (LED + MGIT) |                                                                         |
|          | Uganda                   | National   | $17.08 (LED + LJ) |                                                                         |
|          |                          | National   | $20.58 (LED + MGIT) |                                                                         |
| EUR      | Peru                     | National   | $11.13 (ZN + LJ) |                                                                         |
| SEAR     | India                    | National   | $14.69 (LED + LJ) | $48.23 (Including sensitivity testing)                                 |
| WPR      | China                    | National   | $11.56          |                                                                         |

**Figure 4.** Unit cost in 2010 USD for combined smear and culture test. (1) Directly obtained cost data are in red; imputed cost data are in blue. (2) Cost data were sorted by WHO regions: African Region (AFR), Region of the Americas (AMR), Eastern Mediterranean Region (EMR), European Region (EUR), South-East Asia Region (SEAR) and Western Pacific Region (WPR). (3) For studies with available details on test methods, we labeled them at the end of each bar. (4) [ ] indicates publication year when data collection year is not available. (5) AFB: acid-fast bacillus; LJ: Löwenstein-Jensen; MGIT: Mycobacteria Growth Indicator Tube. aLaboratory running cost is $14.34. Estimated costs incurred by patients are $12.47 (assuming that for taking an examination, a patient has to miss one-day work, take two-way transportation and have one meal outside). b$31.55 is the total cost of $94.66 divided by three combined smear and culture tests.

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Even within the same monitoring method, certain methodological differences may result in cost differences, but also in sensitivity and timing. For example, culture performed in liquid medium, using the MGIT system is known to increase the detection of viable mycobacteria over culture performed in solid LJ or Ogawa medium, while decreasing from 8 weeks to 6 weeks the time required to confirm a culture as negative. Although there was additional cost associated with MGIT in at least 3 studies that compared cost of culture in liquid and solid medium ([13], [24], and [28]), these cost differences may be justified since they accelerate the time to detection and intervention and increase the sensitivity of the test. There are similar differences among the cost and sensitivity of smear microscopy methods [40].

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Table 4. Tradable cost and non-tradable cost from eight studies.

| Author                  | Site (year of study) | Test type                     | Tradable cost components | Non-tradable cost components | Tradable cost (%) | Tradable cost (I) |
|-------------------------|----------------------|-------------------------------|--------------------------|-------------------------------|-------------------|------------------|
| Kamolratanakul et al. [16] | Thailand (1996–1997) | Smear                         | Not available            | Material costs: 2.04 baht     | 0.95%             | 19.24            |
|                         |                      |                               |                          | Overhead cost: 212.19 baht   |                   |                  |
| Sohn et al. [17]        | Thailand (2007–2008) | ZN                            | Equipment: $0.08; reagents and chemicals: $0.04; consumables: $0.22 | Overhead: $1.06; building space: $0.01; staff $0.69 | 16.19%            | 2.06             |
|                         |                      |                               |                          | Overhead: $0.15; building space: $0.01; staff $0.14 | 70.87%            | 1.34             |
| Whitelaw et al. [25]    | South Africa (2009)  | ZN                            | Equipment: $0.02; reagents and chemicals: $0.33; consumables: $0.40 | Overhead: $0.21; building space: $0.01; staff $0.19 | 64.66%            | 2.44             |
|                         |                      |                               |                          | Overhead: $0.81; building space: $0.01; staff $0.47 | 20.86%            | 2.21             |
| Culture                 |                      |                               |                          |                               |                   |                  |
| Kamolratanakul et al. [16] | Thailand (1996–1997) | Culture and sensitivity testing | Material cost: $577.900baht | Overhead cost: 212.19baht | 72.45%            | 23.68            |
| Muller et al. [28]      | Zambia (2006)        | HLJ                           | Consumables: $5.52; equipment: $4.6; consumables, equipment and furniture(included in the overheads ): $2.04 | Staff: $1.44; overheads(excluding consumables, equipment and furniture): $15.68 | 41.53%            | 35.51            |
|                         |                      | CLJ                           | Consumables: $4.62; equipment: $4.12; consumables, equipment and furniture(included in the overheads ): $2.05 | Staff: $1.31; overheads(excluding consumables, equipment and furniture): $15.69 | 38.83%            | 34.49            |
|                         |                      | MMGIT                         | Consumables: $7.14; equipment: $4.05; consumables, equipment and furniture(included in the overheads ): $2.19 | Staff: $1.73; overheads(excluding consumables, equipment and furniture): $16.35 | 42.53%            | 37.88            |
|                         |                      | AMGIT                         | Consumables: $7.13; equipment: $5.48; consumables, equipment and furniture(included in the overheads ): $2.18 | Staff: $1.24; overheads(excluding consumables, equipment and furniture): $16.24 | 45.83%            | 38.44            |
| Chihota et al. [24]     | South Africa (2006–2007) | MGIT                          | Furniture: $0.35; medical equipment: $2.03; non-medical equipment: $0.09; medical supplies: $0.02; non-medical supplies: $0.21 | Buildings: $0.52; staff costs, culture: $6.53; staff costs, non culture: $1.73; overheads: $0.15 | 46.3%             | 21.48            |
|                         |                      | LJ                            | Furniture: $0.45; medical equipment: $0.45; non-medical equipment: $0.09; medical supplies: $2.29; non-medical supplies: $0.22 | Buildings: $0.52; staff costs, culture: $6.64; staff costs, non culture: $1.82; overheads: $0.08 | 28.32%            | 16.98            |
|                         |                      | MGIT+LJ                       | Furniture: $0.45; medical equipment: $2.05; non-medical equipment: $0.09; medical supplies: $6.28; non-medical supplies: $0.23 | Buildings: $0.52; staff costs, culture: $7.60; staff costs, non culture: $1.93; overheads: $0.15 | 47.15%            | 24.86            |
| Dowdy et al. [13]       | Brazil (2006–2008)   | Solid Media (8 patients per week per negative culture) | Culture tubes and media: $0.59; decontamination reagents: $0.83; lab supplies (e.g., pipette tips, centrifuge tubes): $0.53; lab supplies (e.g., mini-pipettes, vortex machine): $1.17; lab equipment (e.g., incubator, freezer): $0.59 | Transportation: $9.61; laboratory personnel: $4.21 | 21.16%            | 19.08            |
|                         |                      | Solid Media (8 patients per week per positive culture) | Culture tubes and media: $0.59; decontamination reagents: $0.83; lab supplies (e.g., pipette tips, centrifuge tubes): $0.53; lab supplies (e.g., mini-pipettes, vortex machine): $1.17; lab equipment (e.g., incubator, freezer): $0.59; Confirmation/speciation: $7.90 | Transportation: $9.61; laboratory personnel: $4.21 | 45.65%            | 27.95            |
### Table 4. Cont.

| Author                  | Site (year of study) | Test type                     | Tradable cost components                                                                 | Non-tradable cost components | Tradable cost (%) | s2010 |
|-------------------------|----------------------|-------------------------------|-------------------------------------------------------------------------------------------|------------------------------|-------------------|-------|
| MGIT (8 patient per week per negative culture) | Moscow (2010)        | Culture tubes and media: $3.00; decontamination reagents: $0.83; cryovials for pellet storage: $0.81; lab supplies (e.g., pipette tips, centrifuge tubes): $0.53; automated MGIT 960 reader: $4.62; lab supplies (e.g., mini-pipettes, vortex machine): $1.00; lab equipment (e.g., incubator, freezer): $0.39 | Transportation: $8.57; laboratory personnel: $3.75 | 47.57% | 25.82 |
| MGIT (8 patient per week per positive culture) | Moscow (2010)        | Culture tubes and media: $3.00; decontamination reagents: $0.83; cryovials for pellet storage: $0.81; lab supplies (e.g., pipette tips, centrifuge tubes): $0.53; automated MGIT 960 reader: $4.62; lab supplies (e.g., mini-pipettes, vortex machine): $1.00; lab equipment (e.g., incubator, freezer): $0.39; confirmation/speciation: $9.18 | Transportation: $8.57; laboratory personnel: $3.75 | 62.3% | 35.69 |
| Balabanova et al. [20]  | Russia (2006–2008)   | MGIT FIND-BD                  | Decontamination: $2.76; equipment: $1.45; medical supplies: $4.58 | Overhead: $1.94; building: $0.42; staff: $0.51 | 75.39% | 15.32 |
| LJ                      | Moscow (2005–2006)   | Decontamination: $2.76; prep LJ: $0.10; equipment: $0.24; medical supplies: $0.05 | Overhead: $4.95; building: $1.07; staff: $1.34 | 29.97% | 18.41 |
| Combined smear and culture | Canada (2005–2006)  | AFB smear & culture on liquid media only | Supplies: $10.07 | Labour costs: $21.83 | 31.57% | 23.88 |

Notes: For studies with detailed information of cost for the included test components, we separated them into two parts: tradable costs and non-tradable costs. All the costs are the original data from selected studies without any conversion and standardization. If the detailed information for overheads is not available, we treated the overheads as non-tradable cost item.
relevant literature in Chinese. China has the highest prevalence of TB after India and the availability of Chinese cost data provides critical information for scaling up the monitoring tests for this large at-risk population. Using existing cost data, we also projected the unit cost of combined tests which could be used as useful reference to policy makers.

We propose a framework for evaluating the quality of unit cost data for TB monitoring tests. The five categories included in the quality score are crucial for determining the generalizability and validity of the cost data. They, may not, however, cover all important aspects. For instance, we only distinguished between the availability and absence of cost components, but did not consider the comprehensiveness of cost components. We assigned each category with the same weight and this may oversimplify the evaluation.

The paucity and low quality of unit cost estimates for TB monitoring in developing countries impose technical challenges in predicting the resource needed for strengthening microbiologic monitoring. As new molecular tests are being rapidly introduced globally to diagnose patients with presumptive TB and drug-resistant TB in one step, evaluation of the costs associated with the change in diagnostic practices – which was not the object of this paper - will be necessary. High quality cost data is especially important for the regions with high incidence of tuberculosis and MDR-TB, where scarce resources must be allocated efficiently. We strongly advocate that more data are collected from these regions, and that cost data collection, estimation, and reporting should follow the protocols proposed by the WHO [34] to improve the validity and comparability.

Supporting Information

Table S1 Databases and search terms of the search strategy. (DOCX)

Table S2 Cost for smear/culture in different regions in China (2010 USD). (DOCX)

Author Contributions

Conceived and designed the experiments: CL CDM. Senior authors: CL CDM. Analyzed the data: CL QL. Wrote the paper: QL CL AS CF DF CDM.

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