**Institution:** University of Birmingham

**Unit of Assessment:** UoA 2, Public Health, Health Services and Primary Care

**Title of case study:** Development of Cochrane reviews for summarising evidence of the accuracy of diagnostic tests have improved patient care and outcomes

**Period when the underpinning research was undertaken:** 2004–2020

**Details of staff conducting the underpinning research from the submitting unit:**

| Name(s): | Role(s) (e.g. job title): | Period(s) employed by submitting HEI: |
|---|---|---|
| Prof. Jon Deeks | Professor of Biostatistics | 2006–present |
| Prof. Yemisi Takwoingi | Professor of Test Evaluation | 2008–present |
| Dr Clare Davenport | Senior Clinical Lecturer in Public Health | 2008–present |
| Dr Jac Dinnes | Senior Systematic Reviewer | 2009–present |
| Prof. Sue Mallett | Professor of Medical Statistics | 2015–2020 |

**Period when the claimed impact occurred:** 1 August 2013–31 December 2020

**Is this case study continued from a case study submitted in 2014?** No

## 1. Summary of the impact

Diagnostic tests are crucial to the clinical management of disease and subsequent outcome for patients. Deeks and the Test Evaluation Research Group (TERG) at the University of Birmingham **have developed a methodological framework for evaluating the accuracy of diagnostic tests** which has transformed the way in which Cochrane and international Health Technology Assessment organisations evaluate the accuracy of diagnostic tests. This method is now the "Cochrane approved methodology". As a result, **over 200 clinical guidelines have been informed** by reviews using TERG methodology as has the **World Health Organisation (WHO) Essential Diagnostics list**. In turn, this has **changed practice** and **led to improved patient outcomes**. We illustrate this using the examples of WHO guideline changes for TB and Malaria.

## 2. Underpinning research

Accurate diagnosis of a patient's medical condition is essential as it determines their clinical care and impacts on health outcome, quality of life and healthcare costs. Therefore, reliable guidance on the accuracy of diagnostic tests is vital. The results of individual **diagnostic test accuracy (DTA) studies** may be misleading and clinical guidelines should ideally be based upon results from all available studies. These can be drawn together using **systematic reviews** that critically appraise the design and execution of the available studies, summarise the strength of the evidence and ultimately estimate the effect of the health technology and the confidence that can be attributed to it. **Cochrane is the largest international organisation preparing systematic reviews for healthcare** and is seen as setting the 'gold standard' for high quality, robust reviews. Initially, Cochrane reviews focused on interventions such as treatments or prevention strategies. Adding systematic reviews of diagnostic test accuracy has presented Cochrane with a unique set of methodological and statistical challenges.

To address these challenges, Deeks led a programme of work with Cochrane to define a methodological approach for Cochrane DTA reviews and to create software tools i) to produce the reviews, ii) to establish a publishing framework, iii) to run a peer-review editorial process and iv) to train researchers to perform DTA reviews. Deeks was awarded a £1.4M NIHR grant 2006–2011 to support this work which has been conducted by the University of Birmingham's **Test Evaluation Research Group (TERG)** and through an international collaboration led by Deeks.

The methodological framework was published in brief in 2008 [R1] and reported in detail in the online Cochrane DTA Reviewers' Handbook [methods.cochrane.org/sdt] with Deeks as lead editor. It is scheduled to be published as a book in 2021. Research outputs from TERG can be divided into two major groups:

1. **Development of the core components of a DTA framework**

**i) Comparing the accuracy of different tests**

Scientifically, the strongest way to compare the accuracy of two tests is to use them both in individual patients and compare the results with a reference standard. However, this is not always possible and one strength of a systematic review is the ability to compare the results of different studies which used the different tests. TERG showed that the second approach leads to different results, leading Cochrane to recommend that **analyses restricted to studies where patients receive all the tests should be done routinely and considered as stronger evidence** [R2].

**ii) Assessing study bias and relevance**

The design and conduct of studies included in a review must be scrutinised to assess whether the findings are free from bias and relevant to the review question. **The Quality Assessment of Diagnostic Accuracy Studies (QUADAS)** tool had been developed to assess this but a revised tool was needed. Deeks and Mallet were part of the steering group that developed the revised tool, **QUADAS-2**, and Davenport was a member of the advisory group throughout its development [R3].

**iii) Pooling results of component studies**

TERG developed and validated statistical models that are suitable for pooling the results of all the studies in a DTA review. They showed that **hierarchical model-based approaches should be used for DTA reviews, with simpler hierarchical models being more valid in situations with few studies or sparse data** [R4].

2. **Application of DTA Reviews in a real-world setting**

TERG have applied the DTA methodology framework to 38 DTA reviews during this REF period. Two exemplars are **rapid diagnostic tests (RDTs)** for **malaria** [R5] and **tuberculosis (TB)** [R6]. In 2019, these diseases were responsible for over 409,000 and 1.4M deaths worldwide, respectively. Both are amongst the United Nations Sustainable Development Goal 3 target to end epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases by 2030. In both conditions, early diagnosis and treatment is essential as it reduces disease severity and transmission, and prevents death. Particularly in low and middle income countries (LMICs), RDTs provide greater access to testing and faster results, such that treatment can begin in the same healthcare visit, with potentially life-saving benefits.

- Our review of **RDTs for *Plasmodium falciparum* malaria** (the most severe form), based on the results of 74 studies, showed that **RDTs are sufficiently accurate to replace microscopy (the standard test), with only small differences between different tests** [R5].
- Our review of **RDTs for TB in children** combined evidence from 49 studies, and assessed two RDTs (Xpert MTB/RIF and the next generation Xpert Ultra) for diagnosis of TB and drug resistance. It showed that these **RDTs accurately detect disease across multiple sample types and also detect drug resistance** [R6].

**3. References to the research (6 maximum)**

**[R1]** Leeflang MMG, **Deeks JJ**, Gatsonis C, Bossuyt PMM. Systematic reviews of diagnostic test accuracy. Annals of Internal Medicine 2008;149(12):889-97. (1007 citations)

**[R2] Takwoingi Y**, Leeflang M, **Deeks JJ**. Empirical evidence of the importance of comparative studies of diagnostic test accuracy. Annals of Internal Medicine 2013;158(7):544-54. doi: 10.7326/0003-4819-158-7-201304020-00006. (134 citations)

**[R3]** Whiting PF, Rutjes AWS, Westwood ME, **Mallett S, Deeks JJ**, Reitsma JB, Leeflang MMG, Sterne JAC, Bossuyt PMM and the QUADAS-2 group. QUADAS-2: A revised tool for the quality

assessment of diagnostic accuracy studies. Annals of Internal Medicine 2011;155(8):529-36. doi:10.7326/0003-4819-155-8-201110180-00009. (6267 citations)
**[R4] Takwoingi Y**, Guo B, **Riley RD**, **Deeks JJ**. Performance of methods for meta-analysis of diagnostic test accuracy with few studies or sparse data. Statistical Methods in Medical Research 2015. DOI: 10.1177/0962280215592269 (140 citations)
**[R5]** Abba K, **Deeks JJ**, Olliaro P, Naing CM, Jackson SM, **Takwoingi Y**, Donegan S, Garner P. Rapid diagnostic tests for diagnosing uncomplicated P. falciparum malaria in endemic countries. Cochrane Database of Systematic Reviews 2011; (7):CD008122. doi:10.1002/14651858.CD008122.pub2. (289 citations)
**[R6]** Kay AW, González Fernández L, **Takwoingi Y**, Eisenhut M, Detjen AK, Steingart KR, Mandalakas AM. Xpert MTB/RIF and Xpert MTB/RIF Ultra assays for active tuberculosis and rifampicin resistance in children. Cochrane Database of Systematic Reviews 2020, Issue 8. Art. No.: CD013359. DOI: 10.1002/14651858.CD013359.pub2. (6 citations)

## 4. Details of the impact

### 1. New methodology adopted for evaluating diagnostic tests

The Cochrane DTA Method developed by TERG [R1–R4] has transformed the way in which Cochrane and international Health Technology Assessment organisations evaluate the accuracy of diagnostic tests. During this REF period:

- **Cochrane has universally adopted the methodology** and used it for 127 DTA reviews (including 38 led or co-authored by TERG) that cover the full breadth of healthcare and diagnostic technology [S1i].
- **Seven health technology assessment organisations** (including those in Europe (2016), Australia (2016), India (2018), Canada (2018) and Sweden (2018)) have endorsed the methodology for their own evaluations of diagnostic tests which they undertake to determine test provision in their regions [S1ii].
- **238 clinical guidelines (205 national and 33 international) on disease diagnosis and monitoring have been written based on evidence** from 80 Cochrane DTA reviews. They were produced by 109 leading professional or public national or international healthcare organisations [S2i] from 22 different countries [S2ii], as well as 16 European and 3 global organisations [S2i].
- **WHO produced the first version of its annual Essential Diagnostics List (EDL**) in 2018 to guide its 193 member states on the most essential diagnostic tests to provide and procure [S3i]. Deeks was appointed a member of the Strategic Advisory Group of Experts to develop the evidence review process for the EDL and assisted with the process for all three versions published 2018, 2019 and January 2021. This process prioritises use of evidence from Cochrane DTA reviews using methods [R1–R4] whenever they are available. **The WHO EDL is used by individual countries to produce their own EDL tailored to their health needs**. For example, in December 2018, the Indian Council for Medical Research published the first draft of an **Indian National Essential Diagnostics List** [S3ii] based upon the WHO EDL.

### 2. Changed WHO guidelines leading to improved practice and patient outcome

Of 238 clinical guidelines informed by Cochrane DTA reviews using TERG methodology, we illustrate the impact this has had on clinical practice and benefit to patients through the examples of TB and Malaria.

**2.i. WHO has updated its guidance** on RDTs to detect TB and resistance to the drugs used to treat it in adults and children, and patients with HIV [S4ia–f], based on five commissioned systematic reviews and their updates, all of which were conducted according to Cochrane DTA methodology [R1–R4; S4ii].

In 2020, WHO consolidated all the guidelines on RDTs for TB [S4i]. R6 informed all of the 11 recommendations on the specific use of the RDTs Xpert MTB/RIF and its next generation test Xpert-Ultra in children. In this consolidated update, WHO:

a) Extended guidance on use of Xpert MTB/RIF from use in only those with multi-drug resistant TB or HIV [S4ib] to use for initial diagnosis of pulmonary TB in all suspected cases in adults and children [S4ia];
b) Gave more specific and certain guidance on the use of both RDTs across a wider range of sample types including those to detect extrapulmonary TB [S4ia];
c) Provided conditional recommendations on repeat testing with these tests in children with signs and symptoms of pulmonary TB [S4ia].

In 2018, WHO **introduced RDTs for TB into its EDL** [S3i] based on their better suitability than conventional methods for TB diagnosis in different settings as indicated by the DTA reviews it commissioned [S4ii]. Subsequently, India has included RDTs for TB in its EDL [S3ii]. The former Senior Scientist in the WHO TB Diagnostics and Laboratory Strengthening Unit has testified of the crucial role of Cochrane DTA reviews in developing WHO's guidelines on TB diagnosis and acknowledged the **impact this has had on patient lives**, stating that RDTs have

- "Allowed rapid and reliable TB diagnostic testing to be decentralised and allow patients to be diagnosed quickly with earlier initiation of appropriate treatment in many low and middle income countries" [S5];
- Enabled "earlier detection of drug resistance" [S5];
- "Reduced mortality from TB among seriously ill persons living with HIV." [S5]

The number of WHO member states that are now meeting WHO targets for good TB drug sensitivity testing has increased by 17% since 2015 to 113 countries [S6]. This includes 17 of the 40 countries with the highest TB burden. Continuous surveillance systems for drug-resistant TB have also replaced periodic national surveys in these countries which further improves access to timely and appropriate treatment, and enables outbreaks of TB to be identified and managed more quickly to prevent transmission. WHO says, "the ongoing shift from reliance on periodic surveys towards continuous surveillance systems is largely due to the increased availability of Xpert MTB/RIF testing at peripheral health facilities." [S6, pp. 49, 53]

**2.ii.** In 2015, **WHO updated its 'guidelines for the diagnosis of malaria'** [S7] solely on the basis of Deeks' 2011 review [R5], stating that "all cases of suspected malaria should have a parasitological test (microscopy or rapid diagnostic test (RDT)) to confirm the diagnosis" [S7). Although individual studies had evaluated RDTs, these were too small to provide convincing evidence of their value. By pooling data from 74 field studies in R5, the WHO guideline team were convinced of the value and the high accuracy of RDTs. Subsequently, this guideline was used to justify inclusion of RDTs for malaria on the WHO EDL [S3i] and in India's national EDL [S3ii].

The WHO African Region carries 94% (215M cases) of the world's malaria burden. **Use of RDTs has tripled in this region** between 2013 and 2018 from 59M to 189M in accordance with WHO guidance underpinned by R5 [S8]. By contrast, use of microscopy has remained fairly constant, meaning that the total number who receive a test for malaria by microscopy or RDT has increased from 118M to 232M. This change in practice has resulted in the following benefits to patients:

a) **Standards of care have improved** as the proportion of people diagnosed with malaria who received a confirmatory test has increased from 37% to 82%. This is important because diagnosis based on symptoms alone risks mis-diagnosis and overuse of anti-malarials that leads to drug resistance.
b) **Detection of malaria has increased** from 128M to 152M per annum enabling increased treatment and better containment of disease.
c) **Mortality from malaria has reduced by 37%** thereby **saving 43,000 lives each year**.

RDTs are only one component of malaria reduction programmes, but it is likely that this reduction in mortality is in part driven by increased accessibility to accurate, earlier and quicker diagnosis with testing from RDTs. Healthcare workers and managers from hospitals in the Republic of Congo testify that **RDTs have made diagnostic testing for malaria available for all patients regardless of gender and age** and say that because the test is "easy to use" it can be used in community care sites as well as the General Hospital, meaning people can be treated

within 5–10Km of where they live. Also, because they are better for diagnosing the type of malaria more patients are receiving effective treatments [S9].

**3. Impacts on Education and Training**

TERG have enabled researchers in academia, government and commercial organisations working as primary authors, reviewers, clinicians, health service researchers, systematic reviewers, statisticians and health economists to perform DTA reviews according to Cochrane methods [R2, R4]. They have done this by developing training courses, online training programmes and computer macros to support their execution [S10]. During this REF period, TERG has run 11 courses in the UK, that have trained more than 300 people, and has run courses in Canada, Amsterdam, India, Austria, Switzerland, Taiwan, USA, South Korea and South Africa that have trained approximately 500 people.

**5. Sources to corroborate the impact**

**S1i.** DTA reviews published in the Cochrane Library
**S1ii.** Table of Health Technology Assessment Organisations citing TERG methods
**S2i.** Professional/public organisations citing Cochrane DTA reviews in guidelines
**S2ii.** Geographical coverage of organisations citing Cochrane DTA review in guidelines
**S3i.** World Health Organization Essential Diagnostics List (2018 and 2019)
**S3ii.** India Essential Diagnostics List
**S4i(a–f).** World Health Organization guidelines for RDTs for TB between October 2013 and December 2020
**S4ii.** Version histories of commissioned systematic reviews that informed WHO TB guidelines and links to the reviews
**S5.** Testimonial from the former Senior Scientist in the WHO TB Diagnostics and Laboratory Strengthening Unit who led the TB diagnostic development process of the World Health Organization Global TB Programme (July 2020).
**S6.** World Health Organization Global Tuberculosis report 2020
**S7.** World Health Organization guidelines for diagnosis of malaria
**S8.** World Health Organization. World Malaria Report and graph showing numbers tested by microscopy and RDT, numbers tested positive by microscopy and RDT, untested but presumed positive and number of deaths
**S9.** Statements from healthcare workers and managers from hospitals in the Republic of Congo (July 2020)
**S10.** Course training materials provided by TERG