Strengthening methods of diagnostic accuracy studies

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Introduction
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General introduction

Faces cringed with frustration as the doctors at a university hospital in Kenya discussed the newly recommended policy of using a rapid test for malaria and only treating test-positive patients. They were reeling from the death of Lulu, a 5-year old girl. A false-negative result with the test they used had resulted in missing malaria and in Lulu's death.

The new test-and-treat policy was introduced in an attempt to curb overdiagnosis of malaria amidst increasing concerns of drug resistance and high costs associated with irrational prescription of anti-malarial drugs. The challenge with complying with the test-and-treat policy is that the risk of mortality from Malaria is high especially in children. Just like Lulu’s case, a missed case of Malaria could easily result in death.

The doctors faced a dilemma. Do we keep following this new policy and let results from our rapid test guide treatment or should we continue to treat presumptively based on clinical suspicion?

The doctors questioned the validity of the evidence on which the test-and-treat strategy was recommended, as they suspected the false negative rates of these rapid tests to be too high. A look through some of the published systematic reviews on the diagnostic tests for malaria revealed some limitations. Many of these reviews discussed the poor reporting of the included primary studies. Poor reporting hampered an assessment of the risk of bias in included studies and the investigation of sources of heterogeneity of the accuracy results of the included primary studies. Besides, the systematic reviews also used different methods of meta-analysis. Could these different methods of meta-analyses have a bearing on the credibility of the pooled measures of accuracy?
A cursory look through a number of abstracts of primary studies included in the reviews further added to the quagmire. Some abstracts presented very optimistic results and conclusions whereas other abstracts presented cautionary conclusions recommending that higher quality studies were needed. Whatever ‘higher quality’ meant?

The above scenario reflects some of the challenges health care workers have in appraising the evidence generated by studies evaluating the accuracy of diagnostic tests. The clinical use of tests based on questionable evidence or exaggerated conclusions may lead to incorrect clinical decisions, compromised patient safety and lead to unnecessary health care costs. It is therefore paramount that the evidence used to recommend diagnostic tests that will guide treatment of patients is generated using the most appropriate and robust methods.

**Central Theme of thesis**

In order to generate credible evidence about the accuracy of diagnostic tests, preferred methods of designing and conducting strong test accuracy studies and reviews have been recommended over the years. In the projects reported in this thesis we systematically assessed how these recommended methods have been applied in reports of recently published primary studies and in systematic reviews of diagnostic test accuracy. We specifically evaluated the methods of reporting in primary studies of diagnostic test accuracy and in systematic reviews of diagnostic test accuracy, we examined methods for assessing risk of bias, performing meta-analyses and investigating publication bias. We further propose recommendations to enhance the use and reporting of appropriate methods.
Outline of thesis

This thesis has three sections. **Part 1 (Chapters 1-3)** presents studies looking into the methods of reporting of primary diagnostic accuracy studies. Systematic reviews, a fundamental part of evidence-based practice, are built upon information presented in reports of primary studies. It is therefore essential that we evaluate how primary studies are reported.

In **chapter 1** we focus on overoptimistic interpretation and reporting of test accuracy studies. Reporting that distorts or misrepresents data-intentionally or unintentionally to make interventions look favourable is called overinterpretation also referred to as ‘spin’. Here, we examine the frequency of overinterpretation and misreporting of results of diagnostic accuracy studies.

In **chapter 2** we assess the frequency of failure to publish and the discrepancies between registered records and corresponding publications in a cohort of test accuracy studies registered in ClinicalTrials.gov. Failure to publish and selective reporting of research findings has been demonstrated in the biomedical literature with studies presenting favourable results being more likely to be published than studies with negative results.

The Standards for Reporting of Diagnostic Accuracy (STARD) was published ten years ago with the intended purpose of improving the transparency and completeness of reporting of diagnostic accuracy studies. In **chapter 3**, we present an opinion article describing the impact STARD has had on the reporting of test accuracy studies and propose ways to improve the current version of this reporting guideline.

**Part 2 (Chapters 4-6)** presents studies evaluating the methods used to assess the risk of bias in studies included in diagnostic reviews, methods used to meta-analyze accuracy measures in diagnostic accuracy studies and methods used to investigate the impact of publication bias in meta-analyses of diagnostic accuracy studies.
Although quality assessment is a key element of a systematic review, we suspected that only few reviews had taken the quality of the included studies into account when discussing the results and drawing conclusions. In chapter 4, we present a cross-sectional study that identified if and to what extent quality assessments of included studies have been incorporated in the conclusions of diagnostic accuracy reviews.

In chapter 5, we present the results of a survey conducted among authors of recently published meta-analyses of diagnostic accuracy studies. To understand why authors used the method of meta-analyses in their publications, we asked these authors about their rationale for selecting the type of methods for meta-analyzing data in their publications. We did this in order to improve further guidance on recommended methods of meta-analyses.

Methods for investigating the impact of publication bias on the results have been developed for intervention reviews but preferred methods are still unclear for diagnostic accuracy reviews. In chapter 6 we present a meta-epidemiological study that assessed if and how publication bias was investigated in meta-analyses of diagnostic accuracy and compared the results of existing statistical methods to investigate publication bias.

Part 3 (Chapters 7-9) contains studies applying the use of these methods in systematic reviews evaluating the accuracy of diagnostic tests for two major parasitic diseases plaguing tropical areas: Malaria and Schistosomiasis

In chapter 7 we report the results of a systematic review evaluating the accuracy of rapid diagnostic tests for the detection of malaria in pregnant women. Chapter 8 presents a systematic review about the diagnostic accuracy of circulating antigen tests and urine reagent strips for diagnosis of active schistosomiasis in endemic areas. Chapter 9 is an opinion article calling for the increased use of systematic reviews of diagnostic test accuracy to support
evidence-based diagnostic practice in Africa; a continent in which the practice of evidence-based care though much needed, is still in its infancy.

Chapter 10 summarises the main findings of the research presented in this thesis, identifies gaps in the existing evidence and proposes recommendations for future research.