Williams L, Drennan VM. Evaluating the efficacy of rapid diagnostic tests for imported malaria in high income countries: A systematic review.

Revised Manuscript submitted to Journal Int Emerg Nurs. Introduction

Emergency department nurses in countries, which are not endemic to malaria, will be familiar with the testing of adult and paediatric patients for malaria who present with fever and have a recent history of travel to a malaria endemic country. In the United Kingdom (UK) this testing is by microscopy [1] which entails three visits to the emergency department (ED) if the first is negative, which is burdensome for patients and the service. However, ED nurses who have worked in malaria endemic countries will know that rapid diagnostic testing (RDT) is common, and the World Health Organisation (WHO) recommends RDT or microscopy for diagnosis and before treatment commences [2]. The need for effective rapid diagnostic tests is ever present, with the current pandemic fast, high-performing field assays are needed so that results are received in a time frame to make a difference [3]. This raised the question as to whether there was evidence supporting the use of RDT for malaria (Plasmodium Falciparum and Plasmodium Vivax) in non-endemic countries. We investigated this question through a systematic review, reported here.

Background

Malaria is a life-threatening disease caused by the transmission of the *Plasmodium* parasite following a bite from an infected, female *Anopheles* mosquito. There are five species of parasite that affect humans. *Plasmodium (P) falciparum* (PF) and *P.*

vivax (PV) are the most prevalent with *P.falciparum* having the potential to cause the most serious illness [4]. Uncomplicated malaria can often have non-specific symptoms, similar to other febrile illnesses [5]. Treatment is specific to the type of parasite [6]. When left untreated the disease can progress to severe malaria within 24 hours [5]. The manifestations of severe malaria can include anaemia, hypoglycaemia, acute kidney injury, acidosis and coma [7]. In 2018 there were 228 million cases globally with approximately 405,000 deaths; the majority caused by *P.Falciparum* [8]. Malaria is endemic in 89 countries; the majority of which are in Africa and South East Asia [8]. Malaria continues to be a concern for non-endemic countries, through imported cases [9]. The number of international travellers visiting countries with a malaria transmission risk is over 125 million per year [10]. In Europe, the disease accounts for a considerable burden of morbidity and mortality [11]. Imported cases throughout non endemic countries vary significantly with France having the highest average annual caseload (n= 2169), followed by UK (n=1898), USA (n=1511) and Italy (n=637) [9].

The National Institute of Clinical Excellence (NICE) guidance for the management of malaria in the UK currently advocates parasitological testing by microscopy as the gold standard for diagnosis, requiring three negative blood films over a 24-48-hour period to exclude malaria [12]. Microscopy is undertaken in a laboratory but due to the low numbers of tests and infrequency in performing them there is often a lack of proficiency in detecting the parasite, particularly at low densities, resulting in poor sensitivity (i.e. low identification of true cases) [13]. Due to the possibility of false negatives at low parasite densities three malaria slides at intervals are recommended to rule out malaria, these incur increased costs for healthcare facilities due to multiple attendances and an increase in laboratory work [14].

Rapid Diagnostic Tests (RDTs) are point of care tests, using finger prick blood with results being available in 15-30 minutes [15]. RDTs are lateral flow immuno-chromatographic antigen detection tests which produce a visible band on a strip of nitro-cellulose, once the antigen is detected. WHO undertakes regular laboratory evaluations of the performance of different types of RDTs to inform endemic countries. The 2018 report of this testing identified that there were now some RDTs performing at high sensitivity with low densities of parasites (<200 parasites/μL) [16].

A 2011 Cochrane review and metanalysis of 74 studies in endemic areas assessing RDT compared to microscopy for *P.Falciparum* reported that RDTs were very accurate in detecting malaria although there were some differences between types of tests designed to detect different antigens. A further Cochrane review and metanalysis in 2014 reviewed 47 studies evaluating the use of RDTs compared to microscopy for uncomplicated *non-falciparum* or *P.Vivax* alone in endemic countries. RDTs designed to detect *P.Vivax* only were very accurate but those testing for non *P. Falciparum* had a low sensitivity (78-89%) There are no systematic reviews for the use of malaria RDTs diagnostic tests in non-endemic countries. We undertook a systematic review of published clinical evidence to address the research question:

Are rapid diagnostic tests accurate for diagnosing imported Falciparum and Vivax malaria in non-endemic, high income countries?

1. Methods

A systematic review was designed and reported here to meet Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards [17].

Studies addressing the research question were identified by systematic searching for keywords in the following electronic databases: CINHAL, Medline, PubMed and Embase from 2009 to 11/2020. The key words were compiled with the support of an informaticist: Rapid Diagnostic Test, RDT*, Point of Care test, Point of Care system, Diagnostic Method, Imported Malaria, *Plasmodium*, *Plasmodium Falciparum*, Imported Malaria, Febrile traveller.

1.1. Inclusion criteria and study selection

Relevant studies were selected according to eligibility criteria using a two-step screening process: (1) title and abstract screening and (2) full-text screening. All the full texts of the potentially relevant citations were examined in parallel by the authors to analyse whether they met all the inclusion criteria. Disagreements were resolved by discussion.

Peer-reviewed articles were considered for analysis if they fitted the following inclusion criteria:

Population: Patients presenting for malaria testing in high income countries as defined by the International Monetary Fund's definition [18].

Intervention: Rapid diagnostic test

Comparison: Microscopy or Microscopy and Polymerase Chain Reaction (PCR)

Outcome: Sensitivity, also called the true positive rate i.e. correctly identifying the patient as having the disease), Specificity, also called the true negative rate i.e.

correctly identifying the patient as disease free), Positive predictive values (the percentage of patients with a positive test who actually have the disease), Negative predictive values (the percentage of patients with a negative test who are disease free), Density of parasitaemia required to achieve > 95% sensitivity. These outcomes were chosen in order evaluate the accuracy of the RDTs reviewed.

Study design: randomised control trials and any quantitative study design that allowed comparison of RDT for malaria with microscopy.

Screening exclusion criteria

Articles were excluded if they did not fulfil one or more inclusion criteria or if they: (1) were not published in the English language; (2) reported on a study from countries that were not defined by the International Monetary Fund as advanced economies [18], (3) did not report empirical findings or were published only in abstract form; and (4) presented literature reviews, commentaries and/or non-peer-reviewed articles.

1.2. Data collection and assessment

Data extraction was based on the Centre of Reviews and Dissemination (2009) guidance [19]. All relevant data was extracted into tables in Microsoft Excel.

Extracted data included:

- Identification features of the study (Author, title, country of origin, year of publication)

- Study characteristics (Aims, study design, recruitment, sample size)

- Participant characteristics (age, ethnicity, gender)

- Intervention (RDT used), comparison (microscopy/PCR) and setting

- Outcome data (Sensitivity, specificity, Positive predictive values, negative predictive values)

- Additional outcomes (Ease of use, range of parasitaemia required to achieve > 95% sensitivity).

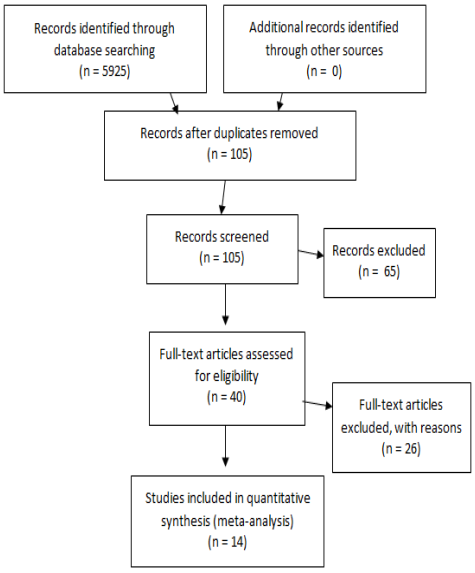
Bias in this review was assessed using the Critical Appraisal Skills Programme (CASP) checklist for diagnostic studies [20]. Risk of bias was scored as high, low or unclear. Each paper was reviewed as to whether the STARD checklist was used in reporting the study. This checklist created by Enhancing the Quality and Transparency Of health Research (EQUATOR) has standards for the reporting of diagnostic accuracy studies and was developed to improve the process and transparency of reporting [21].

A narrative synthesis of results was undertaken with forest plots demonstrating sensitivity and specificity with confidence intervals.

2. Results

The search identified 5925 titles of which 5820 were excluded either as duplicates or based on title alone, 65 studies were excluded after reading the abstract and 26 excluded after reading the full text (see Figure 1 PRISMA diagram). Common themes for exclusion were studies based in endemic settings, evaluating non RDT diagnostic tools or they were based in low income countries.

Figure 1:



2.1. Characteristics of included studies

A total of 14 studies [22-35] were included. The majority were conducted in Belgium [24,25,26, 29,30, 31,34, 35] (table 1). One study was conducted in both France and Malawi, only the results of the study in France have been included as Malawi is an endemic area [23]

Table 1: Characteristics of included studies.

study ID	Ref no	Author	Country	Year	Test	Number.tested
1	22	Bronner et al [ref]	Sweden	2010	MalaQuick Binax Now	635

2	23	Eibach et al [ref]	France and Malawi	2013	VIKIA Malaria Ag Pf/pan	155
3	24	Gillet et al [ref]	Belgium	2009	SD FK80 PF/PV	416
4	25	Gillet et al [ref]	Belgium	2009	SDFK70 Malaria Ag PV	375
5	26	Heutmakers et al. [ref]	Belgium	2012	SDFK90	591
6	27	Houze et al	France	2011	Clearview Malaria pLDH	292
7	28	Houze et al	France	2013	Now ICT Core Malaria Palutop +4 Optimal IT	1311
8	29	Maltha et al	Belgium	2011	SDFK40 SDFK60 Optimal	522
9	30	Maltha et al	Belgium	2010	Carestart Malaria HRP-2/Pldh Combo	590
10	31	Parischa et al	Australia	2013	BinaxNOW/ICT Malaria	388
11	32	Stauffer et al	USA	2009	BinaxNOW	852
12	33	Van DP et al	Belgium	2009	SDFK50/60	452
13	34	Van Dijk et al	Belgium	2009	Palutop+4	613
14	35	Van Dijk et al	Belgium	2010	Immunoquick+4	613

156

157 All studies had a representative cohort of patients included, all symptomatic
158 returning travellers from endemic areas. All studies were assessed using the
159 CASP checklist for diagnostic test studies. None were identified as having high

160 risk of bias in any area. 12 out of 14 studies were identified as having low risk of
161 bias in all areas.

162 Only 8 out of the 14 studies identified that the STARD checklist [21] was used for
163 the reporting of their diagnostic accuracy study.

164 Thirteen types of RDT were evaluated. Most RDTs tested for multiple parasite
165 species as shown in table 2. All RDTs tested for *P Falciparum* (PF), except the
166 SDFK70, which tested for *P.Vivax* (PV) alone. The RDTs evaluated varied in
167 terms of antigen tested (table 7). All but 1 study used both microscopy and
168 Polymerase Chain Reaction (PCR) as the reference standard. PCR detects
169 parasite nucleic acids using polymerase chain reaction [14]

170

171 Table 2: RDTs and Parasite species tested

	Species tested				
Test	Plasmodium Falciparum	Plasmodium Vivax	Plasmodium Ovale	Plasmodium Malariae	Mixed
MalaraQuick [18]	X				X
Binax Now ICT [18, 27, 28]	X				X
Clearview Malaria [23]	X	X	X	X	
Carestart Malaria [26]	X	X	X	X	
SDFK40 [25]	X				

SDFK50 [29]	X				
SDFK70 [21, 27]		X			
SD FK80 PF/PV [20]	X	X			
SDFK90 [22]	X				
VIKIA Malaria [19]	X				X
Core Malaria [22]	X	X			X
Palutop +4 [24, 30]	X	X			X
Optimal IT [24, 25]	X				X
Immunoquick+4 [31]	X	X	X	X	

All studies carried out tests on symptomatic patients returning from endemic areas.

2.2. RDTs and P.Falciparum

There were 18 evaluations of RDTs testing for *P.Falciparum*, verified with either microscopy or microscopy and PCR on 7932 patient samples [22,23,24,26,27,28,29,30,31,32,33,34,35]

Reported sensitivity (i.e. true positive rate) of the RDTs ranged from 67.9% (CI 60.1-81.1) for the SDFK40 RDT to 100% BinaxNow. (CI 92.2-100). The SDFK40 had a lower sensitivity rate than the other tests.

184 The BinaxNow was reported to have the highest sensitivity overall at 100%. It was
185 evaluated in 4 separate studies and achieved a mean sensitivity of 97.5, ranging
186 from 96-100, all of which were above the cut off threshold.

187 Reported specificity (i.e. true negatives) ranged from 93.1% (CI 95.8-96.9) to
188 100% for the VIKIA Malaria RDT (CI 94.6- 100). 8 of the RDTs reached over 95%
189 sensitivity on testing, however 3 of these failed to achieve over 95% in separate
190 studies and 4 of the tests were only trialled once.

191 Figure.1 and 2 are forest plots showing sensitivity and specificity for RDTs tested
192 on P. Falciparum with 95% confidence intervals

193 Figure 1. Forest Plot showing specificity with Confidence intervals for Plasmodium Falciparum

Study ID	RDT
1	BinaxNow
7	Binax Now
10	BinaxNOW
11	BinaxNOW
9	Care Start Malaria
6	Clearview
7	Core Malaria
14	Immunoquick+4
1	MalaQuick
7	Optimal IT
7	Palutop +4
13	Palutop+4
8	SDFK40 Prospective
8	SDFK40 Retrospective
12	SDFK50
3	SD FK80
5	SDFK90
2	VIKIA Malaria Ag Pf

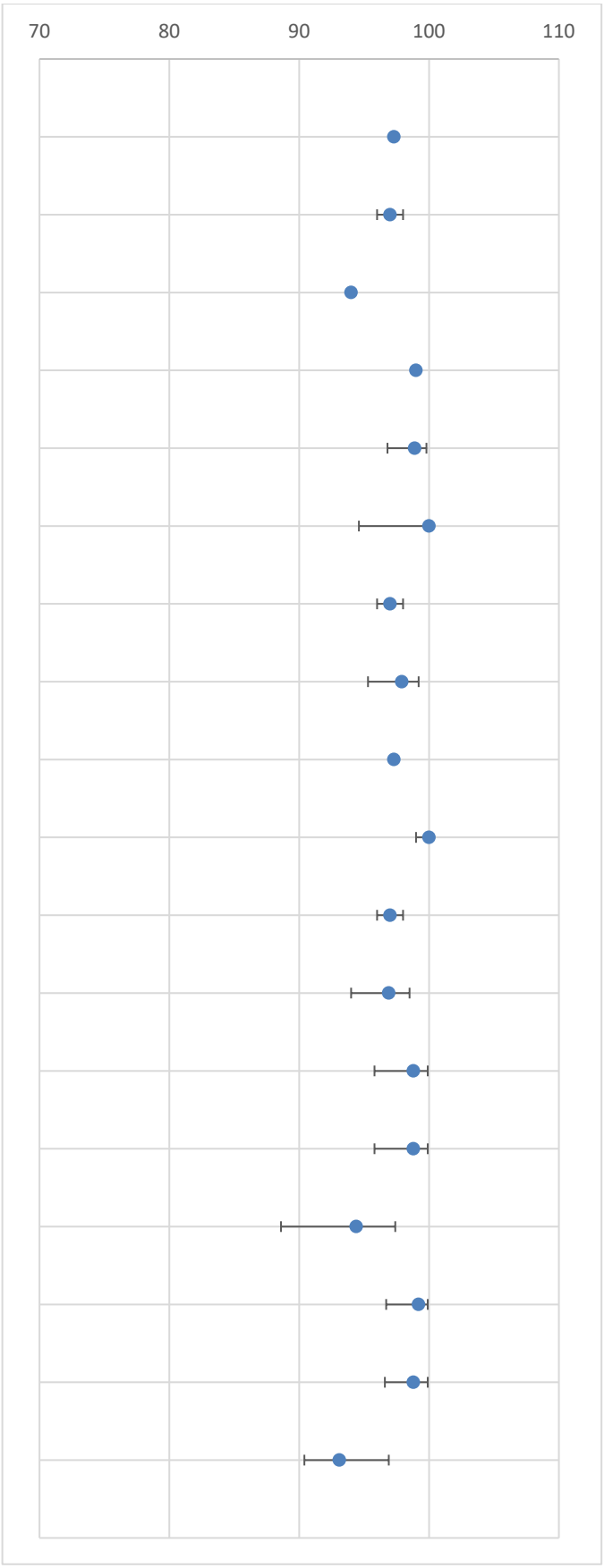
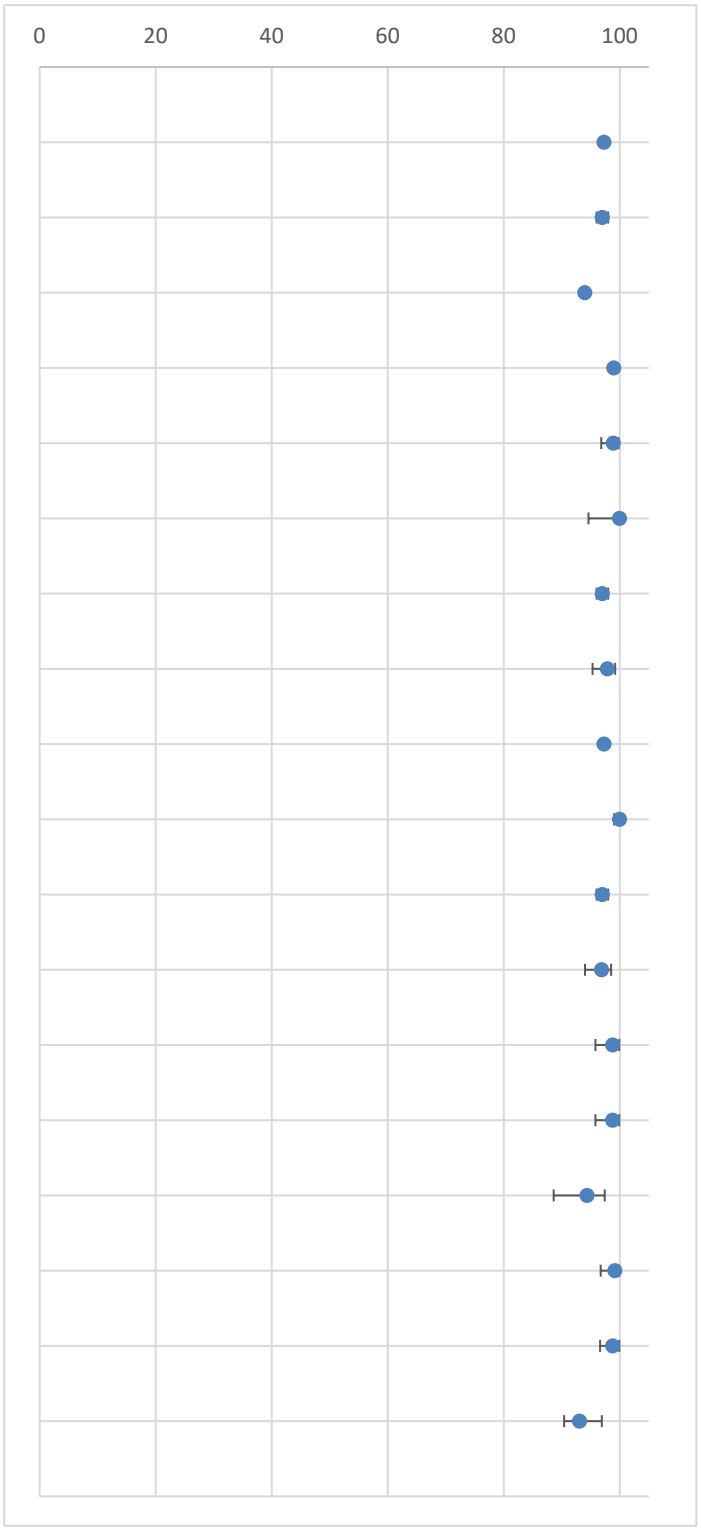


figure 2: Forest Plot showing specificity with Confidence intervals for Plasmodium Falciparum

Study ID	RDT
1	BinaxNow
7	Binax Now
10	BinaxNOW
11	BinaxNOW
9	Care Start Malaria
6	Clearview
7	Core Malaria
14	Immunoquick+4
1	MalaQuick
7	Optimal IT
7	Palutop +4
13	Palutop+4
8	SDFK40 Prospective
8	SDFK40 Retrospective
12	SDFK50
3	SD FK80
5	SDFK90
2	VIKIA Malaria Ag Pf



Positive Predictive Values (PPV) and Negative Predictive Values were only documented for 5 of the 13 tests included for *P. Falciparum* (See forest plots). The Optimal IT was reported with the highest PPV at 98% (CI 96-100) and both the MalaraQuick and Binax Now RDT the lowest at 84.8% (CI not documented for all studies.

Figure 3. Forest plot showing PPV for RDTs testing for Plasmodium Falciparum including CIs

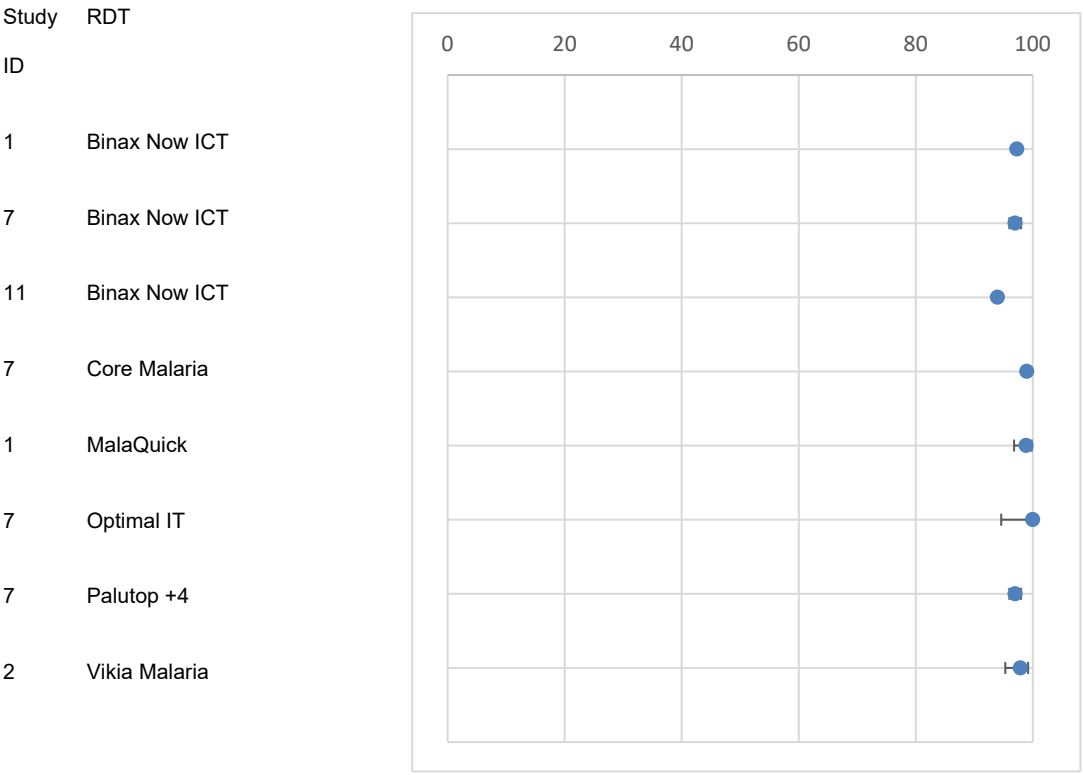
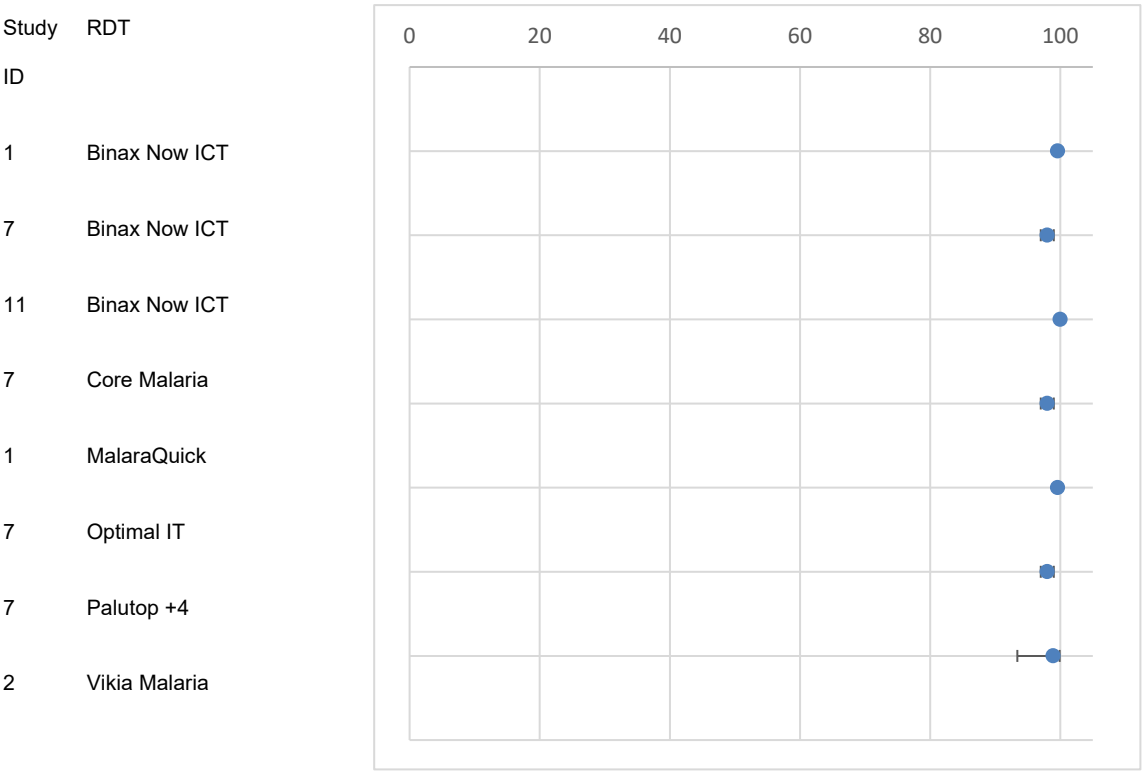


Figure 4. Forest plot showing NPV for RDTs testing for Plasmodium Falciparum including CIs



The SDFK40 [29], SDFK50 [32], SDFK60 [33], SDFK80 [24], SDFK90 [26], Care Start malaria [30] and the Immunoquick +4 [35] had parasite densities documented at point of testing. The SDFK90 required the lowest parasite density in order to achieve over 95% sensitivity (>1-100u/L), both the SDFK50 and 60 achieved over 95% sensitivities at parasite densities >201u/L. The Palutop +4 did not achieve over 95% sensitivity at any parasite density range. The remaining RDTs only achieved over 95% sensitivity at a density >1000u/L.

RDTS and Plasmodium Vivax

There were 9 evaluations of RDTs for testing of *P.Vivax*, verified with either microscopy or microscopy and PCR on 3674 patient samples [22, 24, 25, 27,29, 30, 31 ,34, 35]. 8 different RDTs were evaluated.

None of the RDTs were reported over 95% sensitivity on testing.

The Palutop +4 RDT was reported with the highest sensitivity of 91% (CI 74-100) in a French study [28] but only 66% (CI 55.6-75.1) sensitivity in in a study in Belgium [35]. Parasite densities in the samples could be the source of the discrepancy as they were only reported in the Van Dijk et al study [35]. The same discrepancy was reported in the results for specificity.

Specificity of the RDTs was reported as 98.1 to 100%. The Carestart RDT was reported with the lowest specificity (98.1) and the Clearview Malaria HRP-2/Pldh, SDFK60 and SDFK80 PF/PV and Palutop +4 all reached 100% (see forest plot).

PPV and NPV were only documented for the Core Malaria and the Palutop+ 4 RDTs used to detect *P. Vivax*. The Palutop +4 RDT gave the highest PPV and NPV at 98% and 89% respectively [35].

Figure 5. Forest Plot showing sensitivity with Confidence intervals for Plasmodium Vivax

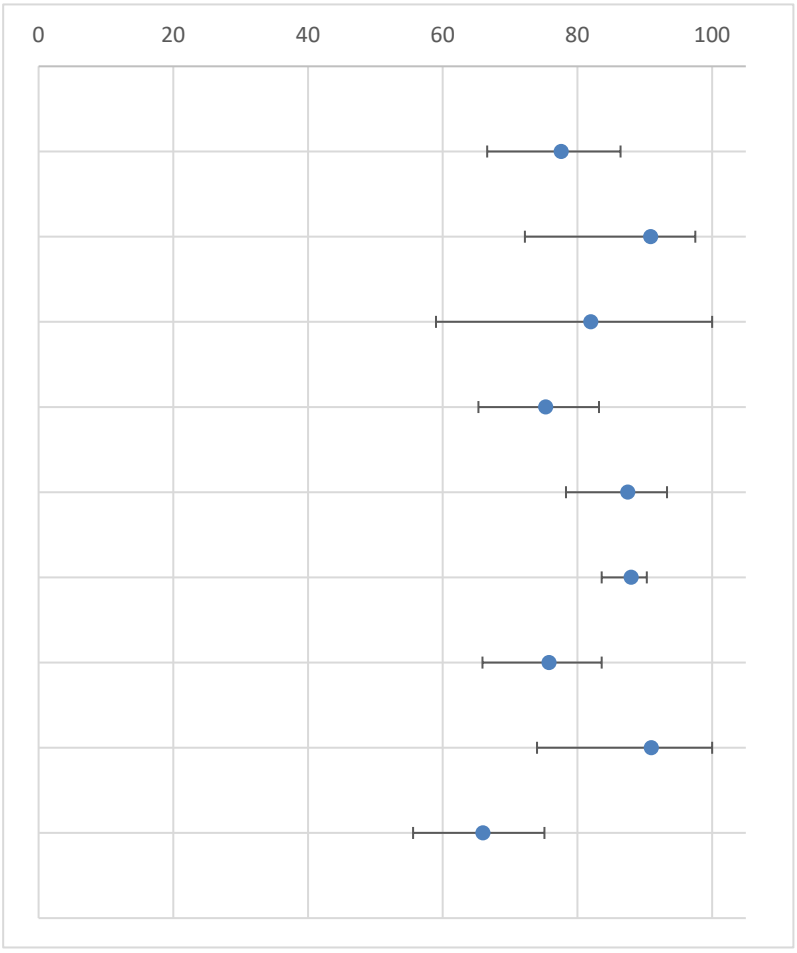
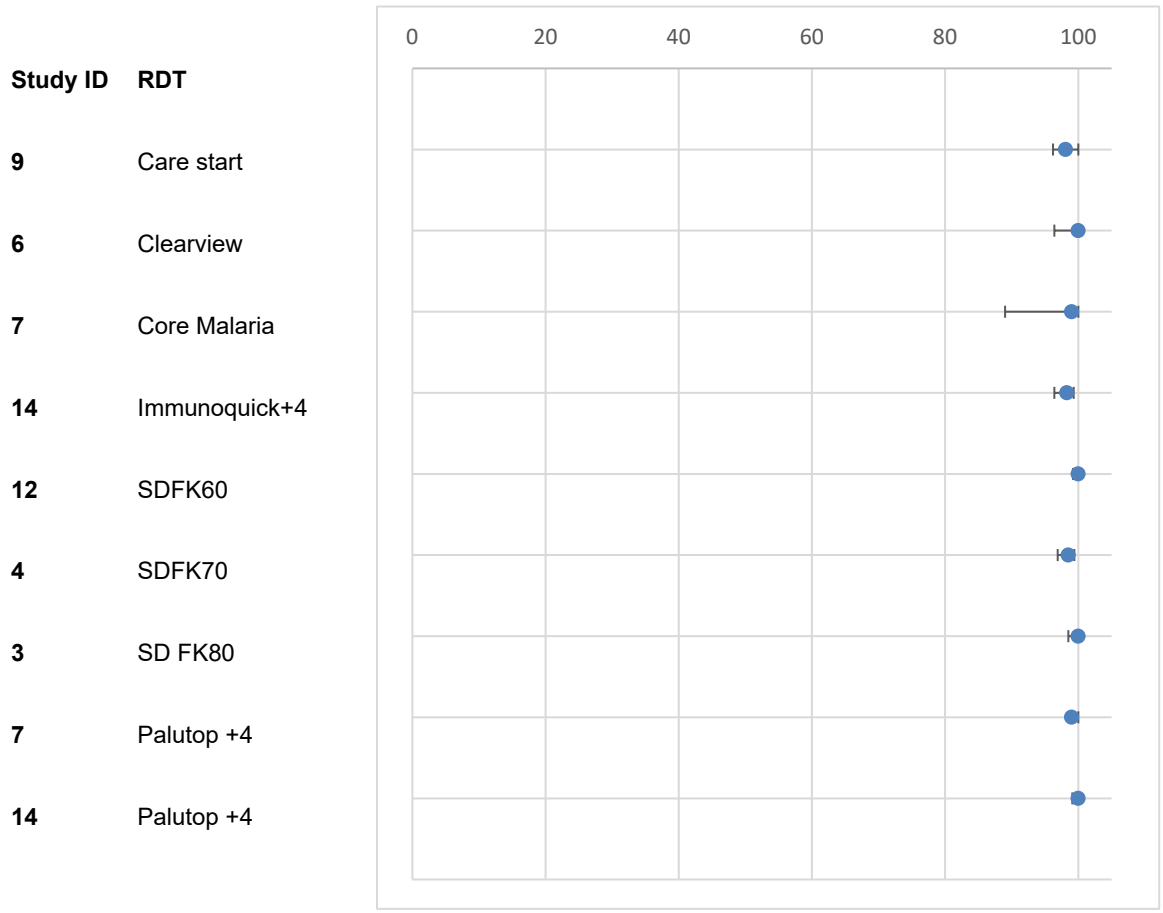


Figure 6. Forest Plot showing specificity with Confidence intervals for Plasmodium Vivax



The SDFK60 [29], SDFK70 [25], SDFK80 [23], Palutop +4 [28, 34] and Immunoquick +4 [35] had parasite densities documented. Only the SDFK70 achieved a sensitivity of 95% or above at a parasite density of >500. None of the other RDTs achieved a sensitivity over 95% at any density. The SDFK70 RDT was the only test included in the review that was to test for *P.Vivax*

specifically, the other tests were to test for *P.Falciparum* and other species, which could be the reason for the ability for the test to perform at a higher level than the others for the particular parasite.

Discussion

This review investigated the diagnostic efficiency of malaria rapid tests in terms of accuracy (sensitivity and specificity) in non-endemic, high income countries. To our knowledge this is the first review examining the effectiveness of RDTs in non-endemic countries with a focus of applicability in ED settings. Fourteen studies were included, the majority conducted in Belgium. It was notable that there was a lack of studies conducted in non-endemic countries with some of the highest rates of malaria. All studies showed low risk of bias when assessed using CASP checklists [18]. Thirteen RDTs were assessed and showed significant variation in results for sensitivity for all malaria species. Higher parasite densities were related to higher sensitivity, with *P.V* only achieving over 95% with parasite densities >500u/L. All tests were showed high specificity for both *PF* and *PV*.

Sensitivity for RDTs for P. *Falciparum* ranged from 67.9% and 100% and specificity between 93.1 -100%. 7 RDTs achieved higher than 95% sensitivity, with the BinaxNow achieving over 95% in 4 separate studies. Higher sensitivity was achieved with higher parasite densities. The accuracy varied widely between different tests, therefore not all tests can be recommended for diagnosis of *P. Falciparum* in practice in non-endemic countries. The BinaxNow consistently produced sensitivities over 95% in 4 different studies, however confidence intervals were not provided in all studies. The Clearview produced

over 95% sensitivity but was only assessed in one study and other RDTs that were tested in more than one study showed significantly different results. Higher sensitivity rates were associated with higher parasite densities which is similar to results from previous research [35]. The best performing RDTs require further assessment to provide stronger evidence of consistent results.

RDTs testing for *Plasmodium Vivax* had sensitivity rates from 66 -91% overall and specificity rates from 98.1 – 100%. However, the SDFK70 achieved over 95% sensitivity for *Plasmodium vivax* with parasite densities over 500u/L. These results indicate that RDTs do not provide sufficient accuracy to be used in clinical practice.

Strengths and weaknesses

This review was undertaken following recognised systematic review guidelines. A comprehensive search was undertaken of four databases with a total of 5925 records reviewed. However, it is recognised that despite a thorough search strategy diagnostic test accuracy studies are often poorly indexed, therefore studies suitable for inclusion may have been missed.

ConclusionsUnderstanding the utility, sensitivity and specificity of different types of diagnostic tests has taken greater significance with the global pandemic for nurses, health professionals and the public. Emergency nurses in non-endemic, high income countries are aware that malaria, rapid, point of care testing would be preferable for adult and paediatric patients compared to three attendances for testing. This review of studies assessing the performance of rapid diagnostic tests in such countries demonstrates that such tests do not yet perform to the same standard of accuracy as that achieved by microscopy. As such there

cannot be any recommendation for change in practice. However, some of the RDTs are reported to have higher performance but only in single studies. Further research and assessment is required of these RDTs in non, endemic, high income countries to help establish the evidence for a method that provides accurate results in a more acceptable and efficient way.

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