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A Systematic Review: Performance of Rapid Diagnostic Tests for the Detection of *Plasmodium knowlesi*, *Plasmodium malariae*, and *Plasmodium ovale* Monoinfections in Human Blood

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Background. Despite the increased use and worldwide distribution of malaria rapid diagnostic tests (RDTs) that distinguish between *Plasmodium falciparum* and non-*falciparum* species, little is known about their performance detecting *Plasmodium knowlesi* (*Pk*), *Plasmodium malariae* (*Pm*), and *Plasmodium ovale* (*Po*). This review seeks to analyze the results of published studies evaluating the diagnostic accuracy of malaria RDTs in detecting *Pk*, *Pm,* and *Po* monoinfections.

Methods. MEDLINE, EMBASE, Web of Science, and CENTRAL databases were systematically searched to identify studies that reported the performance of RDTs in detecting *Pk*, *Pm,* and *Po* monoinfections.

Results. Among 40 studies included in the review, 3 reported on *Pk*, 8 on *Pm*, 5 on *Po*, 1 on *Pk* and *Pm*, and 23 on *Pm* and *Po* infections. In the meta-analysis, estimates of sensitivities of RDTs in detecting *Pk* infections ranged 2%–48%. Test performances for *Pm* and *Po* infections were less accurate and highly heterogeneous, mainly because of the small number of samples tested.

Conclusions. Limited data available suggest that malaria RDTs show suboptimal performance for detecting *Pk*, *Pm,* and *Po* infections. New improved RDTs and appropriately designed cross-sectional studies to demonstrate the usefulness of RDTs in the detection of neglected *Plasmodium* species are urgently needed.

Keywords. malaria; rapid diagnostic test; diagnosis; *Plasmodium knowlesi*; *Plasmodium malariae*; *Plasmodium ovale*; *Plasmodium*.

Despite its preventable and curable nature, malaria continues to be a life-threatening disease, with ongoing transmission in >90 countries [1]. Parasites belonging to the genus *Plasmodium* are responsible for malaria infections. *Plasmodium falciparum (Pf), Plasmodium vivax (Pv), Plasmodium knowlesi (Pk), Plasmodium malariae (Pm),* and *Plasmodium ovale (Po)* target humans as natural hosts [2]. Two forms of *Po*, which have been recently confirmed to be two distinct species, *Plasmodium ovale curtisi* (*Poc*) and *Plasmodium ovale wallikeri (Pow)*, exist [3, 4]. In addition, *Plasmodium cynomolgi* has been reported to cause human infections [5]. Most of the epidemiological studies and operational interventions primarily focus on the two most common species, *Pf* and *Pv*, due to their global burden and mortality rates. Similar efforts on *Pk, Pm,* and *Po* have remained scarce until now, although reports of severe infections with these species have started to accumulate [6]. *Plasmodium ovale* malaria cases with severe conditions and even death have been reported [7, 8], and severe acute renal failure and severe anemia have been shown to be associated with *Pm* infection [9–11]. Recently, *Pk* was reported to be the most common cause of malaria in Malaysia [12]. These observations reinforce the idea that all *Plasmodium* species infecting humans should be of concern if the global targets set by the World Health Organization (WHO) to eliminate malaria due to any species are to be achieved [13].

Microscopy and rapid diagnostic tests (RDTs) are the WHO-recommended tools to confirm the diagnosis of all suspected malaria cases [13]. Histidine-rich protein-2 (HRP2), lactate dehydrogenase (LDH), and aldolase are the targeted malaria antigens used in malaria RDTs [14]. Histidine-rich protein-2 is a *Pf*-specific antigen, whereas aldolase is common to all *Plasmodium* species (pan-specific). *Plasmodium falciparum*–specific, pan-specific, and *Pv*-specific LDH antibodies are also available to be used in commercially available malaria RDTs. Antibodies against these three antigens are often combined in RDTs to distinguish *Pf* and *Pv* from other species or to detect all species at once [14, 15]. Rapid diagnostic tests play a nonnegligible role in the control of malaria by promoting access to rapid diagnosis and appropriate treatment. Especially in settings where the conditions are not favorable for the use of microscopy, RDTs serve as an easy-to-use, cost-effective, and field-ready alternative.

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However, the widespread use of *falciparum*-specific RDTs causes the missed detection of non-*falciparum* species, including *Pk*, *Pm,* and *Po* [16], especially because, in regions where malaria is endemic, individuals are often infected with more than one single *Plasmodium* species (mixed-species infections) [17–19]. This situation undermines the efforts to understand the epidemiological distribution and impact of circulating species. Even though malaria RDTs that also target non-*falciparum* species are available, their performance for the detection of *Pk, Pm,* and *Po* is less well studied than that of *Pf and Pv.* Thereby, there is a knowledge gap regarding the usefulness of currently available malaria RDTs for detection of *Pk*, *Pm*, and *Po* infections.

The objective of this systematic review is to summarize and analyze published information about the performance of malaria RDTs in detecting human monoinfections with the three *Plasmodium* species, *Pk*, *Pm*, and *Po*, in endemic and nonendemic settings. This review aims to highlight the big knowledge gap on the performance of malaria RDTs in detecting these *Plasmodium* species and to help make informed decisions on the use of diagnostic tools to support the elimination of malaria caused by any species.

METHODS

Searched Databases

A systematic approach was used to search the following databases for articles of possible relevance: Medline (PubMed), Web of Science, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL). The search terms and strategy as adapted from an earlier report [15] are outlined in Supplementary Table 1. Searches were carried out in August 2017. Reference lists of all eligible studies were searched for additional relevant articles.

Selection Criteria

The data search was limited to studies with a cross-sectional or a case–control design with any sampling method. Case reports, reviews, editorials, country reports, guidelines, and conference abstracts were not eligible. To impose a focus on currently available malaria RDTs, only studies published during the last 20 years (from 1997 to 2017) were included.

Studies reporting on *Pk*, *Pm*, and/or *Po* human monoinfections were eligible. Studies reporting exclusively on *Pf* and/or *Pv* infections or mixed infections with *Pk*, *Pm*, and/or *Po* were excluded from further analysis. Reports on a single patient with *Pk*, *Pm*, or *Po* monoinfection were excluded from the review to enable meaningful evaluation of test performances. Studies reporting on participants living in endemic areas, as well as international travelers and migrants who had recently been to endemic areas, were included in the review. Studies detecting different *Plasmodium* species with conventional microscopy and/or polymerase chain reaction (PCR) as reference standard were considered eligible. All inclusion and exclusion criteria are summarized in Supplementary Table 2.

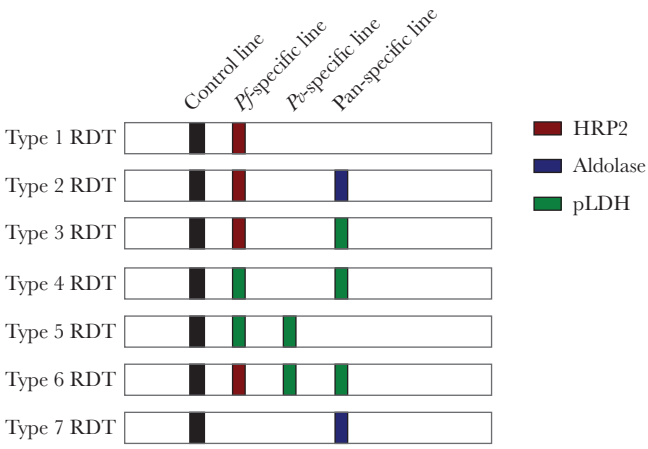


Figure 1. Antigens targeted by rapid diagnostic test (RDT) types included in the review. Only type 2, 3, 4, and 6 RDTs are able to distinguish between *Plasmodium falciparum* (*Pf*) and non-*falciparum* infections. Type 2 tests detect *Pf*-specific histidine-rich protein-2 (HRP2) antigen and panmalarial aldolase, which is expressed by all species. Type 3 tests detect a pan-specific LDH in addition to *Pf*-specific HRP2 antigen. Type 4 RDTs target *Pf*-specific and pan-specific lactate dehydrogenase (LDH) antigens as two separate lines, allowing distinction between *Pf* and non-*falciparum* infections. Type 6 RDTs are 4-band tests that target *Pf*-specific HRP2, *Pv*-specific LDH, and pan-specific LDH [7, 8]. Abbreviations: HRP2, Histidine-rich protein-2; *Pf*, *Plasmodium falciparum*; pLDH, *Plasmodium* lactate dehydrogenase; *Pv*, *Plasmodium vivax*; RDT, rapid diagnostic test.

Studies evaluating any immunochromatography-based RDTs designed for the detection of non-*falciparum* malaria were eligible. Bell and colleagues classified malaria RDTs according to antibody combinations and parasite species detected [14] (Figure 1; Supplementary Table 3). According to this classification, type 2, 3, 4, and 6 tests are able to detect non-*falciparum* infections and to distinguish them from *Pf* (and *Pv* in the case of type 6 RDTs) concurrent infections (Figure 1). Therefore, studies evaluating these four types of RDTs were included in the review. Interpretation of RDT results that were considered eligible for the review is summarized in Table 1. Reports that considered tests positive for *Pk*/*Pm*/*Po* infections when both *Pf*- or *Pv*-specific lines and pan-only lines were visible were excluded from the analysis or re-evaluated to avoid any spurious effect due to cross-reaction between *Pf* (and *Pv* in the case of type 6 tests) infections and pan-specific reagents.

Data Extraction

All titles and abstracts acquired through search were stored in Mendeley reference manager software (version 1.17.10; Mendeley Ltd). As a first step, duplicates were removed from the list; titles and abstracts were then screened, and those that were clearly not suitable for inclusion were excluded. Subsequently, articles were full-text screened, and those that did not comply with eligibility criteria were excluded. All excluded titles were stored, with tags indicating the reason for exclusion, in a separate folder.

Data were extracted by a review author (S. Y.) using a Google Form based on the predefined variables (Supplementary Table 4).

Table 1. Interpretation of rapid diagnostic test results for *Plasmodium knowlesi*, *Plasmodium malariae*, and *Plasmodium ovale* monoinfections

	TP	TN	FP	FN
Type 2/3/4 RDTs				
Microscopy/PCR	Only *Pk*/*Pm*/*Po*	Neg or non-*Pk*/*Pm*/*Po*	Neg or non-*Pk*/*Pm*/*Po*	Only *Pk*/*Pm*/*Po*
RDT	Only pan line visible	No lines visible or *Pf* line visible with or without pan line	Only pan line visible	No lines visible or *Pf* line visible with or without pan line
Type 6 RDTs				
Microscopy/PCR	Only *Pk*/*Pm*/*Po*	Neg or non-*Pk*/*Pm*/*Po*	Neg or non-*Pk*/*Pm*/*Po*	Only *Pk*/*Pm*/*Po*
RDT	Only pan line visible	No lines visible or *Pf* and/or *Pv* line(s) visible with or without pan line	Only pan line visible	No lines visible or *Pf* and/or *Pv* line(s) visible with or without pan line

Tests were considered to be positive for *Plasmodium knowlesi* (*Pk*), *Plasmodium malariae* (*Pm*), and *Plasmodium ovale* (*Po*) infections only if pan-only and control lines but no other lines (*Pf*- or *Pv*-specific lines) were visible. Hence, only patients with pure *Pk*, *Pm*, or *Po* monoinfections as verified with microscopic examination or polymerase chain reaction analysis were considered true positives.

Abbreviations: FN, false positive; FP, false positive; Neg, negative; Pan, all *Plasmodium* species; PCR, polymerase chain reaction; *Pf*, *Plasmodium falciparum*; *Pk*, *Plasmodium knowlesi*; *Pm*, *Plasmodium malariae*; *Po*, *Plasmodium ovale*; *Pv*, *Plasmodium vivax*; RDT, rapid diagnostic test; TN, true negative; TP, true positive.

Data from a random sample of 10% of the articles were extracted independently by a second author (A. C.) for quality check. Any inconsistencies were resolved through discussion between two authors, and final arguments were adopted for the rest of the data. Data were later compiled into an Excel spreadsheet for further analysis, cleaned, and cross-checked. Sensitivity and specificity values and confidence intervals were (re-)calculated using the functionalities available in Review Manager (version 5.3; The Cochrane Collaboration) based on true positives (TPs), true negatives (TNs), false negatives (FNs), false positives (FPs), and total case numbers reported in studies. Corrections were made where necessary.

The Quality Assessment of Diagnostic Accuracy Score 2 framework was implemented to assess the methodological quality of individual studies included in the review [20]. Each question was answered with a "yes," "no," or "unclear" response based on the availability of relevant information in a given study and preset criteria (Supplementary Table 5).

Statistical Analysis and Data Synthesis

Studies were grouped according to the detected *Plasmodium* species and different RDT types for comparative analysis. The estimates of the observed sensitivity and specificity per study in each analysis group were visually summarized in a forest plot for easy-to-read visualization of the variabilities in test accuracy among studies and in a scatter plot of sensitivity versus specificity in cases where both sensitivity and specificity values were reported. Plots were drawn using the plot function and the forestplot package in R (version 3.4; R Foundation for Statistical Computing). Because of a scarce number of full reports on 2 × 2 tables, it was not possible to apply a meta-analysis approach to estimate the expected operating points. However, in the *Pk* publications where sample size was ≥25 cases, the estimate of the summary sensitivities per RDT type was derived by meta-analysis using a random-effects model using the metafor package in R. A similar analysis was not undertaken for *Pm* and *Po* studies because of the substantial heterogeneity observed (mostly linked to large confidence intervals owing to small sample sizes). In the absence of statistical pooling, the findings were presented in a narrative form, including tables and figures to aid in data visualization where appropriate.

The use of Cochrane's Q test or Higgins's I^2 statistics is not recommended for the assessment of heterogeneity across diagnostic accuracy studies because they do not take the threshold effect into consideration [21]. Therefore, heterogeneity was assessed by visual inspection of the forest plots. Subgroup analyses based on age, geographical areas, parasite densities, or any other criteria was not possible due to lack of complete data.

RESULTS

Results of the Search

The initial search allowed the identification of 1080 publications. After removing duplicates, 661 titles were left for screening. Title and abstract screening resulted in the exclusion of 474 titles. The full text of 187 titles was assessed for their eligibility, and 155 of these were excluded. An additional 16 titles, for which the full text was not available, were also excluded. The most common reason for exclusion was the unavailability of data for analysis. Other reasons for exclusion are shown in Figure 2. As a result, 32 articles were included in the review [22–53]. As an additional source of data, articles listed in the references of selected publications were also screened, which resulted in the inclusion of 8 further articles [54–61]. Thus, a total of 40 articles were selected for full data extraction.

Among the 40 articles included in the review, 3 reported on *Pk* [22, 29, 43], 8 on *Pm* [13, 19, 21, 23, 27, 32, 38, 39], 5 on *Po* [23, 25, 30, 31, 54], 1 on *Pk* and *Pm* [32], and 23 on *Pm* and *Po* [24, 26–28, 33, 35–39, 41, 45–47, 49–52, 55–58, 61]. The majority of studies (n = 23) were done in nonendemic settings using samples obtained from imported cases (international travellers

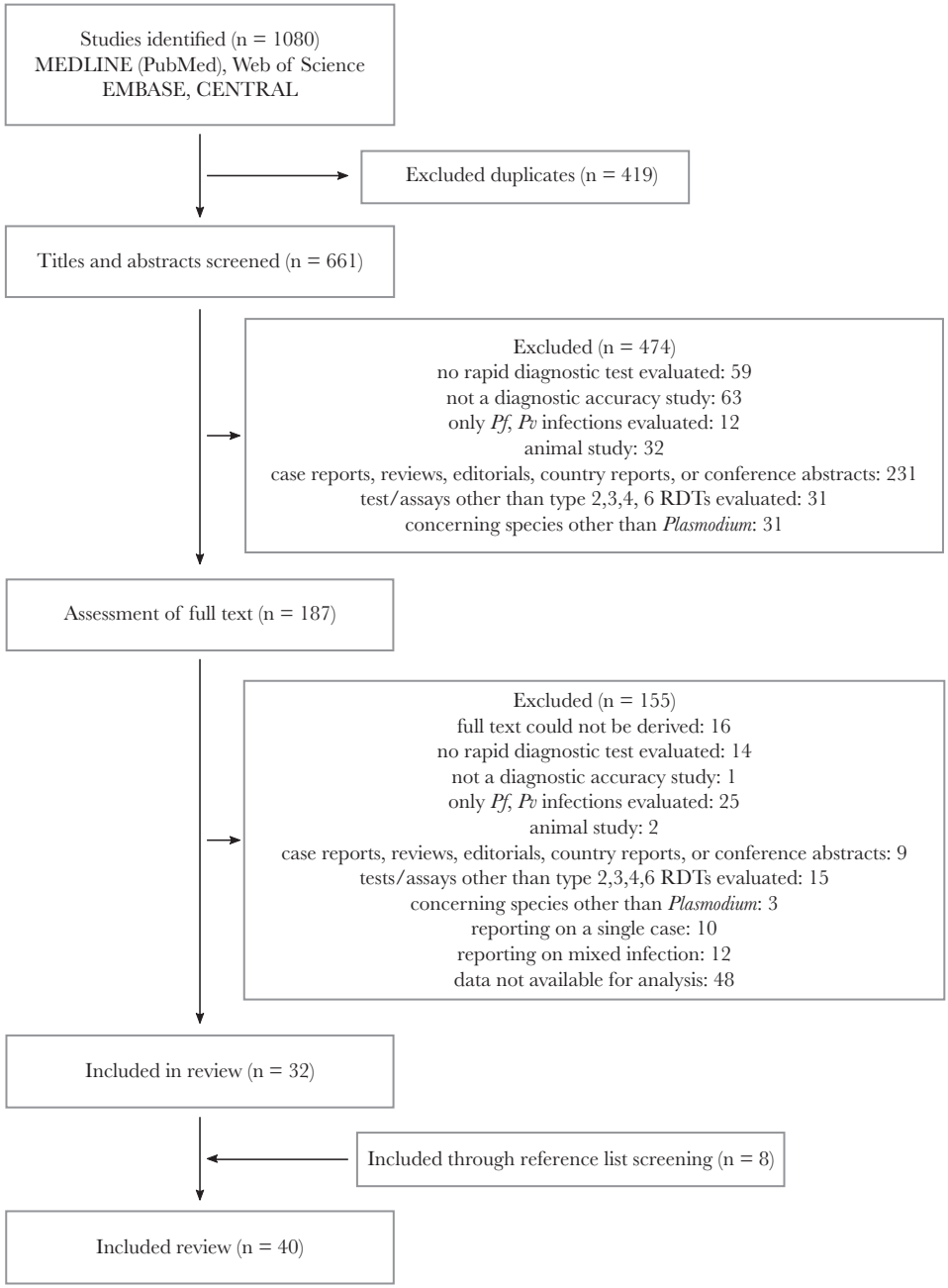


Figure 2. Flow chart of the selection procedure. Forty articles were included in the review. Abbreviations: *Pf*, *Plasmodium falciparum*; *Pv*, *Plasmodium vivax*; RDT, rapid diagnostic test.

or migrants) [23, 24, 26, 28, 30, 33, 35–39, 45, 47, 49–52, 54–58, 61]. Sixteen studies were conducted in endemic settings [22, 25, 29, 31, 32, 34, 40–44, 46, 48, 53, 59, 60]. One study conducted two independent evaluations; one in a nonendemic area and the other in an endemic area [27].

All studies on *Pk*, with the exception of 1, reported on the parasite density estimated in patients, which ranged from 10 parasites per microliter of blood (p/μL) to 911 616 p/μL. The upper range of parasitemia estimated in *Pm*- and *Po*-infected patients did not exceed 9900 p/μL and 16 930 p/μL, respectively.

Methodological Quality of Included Studies

Methodological quality of selected studies varied highly (Figure 3; Supplementary Figure 1). A total number of 25 studies had a cross-sectional design, and 14 used a case–control design. One study did not describe the study design [42]. Three studies tested both archived and fresh samples [29, 35, 38]. In another three studies, the storage conditions of samples prior to testing remained unclear [33, 42, 54]. Among 34 studies that used freshly obtained samples, 14 used consecutive or random enrollment of patients. The rest either failed to

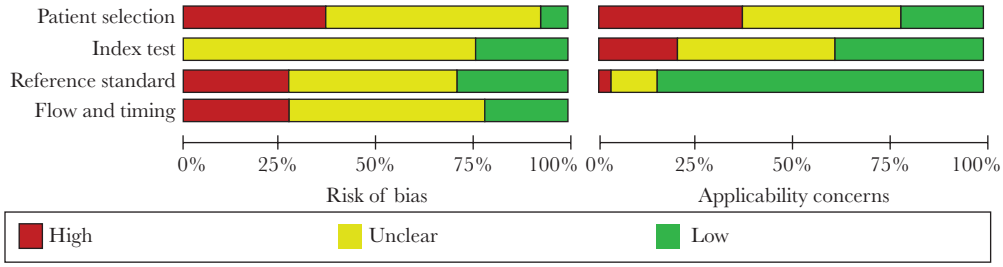


Figure 3. Methodological quality assessment of 40 studies included in the review. Reviewers' assessment of four key domains—patient selection, index test, reference standard, and flow and timing—of the Quality Assessment of Diagnostic Accuracy Score 2 tool is presented in stack bars as the proportion of studies with high/unclear/low risk of bias and with high/clear/low concerns regarding applicability [13].

report on the sampling method or applied convenience sampling. Microscopic examination was used as reference standard in 36 studies, of which 15 used PCR to confirm the species. The remaining 4 studies relied solely on PCR as a reference standard. The level of expertise of microscopists was mentioned in 23 studies, of which 14 engaged >1 microscopist. Only 14 of 40 studies provided adequate data to retrieve full 2×2 tables.

Performance of Rapid Diagnostic Tests with *Plasmodium knowlesi* Monoinfections

All four studies reporting on the performance of RDTs in detecting *Pk* were explicitly designed for this purpose [22, 29, 32, 43]. All studies were undertaken in Malaysia and had a case–control design. One study evaluated both fresh and archived samples [29], whereas the other three relied only on fresh samples. In total, six different test brands were evaluated with different RDT types: two type 2, two type 3, one type 4, and one type 6 RDT. Sensitivities of the tests ranged 0%–74% (Figure 4A). Among all studies, only one study, which assessed two different RDT types, reported on both sensitivity and specificity estimates (Figure 4B) [32].

Sensitivities of type 2 RDTs used for *Pk* detection ranged 23%–29%. Based on analysis of 165 *Pk* cases in three independent evaluations, the summary estimate of sensitivity was 24% (95% confidence interval [CI], 18%–30%) [22, 29]. All fresh samples that tested positive for *Pk* with a type 2 RDT had parasite counts >4412 p/μL of blood [22, 29]. On the other hand, archived samples that were positive for *Pk* had a wide range of *Pk* parasitemia (one RDT positive sample with a parasite density <500 p/μL, four between 500 and 5000 p/μL, and five samples >5000 p/μL) [29].

Sensitivities of type 3 RDTs in *Pk* detection ranged 28%–74%. The meta-analyzed summary estimate of sensitivity was 48% (95% CI, 22%–75%). The summary estimate of sensitivity for type 4 RDTs was 12% (95% CI, 0%–25%), whereas for type 6 RDTs it was 2% (95% CI, 0%–5%).

Performance of Rapid Diagnostic Tests with *Plasmodium malariae* Monoinfections

The median number of *Pm* cases tested in 32 studies was 5 (range, 2–31) (Figure 5A). *Plasmodium malariae* infections were reported in Africa (Cameroon, Uganda, Madagascar, and Mali), Asia (India, Malaysia, and Thailand), and South America (Venezuela). Overall, 12 studies reported on both sensitivity and specificity estimates, as shown in Figure 5B.

Four different type 2 RDT brands were assessed for their accuracy in detecting *Pm* infections in 15 studies. Six studies, which evaluated 27 *Pm* cases in total using 3 different brands, reported sensitivities as 0% [33, 34, 45, 55, 58, 59]. The highest sensitivity reported was 80% (95% CI, 28%–99%), as estimated by evaluating 5 *Pm* cases [53]. Specificities of type 2 RDTs as reported in seven studies ranged 42%–99% [27, 28, 45, 47, 53, 58, 61].

Independent evaluations of nine different type 3 RDT brands in nine studies were carried out [26, 27, 32, 37, 39, 46, 48, 50, 52]. In total, 84 archived samples and 26 fresh samples were tested. Sensitivities ranged 14%–100%. A total of three different type 4 RDT brands, which were assessed in 16 studies, showed a similarly wide range of sensitivities (range, 0%–100%) [26, 32, 35, 36, 38–42, 44, 49, 55–58, 60]. Only two studies evaluated type 6 RDTs for their performance in detecting *Pm* infections [36, 51]. One study carried out evaluations using two different brands [36]. Sensitivities ranged 32%–67%.

Performance of Rapid Diagnostic Tests with *Plasmodium ovale* Monoinfections

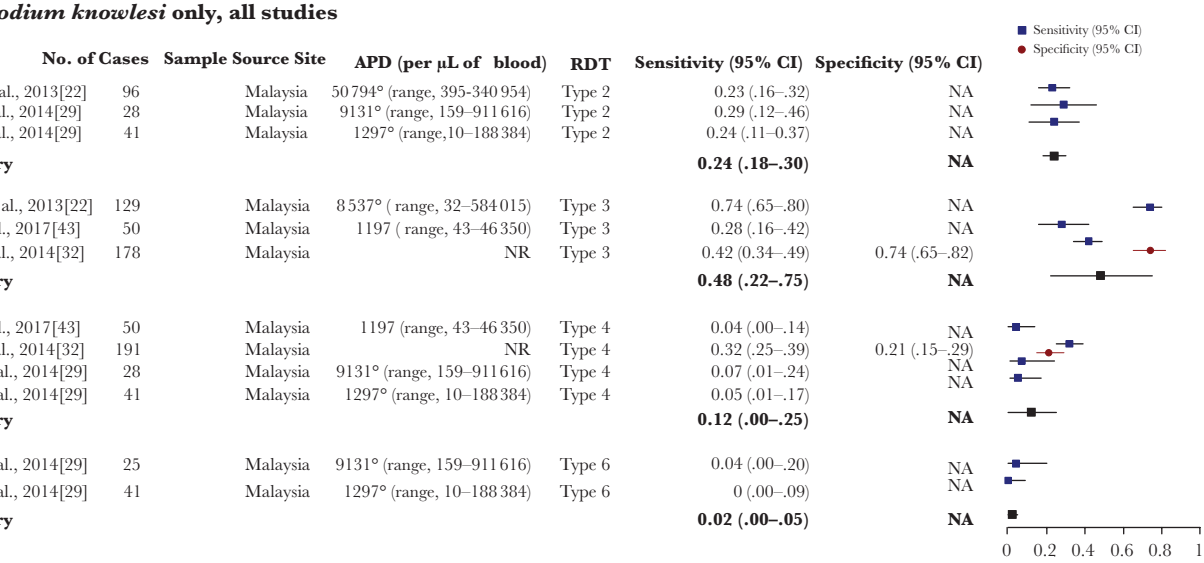
Twenty-eight studies evaluated RDTs with *Po* infections mostly acquired in Africa (Ethiopia, Mali, Gabon) and Asia (India, Thailand) (Figure 6A). Thirteen studies reported on both sensitivity and specificity estimates (Figure 6B).

Seventeen studies evaluated type 2 RDTs for their performance in detection of *Po* mono-infections [23–25, 27, 28, 30, 33, 36, 45, 47, 49, 54–56, 58, 61]. The RDTs used in 5 studies failed to detect any of the *Po* infections in a total of 23 fresh samples positive for *Po* [45, 49, 55, 58, 61]. The rest of the evaluations showed a wide range of sensitivities (range, 20%–100%].

Among 10 studies that evaluated type 3 RDTs, three tested three different brands with a relatively large number of cases (n = 73–80) [37, 50, 52]. Sensitivities in two of these studies were low (18% and 19%) [37, 52], whereas the third study reported a comparatively higher sensitivity (76%) [50]. By contrast, the type 3 tests used in three other studies failed to detect any of the *Po* infections [31, 35, 46]. One study compared the

A ***Plasmodium knowlesi* only, all studies**

Study	No. of Cases	Sample Source Site	APD (per μL of blood)	RDT	Sensitivity (95% CI)	Specificity (95% CI)
Barber et al., 2013[22]	96	Malaysia	50 794° (range, 395-340 954)	Type 2	0.23 (.16–.32)	NA
Foster et al., 2014[29]	28	Malaysia	9131° (range, 159–911 616)	Type 2	0.29 (.12–.46)	NA
Foster et al., 2014[29]	41	Malaysia	1297° (range,10–188 384)	Type 2	0.24 (.11–0.37)	NA
Summary					**0.24 (.18–.30)**	**NA**
Barber et al., 2013[22]	129	Malaysia	8 537° (range, 32–584 015)	Type 3	0.74 (.65–.80)	NA
Piera et al., 2017[43]	50	Malaysia	1197 (range, 43–46 350)	Type 3	0.28 (.16–.42)	NA
Grigg et al., 2014[32]	178	Malaysia	NR	Type 3	0.42 (0.34–.49)	0.74 (.65–.82)
Summary					**0.48 (.22–.75)**	**NA**
Piera et al., 2017[43]	50	Malaysia	1197 (range, 43–46 350)	Type 4	0.04 (.00–.14)	NA
Grigg et al., 2014[32]	191	Malaysia	NR	Type 4	0.32 (.25–.39)	0.21 (.15–.29)
Foster et al., 2014[29]	28	Malaysia	9131° (range, 159–911 616)	Type 4	0.07 (.01–.24)	NA
Foster et al., 2014[29]	41	Malaysia	1297° (range, 10–188 384)	Type 4	0.05 (.01–.17)	NA
Summary					**0.12 (.00–.25)**	**NA**
Foster et al., 2014[29]	25	Malaysia	9131° (range, 159–911 616)	Type 6	0.04 (.00–.20)	NA
Foster et al., 2014[29]	41	Malaysia	1297° (range, 10–188 384)	Type 6	0 (.00–.09)	NA
Summary					**0.02 (.00–.05)**	**NA**



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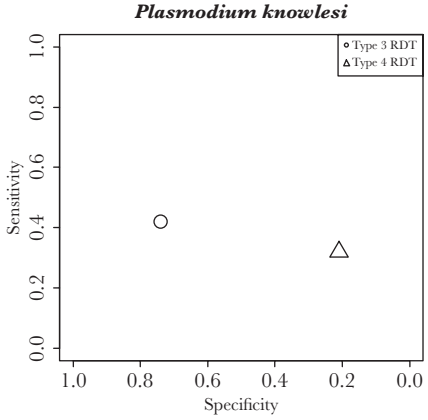


Figure 4. Performance of malaria rapid diagnostic tests (RDTs) for the detection of *Plasmodium knowlesi* mono-infections in human blood. *A*, Forest plot of sensitivity and specificity of RDT types for detection of *Plasmodium knowlesi* (*Pk*) infections. Studies are ordered by sample source site and study ID. *B*, Plot of sensitivity versus specificity as estimated in studies that report on both. Abbreviations: APD, average parasite density of *Pk* cases (° median parasite density); CI, confidence interval; NA, not available; NR, not reported; RDT, rapid diagnostic test.

performances of five different brands using the same set of samples, and, in this case, the sensitivities ranged 7%–100% [39].

Type 4 RDTs were evaluated with *Po* in 12 studies [26, 33, 35, 36, 38, 39, 41, 49, 55–58]. Two studies, which tested 30 and 69 *Po*-positive archived samples, respectively, using two different brands, showed sensitivities of 80% (95% CI, 61%–92%) and 32% (95% CI, 21%–44%), respectively [35, 38]. The number of cases used in the rest of the evaluations did not exceed 18, and sensitivities ranged 0%–77%. Two different brands of type 6 RDTs were, on the other hand, evaluated in two independent studies [36, 51]. One study used archived samples [51], whereas the other used fresh samples [36]. Sensitivity was 5% (95% CI, 2%–13%) when archived samples were tested and 44% (95% CI, 22%–69%) when fresh samples were tested.

DISCUSSION

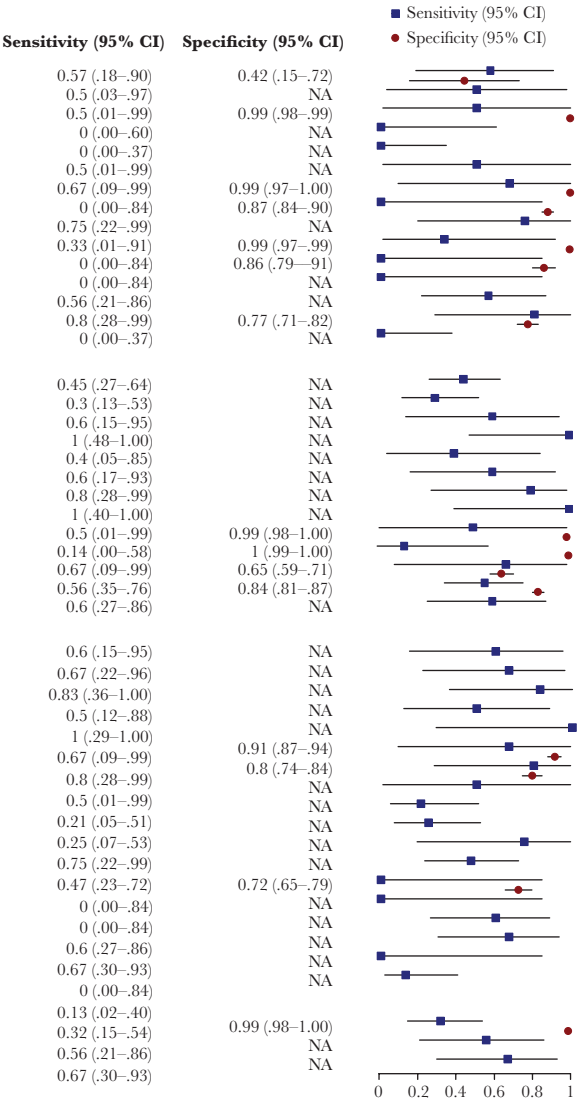
To our knowledge, this review is the first attempt to summarize the available data on the performance of RDTs for the detection of monoinfections due to neglected *Plasmodium* species *Pk*, *Pm*, and *Po* in endemic and nonendemic settings. Summary estimates of sensitivities of type 2, 3, 4, and 6 tests in detecting *Pk* infections were 24%, 48%, 12%, and 2%, respectively. Sensitivities of any RDT types included in the review range from no detection to 100% for *Pm* and *Po* monoinfections. Evidence overall is weak, mainly because of few studies available for *Pk* and highly heterogeneous results obtained from a small number of cases for *Pm* and *Po*. Nonetheless, the current data are still suggestive of low performance of currently available RDTs to detect *Pk*, *Pm*, and *Po* infections.

Similar variable performance of RDTs has previously been demonstrated in the frame of the FIND-WHO global RDT evaluation program [62], although evaluations in this program have been done so far with *Pf* and *Pv* clinical samples only. Annual reports from this program are currently guiding WHO and Global Fund recommendations for procurement of RDTs in endemic settings and are part of the prequalification process

A

***Plasmodium malariae* only, all studies**

Study	No. of Cases	Sample Source Site	APD(per μL of blood)	RDT	Sensitivity (95% CI)	Specificity (95% CI)
Ruas et al., 2017[47]*	7	Africa	NR	Type 2	0.57 (.18–.90)	0.42 (.15–.72)
Bourgeois et al., 2009[24]	2	Africa	NR	Type 2	0.5 (.03–.97)	NA
Eibach et al., 2013b[27]	2	Africa	NR	Type 2	0.5 (.01–.99)	0.99 (.98–.99)
Proux et al., 2001[59]	4	Asia	824 (range, 80-2816)	Type 2	0 (.00–.60)	NA
Haanshuus et al., 2016[34]	9	Asia	NR	Type 2	0 (.00–.37)	NA
Tanizaki et al., 2014[49]*	2	NR	NR	Type 2	0.5 (.01–.99)	NA
Farcas et al., 2003[28]*	3	NR	NR	Type 2	0.67 (.09–.99)	0.99 (.97–1.00)
Richter et al., 2004[45]	2	NR	NR	Type 2	0 (.00–.84)	0.87 (.84–.90)
De Monbrison et al., 2004[56]	4	NR	NR	Type 2	0.75 (.22–.99)	NA
Wiese et al., 2006[61]	3	NR	NR	Type 2	0.33 (.01–.91)	0.99 (.97–.99)
Playford et al ., 2002[58]	2	NR	555(range, 340-770)	Type 2	0 (.00–.84)	0.86 (.79—91)
Iqbal et al., 2002[55]	2	NR	NR	Type 2	0 (.00–.84)	NA
Houzé et al., 2013[36]	9	NR	NR	Type 2	0.56 (.21–.86)	NA
Wongsrichanalai et al., 2003[53]	5	NR	NR	Type 2	0.8 (.28–.99)	0.77 (.71–.82)
Grobusch et al., 2002[33]	8	NR	NR	Type 2	0 (.00–.37)	NA
Vander Palen et al., 2009[50]*	31	Africa	NR	Type 3	0.45 (.27–.64)	NA
Maltha et al., 2010[37]*	23	Africa	NR	Type 3	0.3 (.13–.53)	NA
Maltha et al., 2013[39]*	5	Africa	382 (range, 26–1920)	Type 3	0.6 (.15–.95)	NA
Maltha et al., 2013[39]*	5	Africa	382 (range, 26–1920)	Type 3	1 (.48–1.00)	NA
Maltha et al., 2013[39]*	5	Africa	382 (range, 26–1920)	Type 3	0.4 (.05–.85)	NA
Maltha et al., 2013[39]*	5	Africa	382 (range, 26–1920)	Type 3	0.6 (.17–.93)	NA
Maltha et al., 2013[39]*	5	Africa	382 (range, 26–1920)	Type 3	0.8 (.28–.99)	NA
Tahar et al., 2013[48]	4	Africa	NR (range, 1130–7650)	Type 3	1 (.40–1.00)	NA
Eibach et al., 2013b[27]	2	Africa	NR	Type 3	0.5 (.01–.99)	0.99 (.98–1.00)
Roh et al., 2017[46]	7	Africa	NR	Type 3	0.14 (.00–.58)	1 (.99–1.00)
Grigg et al., 2014[32]*	3	Asia	NR	Type 3	0.67 (.09–.99)	0.65 (.59–.71)
van Dijk et al., 2010[52]*	25	NR	NR	Type 3	0.56 (.35–.76)	0.84 (.81–.87)
Cnops et al., 2011[26]	10	NR	NR	Type 3	0.6 (.27–.86)	NA
Maltha et al., 2013[39]*	5	Africa	382 (range, 26–1920)	Type 4	0.6 (.15–.95)	NA
Ratsimbasoa et al., 2007[60]	6	Africa	NR	Type 4	0.67 (.22–.96)	NA
Ratsimbasoa et al., 2007[60]	6	Africa	NR	Type 4	0.83 (.36–1.00)	NA
Ratsimbasoa et al., 2007[60]	6	Africa	NR	Type 4	0.5 (.12–.88)	NA
Randrianasolo et al., 2007[44]	3	Africa	NR	Type 4	1 (.29–1.00)	NA
Grigg et al., 2014[32]*	3	Asia	NR	Type 4	0.67 (.09–.99)	0.91 (.87–.94)
Pattanasin et al., 2003[41]	5	Asia	NR	Type 4	0.8 (.28–.99)	0.8 (.74–.84)
Tanizaki et al., 2014[49]*	2	NR	NR	Type 4	0.5 (.01–.99)	NA
Maltha et al., 2011[38]**	14	NR	645 (range, 0.1–9900)	Type 4	0.21 (.05–.51)	NA
Heutmekers et al., 2012[35]**	16	NR	473 (range, 0.1–6096)	Type 4	0.25 (.07–.53)	NA
De Monbrison et al., 2004[56]	4	NR	NR	Type 4	0.75 (.22–.99)	NA
Moody et al., 2000[57]	17	NR	NR	Type 4	0.47 (.23–.72)	0.72 (.65–.79)
Playford et al., 2002[58]	2	NR	555 (range, 340–770)	Type 4	0 (.00–.84)	NA
Iqbal et al., 2002[55]	2	NR	NR	Type 4	0 (.00–.84)	NA
Cnops et al., 2011[26]	10	NR	NR	Type 4	0.6 (.27–.86)	NA
Houzé et al., 2013[36]	9	NR	NR	Type 4	0.67 (.30–.93)	NA
Penhalbel et al., 2005[42]**	2	NR	NR	Type 4	0 (.00–.84)	
Metzger et al., 2008[40]	15	South America	87 (range, 3–977)	Type 4	0.13 (.02–.40)	
van Dijk et al., 2009[51]*	25	NR	NR	Type 6	0.32 (.15–.54)	0.99 (.98–1.00)
Houzé et al., 2013[36]	9		NR	Type 6	0.56 (.21–.86)	NA
Houzé et al., 2013[36]	9	NR	NR	Type 6	0.67 (.30–.93)	NA



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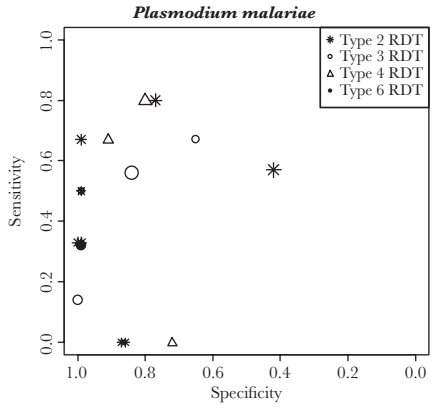
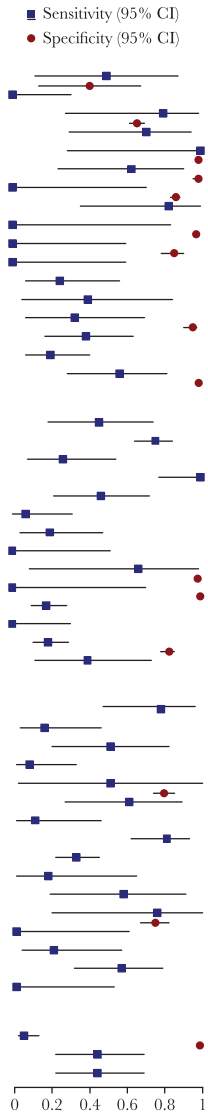


Figure 5. Performance of malaria rapid diagnostic tests (RDTs) for the detection of *Plasmodium malariae* mono-infections in human blood. *A*, Forest plot of sensitivity and specificity of RDT types for detection of *Plasmodium malariae* (*PM*) infections. Studies are ordered by RDT type, sample source site, study design, and study ID. Studies listed have cross-sectional design unless marked with * for case–control design or with ** for unclear design. *B*, Plot of sensitivity versus specificity as estimated in studies that report on both. Size of symbols corresponds to the number of cases evaluated in each study. Abbreviations: APD, average parasite density of *Pk* cases (° median parasite density); CI, confidence interval; NA, not available; NR, not reported; RDT, rapid diagnostic test.

A

***Plasmodium ovale* only, all studies**

Study	No. of Cases	Sample Source Site	APD (per μL of blood)	RDT	Sensitivity (95% CI)	Specificity (95% CI)
Ruas et al., 2017*	6	Africa	NR	Type 2	0.5 (.12–.88)	0.38 (.14–.68)
Tanizaki et al., 2014*	10	Africa	1550	Type 2	0 (.00–.31)	NA
Bouyou Akotet et al., 2013	5	Africa	924 (range, 507–1473)	Type 2	0.8 (.28–.99)	0.66 (.62–.70)
Bourgeois et al., 2009	7	Africa	NR	Type 2	0.71 (.30–.95)	NA
Eibach et al., 2013b	3	Africa	NR	Type 2	1 (.29–1.00)	0.99 (.97–1.00)
Farcas et al., 2003*	9	NR	NR	Type 2	0.63 (.24–.91)	0.99 (.96–1.00)
Richter et al., 2004	3	NR	NR	Type 2	0 (.00–.71)	0.87 (.84–.89)
De Monbrison et al., 2004	6	NR	NR	Type 2	0.83 (.37–.99)	NA
Wiese et al., 2006	2	NR	NR	Type 2	0 (.00–.84)	0.98 (.97–.99)
Playford et al., 2002	4	NR	NR (range, 630–16 930)	Type 2	0 (.00–.60)	0.86 (.79–.91)
Iqbal et al., 2002	4	NR	NR	Type 2	0 (.00–.60)	NA
Bigaillon et al., 2005	12	NR	NR	Type 2	0.25 (.07–.57)	NA
Gatti et al., 2006	5	NR	NR	Type 2	0.4 (.07–.83)	NA
Eibach et al., 2013a	9	NR	NR	Type 2	0.33 (.07–.70)	0.96 (.91–.98)
Houzé et al., 2013	18	NR	NR	Type 2	0.39 (.17–.64)	NA
Grobusch et al., 2002	25	NR	NR	Type 2	0.2 (.07–.41)	NA
Durand et al., 2005	14	NR	NR	Type 2	0.57 (.29–.82)	0.99 (.96–1.00)
Maltha et al., 2011**	13	Africa	1904 (range, 51–5310)	Type 3	0.46 (.19–.75)	NA
Van der Palen et al., 2009*	80	Africa	NR	Type 3	0.76 (.65–.85)	NA
Maltha et al., 2013*	15	Africa	817.5 (range, 51–5930)	Type 3	0.27 (.08–.55)	NA
Maltha et al., 2013*	15	Africa	817.5 (range, 51–5930)	Type 3	1 (.78,1.00)	NA
Maltha et al., 2013*	15	Africa	817.5 (range, 51–5930)	Type 3	0.47 (.22–.73)	NA
Maltha et al., 2013*	15	Africa	817.5 (range, 51–5930)	Type 3	0.07 (.00–.32)	NA
Maltha et al., 2013*	15	Africa	817.5 (range, 51–5930)	Type 3	0.2 (.04–.48)	NA
Getnet et al., 2015	5	Africa	NR	Type 3	0 (.00–.52)	NA
Eibach et al., 2013b	3	Africa	NR	Type 3	0.67 (.09–.99)	0.99 (.98–1.00)
Roh et al., 2017	3	Africa	NR	Type 3	0 (.00–.71)	1 (.99–1.00)
Maltha et al., 2010*	76	Africa; Asia; America	NR	Type 3	0.18 (.10–.29)	NA
Heutmekers et al., 2012**	10	NR	858 (range, 22–7292)	Type 3	0 (.00–.31)	NA
van Dijk et al., 2010*	73	NR	NR	Type 3	0.19 (.11–.30)	0.83 (.79–.86)
Cnops et al., 2011	10	NR	NR	Type 3	0.4 (.14–.73)	NA
Maltha et al., 2011**	13	Africa	1904 (range, 51–5310)	Type 4	0.77 (.46–.95)	NA
Maltha et al., 2011**	13	Africa	1904 (range, 51-5310)	Type 4	0.15 (.02–.45)	NA
Tanizaki et al., 2014*	10	Africa	1,550	Type 4	0.5 (.19–.81)	NA
Maltha et al., 2013*	15	Africa	817.5 (range, 51–5930)	Type 4	0.07 (.00–.32)	NA
Pattanasin et al., 2003	2	Asia	NR	Type 4	0.5 (.01–.99)	0.79 (.73–.84)
Heutmekers et al., 2012**	10	NR	858 (range, 22–7292)	Type 4	0.6 (.26–.88)	NA
Heutmekers et al., 2012**	10	NR	858 (range, 22–7292)	Type 4	0.1 (.00–.45)	NA
Maltha et al., 2011**	30	NR	1331 (range, 19–5930)	Type 4	0.8 (.61–.92)	NA
Heutmekers et al., 2012**	69	NR	974 (range, 10–10 000)	Type 4	0.32 (.21–.44)	NA
De Monbrison et al., 2004	6	NR	NR	Type 4	0.17 (.01–.64)	NA
Moody et al., 2000	7	NR	NR	Type 4	0.57 (.18–.90)	NA
Playford et al., 2002	4	NR	NR (range, 630–16 930)	Type 4	0.75 (.19–.99)	0.74 (.66–.81)
Iqbal et al., 2002	4	NR	NR	Type 4	0 (.00–.60)	NA
Cnops et al., 2011	10	NR	NR	Type 4	0.2 (.04–.56)	NA
Houzé et al., 2013	18	NR	NR	Type 4	0.56 (.31–.78)	NA
Grobusch et al., 2002	5	NR	NR	Type 4	0 (.00–.52)	NA
van Dijk et al., 2009*	73	NR	NR	Type 6	0.05 (.02–.13)	0.99 (.97–.99)
Houzé et al., 2013	18	NR	NR	Type 6	0.44 (.22–.69)	NA
Houzé et al., 2013	18	NR	NR	Type 6	0.44 (.22–.69)	NA



B

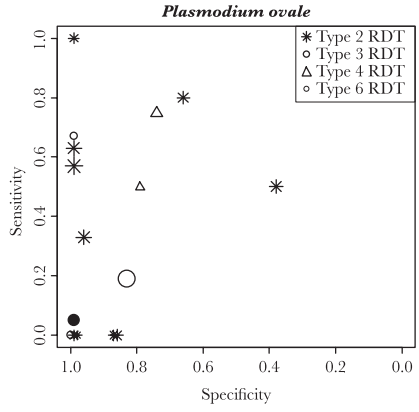


Figure 6. Performance of malaria rapid diagnostic tests (RDTs) for the detection of *Plasmodium ovale* mono-infections in human blood. *A*, Forest plot of sensitivity and specificity of RDT types for detection of *Plasmodium ovale* (*Po*) infections. Studies are ordered by sample source site, study design, and study ID. Studies listed have cross-sectional design unless marked with * for case–control design or with ** for unclear design. Eibach et al [27] has been designated as 2013a and 2013b to distinguish between the first part of the study (2013a), which was conducted in a nonendemic setting, and the second part of the study (2013b), which was conducted in an endemic setting. *B*, Plot of sensitivity versus specificity as estimated in studies that report on both. Size of symbols corresponds to the number of cases evaluated in each study. Abbreviations: APD, average parasite density of *Pk* cases (° median parasite density); CI, confidence interval; NA, not available; NR, not reported; RDT, rapid diagnostic test.

at WHO. Expanding the evaluation to *Pk*, *Pm*, and *Po* clinical samples would not only provide additional RDT performance data but would also guide countries in the selection of the most appropriate RDTs for their epidemiological context.

There is evidence demonstrating that *Pm* and *Po* infections commonly occur as coinfections with *Pf* [4, 63], which would facilitate indirect treatment of malaria due to these species. In fact, if a patient is diagnosed as having malaria due to *Pf*, treatment with artemisinin-based combination therapies (ACTs) could eventually eliminate any coinfection even if it is not specifically detected by microscopy or RDT [64]. However, this would not be the case for *Pv* and *Po* coinfections, for which primaquine would be needed to eliminate hypnozoites. There are currently no RDTs specific to *Pk*, *Pm*, or *Po* infections. Rapid diagnostic tests that are capable of identifying these infections rely on the detection of antigens that are common to all *Plasmodium* species. It has also been shown that *Pk* cross-reacts with *Pf*- and *Pv*-specific pLDH [32, 65]. Thereby, the nonspecific nature of these tests precludes the differentiation of non-*falciparum* species as well as the confirmation of mixed infections. Given the presumed low prevalence and/or limited geographical spread of these species, there is not much effort on the part of RDT manufacturers to develop species-specific tests. However, species-specific RDTs would likely play a pivotal role for case management and epidemiological purposes in the detection of *Pk*, *Pm*, and *Po* infections in resource-limited settings.

Microscopy continues to be the gold standard for malaria diagnosis. However, it is imperfect, especially when it comes to species differentiation [22, 66, 67]. In this review, more than half of the studies (n = 21) relied solely on microscopy for *Plasmodium* detection and species differentiation. Therefore, there is a risk that some of the discordant results in the included studies were misqualified due to the imperfect nature of the reference standard. *Po* and *Pm* infections usually occur at very low parasitemia, which hinders, even more, its detection by microscopy and current RDTs. Similarly, *Pk* infections can occur at low parasitemia as well. Therefore, improved analytical sensitivity should be one of the first requirements when considering the development of new RDTs able to detect clinically significant infections due to *Pk*, *Pm*, and *Po*.

A thorough and comprehensive literature search allowed the identification of 32 studies, and an additional 8 studies were identified by screening the references of included studies, which suggests that some potentially eligible studies could be missed through our search strategy. Potential reasons for this could be the poor indexing of diagnostic accuracy studies and the fact that our search was designed to identify neglected *Plasmodium* infections, which were often not the primary target of studies and therefore were not explicitly mentioned in titles and abstracts. Nevertheless, studies evaluating the performance of diagnostic tests for the detection of these *Plasmodium* species are scarce and, when performed, suboptimal. Appropriately designed studies with an explicit focus on the diagnosis of these three neglected non-*falciparum* species are urgently needed. Such efforts would not only contribute to a better understanding of the performance of current tests but also guide the development of improved diagnostic tools for malaria while shedding light on the actual geographical distribution and epidemiological situation of malaria caused by these *Plasmodium* species.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (http://jid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. World Health Organization. World malaria report 2017 http://apps.who.int/iris/bitstream/10665/259492/1/9789241565523-eng.pdf. Accessed 19 February 2018.
2. Hay SI, Guerra CA, Tatem AJ, Noor AM, Snow RW. The global distribution and population at risk of malaria: past, present, and future. Lancet Infect Dis **2004**; 4:327–36.
3. Sutherland CJ, Tanomsing N, Nolder D, et al. Two nonrecombining sympatric forms of the human malaria parasite *Plasmodium ovale* occur globally. J Infect Dis **2010**; 201:1544–50.
4. Rutledge GG, Böhme U, Sanders M, et al. *Plasmodium malariae* and *P. ovale* genomes provide insights into malaria parasite evolution. Nature **2017**; 542:101–4.
5. Ta TH, Hisam S, Lanza M, Jiram AI, Ismail N, Rubio JM. First case of a naturally acquired human infection with *Plasmodium cynomolgi*. Malar J **2014**; 13:68.
6. Singh B, Daneshvar C. Human infections and detection of *Plasmodium knowlesi*. Clin Microbiol Rev **2013**; 26:165–84.
7. Facer CA, Rouse D. Spontaneous splenic rupture due to *Plasmodium ovale* malaria. Lancet **1991**; 338:896.
8. Lau YL, Lee WC, Tan LH, et al. Acute respiratory distress syndrome and acute renal failure from *Plasmodium ovale* infection with fatal outcome. Malar J **2013**; 12:389.

9. Naqvi R, Ahmad E, Akhtar F, Naqvi A, Rizvi A. Outcome in severe acute renal failure associated with malaria. Nephrol Dial Transplant **2003**; 18:1820–3.
10. Douglaes NM, Lampah DA, Kenangalem E, et al. Major burden of severe anemia from non-*falciparum* malaria species in Southern Papua: a hospital-based surveillance study. PLoS Med **2013**; 10:e1001575; discussion e1001575.
11. Langford S, Douglas NM, Lampah DA, et al. *Plasmodium malariae* infection associated with a high burden of anemia: a hospital-based surveillance study. PLoS Negl Trop Dis **2015**; 9:e0004195.
12. Yusof R, Ahmed MA, Jelip J, et al. Phylogeographic evidence for 2 genetically distinct zoonotic *Plasmodium knowlesi* parasites, Malaysia. Emerg Infect Dis **2016**; 22:1371–80.
13. World Health Organization. World malaria report 2016. http://www.who.int/malaria/publications/world-malaria-report-2016/report/en/. Accessed 4 September 2017.
14. Bell D, Wongsrichanalai C, Barnwell JW. Ensuring quality and access for malaria diagnosis: how can it be achieved? Nat Rev Microbiol **2006**; 4(9 supp):nrmicro1525.
15. Abba K, Kirkham AJ, Olliaro PL, et al. Rapid diagnostic tests for diagnosing uncomplicated non-*falciparum* or *Plasmodium vivax* malaria in endemic countries. Cochrane Database Syst Rev **2014**; 12:CD011431.
16. Doctor SM, Liu Y, Anderson OG, et al. Low prevalence of *Plasmodium malariae* and *Plasmodium ovale* monoinfections among children in the Democratic Republic of the Congo: a population-based, cross-sectional study. Malar J **2016**; 15:350.
17. Molineaux L, Storey J, Cohen JE, Thomas A. A longitudinal study of human malaria in the West African savanna in the absence of control measures: relationships between different *Plasmodium* species, in particular *P. falciparum* and *P. malariae*. Am J Trop Med Hyg **1980**; 29:725–37.
18. Snounou G, Viriyakosol S, Jarra W, Thaithong S, Brown KN. Identification of the four human malaria parasite species in field samples by the polymerase chain reaction and detection of a high prevalence of mixed infections. Mol Biochem Parasitol **1993**; 58:283–92.
19. Snounou G, Pinheiro L, Gonçalves A, et al. The importance of sensitive detection of malaria parasites in the human and insect hosts in epidemiological studies, as shown by the analysis of field samples from Guinea Bissau. Trans R Soc Trop Med Hyg **1993**; 87:649–53.
20. Whiting PF, Rutjes AW, Westwood ME, et al; QUADAS-2 Group. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med **2011**; 155:529–36.
21. Macaskill P, Gatsonis C, Deeks JJ, Harbord RM, Takwoingi Y. Chapter 10: analysing and presenting results. In: Deeks JJ, Bossuyt PM, Gatsonis C, eds. Cochrane handbook for systematic reviews of diagnostic test accuracy version 10. http://srdta.cochrane.org/. Accessed 17 October 2017.
22. Barber BE, William T, Grigg MJ, Piera K, Yeo TW, Anstey NM. Evaluation of the sensitivity of a pLDH-based and an aldolase-based rapid diagnostic test for diagnosis of uncomplicated and severe malaria caused by PCR-confirmed *Plasmodium knowlesi*, *Plasmodium falciparum*, and *Plasmodium vivax*. J Clin Microbiol **2013**; 51:1118–23.
23. Bigaillon C, Fontan E, Cavallo J-D, Hernandez E, Spiegel A. Ineffectiveness of the Binax NOW malaria test for diagnosis of *Plasmodium ovale* malaria. J Clin Microbiol **2005**; 43:1011.
24. Bourgeois N, Boutet A, Bousquet P-J, et al. Comparison of three real-time PCR methods with blood smears and rapid diagnostic test in *Plasmodium* sp. infection. Clin Microbiol Infect **2010**; 16:1305–11.
25. Bouyou Akotet MK, Mawili-Mboumba DP, Madoungou B, Kombila M. Performances of malaria P.f/Pan rapid test device Acon (Pf HRP2/pan aldolase) and malaria Pf rapid test device Acon (Pf HRP2) for the diagnosis of malaria in adults and children living in Gabon, Central Africa. Diagn Microbiol Infect Dis **2013**; 77:58–63.
26. Cnops L, Boderie M, Gillet P, Van Esbroeck M, Jacobs J. Rapid diagnostic tests as a source of DNA for *Plasmodium* species-specific real-time PCR. Malar J **2011**; 10:67.
27. Eibach D, Traore B, Bouchrik M, et al. Evaluation of the malaria rapid diagnostic test VIKIA malaria Ag Pf/Pan in endemic and non-endemic settings. Malar J **2013**; 12:188.
28. Farcas GA, Zhong KJY, Lovegrove FE, Graham CM, Kain KC. Evaluation of the Binax NOW ICT test versus polymerase chain reaction and microscopy for the detection of malaria in returned travelers. Am J Trop Med Hyg **2003**; 69:589–92.
29. Foster D, Cox-Singh J, Mohamad DSA, Krishna S, Chin PP, Singh B. Evaluation of three rapid diagnostic tests for the detection of human infections with *Plasmodium knowlesi*. Malar J **2014**; 13:60.
30. Gatti S, Gramegna M, Bisoffi Z, et al. A comparison of three diagnostic techniques for malaria: a rapid diagnostic test (NOW Malaria), PCR and microscopy. Ann Trop Med Parasitol **2007**; 101:195–204.
31. Getnet G, Getie S, Srivastava M, Birhan W, Fola AA, Noedl H. Diagnostic performance of rapid diagnostic tests for the diagnosis of malaria at public health facilities in north-west Ethiopia. Trop Med Int Health. **2015**; 20:1564–8.
32. Grigg MJ, William T, Barber BE, et al. Combining parasite lactate dehydrogenase-based and histidine-rich protein 2-based rapid tests to improve specificity for diagnosis of malaria due to *Plasmodium knowlesi* and other *Plasmodium* species in Sabah, Malaysia. J Clin Microbiol **2014**; 52: 2053–60.

33. Grobusch MP, Hänscheid T, Zoller T, Jelinek T, Burchard GD. Rapid immunochromatographic malarial antigen detection unreliable for detecting *Plasmodium malariae* and *Plasmodium ovale*. Eur J Clin Microbiol Infect. **2002**; 21:818–20.
34. Haanshuus CG, Chandy S, Manoharan A, et al. A high malaria prevalence identified by PCR among patients with acute undifferentiated fever in India. PloS One **2016**; 11:e0158816.
35. Heutmekers M, Gillet P, Maltha J, et al. Evaluation of the rapid diagnostic test CareStart pLDH Malaria (Pf-pLDH/pan-pLDH) for the diagnosis of malaria in a reference setting. Malar J **2012**; 11:204.
36. Houzé S, Boutron I, Marmorat A, et al. Performance of rapid diagnostic tests for imported malaria in clinical practice: results of a national multicenter study. PloS One **2013**; 8:e75486.
37. Maltha J, Gillet P, Bottieau E, Cnops L, van Esbroeck M, Jacobs J. Evaluation of a rapid diagnostic test (CareStart Malaria HRP-2/pLDH (Pf/pan) Combo Test) for the diagnosis of malaria in a reference setting. Malar J **2010**; 9:171.
38. Maltha J, Gillet P, Cnops L, et al. Evaluation of the rapid diagnostic test SDFK40 (Pf-pLDH/pan-pLDH) for the diagnosis of malaria in a non-endemic setting. Malar J **2011**; 10:7.
39. Maltha J, Gillet P, Heutmekers M, Bottieau E, Van Gompel A, Jacobs J. Self-diagnosis of malaria by travelers and expatriates: assessment of malaria rapid diagnostic tests available on the Internet. PloS One **2013**; 8:e53102.
40. Metzger WG, Vivas-Martínez S, Rodriguez I, et al. Malaria diagnosis under field conditions in the Venezuelan Amazon. Trans R Soc Trop Med Hyg **2008**; 102:20–4.
41. Pattanasin S, Roux S, Chompasuk D, et al. Evaluation of a new *Plasmodium* lactate dehydrogenase assay (OptiMAL-IT (R)) for the detection of malaria. Trans R Soc Trop Med Hyg **2003**; 97:672–4.
42. Penhalbel R de SR, Fugikaha E, Lorenzetti A, et al. Evaluation of an immunochromatography test for malaria diagnosis under different storage conditions. Rev Soc Bras Med Trop **2005**; 38:194–5.
43. Piera KA, Aziz A, William T, Bell D, González IJ, Barber BE, et al. Detection of *Plasmodium knowlesi*, *Plasmodium falciparum* and *Plasmodium vivax* using loop-mediated isothermal amplification (LAMP) in a co-endemic area in Malaysia. Malar J **2017**; 16:29.
44. Randrianasolo L, Tafangy PB, Raharimalala LA, Ratsimbasoa AC, Randriamanantena A, Randrianarivelojosia M. [Rapid diagnostic test for malaria: preliminary study in Madagascar in 2003]. Sante Montrouge Fr **2007**; 17:69–73.
45. Richter J, Göbels K, Müller-Stöver I, Hoppenheit B, Häussinger D. Co-reactivity of plasmodial histidine-rich protein 2 and aldolase on a combined immuno-chromographic-malaria dipstick (ICT) as a potential semi-quantitative marker of high *Plasmodium falciparum* parasitaemia. Parasitol Res **2004**; 94:384–5.
46. Roh ME, Oyet C, Orikiriza P, et al. Asymptomatic *Plasmodium* infections in children in low malaria transmission setting, Southwestern Uganda. Emerg Infect Dis **2016**; 22:1494–8.
47. Ruas R, Pinto A, Nuak J, Sarmento A, Abreu C. Non-*falciparum* malaria imported mainly from Africa: a review from a Portuguese hospital. Malar J **2017**; 16:298.
48. Tahar R, Sayang C, Ngane Foumane V, et al. Field evaluation of rapid diagnostic tests for malaria in Yaounde, Cameroon. Acta Trop **2013**; 125:214–9.
49. Tanizaki R, Kato Y, Iwagami M, et al. Performance of rapid diagnostic tests for *Plasmodium ovale* malaria in Japanese travellers. Trop Med Health **2014**; 42:149–53.
50. Van der Palen M, Gillet P, Bottieau E, Cnops L, Van Esbroeck M, Jacobs J. Test characteristics of two rapid antigen detection tests (SD FK50 and SD FK60) for the diagnosis of malaria in returned travellers. Malar J **2009**; 8:90.
51. van Dijk DPJ, Gillet P, Vlieghe E, Cnops L, van Esbroeck M, Jacobs J. Evaluation of the Palutop+4 malaria rapid diagnostic test in a non-endemic setting. Malar J **2009**; 8:293.
52. van Dijk DPJ, Gillet P, Vlieghe E, Cnops L, Van Esbroeck M, Jacobs J. Evaluation of the Immunoquick+4 malaria rapid diagnostic test in a non-endemic setting. Eur J Clin Microbiol Infect Dis **2010**; 29:577–83.
53. Wongsrichanalai C, Arevalo I, Laoboonchai A, et al. Rapid diagnostic devices for malaria: field evaluation of a new prototype immunochromatographic assay for the detection of *Plasmodium falciparum* and non-*falciparum Plasmodium*. Am J Trop Med Hyg **2003**; 69:26–30.
54. Durand F, Crassous B, Fricker-Hidalgo H, et al. Performance of the Now Malaria rapid diagnostic test with returned travellers: a 2-year retrospective study in a French teaching hospital. Clin Microbiol Infect **2005**; 11:903–7.
55. Iqbal J, Khalid N, Hira PR. Comparison of two commercial assays with expert microscopy for confirmation of symptomatically diagnosed malaria. J Clin Microbiol **2002**; 40:4675–8.
56. De Monbrison F, Gérome P, Chaulet JF, Wallon M, Picot S, Peyron F. Comparative diagnostic performance of two commercial rapid tests for malaria in a non-endemic area. Eur J Clin Microbiol Infect Dis **2004**; 23:784–6.
57. Moody A, Hunt-Cooke A, Gabbett E, Chiodini P. Performance of the OptiMAL malaria antigen capture dipstick for malaria diagnosis and treatment monitoring at the Hospital for Tropical Diseases, London. Br J Haematol **2000**; 109:891–4.
58. Playford EG, Walker J. Evaluation of the ICT malaria P.f/P.v and the OptiMal rapid diagnostic tests for malaria in febrile returned travellers. J Clin Microbiol **2002**; 40:4166–71.

59. Proux S, Hkirijareon L, Ngamngonkiri C, McConnell S, Nosten F. Short communication: Paracheck-Pf: a new, inexpensive and reliable rapid test for *P. falciparum* malaria. Trop Med Int Health **2001**; 6:99–101.
60. Ratsimbasoa A, Randriamanantena A, Raherinjafy R, Rasoarilalao N, Ménard D. Which malaria rapid test for Madagascar? Field and laboratory evaluation of three tests and expert microscopy of samples from suspected malaria patients in Madagascar. Am J Trop Med Hyg **2007**; 76:481–5.
61. Wiese L, Bruun B, Baek L, et al. Bedside diagnosis of imported malaria using the Binax Now malaria antigen detection test. Scand J Infect Dis **2006**; 38:1063–8.
62. World Health Organization. Malaria rapid diagnostic test performance: results of WHO product testing of malaria RDTs: round 7 (2015–2016). Geneva, Switzerland: World Health Organization, **2017**.
63. Dinko B, Oguike MC, Larbi JA, Bousema T, Sutherland CJ. Persistent detection of *Plasmodium falciparum*, *P. malariae*, *P. ovale curtisi* and *P. ovale wallikeri* after ACT treatment of asymptomatic Ghanaian school-children. Int J Parasitol Drugs Drug Resist **2013**; 3:45–50.
64. World Health Organization. Guidelines for the treatment of malaria. 3rd ed. http://www.who.int/malaria/publications/atoz/9789241549127/en/. Accessed 18 September 2017.
65. McCutchan TF, Piper RC, Makler MT. Use of malaria rapid diagnostic test to identify *Plasmodium knowlesi* infection. Emerg Infect Dis **2008**; 14:1750–2.
66. Johnston SP, Pieniazek NJ, Xayavong MV, Slemenda SB, Wilkins PP, da Silva AJ. PCR as a confirmatory technique for laboratory diagnosis of malaria. J Clin Microbiol **2006**; 44:1087–9.
67. Obare P, Ogutu B, Adams M, et al. Misclassification of *Plasmodium* infections by conventional microscopy and the impact of remedial training on the proficiency of laboratory technicians in species identification. Malar J **2013**; 12:113.