Systematic Review and Meta-analysis of Diagnostic Accuracy of Percutaneous Renal Tumour Biopsy

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Systematic review and meta-analysis of diagnostic accuracy of Loop-mediated isothermal amplification (LAMP) methods compared to microscopy, PCR, and rapid diagnostic tests, for malaria diagnosis

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Abstract

Background

Diagnosis is a challenging issue in the way to malaria elimination. LAMP could be an alternative to conventional methods. Then, it is of interest to evaluate the diagnostic accuracy of LAMP for malaria compared to microscopy, PCR, and RDTs.

Methods and design

We searched MEDLINE, Web of Science, and Scopus, from inception to 1st July 2019. Prospective and retrospective, randomized and non-randomized, mono-center and multi-center studies, including symptomatic or asymptomatic patients that reported one LAMP method and one comparator (microscopy, RDT, PCR) were included. PROSPERO registration number: CRD42017075186.

Results

Sixty-six studies published between 2006 and 2019 were included leading to the analysis of 30 641 LAMP tests. The pooled sensitivity of LAMP remained between 96 and 98% whatever the comparator. The pooled specificity of LAMP was around 95%, but is a little higher if best PCR studies are considered. AUC were found to be above 0.98 whatever the subgroup of studies considered and DOR to be around 1000 for all subgroups except for *Plasmodium vivax*.

Conclusion

This meta-analysis confirms that LAMP method is robust for malaria diagnosis both in symptomatic and asymptomatic people. Thus, the impact of LAMP for the control of malaria is expected to be important.

Keywords: Malaria; Diagnosis; Meta-analysis; Loop-mediated isothermal amplification; microscopy; PCR; Rapid diagnostic tests

Background

The global malaria elimination appears to be more difficult to reach than expected (WHO 2018). It will require highly sensitive, reliable and easy-to-perform methods for the diagnosis of malaria (Landier et al. 2016). Malaria diagnosis can be conducted using microscopy, Rapid Diagnosis Tests (RDT), Polymerase Chain Reaction (PCR), or a combination of these methods. Microscopic examination of Giemsa stained thick or thin smears is the reference standard providing its quality can be maintained and a good expertise is available (Billo et al. 2013). However, expert malaria microscopists are less common than needed leading to impaired microscopy-based diagnosis, especially for non-*falciparum* species (Ruas et al. 2017). Limit of detection (LOD) may vary substantially according to the experience and training of microscopists, from a range of 5 to 100 parasites/µL (Zimmerman and Howes 2015). Rapid Diagnosis Tests (RDTs) for malaria (Odaga et al. 2014) have increased the availability of reliable diagnosis in remote areas (Wilson 2013). RDTs are widely used in endemic areas with a positive effect on the management of fever cases, whereas RDTs have definitive limitations. While the sensitivity and specificity of the majority of RDTs are good for *Plasmodium falciparum*, this is not the case for other human malaria species. Besides, RDTs LOD is too high (between 100 to 200 parasites/µL, depending on the test, with the exception of recent Ultrasensitive RDTs) to be useful to detect asymptomatic carriers in case of gametocyte carriage which are the main reservoir of *Plasmodium* parasites responsible for continuing transmission. Lastly, most of RDTs have been designed for the detection of HRP2, leading to an emerging selection of parasite clones deleted in HRP2/3 proteins in South-America and more recently in sub-Saharan Africa, with a risk of false-negative results (Menegon et al. 2017) .

In this context, molecular detection of malaria would be extremely useful to overcome these limitations. The molecular detection of malaria parasites using PCR or Q-PCR has indeed proved its capacity to detect low parasitemia with LOD of 0.05 parasites/µL or less (Roth et al. 2016). A wide range of PCR methods has been developed for the malaria diagnosis, providing valuable information on the parasite biology and pyrogenic threshold. Authors tried to simplify the method to allow large utilization in the malaria endemic areas, but one should consider that these methods are unavailable for point-of-care diagnosis without a subsequent training and equipment (Amir et al.

2018). PCR is still limited to well-equipped centers mostly far from remote endemic areas inconsistent with the need of prompt initiation of a documented treatment of malaria cases.

Loop-mediated isothermal amplification of DNA (LAMP) has been firstly described in 2000 (Notomi et al. 2000) and its first application to malaria diagnosis was in 2006 (Poon et al. 2006). LAMP is an isothermal molecular method using a DNA polymerase from *Bacillus stearothermophilus* which has strand displacement activity leading to DNA auto-cycling without temperature changes. The different tests available are mostly targeting the mitochondrial genome of *Plasmodium* parasite.

This method of DNA amplification is easier and cheaper to perform than PCR since it requires less equipment and lab facilities (Lucchi et al. 2018). It is expected to have a higher sensitivity than microscopy and RDT and excellent likelihood negative value (Ponce et al. 2017). Recent technical developments led to consider LAMP as a suitable tool for diagnosis in endemic and non-endemic areas (Polley et al. 2013a). Among the questions that remain are the place of LAMP method in a diagnosis process according to available resources, malaria transmission level, lab equipment and staff training.

The aim of this systematic review was to evaluate the diagnostic accuracy of Loop-mediated isothermal amplification (LAMP) methods compared to microscopy, PCR and RDTs for malaria diagnosis in symptomatic and asymptomatic patients from endemic and non-endemic areas.

To this end, this systematic review will answer the following questions: (1) when compared to the microscopic examination of blood smears or RDTs (reference standards) and to PCR (standard of truth) what are the performances (sensitivity, specificity, positive predictive value, negative predictive value) of LAMP methods (index method) for detection of human *Plasmodium* parasites? (2) Is there a difference among main *Plasmodium* species when LAMP tests are used for detection? (3) Is there a difference in LAMP tests performances among symptomatic and non-symptomatic patients? (4) Is there a difference in LAMP tests performance among the available methods?

Methods

This systematic review and meta-analysis followed the preferred reporting items for systematic review and meta-analyses (PRISMA) guidelines and the Cochrane handbook for systematic reviews of diagnostic test accuracy (McGrath et al. 2017). The study protocol was registered with the international Prospective Register of Systematic reviews (PROSPERO) on 24 August, 2017 and was last updated on 25 September, 2017 (registration number CRD42017075186).

Search strategy

Literature search strategies was developed using medical subject headings (MESH) in the National Library of Medicine and text word related to malaria diagnosis and LAMP. We searched MEDLINE, (("Lamp"[Journal] OR "lamp"[All Fields]) AND ("malaria"[MeSH Terms] OR "malaria"[All Fields])) Web of Science, and Scopus from inception to 1st July 2019. To ensure literature saturation, we scanned the reference list of included and excluded studies.

Eligibility criteria

Prospective and retrospective, randomized and non-randomized, mono-center and multi-center studies from symptomatic or asymptomatic patients without age limitation that reported at least one LAMP method for malaria diagnosis (*Plasmodium* genus or species) and one comparator (microscopy, RDT, PCR) were included up to July 2019. Studies from malaria endemic or non-endemic areas, and from research, hospital, and tertiary care settings, were included. If a 2x2 table of true positive, false negative, true negative, and false positive counts, was not available, data were extracted from the original article. There was no language limitation for inclusion. Case reports, animal (including mosquitoes) studies, studies using parasites clones from culture or parasite DNA form collection, and methodological studies without clinical samples, were excluded.

Study selection

After searches in the proposed databases have been completed, a single library was created in Zotero (Version 5.0.18, Corporation for Digital Scholarship, Virginia, USA). The duplicates were removed using Zotero and then, checked manually. A Microsoft Excel spreadsheet (Microsoft Corp.,

Redmond, WA, USA) was used to manage data and literature search. Two identical copies of Excel spreadsheets were created and ascribed to two independent reviewers.

The first step was to screen titles and abstracts of selected articles to exclude studies according to the exclusion criteria. Reviewers must justify exclusion of any items in the spreadsheet. A consensus meeting allowed to avoid any divergence between the two spreadsheets. Studies were included for next step if there is any uncertainty. Based on the first selection list, the next step was to read the full texts to exclude studies that did not meet inclusion criteria. This second step was validated by another consensus meeting to select which article will be considered eligible for review. Disagreements were resolved by discussion and reasons for excluding studies were recorded.

A data extraction form was built to compile data from included studies.

Data extraction and checking

Variables such as title, references, authors, country of the study (endemic vs non-endemic), participants (symptomatic vs non-symptomatic), interventions (genus and/or specie specific detection, commercial or in-house method, prospective or retrospective study), comparators (PCR, microscopy, RDT), and number of participants, were recorded. To ensure reproducibility and completeness of data extraction, a predesigned Excel spreadsheet (Microsoft Corp., Redmond, WA, USA) compiling all variables to be extracted was used. Duplicate, overlapping, or companion studies, detected during the data extraction process were excluded. Two investigators (ALB, SP) independently collected the true positive, false positive, true negative, and false negative counts. Disagreements over data extraction were resolved by discussion. Data were centrally checked by an independent operator for completeness, plausibility, and integrity, before synthesis.

Quality assessment

The methodological quality of included studies was evaluated to reduce systematic biases and inferential error of the extracted data. Risk of bias of the including studies was independently assessed by two reviewers (ALB, SP) using the quality assessment of diagnostic accuracy studies (QUADAS-2) (Whiting et al. 2011). QUADAS-2 assesses four areas of bias including patient selection, index test, reference standards, and flow/timing. Risk of bias summary and graph were generated in Review Manager 5 (RevMan version 5.3.5, http://community.cochrane.org/tools/review-production-tools/revman-5) to provide a synthetic analysis of bias. Moreover, predefined sensitivity analyses after excluding studies judged to have potential risk of bias were performed. Studies without high risk of bias for any of the defined parameters were considered for "best studies" subgroup.

Data Synthesis

RevMan 5 was the software used for meta-analysis. Values of test accuracy compared to microscopic examination of blood smears and non-isothermal PCR methods including sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and 95% confidence intervals, using data extracted from sources (True positives, True Negative, False Positive, False negative) or calculated from the data available were computed. Given the general use of microscopic examination of thin or thick blood smears as reference standard, microscopy was considered as the clinical practice comparator. PCR was considered as the standard of truth as it was the most relevant to compare with LAMP; thus, PCR was considered as the direct comparator. RDTs are widely used in endemic malaria areas, but not frequently used as a comparator for sensitive diagnostic tests; thus, RDTs was considered as a second clinical practice comparator. Results of individual study were presented graphically on forest plot, as well as on receiver operating characteristic (ROC) curve. To evaluate overall performances of the LAMP tests, a bivariate (bivariate diagnostic random effect meta-analysis) and univariate analyses (DerSimonian and Laird random effect model) were conducted using R 3.5.2 software (R Foundation for Statistical Computing, Vienna, Austria); summary point estimates of the pairs of sensitivity and specificity with

their 95% confidence interval, diagnostic odd ratios with their 95% confidence interval, and receiver operating characteristic (SROC) curves, were obtained.

Results

Search results

The literature search identified 526 records through three different sources, including 158 from MEDLINE, 168 from SCOPUS, and 200 from Web of sciences (Figure 1). After removal of the duplicates, the remaining studies (n=158) were screened. Fifty-four records (n=54) were excluded as they did not meet the inclusion criteria. The 104 eligible studies were assessed in details. Sixty-six studies were included (Table 1-3). The reasons for exclusion of the 38 studies were the lack of data allowing direct method comparison or the impossibility to extract those data, LAMP targeting gametocytes only or non-human plasmodium species (*P. chabaudi*), detection of single nucleotide polymorphism, non-human samples (monkeys, mosquitos) and reviews.

Study characteristic

Sixty-six studies published between 2006 and 2019 were included leading to 30641 individual LAMP tests compared either to microscopy, RDT or PCR or a combination of these comparators. 51% (34/66) of the studies were retrospective and 10.6% (7/66) were using samples from asymptomatic people. Most of them (41%, 27/66) were conducted in South-East Asian countries, 27% (18/66) in Africa, 24% (16/66) in Europa or North America from malaria imported cases, and 7% in South-America (5/66). The reference methods used for comparison with LAMP was microscopy for 53 studies (19418 tests), PCR for 55 studies (17479 tests) and RDTs for 17 studies (2065 tests). Most of the LAMP tests (33/66) were performed using LoopAmp (Eiken, Tochigi, Japan), 39% (26/66) using an in-house method or other commercial test, and 10% (7/66) using Illumigene Malaria (Meridian Biosciences, Cincinatti, USA). Three methods were used to read LAMP tests averaged among naked-eyes, turbidimetry, or fluorescence. Among these studies, 11 were designed to detect *P. falciparum*, 13 to detect *P. vivax*, and 10 to detect *P. falciparum* and *P. vivax*. Others studies were

designed to detect different combinations of *Plasmodium* species. A vast majority of studies were using blood samples, but saliva and urines were tested in three studies.

Quality and heterogeneity of diagnostic studies

Risk of bias for patient selection was considered low in 56% of the diagnostic studies and high in 36% (Figure 2). Reporting and execution of LAMP was adequate in 97% of the studies (Figure 2). The quality of verification with a reference standard was good in 100% of the studies (Figure 2).

Statistical analysis of heterogeneity found no substantial or moderate heterogeneity between studies included in the analysis of LAMP compared to microscopy and/or PCR, as well as for the sub-group analysis of *P. vivax*. The value of I^2 was 0% according to the bivariate analysis (REML) and <60% according to the univariate analysis (DOR).

Results of synthesis and sensitivity analysis

Table 4 shows the pooled sensitivity and specificity, AUC, DOR and I^2 according to the bivariate analysis (REML) and OR and I^2 according to the univariate analysis (DOR).

<u>LAMP compared to microscopy</u>

Fifty-five studies comparing LAMP with microscopy were included, for a total of 19687 tests. Most of the studies showed a sensitivity > 0.95 (43/55, 78%) and a specificity > 0.95 (33/55, 60%) (Figure 3). There was no difference between pooled sensitivity of all included studies (0.971 [0.965-0.985]) compared to a selection of the best studies (0.974 [0.960-0.984]). Few studies showed lower sensitivity or specificity values mainly due to the use of non-blood samples or *Plasmodium* species-specific tests. Two studies used samples from patients during pregnancy, and six studies tested asymptomatic people. While a decrease in sensitivity and specificity may be expected for pregnant women and asymptomatic people considering the lower parasitemia, no specific impact of pregnancy or asymptomatic malaria was detected (Figure 4). There is no evidence for a positive or negative impact of LAMP providers (either Eiken, Meridian, or in-house) (Figure 5) and the reader methods (either naked-eyes, turbidimeter, fluorescence) (Figure 6).

LAMP compared to PCR

Fifty-seven studies comparing LAMP with PCR were included, for a total of 17996 tests. Most of the studies showed a sensitivity > 0.95 (48/57, 84%) and a specificity > 0.95 (32/57, 56%) (Figure 7). Half of the studies (28/57) have a prospective design and 29 a retrospective design. Ten of these studies were detecting *P. vivax* only (17%) and 9 were detecting *P. falciparum* only (15.8%). Most of the other studies were designed to detect two or more *Plasmodium* species. Eight studies (14%) were designed to test asymptomatic people and 2 (3.5%), to test pregnant women; there was no evidence of an impact of these conditions on LAMP results (Figure 8).

LAMP compared to RDTs

Seventeen studies comparing LAMP with RDTs were included, for a total of 15848 tests. Most of the samples were collected from asymptomatic volunteers (13585 tests (68%), 7/17 studies). The sensitivity was 1.0 in 14/17 (82%) and specificity was > 0.95 in 10/17 studies (59%) (Figure 9). The study designs were prospective for 13/17 studies (76%). The majority of samples were collected from different studies conducted in Zanzibar (9329/15848, 58.8%) between 2014 and 2017.

Overall performance of LAMP tests

The pooled sensitivity of LAMP remained between 96 and 98% whatever the comparator (microscopy PCR, or RDT). The pooled specificity of LAMP was around 95%, but is little higher (98%) if best PCR studies are considered. If the analysis is performed for LAMP tests extracted from a selection of best included studies for microscopy defined as studies presenting the lower risk of bias, the accuracy measures of LAMP were closed to the analysis of the overall population for pooled microscopy and PCR (0.974 [0.960-0.984] compared to 0.977 [0.965-0.985]). AUC were found to be above 0.98 whatever the subgroup of studies considered. For all subgroups of studies, DOR were demonstrated to be around 1 000 using a bivariate analysis. Using univariate analysis, OR were above 1 000 for all subgroups. Interestingly, higher DOR or OR were observed if LAMP was compared to PCR. If the subgroup of studies “vivax” was considered, DOR and OR were much lower, around 500 confirming the difficulty of vivax malaria diagnosis.

Discussion

Strengthening malaria diagnosis should be a priority in endemic and non-endemic areas (Nema et al. 2019). Indeed, malaria elimination is expected by 2030 in many endemic countries, leading to substantial decrease in patient's parasitemia and increase in the proportion of asymptomatic malaria parasites carriers. Microscopy is an appropriate tool when the number of patients suffering malaria is high enough to allow permanent training and experience of microscopists, whereas RDTs are appropriate when the mean parasitemia is over the RDTs' limit of detection. New accurate diagnosis methods are needed to address the new issues related to changing malaria epidemiology. Among these, high sensitivity is a prerequisite. The LAMP method is probably one of the most interesting diagnosis test recently introduced despite its limitation to well-equipped labs with high levels of resources. This method has been tested both in endemic and non-endemic areas in different conditions. The purpose of this study was to compared and analyze the performance of LAMP method versus microscopy, RDTs, and PCR.

We performed an extensive search of all the available studies, without limitation in reference methods, study area, and clinical presentation of tested people, including both symptomatic and asymptomatic. The vast majority of these studies were conducted between 2015 and 2019, while only four studies were conducted before 2010, demonstrating the very recent interest in this diagnosis method. Statistical heterogeneity was tested using the I^2 statistic, which measures the variation across studies due to inter-study heterogeneity. Indeed, heterogeneity were expected to be related to the LAMP method (in-house or commercial, specie-specific detection or not, DNA target used), the method of test reading (automate, naked-eye), the patients (immune or non-immune, area of contamination, levels of parasitemia), and the comparators (microscopy, PCR, RDT). Of note, there were no significant heterogeneity among the studies included in the meta-analysis thus rendering the results conclusive. Moreover, there were no evidence of significant publication biases according to the QUADAS-2. Then, applicability of the test accuracy estimates generated in this study is high due to the high number of studies included leading to approximately 20 000 tests performed for each comparator, to the low risk of bias, and to the absence of heterogeneity of the included studies.

AUC above 0.98 demonstrated that LAMP is a test with an excellent specificity and sensitivity. Whatever the group of studies considered, DOR around 1000 reflected a test with an excellent discriminant power. Concordant OR were found using univariate analysis, thus supporting that the results were robust whatever the method of analysis used. Higher DOR or OR observed if LAMP was compared to PCR may be explained by the fact that LAMP and PCR are both molecular tests whereas microscopy is not; PCR is moreover considered as the direct comparator in this meta-analysis and microscopy as the clinical practice comparator. If the subgroup of studies “vivax” was considered, DOR and OR were much lower indicating that the test is a little less efficient to detect vivax malaria. Among the included studies, LAMP method varied depending on the targeted *Plasmodium* species, the primers sequences, the amplification time, the method for signal detection, the commercial or in-house method, and the samples used (blood, saliva, urine). Despite this, no significant changes in the test performances were observed, except for non-blood samples (saliva, urine) showing lower diagnosis accuracy, as previously demonstrated by biological evidence.

The primary audience of this meta-analysis is clinicians, biologists, public health policy makers, and stakeholders. The results of this study may help them to choose the most appropriate first line diagnosis method depending on the local requirements and availabilities. Microscopic analysis of stained blood smears is the reference for malaria diagnosis since decades. However, its limitations linked to the required skills and the recent availability of new methods may provide an opportunity for changing the malaria diagnosis paradigm. This study gathers evidence for the future of malaria diagnosis and the implementation of LAMP as a reference test for malaria diagnosis.

This meta-analysis has some limitations. First, the search strategy was performed without using search filters, but unpublished data were not taken into account as well as abstract from meetings since all the requested information related to the study quality were not available. Considering the high number of included studies and the absence of heterogeneity among the included studies, it is expected that potential missing studies should not have a significant impact on the meta-analysis results. Second, studies from endemic and non-endemic areas were included and pooled leading to the possibility of bias linked to the level of circulating parasitemia in the studied population. However, the aim of this study was to evaluate the overall diagnosis accuracy of LAMP for malaria

and this question is not related to the level of malaria endemicity. The potential impact of transmission area could be detected by the difference between symptomatic and asymptomatic people. The data analysis showed that there was no difference in diagnosis accuracy of LAMP using blood samples from these two populations. Third, LAMP method was compared to microscopy, RDTs and PCR. None of these methods should be considered as a standard of truth since methodological difference may lead to significant difference in limit of detection or performances. Moreover, the training and experience of microscopy operators have a direct impact on the quality of results. Considering this limitation, PCR is certainly the best comparator for LAMP.

Conclusion

The challenge of malaria diagnosis is moving forward detection of asymptomatic carriers presenting low parasitemia in endemic areas where the transmission is declining. Microscopy and RDTs are highly efficient for the diagnosis of febrile malaria patients, and PCR shows high sensitivity and specificity while its practicability is low. The positioning of malaria LAMP in this context needs to be clarified thus the first step is to compare its performances to the historical methods for both symptomatic and asymptomatic patients. This meta-analysis clearly confirms a very high DOR (>1000) of LAMP compared to microscopy, RDT, and PCR. Malaria LAMP is now widely recommended as a first line method for the diagnosis of imported malaria cases in non-endemic countries due to its high negative predictive value. Same performances are observed testing symptomatic and asymptomatic patients, then the impact of LAMP for the control of malaria in the near future is expected to be important.

Figure 1: Flow chart

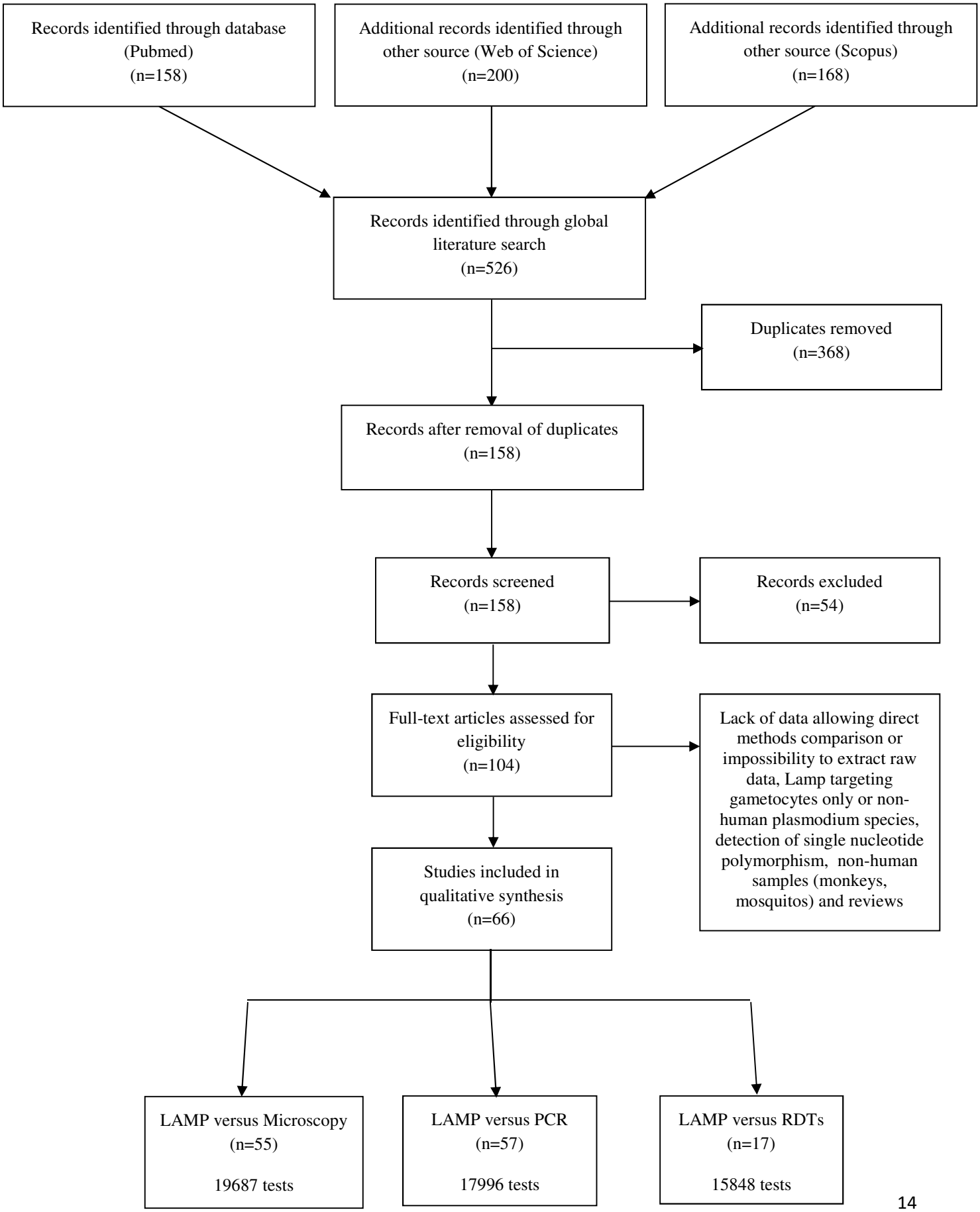


Figure 2: Risk of bias graph of studies included in the meta-analysis

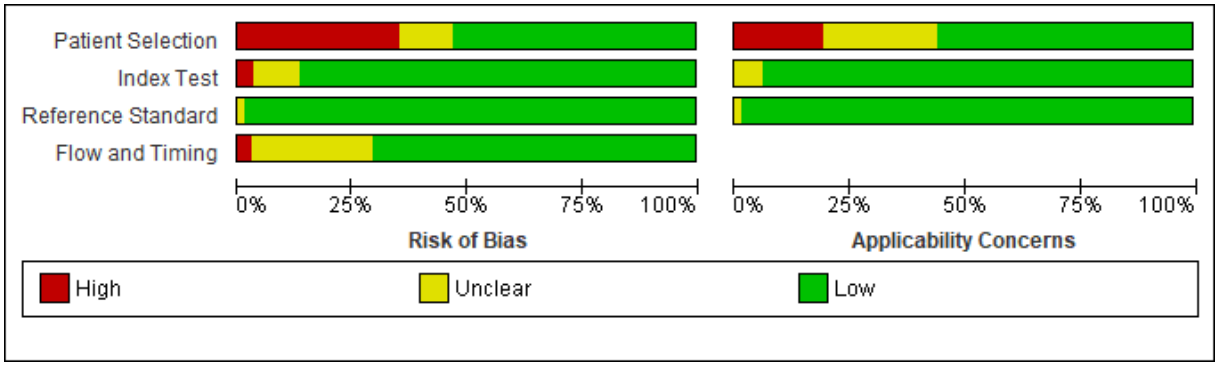
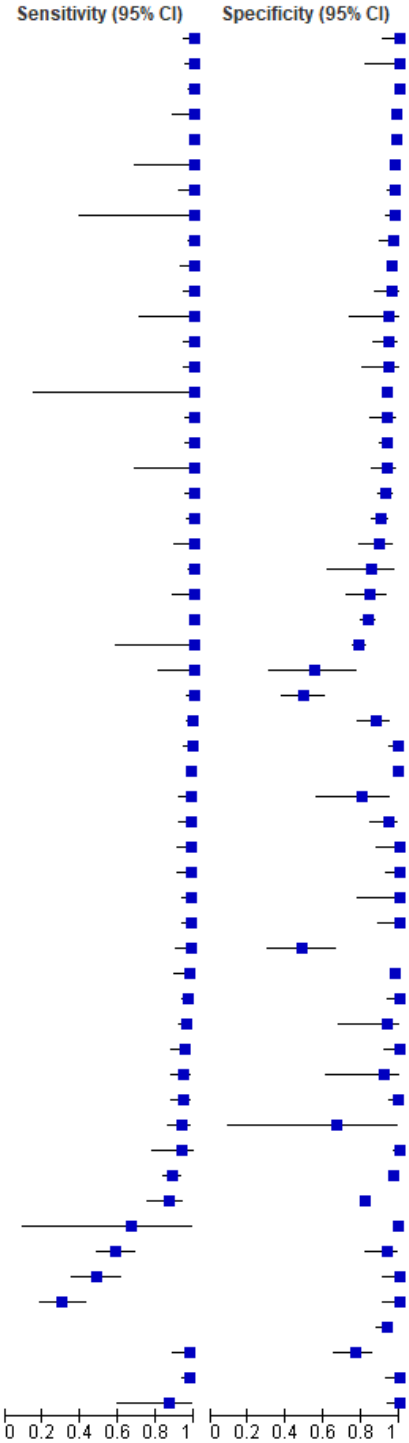


Figure 3: Forest plot of LAMP compared to microscopy

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Najafabadi 2014	68	0	0	40	1.00 [0.95, 1.00]	1.00 [0.91, 1.00]
Piera 2017	73	0	0	19	1.00 [0.95, 1.00]	1.00 [0.82, 1.00]
Aydin-Schmidt (Suspected) 2014	115	1	0	749	1.00 [0.97, 1.00]	1.00 [0.99, 1.00]
Vasquez 2018	31	8	0	492	1.00 [0.89, 1.00]	0.98 [0.97, 0.99]
Viana 2018	226	13	0	761	1.00 [0.98, 1.00]	0.98 [0.97, 0.99]
Sattabongkot 2018	10	81	0	3559	1.00 [0.69, 1.00]	0.98 [0.97, 0.98]
Marti 2015	43	4	0	158	1.00 [0.92, 1.00]	0.98 [0.94, 0.99]
Patel (Asymptomatic) 2014	4	3	0	116	1.00 [0.40, 1.00]	0.97 [0.93, 0.99]
Lau 2016	132	2	0	67	1.00 [0.97, 1.00]	0.97 [0.90, 1.00]
Polley 2013	52	24	0	625	1.00 [0.93, 1.00]	0.96 [0.95, 0.98]
Vincent 2018	62	2	0	51	1.00 [0.94, 1.00]	0.96 [0.87, 1.00]
De Koninck 2017	11	1	0	18	1.00 [0.72, 1.00]	0.95 [0.74, 1.00]
Mohon 2016	69	4	0	67	1.00 [0.95, 1.00]	0.94 [0.86, 0.98]
Poschl 2010	71	2	0	32	1.00 [0.95, 1.00]	0.94 [0.80, 0.99]
Vallejo (Asymptomatic) 2015	2	63	0	978	1.00 [0.16, 1.00]	0.94 [0.92, 0.95]
Rypien 2017	76	4	0	60	1.00 [0.95, 1.00]	0.94 [0.85, 0.98]
Ponce 2017	79	14	0	206	1.00 [0.95, 1.00]	0.94 [0.90, 0.96]
Tegegne 2017	10	5	0	72	1.00 [0.69, 1.00]	0.94 [0.85, 0.98]
Vallejo (Suspected) 2015	80	14	0	184	1.00 [0.95, 1.00]	0.93 [0.88, 0.96]
Oriero (b) 2015	104	23	0	214	1.00 [0.97, 1.00]	0.90 [0.86, 0.94]
Kudiba 2019	33	6	0	52	1.00 [0.89, 1.00]	0.90 [0.79, 0.96]
Kaur 2018	145	3	0	17	1.00 [0.97, 1.00]	0.85 [0.62, 0.97]
Sema 2015	30	8	0	44	1.00 [0.88, 1.00]	0.85 [0.72, 0.93]
Kollenda 2018	177	57	0	289	1.00 [0.98, 1.00]	0.84 [0.79, 0.87]
Girma 2018	7	118	0	437	1.00 [0.59, 1.00]	0.79 [0.75, 0.82]
Hartmeyer 2019	18	9	0	11	1.00 [0.81, 1.00]	0.55 [0.32, 0.77]
Dinzouna-Boutamba 2014	96	41	0	40	1.00 [0.96, 1.00]	0.49 [0.38, 0.61]
Lucchi 2016	135	9	1	64	0.99 [0.96, 1.00]	0.88 [0.78, 0.94]
Mohon 2014	105	1	1	104	0.99 [0.95, 1.00]	0.99 [0.95, 1.00]
Frickmann 2018	235	3	3	759	0.99 [0.96, 1.00]	1.00 [0.99, 1.00]
Singh 2013	68	4	1	16	0.99 [0.92, 1.00]	0.80 [0.56, 0.94]
Han 2007	67	3	1	50	0.99 [0.92, 1.00]	0.94 [0.84, 0.99]
Tao 2011	59	0	1	29	0.98 [0.91, 1.00]	1.00 [0.88, 1.00]
Sirichaisinthop 2011	59	0	1	50	0.98 [0.91, 1.00]	1.00 [0.93, 1.00]
Ocker 2016	116	0	2	15	0.98 [0.94, 1.00]	1.00 [0.78, 1.00]
Chen 2010	115	0	2	30	0.98 [0.94, 1.00]	1.00 [0.88, 1.00]
Singh (saliva) 2013	55	17	1	16	0.98 [0.90, 1.00]	0.48 [0.31, 0.66]
Cheaveau 2018	51	7	1	290	0.98 [0.90, 1.00]	0.98 [0.95, 0.99]
Singh 2017	248	0	9	60	0.96 [0.93, 0.98]	1.00 [0.94, 1.00]
Surabattula 2013	162	1	6	14	0.96 [0.92, 0.99]	0.93 [0.68, 1.00]
Patel (Suspected) 2014	91	0	5	45	0.95 [0.88, 0.98]	1.00 [0.92, 1.00]
Lucchi 2010	89	1	5	11	0.95 [0.88, 0.98]	0.92 [0.62, 1.00]
Poon 2006	96	1	6	99	0.94 [0.88, 0.98]	0.99 [0.95, 1.00]
Yamamura 2009	85	1	6	2	0.93 [0.86, 0.98]	0.67 [0.09, 0.99]
Polley 2010	28	0	2	113	0.93 [0.78, 0.99]	1.00 [0.97, 1.00]
Sattabongkot 2014	177	15	22	466	0.89 [0.84, 0.93]	0.97 [0.95, 0.98]
Serra-Casas 2017	52	198	8	907	0.87 [0.75, 0.94]	0.82 [0.80, 0.84]
Zelman 2018	2	5	1	1487	0.67 [0.09, 0.99]	1.00 [0.99, 1.00]
Britton 2016	56	3	39	44	0.59 [0.48, 0.69]	0.94 [0.82, 0.99]
Najafabadi (saliva) 2014	31	0	33	39	0.48 [0.36, 0.61]	1.00 [0.91, 1.00]
Najafabadi (Urine) 2014	18	0	42	39	0.30 [0.19, 0.43]	1.00 [0.91, 1.00]
Cuadros 2015	0	11	0	151	Not estimable	0.93 [0.88, 0.97]
Lee 2012	46	19	1	62	0.98 [0.89, 1.00]	0.77 [0.66, 0.85]
Lu 2012	160	0	4	50	0.98 [0.94, 0.99]	1.00 [0.93, 1.00]
Lau 2011	13	0	2	59	0.87 [0.60, 0.98]	1.00 [0.94, 1.00]



TP: true positive; FP: false positive; FN: false negative; TN: true negative

Figure 4: SROC of LAMP compared to microscopy according to clinical status of included patients

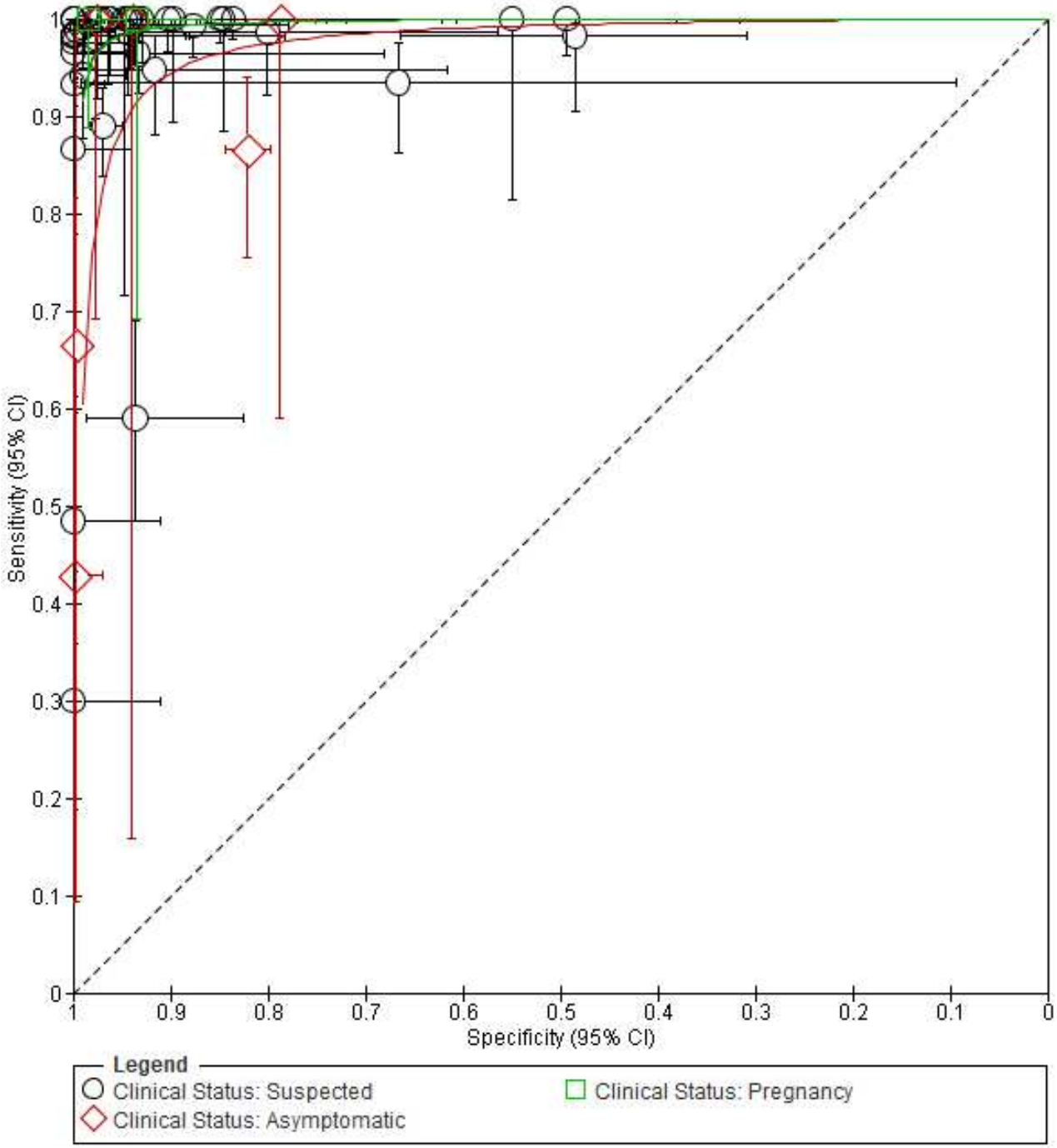


Figure 5: SROC of LAMP compared to microscopy according to LAMP tests providers

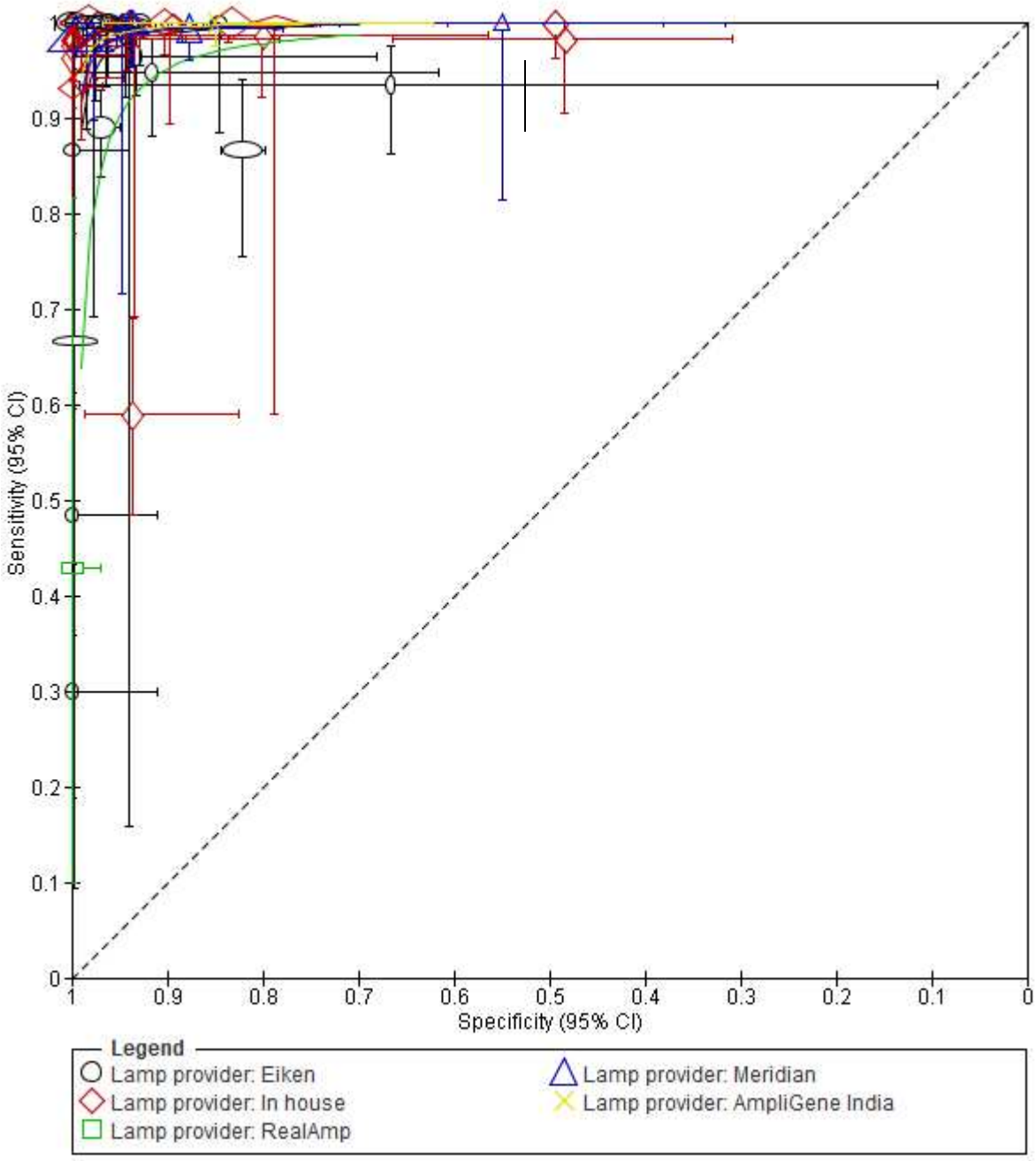
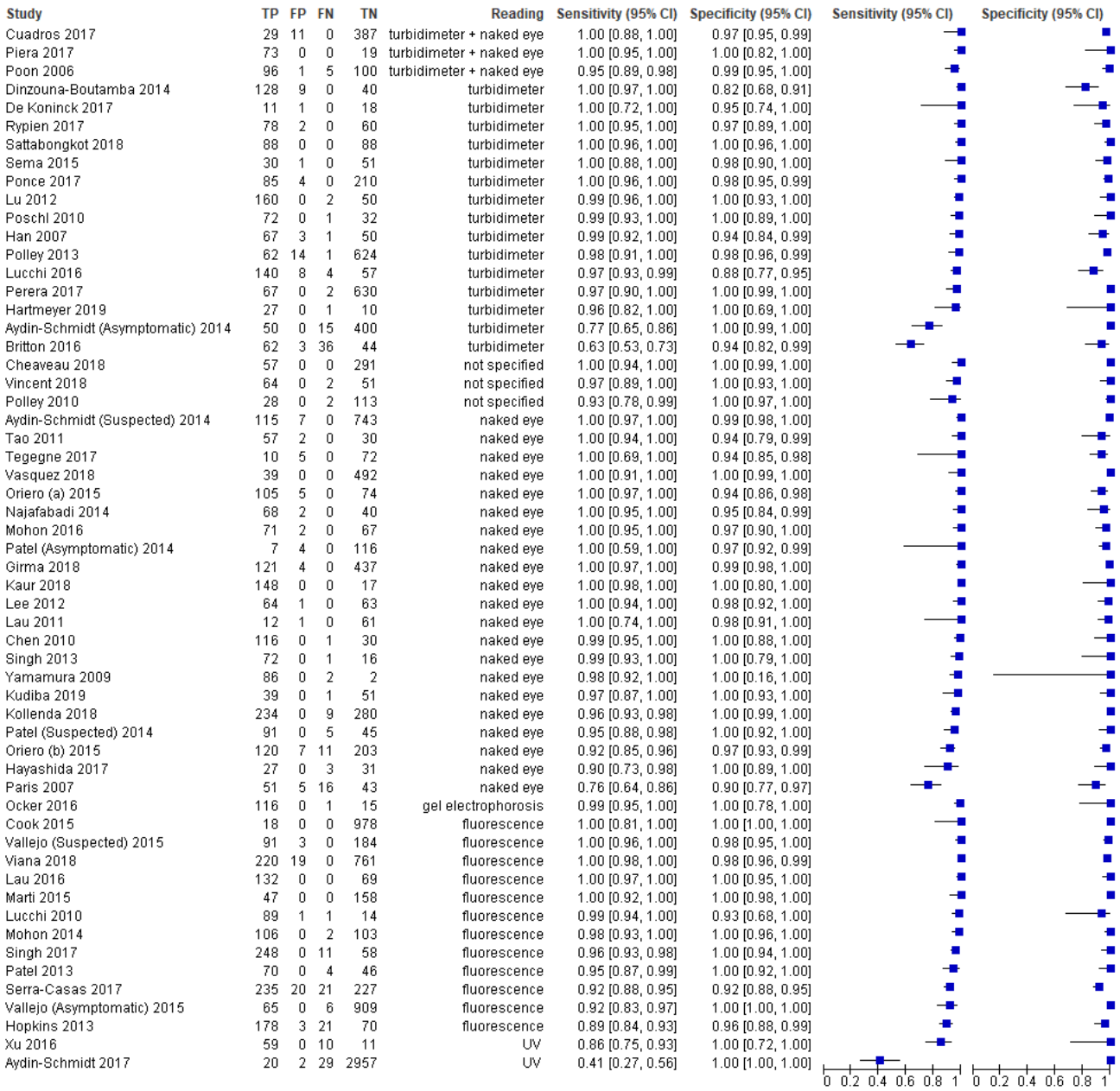


Figure 6: Forest plot and SROC of LAMP compared to microscopy according to reader method



TP: true positive; FP: false positive; FN: false negative; TN: true negative

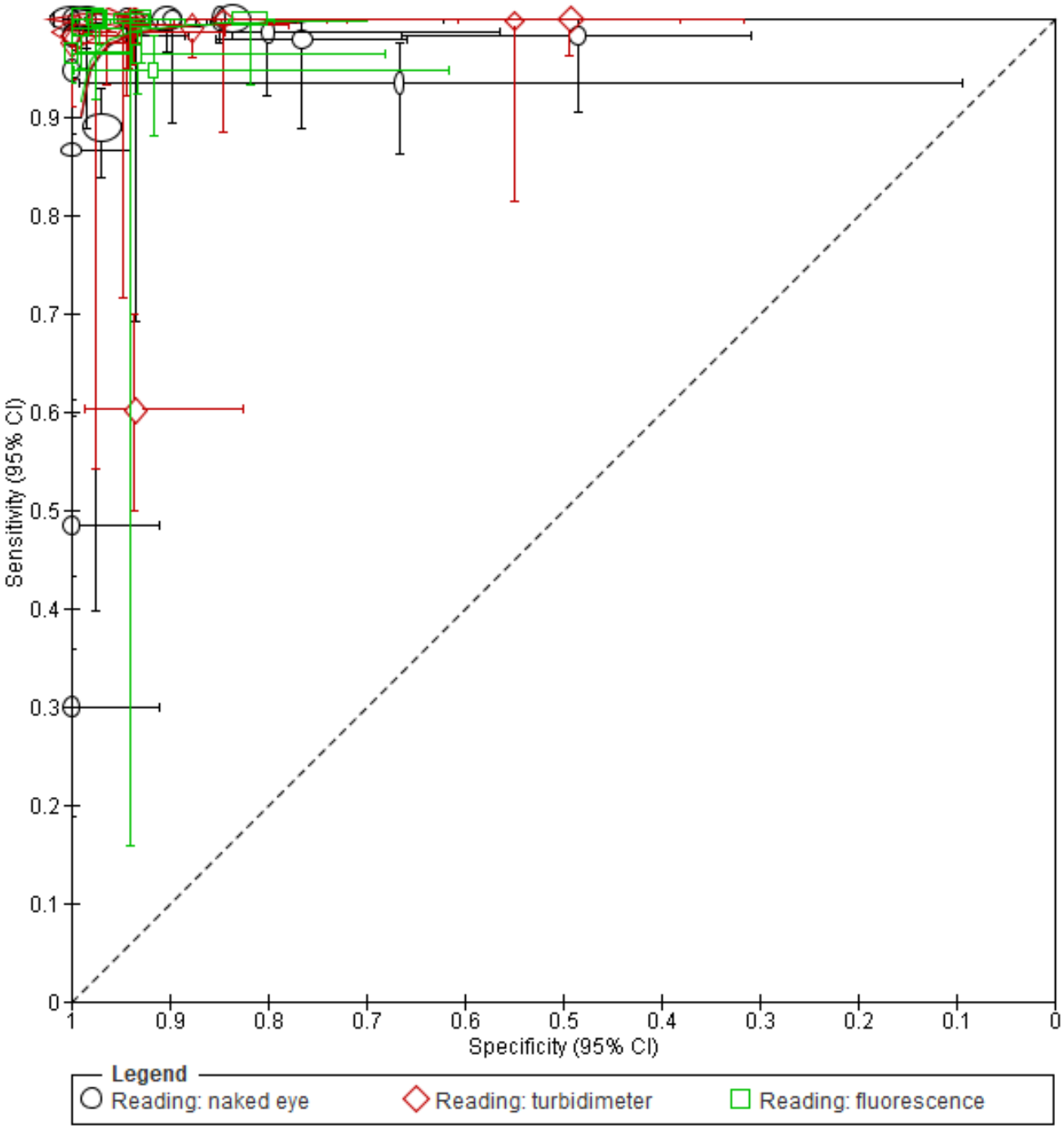
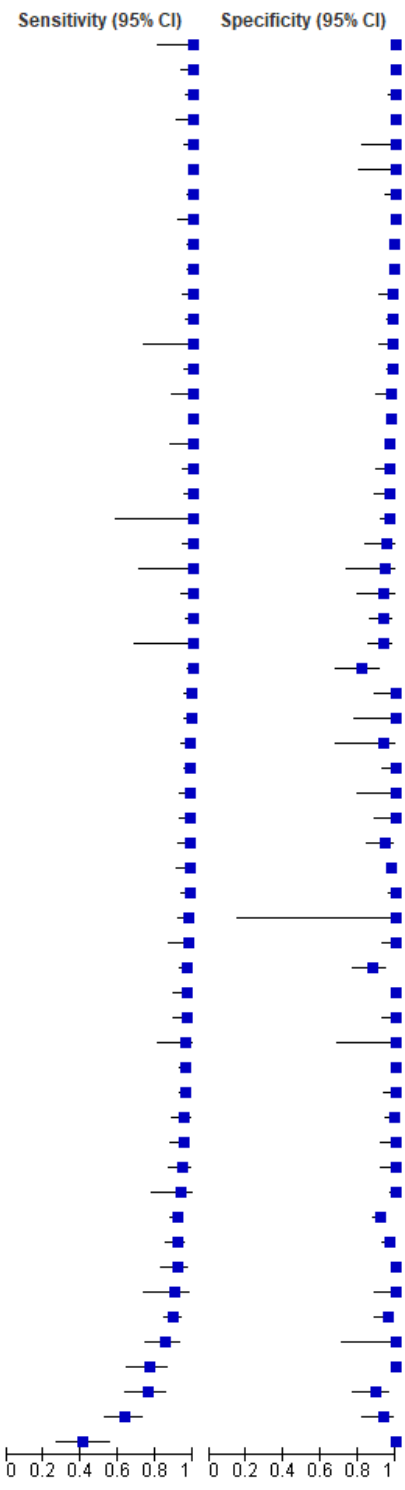

Sensitivity (95% CI)
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
Specificity (95% CI)
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Legend
Reading: naked eye
Reading: turbidimeter
Reading: fluorescence

Figure 7: Forest plot of LAMP compared to PCR

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Cook 2015	18	0	0	978	1.00 [0.81, 1.00]	1.00 [1.00, 1.00]
Cheaveau 2018	57	0	0	291	1.00 [0.94, 1.00]	1.00 [0.99, 1.00]
Sattabongkot 2018	88	0	0	88	1.00 [0.96, 1.00]	1.00 [0.96, 1.00]
Vasquez 2018	39	0	0	492	1.00 [0.91, 1.00]	1.00 [0.99, 1.00]
Piera 2017	73	0	0	19	1.00 [0.95, 1.00]	1.00 [0.82, 1.00]
Kaur 2018	148	0	0	17	1.00 [0.98, 1.00]	1.00 [0.80, 1.00]
Lau 2016	132	0	0	69	1.00 [0.97, 1.00]	1.00 [0.95, 1.00]
Marti 2015	47	0	0	158	1.00 [0.92, 1.00]	1.00 [0.98, 1.00]
Girma 2018	121	4	0	437	1.00 [0.97, 1.00]	0.99 [0.98, 1.00]
Aydin-Schmidt (Suspected) 2014	115	7	0	743	1.00 [0.97, 1.00]	0.99 [0.98, 1.00]
Lee 2012	64	1	0	63	1.00 [0.94, 1.00]	0.98 [0.92, 1.00]
Vallejo (Suspected) 2015	91	3	0	184	1.00 [0.96, 1.00]	0.98 [0.95, 1.00]
Lau 2011	12	1	0	61	1.00 [0.74, 1.00]	0.98 [0.91, 1.00]
Ponce 2017	85	4	0	210	1.00 [0.96, 1.00]	0.98 [0.95, 0.99]
Sema 2015	30	1	0	51	1.00 [0.88, 1.00]	0.98 [0.90, 1.00]
Viana 2018	220	19	0	761	1.00 [0.98, 1.00]	0.98 [0.96, 0.99]
Cuadros 2017	29	11	0	387	1.00 [0.88, 1.00]	0.97 [0.95, 0.99]
Mohon 2016	71	2	0	67	1.00 [0.95, 1.00]	0.97 [0.90, 1.00]
Rypien 2017	78	2	0	60	1.00 [0.95, 1.00]	0.97 [0.89, 1.00]
Patel (Asymptomatic) 2014	7	4	0	116	1.00 [0.59, 1.00]	0.97 [0.92, 0.99]
Najafabadi 2014	68	2	0	40	1.00 [0.95, 1.00]	0.95 [0.84, 0.99]
De Koninck 2017	11	1	0	18	1.00 [0.72, 1.00]	0.95 [0.74, 1.00]
Tao 2011	57	2	0	30	1.00 [0.94, 1.00]	0.94 [0.79, 0.99]
Oriero (a) 2015	105	5	0	74	1.00 [0.97, 1.00]	0.94 [0.86, 0.98]
Tegegne 2017	10	5	0	72	1.00 [0.69, 1.00]	0.94 [0.85, 0.98]
Dinzouna-Boutamba 2014	128	9	0	40	1.00 [0.97, 1.00]	0.82 [0.68, 0.91]
Chen 2010	116	0	1	30	0.99 [0.95, 1.00]	1.00 [0.88, 1.00]
Ocker 2016	116	0	1	15	0.99 [0.95, 1.00]	1.00 [0.78, 1.00]
Lucchi 2010	89	1	1	14	0.99 [0.94, 1.00]	0.93 [0.68, 1.00]
Lu 2012	160	0	2	50	0.99 [0.96, 1.00]	1.00 [0.93, 1.00]
Singh 2013	72	0	1	16	0.99 [0.93, 1.00]	1.00 [0.79, 1.00]
Poschl 2010	72	0	1	32	0.99 [0.93, 1.00]	1.00 [0.89, 1.00]
Han 2007	67	3	1	50	0.99 [0.92, 1.00]	0.94 [0.84, 0.99]
Polley 2013	62	14	1	624	0.98 [0.91, 1.00]	0.98 [0.96, 0.99]
Mohon 2014	106	0	2	103	0.98 [0.93, 1.00]	1.00 [0.96, 1.00]
Yamamura 2009	86	0	2	2	0.98 [0.92, 1.00]	1.00 [0.16, 1.00]
Kudiba 2019	39	0	1	51	0.97 [0.87, 1.00]	1.00 [0.93, 1.00]
Lucchi 2016	140	8	4	57	0.97 [0.93, 0.99]	0.88 [0.77, 0.95]
Perera 2017	67	0	2	630	0.97 [0.90, 1.00]	1.00 [0.99, 1.00]
Vincent 2018	64	0	2	51	0.97 [0.89, 1.00]	1.00 [0.93, 1.00]
Hartmeyer 2019	27	0	1	10	0.96 [0.82, 1.00]	1.00 [0.69, 1.00]
Kollenda 2018	234	0	9	280	0.96 [0.93, 0.98]	1.00 [0.99, 1.00]
Singh 2017	248	0	11	58	0.96 [0.93, 0.98]	1.00 [0.94, 1.00]
Poon 2006	96	1	5	100	0.95 [0.89, 0.98]	0.99 [0.95, 1.00]
Patel (Suspected) 2014	91	0	5	45	0.95 [0.88, 0.98]	1.00 [0.92, 1.00]
Patel 2013	70	0	4	46	0.95 [0.87, 0.99]	1.00 [0.92, 1.00]
Polley 2010	28	0	2	113	0.93 [0.78, 0.99]	1.00 [0.97, 1.00]
Serra-Casas 2017	235	20	21	227	0.92 [0.88, 0.95]	0.92 [0.88, 0.95]
Oriero (b) 2015	120	7	11	203	0.92 [0.85, 0.96]	0.97 [0.93, 0.99]
Vallejo (Asymptomatic) 2015	65	0	6	909	0.92 [0.83, 0.97]	1.00 [1.00, 1.00]
Hayashida 2017	27	0	3	31	0.90 [0.73, 0.98]	1.00 [0.89, 1.00]
Hopkins 2013	178	3	21	70	0.89 [0.84, 0.93]	0.96 [0.88, 0.99]
Xu 2016	59	0	10	11	0.86 [0.75, 0.93]	1.00 [0.72, 1.00]
Aydin-Schmidt (Asymptomatic) 2014	50	0	15	400	0.77 [0.65, 0.86]	1.00 [0.99, 1.00]
Paris 2007	51	5	16	43	0.76 [0.64, 0.86]	0.90 [0.77, 0.97]
Britton 2016	62	3	36	44	0.63 [0.53, 0.73]	0.94 [0.82, 0.99]
Aydin-Schmidt 2017	20	2	29	2957	0.41 [0.27, 0.56]	1.00 [1.00, 1.00]



TP: true positive; FP: false positive; FN: false negative; TN: true negative

Figure 8: SROC of LAMP compared to PCR according to clinical status of included patient

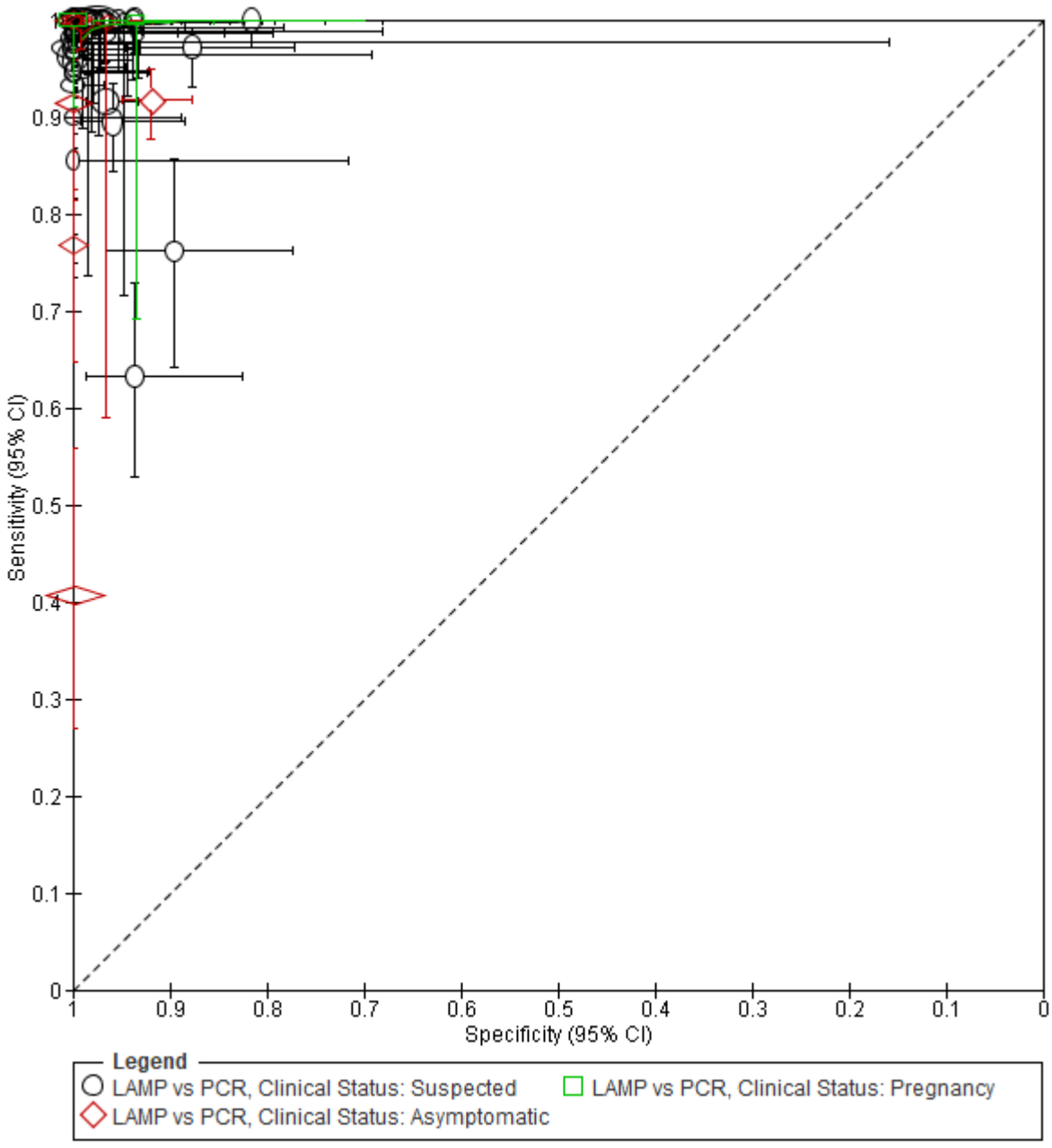
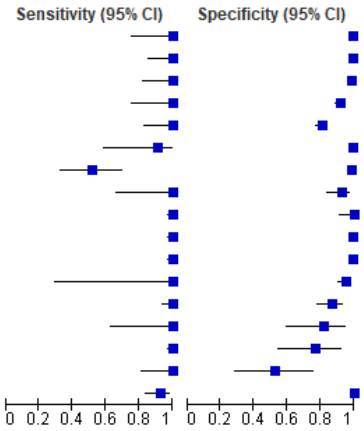


Figure 9: Forest plot and SROC of LAMP versus RDT

Study	TP	FP	FN	TN	Clinical Status	Sensitivity (95% CI)	Specificity (95% CI)
Aydin-Schmidt 2017	13	9	0	2997	Asymptomatic	1.00 [0.75, 1.00]	1.00 [0.99, 1.00]
Tambo 2018	23	24	0	2593	Asymptomatic	1.00 [0.85, 1.00]	0.99 [0.99, 0.99]
Morris 2015	19	46	0	3918	Asymptomatic	1.00 [0.82, 1.00]	0.99 [0.98, 0.99]
Aydin-Schmidt (Asymptomatic) 2014	13	37	0	415	Asymptomatic	1.00 [0.75, 1.00]	0.92 [0.89, 0.94]
Girma 2018	20	105	0	437	Asymptomatic	1.00 [0.83, 1.00]	0.81 [0.77, 0.84]
Cook 2015	10	8	1	978	Asymptomatic	0.91 [0.59, 1.00]	0.99 [0.98, 1.00]
McCreesh 2018	16	27	15	1861	Asymptomatic	0.52 [0.33, 0.70]	0.99 [0.98, 0.99]
Tegegne 2017	9	6	0	72	Pregnancy	1.00 [0.66, 1.00]	0.92 [0.84, 0.97]
Dinzouna-Boutamba 2014	137	0	0	40	Suspected	1.00 [0.97, 1.00]	1.00 [0.91, 1.00]
Oriero (b) 2015	126	1	0	236	Suspected	1.00 [0.97, 1.00]	1.00 [0.98, 1.00]
Aydin-Schmidt (Suspected) 2014	115	6	0	744	Suspected	1.00 [0.97, 1.00]	0.99 [0.98, 1.00]
Cuadros 2015	3	8	0	159	Suspected	1.00 [0.29, 1.00]	0.95 [0.91, 0.98]
Mohon 2016	61	12	0	79	Suspected	1.00 [0.94, 1.00]	0.87 [0.78, 0.93]
De Koninck 2017	8	4	0	18	Suspected	1.00 [0.63, 1.00]	0.82 [0.60, 0.95]
Kaur 2018	143	5	0	17	Suspected	1.00 [0.97, 1.00]	0.77 [0.55, 0.92]
Hartmeyer 2019	18	9	0	10	Suspected	1.00 [0.81, 1.00]	0.53 [0.29, 0.76]
Sattabongkot 2014	65	0	5	147	Suspected	0.93 [0.84, 0.98]	1.00 [0.98, 1.00]



TP: true positive; FP: false positive; FN: false negative; TN: true negative

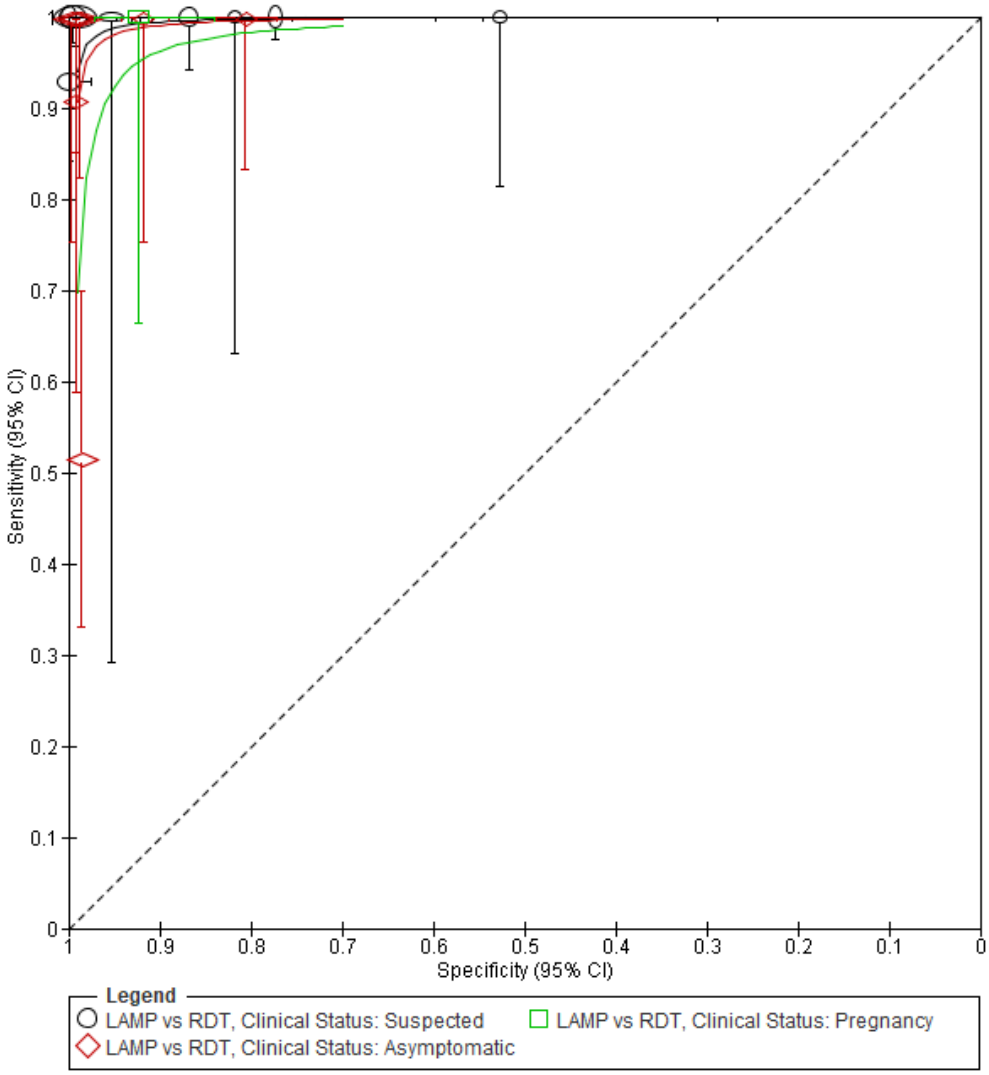


Table 1: List of included studies comparing LAMP to microscopy

	Years	Authors	**TP**	FP	FN	**TN**
1	2014	(Aydin-Schmidt et al. 2014)	**115**	1	0	**749**
2	2016	(Britton et al. 2016b)	**59**	**3**	**39**	**44**
3	2018	(Cheaveau et al. 2018)	**51**	7	1	**290**
4	2010	(Chen et al. 2010)	**115**	0	2	**30**
5	2015	(Cuadros et al. 2015)	**0**	11	0	**151**
6	2017	(De Koninck et al. 2017)	**11**	1	0	**18**
7	2014	(Dinzouna-Boutamba et al. 2014)	**96**	41	0	**40**
8	2018	(Frickmann et al. 2018)	**235**	3	3	**759**
9	2014	(Ghayour Najafabadi et al. 2014)	**68**	0	0	**40**
10	2018	(Girma et al. 2018)	**118**	7	0	**437**
11	2007	(Han et al. 2007)	**67**	3	1	**50**
12	2019	(Hartmeyer et al. 2019)	**18**	9	0	**11**
13	2018	(Kaur et al. 2018)	**145**	3	0	**17**
14	2018	(Kollenda et al. 2018)	**177**	57	0	**289**
15	2019	(Kudyba et al. 2019)	**33**	6	0	**52**
16	2011	(Lau et al. 2011)	**13**	0	2	**59**
17	2016	(Lau et al. 2016)	**132**	0	0	**69**
18	2012	(Lee et al. 2012)	**46**	19	1	**62**
19	2012	(Lu et al. 2012)	**160**	0	4	**50**
20	2010	(Lucchi et al. 2010)	**89**	1	5	**11**
21	2016	(Lucchi et al. 2016)	**135**	9	1	**64**
22	2015	(Marti et al. 2015)	**43**	4	0	**158**
23	2018	(McCreesh et al. 2018)	**16**	27	15	**1861**
24	2014	(Mohon et al. 2014)	**105**	1	1	**104**
25	2016	(Mohon et al. 2016)	**69**	4	0	**67**
26	2015	(Morris et al. 2015)	**19**	46	0	**3918**
27	2016	(Ocker et al. 2016)	**116**	0	2	**15**
28	2015	(Oriero et al. 2015a)	**104**	23	0	**214**
29	2014	(Patel et al. 2014)	**91**	0	5	**45**
30	2017	(Piera et al. 2017)	**73**	0	0	**19**

31	2010	(Polley et al. 2010)	**28**	0	2	**113**
32	2013	(Polley et al. 2013a)	**52**	24	0	**625**
33	2017	(Ponce et al. 2017)	**79**	14	0	**206**
34	2006	(Poon et al. 2006)	**96**	1	6	**99**
35	2010	(Pöschl et al. 2010)	**71**	2	0	**32**
36	2017	(Rypien et al. 2017)	**76**	4	0	**60**
37	2014	(Sattabongkot et al. 2014)	**177**	15	22	**466**
38	2018	(Sattabongkot et al. 2018)	**6**	88	0	**3559**
39	2015	(Sema et al. 2015)	**30**	8	0	**44**
40	2017	(Serra-Casas et al. 2017)	**52**	203	0	**912**
41	2013	(Singh et al. 2013)	**68**	4	1	**16**
42	2017	(Singh et al. 2017)	**248**	0	9	**60**
43	2011	(Sirichaisinthop et al. 2011)	**59**	0	1	**50**
44	2013	(Surabattula et al. 2013)	**162**	1	6	**14**
45	2018	(Tambo et al. 2018)	**23**	24	0	**2593**
46	2011	(Tao et al. 2011)	**59**	0	1	**29**
47	2017	(Tegegne et al. 2017)	**10**	5	0	**72**
48	2015	(Vallejo et al. 2015)	**80**	14	0	**184**
49	2018	(Vásquez et al. 2018)	**31**	8	0	**492**
50	2018	(Viana et al. 2018)	**226**	13	0	**761**
51	2018	(Vincent et al. 2018)	**62**	2	0	**51**
52	2009	(Yamamura et al. 2009)	**85**	1	6	**2**
53	2018	(Zelman et al. 2018)	**2**	5	1	**1487**

Table 2: List of included studies comparing LAMP to PCR

	Years	Authors	**TP**	FP	FN	**TN**
1	2014	(Aydin-Schmidt et al. 2014)	**105**	2	10	**748**
2	2017	(Aydin-Schmidt et al. 2017)	**20**	2	29	**2957**
3	2016	(Britton et al. 2016a)	**62**	3	36	**44**
4	2018	(Cheaveau et al. 2018)	**57**	0	0	**291**
5	2010	(Chen et al. 2010)	**116**	0	1	**30**
6	2015	(Cook et al. 2015)	**10**	3	0	**984**
7	2017	(Cuadros et al. 2017)	**29**	11	0	**387**
8	2014	(Dinzouna-Boutamba et al. 2014)	**128**	9	0	**40**
9	2014	(Ghayour Najafabadi et al. 2014)	**68**	2	0	**40**
10	2018	(Girma et al. 2018)	**121**	4	0	**562**
11	2007	(Han et al. 2007)	**67**	3	1	**50**
12	2019	(Hartmeyer et al. 2019)	**27**	0	1	**10**
13	2017	(Hayashida et al. 2017)	**27**	0	3	**31**
14	2013	(Hopkins et al. 2013)	**178**	3	21	**70**
15	2018	(Kaur et al. 2018)	**148**	0	0	**17**
16	2018	(Kollenda et al. 2018)	**234**	0	9	**280**
17	2019	(Kudyba et al. 2019)	**39**	0	1	**51**
18	2011	(Lau et al. 2011)	**12**	1	0	**61**
19	2016	(Lau et al. 2016)	**132**	2	0	**67**
20	2012	(Lee et al. 2012)	**64**	1	0	**63**
21	2012	(Lu et al. 2012)	**160**	0	2	**50**
22	2010	(Lucchi et al. 2010)	**89**	1	1	**14**
23	2016	(Lucchi et al. 2016)	**140**	8	4	**57**
24	2015	(Marti et al. 2015)	**43**	0	0	**158**
25	2014	(Mohon et al. 2014)	**106**	0	2	**103**
26	2016	(Mohon et al. 2016)	**71**	2	0	**67**
27	2016	(Ocker et al. 2016)	**116**	0	1	**15**
28	2015	(Oriero et al. 2015a)	**100**	5	7	**72**
29	2015	(Oriero et al. 2015b)	**120**	7	11	**203**
30	2013	(Patel et al. 2013)	**70**	0	4	**46**
31	2014	(Patel et al. 2014)	**91**	0	5	**45**
32	2017	(Perera et al. 2017)	**67**	0	2	**630**
33	2017	(Piera et al. 2017)	**73**	0	0	**19**
34	2010	(Polley et al. 2010)	**28**	0	2	**113**
35	2013	(Polley et al. 2013a)	**62**	14	1	**624**
36	2017	(Ponce et al. 2017)	**85**	4	0	**210**
37	2006	(Poon et al. 2006)	**96**	1	5	**100**
38	2010	(Pöschl et al. 2010)	**72**	0	1	**32**
39	2017	(Rypien et al. 2017)	**78**	2	0	**60**
40	2014	(Sattabongkot et al. 2014)	**67**	0	5	**147**

41	2018	(Sattabongkot et al. 2018)	**88**	0	0	**88**
42	2015	(Sema et al. 2015)	**31**	7	0	**44**
43	2017	(Serra-Casas et al. 2017)	**235**	20	21	**227**
44	2013	(Singh et al. 2013)	**72**	0	1	**16**
45	2017	(Singh et al. 2017)	**248**	0	11	**58**
46	2011	(Tao et al. 2011)	**57**	2	0	**30**
47	2017	(Tegegne et al. 2017)	**10**	5	0	**72**
48	2015	(Vallejo et al. 2015)	**64**	17	6	**191**
49	2018	(Vásquez et al. 2018)	**39**	0	0	**492**
50	2018	(Viana et al. 2018)	**220**	19	0	**761**
51	2018	(Vincent et al. 2018)	**64**	0	2	**51**
52	2016	(Xu et al. 2016)	**59**	0	10	**11**
53	2009	(Yamamura et al. 2009)	**86**	0	2	**2**

Table 3: List of included studies comparing LAMP to RDTs

	Years	Authors	**TP**	FP	FN	**TN**
1	2014	(Aydin-Schmidt et al. 2014) (Asymptomatic)	13	37	0	415
2	2014	(Aydin-Schmidt et al. 2014) (Suspected)	115	6	0	744
3	2017	(Aydin-Schmidt et al. 2017)	13	9	0	2997
4	2015	(Cook et al. 2015)	10	8	1	978
5	2015	(Cuadros et al. 2015)	3	8	0	159
6	2017	(De Koninck et al. 2017)	8	4	0	18
7	2014	(Dinzouna-Boutamba et al. 2014)	137	0	0	40
8	2018	(Girma et al. 2018)	20	105	0	437
9	2019	(Hartmeyer et al. 2019)	18	9	0	10
10	2018	(Kaur et al. 2018)	143	5	0	17
11	2018	(McCreesh et al. 2018)	16	27	15	1861
12	2016	(Mohon et al. 2016)	61	12	0	79
13	2015	(Morris et al. 2015)	19	46	0	3918
14	2015	(Oriero et al. 2015b)	126	1	0	236
15	2014	(Sattabongkot et al. 2014)	65	0	5	147
16	2018	(Tambo et al. 2018)	23	24	0	2593
17	2017	(Tegegne et al. 2017)	9	6	0	72

Table 4: Data synthesis of LAMP results compared to microscopy, and/or PCR, or RDT

	LAMP vs microscopy and PCR	LAMP vs microscopy	LAMP vs microscopy (best studies)	LAMP vs PCR	LAMP vs PCR (best studies)	LAMP vs PCR (vivax)	LAMP vs RDT
Bivariate analysis (REML)							
Sensitivity (95%CI.lb-95%CI.ub)	0.977 (0.965-0.985)	0.971 (0.957-0.980)	0.974 (0.960-0.984)	0.971 (0.957-0.980)	0.961 (0.935-0.976)	0.948 (0.800-0.988)	0.966 (0.921-0.986)
Specificity (95%CI.lb-95%CI.ub)	0.947 (0.924-0.964)	0.956 (0.938-0.968)	0.951 (0.927-0.967)	0.956 (0.938-0.968)	0.984 (0.968-0.988)	0.956 (0.865-0.987)	0.964 (0.921-0.984)
AUC	0.985	0.985	0.985	0.985	0.987	0.982	0.984
DOR (2.5%-97.5%)	1061.447 (595.199-1892.929)	913.979 (542.306-1540.381)	959.506 (511.141-1801.169)	913.979 (542.306-1540.381)	1658.503 (824.983-3334.165)	462.891 (76.554-2798.903)	911.208 (295.097-2813.651)
I^2 (%)	0	0	0	0	0	0	0
Univariate analysis (DOR)							
OR (95% CI)	1221.186 (695.726-2143.512)	1102.801 (651.748-1866.015)	1158.573 (619.187-2167.826)	1102.801 (651.748-1866.015)	1772.017 (890.516-3526.096)	504.757 (84.814-3003.993)	943.033 (301.015-2954.371)
I^2 (%)	50.0	63.1	58.6	63.1	64.8	83.9	70.7

Contributions

SP and ALB drafted the manuscript and contributed to the development of the selection criteria, the risk of bias assessment strategy and data extraction criteria. MC performed the statistical analysis. ALB developed the search strategy. SP provided expertise on malaria diagnosis and MC expertise on meta-analysis. All authors read, provided feed-back and approved the final manuscript.

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None

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References

Amir A, Cheong F-W, De Silva JR, Lau Y-L. Diagnostic tools in childhood malaria. Parasit Vectors. 2018 23;11(1):53.

Aydin-Schmidt B, Morris U, Ding XC, Jovel I, Msellem MI, Bergman D, et al. Field Evaluation of a High Throughput Loop Mediated Isothermal Amplification Test for the Detection of Asymptomatic Plasmodium Infections in Zanzibar. PloS One. 2017;12(1):e0169037.

Aydin-Schmidt B, Xu W, González IJ, Polley SD, Bell D, Shakely D, et al. Loop mediated isothermal amplification (LAMP) accurately detects malaria DNA from filter paper blood samples of low density parasitaemias. PloS One. 2014;9(8):e103905.

Billo MA, Diakité M, Dolo A, Diallo M, Poudiougou B, Diawara SI, et al. Inter-observer agreement according to malaria parasite density. Malar J. 2013 Sep 22;12:335.

Britton S, Cheng Q, McCarthy JS. Novel molecular diagnostic tools for malaria elimination: a review of options from the point of view of high-throughput and applicability in resource limited settings. Malar J [Internet]. 2016a Feb 16 [cited 2016 Oct 17];15. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4754967/

Britton S, Cheng Q, McCarthy JS. Novel molecular diagnostic tools for malaria elimination: a review of options from the point of view of high-throughput and applicability in resource limited settings. Malar J. 2016b Feb 16;15:88.

Cheaveau J, Nguyen H, Chow B, Marasinghe D, Mohon AN, Yuan H, et al. Clinical Validation of a Commercial LAMP Test for Ruling out Malaria in Returning Travelers: A Prospective Diagnostic Trial. Open Forum Infect Dis. 2018 Nov;5(11):ofy260.

Chen J-H, Lu F, Lim CS, Kim J-Y, Ahn H-J, Suh I-B, et al. Detection of Plasmodium vivax infection in the Republic of Korea by loop-mediated isothermal amplification (LAMP). Acta Trop. 2010 Jan;113(1):61–5.

Cook J, Aydin-Schmidt B, González IJ, Bell D, Edlund E, Nassor MH, et al. Loop-mediated isothermal amplification (LAMP) for point-of-care detection of asymptomatic low-density malaria parasite carriers in Zanzibar. Malar J. 2015 Jan 28;14:43.

Cuadros J, Pérez-Tanoira R, Prieto-Pérez L, Martin-Martin I, Berzosa P, González V, et al. Field Evaluation of Malaria Microscopy, Rapid Malaria Tests and Loop-Mediated Isothermal Amplification in a Rural Hospital in South Western Ethiopia. PloS One. 2015;10(11):e0142842.

De Koninck A-S, Cnops L, Hofmans M, Jacobs J, Van den Bossche D, Philippé J. Diagnostic performance of the loop-mediated isothermal amplification (LAMP) based illumigene® malaria assay in a non-endemic region. Malar J. 2017 17;16(1):418.

Dinzouna-Boutamba S-D, Yang H-W, Joo S-Y, Jeong S, Na B-K, Inoue N, et al. The development of loop-mediated isothermal amplification targeting alpha-tubulin DNA for the rapid detection of Plasmodium vivax. Malar J. 2014 Jun 30;13:248.

Frickmann H, Hinz R, Rojak S, Bonow I, Ruben S, Wegner C, et al. Evaluation of automated loop-mediated amplification (LAMP) for routine malaria detection in blood samples of German travelers - A cross-sectional study. Travel Med Infect Dis. 2018 Aug;24:25–30.

Ghayour Najafabadi Z, Oormazdi H, Akhlaghi L, Meamar AR, Nateghpour M, Farivar L, et al. Detection of Plasmodium vivax and Plasmodium falciparum DNA in human saliva and urine: loop-mediated isothermal amplification for malaria diagnosis. Acta Trop. 2014 Aug;136:44–9.

Girma S, Cheaveau J, Mohon AN, Marasinghe D, Legese R, Balasingam N, et al. Prevalence and epidemiological characteristics of asymptomatic malaria based on ultrasensitive diagnostics: A cross-sectional study. Clin Infect Dis Off Publ Infect Dis Soc Am. 2018 Nov 26;

Han E-T, Watanabe R, Sattabongkot J, Khuntirat B, Sirichaisinthop J, Iriko H, et al. Detection of four Plasmodium species by genus- and species-specific loop-mediated isothermal amplification for clinical diagnosis. J Clin Microbiol. 2007 Aug;45(8):2521–8.

Hartmeyer GN, Hoegh SV, Skov MN, Kemp M. Use of Loop-Mediated Isothermal Amplification in a Resource-Saving Strategy for Primary Malaria Screening in a Non-Endemic Setting. Am J Trop Med Hyg. 2019 Jan 21;

Kaur H, Sehgal R, Bansal D, Sultan AA, Bhalla A, Singhi SC. Development of Visually Improved Loop Mediated Isothermal Amplification for the Diagnosis of Plasmodium vivax Malaria in a Tertiary Hospital in Chandigarh, North India. Am J Trop Med Hyg. 2018 May;98(5):1374–81.

Kollenda H, Hagen RM, Hanke M, Rojak S, Hinz R, Wassill L, et al. Poor Diagnostic Performance of a Species-Specific Loop-Mediated Isothermal Amplification (LAMP) Platform for Malaria. Eur J Microbiol Immunol. 2018 Sep 28;8(4):112–8.

Kudyba HM, Louzada J, Ljolje D, Kudyba KA, Muralidharan V, Oliveira-Ferreira J, et al. Field evaluation of malaria malachite green loop-mediated isothermal amplification in health posts in Roraima state, Brazil. Malar J [Internet]. 2019 Mar 25 [cited 2020 Feb 3];18. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6434790/

Landier J, Parker DM, Thu AM, Carrara VI, Lwin KM, Bonnington CA, et al. The role of early detection and treatment in malaria elimination. Malar J [Internet]. 2016 Jul 15 [cited 2019 Apr 5];15. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4946177/

Lau Y-L, Fong M-Y, Mahmud R, Chang P-Y, Palaeya V, Cheong F-W, et al. Specific, sensitive and rapid detection of human plasmodium knowlesi infection by loop-mediated isothermal amplification (LAMP) in blood samples. Malar J. 2011 Jul 20;10:197.

Lau Y-L, Lai M-Y, Fong M-Y, Jelip J, Mahmud R. Loop-Mediated Isothermal Amplification Assay for Identification of Five Human Plasmodium Species in Malaysia. Am J Trop Med Hyg. 2016 Feb;94(2):336–9.

Lee P-W, Ji D-D, Liu C-T, Rampao HS, do Rosario VE, Lin I-F, et al. Application of loop-mediated isothermal amplification for malaria diagnosis during a follow-up study in São Tomé. Malar J. 2012 Dec 6;11:408.

Lu F, Gao Q, Zhou H, Cao J, Wang W, Lim CS, et al. Molecular test for vivax malaria with loop-mediated isothermal amplification method in central China. Parasitol Res. 2012 Jun;110(6):2439–44.

Lucchi NW, Demas A, Narayanan J, Sumari D, Kabanywanyi A, Kachur SP, et al. Real-time fluorescence loop mediated isothermal amplification for the diagnosis of malaria. PloS One. 2010 Oct 29;5(10):e13733.

Lucchi NW, Gaye M, Diallo MA, Goldman IF, Ljolje D, Deme AB, et al. Evaluation of the Illumigene Malaria LAMP: A Robust Molecular Diagnostic Tool for Malaria Parasites. Sci Rep. 2016 09;6:36808.

Lucchi NW, Ndiaye D, Britton S, Udhayakumar V. Expanding the malaria molecular diagnostic options: opportunities and challenges for loop-mediated isothermal amplification tests for malaria control and elimination. Expert Rev Mol Diagn. 2018;18(2):195–203.

Marti H, Stalder C, González IJ. Diagnostic accuracy of a LAMP kit for diagnosis of imported malaria in Switzerland. Travel Med Infect Dis. 2015 Apr;13(2):167–71.

McCreesh P, Mumbengegwi D, Roberts K, Tambo M, Smith J, Whittemore B, et al. Subpatent malaria in a low transmission African setting: a cross-sectional study using rapid diagnostic testing (RDT) and loop-mediated isothermal amplification (LAMP) from Zambezi region, Namibia. Malar J. 2018 Dec 19;17(1):480.

McGrath TA, Alabousi M, Skidmore B, Korevaar DA, Bossuyt PMM, Moher D, et al. Recommendations for reporting of systematic reviews and meta-analyses of diagnostic test accuracy: a systematic review. Syst Rev. 2017 10;6(1):194.

Menegon M, L'Episcopia M, Nurahmed AM, Talha AA, Nour BYM, Severini C. Identification of Plasmodium falciparum isolates lacking histidine-rich protein 2 and 3 in Eritrea. Infect Genet Evol J Mol Epidemiol Evol Genet Infect Dis. 2017;55:131–4.

Mohon AN, Elahi R, Khan WA, Haque R, Sullivan DJ, Alam MS. A new visually improved and sensitive loop mediated isothermal amplification (LAMP) for diagnosis of symptomatic falciparum malaria. Acta Trop. 2014 Jun;134:52–7.

Mohon AN, Lee LD-Y, Bayih AG, Folefoc A, Guelig D, Burton RA, et al. NINA-LAMP compared to microscopy, RDT, and nested PCR for the detection of imported malaria. Diagn Microbiol Infect Dis. 2016 Jun;85(2):149–53.

Morris U, Khamis M, Aydin-Schmidt B, Abass AK, Msellem MI, Nassor MH, et al. Field deployment of loop-mediated isothermal amplification for centralized mass-screening of asymptomatic malaria in Zanzibar: a pre-elimination setting. Malar J. 2015 May 17;14:205.

Nema S, Verma AK, Bharti PK. Strengthening diagnosis is key to eliminating malaria in India. Lancet Infect Dis. 2019 Dec;19(12):1277–8.

Notomi T, Okayama H, Masubuchi H, Yonekawa T, Watanabe K, Amino N, et al. Loop-mediated isothermal amplification of DNA. Nucleic Acids Res. 2000 Jun 15;28(12):E63.

Ocker R, Prompunjai Y, Chutipongvivate S, Karanis P. MALARIA DIAGNOSIS BY LOOP-MEDIATED ISOTHERMAL AMPLIFICATION (LAMP) IN THAILAND. Rev Inst Med Trop Sao Paulo. 2016;58:27.

Odaga J, Sinclair D, Lokong JA, Donegan S, Hopkins H, Garner P. Rapid diagnostic tests versus clinical diagnosis for managing people with fever in malaria endemic settings. Cochrane Database Syst Rev. 2014 Apr 17;(4):CD008998.

Oriero EC, Jacobs J, Geertruyden J-PV, Nwakanma D, D'Alessandro U. Molecular-based isothermal tests for field diagnosis of malaria and their potential contribution to malaria elimination. J Antimicrob Chemother. 2015a Jan 1;70(1):2–13.

Oriero EC, Okebe J, Jacobs J, Van Geertruyden J-P, Nwakanma D, D'Alessandro U. Diagnostic performance of a novel loop-mediated isothermal amplification (LAMP) assay targeting the apicoplast genome for malaria diagnosis in a field setting in sub-Saharan Africa. Malar J. 2015b Oct 9;14:396.

Patel JC, Lucchi NW, Srivastava P, Lin JT, Sug-Aram R, Aruncharus S, et al. Field evaluation of a real-time fluorescence loop-mediated isothermal amplification assay, RealAmp, for the diagnosis of malaria in Thailand and India. J Infect Dis. 2014 Oct 15;210(8):1180–7.

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 13;16(1):29.

Polley SD, González IJ, Mohamed D, Daly R, Bowers K, Watson J, et al. Clinical evaluation of a loop-mediated amplification kit for diagnosis of imported malaria. J Infect Dis. 2013a Aug 15;208(4):637–44.

Polley SD, Mori Y, Watson J, Perkins MD, González IJ, Notomi T, et al. Mitochondrial DNA targets increase sensitivity of malaria detection using loop-mediated isothermal amplification. J Clin Microbiol. 2010 Aug;48(8):2866–71.

Ponce C, Kaczorowski F, Perpoint T, Miailhes P, Sigal A, Javouhey E, et al. Diagnostic accuracy of loop-mediated isothermal amplification (LAMP) for screening patients with imported malaria in a non-endemic setting. Parasite Paris Fr. 2017;24:53.

Poon LLM, Wong BWY, Ma EHT, Chan KH, Chow LMC, Abeyewickreme W, et al. Sensitive and inexpensive molecular test for falciparum malaria: detecting Plasmodium falciparum DNA directly from heat-treated blood by loop-mediated isothermal amplification. Clin Chem. 2006 Feb;52(2):303–6.

Pöschl B, Waneesorn J, Thekisoe O, Chutipongvivate S, Karanis P, Panagiotis K. Comparative diagnosis of malaria infections by microscopy, nested PCR, and LAMP in northern Thailand. Am J Trop Med Hyg. 2010 Jul;83(1):56–60.

Roth JM, Korevaar DA, Leeflang MMG, Mens PF. Molecular malaria diagnostics: A systematic review and meta-analysis. Crit Rev Clin Lab Sci. 2016 Mar 3;53(2):87–105.

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 25;16(1):298.

Rypien C, Chow B, Chan WW, Church DL, Pillai DR. Detection of Plasmodium Infection by the illumigene Malaria Assay Compared to Reference Microscopy and Real-Time PCR. J Clin Microbiol. 2017;55(10):3037–45.

Sattabongkot J, Suansomjit C, Nguitragool W, Sirichaisinthop J, Warit S, Tiensuwan M, et al. Prevalence of asymptomatic Plasmodium infections with sub-microscopic parasite densities in the northwestern border of Thailand: a potential threat to malaria elimination. Malar J. 2018 Sep 12;17(1):329.

Sattabongkot J, Tsuboi T, Han E-T, Bantuchai S, Buates S. Loop-mediated isothermal amplification assay for rapid diagnosis of malaria infections in an area of endemicity in Thailand. J Clin Microbiol. 2014 May;52(5):1471–7.

Sema M, Alemu A, Bayih AG, Getie S, Getnet G, Guelig D, et al. Evaluation of non-instrumented nucleic acid amplification by loop-mediated isothermal amplification (NINA-LAMP) for the diagnosis of malaria in Northwest Ethiopia. Malar J. 2015 Jan 28;14:44.

Serra-Casas E, Manrique P, Ding XC, Carrasco-Escobar G, Alava F, Gave A, et al. Loop-mediated isothermal DNA amplification for asymptomatic malaria detection in challenging field settings: Technical performance and pilot implementation in the Peruvian Amazon. PloS One. 2017;12(10):e0185742.

Singh R, Savargaonkar D, Bhatt R, Valecha N. Rapid detection of Plasmodium vivax in saliva and blood using loop mediated isothermal amplification (LAMP) assay. J Infect. 2013 Sep;67(3):245–7.

Singh R, Singh DP, Savargaonkar D, Singh OP, Bhatt RM, Valecha N. Evaluation of SYBR green I based visual loop-mediated isothermal amplification (LAMP) assay for genus and species-specific diagnosis of malaria in P. vivax and P. falciparum endemic regions. J Vector Borne Dis. 2017 Mar;54(1):54–60.

Sirichaisinthop J, Buates S, Watanabe R, Han E-T, Suktawonjaroenpon W, Krasaesub S, et al. Evaluation of loop-mediated isothermal amplification (LAMP) for malaria diagnosis in a field setting. Am J Trop Med Hyg. 2011 Oct;85(4):594–6.

Surabattula R, Vejandla MP, Mallepaddi PC, Faulstich K, Polavarapu R. Simple, rapid, inexpensive platform for the diagnosis of malaria by loop mediated isothermal amplification (LAMP). Exp Parasitol. 2013 Jul;134(3):333–40.

Tambo M, Mwinga M, Mumbengegwi DR. Loop-mediated isothermal amplification (LAMP) and Polymerase Chain Reaction (PCR) as quality assurance tools for Rapid Diagnostic Test (RDT) malaria diagnosis in Northern Namibia. PloS One. 2018;13(12):e0206848.

Tao Z-Y, Zhou H-Y, Xia H, Xu S, Zhu H-W, Culleton RL, et al. Adaptation of a visualized loop-mediated isothermal amplification technique for field detection of Plasmodium vivax infection. Parasit Vectors. 2011 Jun 21;4:115.

Tegegne B, Getie S, Lemma W, Mohon AN, Pillai DR. Performance of loop-mediated isothermal amplification (LAMP) for the diagnosis of malaria among malaria suspected pregnant women in Northwest Ethiopia. Malar J. 2017 19;16(1):34.

Vallejo AF, Martínez NL, González IJ, Arévalo-Herrera M, Herrera S. Evaluation of the loop mediated isothermal DNA amplification (LAMP) kit for malaria diagnosis in P. vivax endemic settings of Colombia. PLoS Negl Trop Dis. 2015 Jan;9(1):e3453.

Vásquez AM, Zuluaga L, Tobón A, Posada M, Vélez G, González IJ, et al. Diagnostic accuracy of loop-mediated isothermal amplification (LAMP) for screening malaria in peripheral and placental blood samples from pregnant women in Colombia. Malar J. 2018 Jul 13;17(1):262.

Viana GMR, Silva-Flannery L, Lima Barbosa DR, Lucchi N, do Valle SCN, Farias S, et al. Field evaluation of a real time loop-mediated isothermal amplification assay (RealAmp) for malaria diagnosis in Cruzeiro do Sul, Acre, Brazil. PloS One. 2018;13(7):e0200492.

Vincent JP, Komaki-Yasuda K, Iwagami M, Kawai S, Kano S. Combination of PURE-DNA extraction and LAMP-DNA amplification methods for accurate malaria diagnosis on dried blood spots. Malar J. 2018 Oct 22;17(1):373.

Whiting PF, Rutjes AWS, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011 Oct 18;155(8):529–36.

WHO. World Malaria Report 2018. World Health Organization; 2018.

Wilson ML. Laboratory diagnosis of malaria: conventional and rapid diagnostic methods. Arch Pathol Lab Med. 2013 Jun;137(6):805–11.

Yamamura M, Makimura K, Ota Y. Evaluation of a new rapid molecular diagnostic system for Plasmodium falciparum combined with DNA filter paper, loop-mediated isothermal amplification, and melting curve analysis. Jpn J Infect Dis. 2009 Jan;62(1):20–5.

Zelman BW, Baral R, Zarlinda I, Coutrier FN, Sanders KC, Cotter C, et al. Costs and cost-effectiveness of malaria reactive case detection using loop-mediated isothermal amplification compared to

microscopy in the low transmission setting of Aceh Province, Indonesia. Malar J. 2018 Jun 1;17(1):220.

Zimmerman PA, Howes RE. Malaria diagnosis for malaria elimination. Curr Opin Infect Dis. 2015 Oct;28(5):446–54.