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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/ μ L (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/ μ L, 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/ μ L 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).

LAMP compared to microscopy

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 compare 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

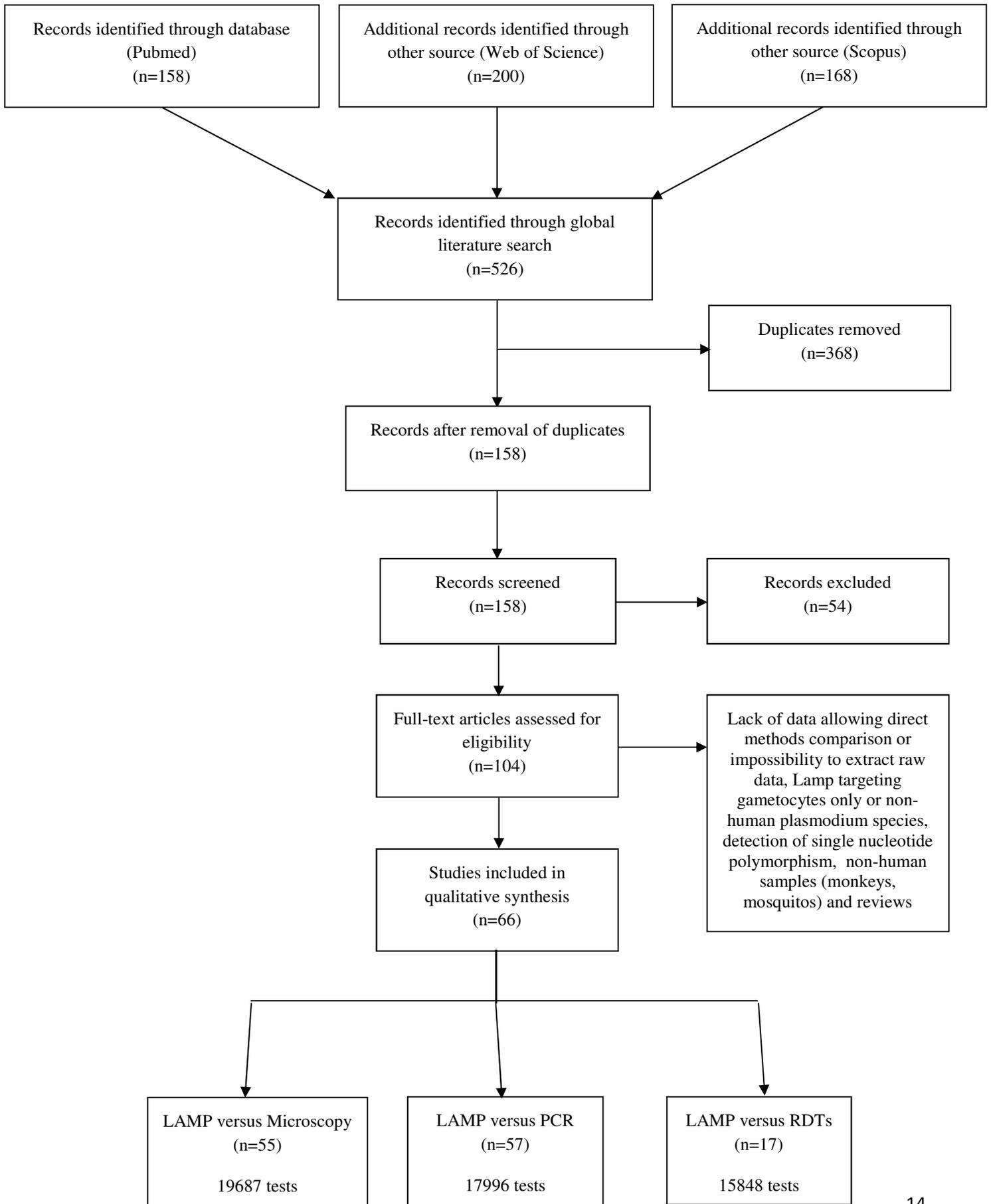


Figure 2: Risk of bias graph of studies included in the meta-analysis

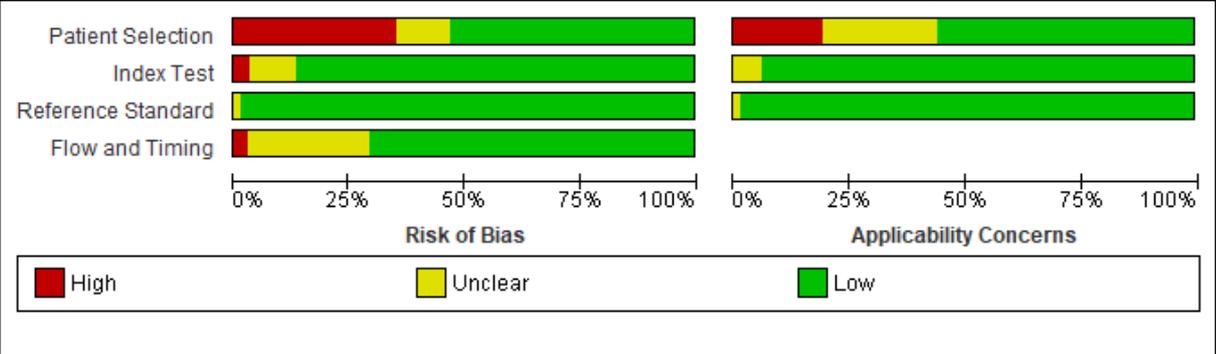
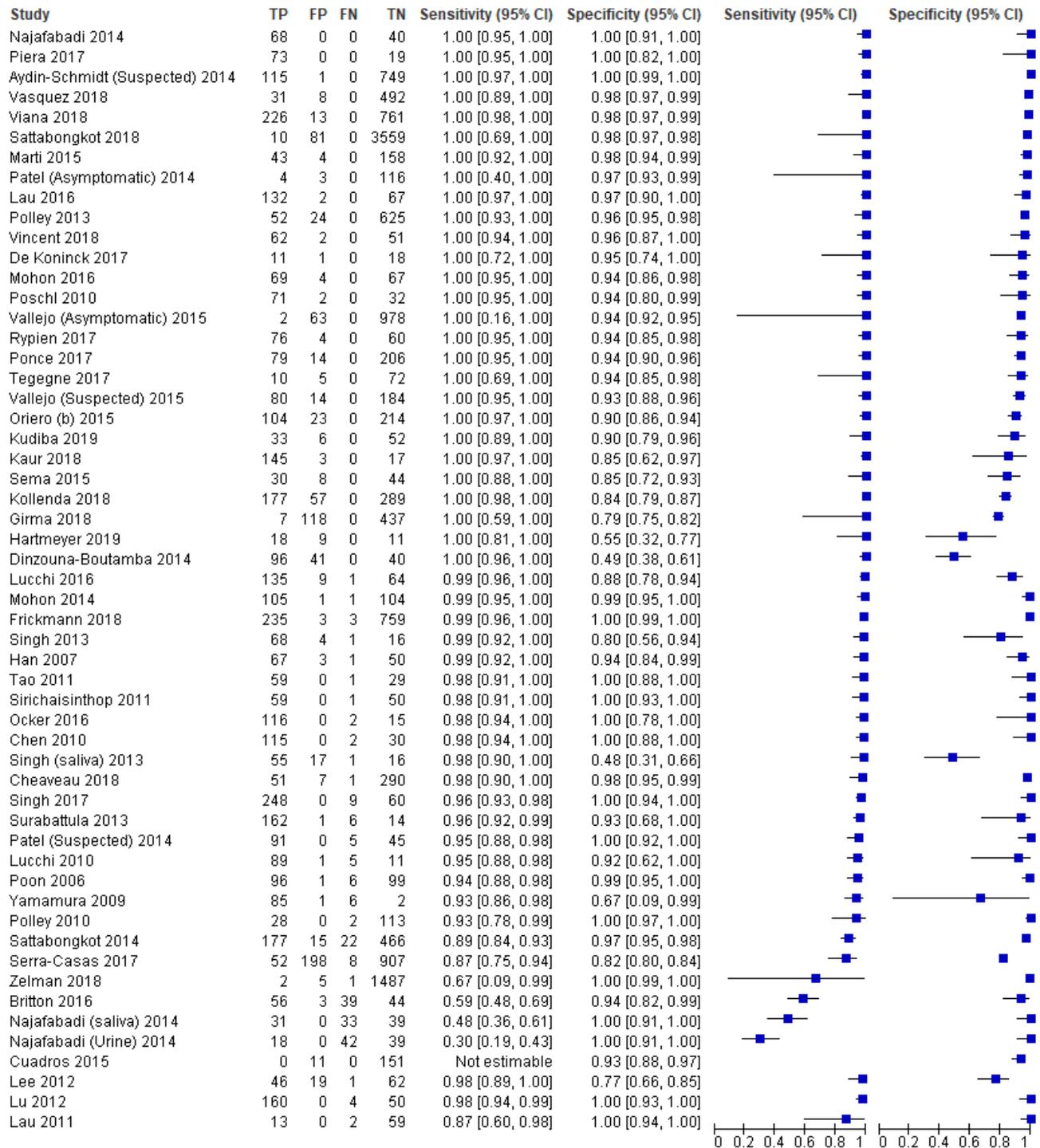


Figure 3: Forest plot of LAMP compared to microscopy



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

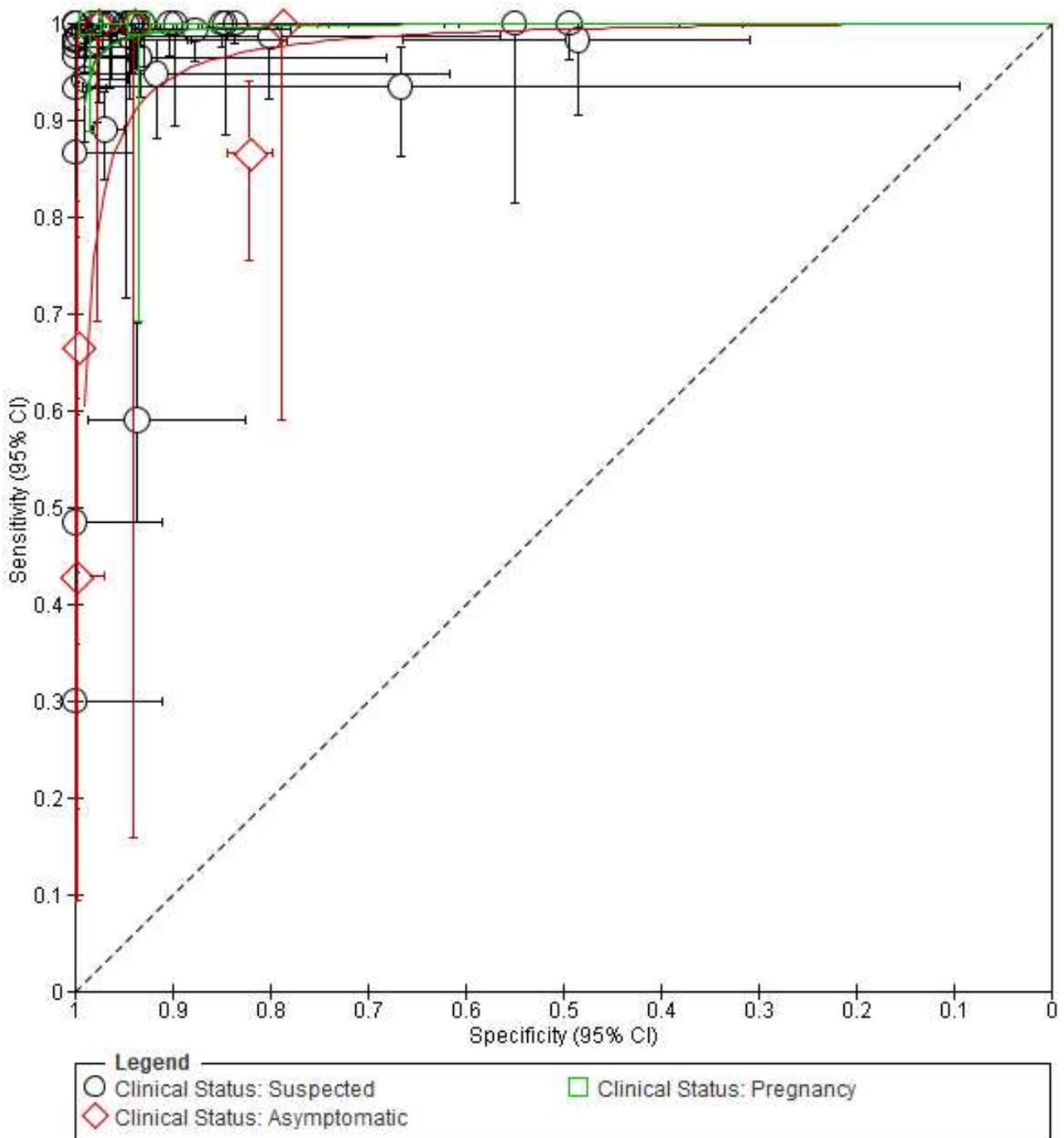


Figure 5: SROC of LAMP compared to microscopy according to LAMP tests providers

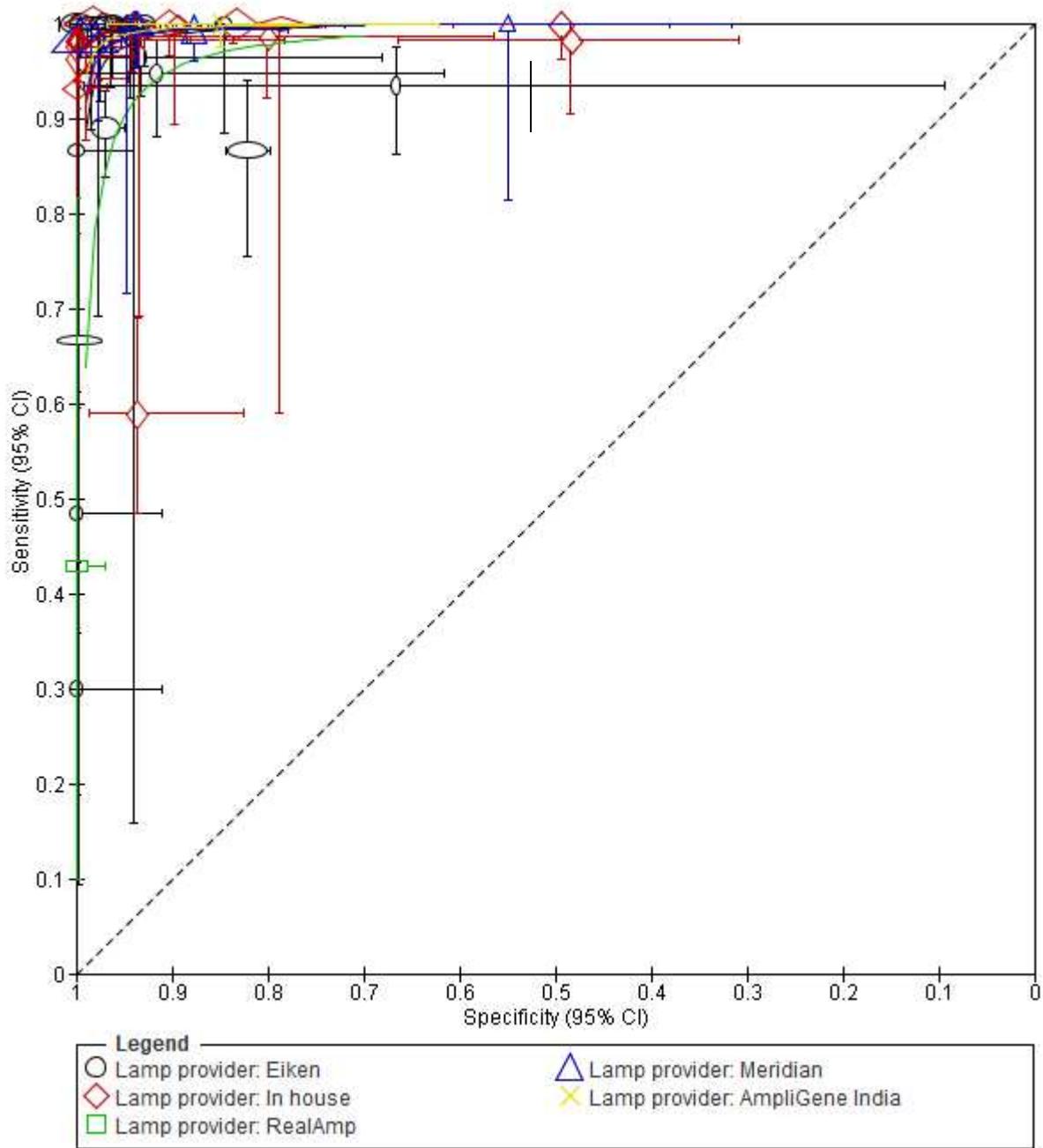
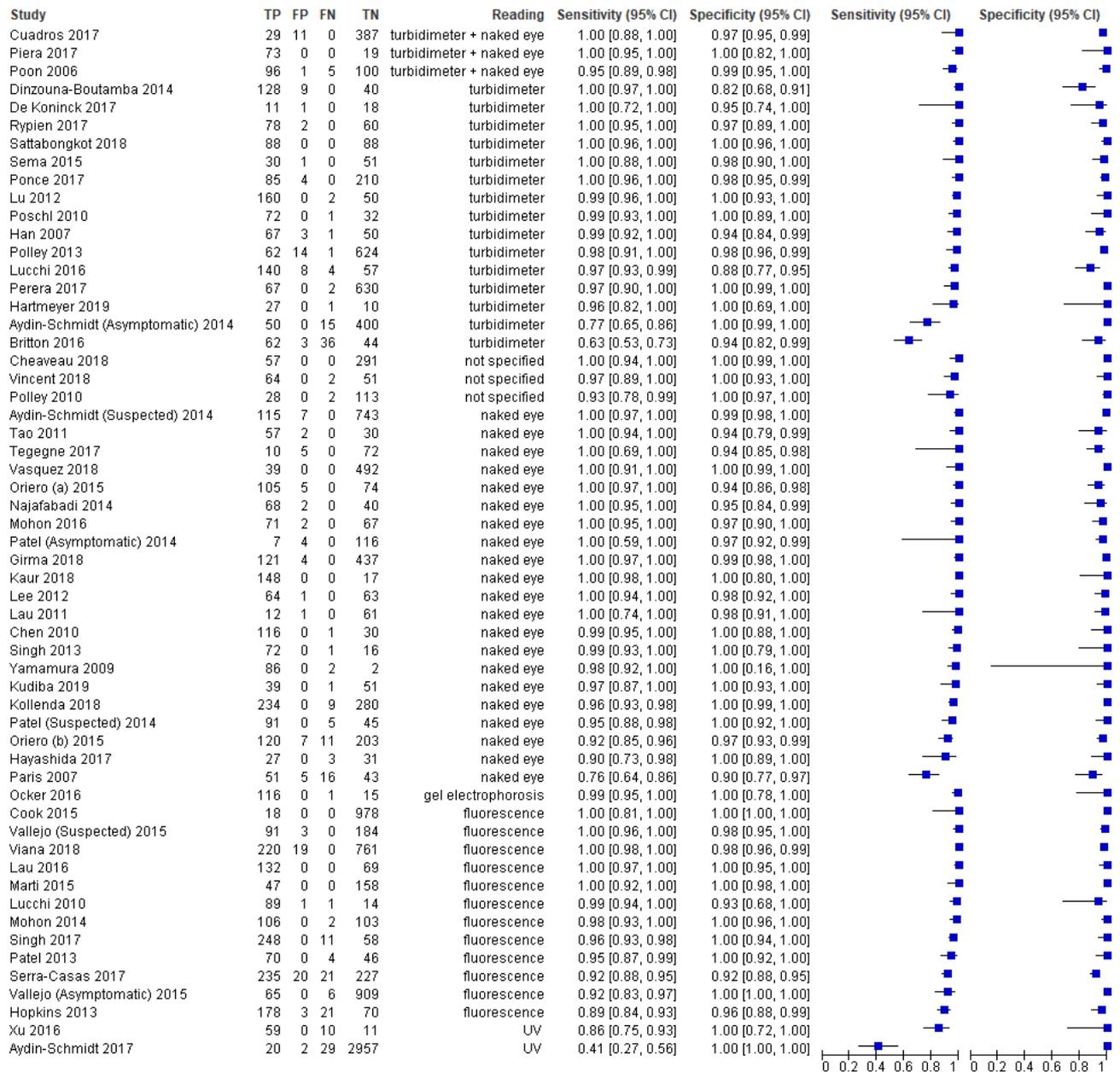


Figure 6: Forest plot and SROC of LAMP compared to microscopy according to reader method



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

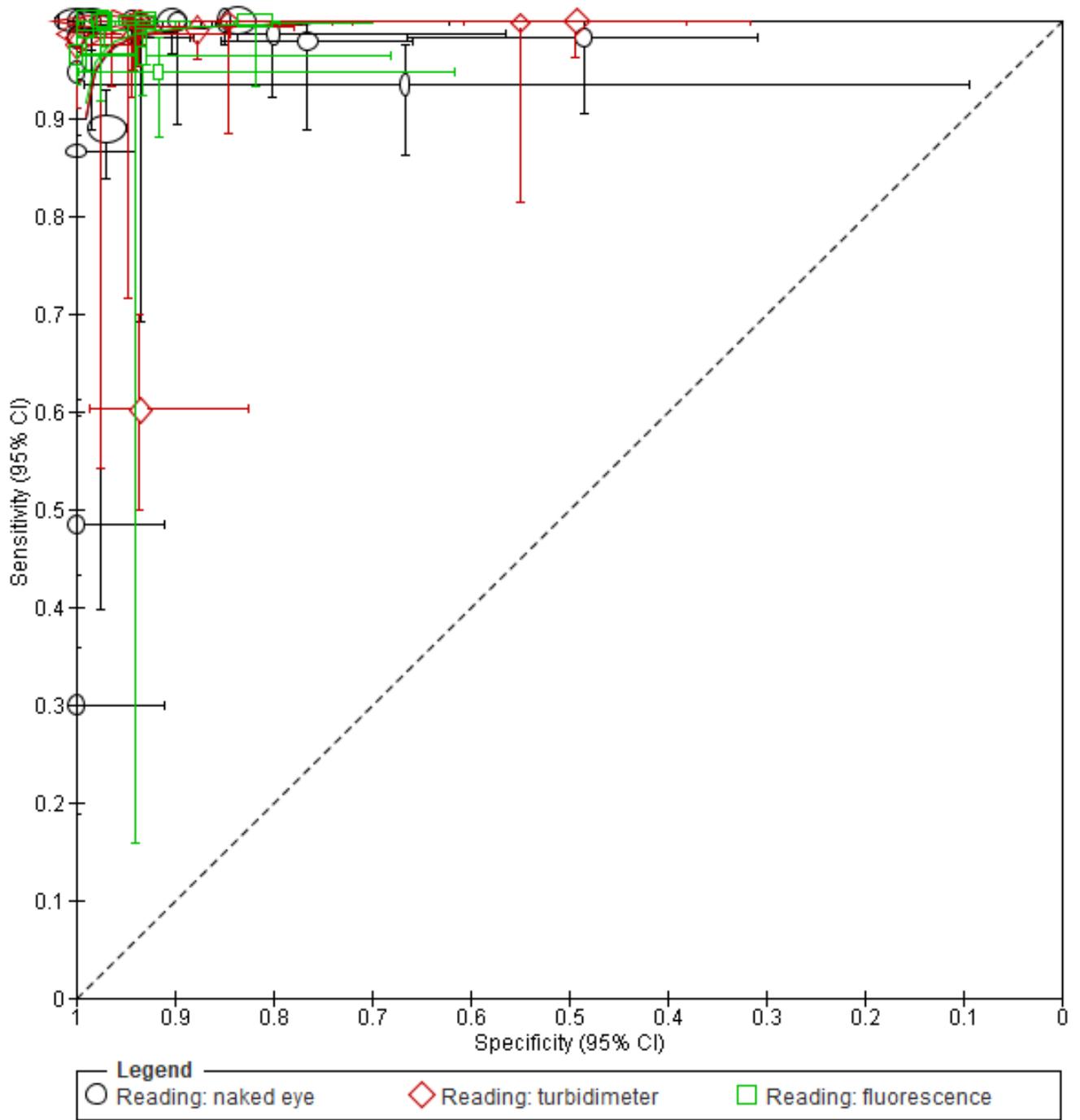
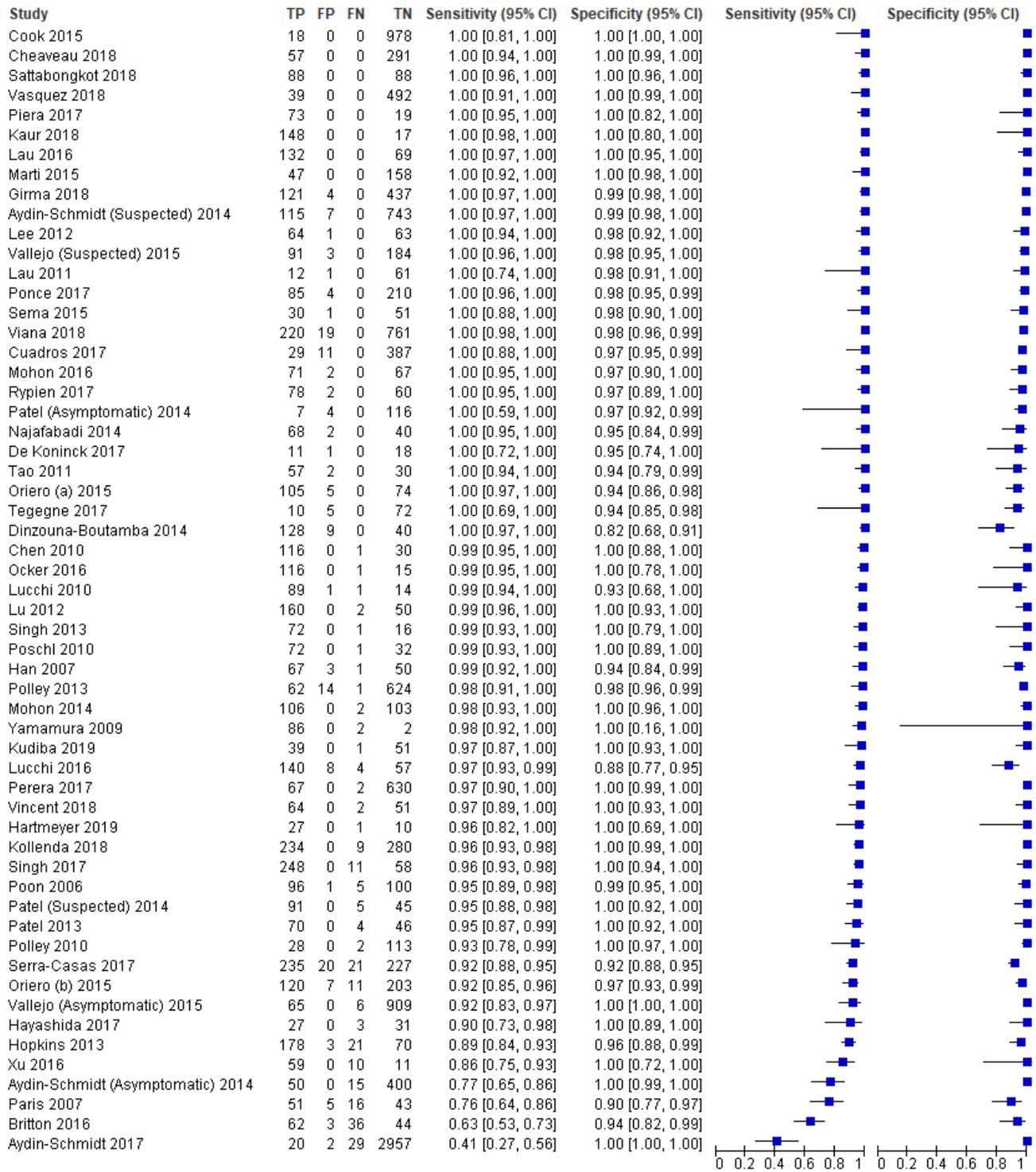


Figure 7: Forest plot of LAMP compared to PCR



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

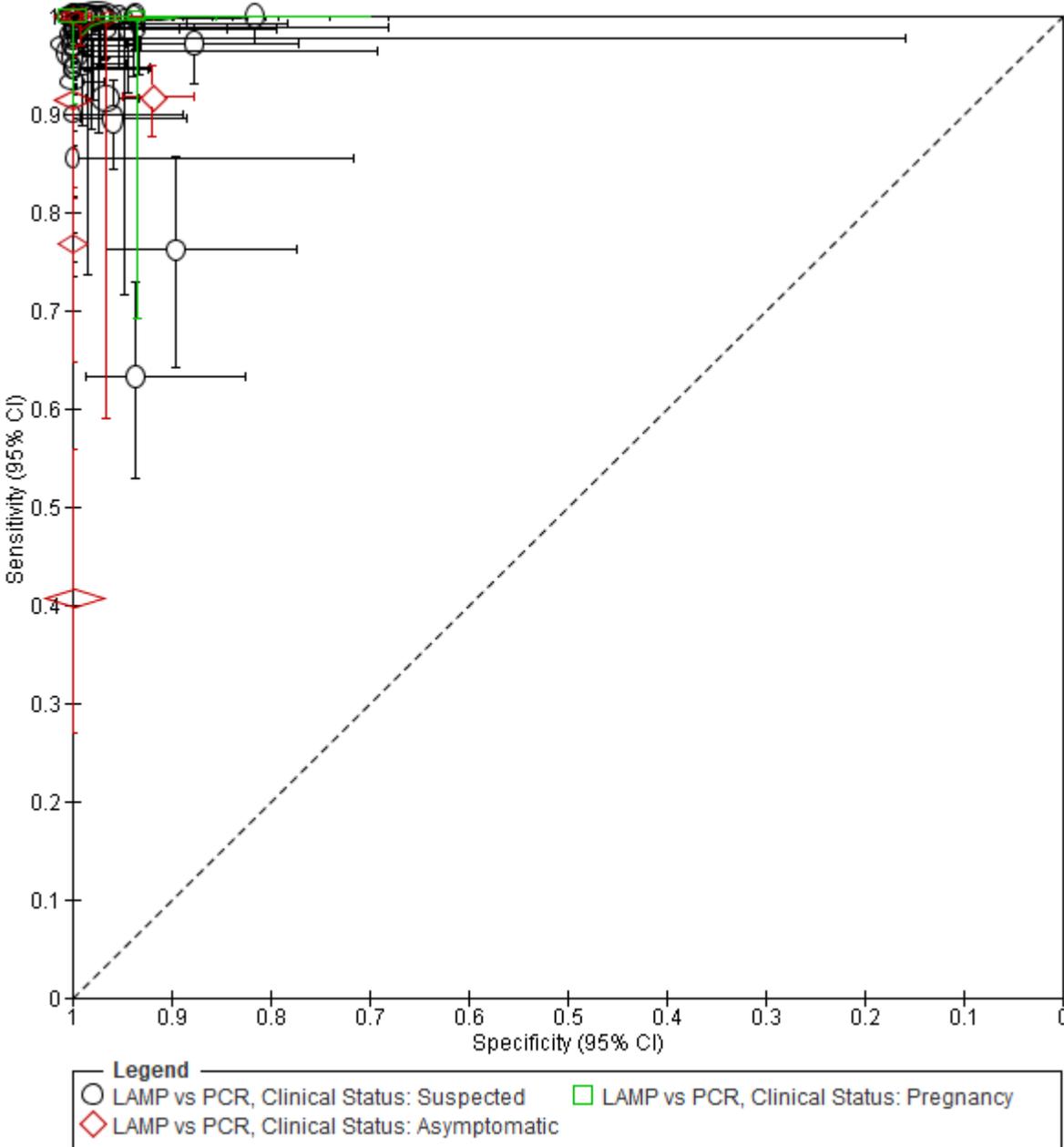
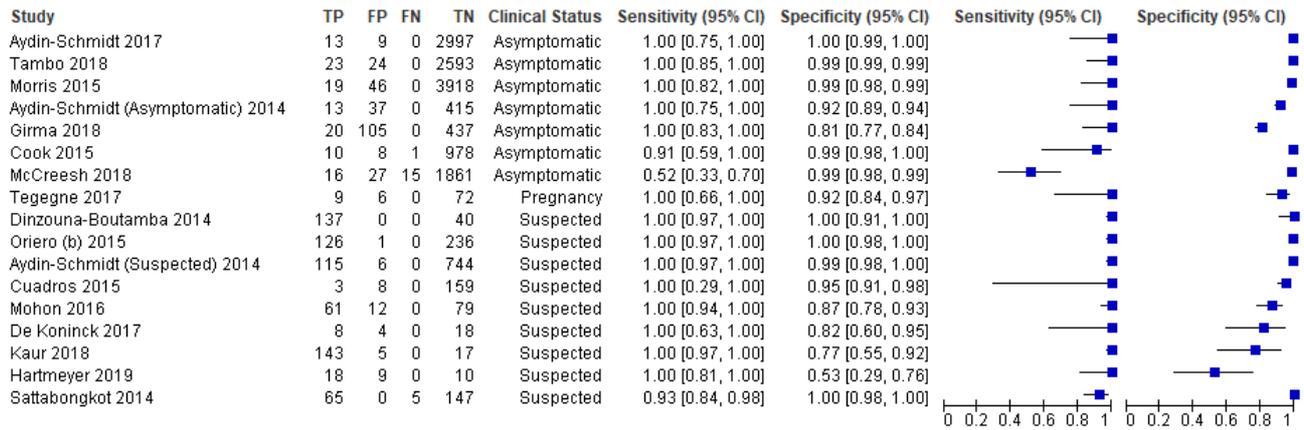


Figure 9: Forest plot and SROC of LAMP versus RDT



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

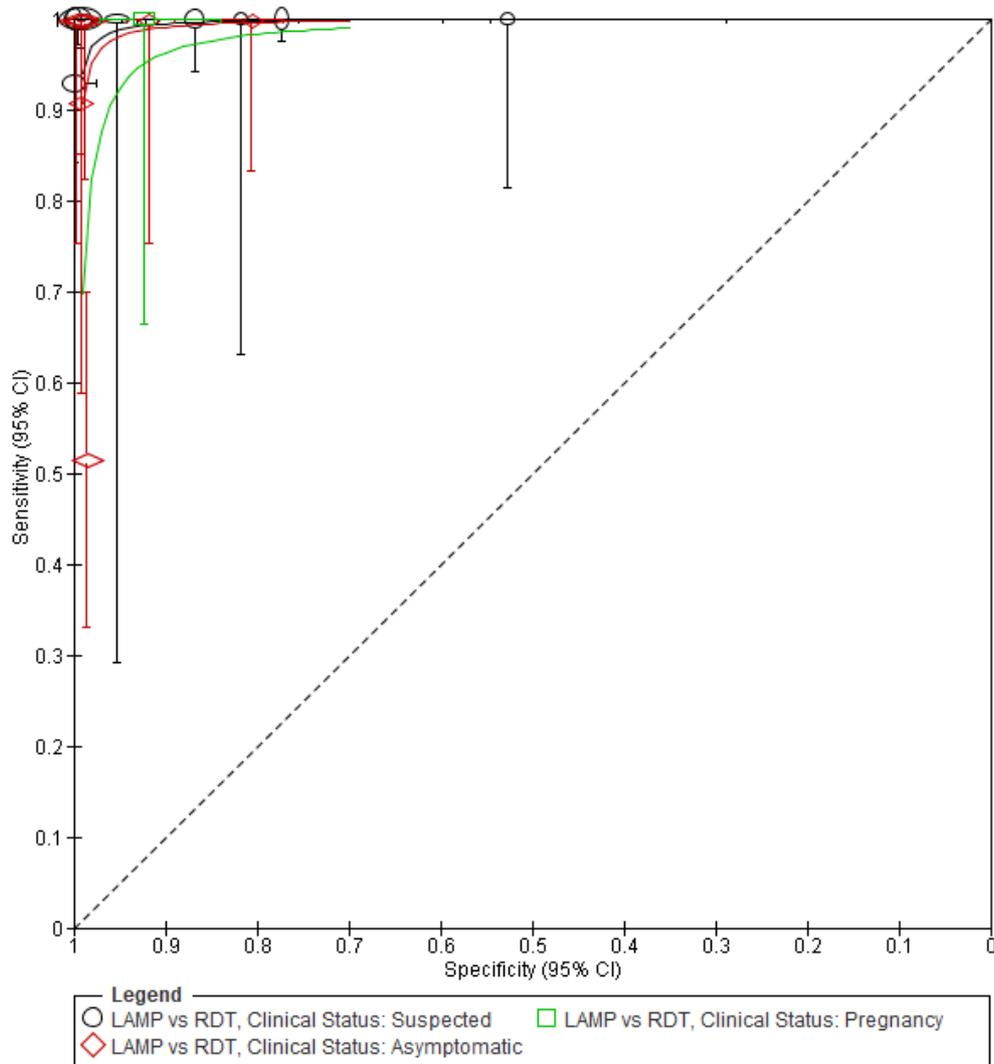


Table 1: List of included studies comparing LAMP to microscopy

	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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