BMJ Global Health

Accuracy of malaria diagnostic tests performed on non-invasively collected samples: a systematic review and meta-analysis

Celestin Danwang ,[1] Jean Jacques Noubiap,[2] Jacob Souopgui ,[3] Jean Gaudart ,[4,5] Jean Cyr Yombi,[6] Annie Robert[1]

To cite: Danwang C, Noubiap JJ, Souopgui J, *et al*. Accuracy of malaria diagnostic tests performed on non-invasively collected samples: a systematic review and meta-analysis. *BMJ Global Health* 2021;**6**:e005634. doi:10.1136/bmjgh-2021-005634

Handling editor Alberto L Garcia-Basteiro

Received 7 March 2021
Revised 6 April 2021
Accepted 30 April 2021

For numbered affiliations see end of article.

Correspondence to
Dr Celestin Danwang; danram07@yahoo.fr

ABSTRACT

Background During the last decade, many studies have assessed the performance of malaria tests on non-invasively collected specimens, but no systematic review has hitherto estimated the overall performance of these tests. We report here the first meta-analysis estimating the diagnostic performance of malaria diagnostic tests performed on saliva, urine, faeces, skin odour ('sniff and tell') and hair, using either microscopy or PCR on blood sample as reference test.

Methods We searched on PubMed, EMBASE, African Journals Online and Cochrane Infectious Diseases from inception until 19 January 2021 for relevant primary studies. A random effects model was used to estimate the overall performance of various diagnostic methods on different types of specimen.

Results Eighteen studies providing 30 data sets were included in the meta-analysis. The overall sensitivity, specificity and diagnostic OR (DOR) of PCR were 84.5% (95% CI 79.3% to 88.6%), 97.3% (95% CI 95.3% to 98.5%) and 184.9 (95% CI 95.8 to 356.9) in saliva, respectively; 57.4% (95% CI 41.4% to 72.1%), 98.6% (95% CI 97.3% to 99.3%) and 47.2 (95% CI 22.1 to 101.1) in urine, respectively. The overall sensitivity, specificity and DOR of rapid diagnostic test for malaria in urine was 59.8% (95% CI 40.0% to 76.9%), 96.9% (95% CI 91.0% to 99.0%) and 30.8 (95% CI:23.5 to 40.4).

Conclusion In settings where PCR is available, saliva and urine samples should be considered for PCR-based malaria diagnosis only if blood samples cannot be collected. The performance of rapid diagnostic testing in the urine is limited, especially its sensitivity. Malaria testing on non-invasively collected specimen still needs substantial improvement.

Key questions

What is already known?

- Malaria diagnostic can be performed on non-invasively collected specimens
- Blood is the biological fluid of choice for malaria diagnosis.

What are the new findings?

- The meta-analysis suggested that sensitivity of PCR in saliva and urine is lower than that reported in the literature when PCR is performed on blood.
- The performance of RDT on urine is lower than the one observed in blood.

What do the new findings imply?

- Malaria testing on non-invasively collected specimen still needs substantial improvement.
- In settings where PCR is available, saliva and urine samples should be considered for PCR-based malaria diagnosis only if blood samples cannot be collected.

INTRODUCTION

Malaria remains a global public health problem with a substantial mortality especially in woman and children under 5 years.[1–3] According to the World Malaria Report 2020, there has been a significant reduction in the burden of malaria over the last two decades, although the Malaria Millennium Development Goal of 90% reduction in global malaria incidence and mortality by 2030 is far to be achieved.[1 4] The facies of malaria transmission and endemicity has changed thoroughly during the last two decades, with some regions like the great Mekong being close to elimination, while others like sub-Saharan Africa still have countries with high endemicity and heterogenous annual transmission pattern.[1]

Accurate diagnosis of malaria is a pillar of malaria control and elimination.[5 6] Prior to the dissemination of rapid diagnostic tests, microscopy and, to a lesser extent, PCR were among the most used methods in the diagnosis of malaria. These methods had the drawback that they require well-trained personnel, ongoing training of the workforce, logistic and equipment that are not always available in developing countries. Although microscopy

remains the gold standard, the advent of rapid diagnostic tests has greatly improved case detection and treatment rates.[7] However, the current diagnostic tests are done on blood samples collected invasively. In some areas, especially in sub-Saharan Africa, the collection of blood sample on which malaria testing is performed, is not an easy task because of blood taboos related to local cultural beliefs, fear of needles and beliefs that HIV test will be conducted on blood collected without consent of the participants when the amount of blood collected is high.[8–11] Moreover, in countries that are in elimination phase, the willingness of asymptomatic patients to go for an invasive test for surveillance purposes may become challenging over time, hence a need for malaria diagnostic tests performed on non-invasively collected specimens.[12 13] These non-invasively collected specimens are also more convenient for research purposes, to support decision making and can be used in management of patients with malaria in hospital.

Recently, several studies have evaluated the accuracy of diagnosing malaria using PCR, ELISA or rapid diagnostic testing (RDT) on non-invasively collected human specimens such as saliva, urine, faeces and hair.[14 15] The current study aimed to systematically review these studies and performed a meta-analysis to determine the overall diagnostic accuracy of malaria diagnostic tests performed on saliva, urine, faeces and hair.

METHODS

This review was registered with PROSPERO (International Prospective Register of Sytematic Reviews) and is reported in accordance with the Preferred Reporting Items for a Systematic Reviews and Meta-analyses of Diagnostic Test Accuracy guidelines.[16]

Search strategy and eligibility criteria

PubMed, EMBASE, Cochrane Infectious Diseases Group Specialised Register and African Journals Online were searched from inception to 19 January 2021 using predefined search strategies adapted for each database (online supplemental tables 1 and 2). We included studies with at least 20 participants reporting on malaria tests performed on non-invasively collected samples regardless of the language, year of publication, design or country. Were considered as non-invasively collected samples all specimens that were obtained without cutting the skin or penetrating any part of the body as defined in the Cambridge dictionary.[17] The 'sniff and tell' method refers to the diagnosis of malaria with dogs. We excluded reviews, letters, commentaries and editorials.

Records retrieved from bibliographic searches were imported in Rayyan online software.[18] After removal of duplicates, the titles and abstracts of remaining records were independently screened for potential inclusion by two reviewers (CD, JJNN). Full texts were then downloaded and assessed for final inclusion. Disagreements were solved through discussion and consensus.

Data extraction and quality assessment

Data were extracted using a preconceived form. They included first author's name, year of publication, country, characteristics of the study population (age distribution and symptoms), index test, reference standard test, type of non-invasive sample, number of true positive, true negative, false positive and false negative cases.

Records reporting the estimation of diagnostic accuracy on two subpopulations, or the ones stratifying the analysis according to a specific criterion, for example, the index test or reference standard used, were splitted into different data sets in order to obtain a single estimation per data set. Thus, the term 'record' refers to one study or article, while 'data set' refers to a substudy.

The Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) was used for the assessment of the risk of bias and applicability of included studies.[19] The QUADAS-2 tool is divided into four sections: patient selection, index test, reference standard, flow and timing. All the four sections are rated in the risk of bias assessment, while all except 'flow and timing' are rated in the applicability concern.[19 20]

An extensive description of the different methods of malaria diagnosis, their principles and techniques are discussed elsewhere.[21–24]

Statistical analysis

All analyses were conducted in R software V.4.0.2. Random effects meta-analysis was performed to determine separately the pooled sensitivity, specificity and diagnostic OR (DOR) using the 'meta' package and the summary receiver operating characteristic curve within the 'MADA' package.[25 26] A subgroup analysis was conducted according to the following variables: the type of specimen (urine, saliva, stool, 'sniff and tell'), the index test used on the non-invasively collected sample, the reference test used on blood and the age of participants. The presence of heterogeneity was assessed with the Cochran statistic and quantified by the I^2.[27 28] Values between 0%–40%, 30%–60%, 50%–90%, 75%–100% were considered as indicative of low, moderate, substantial, considerable heterogeneity, respectively.[29] A $p \leq 0.05$ was considered as statistically significant.

RESULTS

Search results

We retrieved 1607 records from bibliographic searches. Eighteen studies[14 15 30–45] were included, contributing to a total of 36 data sets included in the systematic review and 30 in the meta-analysis (figure 1).

Characteristics of studies in the meta-analysis

Data sets included in the meta-analysis were from 10 countries, mostly from Iran (10 data sets), India (5 data sets) and the Gambia (4 data sets) (online supplemental table 3). The studies were conducted between 2009 and 2020, and they included participants aged between 1 and 80 years. The proportion of male ranged from 29.0% to

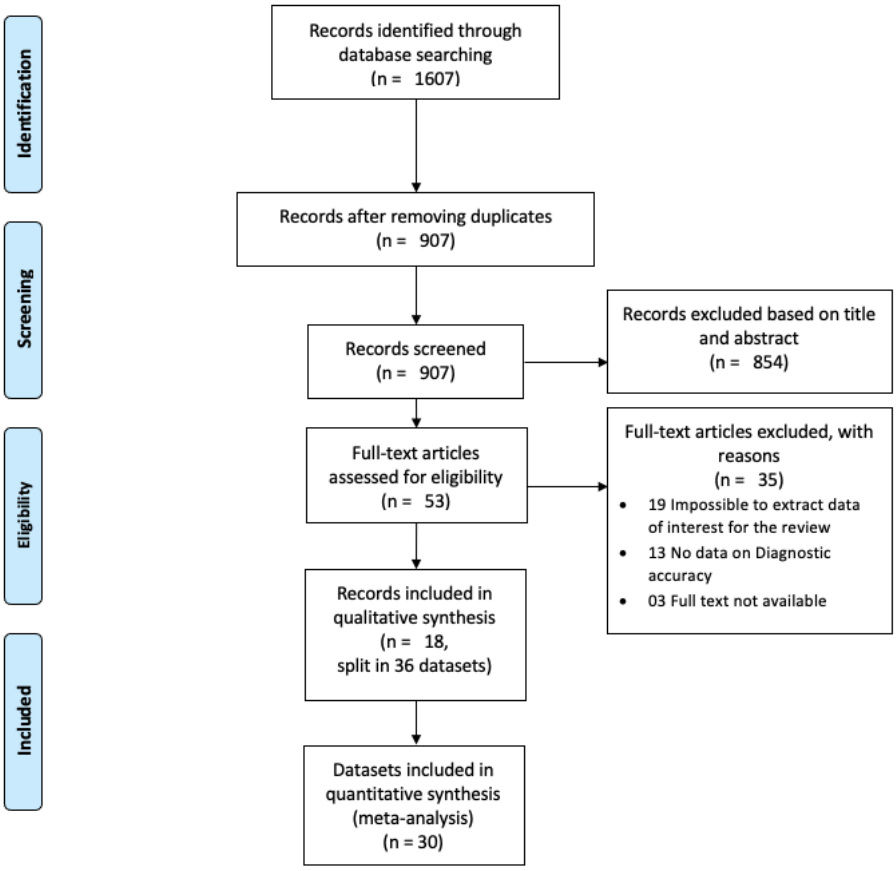


Figure 1 PRISMA flow chart. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

82.4%. Online supplemental table 4 presents the individual characteristics of included studies. The data sets predominantly (17 out of 30) had a moderate risk of bias (figure 2).

Diagnostic accuracy of malaria diagnostic tests performed on saliva

Fourteen data sets were included in the meta-analysis of diagnostic accuracy of tests performed on saliva (online supplemental figures 1–3). Overall (irrespective of the reference test), the pooled sensitivity, specificity and DOR of PCR on saliva were 84.5% (95% CI 79.3% to 88.6%), 97.3% (95% CI 95.3% to 98.5%) and 184.9 (95% CI 95.8 to 356.9), respectively. With PCR on a blood sample as the reference test, PCR on saliva had a pooled sensitivity, specificity and DOR of 87.0% (95% CI 81.8% to 90.9%), 98.6% (95% CI 95.7% to 99.5%), 395.5 (95% CI 117.1 to 1335.8), respectively. When microscopy on a blood sample was considered as the reference test, the pooled sensitivity, specificity and DOR of PCR on saliva were respectively 83.2% (95% CI 76.0% to 88.6%), 96.9% (95% CI 94.3% to 98.3%), 153.4 (95% CI 72.6 to 323.8) (table 1, online supplemental figures 1–3).

Diagnostic accuracy of malaria diagnostic tests performed on urine

Thirteen data sets were included in the assessment of the diagnostic performance of tests conducted on urine (online supplemental figures 4–6). Irrespective of the reference test, the pooled sensitivity, specificity and DOR of, PCR on a urine sample were 57.4% (95% CI 41.4% to 72.1%), 98.6% (95% CI 97.3% to 99.3%) and 47.2 (95% CI 22.1 to 101.1), respectively. With PCR on a blood sample as the reference test, PCR on urine had a pooled sensitivity, specificity and DOR of 70.1% (95% CI: 61.9% to 77.1%), 98.6% (95% CI: 90.6% to 99.8%), 99.5 (95% CI 18.8 to 526.2), respectively. When microscopy of a blood sample was considered as the reference test, the pooled sensitivity, specificity and DOR of PCR on urine were respectively 48.2% (95% CI 28.5% to 68.4%), 98.6% (95% CI 97.1 to 99.3), 46.4 (95% CI 15.2 to 141.7) (table 1).

The pooled sensitivity, specificity and DOR for RDT on urine (irrespective of the reference test) were 59.8% (95% CI 40.0% to 76.9%), 96.9% (95% CI 91.0% to 99.0%) and 30.8 (95% CI 23.5 to 40.4), respectively (table 1). With microscopy of a blood sample as the reference test, RDT on urine had pooled a sensitivity,

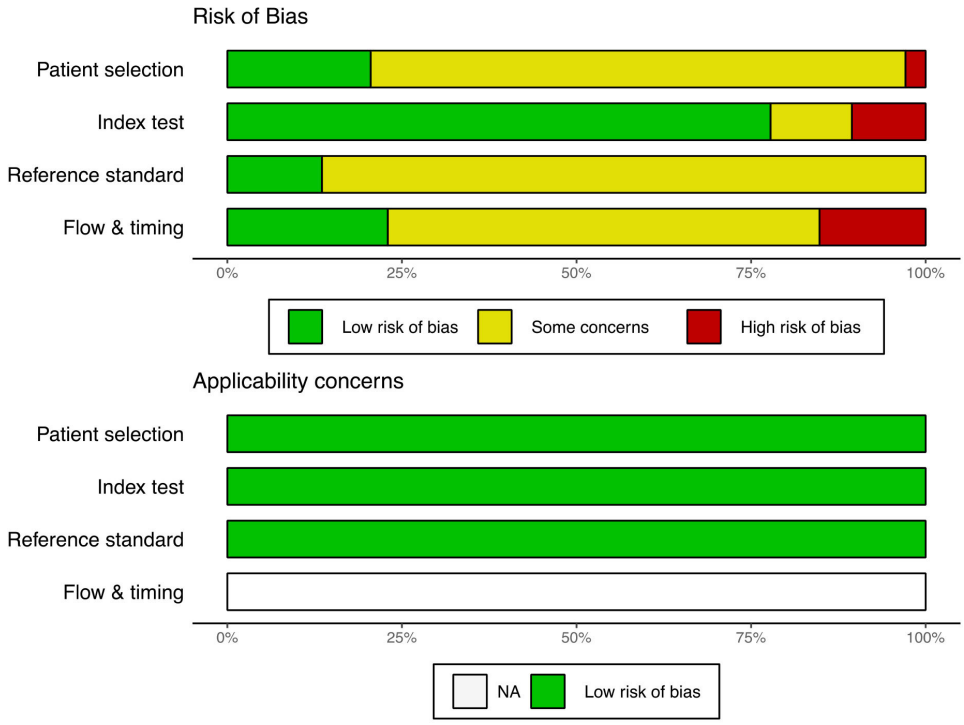


Figure 2 Quality assessment of studies included in the meta-analysis.

specificity and DOR of 71.7% (95% CI 44.9% to 88.7%), 89.9% (95% CI 83.9% to 93.8%), 30.0 (95% CI 22.5 to 40.0), respectively (table 1).

Diagnostic accuracy of the 'sniff and tell' method in children

Five out of the 36 data sets were derived from studies done in children, with two reporting the performance of 'sniff and tell' (including two dogs) method. In studies reporting on 'sniff and tell', malaria positivity was assessed by microscopy while malaria negativity was confirmed by qPCR on blood samples. The pooled sensitivity, specificity and DOR of 'sniff and tell' were 71.7% (95% CI 59.1% to 81.6%), 90.7% (95% CI 86.8% to 93.5%) and 24.6 (95% CI 12.4 to 48.9), respectively (online supplemental figures 7–9).

In leave-one-out analysis, regardless of the reference test, the exclusion of none of the studies significantly changed the pooled diagnostic accuracy of tests performed on the urine or saliva (online supplemental figures 10–16).

Data sets from studies that used ELISA, PCR and RDT on saliva in children were not considered for meta-analysis due to small sample size (less than 20 participants). These data are summarised in online supplemental table 4.

DISCUSSION

This meta-analysis of studies on the performance of malaria diagnostic tests on non-invasively collected samples revealed a lower overall sensitivity of PCR in saliva and urine compared with that reported in the literature when PCR is performed on blood. PCR performance in urine and saliva was better when the reference test in blood was PCR. Probably because only two studies included in the meta-analysis of urine/saliva were conducted in patients that were not symptomatic. Thus, the diagnostic performance estimates are probably representative of those that would be observed among clinical infections with parasite densities above 100/µL. Moreover, the performance of the tests performed on saliva was better than that of the tests conducted on urine. Probably because most saliva studies have used PCR as the index test (71.4% vs 38.5% for urine). When the studies were stratified according to the index test performed on the non-invasively collected sample, regardless of the type of sample, PCR had a higher pooled sensitivity than RDT, LAMP and ELISA tests. In addition, PCR performed better in saliva than in urine when the reference test on blood was PCR.

The higher performance of PCR compared with other tests in the diagnosis of malaria is well established and has been published in several studies and reviews. A meta-analysis showed a pooled sensitivity of PCR of about 98% (95% CI 90% to 99%) when performed on blood samples, which is higher than the sensitivity in saliva found in our meta-analysis.[46] The high sensitivity of PCR in the saliva compare to urine can be due to blood contamination of the saliva as a result of microbleeding in the oral cavity.[37 47 48] It is paramount for research purposes to compare the performance of PCR on saliva samples in which the presence of blood has been formally excluded with the ones in which it has not. One of the alternatives to deal with blood contamination in saliva may be to use supernatant of spun saliva instead of whole saliva to test for malaria as reported in some studies.[37] In addition, a better understanding of the mechanisms of malaria detection in saliva is needed to improve the performance of malaria diagnostic methods at point-of-care.

The performance of RDT on urine appears to be lower than the one observed in blood. Indeed, the average

Table 1 Meta-analysis of diagnostic accuracy of malaria diagnostic tests performed on non-invasively collected samples

	Pooled sensitivity, % (95% CI)	Pooled specificity, % (95% CI)	Pooled DOR, OR (95% CI)	N studies	Heterogeneity for sensitivity (I^2, %)	Heterogeneity for specificity (I^2, %)	Heterogeneity for DOR (I^2, %)
Saliva							
Studies conducted on saliva with PCR as the index test and,	84.5 (79.3 to 88.6)	97.3 (95.3 to 98.5)	184.9 (95.8 to 356.9)	10	68.3	60.1	49.4
▲ PCR in a blood sample as the reference test	87.0 (81.8 to 90.9)	98.6 (95.7 to 99.5)	395.5 (117.1 to 1335.8)	3	0.0	0.0	0.0
▲ Microscopy of a blood sample as the reference test	83.2 (76.0 to 88.6)	96.9 (94.3 to 98.3)	153.4 (72.6 to 323.8)	7	73.9	64.3	56.0
Urine							
Studies conducted on urine with PCR as the index test and,	57.4 (41.4 to 72.1)	98.6 (97.3 to 99.3)	47.2 (22.1 to 101.1)	5	87.9	0.0	0.0
▲ PCR in a blood sample as the reference test	70.1 (61.9 to 77.1)	98.6 (90.6 to 99.8)	99.5 (18.8 to 526.2)	2	0.0	0.0	0.0
▲ Microscopy of a blood sample as the reference test	48.2 (28.5 to 68.4)	98.6 (97.1 to 99.3)	46.4 (15.2 to 141.7)	3	88.3	0.0	23.1
Studies conducted on urine with RDT as the index test and,	59.8 (40.0 to 76.9)	96.9 (91.0 to 99.0)	30.8 (23.5 to 40.4)	9	95.8	95.6	0.0
▲ Microscopy of a blood sample as the reference test	71.7 (44.9 to 88.7)	89.9 (83.9 to 93.8)	30.0 (22.5 to 40.0)	5	96.1	81.2	0.0

DOR, diagnostic OR; RDT, Rapid diagnostic test.

sensitivity and specificity of histidine-rich protein II (HRP2) based RDT of malaria in blood regardless of the reference test are estimated to be 95.0% (95% CI 93.5% to 96.2%) and 95.2% (95% CI 93.4% to 99.4%) respectively,[7] compared with 58.7% (95% CI 25.8% to 85.3%) and 96.5% (95% CI 82.8% to 99.4%) in urine as determined by our meta-analysis. Given that rapid diagnostic tests are among the most accessible and user-friendly methods of malaria diagnostic, the development of highly sensitive and polyvalent tests that can be performed with comparable sensitivity on urine, saliva and blood would significantly increase adherence to diagnostic testing of asymptomatic individuals, particularly in resource-constrained settings and in countries that are in the elimination phase.

In addition to help in the management of malaria cases in hospitals, malaria diagnosis can be done for many purposes, such as to assess the prevalence of malaria in communities, for research activities or to support decision-making in countries or areas that are in the elimination phase and where the detection of the human parasite reservoir can be useful to tailor interventions. Therefore, the diagnosis of malaria and the interpretation of the current findings cannot be made from the sole prism of hospital case management but should be integrated into a broader context.

The molecules detected in non-invasive samples are the same as in blood. For nPCR in saliva for example, 18S rRNA genes, or mitochondrial cytochrome b gene, of *Plasmodium falciparum* and *Plasmodium vivax* were targeted and amplified in most of the studies,[30 31] whereas RDT in saliva and urine target *Pf*HRP2 and pLDH antigens.[14 36] This suggests that the issues faced by blood based RDT tests (regarding *Pf*HRP detection) are the same for tests conducted on non-invasive sample.

This review is written under the premise that non-invasive tests for malaria would be preferable if they were at least as good as the currently available point-of-care tests that use finger-prick blood (RDT or microscopy). However, many of these tests still face the same logistical challenges as blood-based tests, as they require sophisticated equipment and trained personnel. Nevertheless, the use of RDT on non-invasive samples has a substantial advantage over blood as they do not require any expertise for sampling since urine and saliva are directly available, while blood collection requires knowledge of asepsis and good knowledge of finger or phlebotomy blood sampling methods. The samples are painless and do not require psychological preparation of patients to cope with pain as is the case for blood sampling. However, when these tests are not performed immediately after the collection of the non-invasive material, the necessity to store the samples at low temperatures, makes it difficult to perform the tests in routine practice in the communities or at malaria point of care in low/middle-income countries where electricity is often lacking and the number of patients to be tested is large. It is essential that the stability of non-invasive specimens when stored at room temperature is assessed to determine whether their storage at room temperature does not compromise the performance of malaria tests performed on these specimens.

The findings of the current review suggest that the performance of malaria diagnostic tests on non-invasively collected samples still needs to be improved to be comparable with the performance on blood. They call for further research to develop highly sensitive rapid diagnostic tests based on non-invasively collected samples, particularly saliva which can be easily obtained, and for more studies to assess the performance of available tests on saliva and urine.

This review is mainly limited by some heterogeneity observed in the meta-analysis, the source being the multiplicity of reference tests used in the blood, and index tests used on the non-invasive sample, and perhaps the difference in nucleic acid stability in saliva and urine. However, this study is the first meta-analysis on the diagnostic accuracy of malaria tests performed on non-invasively collected samples. A subgroup analysis was conducted by type of specimen, reference blood test and index test to give a broad overview on the performance of this approach in different contexts.

CONCLUSION

In settings where PCR is available, saliva and urine samples may be considered for PCR-based malaria diagnosis only if blood samples cannot be collected, given the lower sensitivity found. The performance of RDT in the urine remain limited, especially its sensitivity. Malaria testing on non-invasively collected specimen still needs substantial improvement, especially for RDT, in order to be considered for widespread use.

Author affiliations
[1]Epidemiology and Biostatistics Unit, Institut de Recherche Expérimentale et Clinique, Université catholique de Louvain, Brussels, Belgium
[2]Centre for Heart Rhythm Disorders, University of Adelaide and Royal Adelaide Hospital, Adelaide, South Australia's, Australia
[3]Department of Molecular Biology, Universite Libre de Bruxelles, Gosselies, Belgium
[4]Aix Marseille Univ, IRD, INSERM, SESSTIM, ISSPAM, Marseille, France
[5]APHM, Hop Timone, BioSTIC, Biostatistics & ICT, Marseille, France
[6]Department of Internal Medicine and Infectious Diseases, Cliniques Universitaires Saint-Luc, Brussels, Belgium

Contributors CD conceived the original idea of the study. CD and JJN selected the studies, extracted the relevant information and synthetised the data. CD and JJN did the literature search. CD performed analyses and wrote the first draft of the paper with inputs from JJN and AR. All authors critically revised successive drafts of the paper and approved the final version.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as online supplemental information.

ORCID iDs
Celestin Danwang http://orcid.org/0000-0002-7976-4331
Jacob Souopgui http://orcid.org/0000-0003-1526-4431
Jean Gaudart http://orcid.org/0000-0001-9006-5729

REFERENCES

1 World malaria report 2020 [online]. Available: https://www.who.int/teams/global-malaria-programme/reports/world-malaria-report-2020 [Accessed 23 Dec 2020].
2 Battle KE, Lucas TCD, Nguyen M, *et al*. Mapping the global endemicity and clinical burden of Plasmodium vivax, 2000-17: a spatial and temporal modelling study. *Lancet* 2019;394:332–43.
3 Weiss DJ, Lucas TCD, Nguyen M, *et al*. Mapping the global prevalence, incidence, and mortality of Plasmodium falciparum, 2000-17: a spatial and temporal modelling study. *Lancet* 2019;394:322–31.
4 World Health Organization. *Global malaria programme. global technical strategy for malaria, 2016-2030*, 2015.
5 World Health Organization. T3: test. treat. track. Scaling up diagnostic testing, treatment and surveillance for malaria [online]. Available: https://www.who.int/malaria/publications/atoz/t3_brochure/en/ [Accessed 23 Dec 2020].
6 Graz B, Willcox M, Szeless T, *et al*. 'Test and treat' or presumptive treatment for malaria in high transmission situations? A reflection on the latest WHO guidelines. *Malar J* 2011;10:136.
7 Abba K, Deeks JJ, Olliaro PL. Rapid diagnostic tests for diagnosing uncomplicated P. falciparum malaria in endemic countries. Cochrane infectious diseases group, editor. *Cochrane Database Syst Rev* 2011.
8 Boahen O, Owusu-Agyei S, Febir LG, *et al*. Community perception and beliefs about blood draw for clinical research in Ghana. *Trans R Soc Trop Med Hyg* 2013;107:261–5.
9 Chatio S, Baiden F, Achana FS, *et al*. Knowledge and perceptions about clinical trials and the use of biomedical samples: findings from a qualitative study in rural Northern Ghana. *PLoS One* 2016;11:e0152854.
10 Cohen J, Cox A, Dickens W, *et al*. Determinants of malaria diagnostic uptake in the retail sector: qualitative analysis from focus groups in Uganda. *Malar J* 2015;14:89.
11 Baiden F, Owusu-Agyei S, Okyere E, *et al*. Acceptability of rapid diagnostic test-based management of malaria among caregivers of Under-Five children in rural Ghana. *PLoS One* 2012;7:e45556.
12 Newton S, Doku V, Geissler W, *et al*. Drawing blood from young children: lessons learned from a trial in Ghana. *Trans R Soc Trop Med Hyg* 2009;103:497–9.
13 Achieng F, Rosen JG, Cherop RY, *et al*. Caregiver and community perceptions and experiences participating in an infant malaria prevention trial of PfSPZ vaccine administered by direct venous inoculation: a qualitative study in Siaya County, Western Kenya. *Malar J* 2020;19:226.
14 Aninagyei E, Abraham J, Atiiga P, *et al*. Evaluating the potential of using urine and saliva specimens for malaria diagnosis in suspected patients in Ghana. *Malar J* 2020;19:349.
15 Al-Shehri H, Power BJ, Archer J, *et al*. Non-invasive surveillance of Plasmodium infection by real-time PCR analysis of ethanol preserved faeces from Ugandan school children with intestinal schistosomiasis. *Malar J* 2019;18:109.
16 McInnes MDF, Moher D, Thombs BD, *et al*. Preferred reporting items for a systematic review and meta-analysis of diagnostic test accuracy studies: the PRISMA-DTA statement. *JAMA* 2018;319:388.
17 NON-INVASIVE | meaning in the Cambridge English Dictionary [online]. Available: https://dictionary.cambridge.org/dictionary/english/non-invasive [Accessed 25 Jan 2021].
18 Ouzzani M, Hammady H, Fedorowicz Z, *et al*. Rayyan-a web and mobile APP for systematic reviews. *Syst Rev* 2016;5:210.
19 Whiting PF, Rutjes AWS, Westwood ME, *et al*. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* 2011;155:529.
20 University of Bristol. Bristol U of. QUADAS-2 [online]. Available: https://www.bristol.ac.uk/population-health-sciences/projects/quadas/quadas-2/ [Accessed 1 Apr 2021].

21 Kasetsirikul S, Buranapong J, Srituravanich W, *et al*. The development of malaria diagnostic techniques: a review of the approaches with focus on dielectrophoretic and magnetophoretic methods. *Malar J* 2016;15:358.
22 World Health Organization. Diagnostic testing [online]. Available: http://www.who.int/malaria/publications/diagnostic_testing/en/ [Accessed 7 Mar 2021].
23 Obeagu EI, Uo C, Is E. Malaria rapid diagnostic test (RDTs). *Ann Clin Lab Res* 2018;06.
24 World Health Organization. Rapid diagnostic tests for malaria [online]. Available: http://www.who.int/bulletin/volumes/93/12/14-151167/en/ [Accessed 1 Apr 2021].
25 Doebler P. mada: meta-analysis of diagnostic accuracy [online], 2020. Available: https://CRAN.R-project.org/package=mada [Accessed 22 Dec 2020].
26 R Documentation. meta-package function [online]. Available: https://www.rdocumentation.org/packages/meta/versions/4.15-1/topics/meta-package [Accessed 22 Dec 2020].
27 Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539–58.
28 Cochran WG. The combination of estimates from different experiments. *Biometrics* 1954;10:101–29.
29 Shim SR, Kim S-J, Lee J. Diagnostic test accuracy: application and practice using R software. *Epidemiol Health* 2019;41:e2019007.
30 Singh R, Singh DP, Gupta R, *et al*. Comparison of three PCR-based assays for the non-invasive diagnosis of malaria: detection of Plasmodium parasites in blood and saliva. *Eur J Clin Microbiol Infect Dis* 2014;33:1631–9.
31 Ghayour Najafabadi Z, Oormazdi H, Akhlaghi L, *et al*. Mitochondrial PCR-based malaria detection in saliva and urine of symptomatic patients. *Trans R Soc Trop Med Hyg* 2014;108:358–62.
32 Mfuh KO, Tassi Yunga S, Esemu LF, *et al*. Detection of Plasmodium falciparum DNA in saliva samples stored at room temperature: potential for a non-invasive saliva-based diagnostic test for malaria. *Malar J* 2017;16:434.
33 Nwakanma DC, Gomez-Escobar N, Walther M, *et al*. Quantitative detection of Plasmodium falciparum DNA in saliva, blood, and urine. *J Infect Dis* 2009;199:1567–74.
34 Wilson NO, Adjei AA, Anderson W, *et al*. Detection of Plasmodium falciparum histidine-rich protein II in saliva of malaria patients. *Am J Trop Med Hyg* 2008;78:733–5.
35 Netongo P, Tchoupe E, Kamdem SD, *et al*. *Evaluation of a homemade saliva kit for the stabilization of Plasmodium DNA at room temperature*, 2020.
36 Oyibo WA, Ezeigwe N, Ntadom G, *et al*. Multicenter pivotal clinical trial of urine malaria test for rapid diagnosis of Plasmodium falciparum malaria. *J Clin Microbiol* 2017;55:253–63.
37 Gbotosho GO, Happi CT, Folarin O, *et al*. Rapid detection of lactate dehydrogenase and genotyping of Plasmodium falciparum in saliva of children with acute uncomplicated malaria. *Am J Trop Med Hyg* 2010;83:496–501.
38 Buppan P, Putaporntip C, Pattanawong U, *et al*. Comparative detection of Plasmodium vivax and Plasmodium falciparum DNA in saliva and urine samples from symptomatic malaria patients in a low endemic area. *Malar J* 2010;9:72.
39 Guest C, Pinder M, Doggett M, *et al*. Trained dogs identify people with malaria parasites by their odour. *Lancet Infect Dis* 2019;19:578–80.
40 Chidi AP, Chishimba S, Kobayashi T, *et al*. Validation of oral fluid samples to monitor serological changes to Plasmodium falciparum: an observational study in southern Zambia. *Malar J* 2011;10:162.
41 Gómez-Luque A, Parejo JC, Clavijo-Chamorro MZ, *et al*. Method for malaria diagnosis based on extractions of samples using non-invasive techniques: an opportunity for the nursing clinical practice. *Int J Environ Res Public Health* 2020;17 doi:10.3390/ijerph17155551
42 Samal AG, Behera PK, Mohanty AK, *et al*. The sensitivity and specificity of a urine based rapid diagnostic test for the diagnosis of Plasmodium falciparum in a malaria endemic area in Odisha, India. *Pathog Glob Health* 2017;111:383–7.
43 Ghayour Najafabadi Z, Oormazdi H, Akhlaghi 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;136:44–9.
44 Oguonu T, Shu E, Ezeonwu BU, *et al*. The performance evaluation of a urine malaria test (UMT) kit for the diagnosis of malaria in individuals with fever in south-east Nigeria: cross-sectional analytical study. *Malar J* 2014;13:403.
45 Olasehinde GI, Fadina I, Ayepola OO, *et al*. Development of saliva based diagnostic method for malaria. *Int J Infec Dis* 2016;45:236.
46 Roth JM, Korevaar DA, Leeflang MMG, *et al*. Molecular malaria diagnostics: a systematic review and meta-analysis. *Crit Rev Clin Lab Sci* 2016;53:87–105.
47 Kamodyová N, Baňasová L, Janšáková K, *et al*. Blood contamination in saliva: impact on the measurement of salivary oxidative stress markers. *Dis Markers* 2015;2015:e479251
48 Kang J-H, Kho H-S. Blood contamination in salivary diagnostics: current methods and their limitations. *Clin Chem Lab Med* 2019;57:1115–24.

Accuracy of malaria diagnostic tests performed on non-invasively collected samples: a systematic review and meta-analysis

APPENDIX

Supplementary Tables

Supplementary figures

Danwang C, *et al. BMJ Global Health* 2021; 6:e005634. doi: 10.1136/bmjgh-2021-005634

Supplementary Table 1. Search strategy for PubMed

Search	**Search terms**
#1	"non-invasive"[tiab] OR "non-blood"[tiab] OR "urine"[tiab] OR "saliva"[tiab]
#2	"malaria"[MeSH Terms]
#3	#1 AND #2
Date: 19 January 2021, 422 citations Restrictions: No	

Supplementary Table 2. Search strategy for EMBASE

Search	**Search terms**
#1	'non invasive':ti,ab,kw OR 'non blood':ti,ab,kw OR urine:ti,ab,kw OR saliva:ti,ab,kw
#2	malaria:ti,ab,kw
#3	#1 AND #2
Date: 19 January 2021, 1185 citations Restrictions: No	

Supplementary Table 3. General characteristics of included studies

Characteristics		N	%
Country where the study was conducted	Iran	10	27.8%
	Nigeria	5	13.9%
	India	5	13.9%
	Cameroon	4	11.1%
	The Gambia	4	11.1%
	Ghana	3	8.3%
	Thailand	2	5.6%
	Rwanda	1	2.8%
	Uganda	1	2.8%
	Zambia	1	2.8%
Settings where the study was conducted	Hospital	31	86.1%
	Community	3	8.3%
	Unclear	2	5.5%
Region where the study was conducted	Africa	20	55.5%
	Outside Africa	16	44.4%
Study design	Cross sectional	33	91.7%
	Case control	3	8.3%
Age groups	Children	5	13.9%
	All age categories	28	77.7%
	Unclear	3	8.3%
Period during which studies were conducted		2008-2020	
Age range (yrs, n=24 studies)		1-80	
Male % (n=27 studies)		29-82.4	

Supplementary Table 4. Individual characteristics of the included studies

Author	Year	Design	Country	Setting	Mean Age	Minimum age	Maximum age	Male %	Characteristic of the population in terms of age and diseases/conditions	Characteristics of patients in terms of fever or other malaria symptoms	Name of the reference (GOLD STANDARD) test	Name of the material for non-invasive test	Name of the test performed on the non-invasive sample	Details about the test performed on the non-invasive sample	TP	FP	TN	FN	Person(s) performing de analysis	Plasmodium Target by the non-invasive test	Transport and storage conditions for the non-invasive sample	Parasite density
Singh_1	2014	Cross sectional	India	Hospital based	NR	1	80	67	All age categories and conditions*	Symptomatic	Microscopy	Saliva	PCR	Nested PCR	83	2	121	12	Experienced worker	Both falciparum and non-falciparum	A sample of 0.5 to 2.0 ml of saliva, collected in sterile plastic vials by the passive drool method immediately after blood collection and stored at 4 °C	Overall parasite density for P. vivax : from 320 to 61,600/µl (geometric mean 4,941 parasites/µl) and P. falciparum 200 to 496,000 (geometric mean 21,850 parasites/µl).
Singh_2	2014	Cross sectional	India	Hospital based	NR	1	80	67	All age categories and conditions	Symptomatic	Microscopy	Saliva	PCR	Singleplex CRS PCR	77	2	121	18	Experienced worker	Both falciparum and non-falciparum	A sample of 0.5 to 2.0 ml of saliva, collected in sterile plastic vials by the passive drool method immediately after blood collection and stored at 4 °C	Overall parasite density for P. vivax : from 320 to 61,600/µl (geometric mean 4,941 parasites/µl) and P. falciparum 200 to 496,000 (geometric mean 21,850 parasites/µl).
Singh_3	2014	Cross sectional	India	Hospital based	NR	1	80	67	All age categories and conditions	Symptomatic	Microscopy	Saliva	PCR	Multiplex CRS PCR	67	1	122	28	Experienced worker	Both falciparum and non-falciparum	A sample of 0.5 to 2.0 ml of saliva, collected in sterile plastic vials by the passive drool method immediately after blood collection and stored at 4 °C	Overall parasite density for P. vivax : from 320 to 61,600/µl (geometric mean 4,941 parasites/µl) and P. falciparum 200 to 496,000 (geometric mean 21,850 parasites/µl).
Ghayour_1	2014	Cross sectional	Iran	Hospital based	NR	NR	NR	NR	All age categories and conditions	Symptomatic	PCR	Urine	PCR		46	1	32	20	Unclear	Both falciparum and non-falciparum	2 ml of blood and 5 ml of urine stored in ethanol at -20°C.	Unclear
Ghayour_2	2014	Cross sectional	Iran	Hospital based	NR	NR	NR	NR	All age categories and conditions	Symptomatic	PCR	Saliva	PCR		60	1	32	6	Unclear	Both falciparum and non-falciparum	2 ml of blood and 2ml of saliva stored in ethanol at -20°C.	Unclear
Mfuh_1	2017	Cross sectional	Cameroon	Hospital based	22	2	76	29	All age categories and conditions	Symptomatic	Microscopy	Saliva	PCR		50	12	157	3	Experienced worker	Falciparum	1 ml of saliva into OMNIgene ®•ORAL (OM-501) kit, stored at room temperature until DNA extraction 2–6 weeks later	Median parasitaemia by age group/ µl of blood: 71,907 (2–10 years); 23,257 (11–20); 26,760 (21–39); 13,600 (> 40)
Mfuh_2	2017	Cross sectional	Cameroon	Hospital based	22	2	76	29	All age categories and conditions	Symptomatic	PCR	Saliva	PCR		64	1	143	14	Experienced worker	Falciparum	1 ml of saliva into OMNIgene ®•ORAL (OM-501) kit, stored at room temperature until DNA extraction 2–6 weeks later	Median parasitaemia by age group/ µl of blood: 71,907 (2–10 years); 23,257 (11–20); 26,760 (21–39); 13,600 (> 40)
Nwakanma_1	2009	Cross sectional	The Gambia	Hospital based	25	10	45	63.2	All age categories and conditions	Symptomatic	Microscopy	Saliva	PCR		37	10	325	14	Experienced worker	Both falciparum and non-falciparum	2-mL of saliva collected into sterile bottles and stored at 4°C–8°C until DNA, usually within 2 h	Unclear
Nwakanma_2	2009	Cross sectional	The Gambia	Hospital based	25	10	45	63.2	All age categories and conditions	Symptomatic	Microscopy	Urine	PCR		16	6	328	34	Experienced worker	Both falciparum and non-falciparum	5-mL of urine collected into sterile bottles and stored at 4°C–8°C until DNA, usually within 2 h.	Unclear

Wilson	2008	Cross sectional	Ghana	Hospital based	NR	1.8	16	42.5	Children	Symptomatic	Microscopy	Saliva	ELISA		13	0	10	17	Unclear	Falciparum	Saliva collected in sterile containers and aliquoted into microcentrifuge tubes and stored at −20°C	Unclear
Aninagyei_1	2020	Cross sectional	Ghana	Hospital based	22.3	6	39	42.7	All age categories and conditions	Symptomatic	RDT	Urine	RDT		22	0	325	269	Unclear	Both falciparum and non-falciparum	30 mL of urine frozen at − 20 °C	Unclear
Aninagyei_2	2020	Cross sectional	Ghana	Hospital based	22.3	6	39	42.7	All age categories and conditions	Symptomatic	RDT	Saliva	RDT		28	0	325	182	Unclear	Both falciparum and non-falciparum	5 mL of saliva frozen at − 20 °C	Unclear
Netongo_1	2019	Cross sectional	Cameroon	Hospital based	27	2	77	24.1	All age categories and conditions	Symptomatic	Microscopy	Saliva	PCR	homemade kit (Formulation f1) to stabilize Plasmodium DNA in saliva stored at room temperature	65	3	15	0	Experienced worker	Both falciparum and non-falciparum	1–2 ml of saliva introduced into equal volume of the homemade DNA stabilization buffer	Not reported
Netongo_2	2019	Cross sectional	Cameroon	Hospital based	27	2	77	24.1	All age categories and conditions	Symptomatic	Microscopy	Saliva	PCR	OMNIgene ® ORAL (S0)	65	4	14	0	Experienced worker	Both falciparum and non-falciparum	1–2 ml of saliva introduced into equal volume of the OMNIgene®ORAL (OM-501) kit (S0)	Not reported
AlShehri	2019	Cross sectional	Uganda	Population-based	6.8	6.6	6.9	50.2	Unclear	Asymptomatic	RDT	Stool	PCR		101	57	52	37	Unclear	Both falciparum and non-falciparum	Two stool samples per participant, filtered through a 212 µm metal mesh then 0.5 g placed in 1 mL of 95% ethanol for the EPF before transfer to the to a foreign lab for DNA extraction	Not reported
Samal	2017	Case control study	India	Hospital based	NR	NR	NR	NR	Unclear	Symptomatic	Microscopy	Urine	RDT		52	3	48	8	Experienced worker	Falciparum	1 ml of urine in a sterile tube. Storage conditions unclear	Unclear
Oyibo_1	2014	Cross sectional	Nigeria	Unclear/No description	18.6	2	80	43	All age categories and conditions	Asymptomatic	Microscopy	Urine	RDT		98	79	909	39	Unclear	Falciparum	Unclear	Unclear
Oyibo_2	2014	Cross sectional	Nigeria	Unclear/No description	18.6	2	80	43	All age categories and conditions	Symptomatic	Microscopy	Urine	RDT		173	58	304	31	Unclear	Falciparum	Unclear	Unclear
Najafabadi_1	2014	Cross sectional	Iran	Hospital based	28	3	57	82.4	All age categories and conditions	Symptomatic	Microscopy	Saliva	PCR		63	1	38	6	Experienced worker	Both falciparum and non-falciparum	Two volumes of absolute ethanol added to 2 ml of saliva, transported to the laboratory and stored at −20◦C	Geometric mean parasite density of positive samples = 3970.7 parasites/ µl (range = 120–94,117 parasites/ µl).
Najafabadi_2	2014	Cross sectional	Iran	Hospital based	28	3	57	82.4	All age categories and conditions	Symptomatic	Microscopy	Urine	PCR		50	0	39	19	Experienced worker	Both falciparum and non-falciparum	Two volumes of absolute ethanol added to 5 ml of urine, transported to the laboratory and stored at −20◦C	Geometric mean parasite density of positive samples = 3970.7 parasites/ µl (range = 120–94,117 parasites/ µl).
Najafabadi_3	2014	Cross sectional	Iran	Hospital based	28	3	57	82.4	All age categories and conditions	Symptomatic	Microscopy	Saliva	LAMP		33	0	39	36	Experienced worker	Both falciparum and non-falciparum	Two volumes of absolute ethanol added to 2 ml of saliva, transported to the laboratory and stored at −20◦C	Geometric mean parasite density of positive samples = 3970.7 parasites/ µl (range = 120–94,117 parasites/ µl).
Najafabadi_4	2014	Cross sectional	Iran	Hospital based	28	3	57	82.4	All age categories and conditions	Symptomatic	Microscopy	Urine	LAMP		21	0	39	48	Experienced worker	Both falciparum and non-falciparum	Two volumes of absolute ethanol added to 5 ml of urine, transported to the laboratory and stored at −20◦C	Geometric mean parasite density of positive samples = 3970.7 parasites/ µl (range = 120–94,117 parasites/ µl).

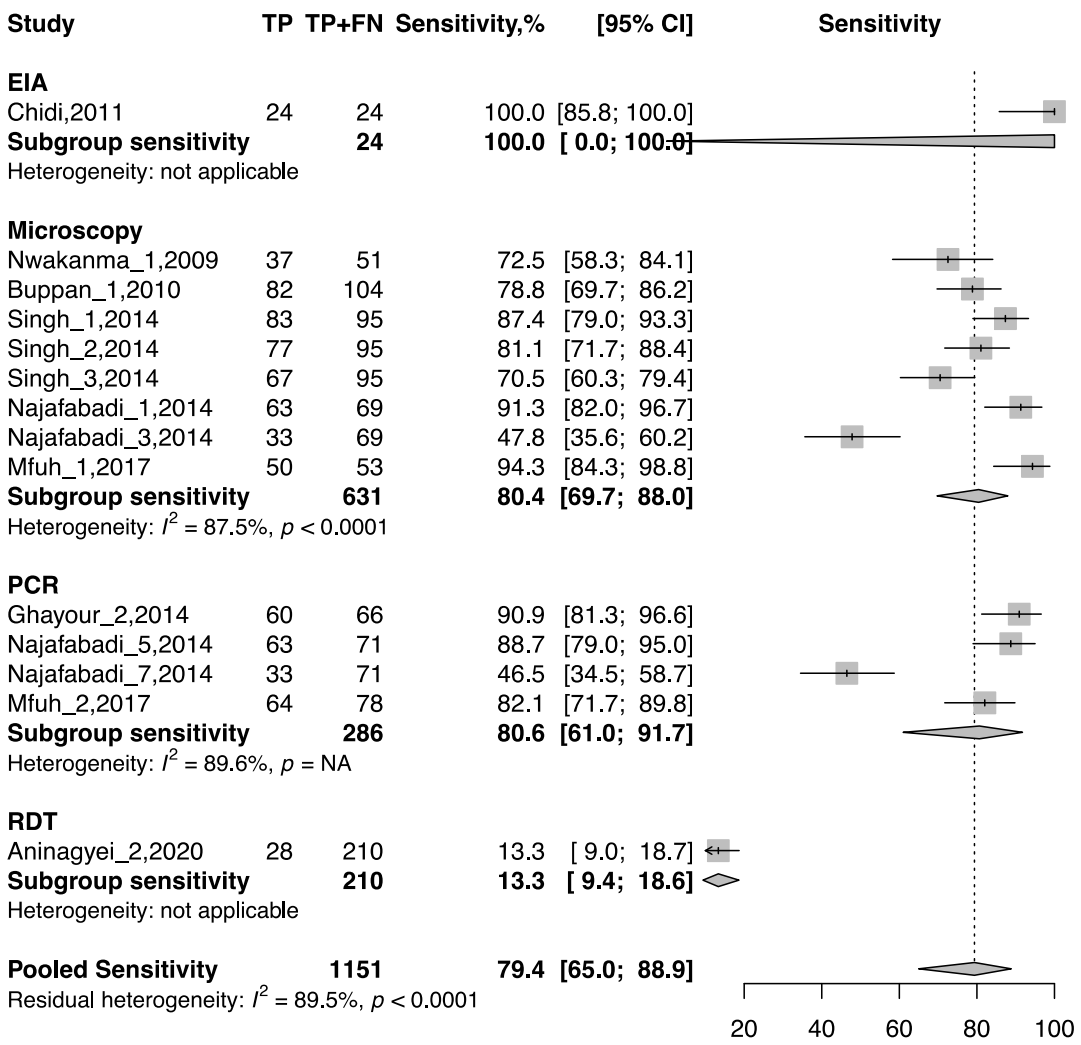
Najafabadi_5	2014	Cross sectional	Iran	Hospital based	28	3	57	82.4	All age categories and conditions	Symptomatic	PCR	Saliva	PCR		63	1	36	8	Experienced worker	Both falciparum and non-falciparum	Two volumes of absolute ethanol added to 2 ml of saliva, transported to the laboratory and stored at −20◦C	Geometric mean parasite density of positive samples = 3970.7 parasites/ µl (range = 120–94,117 parasites/ µl).
Najafabadi_6	2014	Cross sectional	Iran	Hospital based	28	3	57	82.4	All age categories and conditions	Symptomatic	PCR	Urine	PCR		50	0	37	21	Experienced worker	Both falciparum and non-falciparum	Two volumes of absolute ethanol added to 5 ml of urine, transported to the laboratory and stored at −20◦C	Geometric mean parasite density of positive samples = 3970.7 parasites/ µl (range = 120–94,117 parasites/ µl).
Najafabadi_7	2014	Cross sectional	Iran	Hospital based	28	3	57	82.4	All age categories and conditions	Symptomatic	PCR	Saliva	LAMP		33	0	37	38	Experienced worker	Both falciparum and non-falciparum	Two volumes of absolute ethanol added to 2 ml of saliva, transported to the laboratory and stored at −20◦C	Geometric mean parasite density of positive samples = 3970.7 parasites/ µl (range = 120–94,117 parasites/ µl).
Najafabadi_8	2014	Cross sectional	Iran	Hospital based	28	3	57	82.4	All age categories and conditions	Symptomatic	PCR	Urine	LAMP		21	0	37	50	Experienced worker	Both falciparum and non-falciparum	Two volumes of absolute ethanol added to 5 ml of urine, transported to the laboratory and stored at −20◦C	Geometric mean parasite density of positive samples = 3970.7 parasites/ µl (range = 120–94,117 parasites/ µl).
Oguonu	2014	Cross sectional	Nigeria	Hospital based	NR	NR	NR	NR	All age categories and conditions	Symptomatic	Microscopy	Urine	RDT		67	19	96	13	Experienced worker	Falciparum	NR	
Gbotosho_1	2010	Case control study	Nigeria	Hospital based	7.2	0.7	13	NR	Children	Symptomatic	Microscopy	Saliva	PCR		30	2	2	3	Unclear	Falciparum	Whole saliva analysed immediately, or stored at 4°C for 24 hours before analysis	Geometric mean parasite density was 59,179 asexual parasites/µL blood (range =2,463–551,614)
Gbotosho_2	2010	Cross sectional	Nigeria	Hospital based	7.2	0.7	13	NR	Children	Symptomatic	Microscopy	Saliva	RDT		53	0	10	15	Unclear	Falciparum	Whole saliva analysed immediately, or stored at 4°C for 24 hours before analysis	Geometric mean parasite density was 59,179 asexual parasites/µL blood (range = 2,463–551,614)
Buppan_1	2010	Cross sectional	Thailand	Hospital based	20.3	4	60	60.8	All age categories and conditions	Symptomatic	Microscopy	Saliva	PCR		82	11	125	22	Experienced worker	Both falciparum and non-falciparum	1 - 2 ml of saliva, half volume of which was kept on ice during transportation to the lab, and the remaining was preserved by two volumes of absolute ethanol and kept at 25°C - 35°C	Overall parasite density of microscopy positive samples ranged=35-311,395 parasites/ml (geometric mean = 13,920 parasites/ml).
Buppan_2	2010	Cross sectional	Thailand	Hospital based	20.3	4	60	20.3	All age categories and conditions	Symptomatic	Microscopy	Urine	PCR		41	1	135	63	Experienced worker	Both falciparum and non-falciparum	20 ml of midstream urine, half volume of which was kept on ice during transportation to the lab, and the remaining was preserved by two volumes of absolute ethanol and kept at 25°C - 35°C	Overall parasite density of microscopy positive samples ranged=35-311,395 parasites/ml (geometric mean = 13,920 parasites/ml).
Guest_1	2019	Cross sectional	The Gambia	Population-based	NR	5	13	NR	Children	Asymptomatic	Microscopy/PCR	Skin odour	Dog smell	Dog L	22	13	132	8	Dog	Unclear	NA	Unclear
Guest_2	2019	Cross sectional	The Gambia	Population-based	NR	5	13	NR	Children	Asymptomatic	Microscopy/PCR	Skin odour	Dog smell	Dog S	21	14	131	9	Dog	Unclear	NA	Unclear
Olasehinde	2016	Case control study	India	Hospital based	NR	NR	NR	NR	Unclear	Symptomatic	Microscopy	Urine	RDT		13	0	25	62	Two pathologists	Both falciparum and non-falciparum	Unclear	
Chidi	2011	Cross sectional	Zambia	Hospital based	13.5	1	80	55	All age categories and conditions	Unclear	EIA	Saliva	EIA		24	0	29	0	Unclear	Falciparum	Participants' gums were swabbed, and samples were transferred to collection tube with transport buffer	Unclear

																				and stored at room temperature	
Gómez-Luque	2020	Cross sectional	Rwanda	Hospital based	NR	4	31	47.4	All age categories and conditions	Symptomatic	RDT and qPCR	Hair	qPCR		-	-	-	-	Unclear	Falciparum	50 units of hair without root keep in in sterile resealable plastic bags and at room temperature (4 months at 18–24 °C), refrigeration (3 months at 2–6 °C) and freezing (1 month at -20 °C and 1 month at -80 °C)	Unclear

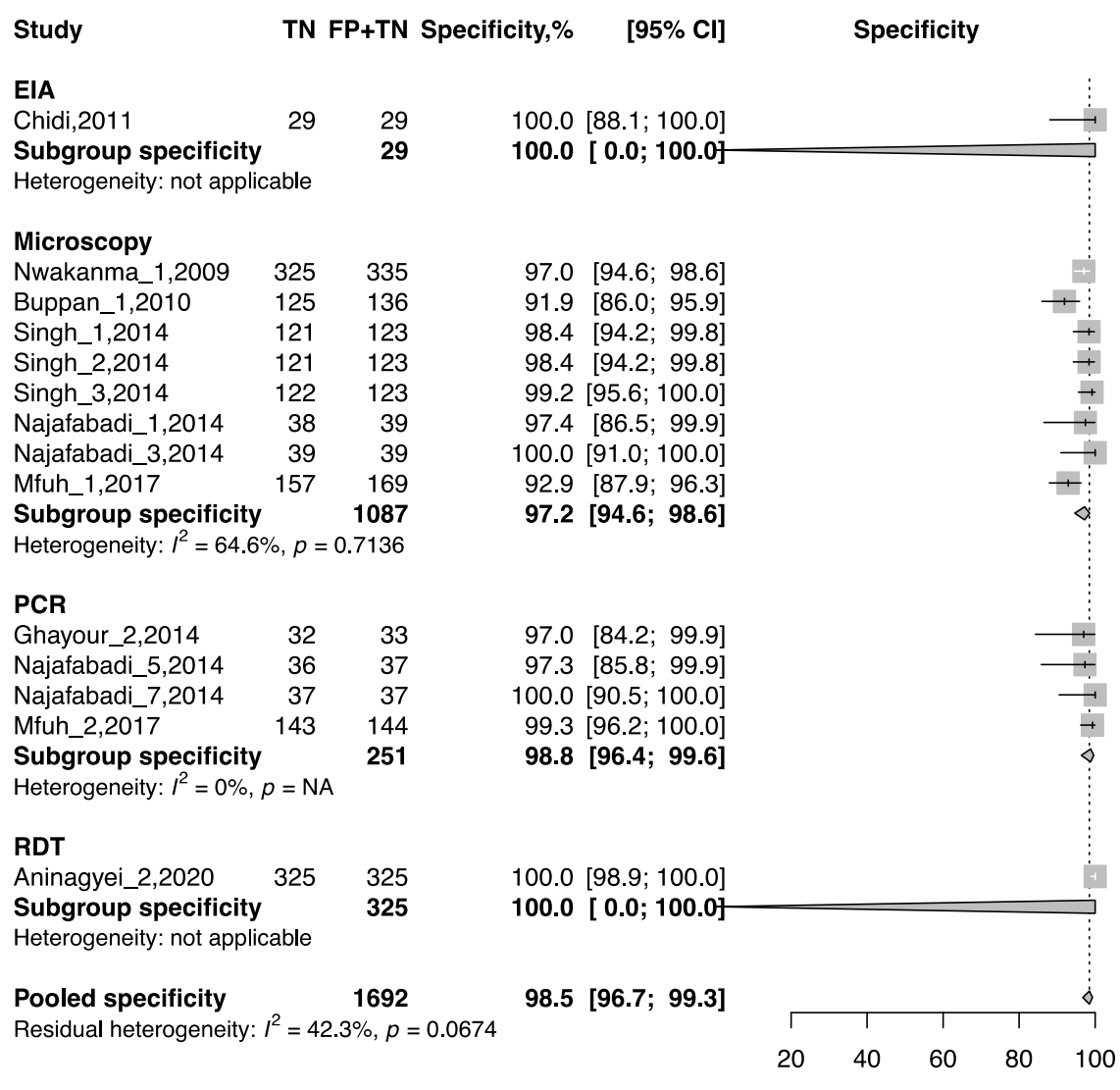
**Condition refers to pregnancy/post-partum or diseases such as sickle cell disease or any other chronic (know or unknow) disease.*

SALIVA

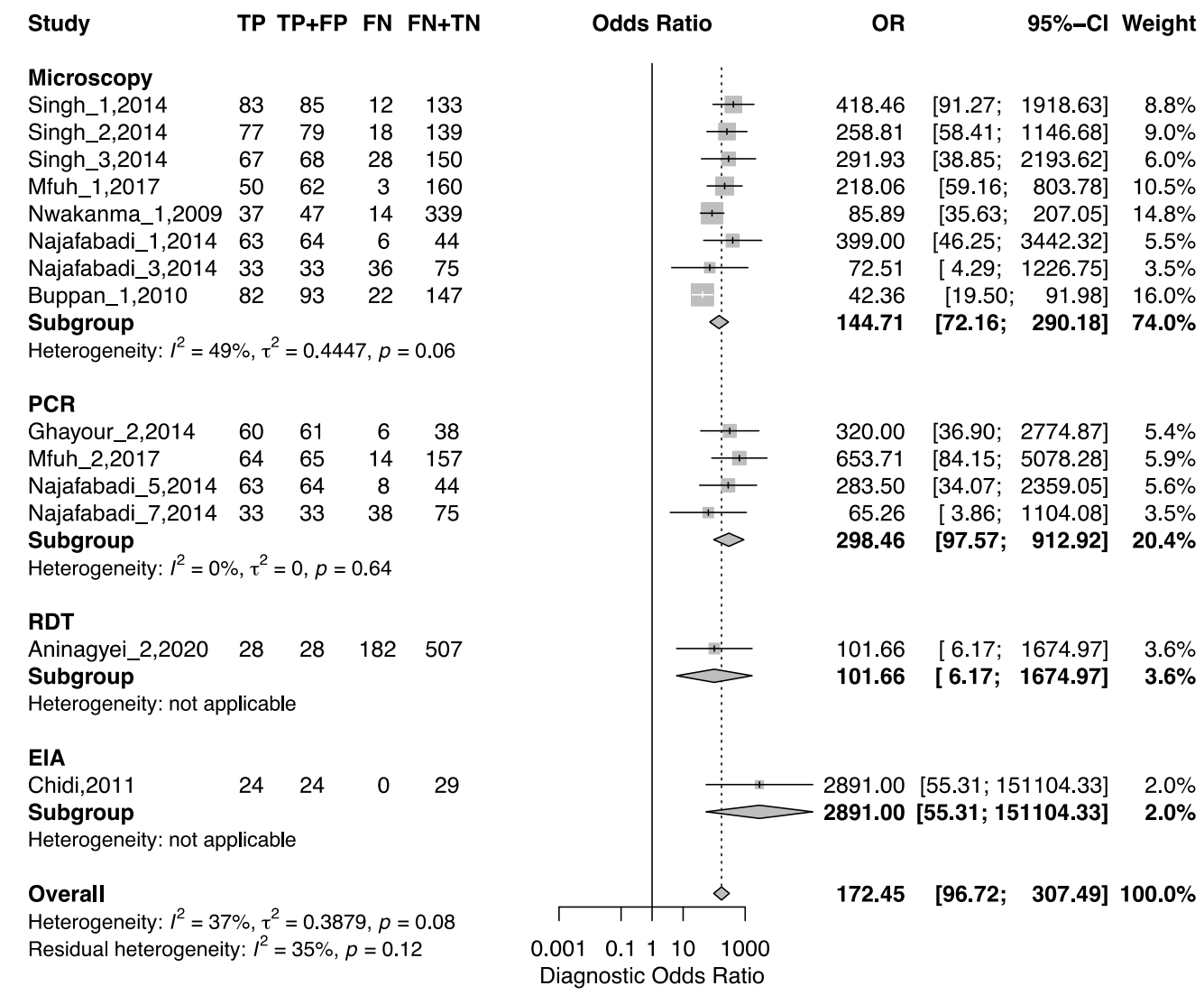
Diagnostic accuracy of tests conducted on saliva according to the reference test performed on blood



Supplementary Figure 1. Sensitivity of tests conducted on saliva according to the reference test performed on blood



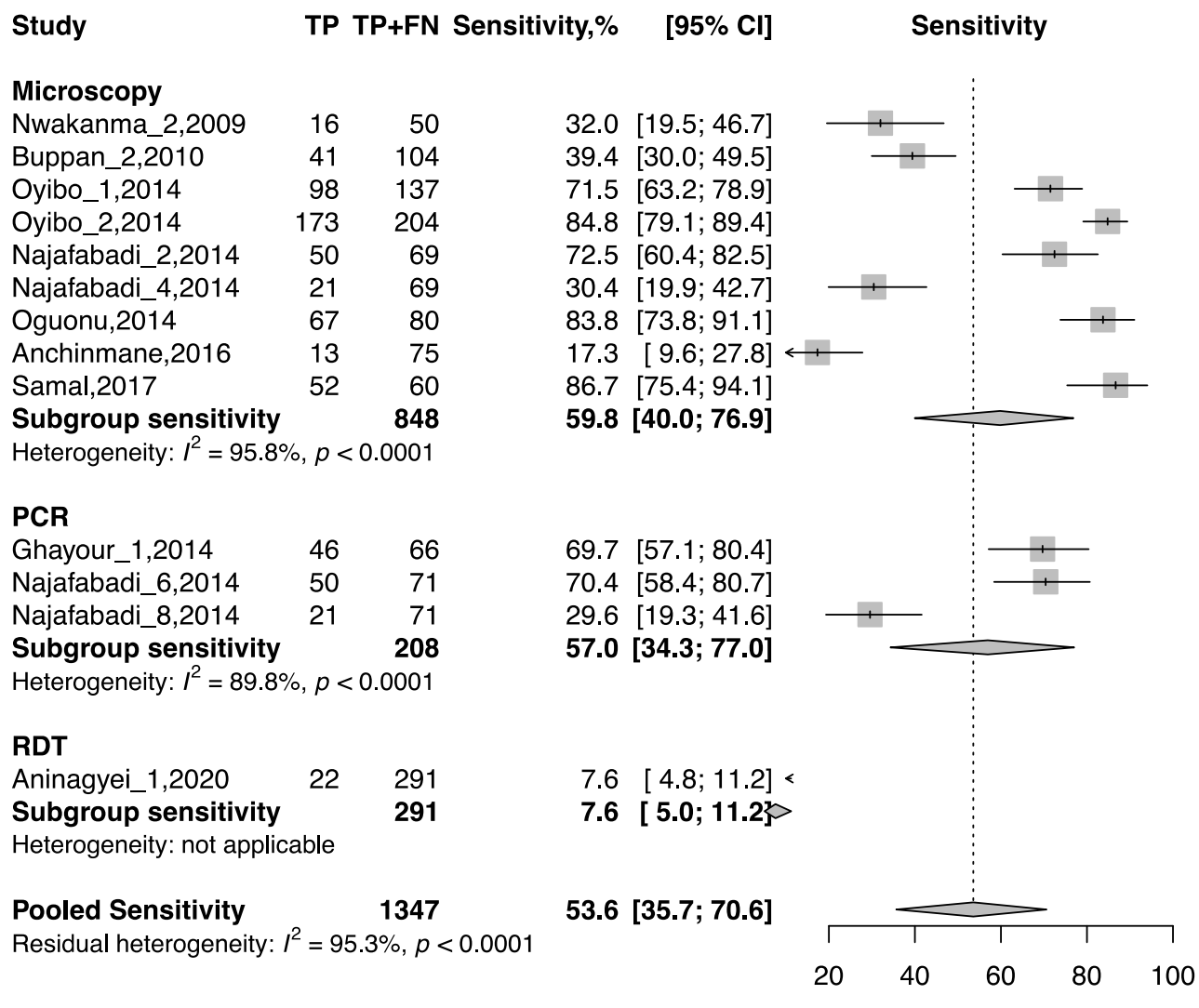
Supplementary Figure 2. Specificity of tests conducted on saliva according to the reference test performed on blood



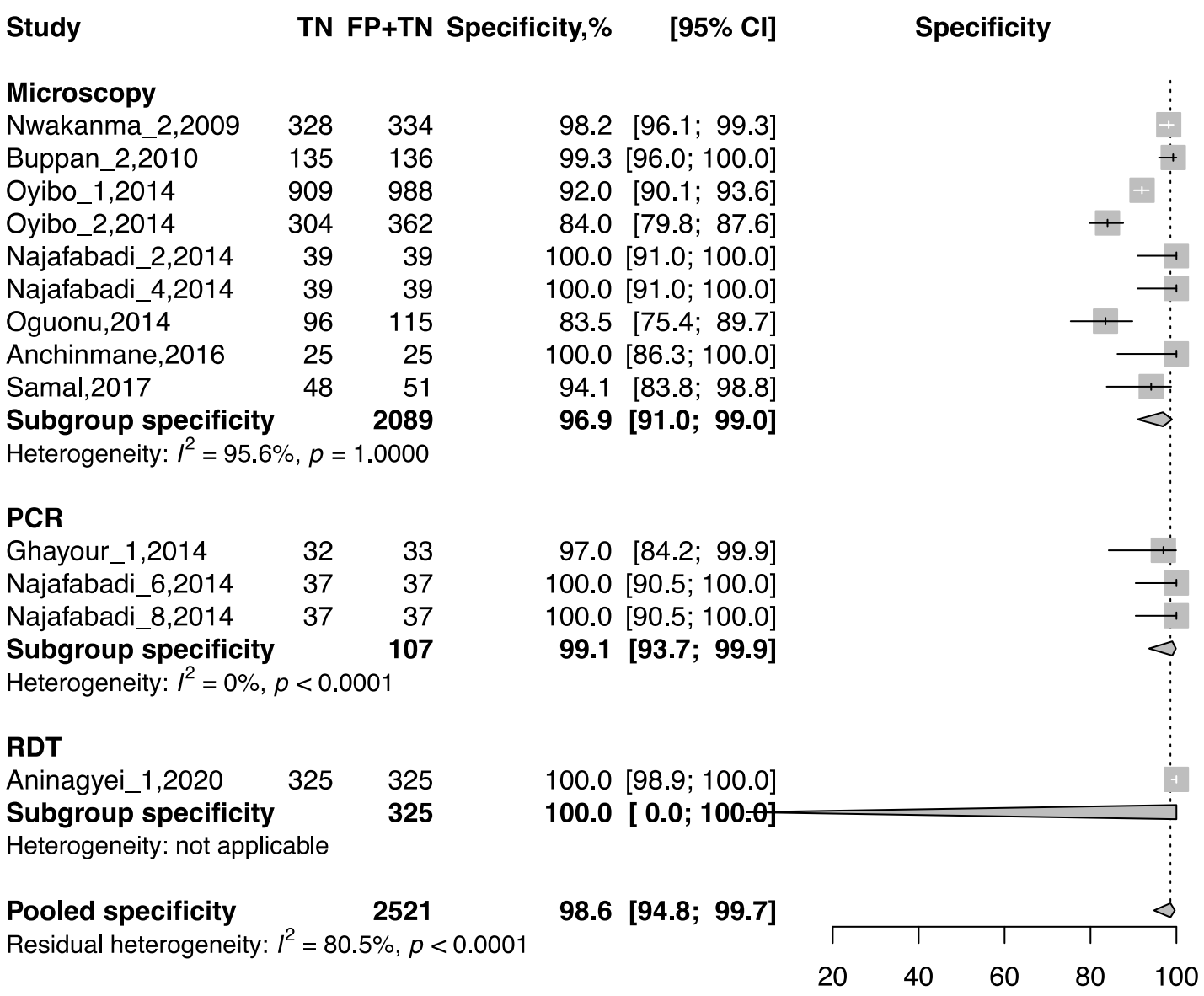
Supplementary Figure 3. DOR of tests conducted on saliva according to the reference test performed on blood

Urine

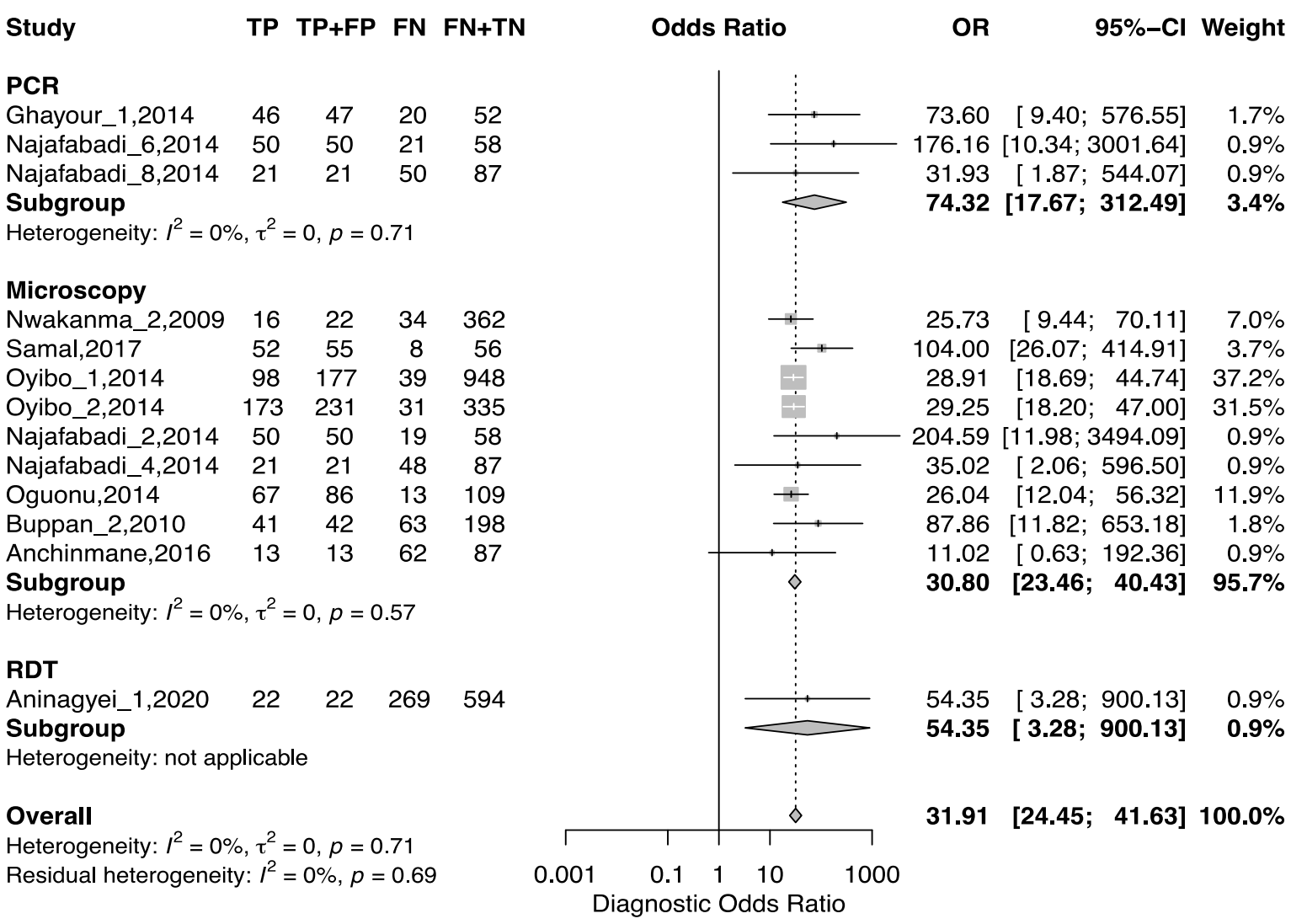
Diagnostic accuracy of tests conducted on urine according to the reference test perform on blood sample



Supplementary Figure 4. Sensitivity of tests conducted on urine according to the reference test perform on blood sample



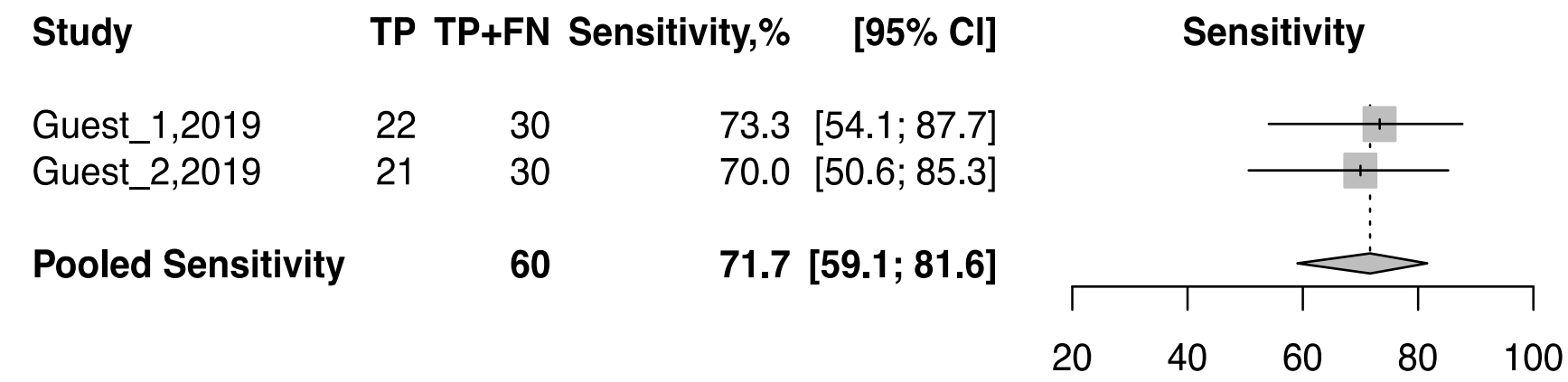
Supplementary Figure 5. Specificity of tests conducted on urine according to the reference test perform on blood sample



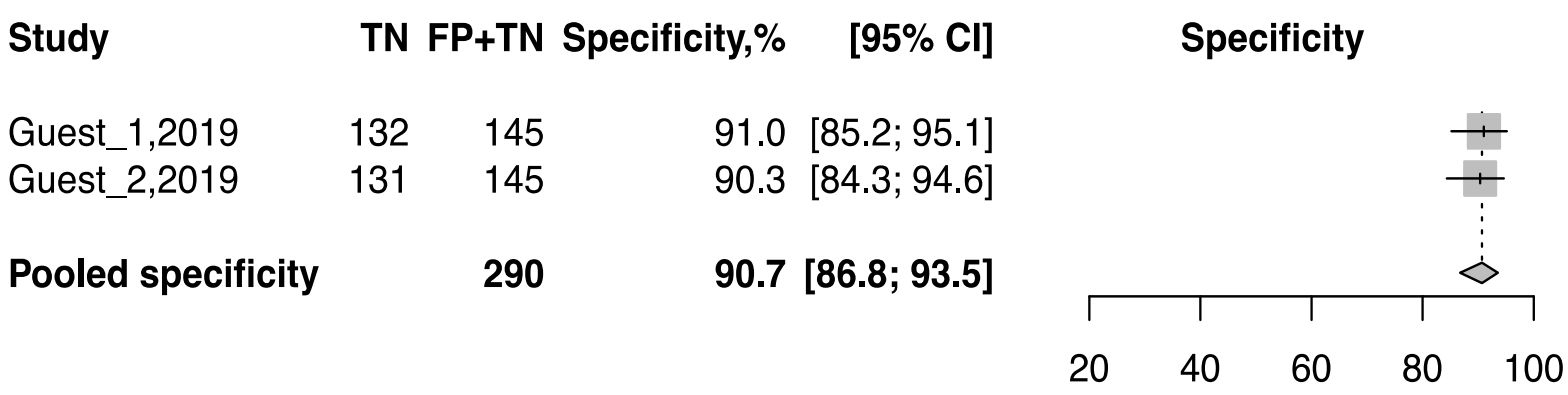
Supplementary Figure 6. DOR of tests conducted on urine according to the reference test perform on blood sample

Studies conducted in children

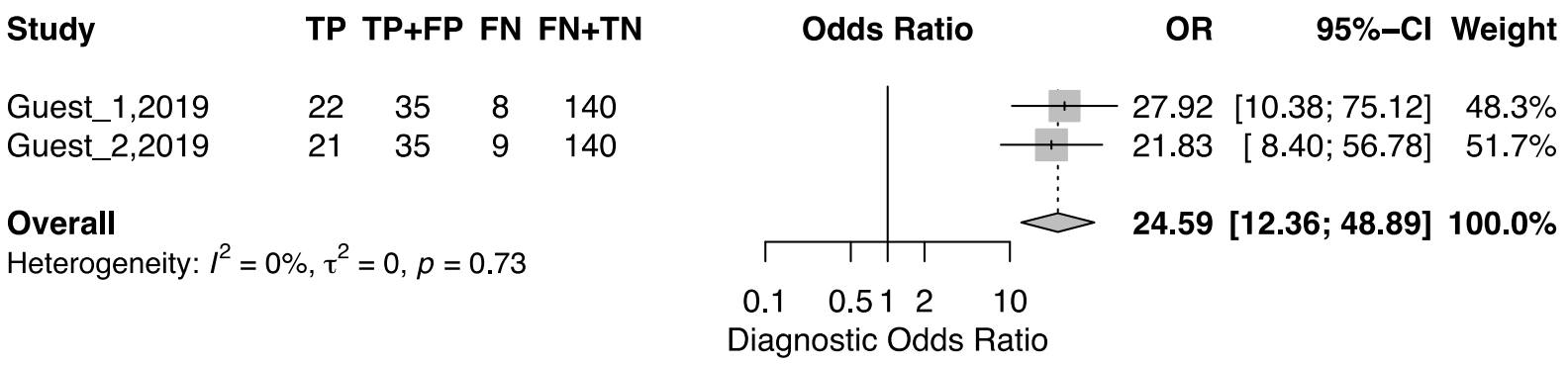
Studies conducted in children: only study on the "sniff and tell" method were eligible for meta-analysis



Supplementary Figure 7. Sensitivity of "sniff and tell" method



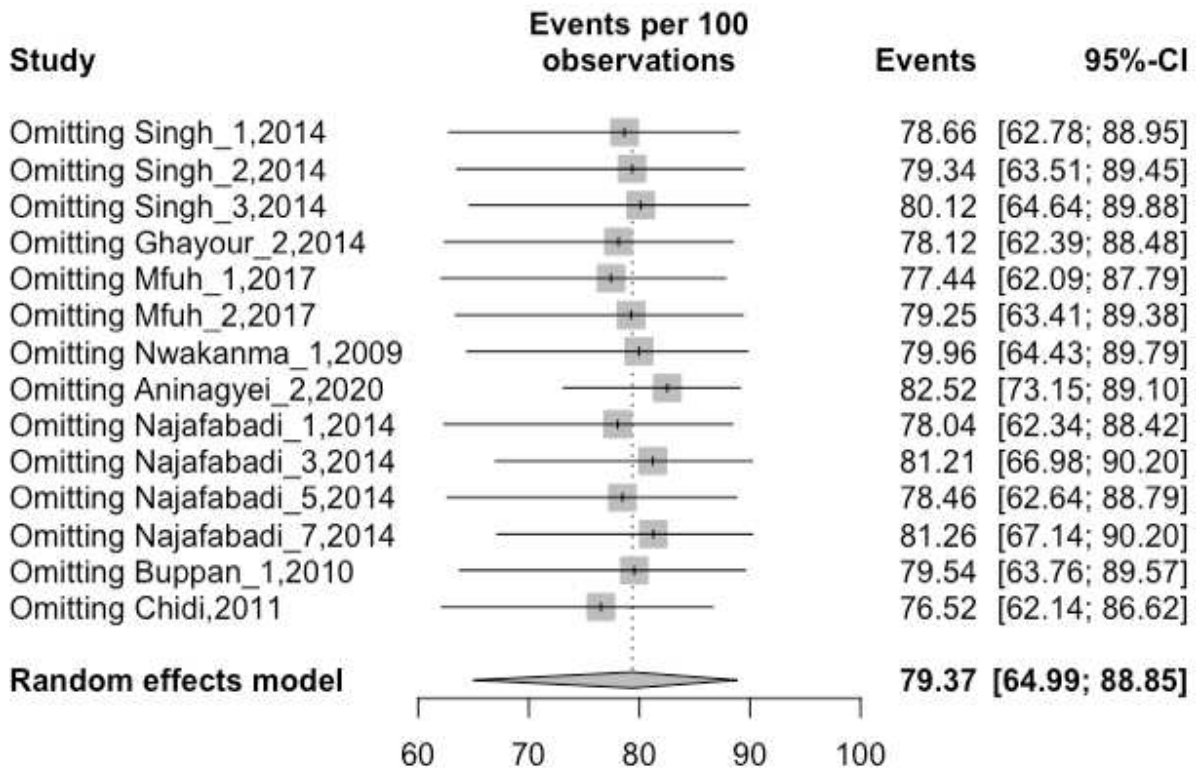
Supplementary Figure 8. Specificity of "sniff and tell" method



Supplementary Figure 9. DOR of "sniff and tell" method

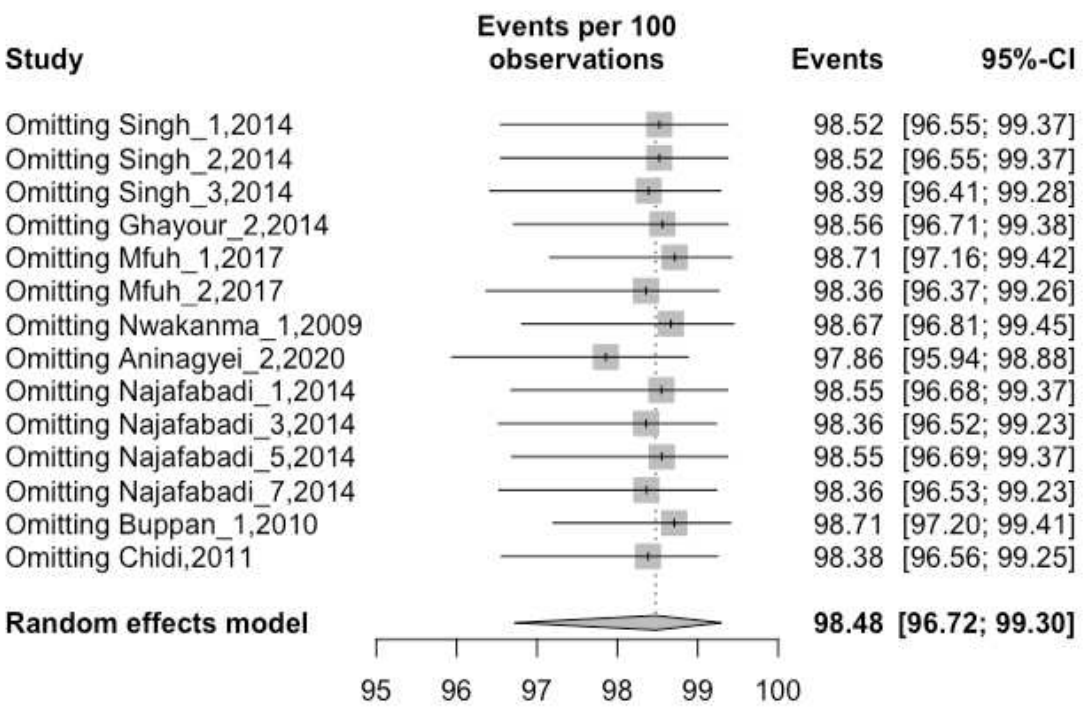
Leave-one-out analysis for studies conducted on saliva

Sensitivity



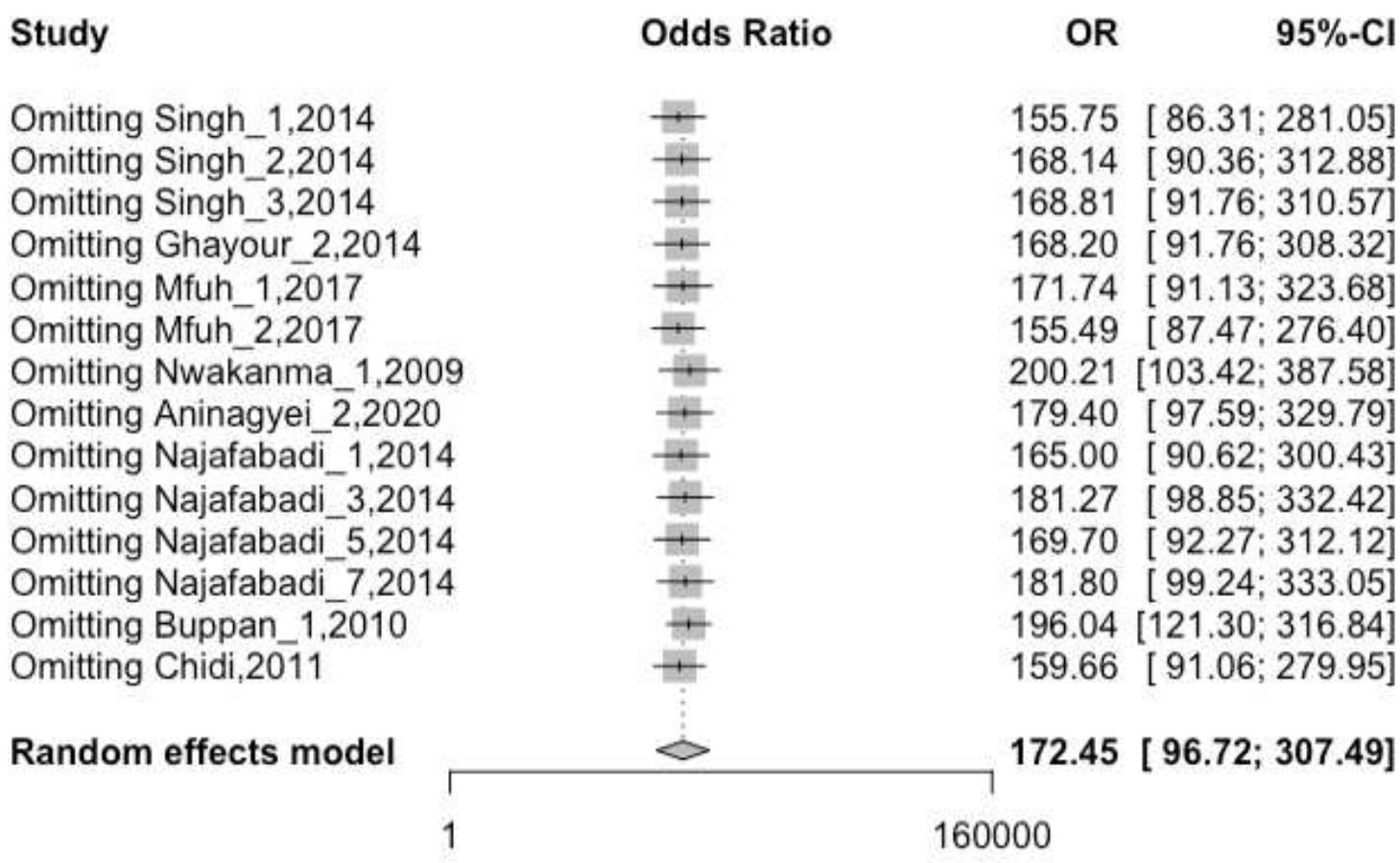
Supplementary Figure 10. Leave-one-out analysis of studies reporting on saliva (sensitivity)

Specificity



Supplementary Figure 11. Leave-one-out analysis of studies reporting on saliva (specificity)

DOR

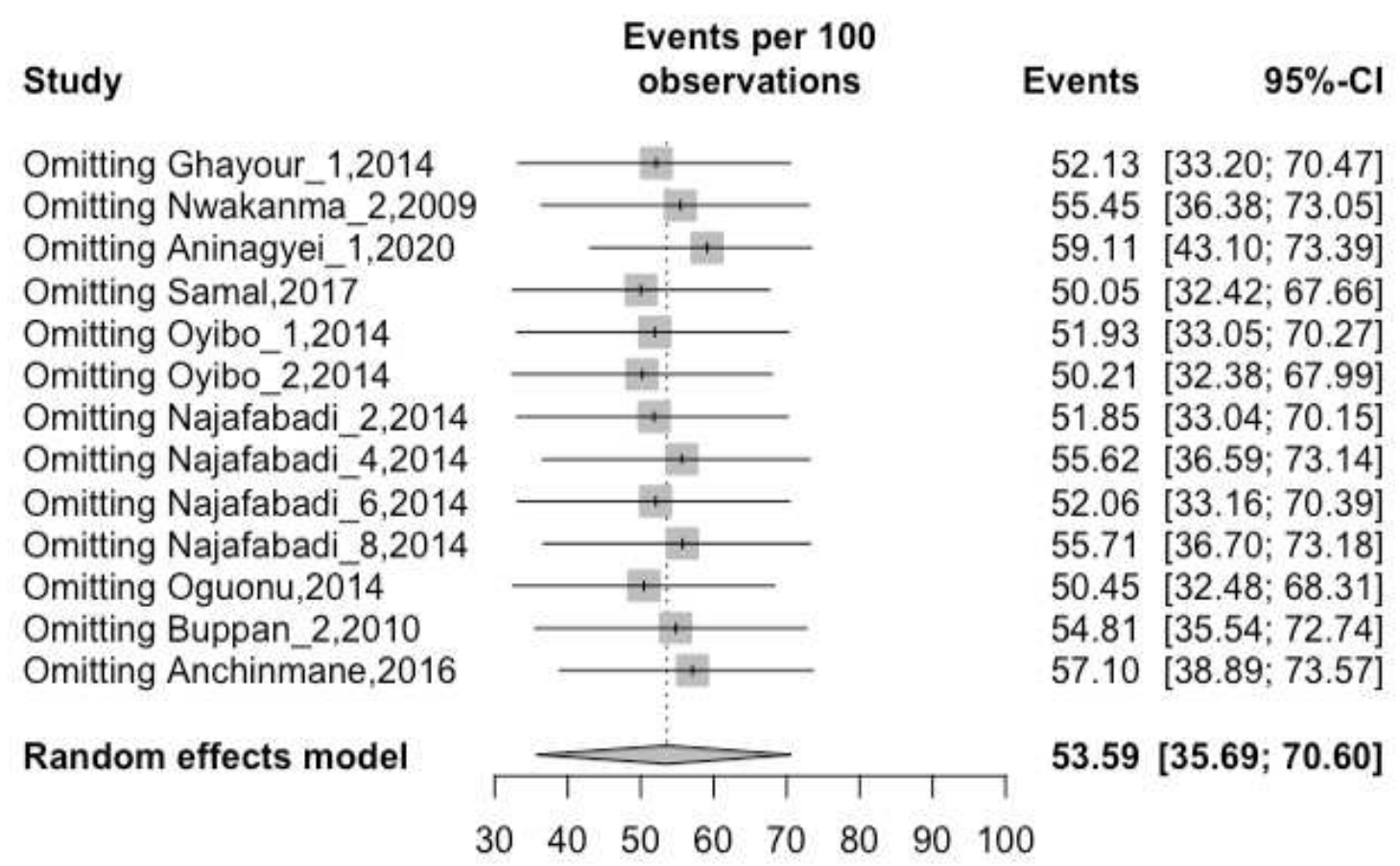


Supplementary Figure 12. Leave-one-out analysis of studies reporting on saliva (DOR)

NB: the leave-one-out analysis was conducted regardless of the reference test used in blood.

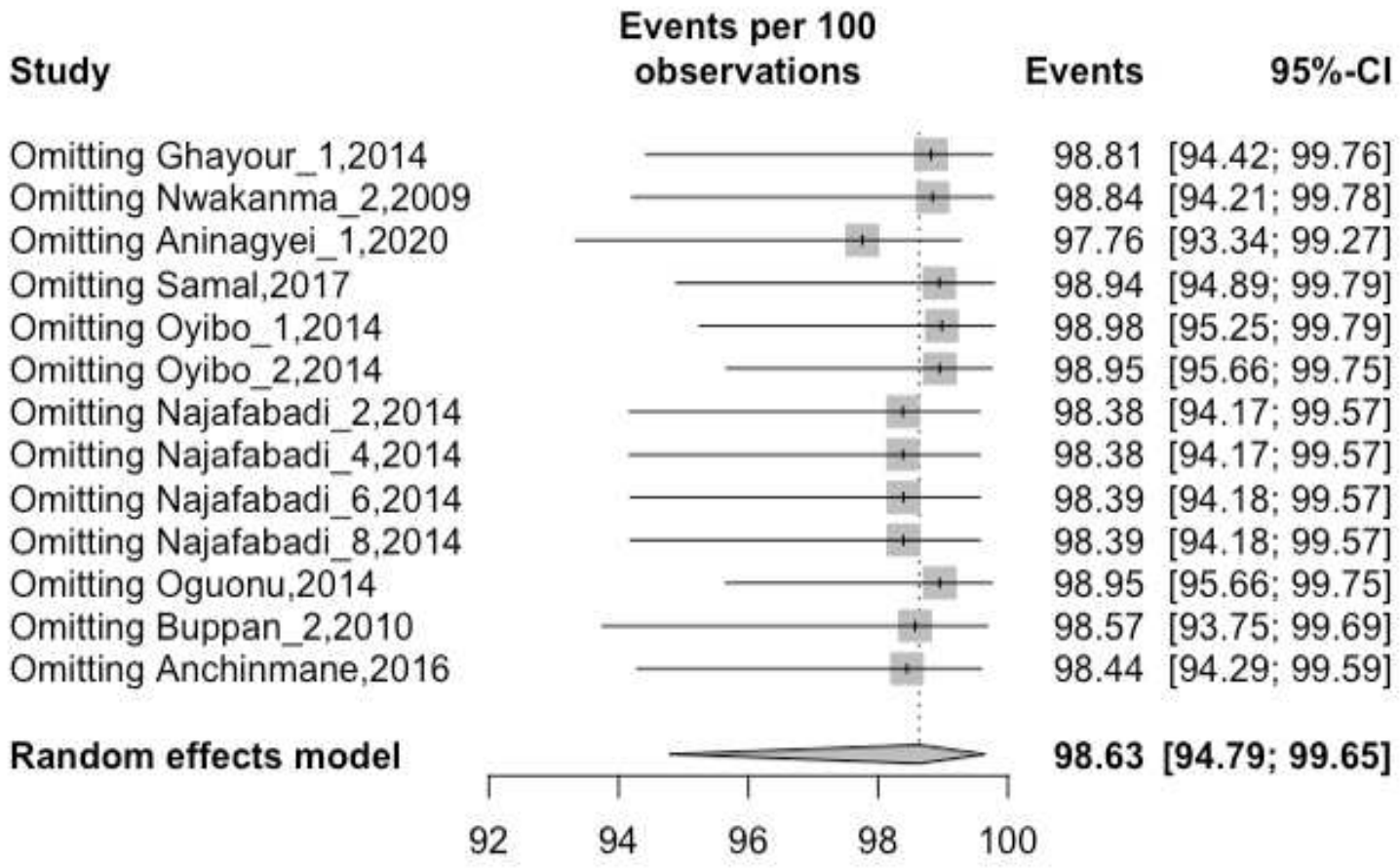
Leave-one-out analysis for studies conducted on urine

Sensitivity



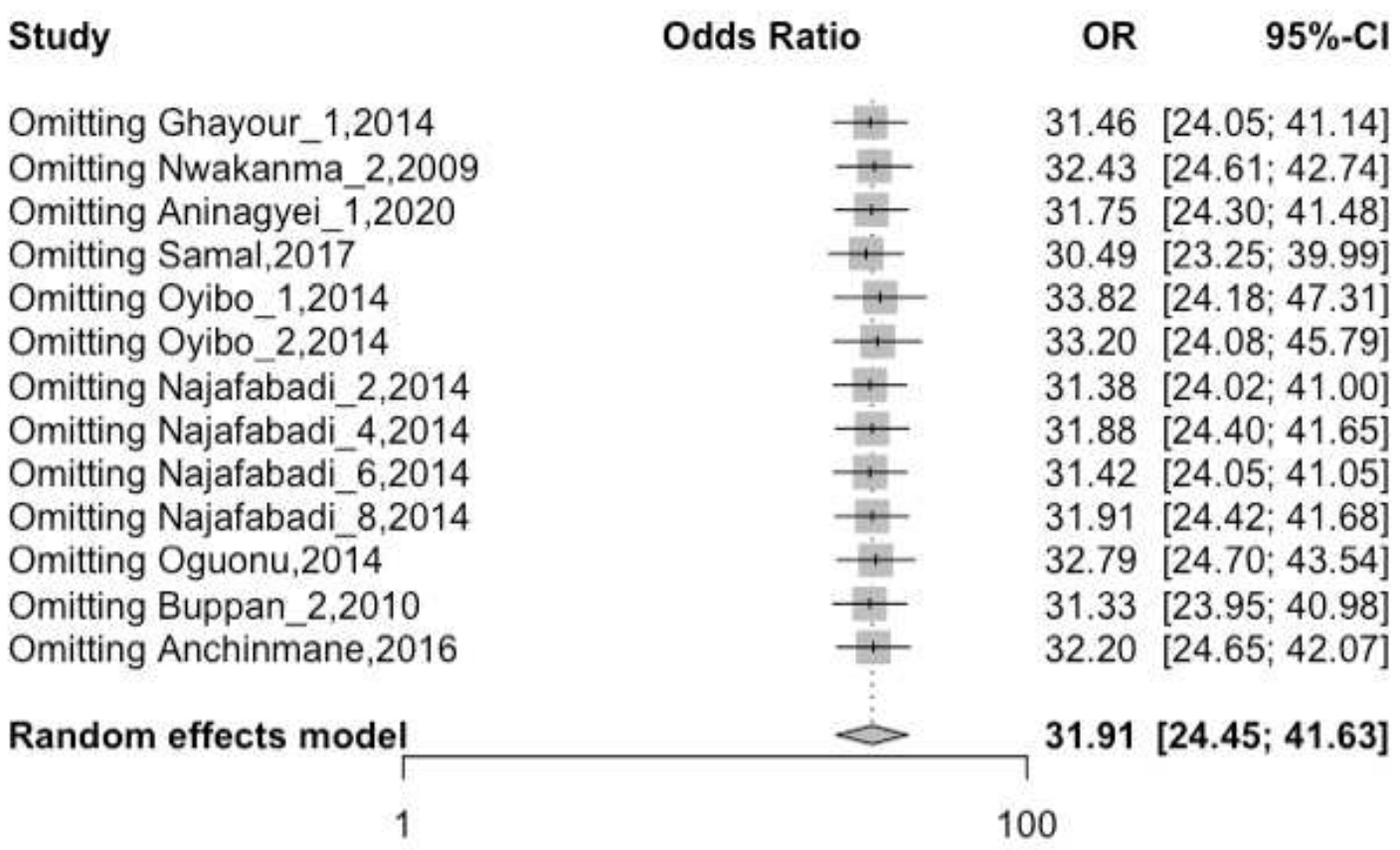
Supplementary Figure 13. Leave-one-out analysis of studies reporting on urine (sensitivity)

Specificity



Supplementary Figure 14. Leave-one-out analysis of studies reporting on urine (specificity)

DOR



Supplementary Figure 15. Leave-one-out analysis of studies reporting on urine (DOR)

NB: the leave-one-out analysis was conducted regardless of the reference test used in blood.