Performance of a novel hematology analyzer in the detection of *Plasmodium* infections in clinical settings: Systematic review

Performance d'un nouvel analyseur d'hématologie dans la détection des infections à *Plasmodium* en milieu clinique : revue systématique

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Summary

Background: Early and accurate diagnosis is crucial for malaria disease effective management. In the current context of global malaria control and elimination, there is a dire need for innovative, easy-to-use, highly sensitive, and automated malaria diagnostic methods. Against this backdrop, this review scrutinized the available data on the diagnostic performance of the hematology analyzer XN-31 compared to other diagnostic methods currently used in malaria diagnosis. **Methods**: The published articles on the diagnostic performance of the hematology analyzer XN-31 in detecting *Plasmodium* infections in clinical settings were systematically searched on major medical databases. The data were reported following the Preferred Reporting Items for Systematic and Meta-analyses (PRISMA) guidelines. **Results**: In total, 279 articles were identified, of which 7 met the inclusion criteria. The overall concordance of XN-31 compared with microscopy and/or rapid diagnostic test (RDT), polymerase chain reaction (PCR), and quantitative buffy coat (QBC) was high (≥ 85%). The overall sensitivity, specificity, positive and negative predictive values of XN-31 were also high (> 80%) regardless of the malaria diagnostic method used. Finally, the parasitemia values of XN-31 showed an excellent correlation with the current malaria clinical diagnostic gold standard (> 0.99). Thus, this latter performance makes the XN-31 as accurate as expert microscopy in the biological diagnosis of malaria. **Conclusion**: This systematic review showed that the XN-31 is an automated rapid, robust, and accurate malaria diagnostic method. However, data on its performance in real conditions of use, especially in malaria endemic countries, should be collected to consolidate its use.

Keywords: *hematology analyzer XN-31, malaria, microscopy, PCR, rapid diagnostic test*

Résumé

Introduction : Un diagnostic précoce et précis est crucial pour une prise en charge efficace du paludisme. Dans le contexte actuel de contrôle et d'élimination du paludisme, il existe un besoin urgent de méthodes innovantes, faciles à utiliser, hautement sensibles et automatisées. Cette revue avait pour objectif de synthétiser les données disponibles sur les performances diagnostiques de l'analyseur d'hématologie XN-31 par rapport aux autres méthodes actuellement utilisées. **Méthodes :** Les articles publiés sur les performances diagnostiques de l'analyseur XN-31 dans la détection des infections à *Plasmodium* ont été systématiquement recherchés dans les principales bases de données médicales. Les données ont été rapportées conformément aux lignes directrices PRISMA (Preferred Reporting Items for Systematic and Meta-analyses). **Résultats :** Au total, 279 articles ont été identifiés, dont 7 répondaient aux critères d'inclusion. La concordance globale du XN-31 par rapport à la microscopie et/ou au test de diagnostic rapide (TDR), à la réaction en chaîne par polymérase (PCR) et à la couche leuco-plaquettaire (QBC) était élevée (≥ 85 %). La sensibilité, la spécificité et les valeurs prédictives globales du XN-31 étaient également élevées (> 80 %) indépendamment de la méthode utilisée. Enfin, les valeurs de parasitémie du XN-31 ont montré une excellente corrélation avec la méthode de référence (> 0,99). **Conclusion :** Cette revue systématique a montré que le XN-31 est une méthode automatisée, rapide, robuste et précise. Cependant, des données sur ses performances dans des conditions réelles d'utilisation, notamment dans les pays d'endémie, doivent être collectées afin de consolider son utilisation.

Mots-clés : *analyseur d'hématologie XN-31, microscopie, paludisme, PCR, test de diagnostic rapide*

BACKGROUND

Malaria infection remains a significant public health problem worldwide, although it is considered one of the oldest infectious diseases [1]. Although malaria morbidity and mortality rates have declined since 2010, significant efforts are needed to achieve the World Health Organization (WHO) global targets by 2030 [2]. Globally in 2022, there were 249 million malaria cases with 608 000 deaths reported [3]. The WHO African region accounted for about 93.6% of cases and 95.4% of deaths [3]. Early and accurate diagnosis of malaria is crucial for effective disease management and vector control [4]. According to the recommendations of the WHO, a prompt malaria diagnosis, either by microscopy or by a malaria rapid diagnostic test (RDT), should be performed in all patients with suspected malaria before treatment is administered [5]. Microscopic examination remains the gold standard test for malaria diagnosis in clinical settings [6]. This method is inexpensive from the point of view of materials and consumables, allows species identification and quantification of parasitemia, and is useful when monitoring clearance of parasitemia [6]. However, this method is time-consuming, requires an experienced microscopist, and there is significant variability in the methods applied across laboratories [7]. Alternatives to microscopic examination include RDTs, which are easy to use and do not require trained personnel [6]. However, in cases of infections with low parasitemia, false negative results may be obtained [8]. In Addition, the sensitivity of RDTs decreases for the detection of *Plasmodium falciparum* due to specific mutations or complete deletion of the gene encoding the histidine-rich target protein 2/3 (HRP2/3) in *P. falciparum* [9–11]. RDTs detecting *Plasmodium* lactate dehydrogenase (pLDH) are also available, but their sensitivity is lower than that of HRP-detecting RDTs [12]. Furthermore, this pLDH-RDT is associated with a high rate of false negative results in the detection of *Plasmodium ovale* [13]. Although polymerase chain reaction (PCR) and loop-mediated isothermal amplification (LAMP) demonstrate greater sensitivity and specificity than RDT and microscopy, their usefulness in low and middle income countries are limited due to intensive sample processing, high costs, and the need for specially trained technologists [4,14]. In the current context of global malaria control and elimination, there is a dire need for innovative, easy-to-use, highly sensitive, and automated malaria diagnostic methods. The XN-31 is an automated hematology analyzer developed by Sysmex (Kobe, Japan) to support the diagnosis of malaria in whole blood samples in clinical settings [15]. This method uses fluorescence flow cytometry technology to quantify malaria-infected red blood cells (MIRBCs) in human blood, specifically identifying RBCs containing nucleic acids [16,17]. Combined with a complete blood count (CBC), XN-31 automatically calculates parasitemia shown as malaria-infected red blood cells in percentage “MI-RBC%” and in number per microliter “MI-RBC#/µL”. It also allows *Plasmodium* identification at the species level [18]. The hematology analyzer XN-31 has been approved as a malaria diagnostic method in several countries such as Kenya, European Union countries, and Japan [15]. This method has recently been integrated into the landscape of malaria diagnostic methods in many reference hospitals in Burkina Faso. Against this backdrop, this review scrutinized the available data on the diagnostic accuracy of the hematology analyzer XN-31 in comparison to other methods currently used for malaria diagnosis.

METHODS

❖ Search strategy and selection criteria

A computerized review was undertaken to assess the performance of the hematology analyzer XN-31 in detecting *Plasmodium* infections was performed by two independent reviewers using PubMed, ScienceDirect, and Google Scholar databases. The search for articles covered the period from March 17 to May 14, 2024. The search utilized the keywords "XN-31", or "hematology analyzer XN-31" combined with "malaria" or "*Plasmodium*" to retrieve relevant reports. Only original articles reporting the performance of the hematology analyzer XN-31 in the detection of *Plasmodium* infections in venous blood were eligible for this review. This performance included all articles addressing the sensitivity, specificity, negative and positive predictive values, efficiency, and correlation of the hematology analyzer XN-31 compared to other diagnostic methods currently used in malaria diagnosis. All articles published in English and French languages were screened based on the title and/or abstract and if necessary, the full-text to assess their potential eligibility. The full-text articles included were checked electronically and duplicates were

removed. Disagreement between the two independent reviewers was resolved by discussion and consensus and if necessary, by involving a third reviewer. No restriction was imposed on the study design, the type of study, and the date of publication of the articles. The data were reported following the Preferred Reporting Items for Systematic and Meta-analyses (PRISMA) guidelines [19].

❖ **Data synthesis**

The relevant data were summarized according to the sensitivity, specificity, negative and positive predictive values, efficiency, intraclass correlation coefficient (ICC), coefficient of determination, and correlation coefficient of the hematology analyzer XN-31 compared to other malaria diagnostic methods. This data was also summarized according to the key methodological, demographic, and clinical data from each included study.

RESULTS

❖ **Search results**

A total of 279 citations were identified from PubMed (n = 17), ScienceDirect (n = 224), and Google Scholar (n = 38). After screening the titles and abstracts, 245 citations were excluded. Among the 34 articles retained, 11 duplicate articles were removed. Out of 23 full-text articles, 16 were excluded based on eligibility criteria. Thus, finally, 7 articles were included in this systematic review (Figure 1).

❖ **Description of key methodological, demographic, and clinical data from included studies**

Table 1 summarizes the key methodological, demographic, and clinical data from each included study. This summary showed a lack of harmonization of the methods used to assess the clinical performance of the hematology analyzer XN-31. Of the 7 studies included in this review, the performance evaluation of the hematology analyzer XN-31 was carried out in 42.86% (3/7) of cases using the prototype device and the remaining 57.14% (4/7) using the approved device. Furthermore, three of the seven (42.86%) studies included in this review assessed the performance of the hematology analyzer XN-31 on imported malaria. The time between sampling and processing with XN-31 varied across studies. Two types of RDTs targeting the histidine-rich protein 2 (HRP2) antigen-specific to *P. falciparum* (Pf) and either the pan-malarial antigen common to *P. falciparum*, *P. vivax*, *P. ovale*, and *P. malariae* for Pf/PAN (HRP2/pLDH) antigens or *Plasmodium* lactate dehydrogenase of *P. vivax* for Pf/Pv (HRP2/pLDH) antigens were identified in this review.

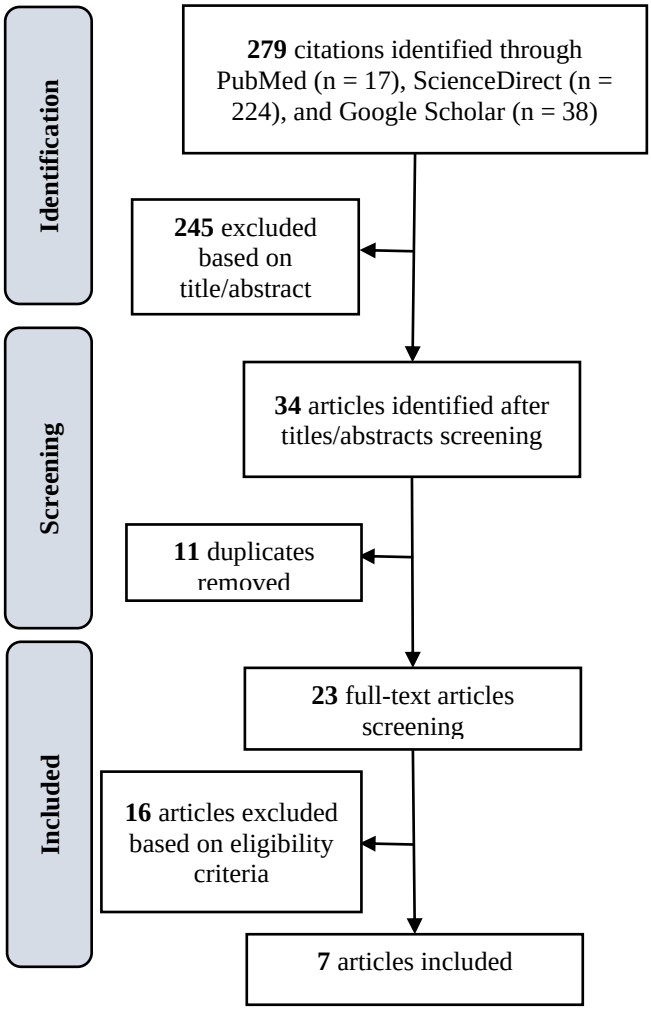

Figure 1. Flow chart of articles selected for the systematic review on the performance of the hematology analyzer XN-31 in the detection of *Plasmodium* infections in clinical settings [19].

The accuracy of XN-31 was compared to that of microscopy in 4 studies [18,20–22], to the RDT in 3 studies [18,20,21] and to PCR in three studies [20,21,23]. Only one study compared the performance of XN-31 with LAMP [18]. The performance of XN-31 against combined reference methods (expert microscopy plus PCR) was reported in one study [24] and RDT plus PCR plus quantitative buffy coat in another one [25]. The study population consisted mainly of adults over 20 years old. Finally, only one study clearly indicated having included severe malaria cases.

- **Performance of the hematology analyzer XN-31 in the detection of *Plasmodium* infections in clinical settings**

The table 2 depicts the sensitivity, specificity, and positive/negative predictive values of the hematology analyzer XN-31 for the detection of *Plasmodium* infections in clinical settings compared with other malaria diagnostic methods. The overall sensitivity of XN-31 regardless of the malaria diagnostic method used ranged from 81.8 to 100%. However, when considering only the values of approved XN-31, this sensitivity ranged from 91.74 to 100%. The sensitivity of approved XN-31 was even higher (95.05–100%) when the reference method used was high-performance such as PCR or LAMP. Regarding specificity, except for the study by Tiwari et *al*., which reported a specificity of 72.7% on an approved XN-31 device, the overall specificity of XN-31 ranged from 98.11 to 100%. The positive predictive value (PPV) regardless of the malaria diagnostic method used, ranged from 88.9 to 100%. As observed with sensitivity, the PPV of XN-31 was higher (97.35 to 100%) when compared to high-performance reference method (PCR or LAMP). Finally, the negative predictive value (NPV) regardless of the malaria diagnostic method used ranged from 95.08 to 100%. Zuluaga-Idárraga et *al*. assessed the performance of XN-31 in the detection of *P. falciparum* or *P. vivax*. The sensitivity, specificity, PPV, and NPV ranged from 84.4 to 90.13%, 99.1 to 99.62%, 96.66 to 98.59%, and 95.48 to 97.21%, respectively, for *P. falciparum*. This performance of XN-31 with *P. vivax* ranged from 91.94 to 98.25%, 98.32 to 98.93%, 80.43 to 87.02%, and 99.36 to 99.87% for the sensitivity, the specificity, the PPV, and the NPV, respectively. Khartabil et *al*. assessed the efficiency of XN-31 against reference combined methods (RDT, PCR, and QBC). The efficiency of XN-31 compared to the reference combined methods was 96% [25]. Zuluaga-Idárraga et *al*. assessed the concordance of parasitemia between the XN-31 and the microscopy. This concordance was good with an intraclass correlation coefficient (ICC) of 0.85 for the concordance between the XN-31 (MI-RBC#/µL) and the thick blood smear and excellent (0.98) between the XN-31 (MI-RBC%) and the thin blood smear [20]. Komaki-Yasuda et *al*. determined the correlation coefficient between XN-31 (MI-RBC%) and microscopic values. These values were found to be highly correlated with a correlation coefficient > 0.99 [23]. The coefficient of determination (R^2) reported between the XN-31 and the microscopy by Picot et *al*. was also very high (0.96) [18]. Available data showed that 3.08% (228/7398) of the samples analyzed with XN-31 yielded "indeterminate" results. Of these indeterminate results, 95.17% (217/228) were confirmed negative by PCR and/or microscopy or RDT [20,21,23–25].

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DISCUSSION

This systematic review aimed to assess the accuracy of the hematology analyzer XN-31 developed by Sysmex compared to current major malaria diagnostic methods (microscopy, RDT, PCR, LAMP, and QBC) in the detection of *Plasmodium* infections in clinical settings. The overall sensitivity, specificity (except for the study of Tiwari et *al*.), positive and negative predictive values of XN-31 was good (> 80%) regardless of the malaria diagnostic method used [18,20–25]. The overall concordance of XN-31 was also good (≥ 85%) [20,25]. Finally, the parasitaemia values of XN-31 showed an excellent correlation with the current malaria clinical diagnostic gold standard (> 0.99) [23]. Thus, this latter performance makes the XN-31 as accurate as expert microscopy in the diagnosis of malaria. To these performances, we must add a rapid processing time of approximately one minute to analyze each sample, the automated analysis and its ability to monitor the decrease in the parasitic load once antimalarial treatment has been initiated [26]. In view of these good performances, XN-31 expands the range of current malaria diagnostic methods. This automated malaria diagnostic method could play an important role in malaria endemic regions where the number of expert microscopists is decreasing with the decline in number of malaria cases [18]. In non-endemic countries, XN-31 could provide reliable results in a setting where experienced microscopists are lacking due to the limited number of malaria cases per year [25]. However, large-scale studies in real conditions of use, particularly in endemic countries, must be conducted to validate the performance of XN-31. Indeed, the number of studies carried out on the approved version of XN-31 are largely lacking, particularly in endemic countries where only two clinical studies are currently reported [22,24]. Furthermore, most published studies on the performance of XN-31 have focused on

adult populations or imported malaria cases [18,20–25]. The most vulnerable groups, namely children under 5 years of age and pregnant women, who bear the greatest burden of morbidity and mortality attributable to malaria, particularly in sub-Saharan Africa [3], are largely absent from these studies.

This is all the more important because in malaria-endemic countries there is overlap with other parasitic diseases. Furthermore, more than 80% of people with sickle cell disease live in sub-Saharan Africa, where most deaths due to malaria occur [27]. This health condition is associated with the increase of indeterminate results with XN-31 [26]. The number of malnutrition cases and premature newborns reported to be associated with the occurrence of indeterminate results with XN-31 is also prevalent in malaria-endemic countries [25]. In addition, in these endemic malaria countries, complex diagnostic scenarios with mixed *Plasmodium* species infections or co-infection with other parasitic and non-parasitic infections are possible. These situations could favor the occurrence of indeterminate results or false positive results with XN-31 [21]. These latter scenarios coupled with reagent shortage, machine breakdown, or computer issues, particularly in low and middle income countries suggested that XN-31 should be combined with the current malaria diagnostic method and not completely supplant these methods [18].

All these shortcomings require large-scale studies to be carried out specifically on priority target populations defined by the WHO (children under 5 years of age and pregnant women) in endemic countries, particularly in sub-Saharan Africa [3]. Such studies on the performance of XN-31 in countries with the highest malaria burden will help the establishment of clear recommendations for its use in routine clinical practice.

CONCLUSION

This systematic review showed that the hematology analyzer XN-31 is an automated rapid, robust, and accurate malaria diagnostic method. However, data on its performance in real conditions of use, especially on target populations defined by WHO in high malaria endemic countries, are needed to support its large-scale implementation in routine clinical practice. This new method should not be used as the sole method for diagnosing malaria but rather as an additional diagnostic tool within the currently existing diagnostic arsenal. Finally, the ability of XN-31 to identify red blood cells containing nucleic acids combined with its ability to provide white blood cell counts support its use in reference laboratories.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest regarding this article.

AUTHORS' CONTRIBUTIONS

Ouédraogo DF, Yerbanga IW, and Nagalo A designed the study. Ouédraogo DF and Yerbanga IW selected, extracted, and synthesized data. ODF and YWI wrote the manuscript. All authors revised the final version of the manuscript. All authors read and approved the final manuscript.

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Table 1: Summary of key methodological, demographic and clinical data from each included studies

Authors, date of publication	Country	Malaria endemic country?	Type of study	Age	Sample size	Severity of malaria	Time between sampling and processing with XN-31	Type of RDT	XN-31 compared with	Reference
Tiwari et *al*., 2024	India	Yes	Cross-sectional	Median age: 32 years (IQR, 18–65) in BD, and 40 years (IQR 17–60) in MS patients	5005 in BD group and 82 in malaria suspected patients' group	-Asymptomatic (BD) -NA in malaria suspected patients	Within 24 h of blood collection	NA	MI	**[22]**
Picot et *al*., 2022	France	No	Cohort study*	Median age = 36 years (range, 1–89)	357	Uncomplicated	NA	Pf/PAN (HRP2/pLDH) Ag	MI, RDT and LAMP	**[18]**
Khartabil et *al*., 2022	Netherlands	No	Cohort study*	-	112	NA	Freshly collected blood specimens	Pf/PAN (HRP2/pLDH) Ag	Combined methods***	**[25]**
Komaki-Yasud et *al*.*., 2022	Japan	No	Cross-sectional	NA	80	NA	Within 24 h of blood collection	Pf/PAN (HRP2/pLDH) Ag	PCR	**[23]**
Kagaya et *al*.*, 2022	Kenya	Yes	Cross-sectional	Median age (IQR): 23 years (5–36)	171	NA	NA	Pf/Pv (HRP2/pLDH Ag	MI, RDT and PCR	**[21]**
M'baya et *al*., 2021	Malawi	Yes	Cross-sectional	-	5281	Asymptomatic (BD)	within 24–72 h of blood collection	-	Combined methods****	**[24]**
Zuluaga-Idárraga et *al*.*, 2021	Colombia	Yes	Cross-sectional	> 2 years old	1754	Uncomplicated and severe malaria	NA	Pf/Pv (HRP2/pLDH Ag	MI, RDT, PCR	**[20]**

*Performance evaluation of the hematology analyzer XN-31 was carried out in prototype device; **Inclusion of samples collected at admission and during follow-up; ***: performance evaluation of the XN-31 hematology analyzer against reference combined methods (RDT, PCR, and quantitative buffy coat); ****: performance evaluation of the XN-31 hematology analyzer against reference combined methods (expert microscopy and PCR); BD: blood donors; IQR: Interquartile range; LAMP: loop-mediated isothermal amplification; MI: microscopy; MS: malaria suspected; NA: not available; PCR: polymerase chain reaction; Pf/PAN (HRP2/pLDH) Ag: The test targets the histidine-rich protein II (HRPII) antigen specific to *P. falciparum* and a pan-malarial antigen common to all four malaria species capable of infecting humans namely *P. falciparum*, *P. vivax*, *P. ovale*, and *P. malaria*; P.f/P.v Ag: Qualitative and differential test for the detection of histidine-rich protein II (HRP-II) antigen of *P. falciparum* and *P. vivax* lactate dehydrogenase (pLDH) in human whole blood; RDT: rapid diagnostic test

Table 2: Performance (sensitivity, specificity, positive/negative predictive values) of the hematology analyzer XN-31 in the detection of *Plasmodium* infections in clinical settings

Authors		Sensitivity of XN-31 compared with								Reference
		Microscopy		RDT		PCR		LAMP		
		Values (%)	95%CI	Values (%)	95%CI	Values (%)	95%CI	Values (%)	95%CI	
Picot et *al.*	All data	100	97.13–100	91.74	88.87–94.37	-	-	96.16	93.40–98.92	[18]
	Admission data	98.98	96.14–100	95.96	93.21–98.71	-	-	95.05	92.32–97.78	
Komaki-Yasuda et *al.*		-	-	-	-	97	-	-	-	[23]
Kagaya et *al.*		100	71.3-100	100	74–100	81.8	59.7–94.8	-	-	[21]
M'baya et *al.**		100 (CI95%: 96-100)								[24]
Tiwari et *al.*	WB donors	100	-	-	-	-	-	-	-	[22]
	MS patients	100	-	-	-	-	-	-	-	
Zuluaga-Idárraga et *al.*	All data	98.09	96.51–99.08	97.23	95.4–98.48	90.00	87.24–92.34	-	-	
	PF only	89.74	86.3–92.57	90.13	86.7–92.92	84.4	80.42–87.85	-	-	
	PV only	98.25	93.81–99.79	97.37	92.5–99.45	91.94	85.67–96.06	-	-	
		Specificity of XN-31 compared with								
		Microscopy		RDT		PCR		LAMP		
		Values (%)	95%CI	Values (%)	95%CI	Values (%)	95%CI	Values (%)	95%CI	
Picot. et *al.*	All data	98.39	95.56–100	99.15	96.30–100	-	-	98.72	95.88–100	[18]
	Admission data	100	97.13–100	98.94	96.10–100	-	-	99.47	96.62–100	
Komaki-Yasuda et *al.*		-	-	-	-	100	-	-	-	[23]
Kagaya et *al.*		98.6	95.2-99.8	100	96.3–100	100	96.2–100			[21]
M'baya et *al.**		99.9 (CI95%: 99.4-99.997)								[24]
Tiwari et *al.*	WB donors	100	-	-	-	-	-	-	-	[22]
	MS patients	72.7	-	-	-	-	-	-	-	
Zuluaga-Idárraga et *al.*	All data	99.83	99.4–99.98	98.11	97.18–98.8	99.83	99.38–99.98	-	-	[20]
	PF only	99.62	99.12–99.88	99.1	98.43–99.53	99.54	98.99–99.83	-	-	
	PV only	98.93	98.3–99.38	98.32	97.56–98.89	98.91	98.26–99.36	-	-	
		PPV of XN-31 compared with								
		Microscopy		RDT		PCR		LAMP		
		Values (%)	95%CI	Values (%)	95%CI	Values (%)	95%CI	Values (%)	95%CI	
Picot et *al.*	All data	96.46	93.69–99.22	98.23	95.41–100	-	-	97.35	94.55–100	[18]
	Admission data	100	97.13–100	97.94	95.13–100	-	-	98.97	96.13–100	
Khartabil et *al.***		100								[25]
Komaki-Yasuda et *al.*		-	-	-	-	100	-	-	-	[23]
Kagaya et *al.*		88.9	65.3-98.6	100	74–100	100	74–100	-	-	[21]
Zuluaga-Idárraga et *al.*	All data	99.61	98.6–99.95	95.53	93.37–97.15	99.61	98.6–99.95	-	-	[20]
	PF only	98.59	96.74–99.54	96.66	94.23–98.26	98.21	96.15–99.34	-	-	
	PV only	86.82	79.74–92.13	80.43	72.83–86.69	87.02	80.04–92.26	-	-	
		NPV of XN-31 compared with								
		Microscopy		RDT		PCR		LAMP		
		Values (%)	95%CI	Values (%)	95%CI	Values (%)	95%CI	Values (%)	95%CI	
Picot et *al.*	All data	100	97.13–100	95.9	93.03–98.65	-	-	95.08	92.35–97.80	[18]
	Admission data	99.48	96.62–100	97.91	95.10–100	-	-	97.38	94.59–100	
Khartabil et *al.***		100%								[25]
Komaki-Yasuda et *al.*		-	-	-	-	98	-	-	-	[23]
Kagaya et *al.*		100	96.3-100	100	96.3-100	97.3	93.1–99.2	-	-	[21]
Zuluaga-Idárraga et *al.*	All data	99.17	98.49–99.6	98.84	98.07–99.37	95.29	93.94–96.42	-	-	[20]
	PF only	97.04	95.99–97.88	97.21	96.18–98.02	95.48	94.23–96.53	-	-	
	PV only	99.87	99.54–99.98	99.81	99.45–99.96	99.36	98.82–99.69	-	-	

WB: whole blood; MS: malaria suspected; PF: *P. falciparum*; PV: *P. vivax*; CI: confidence interval; LAMP: loop-mediated isothermal amplification; PCR: polymerase chain reaction; RDT: rapid diagnostic test; NPV: negative predictive value; PPV: positive predictive value; *: performance evaluation of the XN-31 hematology analyzer against reference combined methods (expert microscopy and PCR); **: performance evaluation of the XN-31 hematology analyzer against reference combined methods (RDT, PCR, and quantitative buffy coat)