Accuracy of SD Malaria Ag P.f/Pan® As A Rapid Diagnosis Test of Malaria in French Amazonia

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Abstract

Background

French Guiana (FG) is, with Mayotte island, one of the two French overseas territories where malaria is still endemic. Ten years ago, French health authorities implemented a strategy to eradicate malaria disease in the region. The current incidence rate is 0,74‰ inhabitants, and *Plasmodium Vivax* is widely predominating even though *Plasmodium Falciparum* is still present due to imported cases, mainly from the Africa continent. In FG, RDT (SD Malaria Ag Pf/Pan®) test is based on detection of pan-pLDH, PfHRP2, and PfHRP3 antigens. While, in South America, the share of deletion of PfHRP2 gene is significantly increasing. So, we wondered if RDTs remained reliable in this context.

Methods

Our study is a retrospective analysis conducted over four years and analyzed 12880 rapid diagnosis tests (RDTs) whose result was compared with Blood Film Tests (BFTs) sampled for malaria diagnosis.

Results

The global assessment of the diagnosis accuracy of RDT in the diagnosis of malaria shows PPV (Positive Predictive Value) and NPV (Negative Predictive Value) more than 95%, except for PPV of RDT in the diagnosis of malaria to *P falciparum* (88%). Overall, the concordance rate between RDT and BFT (positive/positive; negative/negative) was 99.5%. The PPV of the RDT in the follow-up of patients diagnosed with *P falciparum* was the lowest during the 28 first days after diagnosis. The PPV of the RDT in the follow-up of patients diagnosed with *P vivax* was the lowest during the 21 first days after diagnosis. The global sensitivity of SD Malaria Ag Pf/Pan® test was, on average, 96% (88.2 – 1) for *P falciparum* and 93% (90.6 – 94.2) for *P vivax*. The global specificity was high, with a rate of 99.8% (99.5 – 1) for all species included.

Conclusion

SD Malaria Ag Pf/Pan® is still a reliable rapid test used for the first-line diagnosis in remote healthcare centers. The test reading should be nuanced by the recent medical history of patients and the date of arrival in FG. RDT result has always to be confirmed by BFT that is still the gold standard for the malaria diagnosis. FG is still a PfHRP2 gene deletion-free area.

Background

WHO ranked malaria as a communicable disease among world public health priorities. In 2017, malaria was still the most prevalent parasitic disease, with 1,4 billion people remaining at risk worldwide [2]. The year after, the number of malaria cases was estimated at 228 million, with 405.000 deaths worldwide, with a large predominance on the African continent. The global incidence declined between 2010 and 2018 with 57 cases/1000 inhabitants against 71 cases/1000 in 2010 then stayed at the same level until 2018. In the Americas region, the Malaria incidence is increasing since 2016, mainly due to the epidemic situation in Venezuela [3,4]. *Plasmodium Vivax* is predominating in the Americas Region, accounting for 75% of malaria cases [3]. With Mayotte island, French Guiana (FG) is one of the two French overseas territories where malaria is still endemic [5]. In FG, efforts to fight malaria since the 1950s and the control strategies implemented to the Guiana Shield [6] have led to a significant reduction of yearly recorded cases [7]. In 2019, the number of recorded malaria cases was the lowest for more than ten years, with 212 identified patients in the public IT healthcare system. Thus, the malaria incidence rate is 0,74‰ inhabitants [8]. Previously in FG, *Plasmodium falciparum* was accountable for the majority of cases. However, within the last twenty years, the

distribution of *Plasmodium species* changed with a vast rate of diagnosed *Plasmodium Vivax* [7,9]. Despite a very encouraging figure with very low malaria transmission in the coastal and urban areas, the malaria risk is still endemic in FG. The country's inland sites experience higher levels mainly related to socially marginalized and isolated populations.

Among lab methods used for malaria parasite detection and exposure, only rapid diagnosis tests (RDT) and blood films test (BFT) are currently available for daily practice. Molecular methods are recommended for the submicroscopic detection of malaria parasites. Serology is recommended for the survey and elimination assessment when the parasite prevalence reaches a level lower than 1%. RDT is based on detection of pan-pLDH, PfHRP2 and PfHRP3 antigens. However, there is an increasing rate of deletion of the PfHRP2 gene worldwide, threatening the ability to diagnose patients infected with *Plasmodium falciparum*, responsible for numerous false negatives in RDT results (<https://www.who.int/malaria/publications/>). In South America, the distribution of PfHRP2 gene deletion varies with free countries and areas where the deletion rate is over 30%. In French Guiana, the unique study performed on 140 isolates of *Plasmodium falciparum* did not find PfHRP2 deletion but 4.5% PfHRP3 deletion [10].

With a unique study including a small cohort of RDTs and the knowledge from surrounding countries, we wondered if results were still reliable. We gathered the large number of RDTs from 2016 to 2019 to get a significant level for the validation of statistics. This study aims to evaluate the diagnostic relevance of RDT used in the diagnosis of malaria in French Guiana.

Methods

Our study is a retrospective analysis conducted over four years (January 2016 to December 2019) in the microbiology laboratory of the Cayenne General Hospital. It includes all RDT and BFT sampled for malaria diagnosis. Cayenne General Hospital is a 742-beds health facility that provides first-line medical care for an urban population of 150,000 inhabitants. It manages 18 delocalized prevention and healthcare centers providing care for almost 50,000 inhabitants. Thereby, it is also a referral center for a larger population coming from all over French Guiana and the border countries.

Data collection

Data were collected from the computerized database of the microbiology laboratory of the Cayenne General Hospital. They include the date of the tests, the result of the RDT, and concomitant BFT.

In a first step, we included all files with a RDT and a concomitant BFT. We excluded all files with a BFT without a concomitant RDT, and we put apart all files where concomitant RDT/BFT were sampled during the six months following the diagnosis of malaria.

In a second step, we analyzed all files where concomitant RDT/BFT were sampled during the six months following malaria diagnosis.

Microbiological technique

RDT was based on the SD Malaria Ag P.f/Pan® (Standard Diagnostics Inc.), which detects the presence of pan-pLDH and PfHRP2 antigens [10].

BFT is the gold standard for the diagnosis of malaria. It was based on microscopic examination of blood. It is the mainstay of malaria diagnosis [11]. Two sorts of blood film are traditionally used. Thin films allow species identification with better identification of the parasite. Thick films allow the screening of a larger blood volume and are

about eleven times more sensitive than thin films. Both smears should be used when attempting to make a definitive diagnosis of malaria [15]. Indeed, thick films allow the diagnosis of infection with a low level of parasites, whereas thin films allow better identification of the responsible parasite.

Thick and thin blood films were prepared within one hour of blood collection. Thick blood films were stained with Giemsa diluted at 10%, while thin blood films were stained using a rapid method (RALH 555, RAL Diagnostics). Two hundred fields of the thin blood film were examined before classifying the thin smear-negative, then 1000 counted white blood cells (WBCs) from the thick smear were observed before classifying the sample as negative [10]. The parasite density estimation was based on an assumed 6,000 WBC/ml of blood [10].

Statistical analysis

Results are reported as mean and standard deviation or numbers with percentages. We calculated the sensitivity, specificity, positive and negative predictive values, Youden test, and the Q coefficient of Yule to assess the diagnosis value of RDT in the diagnosis of confirmed malaria by BFT. All statistical analyses were carried out with Excel (2010 Microsoft corporation, Redmond, USA) and IBM SPSS Statistics for Windows, version 24 (IBM Corp., Armonk, NY, USA).

Ethical consideration

Our study is a retrospective that did not require individual consent according to the French law regarding research conforming to MR-003 (JORF no. 0160 du 13 juillet 2018. texte no. 109). Our database has been registered at the Commission National de l'Informatique et des Libertés (registration n° 2219819), in compliance with French law on electronic data sources

Results

During the study period, 12984 samples of blood films for the diagnosis of malaria were ordered. A concomitant BFT and RDT were sampled in 12880 cases. About them, 10873 cases (84.4%) fulfilled our inclusion criteria (Figure 1).

The average number of RDTs and BFTs per year was 2718±394 tests. The average number of RDTs and BFTs per month was 1073±105 tests. RDT was performed in 10873 cases and was positive in 773 cases (7.1%) with identification of *P falciparum* in 125 cases (16.1% of positive tests) and to *P vivax* in 648 cases (83.9% of positive tests). BFT was performed in 10873 cases and was positive in 791 cases (7.3%) with identification of *P falciparum* in 105 cases (13.3% of positive tests), and to *P vivax* in 673 cases (85.1% of positive tests), to both of them in 10 cases (1.3% of positive tests), and *P ovale* in 2 cases (0.3% of positive tests).

The global assessment of the diagnosis accuracy of RDT in the diagnosis of malaria shows PPV and NPV more than 95%, except for PPV of RDT in the diagnosis of malaria to *P falciparum* (88%). Figure 2 shows the diagnosis accuracy of RDT in the diagnosis of malaria independently of the plasmodium species identification.

The yearly assessment of the diagnosis accuracy of RDT in the diagnosis of malaria, of malaria to *P falciparum*, and of malaria to *P vivax* is reported in Table 1. The yearly assessment of the diagnosis accuracy of RDT in the diagnosis of malaria to *P falciparum* shows a drop-down in the PPV in 2017 but an increase after that (Figure 3).

Table 1: Evolution of RDT quality criteria yearly

Year	Comparaison variable	Nb	TP	FP	TN	FN	Ss	Sp	PPV	NPV	Q	Youden
2016	RDT	3276	104	6	3164	2	0.981	0.998	0.945	0.999	1.000	0.979
	RDT /P falciparum		30	5	3237	4	0.882	0.998	0.857	0.999	1.000	0.881
	RDT /P vivax		71	4	3196	5	0.934	0.999	0.947	0.998	1.000	0.933
2017	RDT	2462	297	10	2144	11	0.964	0.995	0.967	0.995	1.000	0.960
	RDT /P falciparum		37	9	2415	1	0.974	0.996	0.804	1.000	1.000	0.970
	RDT /P vivax		258	3	2185	16	0.942	0.999	0.989	0.993	1.000	0.940
2018	RDT	2714	265	3	2430	16	0.943	0.999	0.989	0.993	1.000	0.942
	RDT /P falciparum		33	1	2680	0	1.000	1.000	0.971	1.000	1.000	1.000
	RDT /P vivax		232	2	2464	16	0.935	0.999	0.991	0.994	1.000	0.935
2019	RDT	2421	87	1	2324	9	0.906	1.000	0.989	0.996	1.000	0.906
	RDT /P falciparum		10	0	2411	0	1.000	1.000	1.000	1.000	1.000	1.000
	RDT /P vivax		77	1	2335	8	0.906	1.000	0.987	0.997	1.000	0.905

RDT: Rapid diagnosis tests, Nb: Number of cases, TP: True positive, FP: False positive, TN: True negative, FN: False negative, Ss: Sensitivity, Sp: Specificity, PPV: Positive Predictive Value, NPV: Negative Predictive Value

Overall, the concordance rate between RDT and BFT (positive/positive; negative/negative) was 99.5%. It was the highest in 2016 (99.8%) and the lowest in 2017 (99.1%) (Figure 4).

The concordance rate between RDT and BFT (positive/positive; negative/negative) in the diagnosis of *P falciparum* was 99.8%. It was at 99.6% in 2017 (the lowest) and 100% in 2018-2019. The concordance rate between RDT and BFT (positive/positive; negative/negative) in the diagnosis of *P vivax* was 99.3%. It was at 99.1% in 2017 (the lowest) and 99.5% in 2016 and 2019.

During the study period, 2007 cases (15.6%), the RDT and the BFT were performed as part of the follow-up of patients diagnosed with malaria. The PPV of the RDT was the lowest during the 42 first days (6 weeks) after diagnosis (Figure 5).

The PPV of the RDT in the follow-up of patients diagnosed with *P falciparum* was the lowest during the 28 first days after diagnosis. The PPV of the RDT in the follow-up of patients diagnosed with *P vivax* was the lowest during the 21 first days after diagnosis (Table 2).

Table2: Evolution of RDT quality criteria during four months all species included

Time (days)	Nb	TP	FP	TN	FN	Ss	Sp	PPV	NPV	Q	Youden
0 to 7	992	116	61	803	12	0.906	0.929	0.655	0.985	0.984	0.836
8 to 14	221	6	7	208	0	1.000	0.967	0.462	1.000	1.000	0.967
15 to 21	123	9	4	109	1	0.900	0.965	0.692	0.991	0.992	0.865
22 to 28	91	20	0	70	1	0.952	1.000	1.000	0.986	1.000	0.952
28 to 35	76	25	1	48	2	0.926	0.980	0.962	0.960	0.997	0.906
36 to 42	64	19	0	44	1	0.950	1.000	1.000	0.978	1.000	0.950
43 to 49	46	10	1	35	0	1.000	0.972	0.909	1.000	1.000	0.972
50 to 56	33	7	0	26	0	1.000	1.000	1.000	1.000	1.000	1.000
57 to 90	151	29	0	119	3	0.906	1.000	1.000	0.975	1.000	0.906
91 to 120	86	14	0	72	0	1.000	1.000	1.000	1.000	1.000	1.000

RDT: Rapid diagnosis tests, Nb: Number of cases, TP: True positive, FP: False positive, TN: True negative, FN: False negative, Ss: Sensitivity, Sp: Specificity, PPV: Positive Predictive Value, NPV: Negative Predictive Value

Discussion

Even though FG is still not concerned by this FpHPR2 gene deletion [10], the phenomenon of immigration from neighboring countries and over might introduce species carrying the genetic mutation. Our study aimed to assess the accuracy of SD Malaria Ag P.f/Pan® test, which is the RDT currently used in remote healthcare centers of FG, in the rapid diagnosis of malaria. The SD Malaria Ag P.f/Pan® test was sufficiently accurate for diagnosing malaria in suspected patients and the routine monitoring and the detection of passive cases in malaria low transmission areas (Orientation note about malaria diagnosis in the context of low transmission rate, September 2014, WHO). Diagnosing malaria is an emergency to early introduce a curative treatment and prevent an adverse evolution that, in some cases, could lead to death. Microscopic blood smear examination is still the gold standard, but high-quality RDTs can be used, at first, due to their efficacy, large availability, and cheap cost (*WHO. Quality assurance for microscopy: malaria microscopy quality assurance manual. Genève, 2009*). In FG remote areas, the only way to quickly diagnose malaria disease remains RDTs. The choice of the SD Malaria Ag P.f/Pan® in FG was based on the comparison of performance provided by the WHO reports but not on entomological studies made in FG.

(https://www.who.int/diagnostics_laboratory/evaluations/pq-list/malaria/public_report/en/).

In FG, the implementation of a malaria control strategy allowed to reduce the number of recorded malaria cases by 82% during the last ten years, with 3344 cases in 2009 and 212 cases in 2019 (<https://www.guyane.ars.sante.fr>). In 2011, among 1209 cases reported *P falciparum* and *P vivax* represented respectively 31% and 68.5% [10]. In 2019, among the 212 recorded malaria cases, only 6% were *P falciparum* (13 cases). Forty-two cases were hospitalized, and only 2 cases developed a complicated clinical picture (one with *P falciparum* and one with *P vivax*) (<https://www.guyane.ars.sante.fr/paludisme-1>). In our study, the average share of confirmed (BFT test) *P falciparum* decreased significantly with 13.3% of positive tests (minus 17.7%), while confirmed *P vivax* cases raised with 85.1% of positive tests (plus 16.6%) (<https://www.guyane.ars.sante.fr/system/files/2017-06/palu%20plan%202015-2018.pdf>).

Our study recorded all RDT's performed and compared them to BFT regardless of whether it was a first-line diagnostic test or a monitoring test during the curative treatment. The global sensitivity of SD Malaria Ag P.f/Pan® test was, on

average, 96% (88.2 – 1) for *P falciparum* and 93% (90.6 – 94.2) for *P vivax*. The sensitivity can be affected by a low rate of parasitemia in the bloodstream [1]. The global specificity was high, with a rate of 99.8% (99.5 – 1) for all species included. In our database, among 12880 concomitant RDT and BFT tests, 10873 tests (84.4%) represented first-line diagnosis tests, and 2007 RDTs were performed during the follow-up period. The latter affected results of the VVP, which was on average 97% (94.5 – 98.9) but significantly different for *P falciparum* and *P vivax* with respectively 88% (80.4 – 1) and 98% (94.7 – 99.1).

Most of RDTs performed during the follow-up period were done during the two first years, which can explain the annual variation of the PPV. Furthermore, there is a significant variation of the global PPV week after week during the first 28 days of our study. It is also explained by the number of false positives related to the persistence of the protein-encoding for *Plasmodium* in the blood. In our study, we have not collected clinical information. Consequently, we were not able to determine if there were an immunological factor or infectious agents to explain the calculated PPV [12,13]. Thus, a positive result of the RDT must be confirmed by a BFT. On the ground, there is a real risk of not making the correct diagnosis by placing too much importance on the rapid test result in case of positivity.

The negative predictive value was, on average, 99.7% (99.3 – 99.5) without a significant difference between *P falciparum* and *P vivax*. A low density of parasitemia can affect the accuracy of the NPV [14]. It was not the case in our study where we did not find false-negative results. We can deduce that the negativity of SD Malaria Ag Pf/Pan®, used as a first-line diagnosis test, allowed to reasonably eliminate malaria diagnosis even though perform BFT remains the gold standard.

In our study, 2007 concomitant RDT/BFT tests were carried during the follow-up period of patients during treatment. Our results have shown that the RDT result was still in the majority positive up to 28 days, even though parasites were no longer detectable with BFT. The literature emphasizes a remaining RDT positivity up to 63 days after treatment. Previous findings mention that PfHRP2 RDTs are still positive after treatment for longer than combination or pLDH RDTs [15]. This is explained by a slower degradation of PfHRP2 compared to pLDH after parasite elimination [15,16]. Indeed, PfHRP2 antigen, which is progressively eliminated from the bloodstream, can be responsible for false positives [17,18]. In opposition, pLDH is quickly eliminated after one week from the bloodstream [19]. Thus, the initial parasite density influence false positives result and PfHRP2 persistence [16].

Furthermore, patients benefiting from ACT treatment have a higher probability of remaining positive to RDTs than those who received non-ACT drugs [16]. In practice, the persistence of positivity of RDT after treatment makes it obsolete for monitoring. Thus, the SD Malaria Ag Pf/Pan® test should not be used to assess the efficiency of the treatment set up in these conditions.

During the last two years, the majority of malaria cases in FG were autochthonous (83% first-quarter 2019, 78% first-quarter 2020) while the remaining part was from Brazil (range 9 to 14 %), Suriname (range 2 to 5 %), or Africa (range 2 to 7%) [8]. Illegal gold miners (garimpeiros) inside the rainforest and native populations at border areas between Suriname and Brazil are at risk of malaria resurgence [7,20,21]. The epidemic of malaria experienced a pic in 2017 at the Amazonian border between FG and Brazil. Multifactorial causes were pointed out, such as migration matters from Brazil and Venezuela, local politics, logistics issues, and others [22]. Most cases occurred in forest areas except Saint Georges d'Oyapock at Brazil's border (Amapà region). <https://www.guyane.ars.sante.fr/paludisme-1>. In FG, the malaria incidence is low, so that all patients with positive RDT tests are considered as recently infected. However, in 2015, Orpal-1, a study carried out on a population of 421 gold miners, has shown that the wide majority were Brazilian citizens (93.8%). This study has shown that the prevalence of carriage, determined by PCR, was 22.3% (95% CI: 18.3 – 26.3) to 84% asymptomatic. Species identified were *P falciparum* and *P vivax*, 47.9% and 37.2%, respectively with 10.6% co-infections. Thus, there is a real risk of periodic reintroduction of the disease in FG [23]. It is estimated that

illegal gold miners are around 10.000 people (www.guyane.gouv.fr). Orpal-1 results with only 4.2% of the group, targeted as accountable for malaria cases spreading in FG, might be non-representative of the reality. Further investigations are required to clarify this key point.

By the way, in the Brazilian Amazon basin, the lack of PfHRP2 protein is very variable. The isolates collected in Acre state had the highest percentage of deletions with 31.6% (95% CI: 21.6-43.1), while in Rondonia state, the prevalence of deletion was only 3.3% (95% CI: 0.4-11.5) and absent in Para state [24] but 100% of deletion for Pf HRP3 [25]. In 2013, within the annual meeting of AMI/RAVDERA, in Lima, Peru, CDC reported in the Macapa region 9% of PfHRP2 deletion (only 13 samples were screened) and 36% of PfHRP3 deletion. More globally, during the same meeting, CDC mentioned PfHRP2 deletion in 14% of cases in Brazil, 14.1% in Suriname, 33.3% in Peru, 7.5% in Colombia, and 4% in Bolivia [26]. Moreover, there is no accurate data about imported malaria cases except the distribution shares that may depend on immigration waves (www.guyane.ars.sante.fr). Besides, we do not know the immigration journey of patients and if they are coming from endemic countries with a significant rate of PfHRP2 deletion. In theory, it represents a risk of false-negative tests that should be better estimated by further studies [27].

Conclusion

SD Malaria Ag P.f/Pan® is still a reliable rapid test used for the first-line diagnosis in remote healthcare centers. However, it must no longer be used during the follow-up period of patients diagnosed with malaria. The test reading should be nuanced by the recent medical history of patients and the arrival date in FG. RDT result has always to be confirmed by BFT that is still the gold standard for the malaria diagnosis. FG is still a PfHRP2 gene deletion-free area. However, uncontrolled migratory flows might increase the risk of malaria reintroduction in the territory and thwart the strategy put in place with the possibility to import new species that might impact the efficiency of the test.

Abbreviations

ACT: Artemisinin-based combination therapy

BFT: Blood Film Tests

CDC: Centers for Disease Control and Prevention

FG: French Guiana

FN: False negative

FP: False positive

IT: Information Technology

Nb: Number

NPV: Negative Predictive Value

PPV: Positive Predictive Value

RDT: Rapid diagnosis tests

Sp: Specificity

Ss: Sensitivity

TN: True negative

TP: True positive

WBC: White blood cells

WHO: World Health Organization

Declarations

- **Ethics approval and consent to participate:** Since our study is retrospective, it did not require individual consent according to the French law regarding research conforming to MR-003 (JORF no. 0160 du 13 juillet 2018. texte no. 109). Our database has been registered at the Commission National de l'Informatique et des Libertés (registration n° 2219819), in compliance with French law on electronic data sources.
- **Consent for publication:** At admission to our hospital, an information booklet was distributed to all patients or their relatives stating that their data can be used for research and publication purposes and that they can object to that. No person was unconsented.
- **Availability of data and materials:** The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.
- **Competing interests:** The authors declare that they have no competing interests.
- **Funding:** Not applicable
- **Authors' contributions**

JMP: Conceptualization, methodology, project administration, data curation, formal analysis.

SL: Data curation.

SH: Project administration.

AF: Data curation.

DB: Data curation, formal analysis.

FD: Conceptualization.

HK: Conceptualization, methodology, project administration, data curation, formal analysis.

MD: Conceptualization, methodology, project administration.

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Figures

Figure 1

The flow chart of the study (N=Number of cases)

Figure 2

The diagnosis accuracy of RDT in diagnosing malaria according to the plasmodium species identification. (RDT: Rapid diagnosis tests, Ss: Sensitivity, Sp: Specificity, PPV: Positive Predictive Value, NPV: Negative Predictive Value)

Figure 3

The diagnosis accuracy of RDT in the diagnosis of *Plasmodium falciparum* according to the year of the study. (RDT: Rapid diagnosis tests, Ss: Sensitivity, Sp: Specificity, PPV: Positive Predictive Value, NPV: Negative Predictive Value)

Figure 4

The concordance rate of RDT compared to BFT in the diagnosis of malaria independently of the plasmodium species identification according to the year of the study.

Figure 5

diagnosis accuracy of RDT in the follow-up period of malaria independently of the plasmodium species identification.