

Sensitivity and specificity of malaria rapid diagnostic tests based on histidine-rich protein 2 antigen or *Plasmodium* lactate dehydrogenase: prospective diagnostic evaluation, Niger



M Coldiron¹, B Assao², C Langendorf¹, N Sayinzoga-Makombe², I Ciglenecki³, R de la Tour³, E Piriou⁴, M Yarima Bako⁵, A Mumina⁶, O Guindo², A-L Page¹, RF Grais¹

¹Epicentre, Paris, France; ²Epicentre, Maradi, Niger; ³Médecins Sans Frontières (MSF), Geneva, Switzerland; ⁴MSF, Amsterdam, The Netherlands; ⁵Ministère de la Santé Publique, Magaria, Niger; ⁶MSF, Niamey, Niger

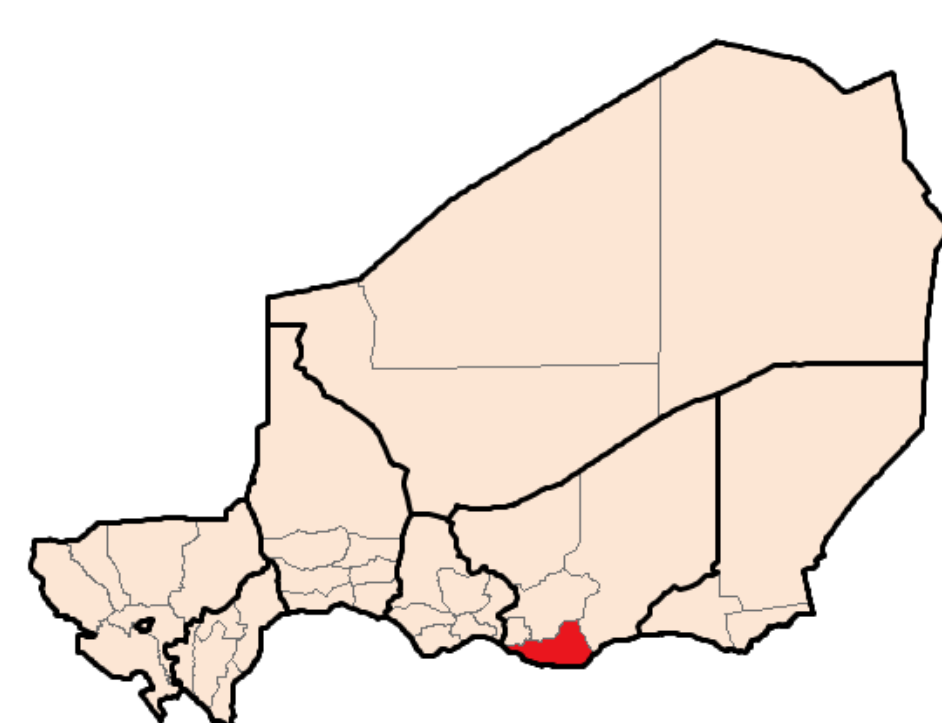
INTRODUCTION

RDTs for malaria

- The median time for a histidine-rich protein 2 antigen (HRP2) test to become negative after an effective treatment is 35-42 days; it is only 2 days for *Plasmodium* lactate dehydrogenase (pLDH) test¹
- This difference likely leads to pLDH tests having a higher specificity in high-transmission environments^{1,2}
- The Carestart pLDH(pan) RDT has performed well in WHO rapid diagnostic test (RDT) evaluations,³ and is being introduced by MSF into its projects in high-transmission zones
- A large number of false-positive pLDH RDTs compared to microscopy prompted a formal evaluation in Magaria, Niger

Magaria Health District, Zinder Region, Niger

- Population 744 268, one of the most populated districts in Niger, but strongly rural
- MSF supports Ministry of Health hospital and peripheral health centers since 2009
- Area has received seasonal malaria chemoprevention (SMC) since 2013



OBJECTIVE

Estimate the performance (sensitivity, specificity, positive predictive value and negative predictive value) of the CareStart pLDH and SD Bioline HRP2 malaria RDTs, during both the high and low transmission seasons in Magaria, Niger

METHODS

- Prospective, health-center based diagnostic test evaluation
- Two seasons:
 - High season: 3-28 October 2017
 - Low season: 28 January-31 March 2018
 - High season timing covered an entire SMC cycle
- Study sites: Magaria (high and low season) and Dantchiao (low season only) Integrated Health Centers
- Study population: children aged 3-59 months presenting with fever (37.5°C axillary) or history of fever in preceding 24 hours; children with signs of severity were excluded
- Gold standard: microscopy
- Fingerstick blood collection for thick/thin smears and both RDTs
- RDTs performed according to manufacturer's instructions, with photographs taken at time of reading
- Double-reading of slides by blinded technicians with external QC at WHO-certified center of excellence
- Target sample size: 279 true positives during each season
- Ethical approval from MSF-ERB and National Health Research Ethics Committee of Niger

¹ Grandesso F et al. Malaria J 15, 496 (2016)

² Maltha J et al. Malaria J 13, 20 (2014)

³ WHO/FIND, Round 6. (2015)

RESULTS

Table 1: Description of parasitemia

	High season (N=539)	Low season (N=1407)
<i>P. falciparum</i> parasitemia, n(%)	246 (46)	155 (11)
Median parasitemia in parasites/μl, (IQR)	12684 (2682-50958)	624 (119-3010)
<200	11 (4)	54 (35)
200-1999	42 (17)	54 (35)
2000-19999	179 (73)	46 (30)
≥200000	14 (6)	1 (1)

Table 2: Performance characteristics of RDT'S

Characteristic Test	High season			Low Season		
	N [†]	Value	95%CI	N [†]	Value	95%CI
Sensitivity						
pLDH	246	99.2	97.0-99.9	155	91.0	85.3-95.0
HRP2	246	99.2	97.1-99.9	155	85.8 [‡]	79.3-90.9
Specificity						
pLDH	293	58.0	52.1-63.8	1252	92.6	91.1-94.0
HRP2	293	57.4	51.5-63.1	1252	93.5	91.9-94.8
PPV						
pLDH	361	66.3	61.1-71.2	233	60.5	53.9-66.8
HRP2	370	66.3	61.2-71.1	215	61.9	55.0-68.4
NPV						
pLDH	169	98.8	95.8-99.9	1173	98.8	98.0-99.3
HRP2	169	98.8	95.8-99.9	1192	98.2	97.2-98.8

^{*} PPV: positive predictive value; NPV: negative predictive value

[†] For sensitivity, N represents all true positives; for specificity, N represents all true negatives; for PPV, N represents all test positives; and for NPV, N represents all test negatives

[‡] Exact McNemar test p=0.008

Table 3: Sensitivity by parasite density

Test Parasites/μl	High season			Low Season		
	N with given parasitemia	Value	95%CI	N with given parasitemia	Value	95%CI
pLDH	246	99.2	97.0-99.9	155	91.0	85.3-95
<200	11	81.8	48.2-97.7	54	81.5	68.6-90.
200-1999	42	100	91.4-100	54	94.4	84.6-98.
2000-19999	179	100	97.9-100	46	97.8	88.5-99.
≥200000	14	100	76.8-100	1	100	2.5-100
HRP2	246	99.2	97.1-99.9	155	85.8	79.3-90
<200	11	81.8	48.2-97.7	54	75.9	62.4-86.
200-1999	42	100	91.6-100	54	85.2	72.9-93.
2000-19999	179	100	98.0-100	46	97.8	88.5-99.
≥200000	14	100	76.8-100	1	100	2.5-100

- No differences in performance by sex, age, production lot, or time since most recent SMC distribution
- 99.1% concordance between HRP2 and pLDH in high season, 98.7% in low season

DISCUSSION AND CONCLUSION

- Unexpectedly low specificity and PPV of pLDH
- Unexpectedly low sensitivity of HRP2 during low season
- Few simple explanations
- Similar studies outside of SMC contexts would provide more information.