

Centre universitaire de médecine générale et santé publique Lausanne

The use of malaria Rapid Diagnostic Tests (mRDT) in travelers

Blaise Genton

Policlinique de médecine tropicale, voyages et vaccinations

Menu

- Etiology of fever in travelers: deleted submitted
- Use of mRDT in clinical management
- Performance of mRDT
- Limitations (prozone, HRP2 deletions)
- Us-mRDT
- Self-diagnosis by travelers

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Is there a better malaria diagnostic test for travelers?

A reliable test available at time and place of need...





Antigen targets for mRDTs

Table 3. Antigen targets of rapid diagnostic tests for malaria								
Di	HRP2		Aldelese					
Plasmodium species		pLDH-Pf	pLDH-pan	pLDH-Pvom	pLDH-Pv	Aldolase		
P. falciparum	Х	Х	Х			х		
P. vivax			Х	Х	Х	Х		
P. malariae			Х	Х		Х		
P. ovale			Х	Х		Х		

HRP2 - histidine-rich protein 2

pLDH - Plasmodium lactate dehydrogenase

Pf – P. falciparum

pan - all Plasmodium species

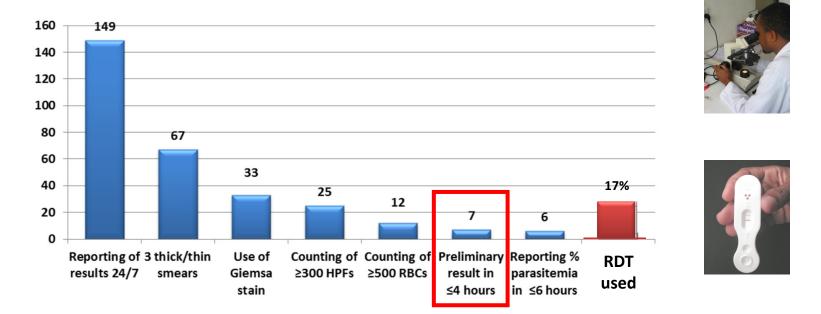
Pvom - P. vivax, ovale and malariae

Pv – P. vivax



Quality of microscopy in non-endemic countries

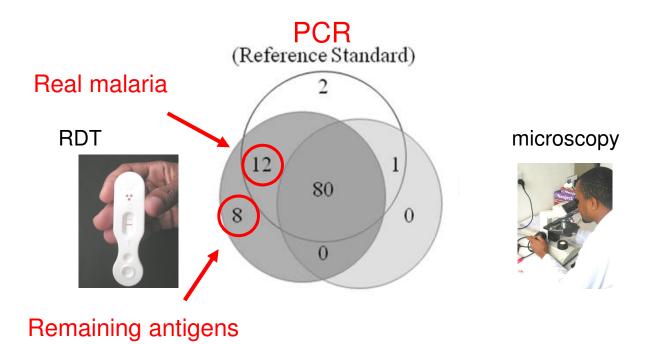
State of malaria diagnostic testing at clinical laboratories in the United States, 2010: a nationwide survey



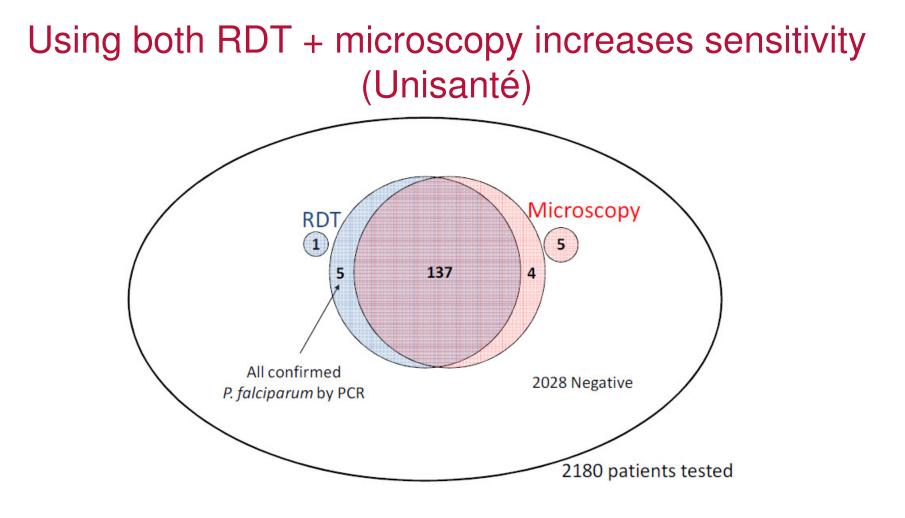
Abanyie et al, Malaria J 2011

Performance of mRDTs

Travelers or migrants attending 3 hospitals in Minnesota, USA

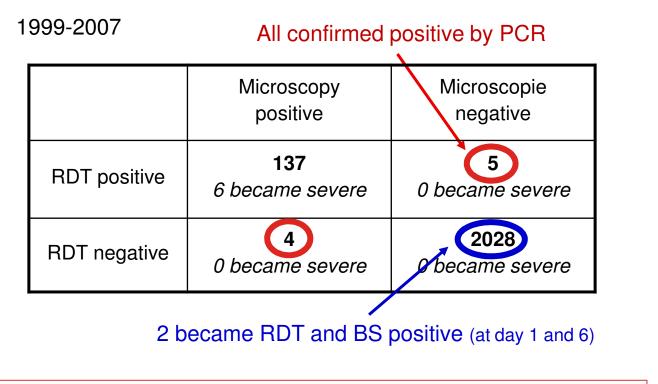


Stauffer et al, CID 2009



Rossi et al, Malaria J 2012

Diagnostic strategy (Unisanté)



Median time to first result saved = 2.1 hours (IQ 1.4 - 5.1)

Rossi et al, Malaria J 2012

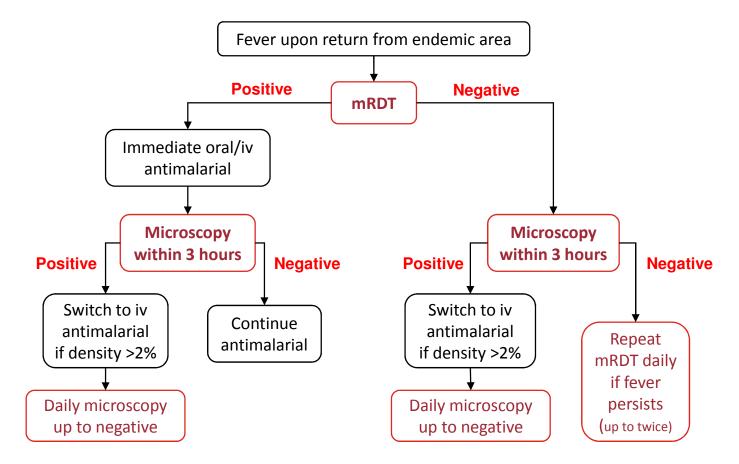
Oucome before and after implementation of mRDT

Outcome	Pre-mRDT	Post mRDT
Time to positive result	10.7h	1.3h
Time to positive Pf result	8.2h	0.5h
Time to initiation treatment or discharge	12.6h	7.3h

Enane et al, JPIDS 2019

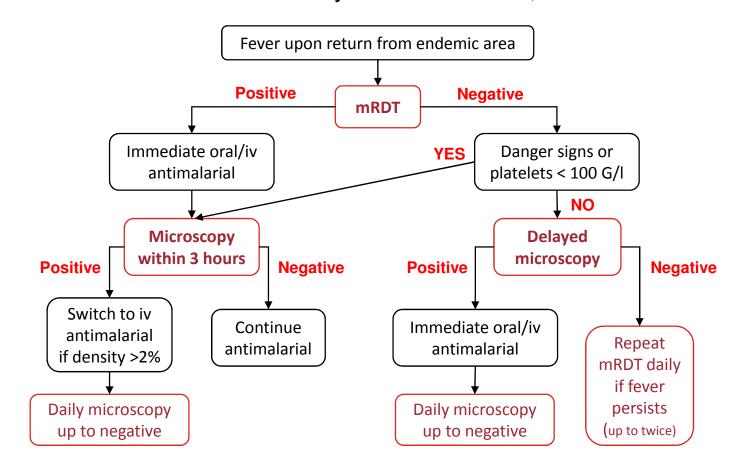


Diagnostic strategy during the day for the last 20 years in Lausanne, Switzerland



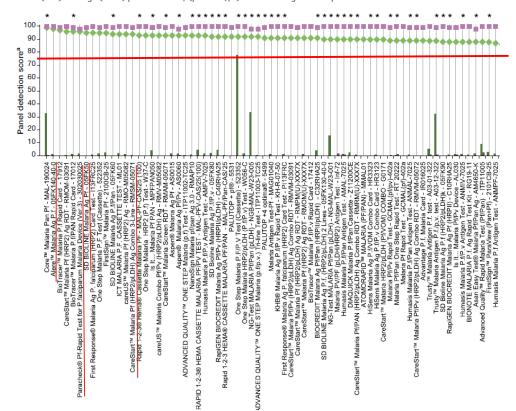


Diagnostic strategy at night / WE for the last 20 years in Lausanne, Switzerland



WHO/FIND product testing for *P Falciparum* malaria Round 7 (2016)

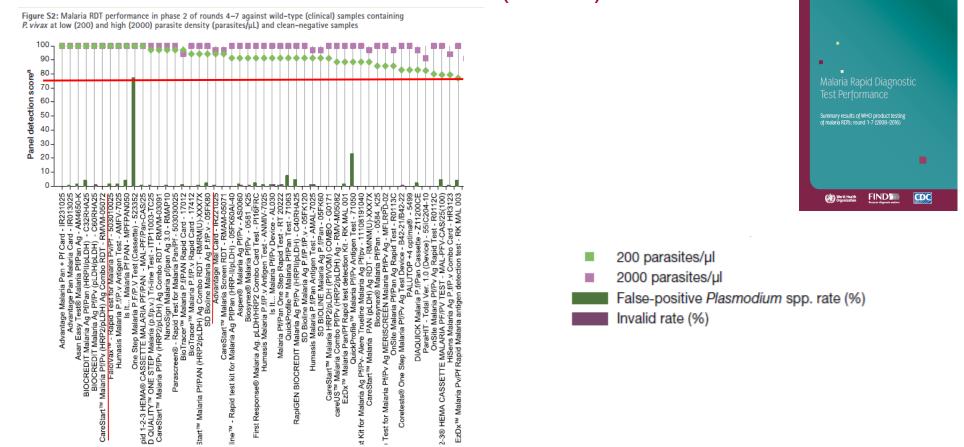
Figure S1: Malaria RDT performance in phase 2 of rounds 4–7 against wild-type (clinical) samples containing *P. falciparum* at low (200) and high (2000) parasite density (parasites/µL) and clean-negative samples

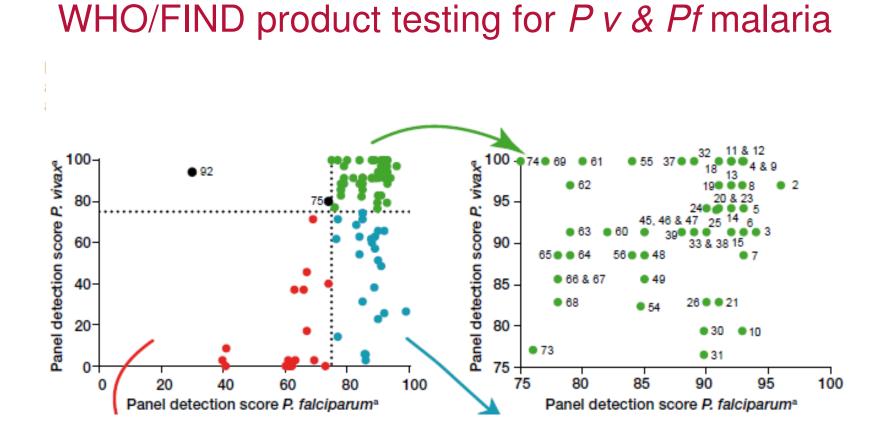




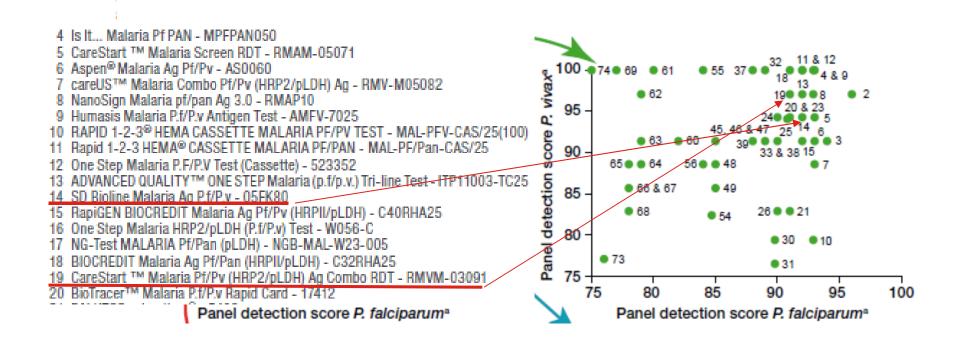
200 parasites/µl 2000 parasites/µl False-positive *Plasmodium* spp. rate (%) Invalid rate (%)

WHO/FIND product testing for *P vivax* malaria Round 7 (2016)

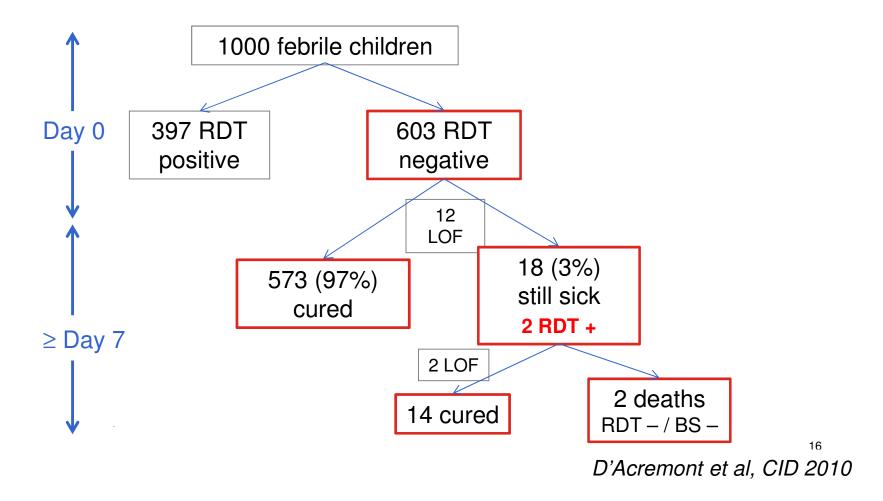




WHO/FIND product testing for P v & Pf malaria



Clinical outcome of children managed with mRDT in Tanzania



mRDT and the prozone effect

Brands/manufacturers	P. falciparum antigen targeted	Number of samples tested	Total number of samples with prozone (%)	HRP-2 or Pf-pLDH line intensity for undiluted prozone positive samples			
				Negative	Faint	Weak	
Paracheck-Pf	HRP-2	76	29 (38.2)	3	5	21	
ICT Malaria	HRP-2	76	27 (35.5)	1	10	16	
SD Malaria Antigen Pf FK50	HRP-2	76	25 (32.9)	-	-	25	
Hexagon Malaria Combi	HRP-2	72	12 (16.7)	-	-	12	
SD Malaria Ag Pf/Pan FK60	HRP-2	76	6 (7.9)	-	-	6	
Malaria Pan/Pv/Pf Rapid Device	HRP-2	75	5 (6.7)	-		5	
SD Malaria pLDH FK40	Pf-pLDH	76	-	-	-	-	
CareStart Malaria pLDH	Pf-pLDH	76		-	100	-	

- The prozone effect exist for HRP2 but not for pLDH bands
- It rendered the band negative in 4/451 (0.9%) of >4% density samples
 - \rightarrow An HRP2 / pLDH combo test should be preferably used
 - → Microscopy should always be performed in patients who present signs or laboratory features of severe malaria



Gillet et al, Malar J 2011

HRP2 deleted parasitesold news in South America ()

OPEN OACCESS Freely available online

January 2010 | Volume 5 | Issue 1 | e8091



A Large Proportion of *P. falciparum* Isolates in the Amazon Region of Peru Lack *pfhrp2* and *pfhrp3*: Implications for Malaria Rapid Diagnostic Tests

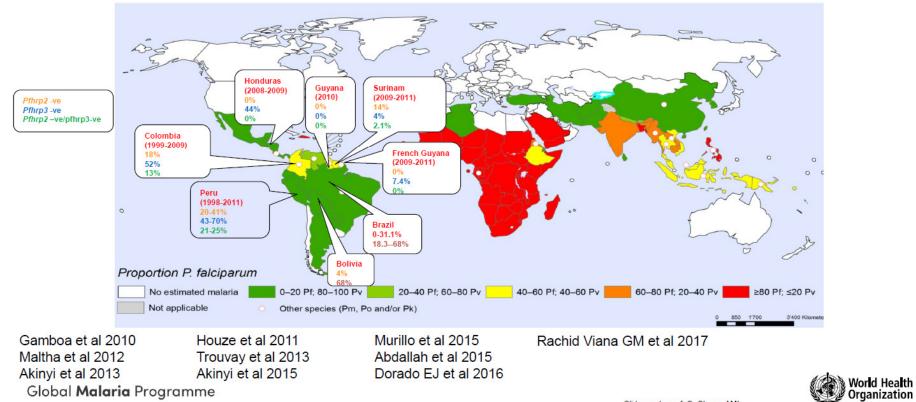
Dionicia Gamboa^{1,2}, Mei-Fong Ho^{3,9}, Jorge Bendezu¹, Katherine Torres¹, Peter L. Chiodini⁴, John W. Barnwell⁵, Sandra Incardona⁶, Mark Perkins⁶, David Bell^{6,7}, James McCarthy^{3,8}, Qin Cheng^{9,10}*

- Recommendations against use of HRP2 based RDTs
- Urgent need for investigation of the abundance and geographic distribution of these parasites in Peru and neighboring countries.

41% (61/148) isolates lacked *pfhrp2;* 21% lacked both *pfhrp2* and 3



Parasites Lacking HRP2/3 in Central and South America



Slide courtesy of Q. Cheng, AMI

HRP2 deletions Africa (2017)

Published:

Mali (2012) Senegal (2013) Ghana (2016) DRC (2016) Rwanda (2017)

Unpublished (2016): Eritrea (pre-submission) Mozambique (submitted) Zambia Uganda

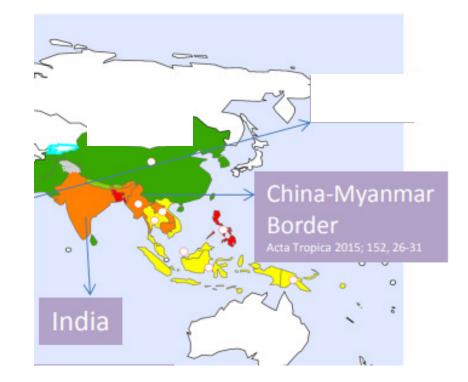




Global Malaria Programme

HRP2 deletions Asia (2017)

China India Bangladesh

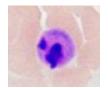


mRDT and HRP2/3 deletions

- In most settings, deletion of HRP2/3 not main cause of false-neg. results
- More likely due to procurement, poor-quality RDTs, use of wrong comparator
- More studies required to determine true prevalence of these mutations
- No reports of parasites failing to express pLDH or aldolase
 => Use mRDT combining HRP2 & pLDH

Sensitivity of mRDT for *P* knowlesi (PCR standard)

	<i>P. Falc</i> n= ⁻	iparum 121	P. Vivax n=41	P. Knowlesi n=129	
Band	Pf-HRP2		Pan-pLDH		
All patients	98% 91%		95%	74%	
No pre-referral treatment	-	90%	100%	88%	
Severe patients	100%	100% 100%		95%	
Band			Pan-aldola	se	
All patients		44%	56%	23%	



Barber et al, J clin Microbiol 2013

Serial testing in travelers: is it useful ?

- 2/2028 (0,2%) patients initially *Pf* negative became RDT and BS positive at day 1 and 6
- 5/384 (1.3%) malaria cases were diagnosed after first set of negative test results (1 Pf, 4 Pv and 1 Po)

Now that both RDT and microscopy are performed in most places:

- → It is less essential to repeat malaria tests, especially when an alternative diagnosis has been documented
- → Using PCR in febrile travelers would probably not help to detect more malaria cases

Rossi et al, Malar J 2012; Pasricha et al, Am J Trop Med Hyg 2013

Would ultrasensitive mRDT (us-mRDT) be useful in travelers?



Alere[™] Malaria Ag P.f Ultra Sensitive

7 Euros...



The Alere™ Malaria Ag P.f test is 10 times more

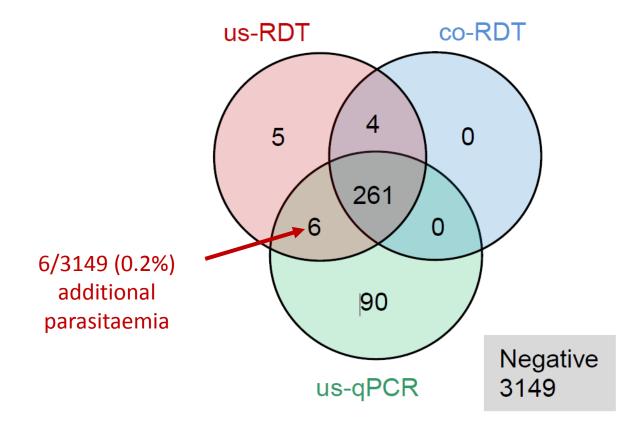
1'000 100 10 1 0.1 neg

Alere[™] Malaria Ag P.f Ultra Sensitive

The Alere™ Malaria Ag P.f test is 10 times more sensitive than current malaria rapid diagnostic tests

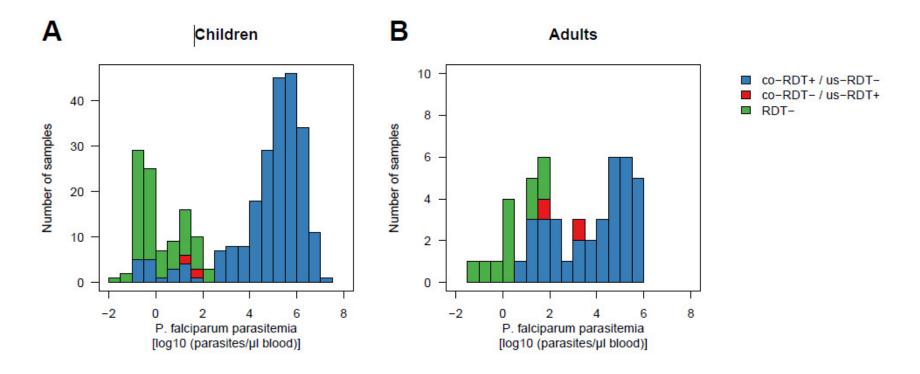


Would us-mRDT be useful in travelers?

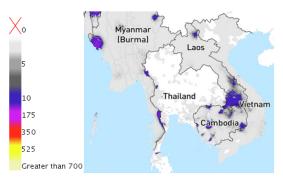


Hofmann et al, J Infect Dis 2019

Distributions of parasite density in febrile children and adults in Dar es Salaam, Tanzania



Standby emergency treatment and mRDTs in travelers



Very low to moderate risk malaria zones



Long term travel/work



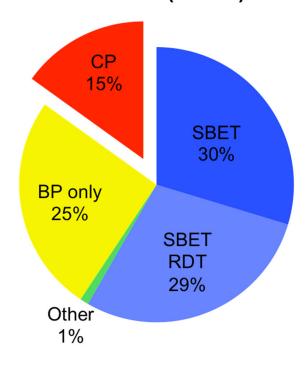
Changing itineraries



Remote areas

Choices of travelers leaving to moderate-low endemicities

Choices (n=391)

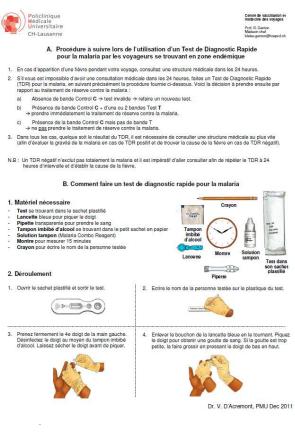


Voumard et al, Mal J 2015

Travelers proposed mRDT

Reasons to propose mRDT (multiple entries possible)	All travellers included n= 691	
Long-term travellers (> 3 months)	478 (69%)	
Travel to remote areas	397 (57%)	
Request by the traveller	117 (17%)	
Health care professionals	97 (14%)	
Humanitarian work	77 (11%)	
Prophylaxis refused	68 (10%)	
Short-stay frequent traveller	30 (4%)	
Others: travel with children pregnancy (known/desired) expatriates VFR serious drug interactions	52 (8%) 12 8 8 2 2 2	

Berthod et al, Mal J 2017



Policlinique Médicale Universitaire CH-Lausanne

Centre de vaccination e médecine des voyages

8.84 PT 8.147 8.142.231

son sache plastifié

Solution

tampor Test dans

Prof. B. Genton Médecin chef

Prosser avec 2 doigts le tube de la pipette du côté carré pour faire sortir l'air. Toucher la goutte de sang avec la ponte de la postet. Relacher douvernent la pression sur le tube de la pipette pour y faire monter le sang jusqu'à la première ligne.



la pipette)



7. Ajoutez 5 gouttes de solution tampon dans la grande chambre ronde de la casette

-



Remarque : Ne pas jeter le matériel avec du sang (lancette, pipette et tampon imbibé d'alcool) directement dans la poubelle. Les mettre dans le sachet plastifié pour les protéger et éviter que quelqu'un se contamine par mégarde avec le sang.

3. Interprétation du résultat (grande fenêtre ovale)

Bande de contrôle C : la ligne du côté C doit toujours apparaître. - Si elle n'est pas présente le test s'avère INVALIDE ! Il faut alors le refaire avec un nouveau test.

Bandes de test T :

Sta 2+0 0 - 0 0

- Si 1 ou même 2 bandes apparaît(ssent) du côté T, le test est POSITIF pour la malaria. - Si aucune bande n'apparaît du côté T, le test est NEGATIF pour la malaria.

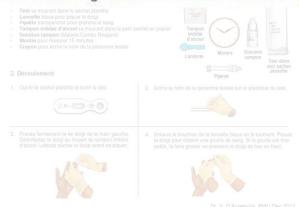


Décharge : Les TDR sont fait sous la seule responsabilité du voyageur et lui sont vendus sur sa demande. La Policlinique Médicale Universitaire n'est pas responsable des conséquences potentielles.

Dr. V. D'Acremont, PMU Dec 2011



 Dans tous les cas, quelque soit le résultat du TDR, il est nécessaire de consulter une structure médicale au plus vite (afin d'évaluer la gravité de la malaria en cas de TDR positif et de trouver la cause de la fièvre en cas de TDR négatif).



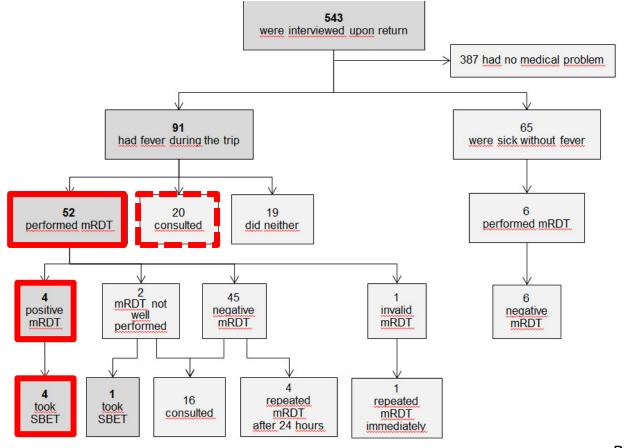
Remarque : Ne pas jeter le maté Les mettre dans le sac			
		T, le test est POSITIF pour la m NEGATIF pour la malaria.	
Test P pour la		Test NEGATIF pour la malaria	Test INVALIDE Pas de bande côté C (même
			s'il y a une bande côté T)
	1		
			ou

Décharge : Les TDR sont fait sous la seule responsabilité du voyageur et lui sont vendus sur sa demand

r. V. D'Acremont, PMU Dec 2011

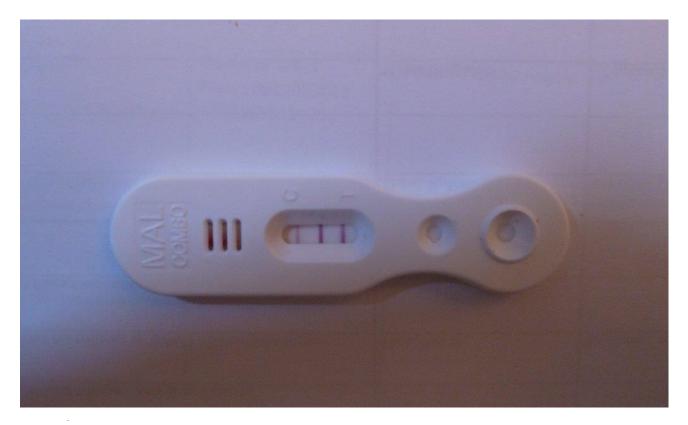


Interview upon return (744 proposed)



Berthod et al, Mal J 2017

Aweil, South Sudan 2014



Would you take mRDT again for the next trip ?

488 (93%) travellers would take mRDT again	55 (7%) travellers would NOT take mRDT
220 'reassuring'	9 'Good health infrastructures on site' (but one would take mRDT if travel with children)
53 'to avoid unnecessary treatment'	7 'I am not at risk', 'I avoid risk areas'
28 'especially useful when travelling with children '	5 'prophylaxis will be enough'
11 'convenient, practical'	5 'useless'
8 'help to react more quickly, autonomy'	4 'Protection against mosquitoes bites will be enough'
1 'I will take prophylaxis and RDT, even in a low risk area, because I had malaria'	1 'enough knowledge of malaria'
167 No reason mentioned	24 No reason mentioned

Self-diagnosis by travelers and expatriates?

Observations:

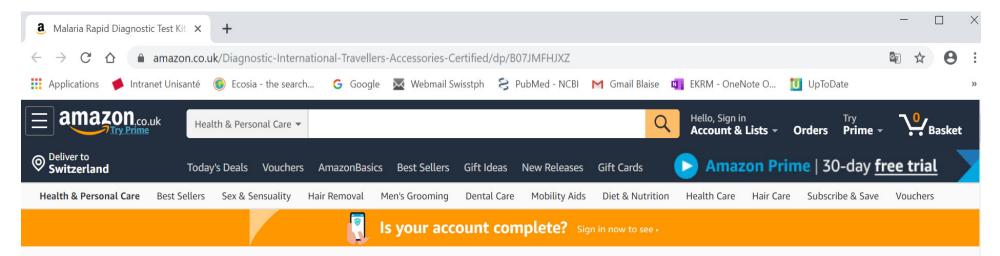
- Main reason for declining mRDTs = fear of self-pricking
- Most difficult step = blood aspiration \rightarrow choose easy-to-use transfer device
- Unexpected reasons for considering mRDTs (drug interactions, early pregnancy)

Conclusion:

- Most of the travelers used mRDT according to instructions given
- Those who did not strictly adhere had reasonable reasons to do so
- Travelers felt more secure, especially when traveling with children
- \downarrow mis-diagnosis and inappropriate treatment by travelers and local clinics

 \rightarrow If travel clinics do not take the lead, travelers will take it!

Berthod et al, Malaria J 2017



Customers who viewed Malaria Rapid Diagnostic Test Kit for International Travellers. 3 Tests... also viewed



One Step: 5 x GP/Medical Professional Malaria Diagnostic Test Packs

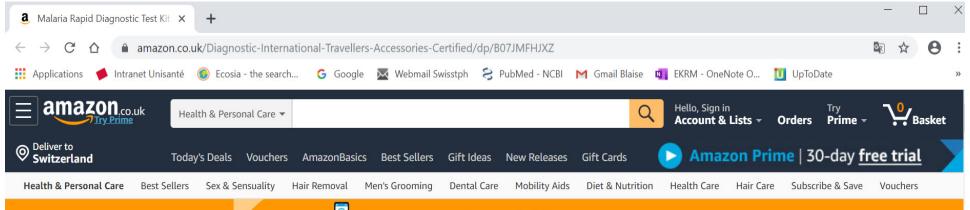
£7.89 1 used and new from £7.89



One Step: 10 x GP/Medical Professional Malaria Diagnostic Test Packs ★★★★☆³ £10.99 1 used and new from £10.99



Malaria Test £45.11 **√prime** 2 used and new from £45.11



Is your account complete? Sign in now to see.



Malaria Rapid Diagnostic Test Kit for International Travellers. 3 Tests & All Accessories, Detailed User Guide, 16 pg Malaria Guide. Assembled in UK. CE Certified. Exp 31/7/2021. Only 300g. by Malarex Ltd

Price: £30.00 & FREE Delivery in the UK. Delivery Details

Get a £20 gift card upon approval for the Amazon Platinum Mastercard. Terms apply. Note: This item is eligible for click and collect. Details

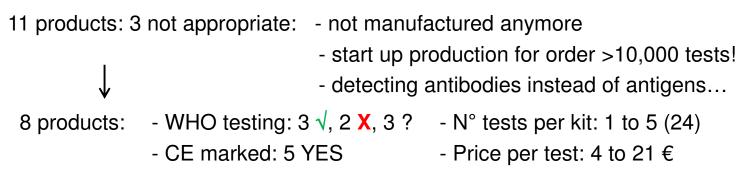
1 new from £30.00

 > Malaria kills nearly half a million people per year. Late diagnosis allows malarial parasites to reproduce unchecked in the blood stream and overwhelm the organs until death ultimately occurs. This is a must-have kit for anyone travelling to a



41

mRDTs available on internet for self-diagnosis



	Number of samples identified (%)				False positive lines			
	P. falciparum		P. vivax	P. ovale	P. malariae	Pv, Po and Pm (n = 35)	malaria ne	gative (n = 10
RDT product	PD <1,000/μl (n = 15)	$PD > 1,000/\mu I$ (n = 40)	(n = 15)	(n = 15)	(n = 5)	Pf test line	Pf test line	Pan/Pv test line
CareStart	15 (100)	40 (100)	15 (100)	4 (26.7)	3 (60.0)	4 (11.4)		
Immunoquick	15 (100)	40 (100)				4 (11.4)		
Labstix	15 (100)	40 (100)	15 (100)	15 (100)	15 (100)	33 (94.3)*	8 (80.0)	8 (80.0)
OneStep	15 (100)	40 (100)	12 (80.0)			28 (80.0)	7 (70.0)	3 (30.0)
OptiMAL	11 (73.3)	39 (97.5) [†]	13 (86.7) [‡]	1 (6.7)	3 (60.0)	2 (5.7)	1 (10.0)	1 (10.0)
Sanitoets	13 (86.7)	39 (97.5) [†]	12 (80.0) [§]	7 (46.7)	2 (40.0)	2 (5.7)* > 1 Pf	remaining	antigens
SDFK63	15 (100)	40 (100)	15 (100)	1 (6.7)	3 (60.0)	3 (8.6)*	, in the second s	
TODA	15 (100)	40 (100)	14 (93.3)	3 (20.0)	4 (80.0)	1 (2.9)*		1 (10.0)

Maltha et al, Plos One 2013

Take home message

- Microscopy & mRDT have similar diagnostic performance for malaria
- A safe strategy to manage imported malaria is to use mRDT & microscopy (sequentially if necessary); it saves time and ressources
- The prozone effect exists for HRP2 band of mRDT but not pLDH
- HRP2 deletion is widespread

→need to use a combo *Pf*-HRP2 / *Pan*-pLDH test

- Us-mRDT do not add much for the management of clinical cases
- mRDT for self-diagnosis of travelers is safe and useful, provided good oral and written information is provided and a blank run is performed
- mRDT ordered on the internet are not all reliable

