FIND

Because diagnosis matters

Plasmodium vivax: challenges in diagnosis, treatment, and elimination

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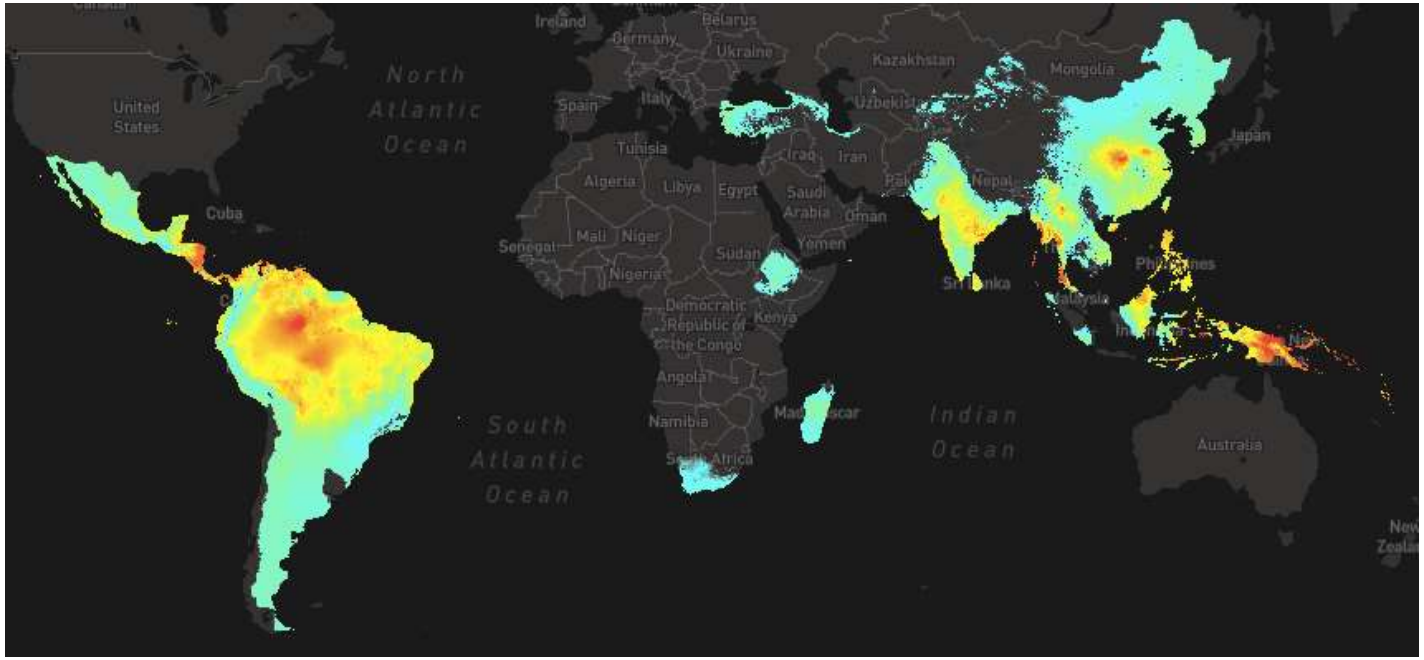
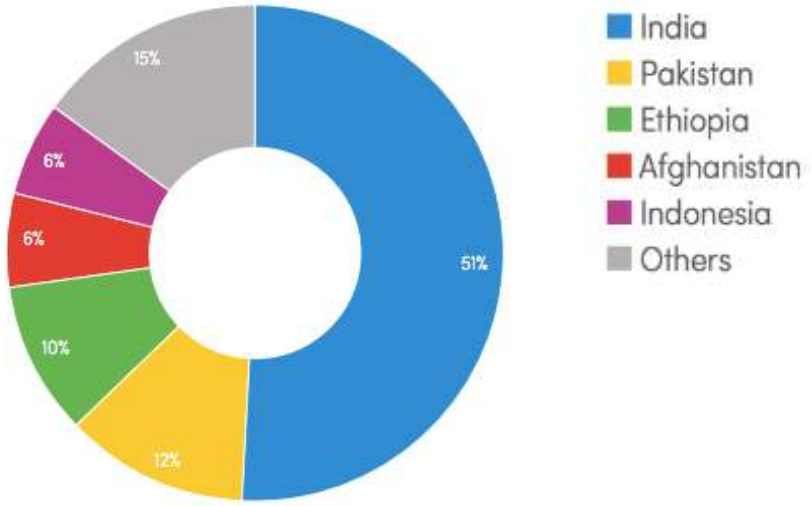
HUMAN's Expert Meeting, ASTMH 2018, New Orleans

Key *Plasmodium vivax* epidemiological figures

- *P. vivax* and *P. falciparum* co-exist in most malaria endemic countries
- *P. vivax* represents 4% of the estimated 216 million of malaria cases worldwide in 2016
- But 36% of all cases outside of sub-Saharan Africa (WHO) and 64% of them in the Americas



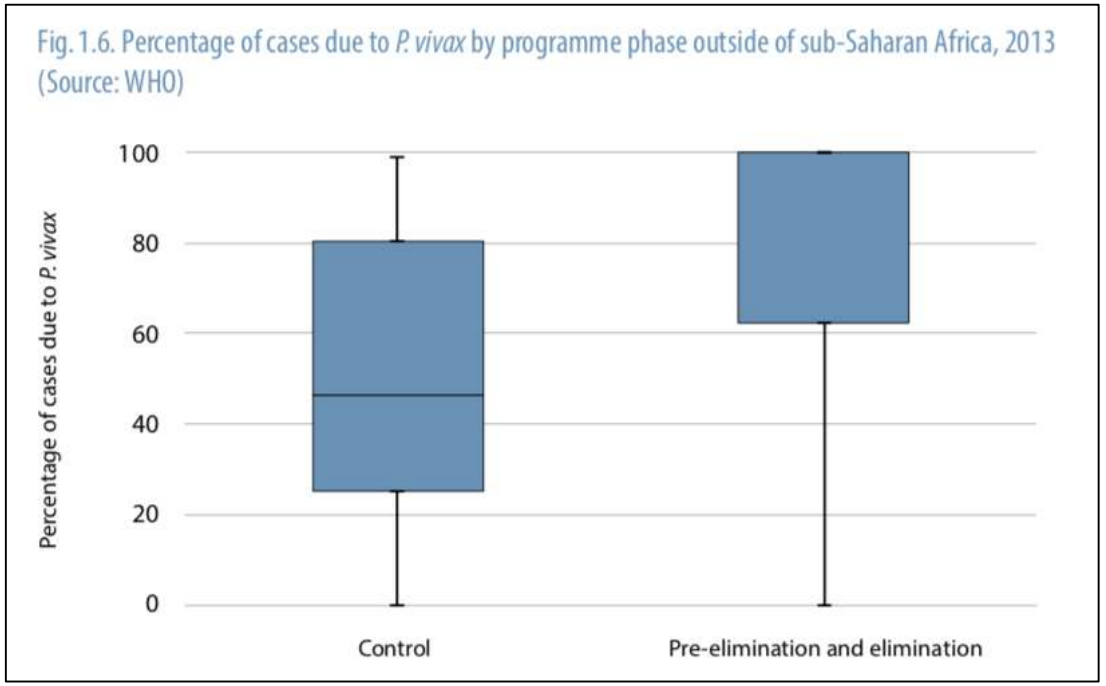
Estimated levels of *Plasmodium vivax* malaria endemicity within the limits of stable transmission (https://map.ox.ac.uk)



Estimated country share of total *P. vivax* malaria cases (WHO)

Key *Plasmodium vivax* epidemiological figures

- In area co-endemic with *P. falciparum*, *P. vivax* incidence decreases more slowly than that of *P. falciparum*
- *P. vivax* relative prevalence increases and is the main malaria species in a majority of countries contemplating elimination.



WHO

P. vivax has been a neglected malaria species for a long time

- Despite keeping **a third of the world population** at risk of infection, *P. vivax* has been **neglected** for the past 60 years on the false assumption that this is a benign form of malaria.

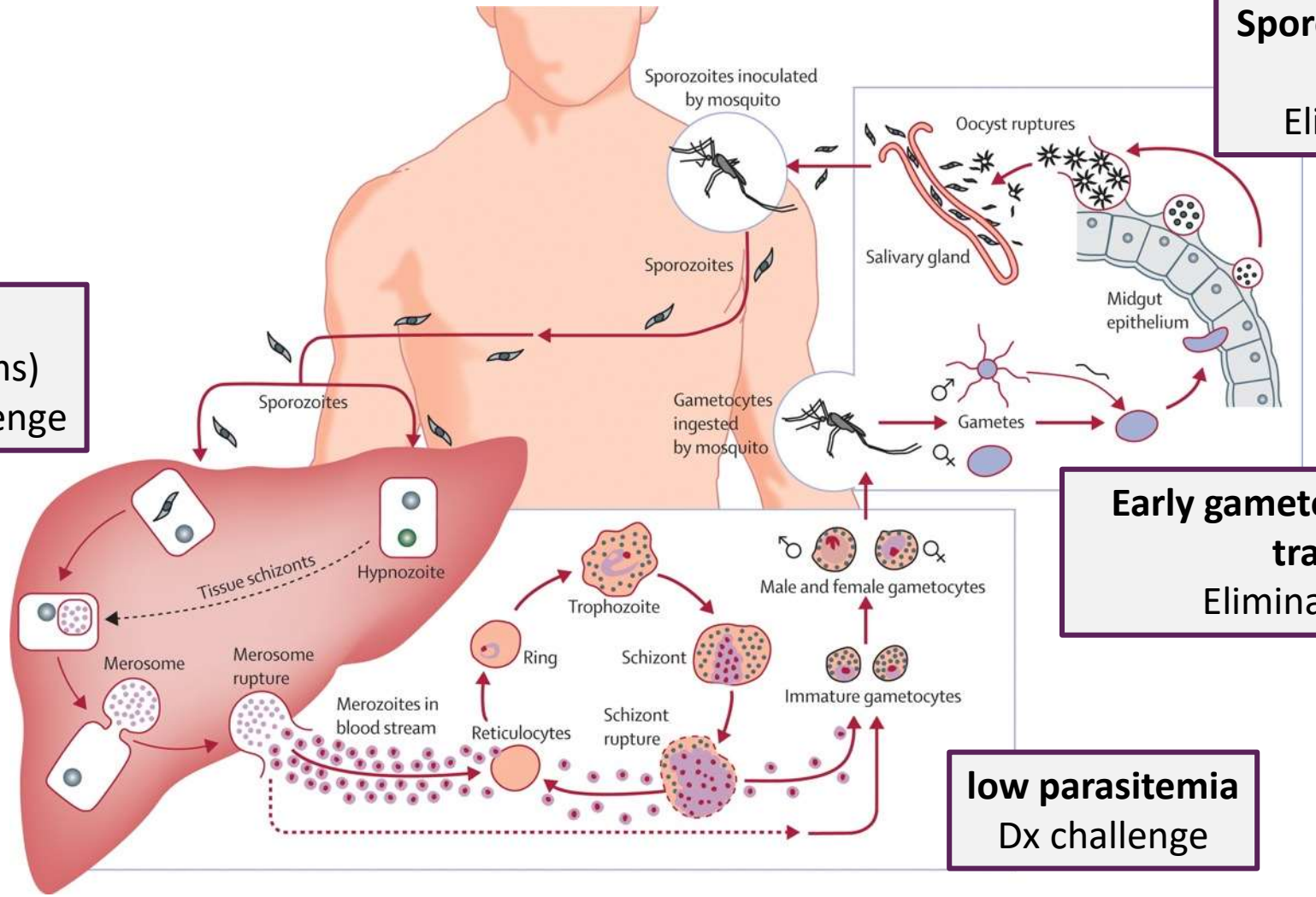
- *Single episode of P. vivax during the 1st trimester: risk of miscarriage increased four-fold (McGready et al., 2012)*
- *P. vivax accounted for 3.1% of global spending in malaria research and development during 2007 to 2009 (PATH, 2011)*
- *ADDITIONAL EVIDENCE OF SEVERITY AND NEGLECT*

> *"The weight of evidence now available leaves no doubt that vivax malaria in many settings often occurs in association with a pernicious and threatening course of illness, which does not assign cause and effect but instead, acknowledges real consequences without regard to their specific genesis." (K. Baird, 2014)*

P. vivax is a very specific malaria with specific challenges

Sporogony occurs at lower temperature
Elimination challenge

Hypnozoites
(resting liver stage forms)
Rx and Elimination challenge

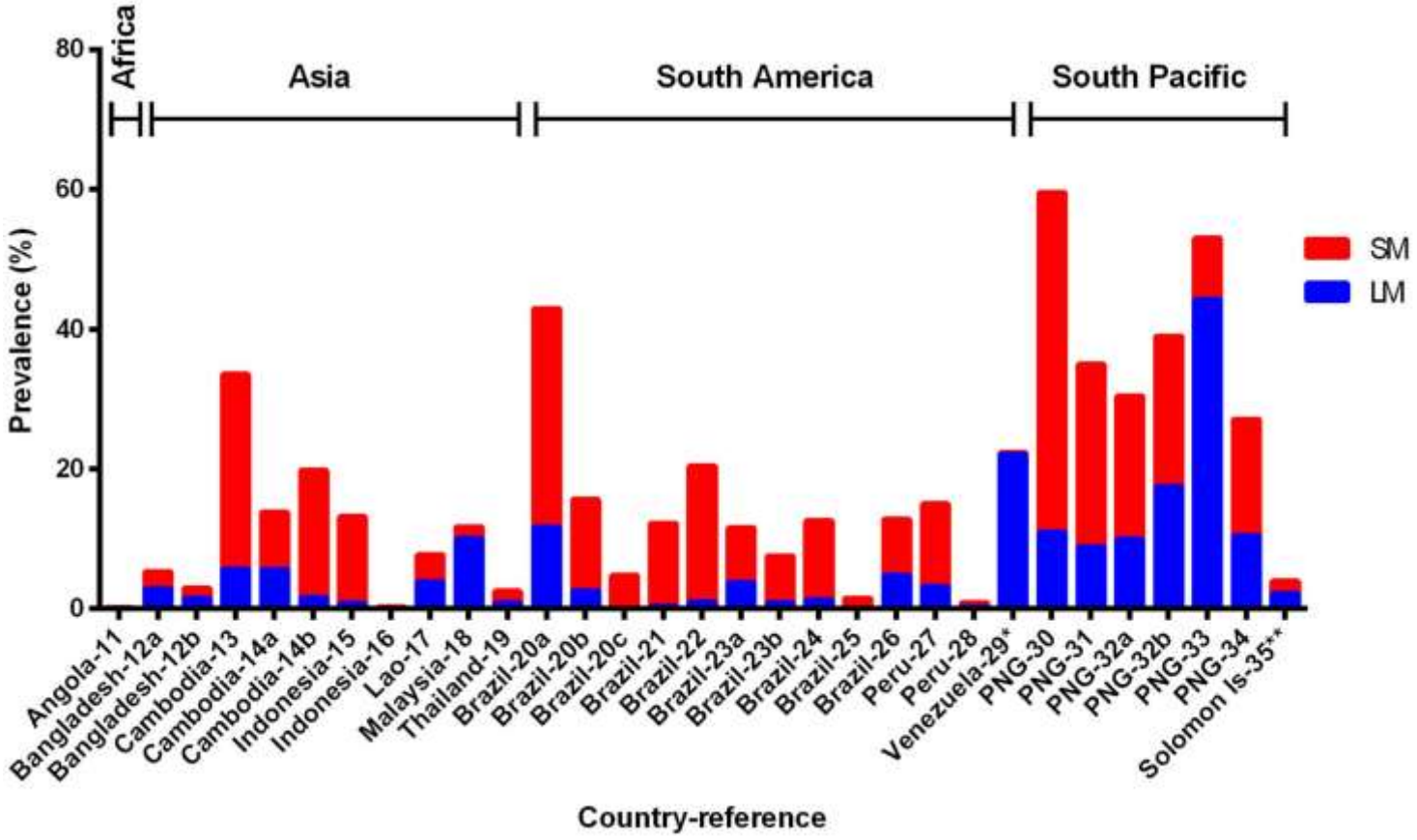


Early gametocytes and effective transmission
Elimination challenge

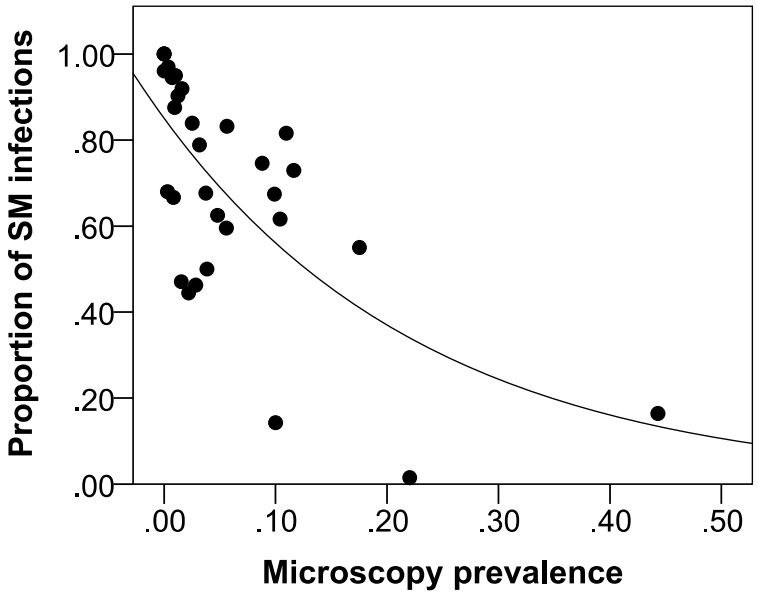
low parasitemia
Dx challenge

The Lancet Infectious Diseases 2009 9, 555-566DOI: (10.1016/S1473-3099(09)70177-X)

Similar to *P. falciparum*, asymptomatic infections are common

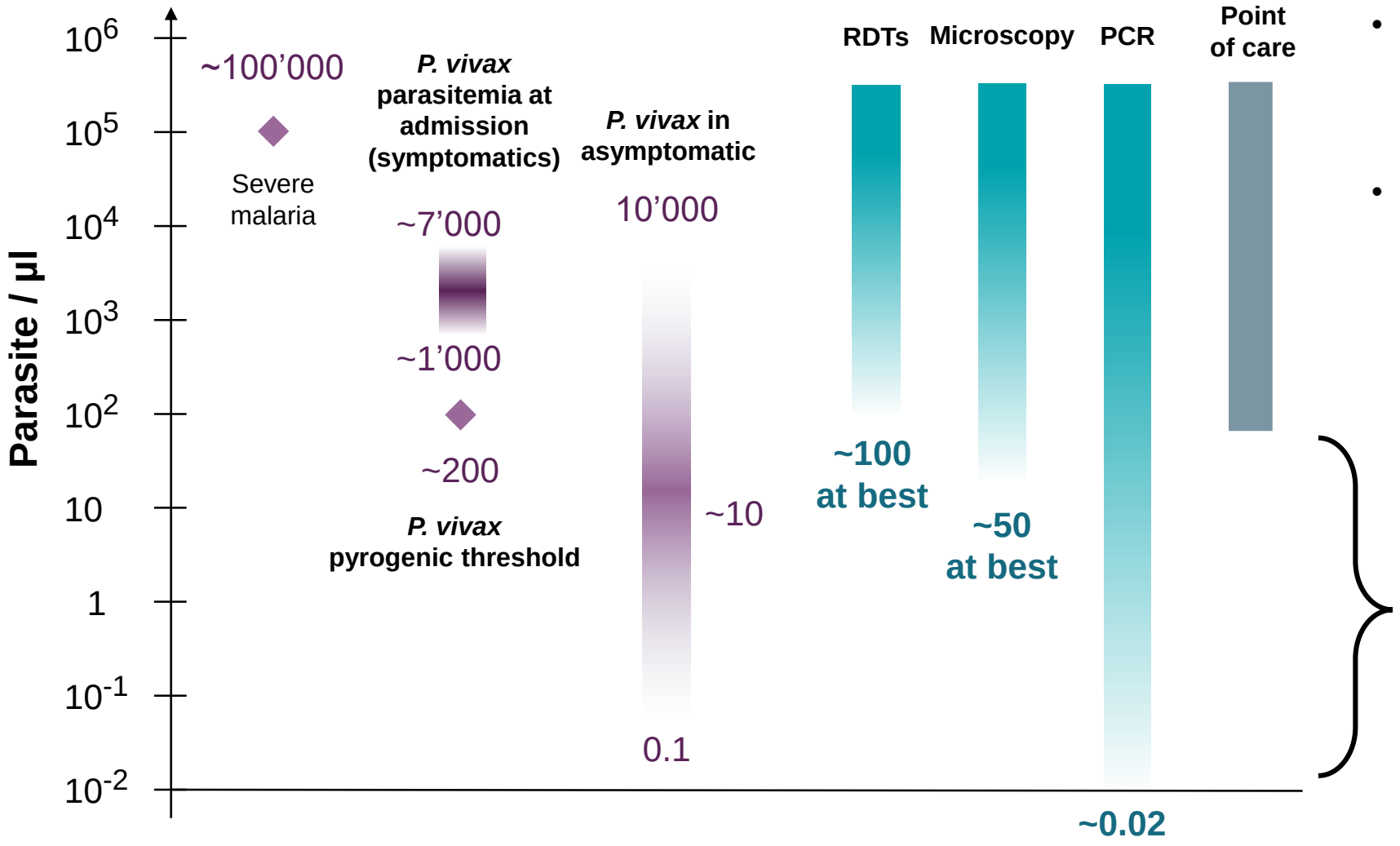


very low parasitemia
Dx challenge



Cheng *et al.* 2015

P. vivax diagnosis challenges



- **Microscopy**
  - *P. vivax* often reported as *P. falciparum*
- **RDTs**
  - *P. vivax* specific RDT rely on the detection of Pv-LDH
  - Only two *P. vivax* specific WHO PQ products

Gap in point-of-care highly sensitive diagnostic

Potential answers

RTD
Limited performances
POC format

“an improved RDT”
High-sensitivity RDT
(**HS-RDT**)

- HRP2-based RDT with a 10X improved analytical sensitivity
- No such RDT exist today for *P. vivax* but some are in development

“a simplified PCR”
Loop mediated isothermal amplification
(**LAMP**)

PCR
Excellent performances
Lab format

- Simple equipment and sample processing
- No cold chain required, naked-eye read-out
- **60 µL of capillary blood**
- **LOD in the range of 1 to 5 p/µL**
- **Time to result is 1h**
- **Commercial kit for *P. vivax* becoming available**

Analytical and clinical performances of a *P. vivax* specific LAMP kit

Laboratory evaluation at the Hosptial for Tropical Diseases (UK)

- Analytical sensitivity evaluated using *P. vivax* frozen whole blood samples at varying parasitemia
- Samples at 5 p/µL are consistently detected
- Samples at 0.5 p/µL are detected in half or more of all reactions
- Analytical sensitivity appears similar to that of the Pan-LAMP kit

Species	Parasitaemia (p/µL)	Pv-LAMP + reactions	Pan-LAMP + reactions
P. vivax	20	6/6	6/6
P. vivax	10	6/6	6/6
P. vivax	5	6/6	6/6
P. vivax	1	5/6	3/6
P. vivax	0.5	3/6	5/6
P. vivax	0.1	1/6	3/6
Negative blood	n/a	0/6	0/6
No template ctl*	n/a	0/6	0/6
Negative ctl	n/a	0/6	0/6
Positive ctl	n/a	n/a	6/6

Sonia M. Herrera et al. submitted

Analytical and clinical performances of a *P. vivax* specific LAMP kit

Laboratory evaluation at the Hosptial for Tropical Diseases (UK)

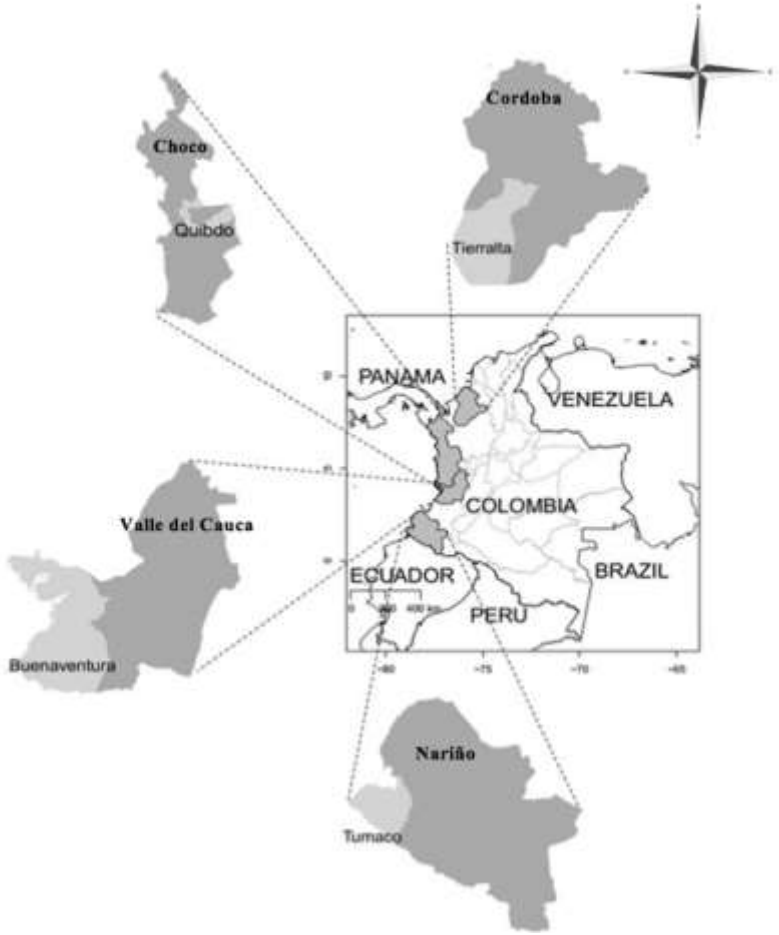
- Analytical specificity evaluated using a range of *Plasmodium* species and matching negative specimens
- Pv-LAMP assay show perfect specificity

Species	Parasitaemia (p/µL)	Pv-LAMP + reactions	Pan-LAMP + reactions
P. falciparum	~19,000	0/6	6/6
P. falciparum	20	0/6	6/6
P. malariae	20	0/6	6/6
P. malariae	20	0/6	6/6
P. ovale	20	0/6	6/6
P. ovale	20	0/6	6/6
P. ovale	1,000	0/2	2/2
P. ovale	5,000	0/2	2/2
P. ovale	10,000	0/2	2/2
P. knowlesi	350,000	0/6	6/6
P. knowlesi	350,000	0/6	6/6
Negative blood 1	n/a	0/6	0/6
Negative blood 2	n/a	0/6	0/6
Negative blood 3	n/a	0/6	0/6
Negative blood 4	n/a	0/6	0/6
Negative blood 5	n/a	0/6	0/6
Negative blood 6	n/a	0/6	0/6
Negative blood 7	n/a	0/6	0/6
No template ctl*	n/a	0/6	0/6

Sonia M. Herrera et al. submitted

Analytical and clinical performances of a *P. vivax* specific LAMP kit

Clinical evaluation in Colombia in collaboration with the Caucaseco Scientific Research Center



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Analytical and clinical performances of a *P. vivax* specific LAMP kit

Retrospective Clinical evaluation in Peru

P. vivax treatment challenges

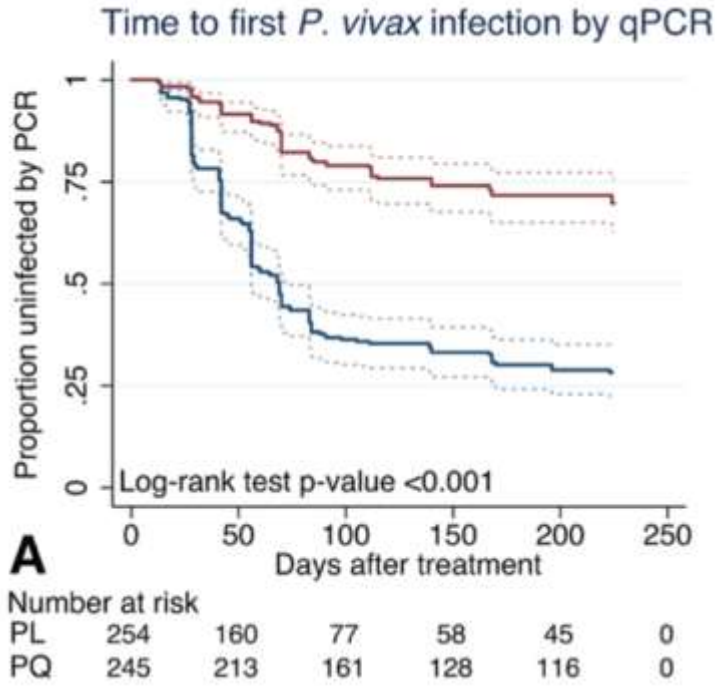
Recommended treatment for Pv: CQ or ACT
Not much resistance, so less of a challenge than for Pf

Real challenge is Rx for hypnozoites:
PQ only option for 60 years
Now TQ coming up but same G6PD liability
Encouraged the development of better test for G6PDd, this wil facilitate the implementation of radical cure Rx
No new anti relapse drug in the pipeline

P. vivax elimination challenges

Hypnozoites:
Allow to bridge transmission seasons, explaining the geographical spread of this species
Is the source of up to 95% of all blood stage infection: majority are relapses

There is no Dx for hypnozoites
Wait for relapse and provide radical cure, but doesn't prevent transmission
Mass drug administration: costly, challenging, exposing 90% of target population to unnecessary treatments
A Dx for hypnozoite would be ideal, FIND working on a serology based approche in collaboration with I. Mueller



Robinson *et al.* 2015

Conclusions

- *P. vivax* poses a number of very specific diagnosis, treatment, and elimination challenges
- Better diagnostic tests for both **clinical case management** and **elimination** are required
- **A *P. vivax* specific LAMP commercial kit**
  - will facilitate the identification of low density, asymptomatic infections
  - is best suited in countries approaching elimination
  - will complement existing kits for Pan detection and *P. falciparum* detection
- **The potential of LAMP for malaria not fully exploited:**
  - High costs
  - Lack of clear recommendations and policy around highly sensitive diagnostics for malaria
  - Lack of implementation guidelines and case-study with demonstrated impact on prevalence/transmission

Acknowledgements

DFAT
Colombia
HTD
Eiken

Australian Government
Department of Foreign Affairs and Trade