DIAMETER:

Diagnostics for Malaria Elimination Toward Eradication

Developing an ultra-sensitive HRP2 infection-detection test to support malaria elimination



Photo: © 2012, Diana Mrazikova/Networks/Senegal, courtesy of Photoshare

International Conference on Parasitology
Philadelphia, August 25, 2015

PATH

PATH is a leader in global health innovation



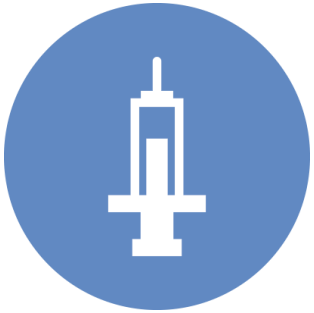
We harness
entrepreneurial insight,
scientific and public health expertise,
and passion for health equity…

…to save the lives
of women and children.

PATH/Aaron Joel Santos

Core expertise across five platforms

Innovation happens here



Vaccines



Drugs



Diagnostics



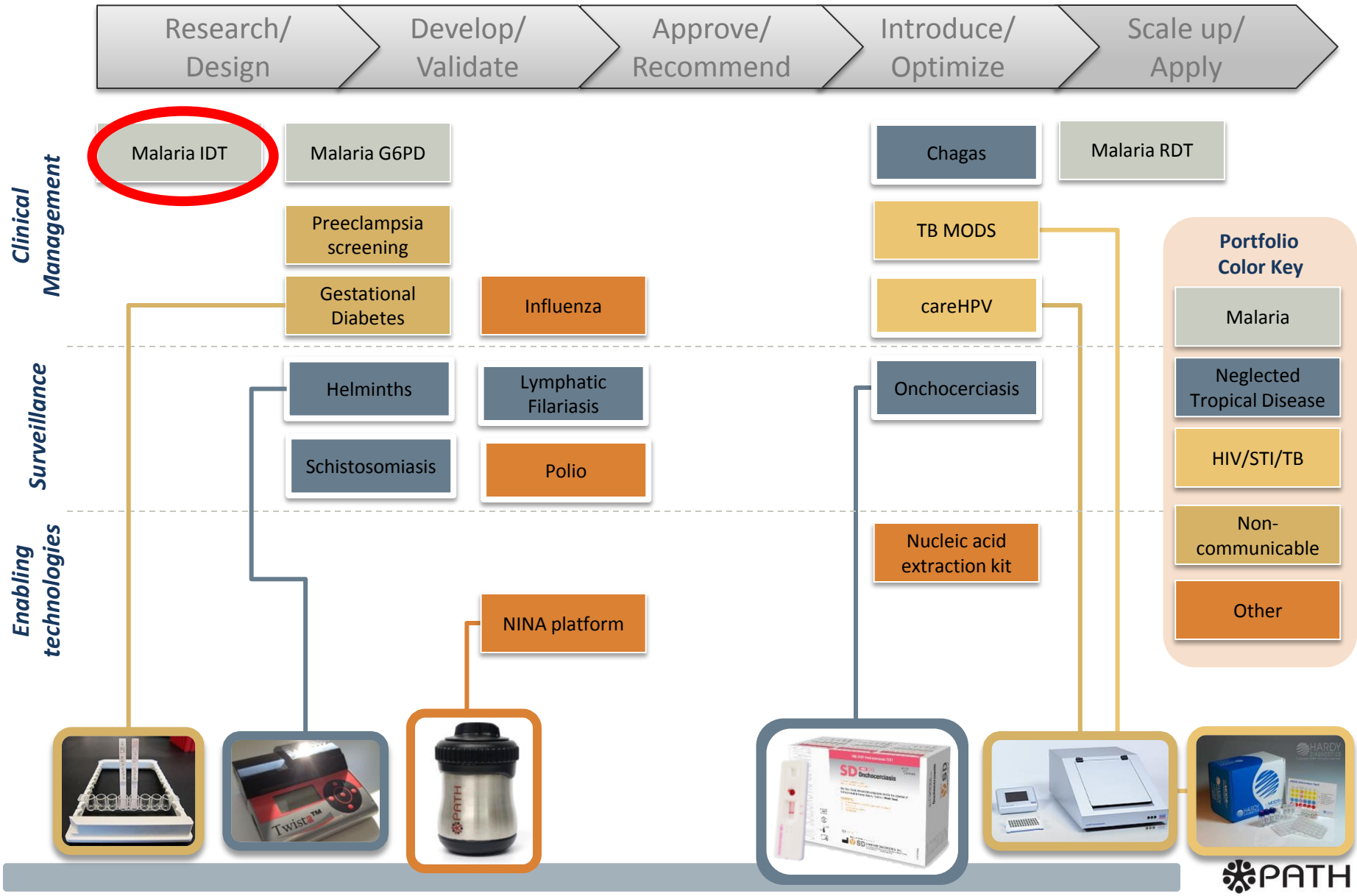
Devices



System and
Service Innovations

PATH

Diagnostics Product Portfolio



Aim and focus

- The aim of DIAMETER is translational science: to enable access to the most appropriate malaria diagnostic tools to support malaria elimination

- The current focus of the Bill & Melinda Gates Foundation IDT Development Initiative is on commercializing a high quality, robust, low cost, easy to use, qualitative, highly sensitive *Pf* IDT by 2017

- Target product profile (TPP) essentials:
  - The primary target analyte is HRP2
  - The required limit of detection (LOD) is 10x improvement (~80 pg/ml HRP2) using up to 50 µl whole blood from a finger stick
  - The format is lateral flow immuno-chromatographic strip assay

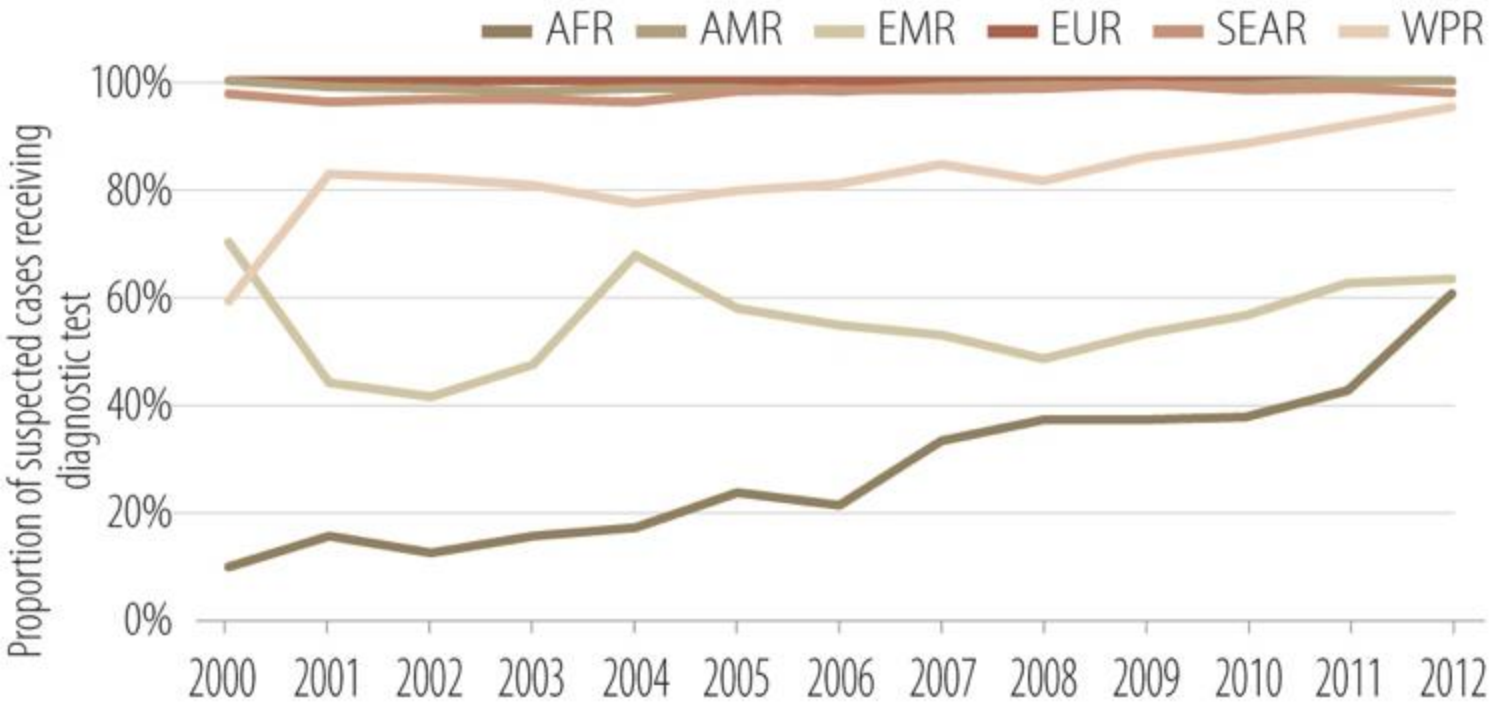
Target product profile as the guide

- Current vision of success
- Dynamic and updated as the landscape evolves
- Starts with an understanding of the current market



Malaria diagnostic market

Steady increase in the number of diagnostic tests performed globally in recent years



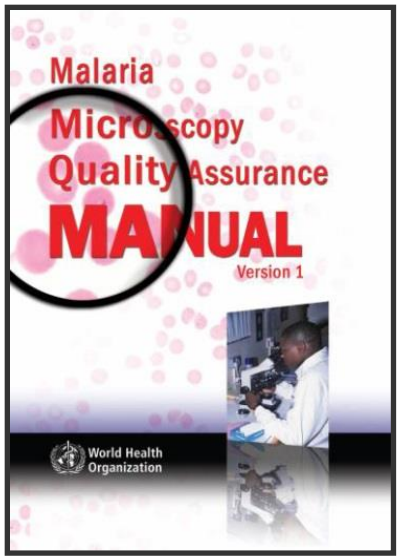
AFR, African Region; AMR, Region of the Americas; EMR, Eastern Mediterranean Region; EUR, European Region; RDT, rapid diagnostic test; SEAR, South-East Asia Region; WPR, Western Pacific Region

Image: National programs reporting to the World Health Organization, World Malaria Report 2013

Microscopy: the gold standard?



Diagnostic standard 1900



Addresses variation due to:

- Technique
- Slide prep
- Interpretation

But what about biological variation?



Diagnostic standard 2015

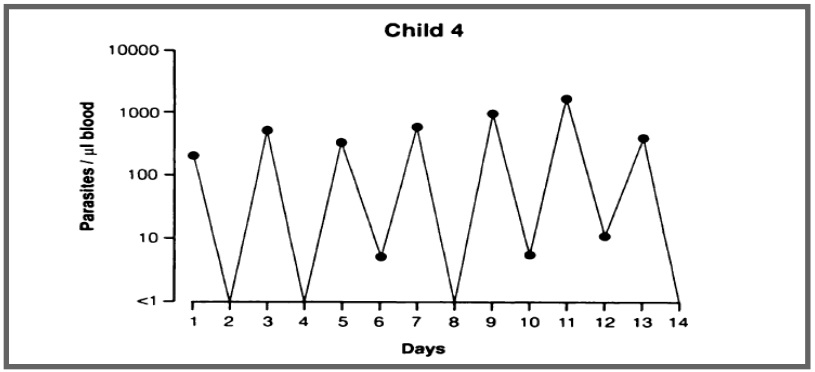


Image: Farnert, 1997

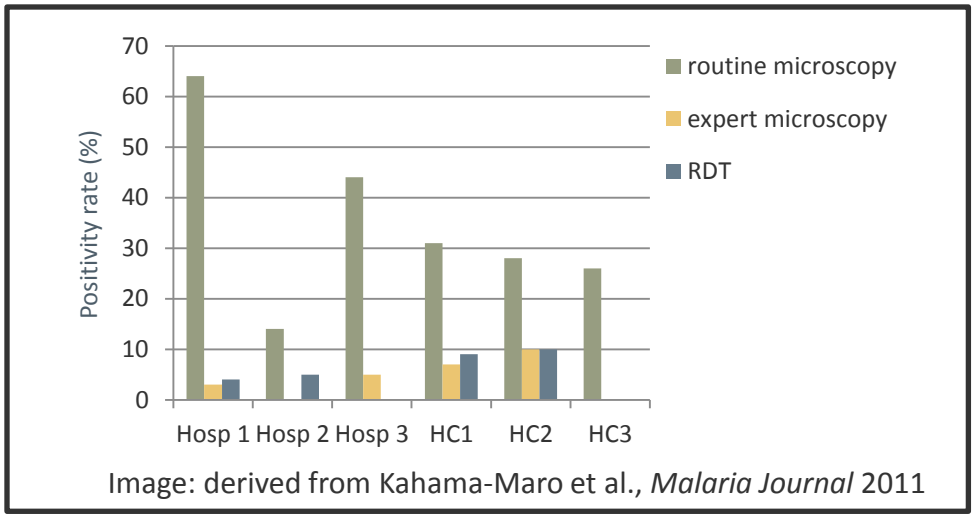


Image: derived from Kahama-Maro et al., *Malaria Journal* 2011

Malaria diagnostic market

Steady increase in the RDT market

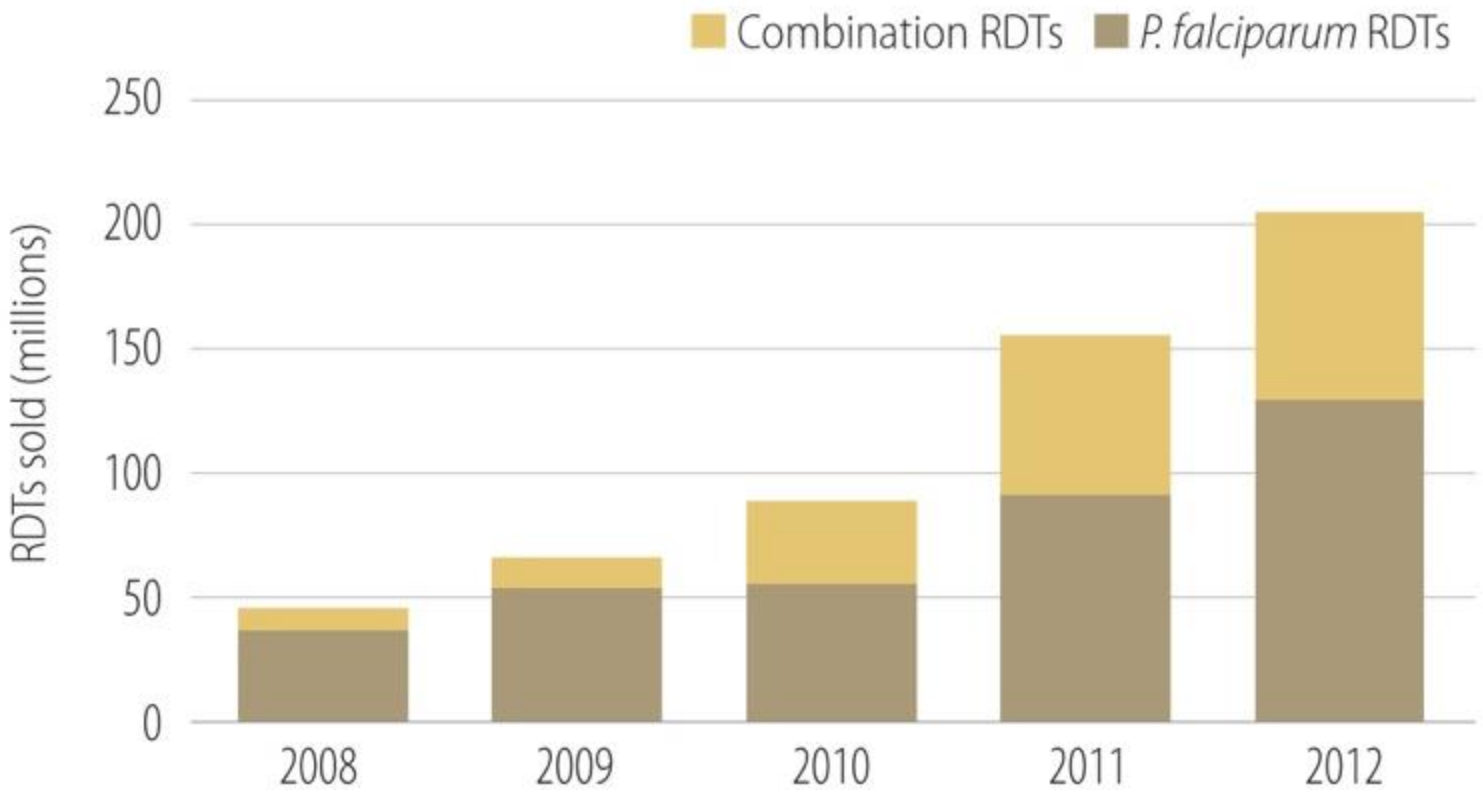


Image: Manufacturer reporting to the WHO, World Malaria Report 2013

Malaria diagnostic market

Prices have dropped steadily

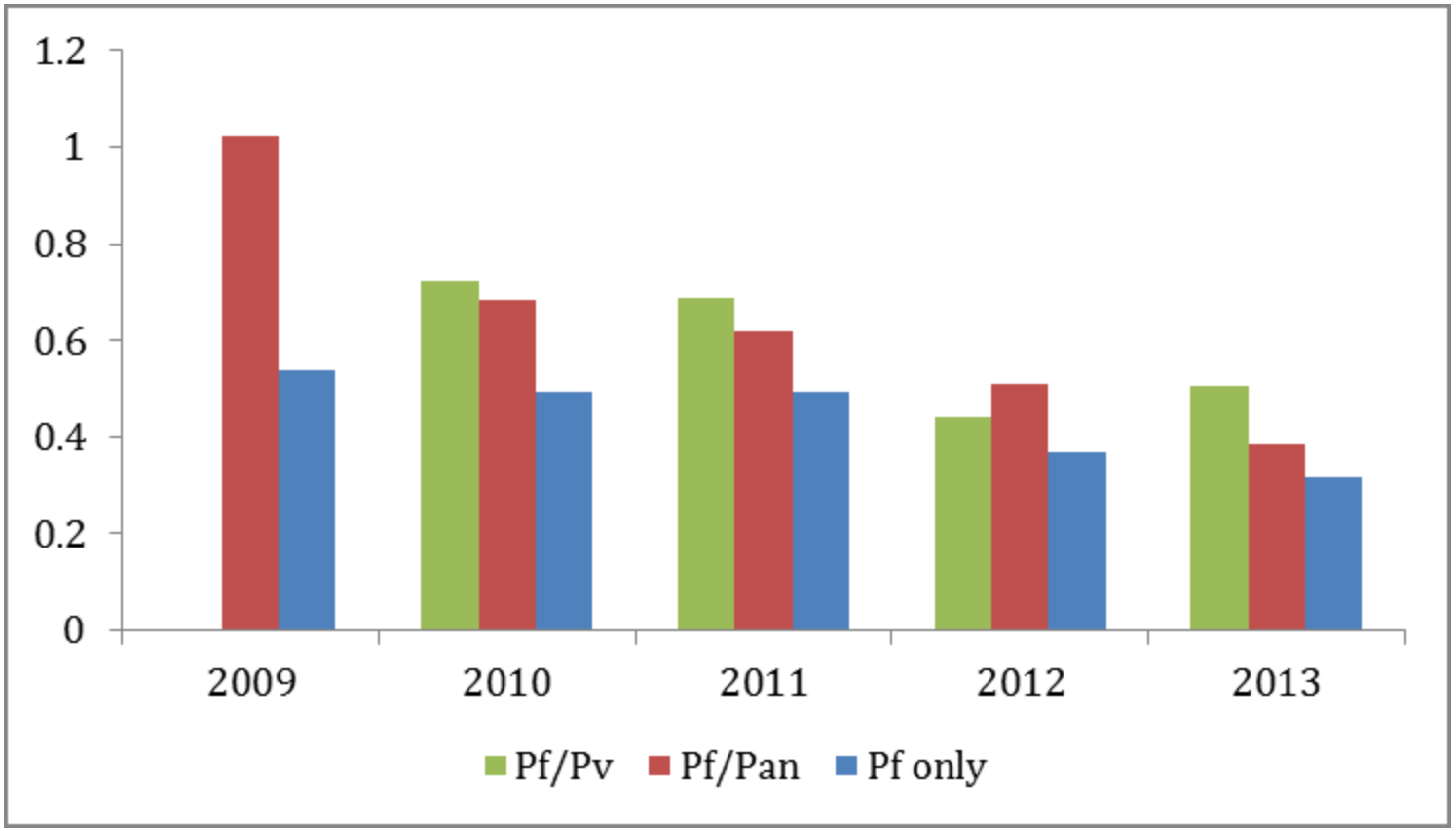
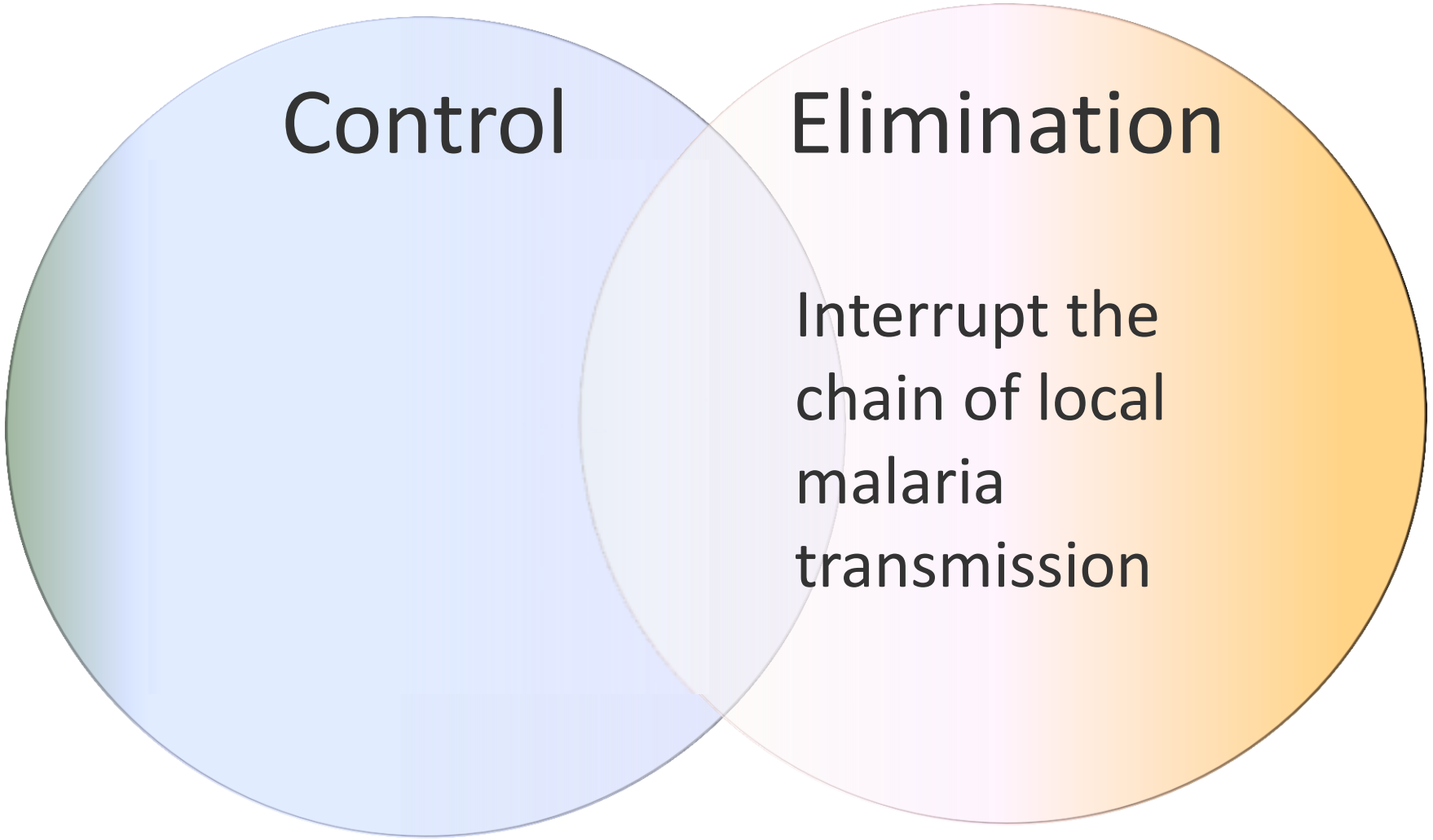
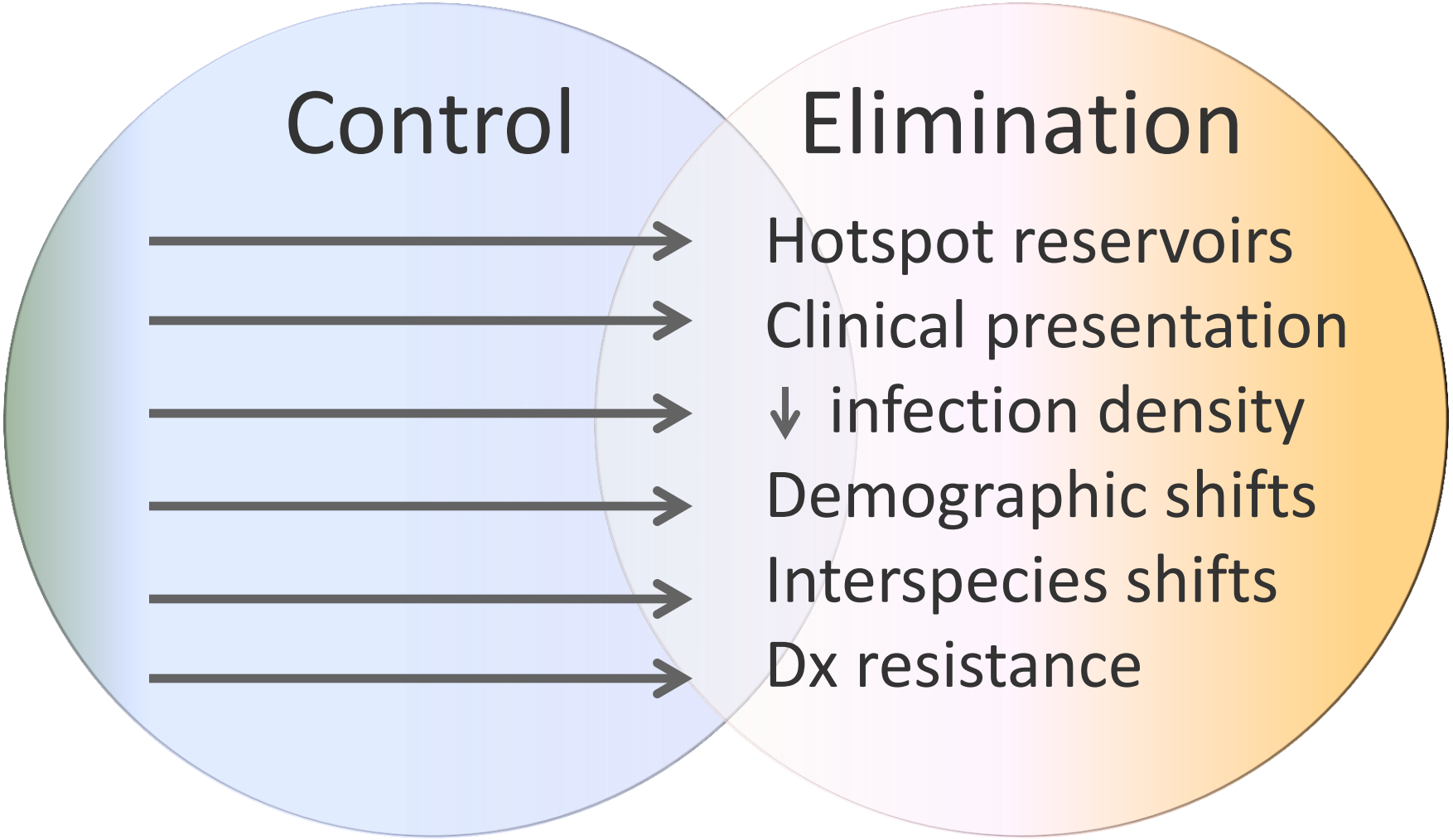


Image: Clinton Health Access Initiative/procurement data analysis 2009–2013

New goals: moving from control to elimination



Dynamic epidemiology



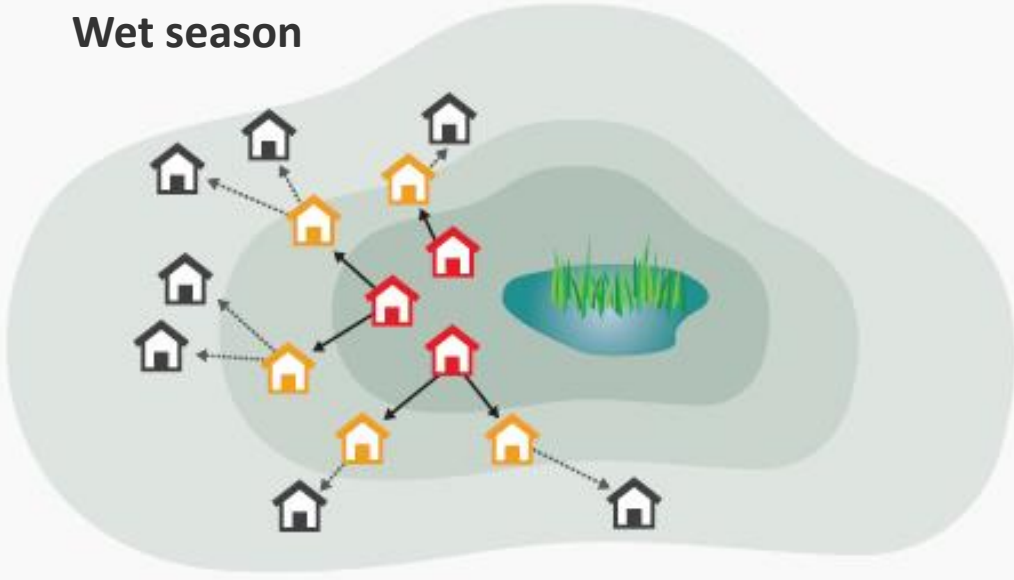
Hotspot reservoirs

Dry season





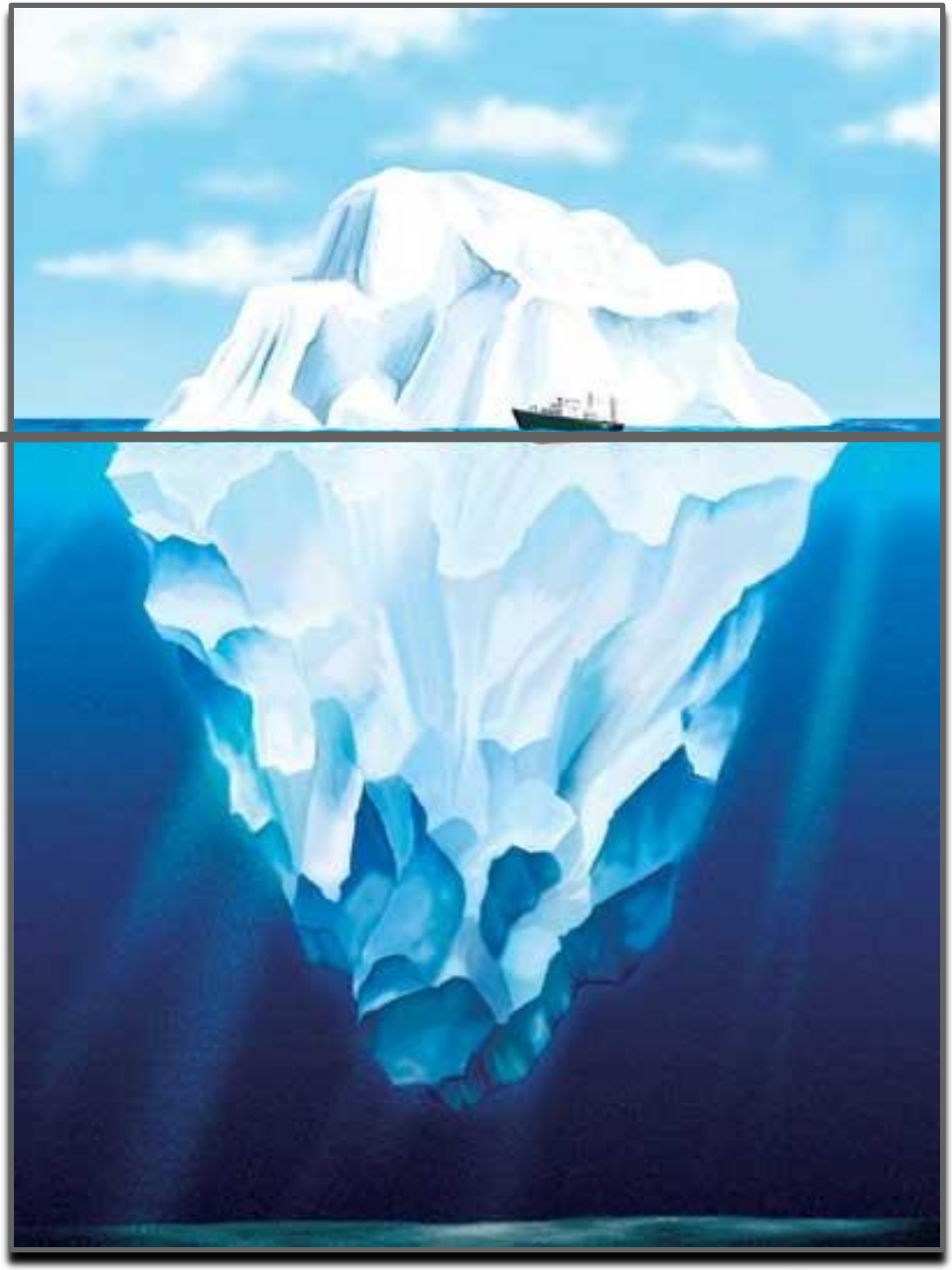
Wet season



Images: Bousema, 2012

Clinical presentation

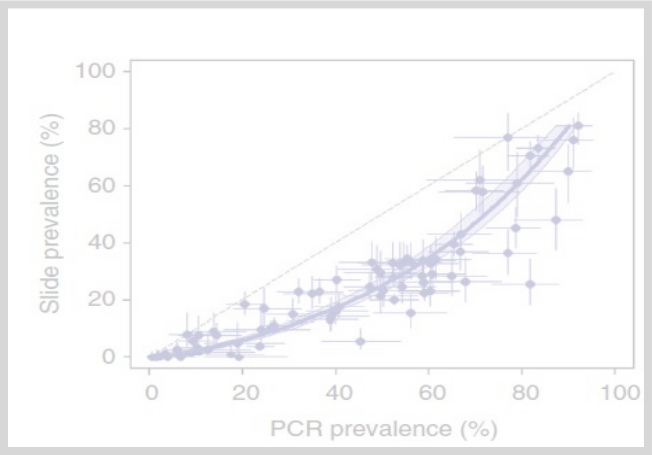
Symptomatic



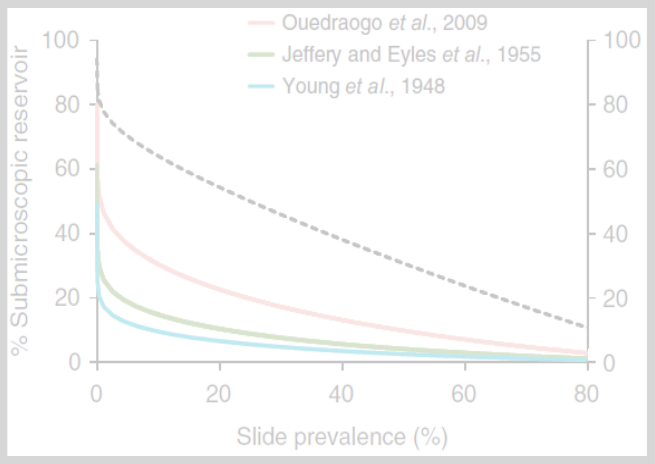
Asymptomatic

Image: http://community-roundtable.com/2009/08/the-iceberg-effect-of-community-management/

Infection density



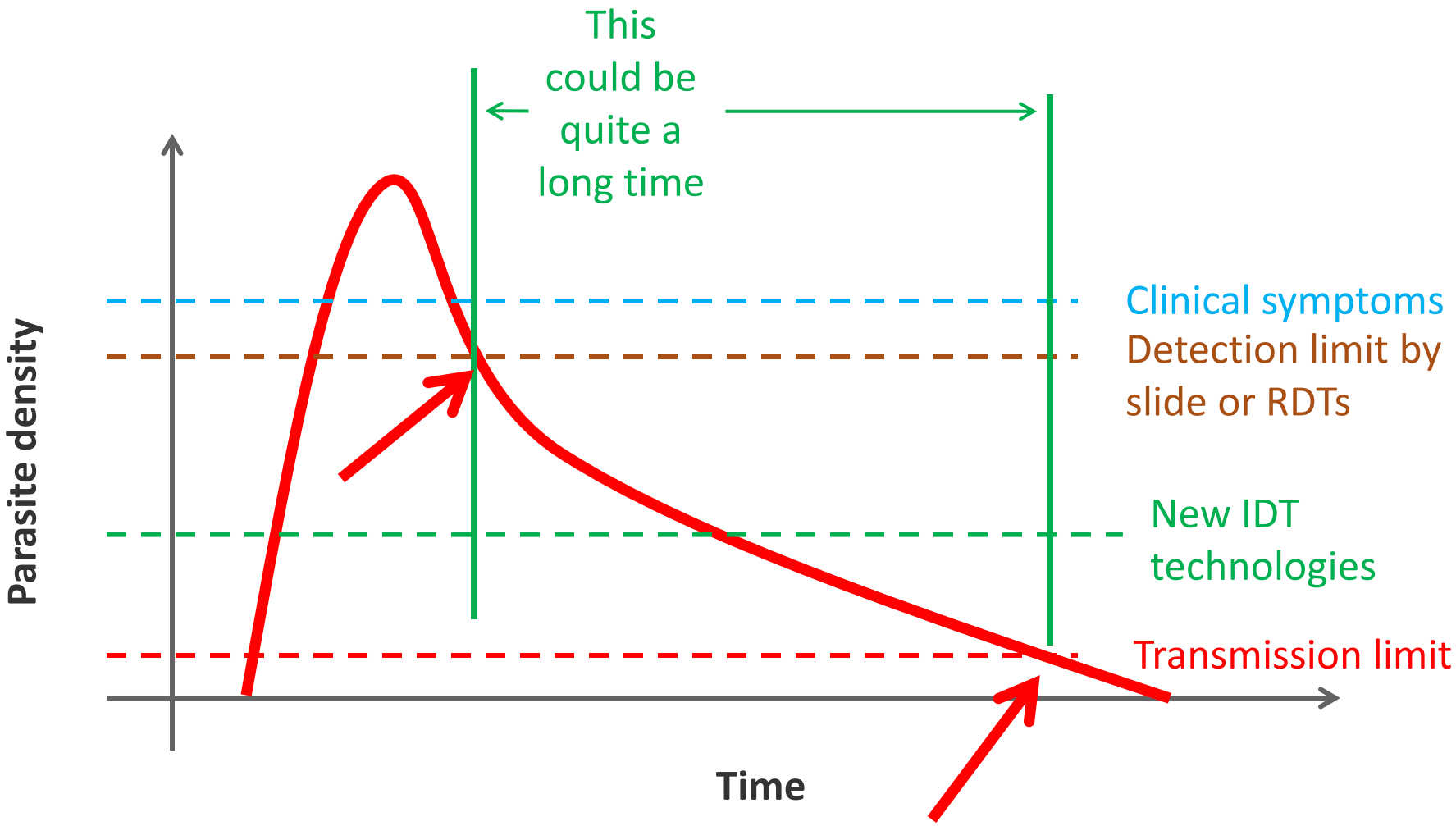
Proportion of submicroscopic carriers varies with prevalence. Proportion ranges up to 80% in low-transmission settings.



Submicroscopic carriers are estimated to be the source of more than 20% of mosquito infections in low-prevalence settings.

Image: Okell, *Nature Communications*, 2012

Detectability



Shift in species proportions

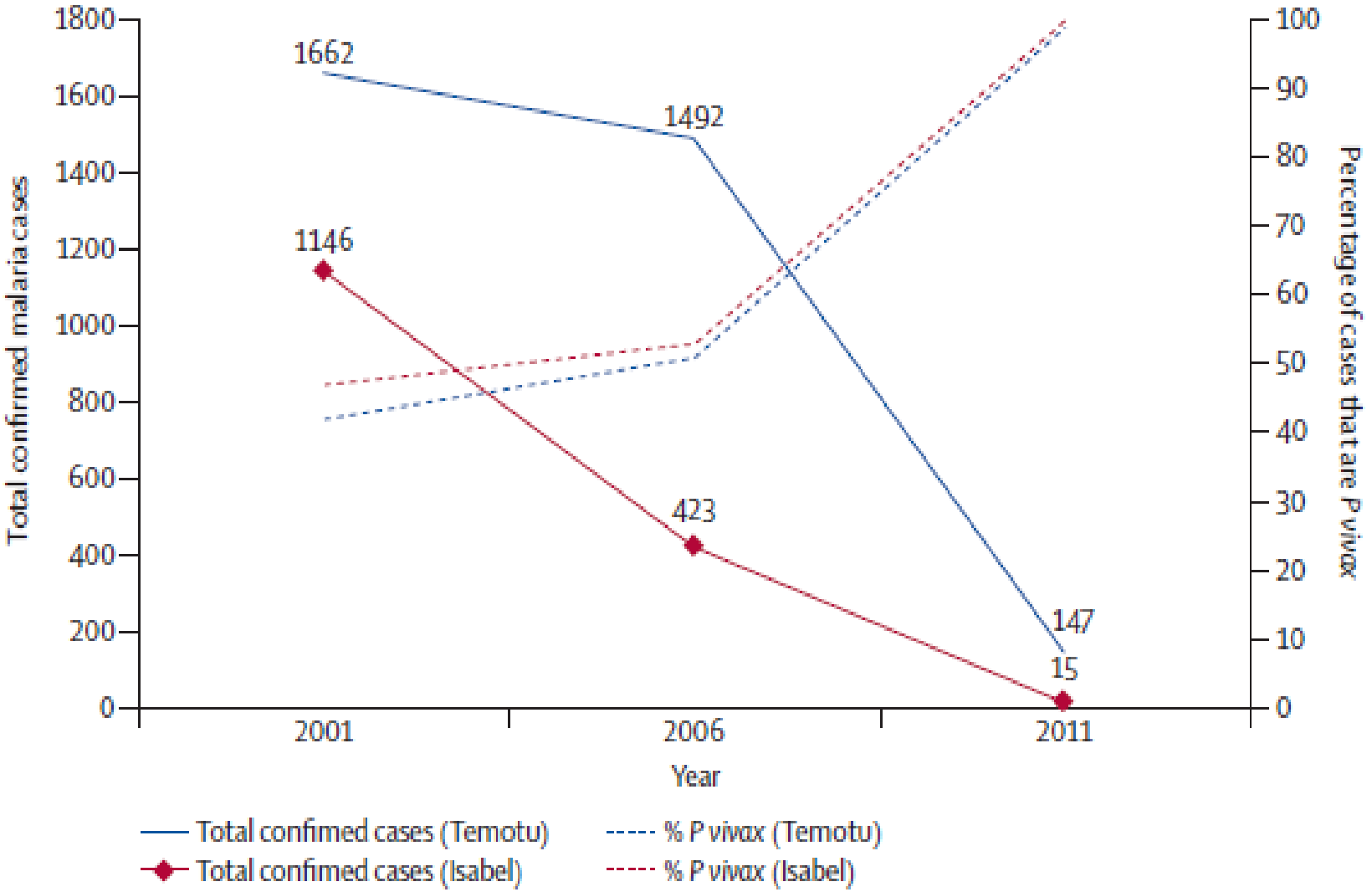


Image: Cotter, 2013

Resistance is not just about drugs and insecticides

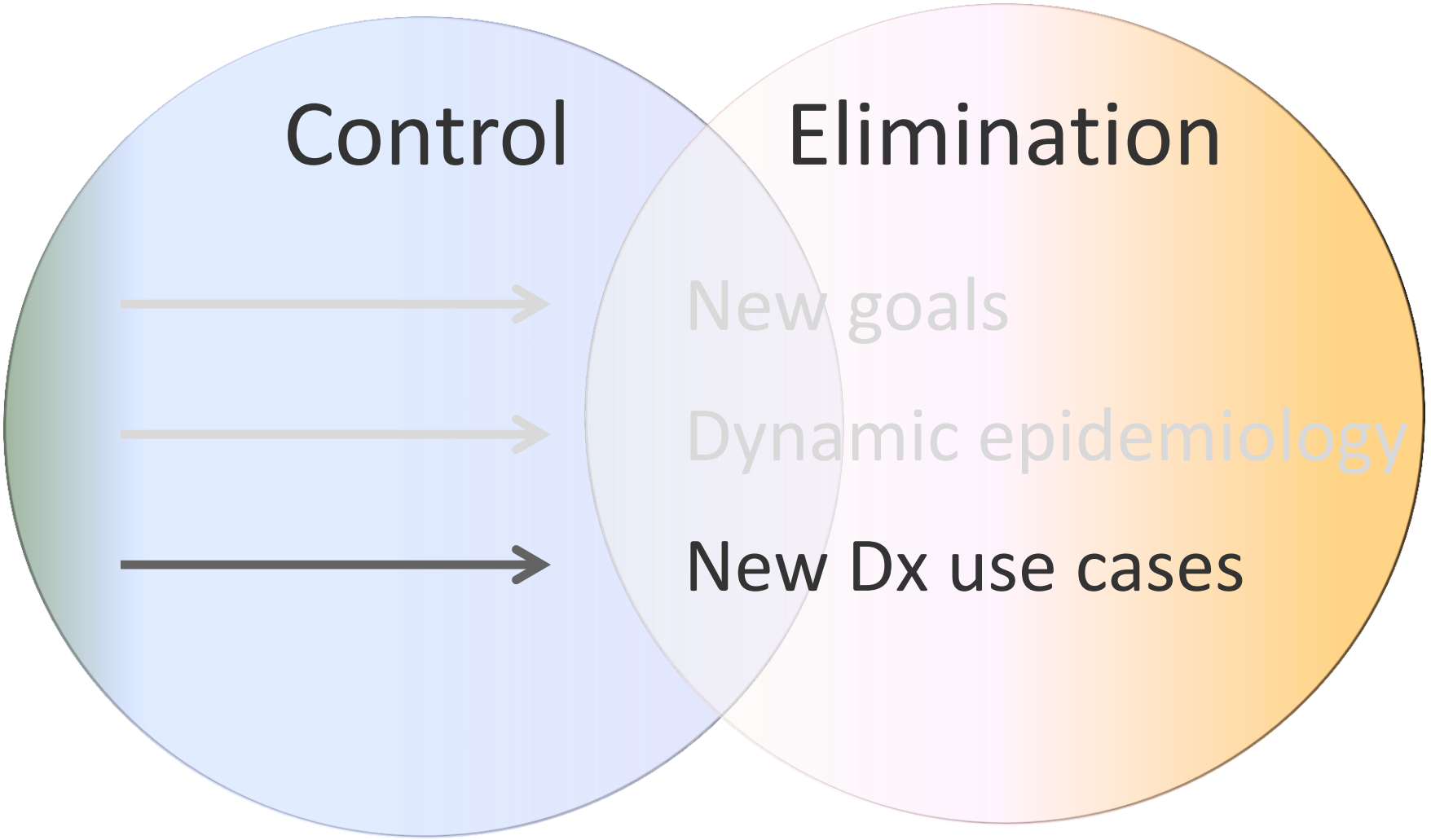
HRP2 deletions?

…the last person standing with malaria may be the least detectable!



Photo: Malaria Journal

Evolution from control to elimination



Target product profile as the guide



Use cases

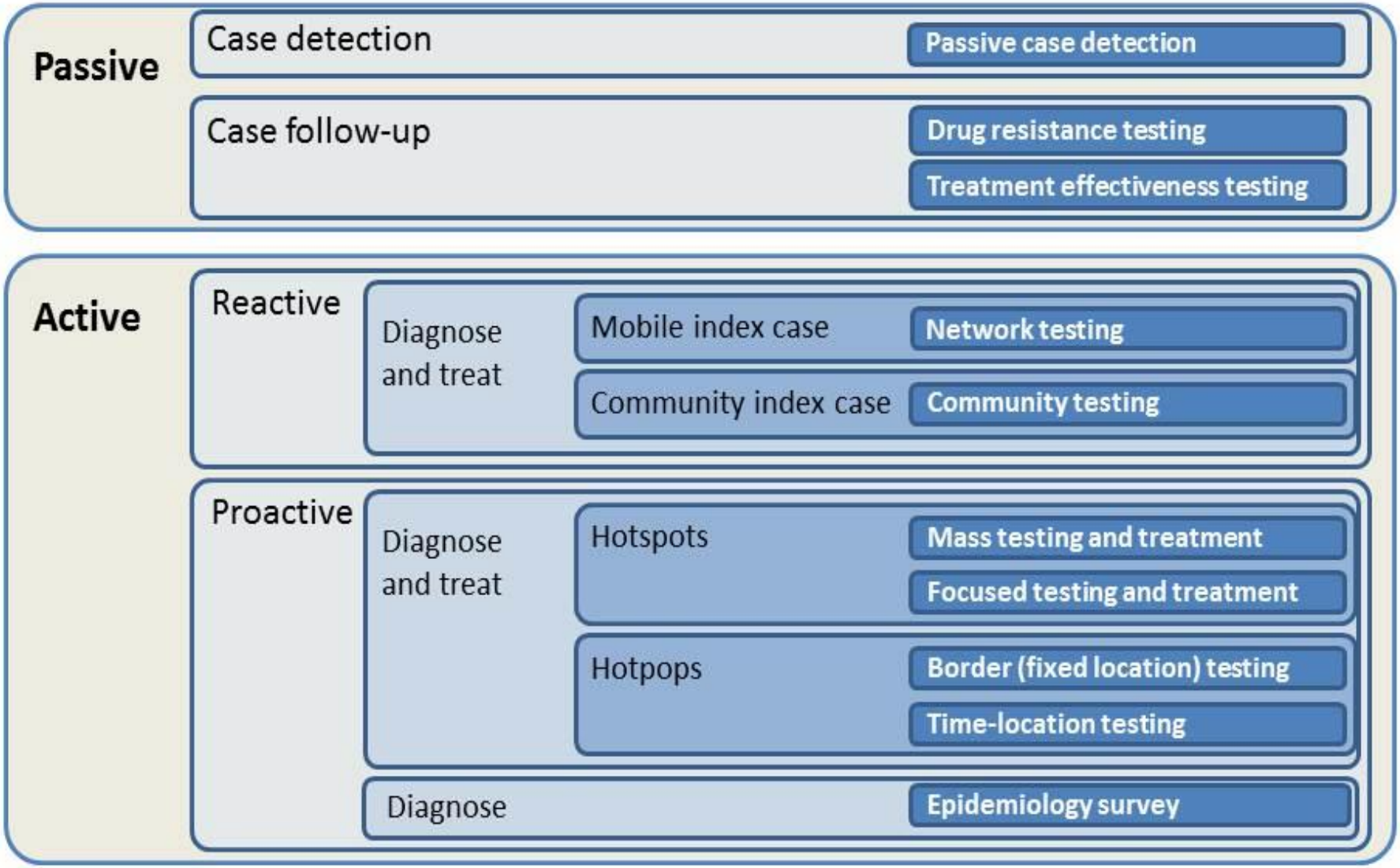
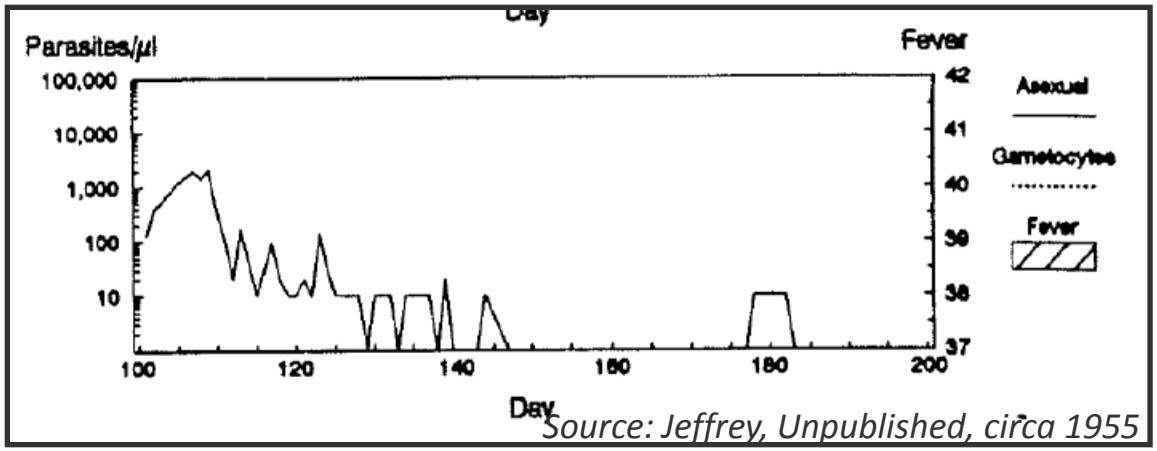
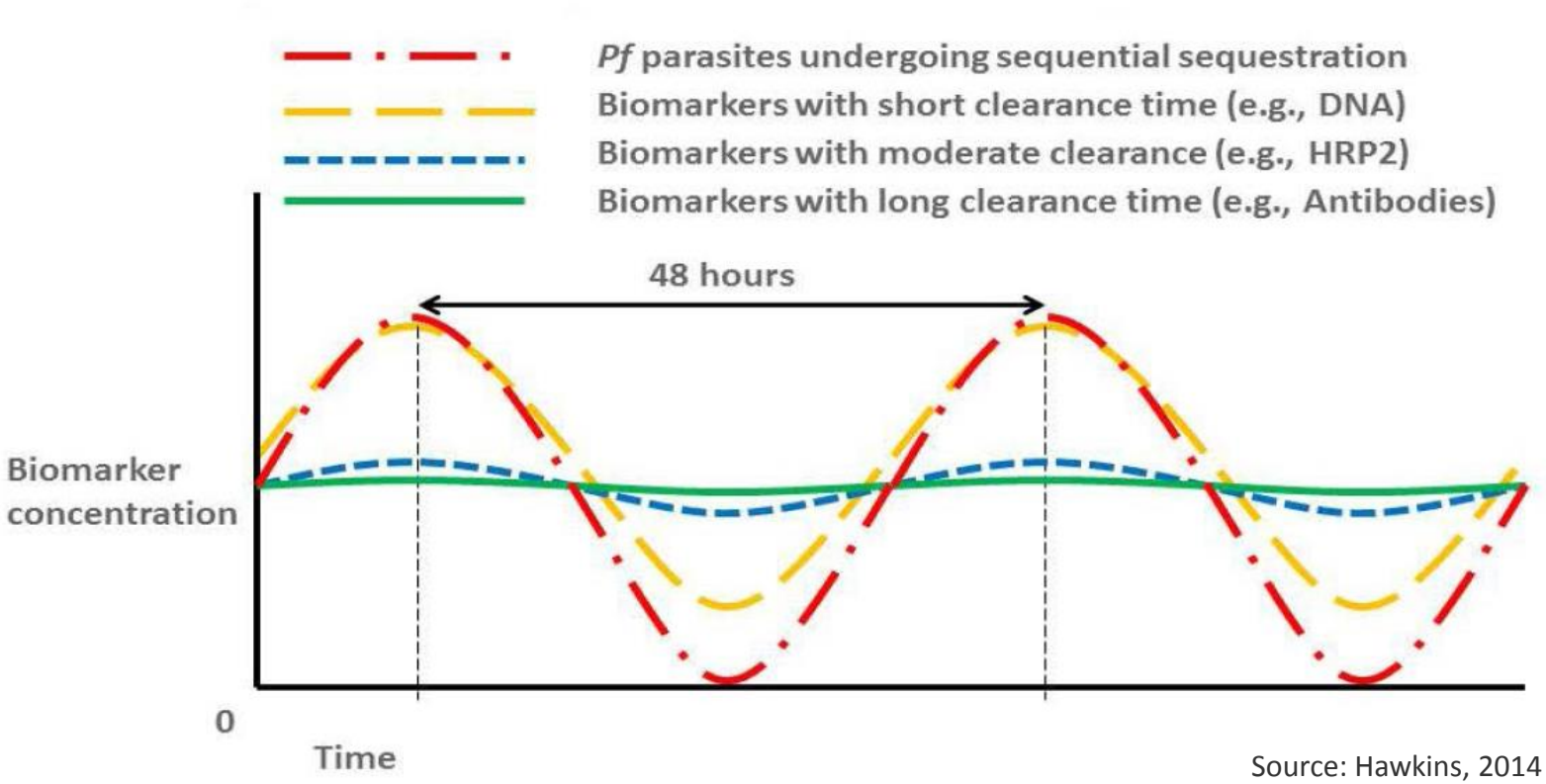


Image: Tietje, 2013

Biomarkers



Source: Jeffrey, Unpublished, circa 1955



Source: Hawkins, 2014

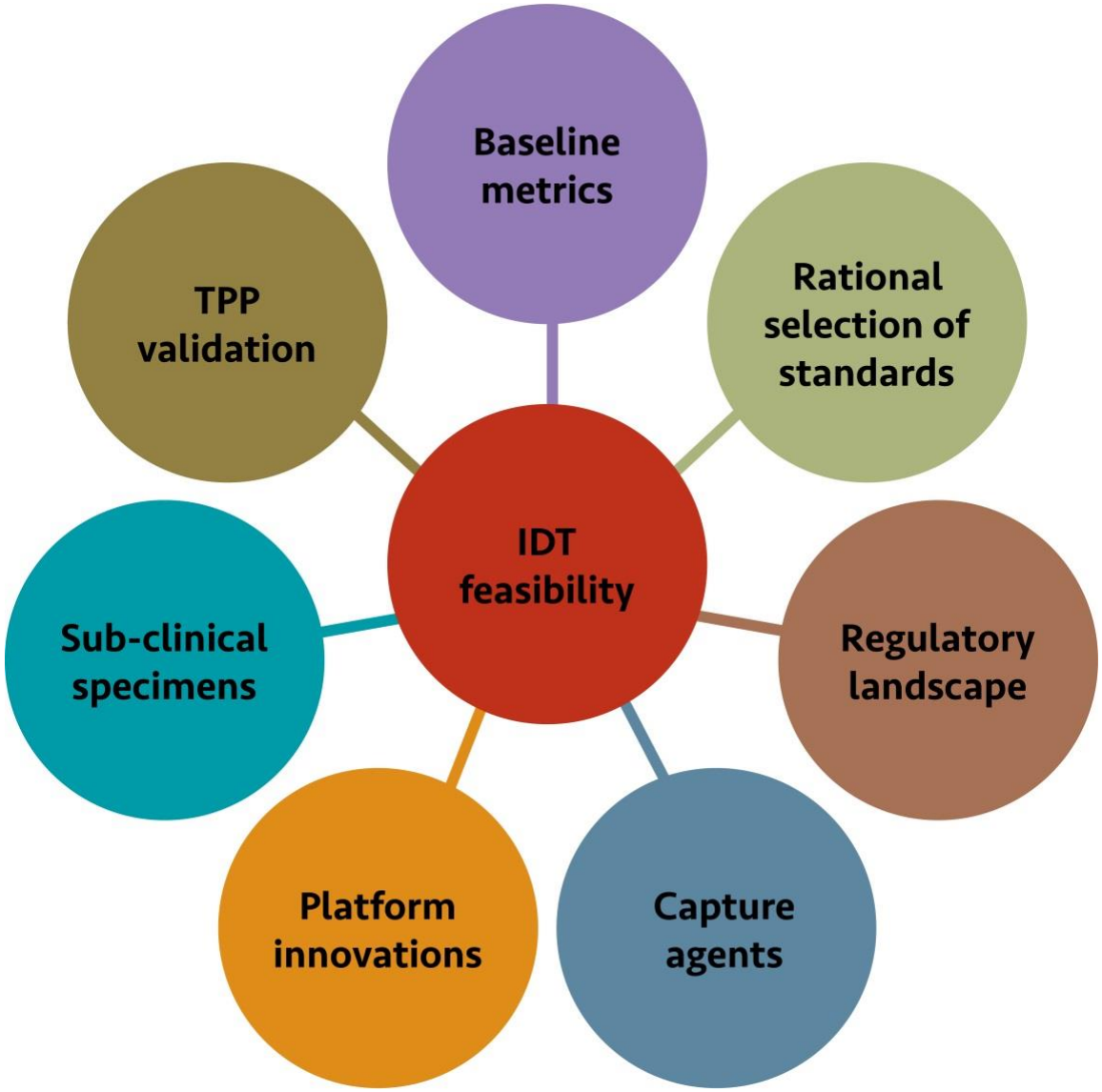
Target product profile

Variable	Minimum requirement
1.0 Design	
1.1 Format	Lateral flow immunochromatographic strip in cassette format
1.2 Target analyte	*Pf* HRP2
1.3 Sample type/collection	Peripheral whole blood from finger stick (heel prick for infants)
1.4 Sample volume	1-50 µl
1.5 Detection	High-contrast, clear results for naked-eye, indoor and outdoor reading; reader compatible
2.0 Performance	
2.1 Species differentiation	*Pf* only
2.2 Analytical sensitivity/limit of detection	100 pg *Pf*HRP2/ml in whole blood (recombinant HRP2 will be provided)
2.3 Diagnostic/clinical sensitivity	95% on provided HRP2 panels
2.4 Diagnostic/clinical specificity	90% on provided HRP2 panels
2.5 Target shelf life/stability	24 months at temperatures between 2°C and 30°C; stable for 2 weeks at 40°C
2.6 Ease of use	One or fewer timed steps; instructions should include diagram of method and results interpretation
2.7 Ease of results interpretation	Clear positive/negative readout in indoor and outdoor lighting conditions; language-appropriate instructions
2.8 Operating temperature	20°C to 35°C
3.0 Regulatory	
3.1 Product registration path	• Target country regulatory requirements • World Health Organization prequalified

Feasibility phase

Goal:

Evaluate technical feasibility of a high quality, robust, low cost, easy to use, qualitative, highly sensitive *Pf*HRP2 RDT by Q1 2017.



What's the LOD for commercial RDTs?

Baseline metrics

WHO Product Testing

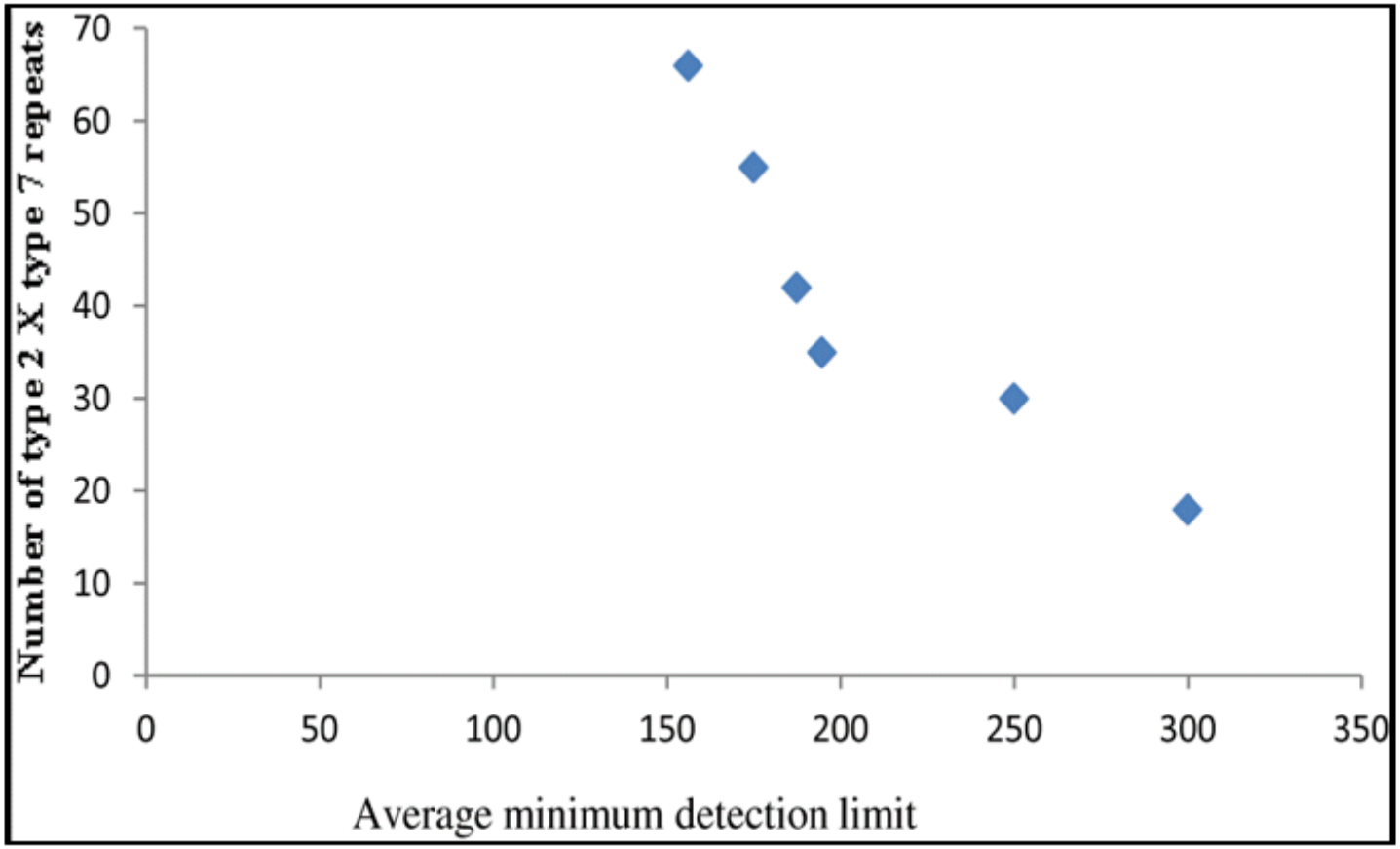
- 5 rounds
- More than 200 RDTs were tested in the last 6 years
- Geographically diverse specimens diluted to 200 p/ul

HRP2 is highly polymorphic

Rational selection of standards

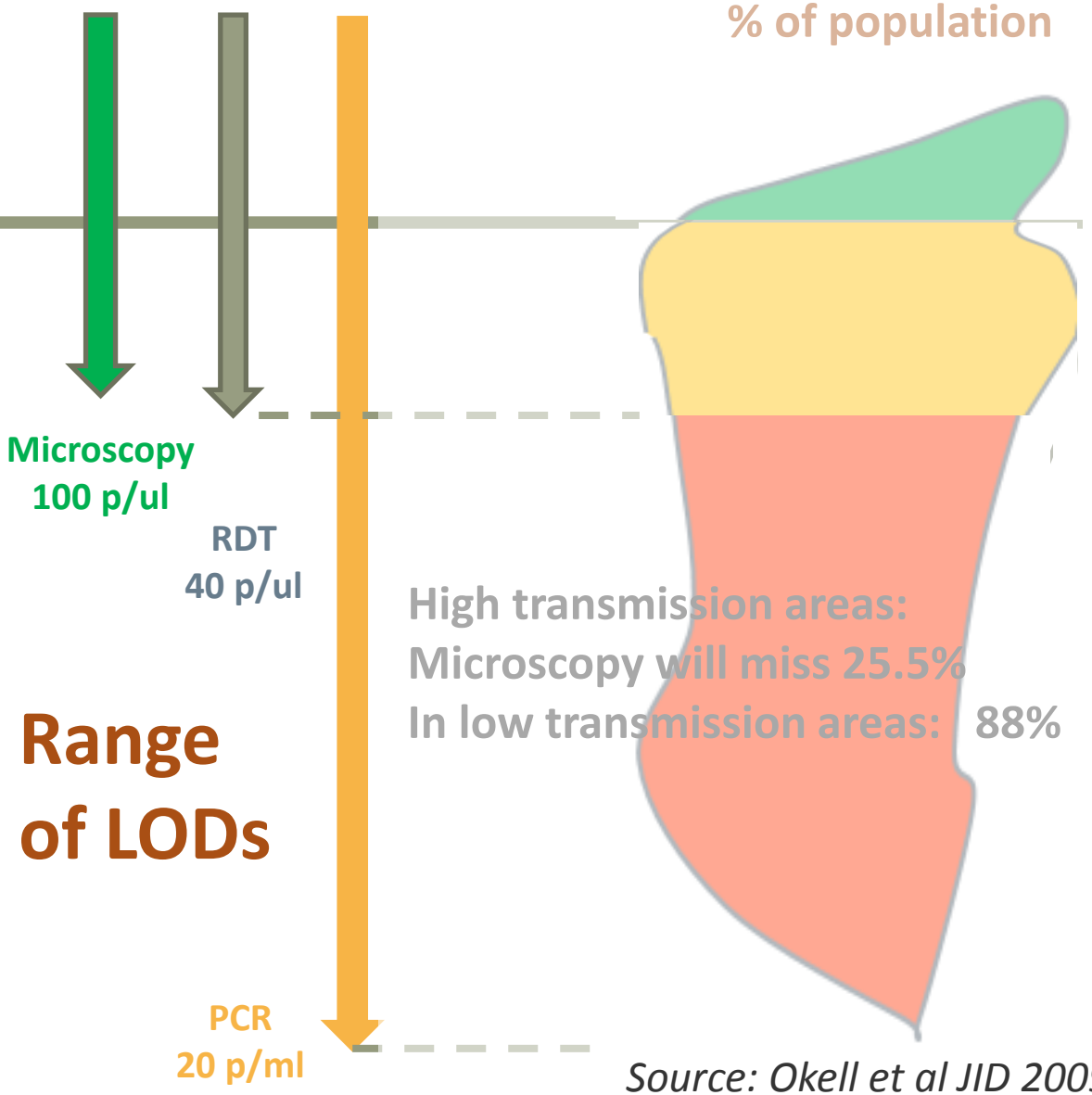
What does this mean?

- HRP2 is highly mutagenic and structurally variable
- Variations include the type and number of repeat epitopes that are targeted by RDTs



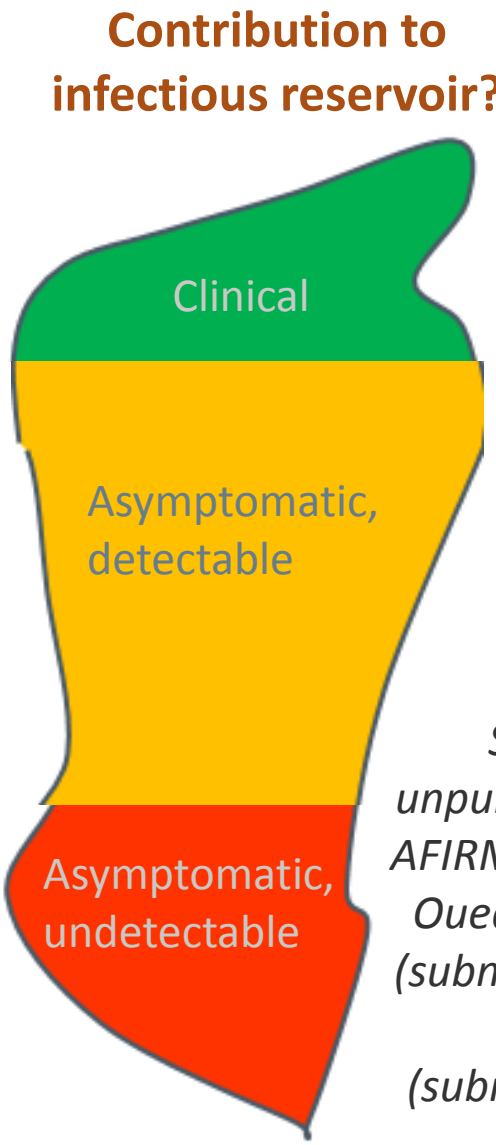
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Infected vs infectious



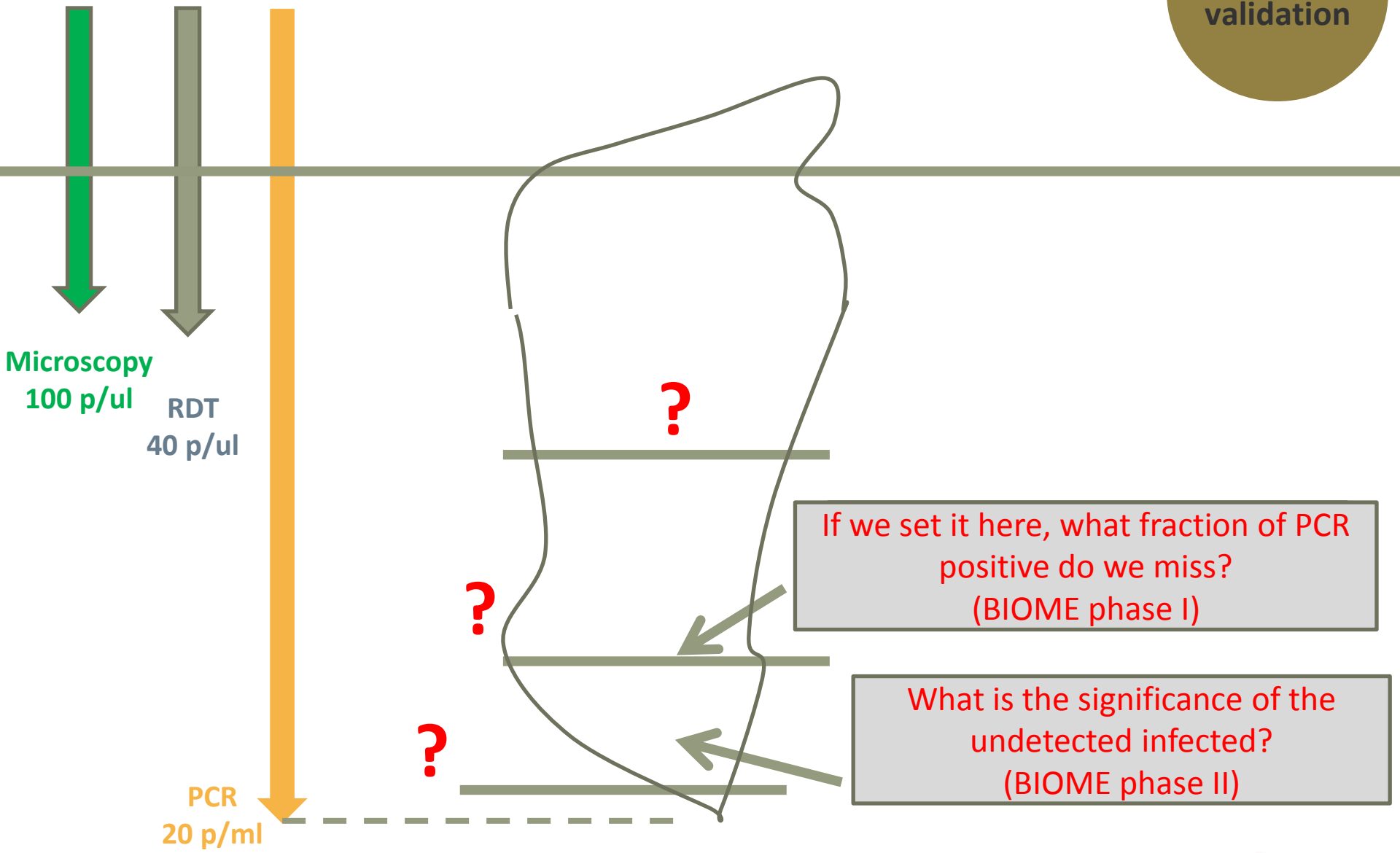
Range of LODs

Source: Okell et al JID 2009



Source: unpublished AFIRM data, Ouedraogo (submitted); Slater (submitted)

Biomarkers for malaria elimination (BIOME)

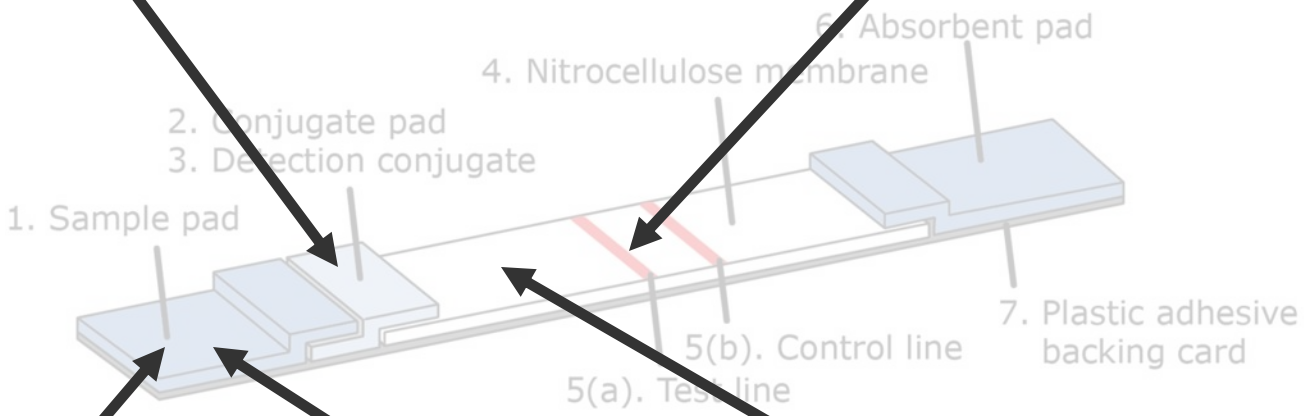


Building a better RDT

Platform innovations

Alternative reporters:
e.g., latex, cellulose, fluorescence

Advanced capture agents:
native immunogens, phage-display, fAb



Non-invasive sample:
saliva, oral fluids

Workflow innovation:
e.g., Chembio dual path platform

Sample preparation:
concentrating technologies

Technology candidates selected for feasibility

Platform innovations

14 proposals screened in targeted RFP (June 2014)

Decision whether to proceed with development (Q4 2015)

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Project DIAMETER Team

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Kate Misiuda: Project assistant
Gonzalo Domingo: Advisor
Jenny Richards: Project Manager
Smita Das: Scientist
Ihn Kyung Jang: Scientist Officer
Bhavya Gowda: Market analyst
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Robbie Baker: Lab Technician
Becky Barnes: Lab Technician
Tamoka Nakamura: Data analyst
Howard Lakougna: Scientist



Photo: PATH/Laura Newman



Thank you

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