Towards *P. vivax* elimination

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Global *P. vivax* distribution

- Geographically most widely distributed malaria parasites
- > 2 billion people at risk of infections
- > 80 million clinical cases
- Now predominant parasites outside Africa.

*P. vivax* worldwide distribution in 2010
The elimination ‘challenge’

• In 2013 and 2014, the leaders of Central American and East-Asian countries formally declared their commitment to eliminate malaria from their regions by 2020 and 2030, respectively

• In all their countries *P. vivax* is now the predominant malaria parasites
The challenge

• The biology of *P. vivax*, with
  – it’s ability to relapse from long-lasting ‘dormant’ liverstages
  – it high transmissibility through continuous production of of gametocytes and rapid development in mosquito is thought to render it more resistant to elimination

• Yet, we still have limited understanding of *P. vivax* biology and epidemiology and lack tools directly targeting *P. vivax*.

Key gaps in the knowledge of *Plasmodium vivax*, a neglected human malaria parasite

Ivo Mueller, Mary R Galinski, Kevin Blund, Jane M Carlton, Dhanpat K Kocher, Pedro L Alonso, Fernando A del Portillo

Mueller et al 2009, Lancet Infect. Dis
Highly endemic *P. vivax* malaria in Papua New Guinea
**P. vivax** malaria is not (always) ‘benign’

- 5-times lower incidence of severe **P. vivax** in children 1-4 yrs, but
- Comparable symptomatology
- Similar case fatality for Pf and Pv but higher in mixed infections
**P. vivax affects mostly young children**

- **3 – 21mths**
  - 3-15 months:
    - *P. falciparum*: 0.28 / yr
    - *P. vivax*: 0.82 / yr
  - 15-21 months:
    - *P. falciparum*: 0.42 / yr
    - *P. vivax*: 0.75 / yr

- **1 - 4yrs**
  - Lin et al 2010 PLoS One

- **5 - 14yrs**
  - Michon et al 2007 AJTMH
Immunity to \( P. \text{ vivax} \) is acquired more rapidly than to \( P. \text{ falciparum} \)

Association of antibodies with risk of infections and illness

\[ \text{Children 1-4 yrs. of age} \]

\[ \text{Children 5-14 yrs. of age} \]

Stanisic et al, 2013 PLoS NTD
Stanistic et al 2015, Infect. Immun

King et al 2008, PNAS
**P. vivax** populations show large global but little local genetic structure

Global **P. vivax** population structure

Population genetic analyses using panel of 10 microsatellite markers for each species

PNG *falciparum & vivax* population structures


What causes this difference between *P. vivax* and *P. falciparum*?
The key to understanding *Plasmodium vivax* – the Hypnozoite

(Source: Mueller et al., 2009)
The *P. vivax* elimination challenge
Comparative epidemiology of *P. falciparum* and *P. vivax* transmission (TransEPI Consortium)

**Overall aim:** Gain an better understanding of the dynamics of malaria transmission in 3 non-Africa settings

**Objective 1:** Determine the relationship between asexual and sexual *Pf* and *Pv* parasites in general population

**Objective 2:** Investigate the longitudinal dynamics of sexual and asexual parasites in longitudinal cohort studies

**Objective 3:** Determine in the relationship between gametocyte density and mosquito infectivity

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**Obj. 1:** Despite variable levels of transmission, ~80% of all infections are asymptomatic and 50-90% are gametocyte positive

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**Blood collection**

- Plasma/PBMCs

Plasma/PBMCs

**DNA sample**

200-300 ul

Plasmodium genus specific qPCR

TaqMan assays to detect and quantify *Plasmodium* species (*P. vivax*, *P. falciparum*, *P. malariae*, *P. ovale*)

**RNA sample (RNAprotect)**

50 ul

**RNA extraction from *P. vivax* / *P. falciparum* positive samples**

Detection and gametocyte specific RNA transcripts by *Pvs2* and *Pfs2* rt-PCR

**Additional screening and genotyping:**

- *P. vivax* msp1F3 and MS16
- *P. falciparum* msp2 nested PCR

**MOI and mFOI**

Control for gDNA contamination by qPCR (DNA based), control for successful RNA extraction by rt-qPCR (RNA based, *Plasmodium* genus specific)
P. vivax infection and P. falciparum infection in Solomon Islands paediatric cohort study

ACD visits: 1058 P. vivax infections & 27 P. falciparum infections
98% of *P. vivax* and 88% of *P. falciparum* infections are asymptomatic.

71% of *P. vivax* and 35% of *P. falciparum* infections are submicroscopic.
Transmission at low transmission

**Solomon Island:**
- PR 12%
- >1 infection 35%
- ≥2 infection: 21%
(Data: Waltmann & Quah)

**Western Thailand:**
- PR 4%
- >1 infection 11%
- ≥2 infection: 7%
(Data: Nuitragool, Sattabongkot & Singhasinavon)

**Manaus, Brazil:**
- PR 4%
- >1 infection 10%
(Data: Kuehn, Monteiro, Karl & Lacerda)
Transmission patterns in Manaus, Brazil

Clinical *P. vivax* episodes

Infections detected by PCR

(Data: Karl, Kuehn, Monteiro & Lacerda)
The ‘diagnostic dilemma’ in MDA interventions

- Treating only parasite positive individual will miss ~2/3 of people that are likely to relapse

- Treating the entire population will expose 65-90% of the population to drugs they do not need, but may have side effect.
  - Too costly, logistically challenging, difficult to get compliance, potential SAEs, etc.
The *P. vivax* elimination challenge

How to efficiently eliminate *P. vivax* when

- hypnozoites contribute ~80% of all infections
- hypnozoites carriers can not be identified
- vast majority of infections are asymptomatic, and
- even submicroscopic infections contribute to maintaining transmission
- The only class of drug we have is potentially toxic an in-effective in upto 10+% of patients?
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