Malaria Transmission:
When a little is Enough

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Malaria – the current state of play
• Malaria – current state of play
• Malaria infections – more than we thought
• Malaria transmission – the infectious reservoir
• Transmission reduction – targeting infectivity
• Conclusions

Bhatt et al., Nature 2015

Trends of declining malaria – linked to increasing net coverage and provision of ACT

Neither intervention is at optimal coverage

Malaria – the current state of play
• Artemisinin resistance – increased parasite clearance time
• Insecticide resistance widespread in S Africa

Ranson et al., Trends Parasitol 2016; TRAC, NEJM 2014
Malaria - the current state of play

WHO World Malaria Report 2018

Current investment is insufficient with significantly less per person at risk invested now than previously

Bending the curve

Alternative strategies and targeting transmission

Malaria infections: The more you look the more you see...

• Large number of studies (n~300) reporting infections beneath the limit of microscopy and latterly RDT

• Nucleic acid amplification tests (NAAT) such as PCR detect at least twice as many infections as microscopy or RDT

• Sensitivity of microscopy increases with P0 prevalence

Whittaker et al under review

Malaria infections: Submicroscopic infections and age

Microscopy

RDT 5% 5-20% 20-50%

Both RDT and microscopy show more discordance at lower transmission levels


Malaria infections

• Do we understand enough about natural infections and their infectivity?

• Symptomatic - readily detectable with concurrent symptoms

• Asymptomatic - no symptoms at the time of sampling
  • Patent/detectable by RDT or microscopy (~100 parasites/ul)
  • Subpatent/submicroscopic - infections that are below the limit of detection of conventional diagnostics

Malaria infections: submicroscopic infections and transmission level

Microscopy

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Malaria transmission: gametocytes

- The vast majority of asymptomatic infections have gametocytes
- Specifically detecting gametocytes may have limited utility
- Gametocyte density loosely associated with asexual parasitaemia
- Gametocyte densities highest in younger age groups

Malaria Transmission: assessing infectiousness to mosquitoes

- Measurement of infectiousness is typically done using mosquito feeding experiments
- Colony (or rarely F1) mosquitoes fed on blood from potentially infectious individuals
- Mosquitoes dissected 7 days later for presence of infection
- Because of the relative logistical complexity these studies are comparatively rare and on small numbers of samples.

Malaria transmission: gamectocyte density & infection

- Many submicroscopic gametocyte carriers infect mosquitoes
- Infection rates increase above ~5 gametocytes/µL
- Estimating male and female gametocytes improves prediction of infection rates
- Deviation from the best fit association is indication of reduced infectivity (immunity & drugs)

Malaria transmission: Sex & Drugs

- Antimalarial drugs have varying effects on gametocytes
- ACT have marked effect
- Methylene blue appears to affect male gametocytes and Primaquine females

The infectious reservoir of malaria

Do submicroscopic infections contribute to the infectious reservoir?
Malaria transmission: historical reservoir estimates

- Cross sectional surveys in wet and dry season with mosquito feeding (Burkina Faso, Kenya)
- Assessments of natural mosquito biting rates

Goncalves et al. Nature Comm 2017
Guelbeogo et al. Elife 2018

Malaria transmission: recent reservoir estimates

- Cross sectional surveys in wet and dry season with mosquito feeding (Burkina Faso, Kenya)
- Assessments of natural mosquito biting rates

Malaria transmission: questions remain...

- More data are needed from low endemic sites (ideally combined with transmission networks at molecular level)
- Longitudinal data on parasite kinetics and infectiousness of natural infections remain limited
- Whilst mosquito biting is higher in adults there are significant variations within household and between season
- Variability in transmissibility of parasite clones
- Laboratory data suggest mosquitoes with more oocysts are more infectious

Malaria transmission: natural infection dynamics - modelled

Transmission reduction: Do we need to target the reservoir?

No
- Submicroscopic infections infect mosquitoes infrequently
- Data from SE Asia suggest clinical cases considerably more infectious than low density
- Settings eliminating without specifically targeting
- Improving/enhancing case management seems to have significant effect on transmission in some settings

Yes
- Low density infections are still infectious and predominate in some settings
- High density asymptomatic infections in African settings
- Elimination in mainly low endemic with historically low transmission
- Case management alone may not reduce all transmission and/or sufficiently rapidly
- Drug resistance
Transmission reduction: what can we do?

- How can the information on parasite carriage and infectivity be used at programme level?
- What effects do different control approaches have on parasite densities, carriage, age distribution and the infectious reservoir?
- Is targeting clinical infections at clinics sufficient?
- Mild symptoms commonly occur upon infection can these be detected with enhanced community case management before gametocytes arise?
- Infections that are initially asymptomatic and missed by CCM maybe detected/removed by screening and treatment?
- Infections need to be treated/cleared (MDA) such that new infections illicit symptoms?

Transmission reduction: Targeting everyone

- Zambia - 3 rounds of MDA (DHA-P) delivered in 30 health facility catchment areas
- Mass drug administration shown to be effective reducing prevalence and incidence
- Questions around cost/coverage/sustainability
- New HSRDT may change this profoundly and make MDA a more viable option

Transmission reduction: demographic targeting

- SMC with SP/AQ in Senegal
- Effects on incidence and parasite prevalence when age range extended
- School based intervention in Uganda
- Significant reduction in prevalence in individuals in environs of treated schools

Transmission reduction: Targeting symptomatics

- Effective case management to catch infections early but will depend on the ratio between symptomatic/asymptomatics
- 21 villages in Northern Cambodia compared clinic derived incidence and community prevalence
- Surveys identified a number of villages with significant infections not detected by CCM
- Requires detailed epidemiological surveillance & stratification

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The reservoir: finding the right analogy

Targeting the reservoir

• What is the imperative to target the reservoir?
• What is the capacity to target the reservoir?

Now it is to these gametocytes that an extreme interest attaches, because it is to them, that we owe the solution of the malaria problem.”

Sir Ronald Ross, 1900
Malaria and mosquitoes
Nature. Vol 61(1587)
p.523

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