Slide 1

Malaria Transmission:

When a little is Enough

Chris Drakeley
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LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

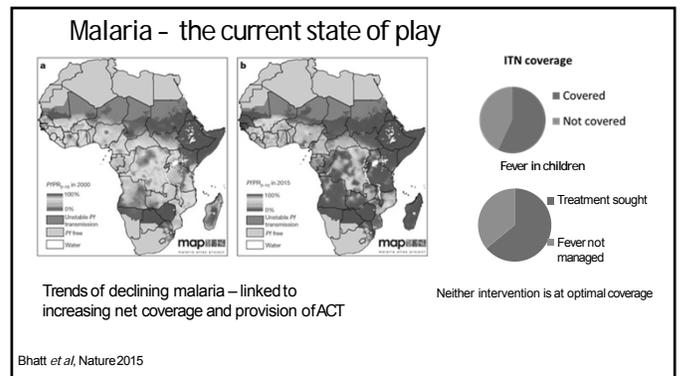Malaria centre

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Disclaimer

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Slide 3

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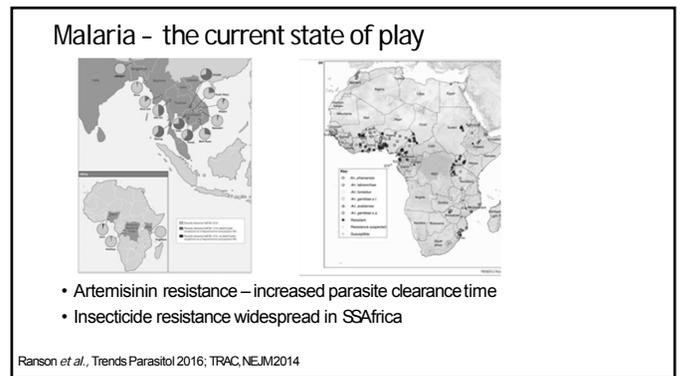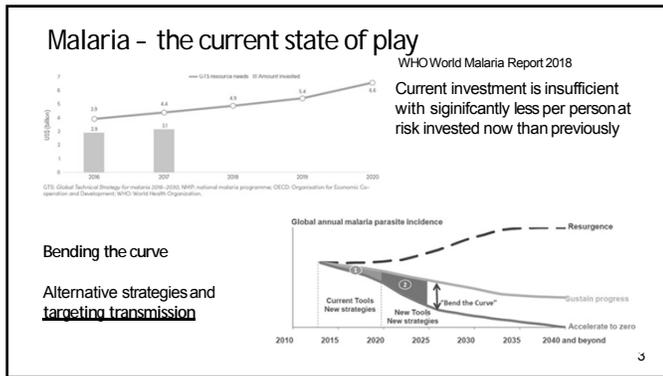- Transmission reduction – targeting infectivity
- Conclusions

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Malaria – the current state of play

ITN coverage
- Covered
- Not covered

Fever in children
- Treatment sought
- Fever not managed

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

Neither intervention is at optimal coverage

Bhatt *et al*, Nature 2015

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Malaria – the current state of play

- Artemisinin resistance – increased parasite clearance time
- Insecticide resistance widespread in SS Africa

Ranson *et al.*, Trends Parasitol 2016; TRAC, NEJM 2014

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Malaria – the current state of play

WHO World Malaria Report 2018

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

GTS :Global Technical Strategy for malaria 2016–2030; NMAP: national malaria programme; OECD: Organisation for Economic Co-operation and Development; WHO: World Health Organization.

Bending the curve

Alternative strategies and <u>targeting transmission</u>

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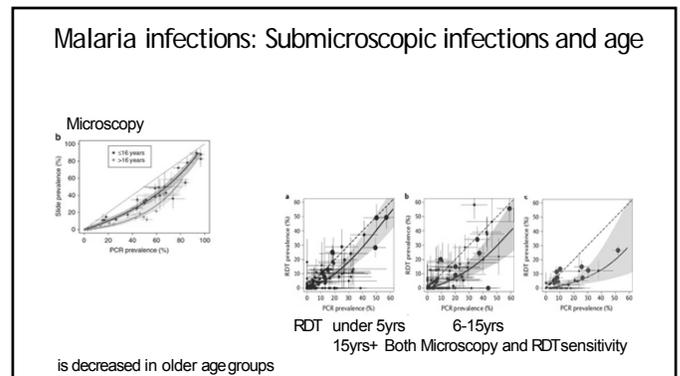### Malaria infections: The more you look the more you see...

- 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 PCR prevalence
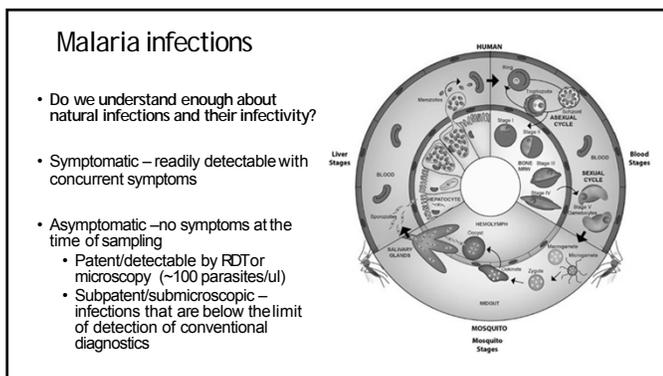
Whittaker et al *under review*

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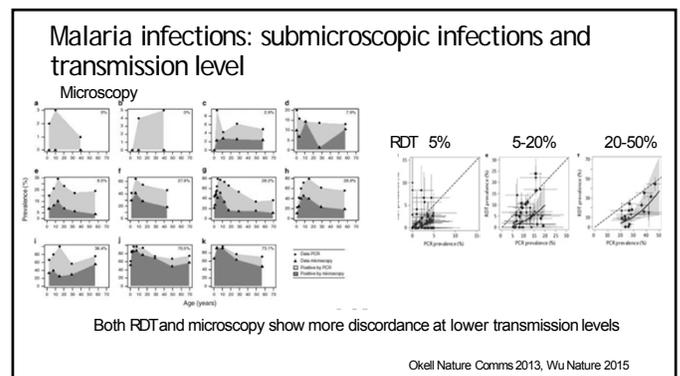- Transmission reduction – targeting infectivity
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Malaria infections: Submicroscopic infections and age

Microscopy

RDT   under 5yrs   6-15yrs

15yrs+ Both Microscopy and RDT sensitivity

is decreased in older age groups

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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

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Malaria infections: submicroscopic infections and transmission level

Microscopy

RDT 5%   5-20%   20-50%

Both RDT and microscopy show more discordance at lower transmission levels

Okell Nature Comms 2013, Wu Nature 2015

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Malaria Transmission: gametocyte 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)

Goncalves et al, Nature Comm 2017; Bradley *et al*. eLife 2018

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Malaria transmission: gametocytes

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

The epidemiology of *Plasmodium falciparum* gametocytes: weapons of mass dispersion

Chris Drakeley[1], Colin Sutherland[1], J. Teun Bousema[2], Robert W. Sauerwein[2] and Geoffrey A.T. Targett[1]

WWARN, BMC Med 2016;
Goncalves et al, Nature Comm 2017

AFRICA

ASIA

Parasites/μl   Haemoglobin g/dL

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Malaria transmission: Sex & Drugs

- Antimalarial drugs have varying effects on gametocytes
- ACT have marked effect

Drug(s)*	Median gametocyte prevalence (% [IQR]) on day 7 for those who were gametocyte free on day 0	Median gametocyte prevalence (% [IQR]) for those who were gametocyte carriers on day 0	
		Day 7	Day 14
Non-ACT drugs			
CQ	35 (26–44)	76 (67–88)	60 (43–83)
SP	55 (47–62)	87.2 (78.3–97.5)	71.4 (54.0–83.0)
AQ	15 (8–23)	69 (58–74)	37 (22–46)
SP + CQ	39 (38–44)	89 (58–100)	60 (33–74)
SP + AQ	10 (7–19)	56 (33–78)	33 (24–43)
ACT regimens			
SP + AS	8 (5–18)	38 (25–60)	18 (17–75)
AQ + AS	5 (0–13)	35 (30–40)	13 (0–41)
MQ + AS	1 (1–3)	13 (3–30)	1 (0–9)
AL	2 (1–4)	20 (18–41)	16 (4–19)
DHA-PPQ	4 (3–5)	33 (15–49)	23 (17–26)
ACT-PQ regimens			
SP + AS + PQ	0 (0–0)	20 (0–40)	0 (0–0)

Methylene blue appears to affect male gametocytes and Primaquine females

Bousema CMR 2011, Roh Lancet ID 2018

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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.

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The infectious reservoir of malaria

Do submicroscopic infections contribute to the infectious reservoir ?

Stone *et al*. Trends Parasitol 2017

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Malaria transmission: historical reservoir estimates

Table 1. Summary of studies assessing the malaria infectious reservoir where recruitment was conducted without regard for parasite status[a]
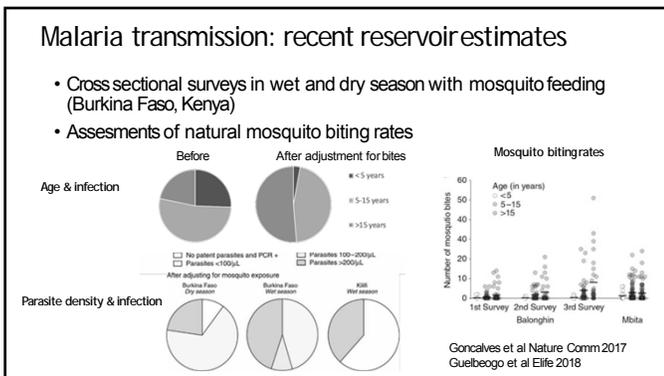
Study location	Local transmission setting	Feeding method	Assay end point[a]	Species	Prevalence of infectiousness (%)[a]	Proportional contribution to reservoir by age group (%)[a]				Mosquito infection probability[a]	Refs
						1–4	5–9	10–19	≥20		
Papua New Guinea	Moderate perennial	Direct and membrane	Oocysts	Anopheles farauti	3.8	22.7	32.9	30.3	14.2	0.013	[19]
						1–4	5–14	≥15			
Liberia	Intense perennial	Direct	Oocysts	Anopheles gambiae	10.6	40.5	28.4	31.1		0.023	[16]
Kenya	Intense perennial	Direct	Oocysts and CSP ELISA	A. gambiae	10.1	23.2	36.1	40.7		0.010	[17]
Burkina Faso	Intense seasonal	Membrane	Oocysts	A. gambiae	48.0	ND[†]	39.7	60.3		0.055	[77]
Cameroon (Bondi)	Intense seasonal	Direct	Oocysts	A. gambiae	7.4	28.8	49.2	21.9		0.024	[18]
Cameroon (Mengang)	Intense seasonal	Direct	Oocysts	A. gambiae	8.2	34.7	33.9	31.4		0.011	[18]
Senegal	Low, unstable	Direct	Oocysts	Anopheles arabiensis	8.7	ND[†]	51.8	48.2		0.002	[32]

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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

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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

Goncalves et al Nature Comm 2017
Guelbeogo et al Elife 2018

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Malaria transmission: natural infection dynamics - modelled

Drakeley et al, Malaria Elimination INTECH 2018
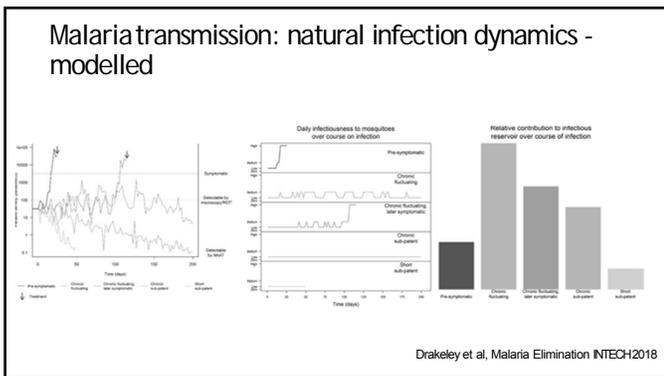
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Transmission reduction: Do we need to target the reservoir?

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

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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 is 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 may be detected/removed by screening and treatment?
- Infections need to be treated/cleared (MDA) such that new infections ilicit symptoms?

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Transmission reduction: Targeting everyone

Table 3. Cumulative Malaria Infection Incidence by RDT Among Individuals ≥3 Months Old in Cohort Households Followed Up Monthly From December 2014 to May 2015

- 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 HS-RDT may change this profoundly and make MSAT a more viable option

Eisele, JID 2016

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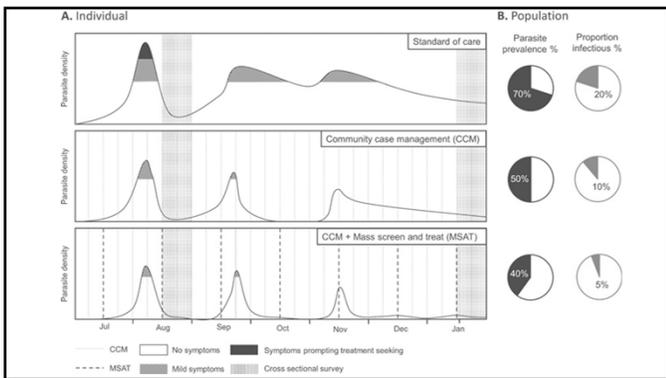
Transmission reduction: demographic targeting

- SMC with SP-AQ in Senegal
- Effects on incidence and parasite prevalence when age range extended

- School based in intervention in Uganda
- Significant reduction in prevalence in individuals in environs of treated schools

Cisse et ak 2017, Staedke et al 2018

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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 significant infections not detected by CM

Requires detailed epidemiological surveillance & stratification

Falq Malaria Journal 2016

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The reservoir- finding the right analogy

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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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Thanks to…

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