Ivermectin for malaria elimination: 2016, a year of exponential growth

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Outline

- High-level assessments
- Insectary-based work
- Clinical trials
- Antimalarial effect?
- Formulations
- Veterinary use
- Ongoing work
- Priorities and critical milestones

High-level assessments

Malaria Policy Advisory Committee Meeting
14–16 September 2016, Geneva, Switzerland
Background document for Session 9

World Health Organization

Ivermectin for malaria transmission control

Technical consultation meeting report
WHO Headquarters, Geneva 30 March–1 April 2016

- **Technical consultation:**

  "Ivermectin for malaria transmission control"

  - Define the key missing data to make a policy recommendation through
  - Development of a target product profile (TPP) for ivermectin as a tool to reduce malaria transmission.

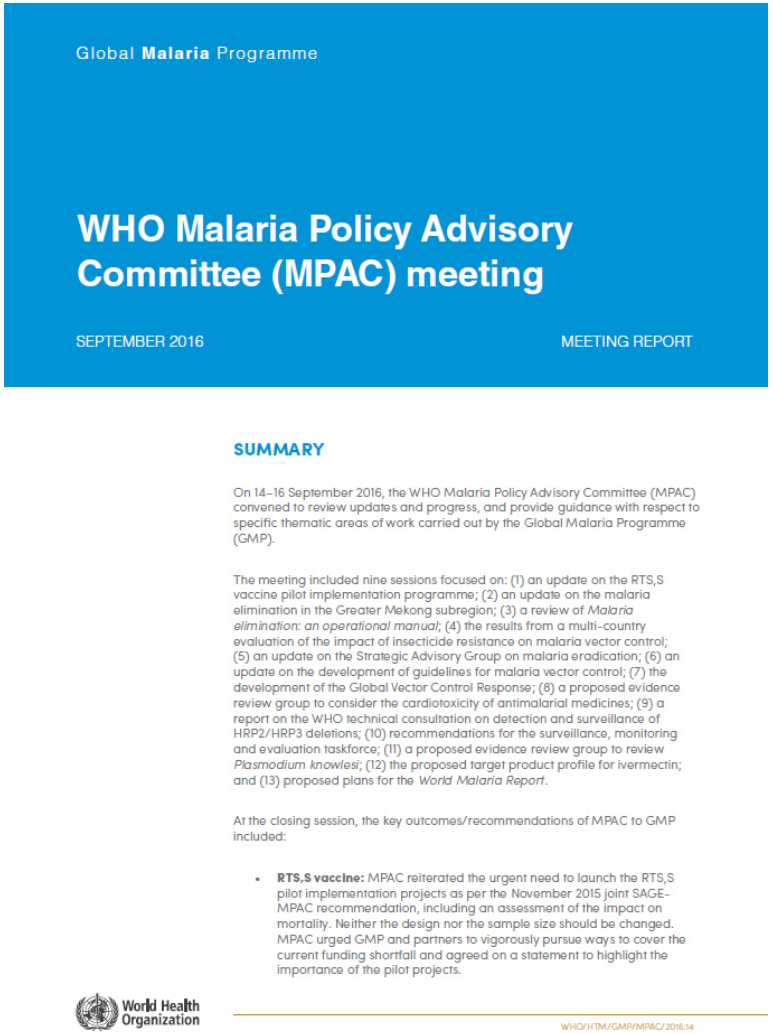
High-level assessments

Efficacy	Desired	Minimally acceptable
In combination with an ACT and core vector control interventions *(Target product antimalarial + ivermectin)*	A significant reduction in incidence of clinical malaria 12 months after a single intervention in combination with ACT MDA and core vector control measures	A significant reduction in infection incidence 12 months after three interventions given at monthly intervals in combination with an ACT MDA and core vector control measures
Stand-alone insecticide *(ivermectin as a target candidate)*	At least 20% reduction in the incidence of clinical malaria, lasting for at least 1 month after a single round of MDA irrespective of baseline transmission levels	*In areas of moderate to high transmission:* At least 20% reduction in the infection incidence in children under 5, lasting for at least 1 month following a single regimen *In areas of low transmission:* A significant reduction in infection incidence, lasting for at least 1 month following a single regimen

- Background document + draft TPP

High-level assessments

- Presented to MPAC (September 2016)
- Feedback on TPP
- TPP as objective NOT recommendation
- Review and re-submit



Global **Malaria** Programme

WHO Malaria Policy Advisory Committee (MPAC) meeting

SEPTEMBER 2016 MEETING REPORT

SUMMARY

On 14–16 September 2016, the WHO Malaria Policy Advisory Committee (MPAC) convened to review updates and progress, and provide guidance with respect to specific thematic areas of work carried out by the Global Malaria Programme (GMP).

The meeting included nine sessions focused on: (1) an update on the RTS,S vaccine pilot implementation programme; (2) an update on the malaria elimination in the Greater Mekong subregion; (3) a review of *Malaria elimination: an operational manual*; (4) the results from a multi-country evaluation of the impact of insecticide resistance on malaria vector control; (5) an update on the Strategic Advisory Group on malaria eradication; (6) an update on the development of guidelines for malaria vector control; (7) the development of the Global Vector Control Response; (8) a proposed evidence review group to consider the cardiotoxicity of antimalarial medicines; (9) a report on the WHO technical consultation on detection and surveillance of HRP2/HRP3 deletions; (10) recommendations for the surveillance, monitoring and evaluation taskforce; (11) a proposed evidence review group to review *Plasmodium knowlesi*; (12) the proposed target product profile for ivermectin; and (13) proposed plans for the *World Malaria Report*.

At the closing session, the key outcomes/recommendations of MPAC to GMP included:

- **RTS,S vaccine:** MPAC reiterated the urgent need to launch the RTS,S pilot implementation projects as per the November 2015 joint SAGE-MPAC recommendation, including an assessment of the impact on mortality. Neither the design nor the sample size should be changed. MPAC urged GMP and partners to vigorously pursue ways to cover the current funding shortfall and agreed on a statement to highlight the importance of the pilot projects.

World Health Organization

WHO/HTM/GMP/MPAC/2016.14

High-level assessments

- **malERA refresh**

MALARIA ERADICATION SCIENTIFIC ALLIANCE

- Panel “Diagnostics, drugs, vaccines and vector control in malaria elimination and eradication”

High-level assessments

Medicines for Malaria Venture

- **New developments in TC and TPP**
- TCP-6 (Endectocides)

Burrows et al. Malar J (2017) 16:26
DOI 10.1186/s12936-016-1675-x

Malaria Journal

REVIEW Open Access

New developments in anti-malarial target candidate and product profiles

Jeremy N. Burrows[1], Stephan Duparc[1], Winston E. Gutteridge[2], Rob Hooft van Huijsduijnen[1], Wiweka Kaszubska[1], Fiona Macintyre[1], Sébastien Mazzuri[3], Jörg J. Möhrle[1] and Timothy N. C. Wells[1*]

Recent and ongoing work

MESA Track

MESA Track is a living database which captures research projects and institutions' research portfolios in malaria elimination and eradication.

Please, reach out to become part of MESA Track. Read about MESA Track methodology.

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Insectary-based work

- *Anopheles aquasalis (LC50~ 47 ng/ml)*
- *Anopheles darlingi (poster at ASTMH)*

Sampaio *et al. Malar J (2016) 15:491*
DOI 10.1186/s12936-016-1540-y

Malaria Journal

RESEARCH Open Access

Filling gaps on ivermectin knowledge: effects on the survival and reproduction of *Anopheles aquasalis*, a Latin American malaria vector

Vanderson S. Sampaio[1,2,3*], Tatiana P. Beltrán[1,2], Kevin C. Kobylinski[4], Gisely C. Melo[2], José B. P. Lima[5], Sara G. M. Silva[1], Íria C. Rodriguez[1], Henrique Silveira[1,6], Maria G. V. B. Guerra[1,2], Quique Bassat[7,8], Paulo F. P. Pimenta[1,9], Marcus V. G. Lacerda[1,10] and Wuelton M. Monteiro[1,2]

Insectary-based work

- *Anopheles dirus (LC50~ 55 ng/ml)*
- *Anopheles minimus (LC50~ 12 ng/ml)*
- *Anopheles sawadwongporni (LC50~ 25 ng/ml)*
- *Anopheles campestris (LC50~ 25 ng/ml)*

Data from Kobylinski presented at ASTMH

Clinical trials

IVERMAL

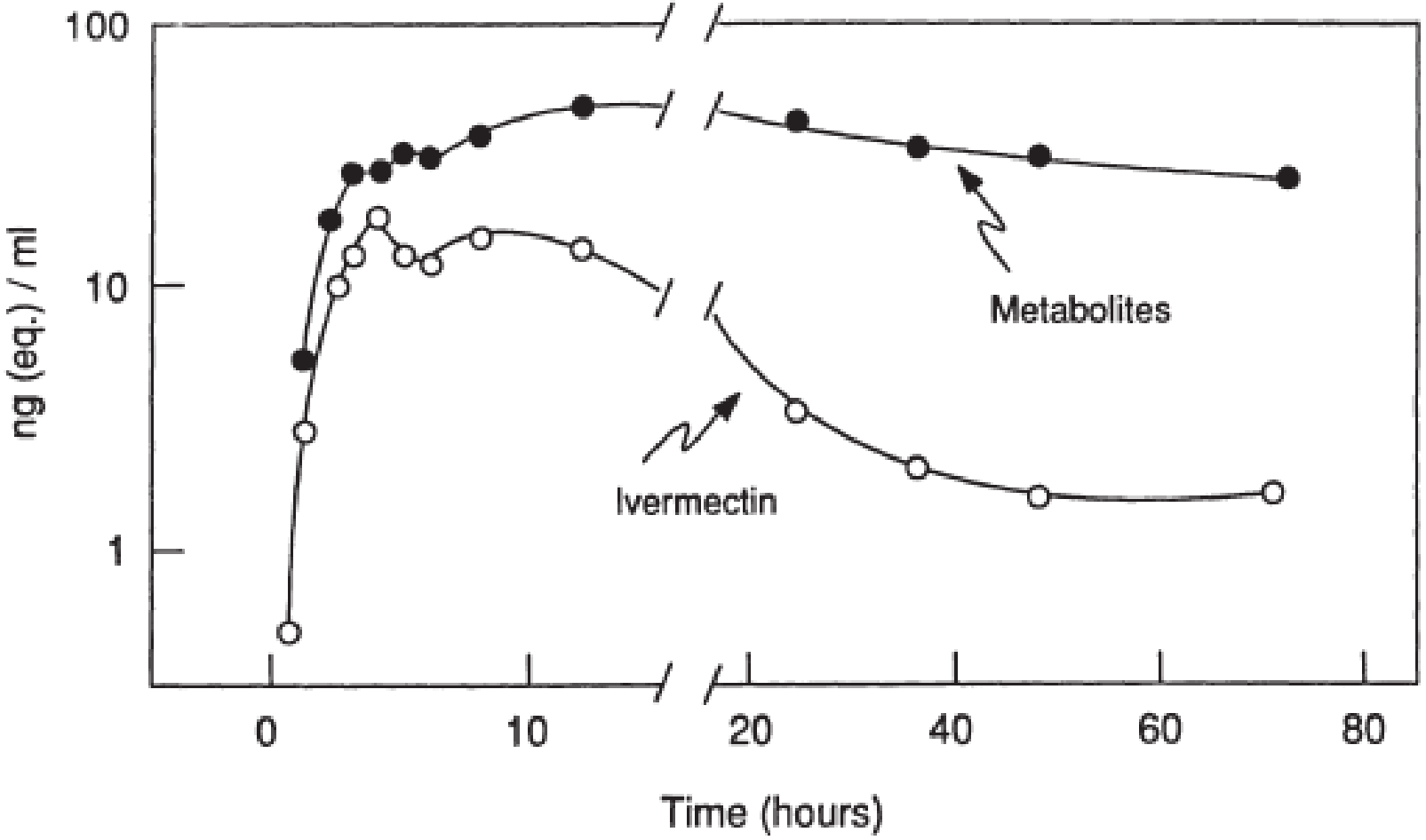
JMIR RESEARCH PROTOCOLS Smit et al

Protocol

Efficacy and Safety of High-Dose Ivermectin for Reducing Malaria Transmission (IVERMAL): Protocol for a Double-Blind, Randomized, Placebo-Controlled, Dose-Finding Trial in Western Kenya

Menno R Smit[1], MD, MPH; Eric Ochomo[2], PhD; Ghaith Aljayyoussi[1], PhD; Titus Kwambai[2,3], MSc, MD; Bernard Abong'o[2], MSc; Nabie Bayoh[4], PhD; John Gimnig[4], PhD; Aaron Samuels[4], MHS, MD; Meghna Desai[4], MPH, PhD; Penelope A Phillips-Howard[1], PhD; Simon Kariuki[2], PhD; Duolao Wang[1], PhD; Steve Ward[1], PhD; Feiko O ter Kuile[1], MD, PhD

- Protocol published
- Part of results presented at ASTMH (M. Smit)
  - No adverse events in combination with DHA-PIP
  - No adverse events at 600 mcg/kg x 3
  - Measurable effect for 28 days
  - Effect longer than drug in plasma (metabolites)



Fink & Porras 1989

Clinical trials

RIMDAMAL

- Part of results presented at ASTMH (B. Foy)
  - Cluster-randomized trial
  - 200 mcg/kg every three weeks x 6 doses
  - Intervention in >5s outcome in < 5s
  - 20% incidence reduction (<5s) by ACD
  - 50% in some groups

Clinical trials

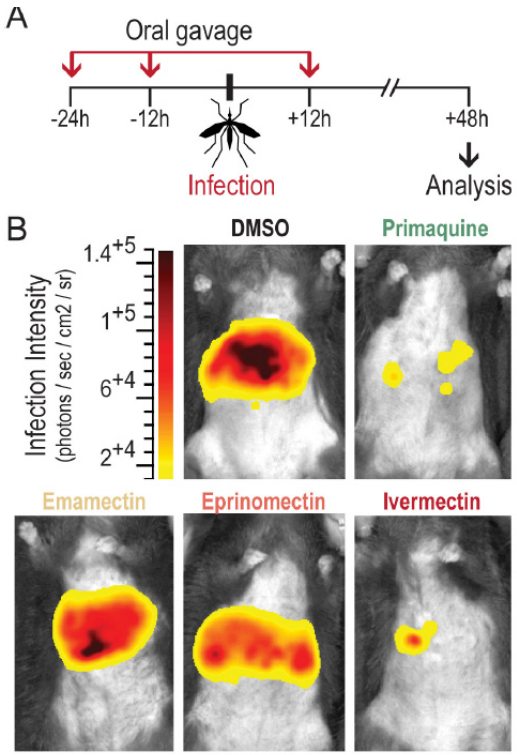
IMSEA

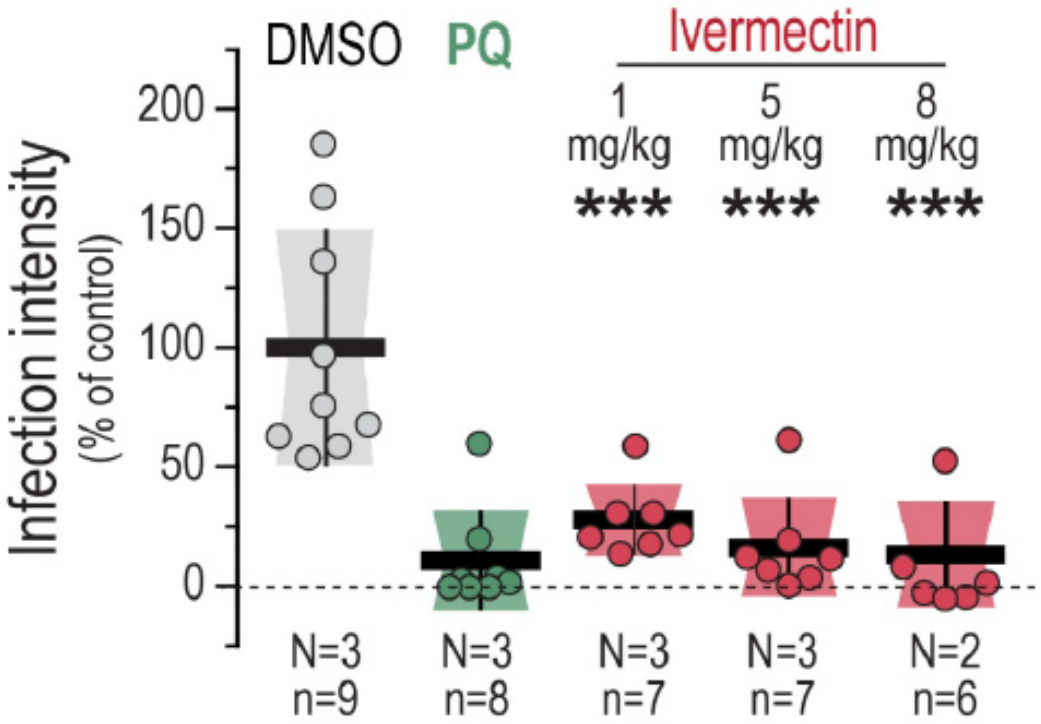
- Part of results presented at ASTMH (Kobylinski)
  - 16 volunteers
  - 7 sequencial treatments
  - IVM+DHA-PQP+PQ+ABZ
  - Safety
  - Mosquito mortality

Antimalaria effect

Inhibition of *Plasmodium* liver infection by ivermectin

Mendes et al. AAC. Nov 2016

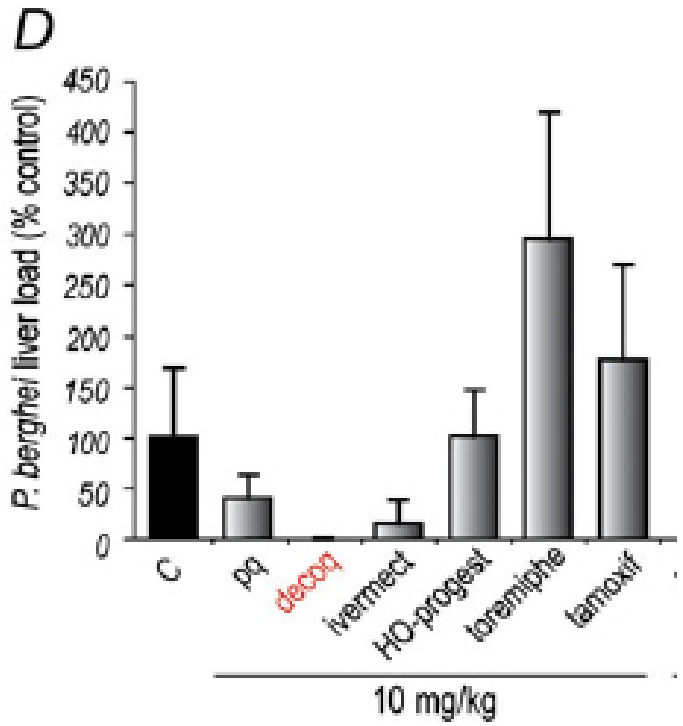




Antimalaria effect

Ivermectin and *Plasmodium*

Da Cruz et al. JID. Apr 2012



MAJOR ARTICLE

Drug Screen Targeted at *Plasmodium* Liver Stages Identifies a Potent Multistage Antimalarial Drug

Filipa P. da Cruz,[1] Cécilie Martin,[2] Kathrin Buchholz,[3] Maria J. Lafuente-Monasterio,[4] Tiago Rodrigues,[5] Birte Sönnichsen,[2] Rui Moreira,[6] Francisco-Javier Gamo,[4] Matthias Marti,[3] Maria M. Mota,[1] Michael Hannus,[2] and Miguel Prudêncio[1]

[1]Instituto de Medicina Molecular, Faculdade de Medicina, Universidade de Lisboa, Portugal, and [2]Cenix BioScience GmbH, Dresden, Germany; [3]Department of Immunology and Infectious Diseases, Harvard School of Public Health, Boston, Massachusetts; [4]Tres Cantos Medicine Development Campus, Diseases of the Developing World, GlaxoSmithKline, Tres Cantos, Madrid, Spain; [5]Department of Chemistry and Applied Biosciences, Institute of Pharmaceutical Sciences, ETH Zürich, Switzerland; and [6]iMed.UL, Faculdade de Farmácia, Universidade de Lisboa, Portugal

Formulations

Bellinger et al. Science translational medicine. Nov 2016

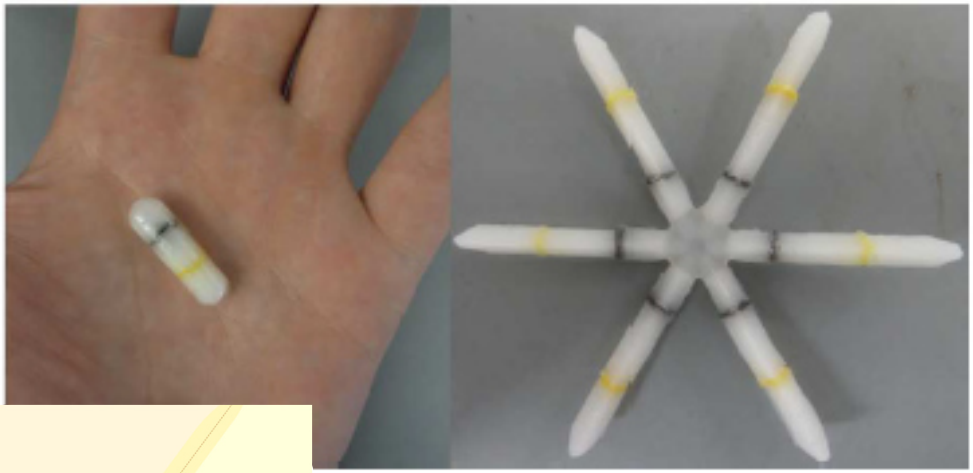
SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

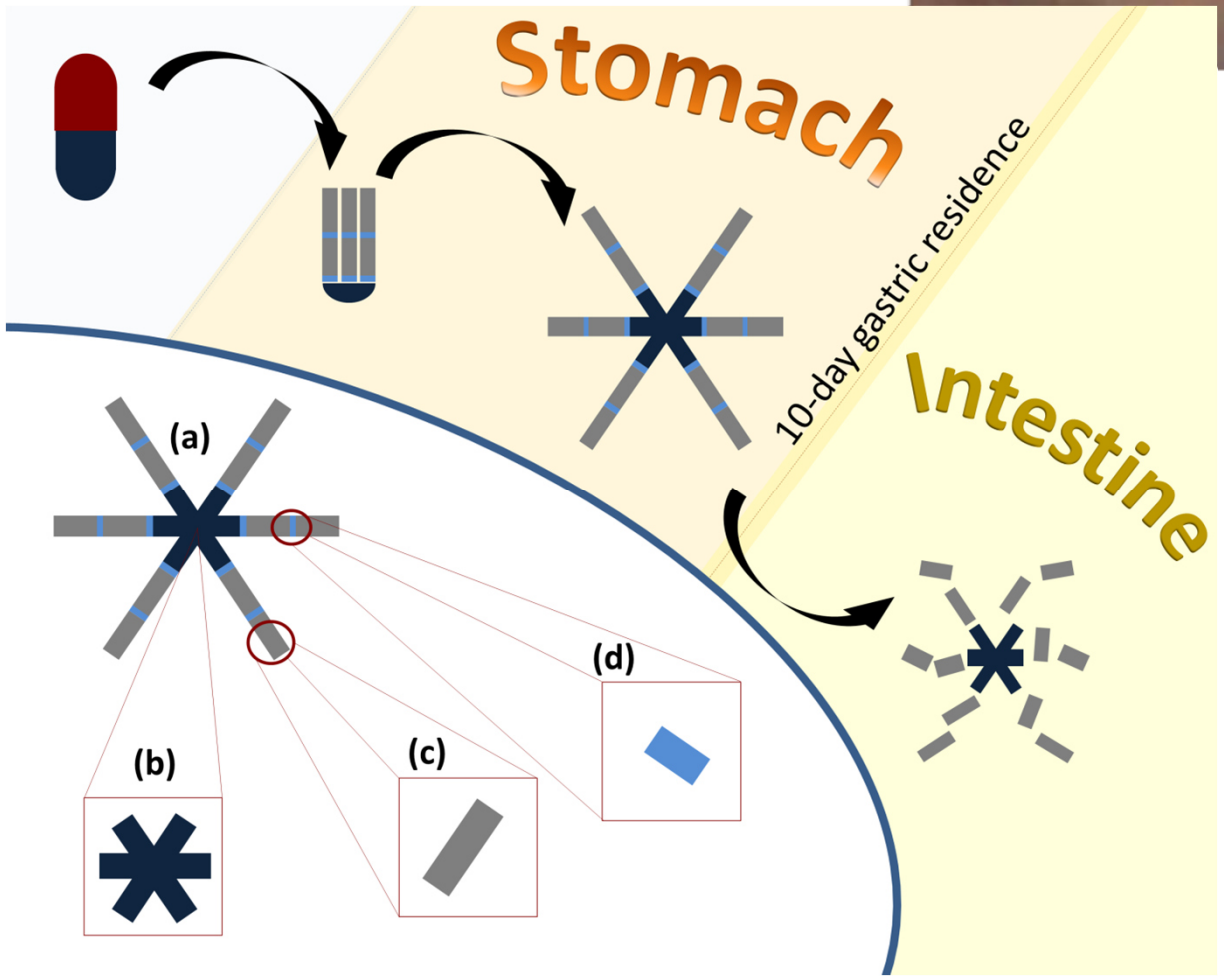
DRUG DELIVERY

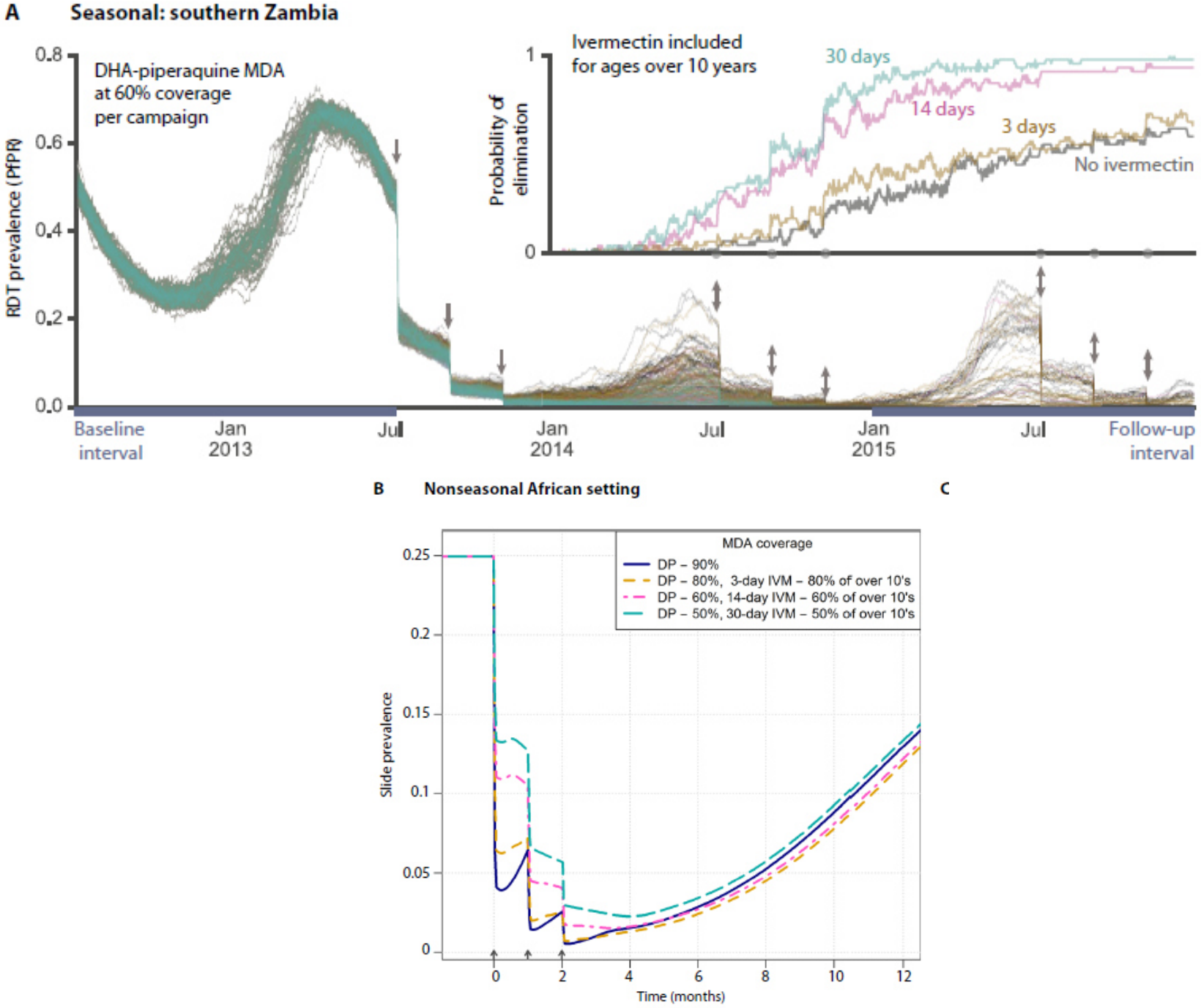
Oral, ultra–long-lasting drug delivery: Application toward malaria elimination goals

Andrew M. Bellinger,[1,2,3]* Mousa Jafari,[1]* Tyler M. Grant,[1,3]* Shiyi Zhang,[1]*† Hannah C. Slater,[4] Edward A. Wenger,[5] Stacy Mo,[1] Young-Ah Lucy Lee,[1] Hormoz Mazdiyasni,[1] Lawrence Kogan,[1] Ross Barman,[1] Cody Cleveland,[1,6] Lucas Booth,[1] Taylor Bensel,[1] Daniel Minahan,[1] Haley M. Hurowitz,[1] Tammy Tai,[1] Johanna Daily,[7] Boris Nikolic,[8] Lowell Wood,[5] Philip A. Eckhoff,[5] Robert Langer,[1,9,10]‡ Giovanni Traverso[1,6,11]‡

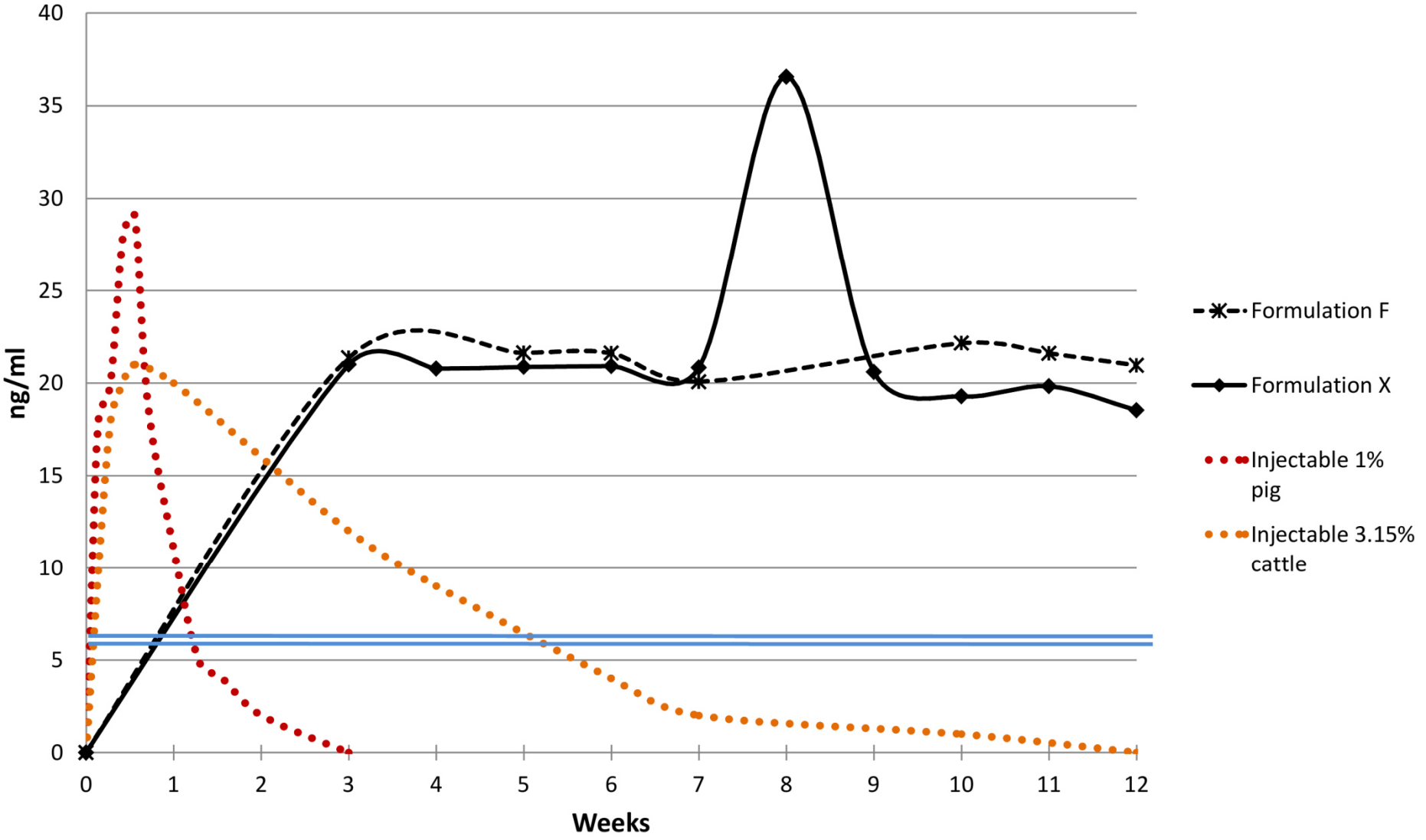
Formulations






A
Seasonal: southern Zambia
DHA-piperaquine MDA
at 60% coverage
per campaign
RDT prevalence (PfPR)
0.8
0.6
0.4
0.2
0.0
Ivermectin included
for ages over 10 years
Probability of elimination
1
0
30 days
14 days
3 days
No ivermectin
Baseline interval
Jan 2013
Jul
Jan 2014
Jul
Jan 2015
Jul
Follow-up interval
B
Nonseasonal African setting
C
MDA coverage
DP – 90%
DP – 80%, 3-day IVM – 80% of over 10's
DP – 60%, 14-day IVM – 60% of over 10's
DP – 50%, 30-day IVM – 50% of over 10's
Slide prevalence
0.25
0.2
0.15
0.1
0.05
0
0
2
4
6
8
10
12
Time (months)

Formulations



Chaccour et al. AAC. 2016

Formulations

- A new dosing paradigm?
- Weight-based dosing – veterinary
- Hampers combinations / co-formulations

- New 18/36 mg tablets
  - Not just a bigger tablet
  - Dose range vs fixed dose

Veterinary use

RESEARCH Open Access

Administration of ivermectin to peridomestic cattle: a promising approach to target the residual transmission of human malaria

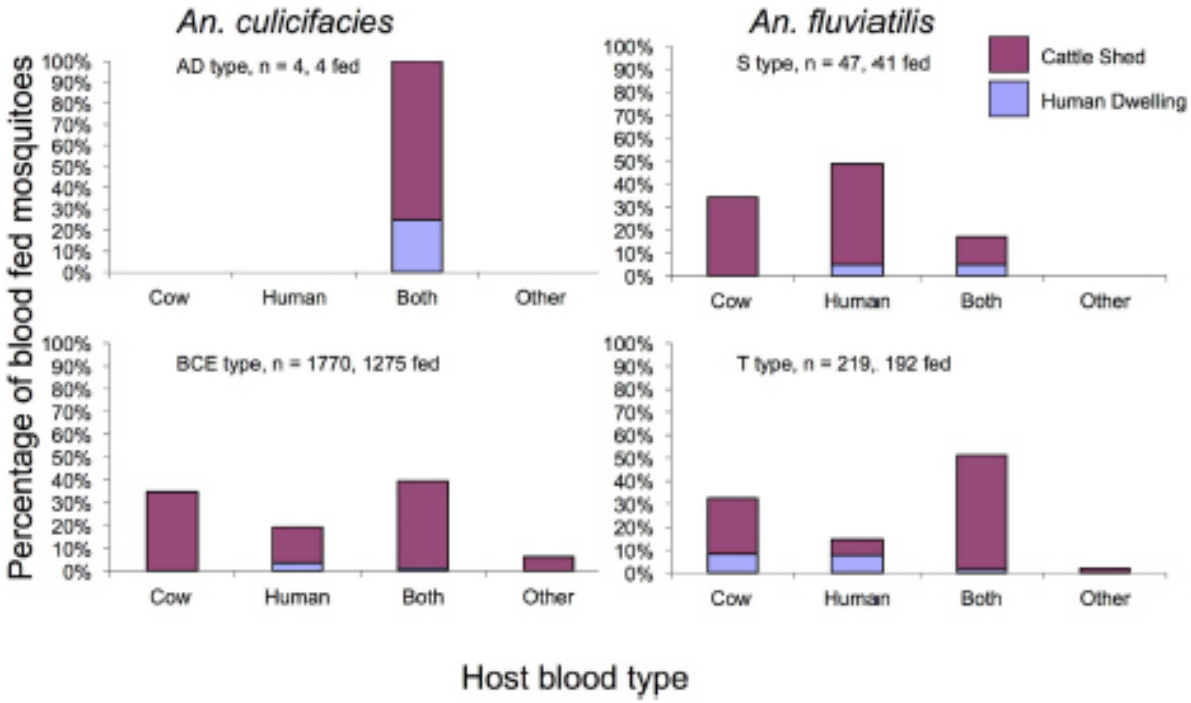
Hermann S. Pooda[1,2,5*], Jean-Baptiste Rayaisse[1], Domonbabele François de Sale Hien[3], Thierry Lefèvre[3,4], Serge R. Yerbanga[3], Zakaria Bengaly[1], Roch K. Dabiré[3], Adrien M. G. Belem[5], Issa Sidibé[1,2], Philippe Solano[6] and Karine Mouline[3,4]

RESEARCH Open Access

Treatment of livestock with systemic insecticides for control of *Anopheles arabiensis* in western Kenya

Richard M. Poché*, Dylan Burruss, Larisa Polyakova, David M. Poché and Rajesh B. Garlapati

Veterinary use



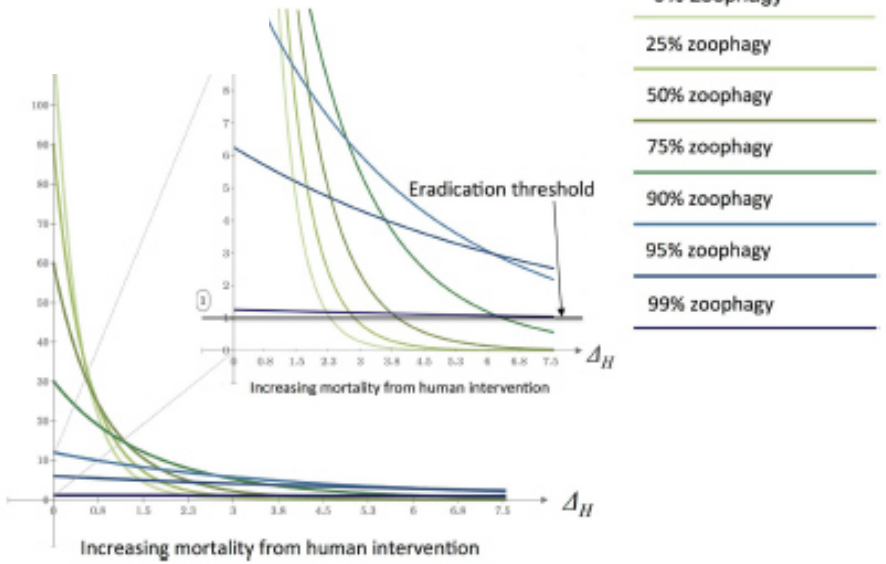
SCIENTIFIC REPORTS

OPEN

Increasing the potential for malaria elimination by targeting zoophilic vectors

Received: 31 August 2016
Accepted: 07 December 2016

Jessica L. Waite[1,*], Sunita Swain[2,*], Penelope A. Lynch[3,*], S. K. Sharma[4], Mohammed Asrarul Haque[2], Jacqui Montgomery[5] & Matthew B. Thomas[1]



Veterinary use

Njoroge *et al. Parasites & Vectors* (2017) 10:18
DOI 10.1186/s13071-016-1957-8

Parasites & Vectors

RESEARCH Open Access

Exploring the potential of using cattle for malaria vector surveillance and control: a pilot study in western Kenya

Margaret M. Njoroge[1*], Inaki Tirados[2], Steven W. Lindsay[3], Glyn A. Vale[4], Stephen J. Torr[2,5] and Ulrike Fillinger[1]

Ongoing work

- Modelling based on new data
- Pharmacoenhancement and Synergism
- Congressionally Directed Medical Research Program (> US$ 6.900.000)

Priorities

- Technical
  - PK gaps - dosing
  - Metabolites
  - Other endectocides
- Study design
  - Outcomes and size
- Regulatory & Policy
  - A sponsor?
  - Path forward

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