Rectal artesunate: lives not saved?

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wellcome

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Tropical Health Network

32 years ago.....

TRANSACTIONS OF THE ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE (1992) **86**, 582–583

Comparison of artemisinin suppositories with intravenous artesunate and intravenous quinine in the treatment of cerebral malaria

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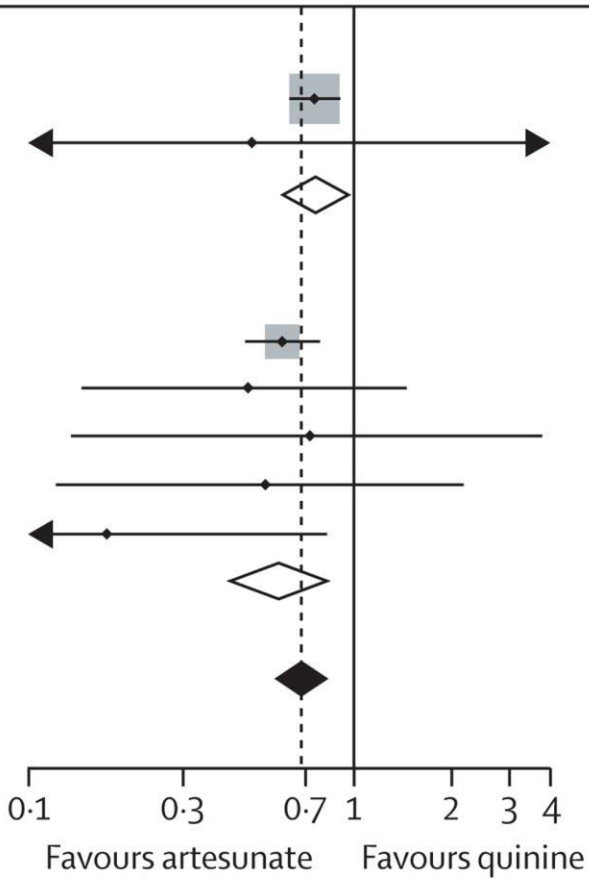
Abstract

Seventy-nine comatose cerebral malaria patients given standard supportive treatment were randomized to receive specific antimalarial chemotherapy of intravenous quinine, intravenous artesunate, or artemisinin suppositories. Artesunate and artemisinin reduced peripheral asexual parasitaemia significantly more rapidly than quinine (90% clearance time 16 h, 18·9 h and 34·5 h respectively), but did not significantly reduce the duration of coma or mortality. The rapid lowering of peripheral parasitaemia may not ameliorate complications already present. These results demonstrate that artemisinin suppositories are as effective as artesunate and quinine given intravenously, and have economic and practical advantages for the treatment of severe malaria in areas remote from major medical centres. However, large numbers of patients will need to be studied if differences in mortality between the 3 treatment groups are to be demonstrated.

Development of rectal artesunate starts in late

Artesunate is the best treatment for severe malaria

	Artesunate	Quinine	OR (95% CI)*; p value
Africa			
AQUAMAT 2010	230/2712 (8·5%)	297/2713 (10·9%)	0·75 (0·63–0·90); 0·002
Sudan (2010)[16]	1/33 (3%)	2/33 (6·1%)	0·48 (0·01–9·85); 0·56
Subtotal (test for heterogeneity: χ^2=0·06, df=1, p=0·81)			**0·75 (0·59–0·95); 0·002**
Asia			
SEAQUAMAT (2005)[7]	107/730 (14·7%)	164/731 (22·4%)	0·60 (0·45–0·79); 0·0002
Thailand (2003)[15]	7/59 (11·9%)	12/54 (22·2%)	0·47 (0·14–1·44); 0·14
Vietnam (1997)[14]	4/37 (10·8%)	5/35 (14·3%)	0·73 (0·13–3·75); 0·66
Vietnam (1992)[13]	5/31 (16·1%)	8/30 (26·7%)	0·53 (0·12–2·17); 0·32
Burma (1992)[12]	2/24 (8·3%)	23/67 (34·3%)	0·17 (0·02–0·83); 0·02
Subtotal (test for heterogeneity: χ^2=1·80, df=4, p=0·77)			**0·58 (0·41–0·81); 0·00005**
Overall (test for heterogeneity: χ^2=4·51, df=6, p=0·61)			**0·69 (0·57–0·84); <0·00001**
Heterogeneity between continents: χ^2=2·65, df=1, p=0·10			

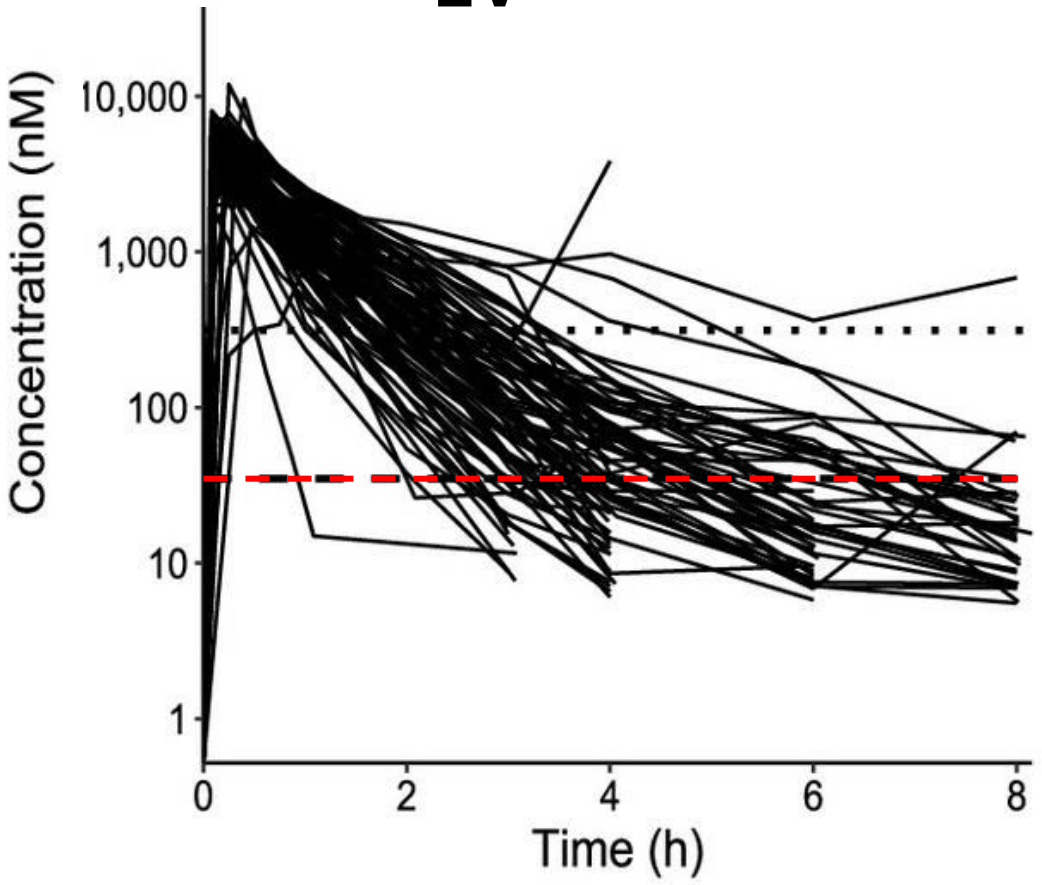


Pharmacology of rectal artesunate

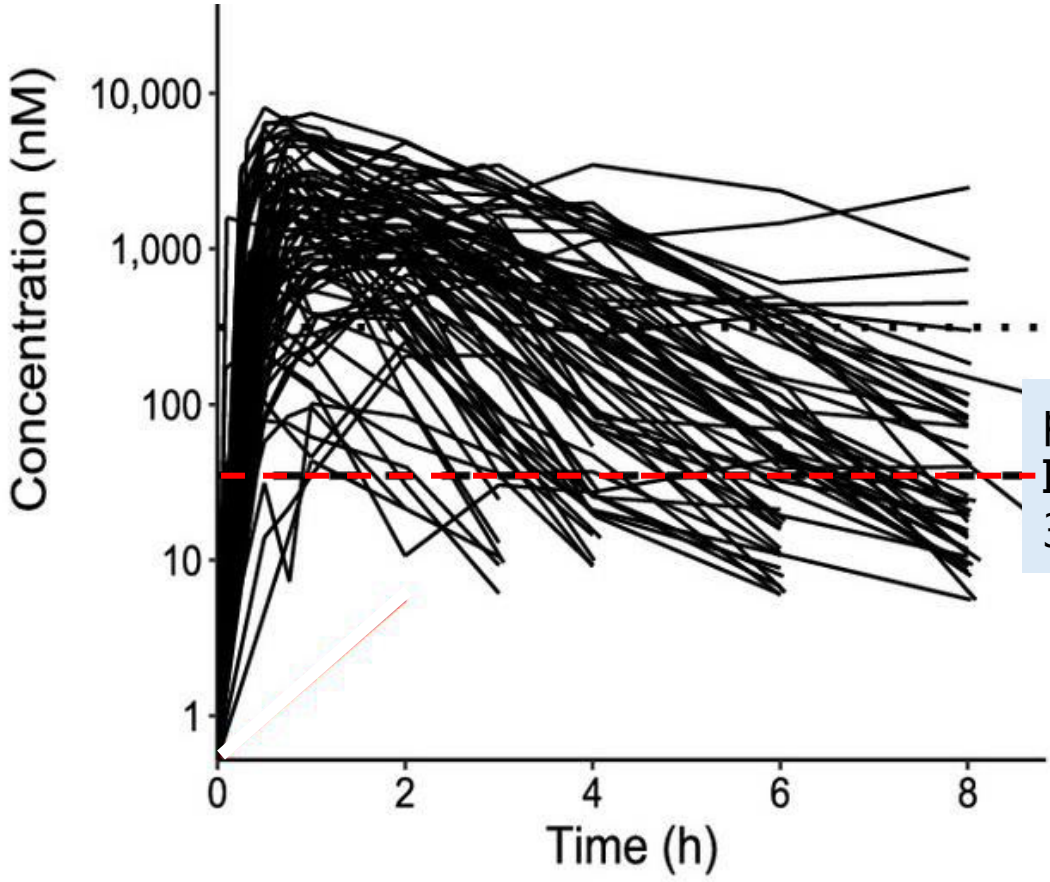
DHA accounts for the majority of the antimalarial effect

Variable absoption of the rectal formulation is offset by a 3-4 fold higher dose

IV



Rectal



putative IC_{50} = 34.9 nM

Main points

- Artesunate and DHA have same parasiticidal properties, ***irrespective*** of route of administration
- Severe malaria can be treated with rectal artesunate suppositories alone if parenteral administration not possible
- Follow-up treatment with IV artesunate is ***not*** a pre-requisite for suppositories to be effective

The rectal artesunate fiasco

World Health Organization

The use of rectal artesunate as a pre-referral treatment for severe *P. falciparum* malaria

JANUARY 2022 INFORMATION NOTE

- **Countries that have not yet introduced pre-referral RAS but are considering doing so should withhold implementation** and await further guidance from WHO on the criteria that need to be met to ensure the safe and efficacious use of RAS.

- **Countries that have already adopted and are deploying pre-referral RAS** should **urgently** review in detail the conditions under which it is currently being used. This includes all three steps along the cascade of care: (i) diagnosis and administration of RAS; (ii) immediate referral; and (iii) complete treatment with at least 24 hours of injectable artesunate and a three-day ACT. Countries that have already adopted pre-referral RAS are encouraged to **withhold further expansion** of its use until further guidance from WHO.

January 202

RESEARCH ARTICLE Open Access

Effectiveness of rectal artesunate as pre-referral treatment for severe malaria in children under 5 years of age: a multi-country observational study

Manuel W. Hetzel[1,2*], Jean Okitawutshu[1,3], Antoinette Tshefu[3], Elizabeth Omoluabi[4], Phyllis Awor[5], Aita Signorell[1,2], Nina C. Brunner[1,2], Jean-Claude Kalenga[3], Babatunde K. Akano[4], Kazeem Ayodeji[4], Charles Okon[4], Ocheche Yusuf[4], Proscovia Athieno[5], Joseph Kimera[5], Gloria Tumukunde[5], Irene Angiro[5], Giulia Delvento[1,2], Tristan T. Lee[1,2], Mark J. Lambiris[1,2], Marek Kwiatkowski[1,2], Nadja Cereghetti[1,2], Theodoor Visser[6], Harriet G. Napier[6], Justin M. Cohen[6], Valentina Buj[1,7], Christian Burri[1,2†] and Christian Lengeler[1,2†]

*"Implemented at scale to the recommended target group, **pre-referral RAS had no beneficial effect on child survival** in three highly malaria-endemic settings. RAS is unlikely to reduce malaria deaths unless health system issues such as referral and quality of care at all levels are addressed."*

Incorrect

CORRESPONDENCE Open Access

The CARAMAL study could not assess the effectiveness of rectal artesunate in treating suspected severe malaria

James A. Watson[1,2*], Thomas J. Peto[2,3] and Nicholas J. White[2,3]

Cannot assess effectiveness from these data due to confounding

CARAMAL

The main problems

1. Observational study-*extremely* heterogeneous
2. No prespecified analytical plan
3. Major concerns over selection bias
4. Major concerns over ascertainment bias
5. Temporal confounding
6. Biological implausibility of causality
7. Misdiagnosis

Cannot, and therefore should not, be used to ascribe causality

The WHO External Independent Review committee agrees

"The technical review identified several issues in the design of the CARAMAL study, which have left it susceptible to a number of biases and made the results difficult to interpret, particularly in terms of the impact of RAS on mortality and referral completion."

"There is no evidence that the increased CFR observed in Nigeria in the post-RAS period was due to RAS."

The use of rectal artesunate as a pre-referral treatment for severe *Plasmodium falciparum* malaria

2023 update

For successful treatment of suspected severe malaria in children, the administration of a single dose of RAS *must be followed by immediate transfer to an appropriate facility* for intensive nursing care and treatment with injectable artesunate, followed by a full three-day course of an artemisinin-based combination therapy (ACT) once the patient can tolerate oral medication.

Risk mitigation

A. Countries that are already implementing or considering implementation of RAS for pre-referral treatment of severe malaria need:

- to strengthen all aspects of the continuum of care for a severely sick child – from community health workers being adequately trained and stocked for giving RAS in the areas where it is most needed, to ensuring rapid transfer and access to referral facilities where a complete course of post-referral treatment is given following WHO recommendations for the treatment of severe malaria;
- to ensure support for adequate supply chain management and referral systems from community health workers and health facilities to referral treatment centres, which is essential for achieving the intended impact of RAS;
- to address barriers to referral completion, as this will improve outcomes not only for severe malaria but also for other severe diseases; and
- to ensure effective community sensitization to increase understanding of severe malaria, its causes, how dangerous it is for children, how to recognize danger signs and the need to promptly seek care if such signs are present.

Pre-referral treatment with rectal artesunate of children with suspected severe malaria: a field guide

World Health Organization

3.2 Minimal essential requirements for RAS

To be effective, RAS requires minimal health system elements (Table 1). Countries should not base a decision to use on these requirements but rather work to strengthen the health system for optimal RAS implementation.

Table 1. Essential minimum considerations for RAS deployment

N= 39!

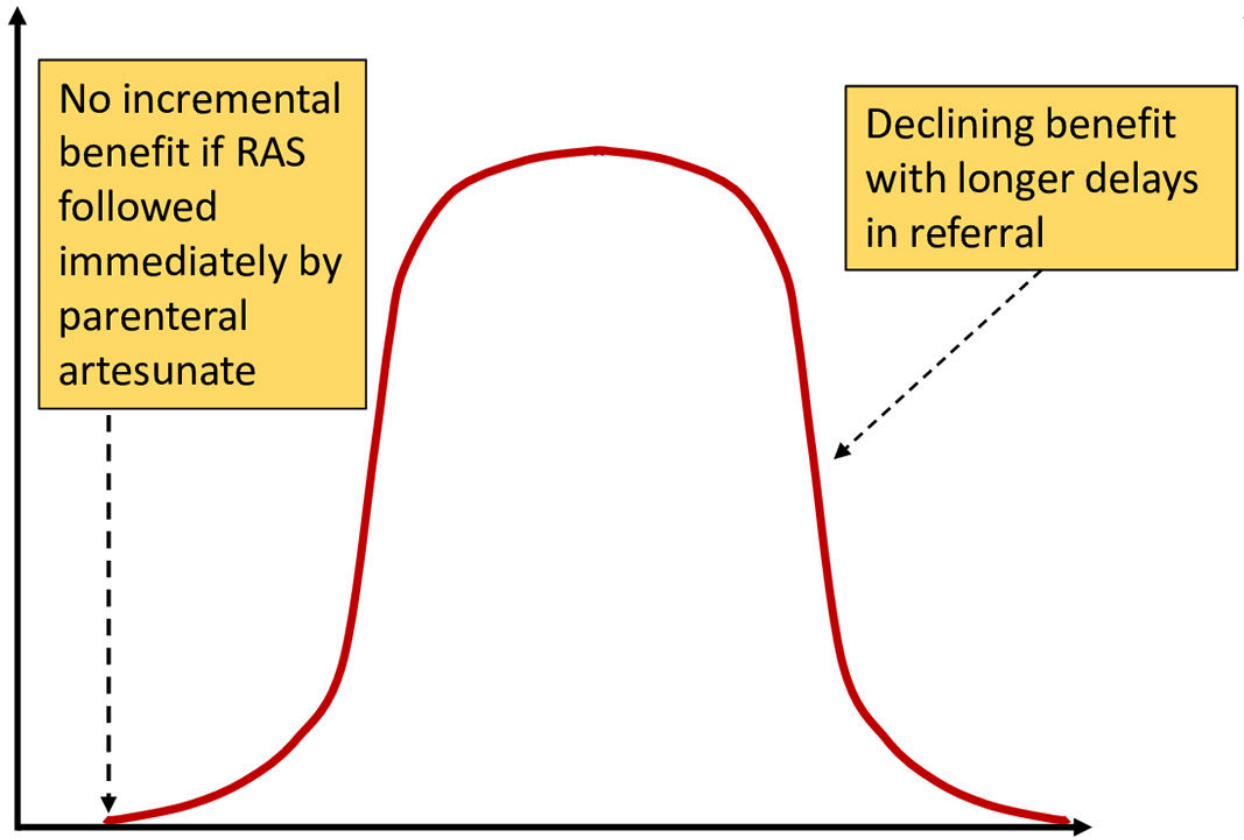
18. Patients should be referred directly to a facility that can offer emergency care and adequate post-referral treatments (in the case of severe malaria usually secondary or tertiary facilities)

20. System for referral to adequate facilities should be strengthened (with consideration of referral facility capacity and resources to alleviate financial barriers of referral)

22. Affordable referral support (e.g. subsidized transport)

A: WHO MPAG view

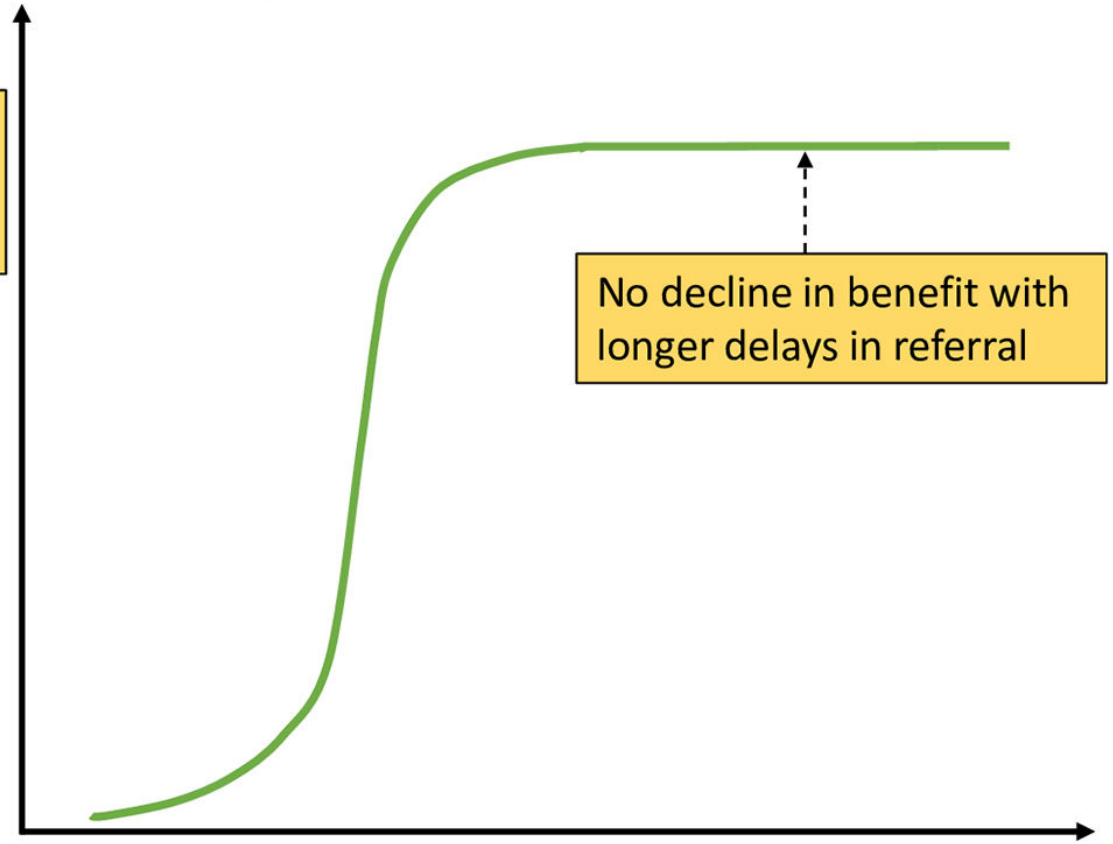
Life saving benefit



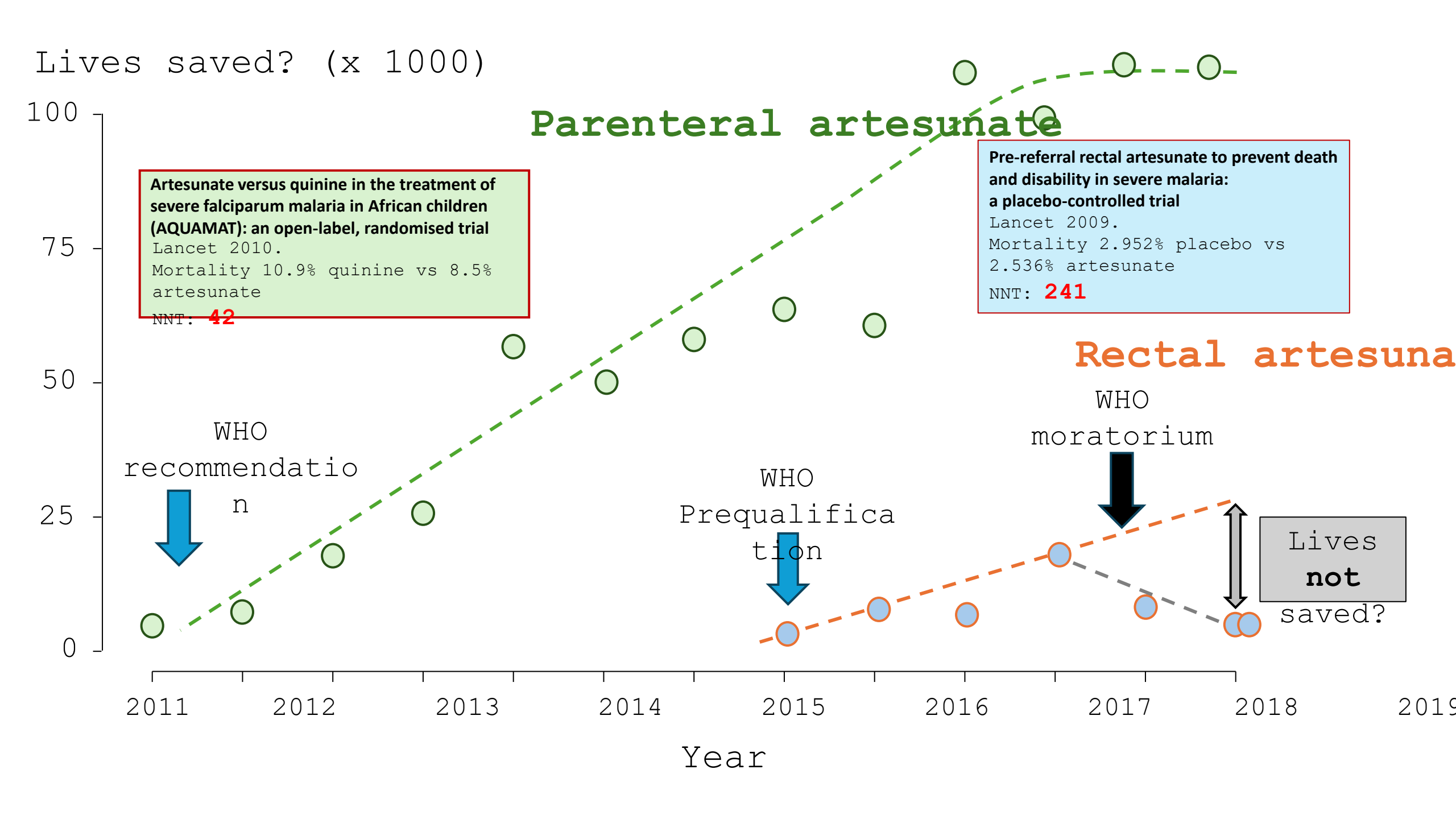
Referral delay following RAS administration

B: Our view

Life saving benefit



Referral delay following RAS administration


Lives saved? (x 1000)
100
75
50
25
0
Parenteral artesunate
Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open-label, randomised trial
Lancet 2010.
Mortality 10.9% quinine vs 8.5% artesunate
NNT: 42
Pre-referral rectal artesunate to prevent death and disability in severe malaria: a placebo-controlled trial
Lancet 2009.
Mortality 2.952% placebo vs 2.536% artesunate
NNT: 241
Rectal artesuna
WHO recommendation
WHO Prequalification
WHO moratorium
Lives not saved?
2011
2012
2013
2014
2015
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2017
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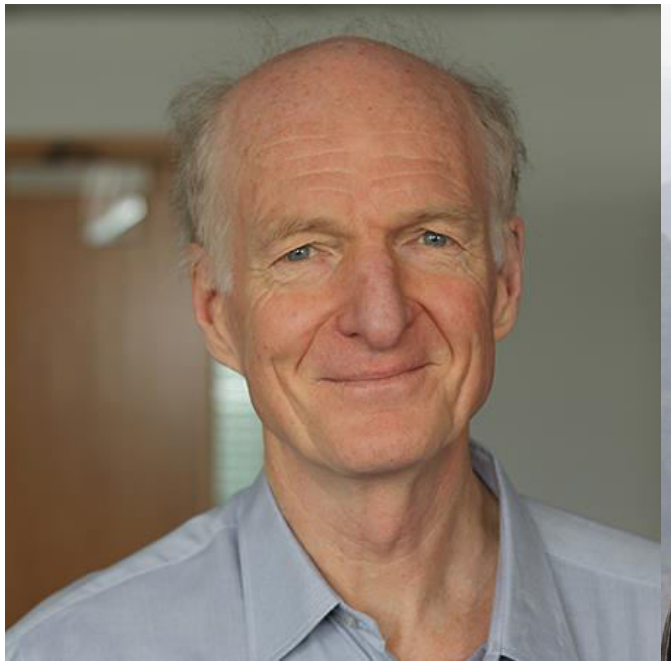
2019
Year



Nick White Tom Peto

Acknowledgements

MMV Medicines for Malaria Venture

POLICY FORUM

Rectal artesunate suppositories for the pre-referral treatment of suspected severe malaria

James A. Watson[1,2]*, Thomas J. Peto[2,3], Nicholas J. White[2,3]