Malaria imported to Belgium: new challenges

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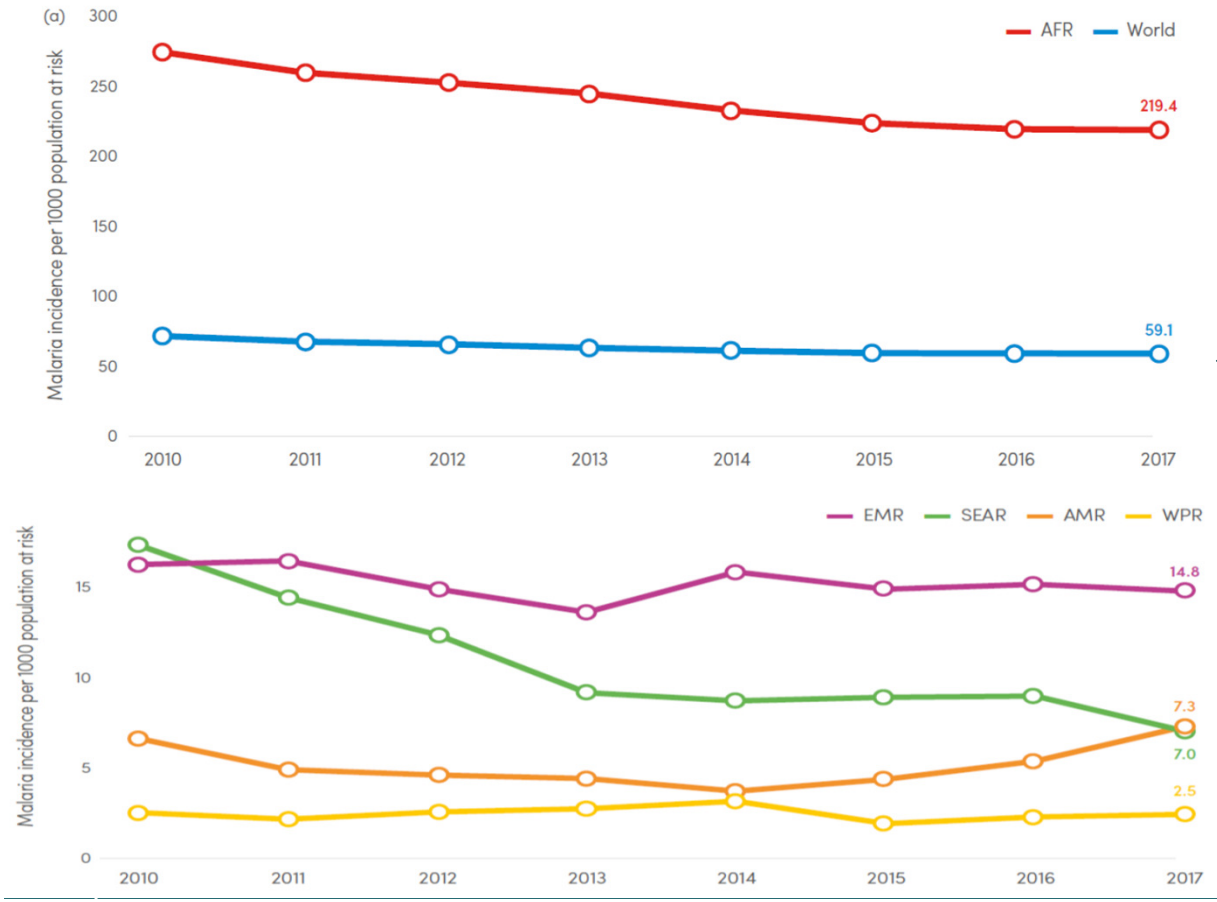
13TH NATIONAL SEMINAR ON TRAVEL MEDICINE
BRUSSELS, 10 OCT 2019

Outline

- Epidemiology of malaria in Belgium
- New epidemiological challenges
- Management of malaria in Belgium
- Emerging challenges in management

Malaria case incidence rate (/1000 p.y), globally



- 18% decrease since 2010
- Stagnation since 3 years

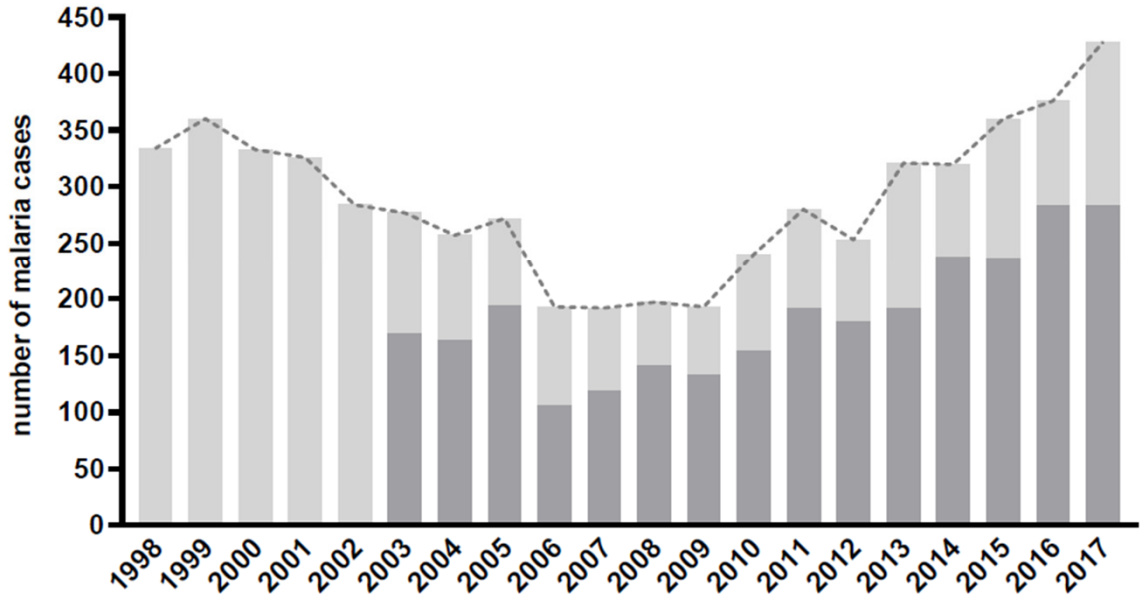
WHO World Report 2018

Malaria trends in Europe

- **Top cause of travel-associated morbidity and mortality**
  - 10,000-30,000 cases globally in non-endemic areas; Tatem AJ *Lancet Infect Dis* 2017
- **Increasing** of reported cases in Europe
  - (5,897 in 2012 and 8,401 in 2017: 40% increase; *ECDC Malaria Report 2017*)
- **Underestimation**
  - reporting not compulsory in several countries (Belgium, France, UK)

Malaria trends in Belgium: Sciensano/ITM ref lab

Figure 1



Additional data sent directly to Sciensano

Data aggregated at Reference Lab ITM

> 2.5 infections/100,000 inhab.

Rovira-Vallbona E. *Trav Med Infect Dis* In press

Malaria trend in Belgium: Sciensano/ITM

- Surveillance based on a network of sentinel laboratories
  - Voluntary base
  - “Stable” contributors over the years
  - Very limited epidemiological metadata (age, sex, region of diagnosis)
  - No clinical data about presentation, drug exposure, outcome
- No mandatory notification, except for autochthonous malaria

Rovira-Vallbona E. *Trav Med Infect Dis* In press

Malaria trend in Belgium: severe cases (WHO 2000)

Any sign of cerebral dysfunction

Severe anemia (hemoglobin < 7 g/dl)

Oligo-anuria < 400 ml/day

Jaundice

Shock

Bleeding/DIC

Table 1. Clinical and biological criteria for severe malaria according to the 2000 World Health Organization definition with modifications (see * and †).

Clinical criteria
Impaired consciousness: Glasgow Coma Scale score <11*
Respiratory distress: requirement for noninvasive and/or endotracheal mechanical ventilation or spontaneous breathing with PaO_2 <60 mm Hg (if FiO_2 ≥0.21) †, and/or respiratory rate >32/min*
Multiple convulsions
Circulatory collapse: systolic blood pressure <80 mm Hg despite adequate volume repletion
Abnormal bleeding
Jaundice: clinical jaundice or bilirubin >50 µmol/L
Macroscopic hemoglobinuria: if unequivocally related to acute malaria (patients with blackwater fever were not included)
Laboratory criteria
Severe anemia: hemoglobin <5 g/dL
Hypoglycemia: blood glucose <2.2 mmol/L
Acidemia (pH<7.35) or acidosis (serum bicarbonate <15 mmol/L)
Hyperlactatemia: arterial lactate >5 mmol/L
Hyperparasitemia ≥4%
Renal impairment: serum creatinine >265 µmol/L or blood urea nitrogen >17 mmol/L*

*Coma scale criteria of 11 instead of 9; respiratory rate >32/minute and blood urea nitrogen > 17 mmol/L are modifications according to the SEAQUAMAT group [8].
†The requirement for noninvasive and/or endotracheal mechanical ventilation or spontaneous breathing with PaO_2 <60 mm Hg (if FiO_2 ≥0.21) was used specifically for this study.
doi:10.1371/journal.pone.0013236.t001

Risk factors for severe malaria

Severe Imported *Plasmodium falciparum* Malaria, France, 1996–2003

Elise Seringe, Marc Thellier, Arnaud Fontanet, Fabrice Legros, Olivier Bouchaud, Thierry Ancelle, Eric Kendjo, Sandrine Houze, Jacques Le Bras, Martin Danis, and Rémy Durand, for the French National Reference Center for Imported Malaria Study Group[1]

- Retrospective study
- 21,888 *P. falciparum* malaria, including 862 (4%) severe cases
- Independent risk factors for severity
  - Age (> 60 years)
  - European origin
  - Absence of chemoprophylaxis
  - Time to diagnosis (4 to 12 days)
  - First visit to GP

Malaria trend in Belgium: National Institute Health & Disability Insurance (RIZIV/INAMI)

		2010	2011	2012	2013	2014	2015	2016	2017	2018
	Data from hospital stays									
Data source : RHM	Hospital stays with a diagnostic: malaria ICD9 084 until 2014 From 2016 ICD10 : B50 to B54	340	366	320	390	400	Poor quality data: will not be available for analysis	396	421	Data available in May 2020
	Total cost hospital stays INAMI/RIZIV (€)								1.483.236	
Data source : SHA	Hospital stays with artesunate reimbursed(CNK 7706336)				0	8	21	39	35	Data available in May 2020
	Artesumate delivered									
Data source: Social insurance companies	Number of patients					8	15	40	34	40
	Cost for INAMI/RIZIV (€)					3.965	9.729	52.683	39.006	40.479

Source: courtesy NIHDI

Malaria trend in Belgium: severe cases

SEVERE MALARIA
I.V. ARTESUNATE TREATMENT
CASE REPORTING FORM

For Belgium: Dr Emmanuel Bottieau, Institute of Tropical Medicine (ebottieau@itg.be)

Please send this form by mail - You may save the form on your computer for your own reference.

Name Clinic	Patient ID of local site:	
…….	……..	
Section 1 – Demographic and patient data		
Date of presentation to clinic/hospital (format: dd-mm-yyyy)		
Month/Year of birth (format: mm-yyyy)		
Sex		M / F
Country of permanent residence		
Patient Status		European resident / Immigrant
Country where infection was acquired		
Chemoprophylaxis		Yes / No
Compliance		Yes / No
Purpose of travel		VFR / Tourism / Business / Other
Pre-treatment criteria of severe malaria according to WHO definition (tick at least one):	☐ **Hyperparesitaemia (>10% of RBC or >500 000/µl)** ☐ **Hyperparesitaemia (>4% of RBC or >200 000/µl)** ☐ **Cerebral malaria (obnobulation or coma)** ☐ **Convulsions** ☐ **Acute renal failure (urine output <400/24h or creatine >2,5 mg/dl)** ☐ **Respiratory failure or ARDS** ☐ **Circulatory collapse (Shock)**	☐ **Anaemia (Hb <8 mg/dl)** ☐ **Very low platelet count (PLT < 20.000/ml)** ☐ **Spontaneous bleeding, DIC** ☐ **Hypoglycaemia (<40 mg/dl)** ☐ **Acidosis (pH <7.25)** ☐ **Jaundice (bilirubin >3 mg/dl or >50µmol/l)** ☐ **ALAT/ASAT >3 x UNL**
Significant pre-existing comorbidities of the patient (*e.g.* *functional asplenism, HIV coinfection…*)		

- ✓ IV artesunate indications well respected by Belgian physicians
- ✓ Good surrogate for severe cases

AIP: € 60,00 (excl. BTW) per verpakking	Z-Index: 15654591

Source: courtesy Dr Clerinx J. & NIHDI

Malaria trend in Belgium: hospital/severe cases (NIDHI)

- 421 admissions in 2017 (ICD9-ICD10)
- Increasing trend since 2010
- 40 IV artesunate treatments administered in 2017 (**10% of admitted cases**)
- Annual hospital costs related to malaria: **1,500, 000** euros
- Data limited to hospital care

Source: courtesy NIHDI

Severe malaria in Belgium: historical series

Eur J Clin Microbiol Infect Dis (2006) 26:181–188
DOI 10.1007/s10096-007-0264-x

ARTICLE

Selective ambulatory management of imported falciparum malaria: a 5-year prospective study

- Prospective study (2000-2005)
- 387 *P. falciparum* cases

- 25% of VFR travelers
- 33% seen first by GP
- 60% of diagnostic delay (> 3 days)
- 15% of severe cases

Bottieau E et al. *Eur J Clin Microbiol Infect Dis* 2006

Severe malaria in GeoSentinel travel clinics

- Retrospective analysis of surveillance data
- 5,689 malaria, including 4,011 *P. falciparum* cases
  - 62% admissions
  - 441 severe cases (11% of *Pf*)

Malaria trend in Belgium: causes of increase ?

- Clinical experience
  - "Most cases of malaria occur in travellers visiting friends and relatives (VFR)"
- High proportion of VRFs in all recent surveys
  - "Assessing the burden of key infectious disease affecting migrants in the EU"; ECDC 2014
  - Angelo KM et al. Malaria in international travelers: a GeoSentinel analysis
    - 53% of 5689 malaria cases (2003-2016) were VFR travelers
- VFRs as contributors of the increase
  - De Gier B et al. Increase in imported malaria in the Netherlands in asylum seekers and VFR travellers. *Malaria J* 2017

Malaria trend in Belgium: causes of increase ?

de Gier *et al. Malar J (2017) 16:60*
DOI 10.1186/s12936-017-1711-5

Malaria Journal

RESEARCH Open Access

Increase in imported malaria in the Netherlands in asylum seekers and VFR travellers

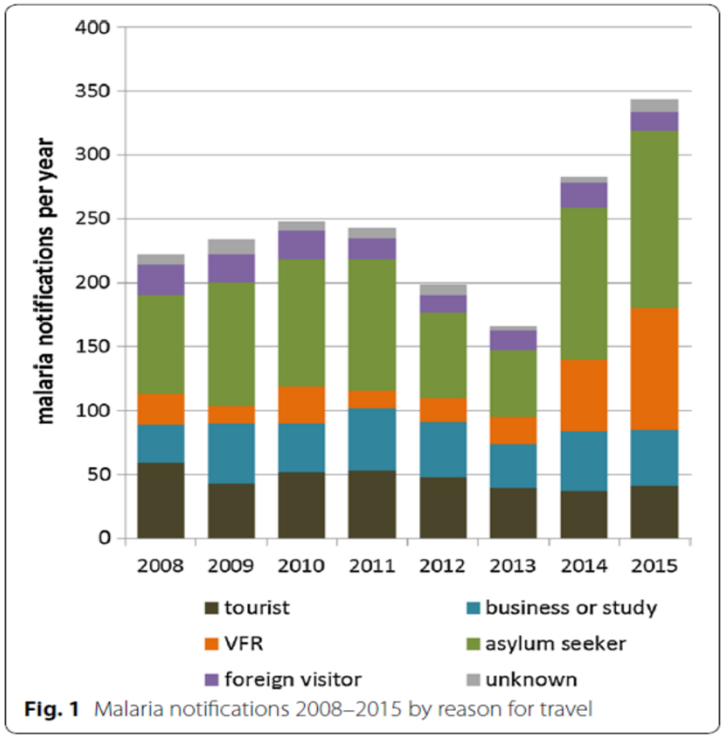
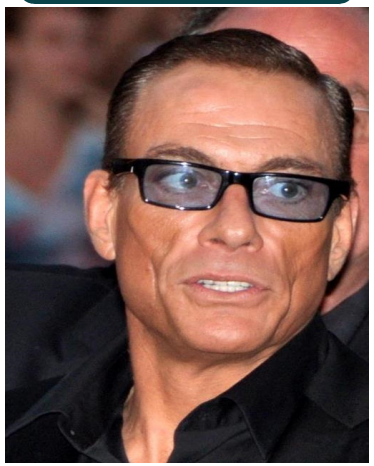


Fig. 1 Malaria notifications 2008–2015 by reason for travel

De Gier B. et al. *Malaria J* 2017

Malaria prevention in Belgium: A-B-C-D

Awareness



Bite prevention

Chemoprophylaxis

- Atovaquone/proguanil
- Doxycycline
- (Mefloquine)

Diagnosis

Malaria diagnosis in Belgium

- Good quality of microscopy in Belgium for diagnosis of *P. falciparum*

Loomans *et al. Malar J* (2019) 18:104
https://doi.org/10.1186/s12936-019-2731-0

Malaria Journal

RESEARCH Open Access

Accuracy of malaria diagnosis by clinical laboratories in Belgium

Excellent diagnosis of *P. falciparum* malaria

- Use of LAMP assay as very sensitive screening tool ?

De Koninck *et al. Malar J* (2017) 16:418
DOI 10.1186/s12936-017-2065-8

Malaria Journal

RESEARCH Open Access

Diagnostic performance of the loop-mediated isothermal amplification (LAMP) based illumigene® malaria assay in a non-endemic region

914 Tijdschr. voor Geneeskunde, 75, nr. 14-15, 2019
doi: 10.2143/TVG.75.14-15.2002890

Overzicht

Screening naar malaria: LAMP-test als sensitiever alternatief voor de dikdruppeltest en implementatie hiervan in het UZ Gent

B. Zwaenepoel[1], J. Philippé[2], S. Callens[1,3]

Treatment severe malaria (2019)

Artesunate (AS) IV, followed by artemisinin-based combination therapy (ACT)

- Clinically superior to quinine (improved survival) in endemic settings
  - SEAQUAMAT; *Lancet* 2005
  - AQUAMAT *Lancet* 2010
- Clinical benefit also in Europe

Intravenous Artesunate Reduces Parasite Clearance Time, Duration of Intensive Care, and Hospital Treatment in Patients With Severe Malaria in Europe: The TropNet Severe Malaria Study

Florian Kurth,[1] Michel Develoux,[2] Matthieu Mechain,[3] Jan Clerinx,[4]

Clinical Infectious Diseases® 2015;61(9):1441–4

70 AS vs 115 Q

Reduction by at least 1 day of fever, ICU and hospital duration

Treatment uncomplicated malaria (2019)

First-line

3 or 4 tab OD
fasting

Dihydroartemisinin/piperaquine

4 tab BID
with food

Artemether/lumefantrine

Second-line

4 tab OD
with food

Atovaquone/proguanil

Third-line

Quinine +

doxycycline

OR clindamycine

Treatment uncomplicated malaria (2019)

Bouchaud *et al. Malaria Journal* 2012, **11**:212
http://www.malariajournal.com/content/11/1/212

MALARIA JOURNAL

RESEARCH Open Access

Therapy of uncomplicated falciparum malaria in Europe: MALTHER – a prospective observational multicentre study

ACTs
n=59

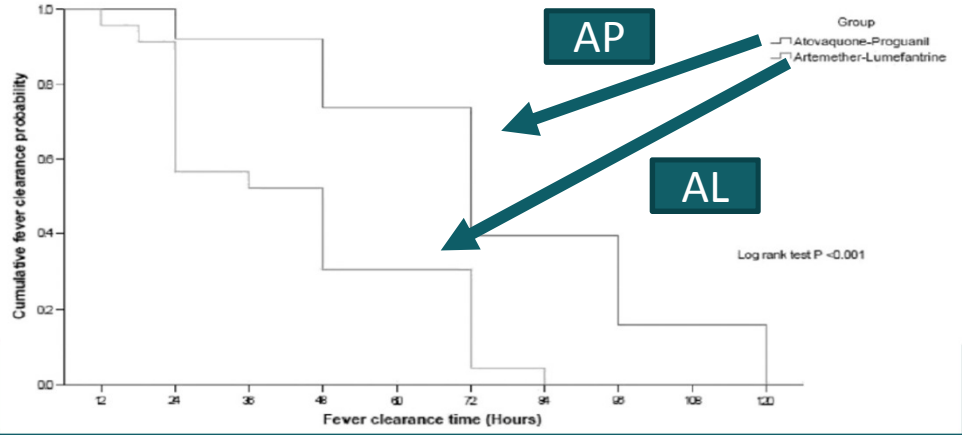
Shortest parasite and fever clearance time

Am. J. Trop. Med. Hyg., 92(1), 2015, pp. 13–17
doi:10.4269/ajtmh.14-0249

Artemether-Lumefantrine Compared to Atovaquone-Proguanil as a Treatment for Uncomplicated *Plasmodium falciparum* Malaria in Travelers

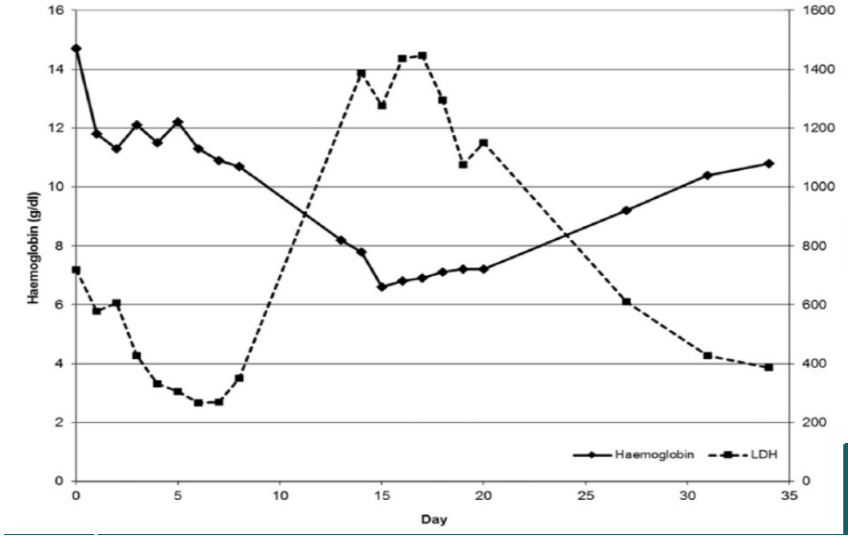
Shirly Grynberg, Tamar Lachish, Eran Kopel, Eyal Meltzer, and Eli Schwartz*

Retrospective
AL (n= 25) vs AP (n=44)



New challenges: artemisinin-related toxicity

- **Post-artesunate delayed hemolysis (PADH) after severe malaria in travelers**
  - Zoller T. et al. *Emerg Infect Dis* 2011; retrospective; 6/25 (24%)
  - Kreeftmeijer-Vegter AR et al. *Malaria J* 2012; retrospective; 7/55 (13%)
  - Kurth F et al. Malaria J 2017; retrospective 19/70 (27%)
  - Jaureguiberry S et al. *Emerg Infect Dis* 2015; **prospective**; 21/78 (**27%**)



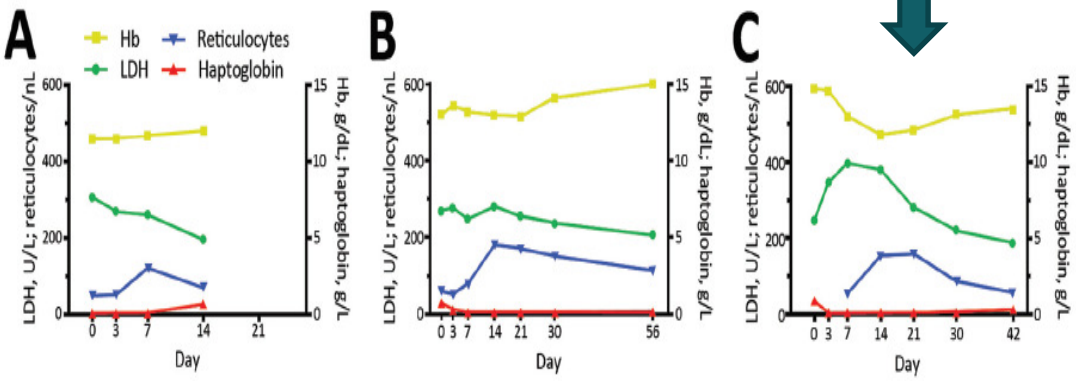
- 15% had a hemglobin level drop below 7 g/dl
- Other persistent hemolysis than PADH

New challenges: artemisinin-related toxicity

- **PADH after severe malaria in endemic countries**
  - Rolling T et al. *J Infect Dis* 2014; prospective; 5/72 (7%)
  - Burri C et al. *Am J Trop Med Hyg* 2014; prospective; 22/201 (11%)
- **PADH after ACT for uncomplicated malaria**
  - Kurth F et al. Emerg Infect Dis 2016; prospective; 8/20 (40%)

Mean Hb drop: 1.3 g/dl

Hemolysis after Oral Artemisinin Combination Therapy for Uncomplicated *Plasmodium falciparum* Malaria



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New challenge: late ACT failure

Clinical Infectious Diseases
MAJOR ARTICLE

High Rate of Treatment Failures in Nonimmune Travelers Treated With Artemether-Lumefantrine for Uncomplicated *Plasmodium falciparum* Malaria in Sweden: Retrospective Comparative Analysis of Effectiveness and Case Series

Klara Sondén,[1] Katja Wyss,[1,2] Irina Jovel,[3] Antero Vieira da Silva,[4] Anton Pohanka,[4,5] Muhammad Asghar,[1] Manijeh Vafa Homann,[1] Lars L. Gustafsson,[4,5] Urban Hellgren,[6,7] and Anna Färnert,[1,6]

N=5 late failures, in Sweden
(2012-2015)
No resistance found

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pfk13-Independent Treatment Failure in Four Imported Cases of *Plasmodium falciparum* Malaria Treated with Artemether-Lumefantrine in the United Kingdom

Colin J. Sutherland,[a,b] Paul Lansdell,[a] Mandy Sanders,[c] Julian Muwanguzi,[b]

N=4 late failures, in UK
(2015-16)
No resistance found

Am. J. Trop. Med. Hyg., 100(4), 2019, pp. 828–834
doi:10.4269/ajtmh.18-0722

Imported Malaria at a Referral Hospital in Tokyo from 2005 to 2016: Clinical Experience and Challenges in a Non-Endemic Setting

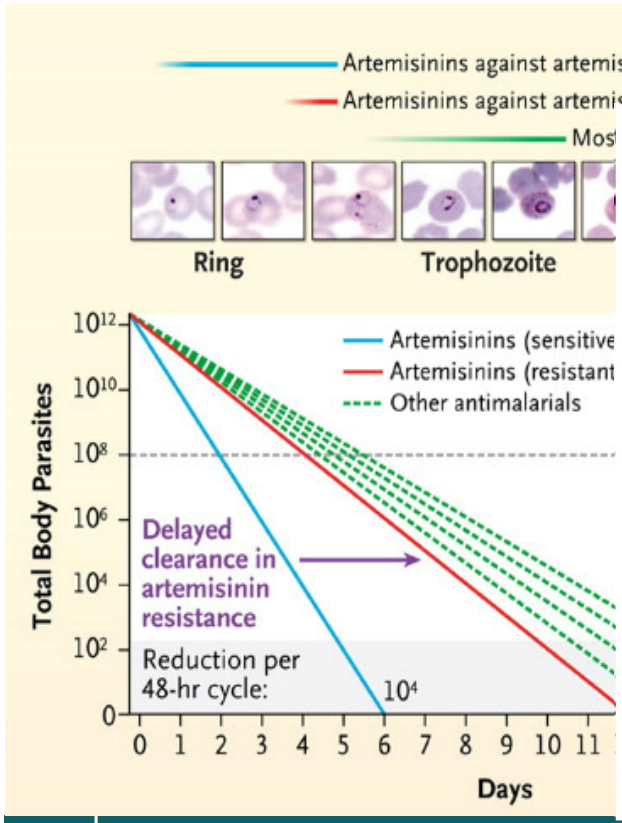
Saho Takaya,[1] Yasuyuki Kato,[1]* Yuichi Katanami,[1] Kei Yamamoto,[1] Satoshi Kutsuna,[1] Nozomi Takeshita,[1] Kayoko Hayakawa,[1]

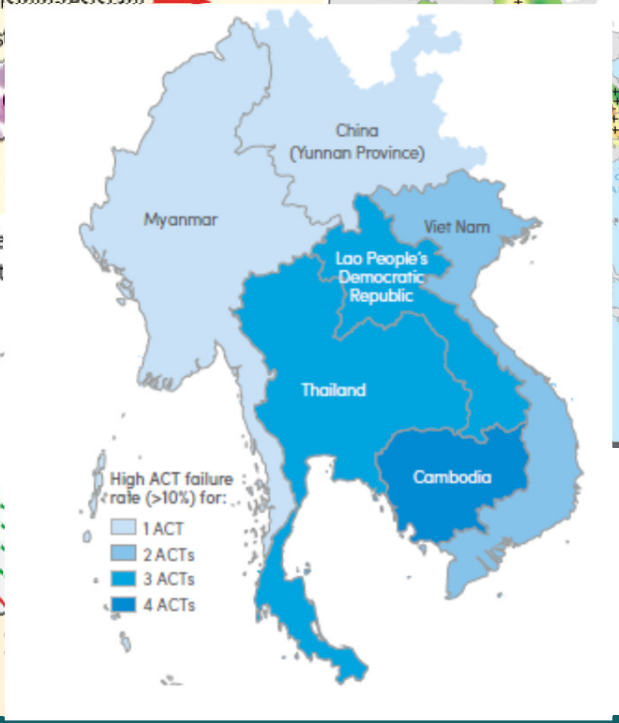
N=4 late failures, in Japan
(2005-2016)
Resistance not tested

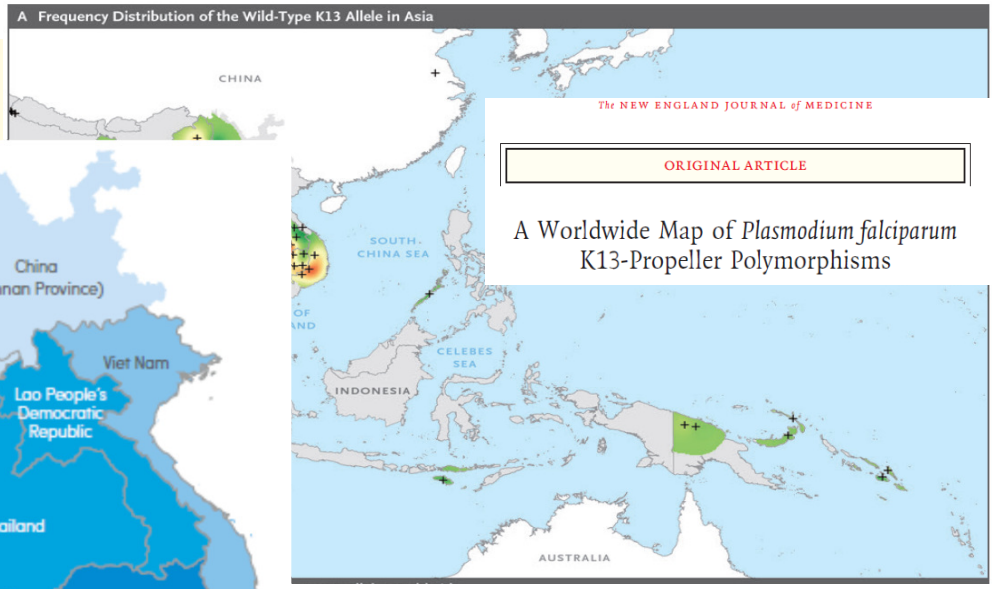
New challenge: late ACT failure in Belgium (2014-2017)

General characteristics	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Gender	male	male	female	male	female	male
Age (years)	40	50	56	33	39	38
Weight (kg)	86	86	62	95	60	81
Country of birth	Belgium	Belgium	Belgium	Belgium	Belgium	Belgium
Chemoprophylaxis	No	No	No	No	No	No
First episode (day 0)						
Days with fever before diagnosis	4	4	7	6	4	1
Parasitaemia at diagnosis	300,138	152,601	1,242,537	98,714	842,771	1521[a]
Criteria of severe malaria	disorientation; hyperparasitaemia	disorientation; kidney failure	hyperparasitaemia	disorientation; kidney failure	shock; kidney failure; hyperparasitaemia	none
Treatment	AS (2 days) + DP	AS (3 days) + AL	AS (1 day) + AL	AS (1 day) + AL	AS (1 day) + AL	AL
Recurrent episode						
Days after first diagnosis	37	35	25	15	20	23
Days with fever before diagnosis	2	1	2	2	2	1
Parasitaemia at diagnosis	34,474	35,454	14,737	19	1951	(0.5%)[b]
Criteria of severe malaria	none	none	none	none	none	none
Treatment	QN-doxy	AP	AP	AP	AP	QN-doxy

New challenge: artemisinin resistant malaria in SE Asia





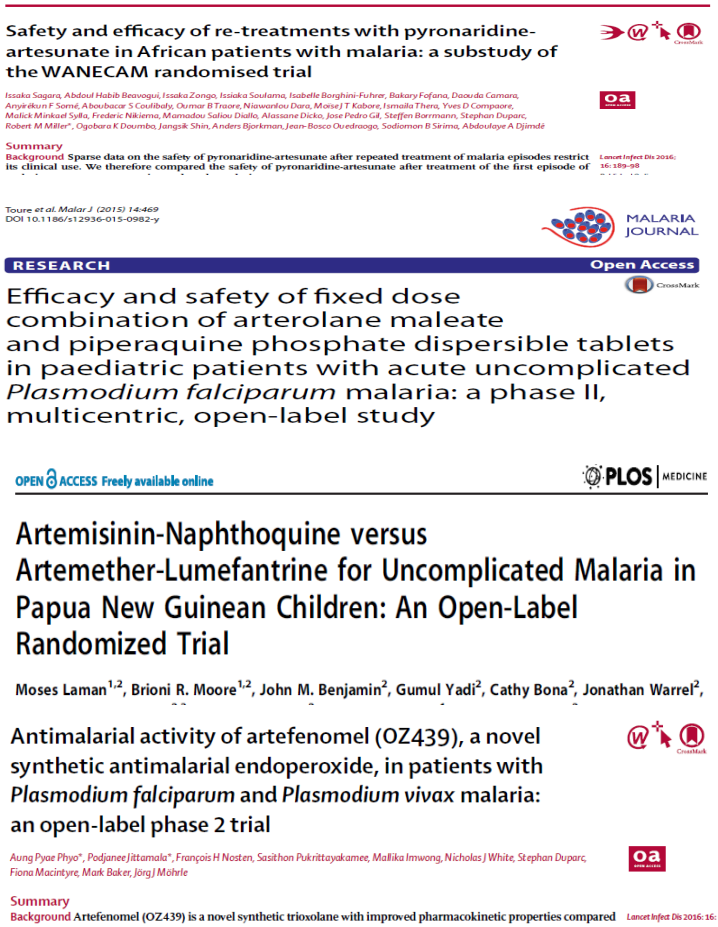


Dondorp AM et al. *N Engl J Med* 2011

Menard D et al. *N Engl J Med* 2016

Threat of artesunate resistance: new ACTs ?

- *Artesunate-pyronaridine* — 3-day
- *Arterolane-piperaquine* — 3-day
- *Artemisinin-naphthoquine* — 3-day; SD?
- *Artefenomel (OZ439)* — SD?



Safety and efficacy of re-treatments with pyronaridine-artesunate in African patients with malaria: a substudy of the WANECAM randomised trial

Issaka Sagara, Abdoul Habib Beavogui, Issaka Zongo, Issiaka Soulama, Isabelle Borghini-Fuhrer, Bakary Fofana, Daouda Camara, Anyirékun F Somé, Aboubacar S Coulibaly, Oumar B Traore, Niawanlou Dara, Moïse J T Kabore, Ismaïla Thera, Yves D Compaore, Malick Minkaïl Sylla, Frederic Nikiema, Mamadou Saliou Diallo, Alassane Dicko, Jose Pedro Gil, Steffen Borrmann, Stephan Duparc, Robert M Miller*, Ogobara K Doumbo, Jangsik Shin, Anders Bjorkman, Jean-Bosco Ouedraogo, Sodiomon B Sirima, Abdoulaye A Djimdé

Summary

Background Sparse data on the safety of pyronaridine-artesunate after repeated treatment of malaria episodes restrict its clinical use. We therefore compared the safety of pyronaridine-artesunate after treatment of the first episode of

Lancet Infect Dis 2016; 16: 189–98

Toure et al. Malar J (2015) 14:469
DOI 10.1186/s12936-015-0982-y

MALARIA JOURNAL

RESEARCH Open Access

Efficacy and safety of fixed dose combination of arterolane maleate and piperaquine phosphate dispersible tablets in paediatric patients with acute uncomplicated *Plasmodium falciparum* malaria: a phase II, multicentric, open-label study

OPEN ACCESS Freely available online

PLOS | MEDICINE

Artemisinin-Naphthoquine versus Artemether-Lumefantrine for Uncomplicated Malaria in Papua New Guinean Children: An Open-Label Randomized Trial

Moses Laman[1,2], Brioni R. Moore[1,2], John M. Benjamin[2], Gumul Yadi[2], Cathy Bona[2], Jonathan Warrel[2],

Antimalarial activity of artefenomel (OZ439), a novel synthetic antimalarial endoperoxide, in patients with *Plasmodium falciparum* and *Plasmodium vivax* malaria: an open-label phase 2 trial

Aung Pyae Phyo*, Podjanee Jittamala*, François H Nosten, Sasithon Pukrittayakamee, Mallika Imwong, Nicholas J White, Stephan Duparc, Fiona Macintyre, Mark Baker, Jörg J Möhrle

Summary

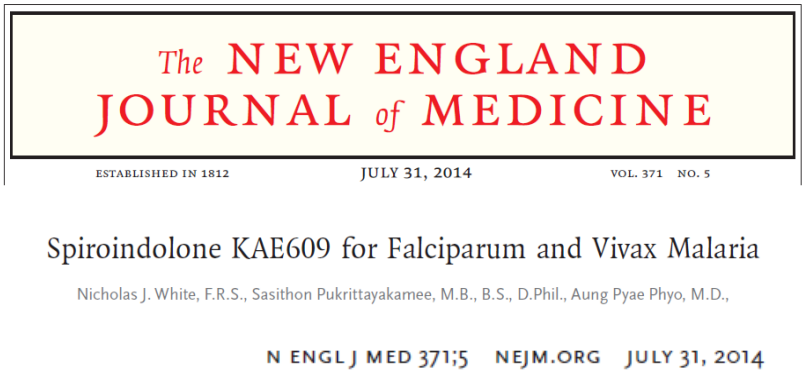
Background Artefenomel (OZ439) is a novel synthetic trioxolane with improved pharmacokinetic properties compared

Lancet Infect Dis 2016; 16: 61–69

Threat of artesunate resistance: new class of drugs ?

– *Spiroindolone KAE609*

Phase 2 (n=21 cases): “safe and effective”



– *Imidazolopiperazine KAF156*

Phase 2 (n=43 cases): “safe and effective”

Conclusions (1): emerging epidemiological challenges

- **Increasing burden of malaria in Belgium**
  - **Unclear reasons due to limited surveillance data**
  - **VFR contribution?**

- **Stable proportion of severe cases**
  - **Good quality of diagnosis**
  - **Diagnostic delays ? (patient ? doctor?)**

Conclusions (2): emerging clinical challenges

- **Artemisinin-related toxicity**
  - Delayed/persisting hemolysis
  - Risk factors ? Management?
- **Treatment failures**
  - No early treatment failure reported in Europe so far
  - Late treatment failure due to non-adherence? subtherapeutic partner drug concentration? resistance?
- **Spread of resistance to artemisinin**
  - Need for molecular surveillance?