

# Wat als artemisinine-combinatietherapie faalt?

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- 29 mei 2017
  - 43-jarige man met koorts
  - **Voorgeschiedenis**
    - 13-05-2017 opname in Canisius-Wilhelmina Ziekenhuis
    - Malaria tropica infectie, waarvoor artemether-lumefantrine
    - Na 4 dagen dikke druppel negatief
- 13 september 2017
  - 24-jarige man met koorts
  - **Voorgeschiedenis**
    - 26-08-2017: opname in Admiraal de Ruyter Ziekenhuis
    - Malaria tropica infectie, waarvoor artemether-lumefantrine
    - Na 3 dagen dikke druppel negatief

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# Casus

- **Anamnese**

- 1 maand geleden in Gabon gedurende 14 dagen
- Geen malariaprofylaxe
- Hoofdpijn, spierpijn, misselijkheid, koorts, koude rillingen, nachtzweeten; gelijk aan eerdere klachten

- **Anamnese**

- 3 weken eerder gedurende 3 weken in Zuid-Afrika en Swaziland geweest
- Geen malariaprofylaxe
- Acut ontstane koorts en malaise; gelijk aan eerdere klachten

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# Casus

- **Lichamelijk onderzoek**

- Matig zieke man, 96 kg
- Lichte tachycardie: 100 bpm
- Temperatuur 40.2°C

- **Aanvullend onderzoek**

- Hb 7.4 mmol/L, leukocyten  $4.5 \times 10^9/L$ , trombocyten  $214 \times 10^9/L$ , LDH 725 U/L, kreatinine 116  $\mu\text{mol/L}$ , CRP 42 mg/L

- Dikke druppel: *P. falciparum*, parasitemie 1.12%

- **Lichamelijk onderzoek**

- 95 kg
- Temperatuur 39.4°C

- **Aanvullend onderzoek**

- Hb 9.7 mmol/L, leukocyten  $7.6 \times 10^9/L$ , trombocyten  $223 \times 10^9/L$   
CRP 32 mg/L

- Dikke druppel: *P. falciparum*, parasitemie 0.3%

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# Casus

- **Werkdiagnose**
  - Therapiefalen van artemether-lumefantrine bij *P. falciparum* infectie

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# Casus

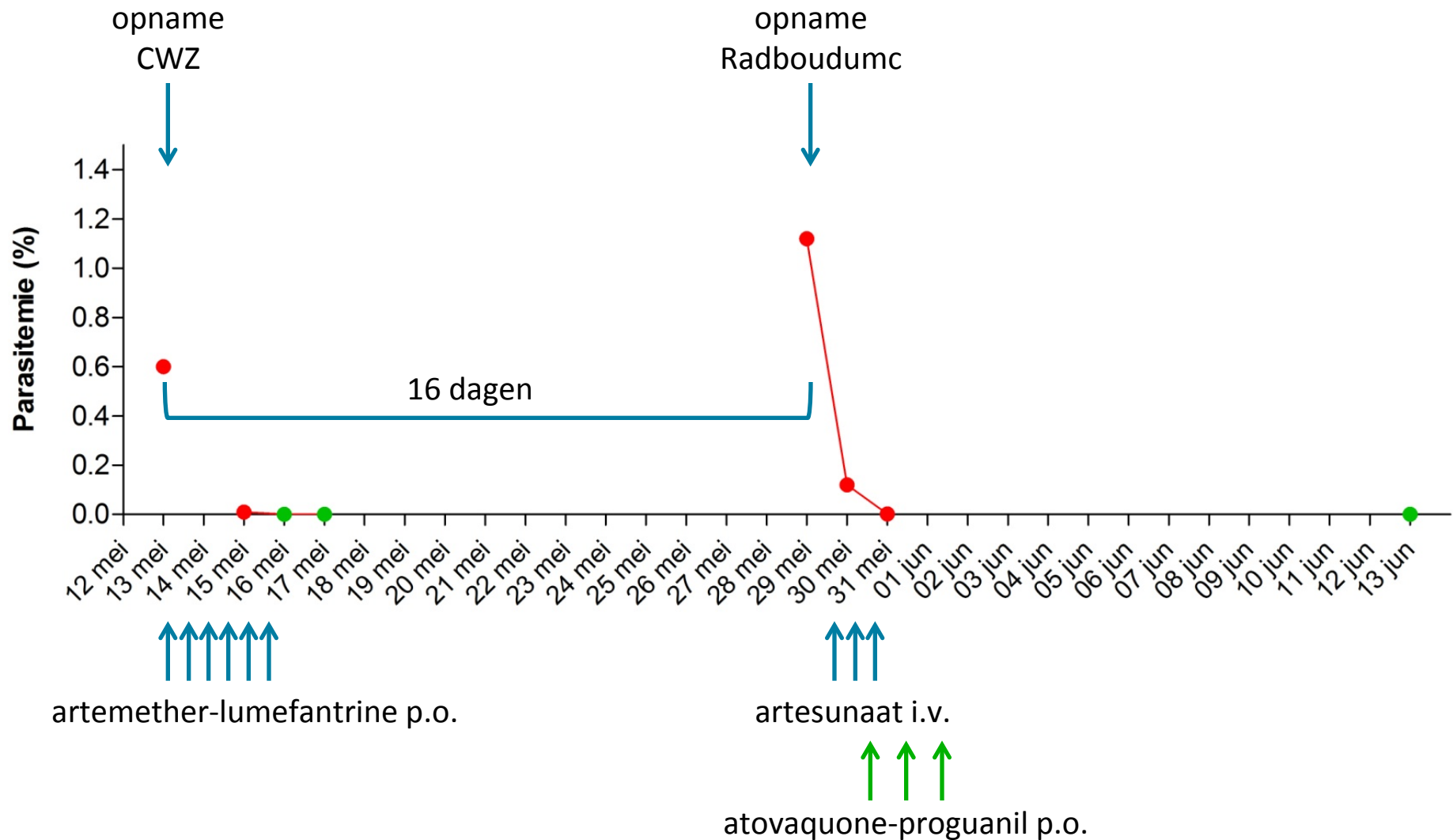
- **Beleid**

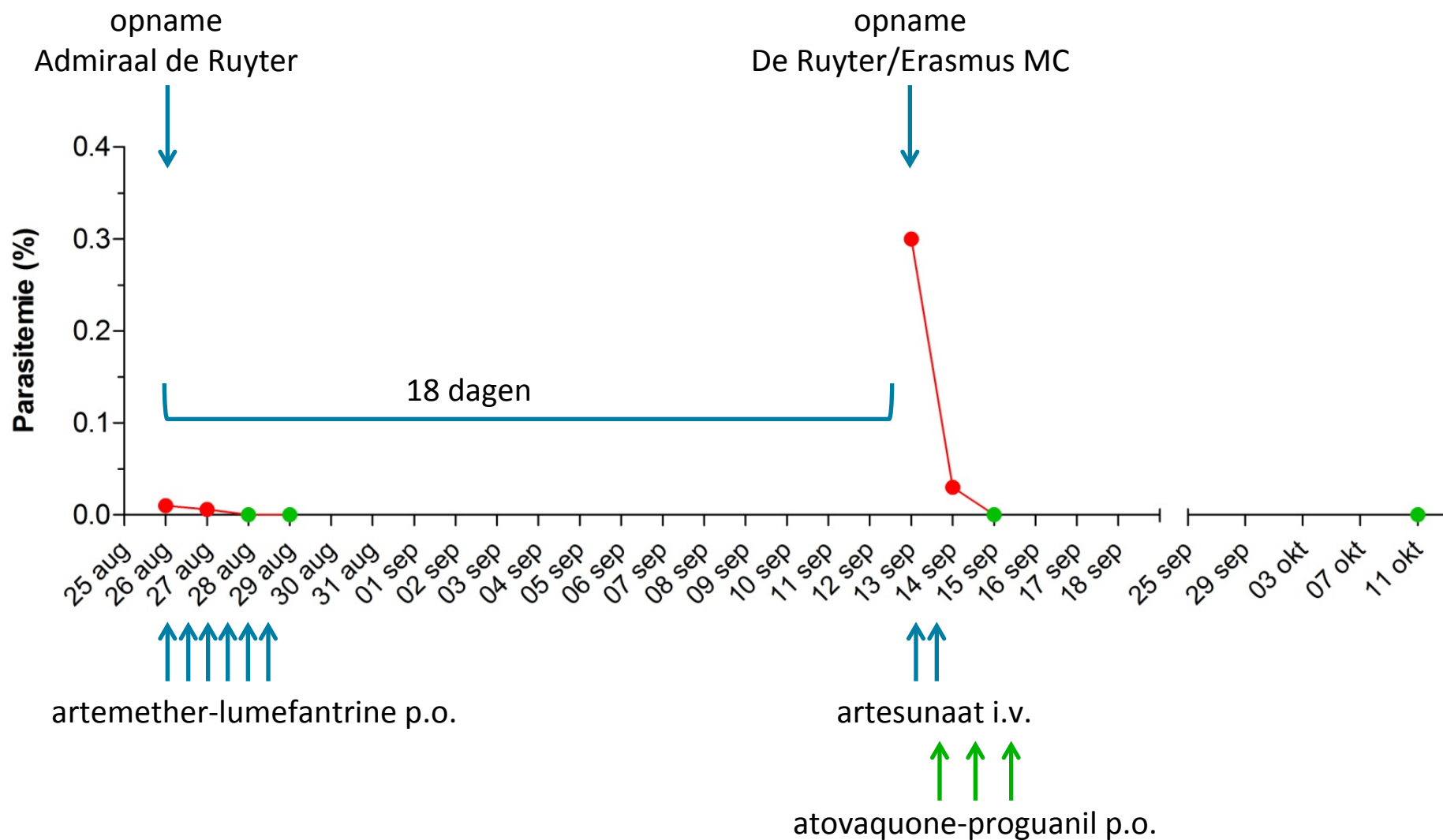
- Start artesunaat 2.4 mg/kg i.v.
- Na 3 giften artesunaat i.v. switch  
→ atovaquone-proguanil (Malarone®) oraal 4 tabletten/dag gedurende 3 dagen (volledige kuur)
- Ontslag na 2 dagen (31 mei)

- **Beleid**

- Start artesunaat 2.4 mg/kg i.v.
- Na 2 giften artesunaat i.v. switch  
→ atovaquone-proguanil (Malarone®) oraal 4 tabletten/dag gedurende 3 dagen (volledige kuur)
- Ontslag na 2 dagen (15 sep)

# Radboudumc

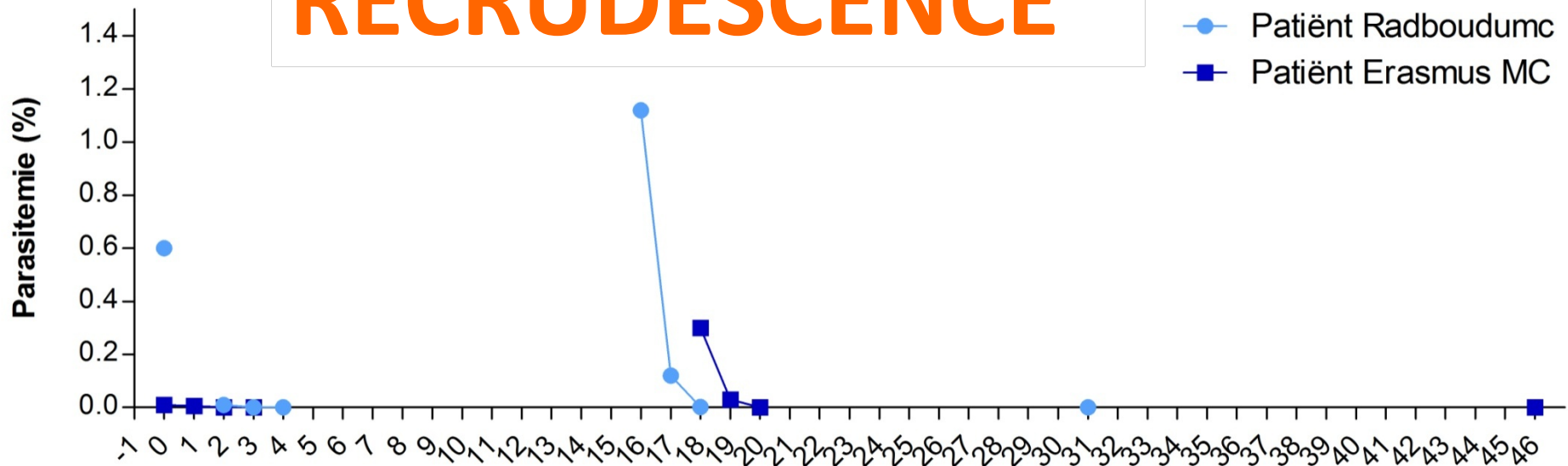






# Overview

## RECRUDESCENCE



### CDC:

'A repeated attack of malaria due to the survival of malaria parasites in red blood cells'

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$$N = 2$$

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# Efficacy van AL

- (Semi)-immune kinderen
  - Overall efficacy ~97%
- Non-immune reizigers
  - Overall efficacy ~95%
  - Minder goed gedocumenteerd
  - Diverse rapporten van therapiefalen



# Therapiefalen na AL

**Table 5. Published Reports of Artemether-Lumefantrine (AL) Treatment Failures and Studies of AL Effectiveness in Travelers Diagnosed in Malaria-Free Areas and Including Only the 3-Day AL Treatment Regimen**

| Reference              | Country                          | Study Design               | Patients, No. | Median Weight, kg | Male Sex, % | Age, y | Effectiveness of AL | Treatment Failures (AL), No. (%) | Median Weight, kg (Range) |
|------------------------|----------------------------------|----------------------------|---------------|-------------------|-------------|--------|---------------------|----------------------------------|---------------------------|
| All Study Subjects     |                                  |                            |               |                   |             |        |                     | Only Cases of Failure            |                           |
| Hatz, 2008 [4]         | Multicenter, Europe and Colombia | Prospective observational  | 165           | 73                | 68.5        | 17–66  | 96 (90.8–99.8)      | 6/165 (3.6%)                     | 85 (73–97)                |
| Mizuno, 2009 [6]       | Japan                            | Case report                | 1             | NA                | Yes         | 58     | NA                  | 1                                | NA                        |
| Repetto, 2011 [8]      | Italy                            | Case report                | 1             | NA                | Yes         | 32     | NA                  | 1                                | NA                        |
| Färnert, 2012 [9]      | Sweden                           | Case report                | 1             | 77                | Yes         | 57     | NA                  | 1                                | 77                        |
| Kutsuna, 2014 [7]      | Japan                            | Restrospective descriptive | 19            | NA                | NA          | NA     | NA                  | 3/19 (15.7%)                     | NA                        |
| Gray, 2015 [18]        | United States                    | Retrospective descriptive  | 98            | 71                | 58.6        | 1–88   | 95 (91.3–99.4)      | 4/98 (4.1%)                      | NA                        |
| Grynberg, 2015 [5]     | Israel                           | Retrospective comparative  | 25 AL, 44 AP  | NA                | 93.0        | ≥18    | NA                  | 1/25 (4%)                        | NA                        |
| Bochaud, 2016 [19]     | Multicenter, Europe              | Prospective observational  | 504 (39 AL)   | NA                | NA          | ≥18    | NA                  | 1/39 (2.6%)                      | NA                        |
| Sondén (current study) | Sweden                           | Retrospective descriptive  | 95            | 75                |             | ≥18    | 94.7 (88.1–98.3)    | 5/95 (5.2%)                      | 77 (70–121)               |

Abbreviations: AL, artemether-lumefantrine; AP, atovaquone-proguanil; NA, not available.

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# Therapiefalen – CID 2017

- Volwassen reizigers met ongecompliceerde *P. falciparum* malaria
- Behandeld met artemether-lumefantrine (AL)
- AL vaker laat therapiefalen dan bij mefloquine
  - Opnieuw parasitemie 7-42 dagen na microscopie negatief
  - 5.2% (5 / 95 patiënten)
- Allemaal non-immune, volwassen, Europese mannen
  - 27% failure rate



# Therapiefalen – CID 2017

## Risicofactoren:

1. Non-immuun
2. Volwassen mannen (> ~70kg)

**Table 3. Clinical Parameters at the Time of Admission and Treatment Regimens in Travelers With Artemether-Lumefantrine Treatment Failures After Treatment for Uncomplicated *Plasmodium falciparum* Malaria**

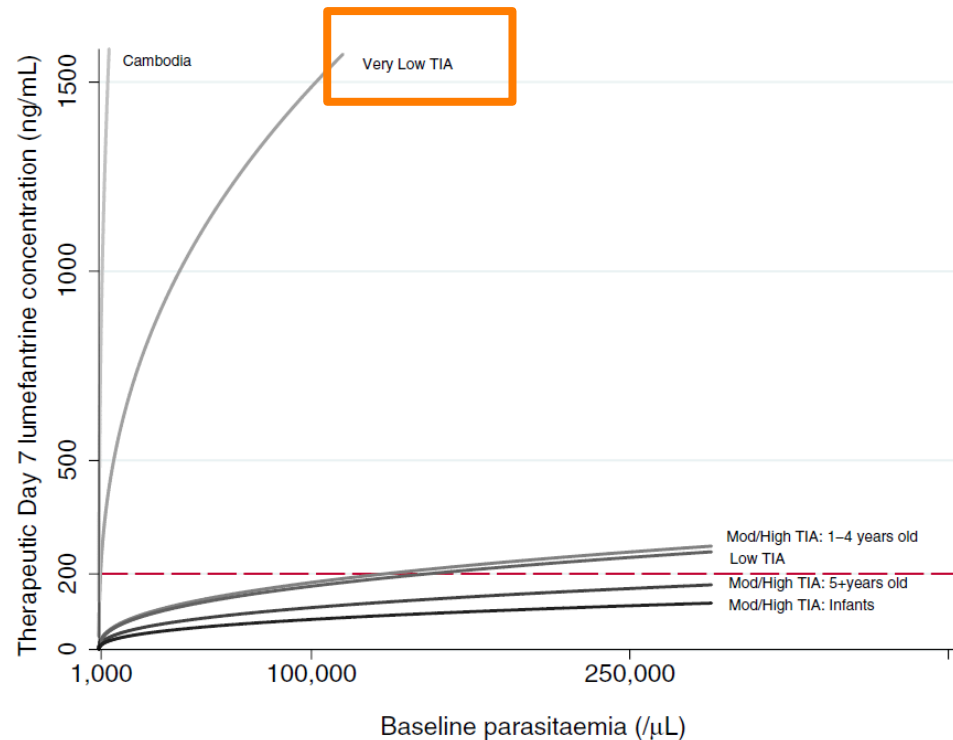
| Parameter                         | Case 1                         | Case 2                           | Case 3                  | Case 4             | Case 5                                     | Case 6 & 7 |
|-----------------------------------|--------------------------------|----------------------------------|-------------------------|--------------------|--------------------------------------------|------------|
| Body weight, kg                   | 77                             | 70                               | 121                     | 69                 | 78                                         | 96 95      |
| Age, y                            | 58                             | 43                               | 38                      | 32                 | 20                                         |            |
| Sex                               | Male                           | Male                             | Male                    | Male               | Male                                       |            |
| Country of birth                  | Sweden                         | France                           | Sweden                  | Sweden             | Sweden                                     |            |
| Country visited                   | Tanzania                       | Ghana                            | Tanzania and Mozambique | Gambia             | Thailand, Cambodia, Vietnam, and Indonesia |            |
| Year of diagnosis                 | 2012                           | 2013                             | 2014                    | 2015               | 2015                                       |            |
| First admission                   |                                |                                  |                         |                    |                                            |            |
| Parasitemia, %                    | 0.1                            | 2.1                              | 0.7                     | 1.4                | 0.3                                        |            |
| Signs of severity                 | None                           | None                             | None                    | None               | None                                       |            |
| Treatment                         | AL                             | AL                               | AL                      | AL                 | AL                                         |            |
| Second admission                  |                                |                                  |                         |                    |                                            |            |
| Days from initial treatment start | 24                             | 25                               | 28                      | 20                 | 20                                         | 16 18      |
| Parasitemia, %                    | 2.0                            | 0                                | 0.0                     | 0.9                | 0.2                                        |            |
| Fever at admission                | Yes                            | Yes                              | Yes                     | Yes                | Yes                                        |            |
| Signs of severity                 | Low blood pressure<br>Jaundice | Hyperparasitemia >5%<br>Jaundice | None                    | Jaundice           | None                                       |            |
| Treatment                         | MQ                             | IV quinine                       | AL                      | IV artesunate + AL | AL (5 d)<br>+ doxycycline                  |            |

Abbreviations: AL, artemether-lumefantrine; IV, intravenous; MQ, mefloquine.

# Non-immuun

- ↑ therapiefalen bij ↓ transmissie (en dus ↓ populatie-immuniteit)

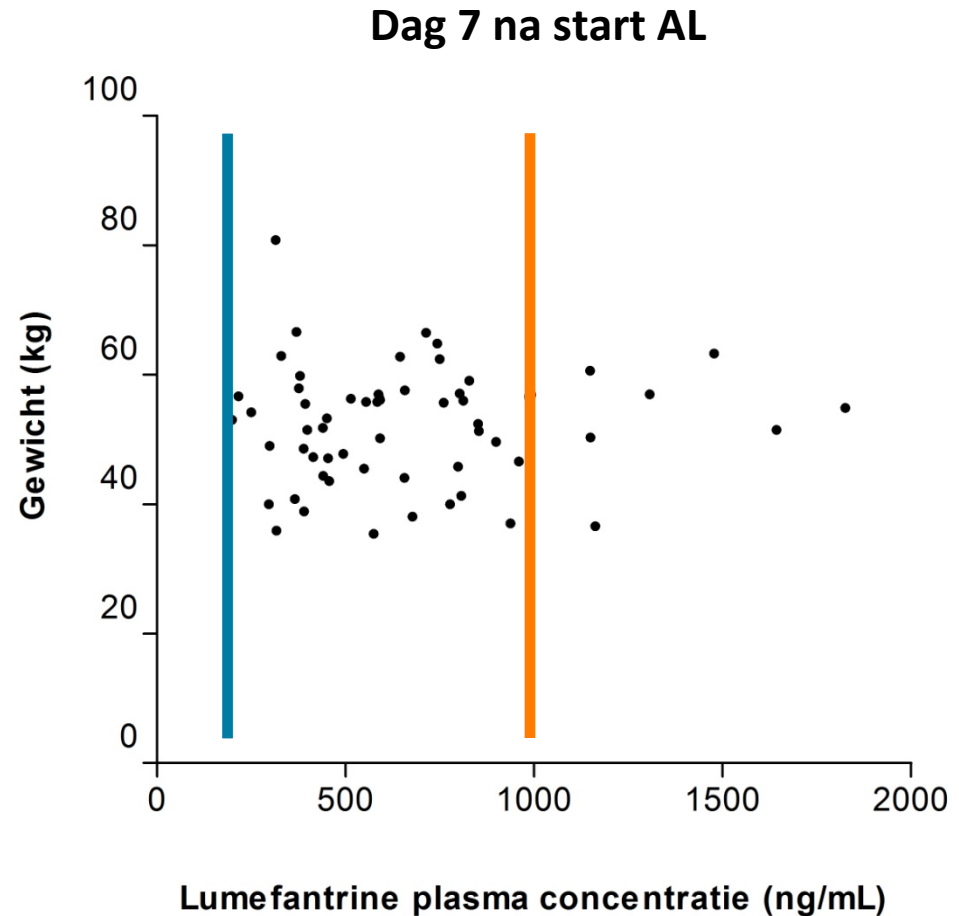
- Hoge concentratie lumefantrine (>1000 ng/mL op dag 7) nodig bij patiënten in very low transmission areas met lage parasitemie



**Fig. 3** Predicted day 7 lumefantrine concentrations needed to achieve a 95 % cure rate by day 42. Results are derived from multivariable Cox regression model (Table 3) for key patient populations. A zero study site effect was assumed. TIA, transmission intensity area

# Gewicht

- Novartis:
  - 'Demographic characteristics such as sex and weight appear to have no clinically relevant effects on the pharmacokinetics of Coartem.'
- Burkina Faso
  - Pearson  $r = 0.04$  (ns)





# Gewicht

- In vitro is 99.7% van lumefantrine gebonden aan plasma-eiwitten



- 2008: nadat AL op de markt is gebracht is een evaluatie van de efficacy nodig in populaties met hoger lichaamsgewicht

≥35 kg



# Gewicht

- Evaluatie van AL efficacy
  - Gepoolde analyse
  - Malaria-endemische gebieden
- Associatie tussen lumefantrine dosering en risico op recrudescence
- Laagste AL efficacy in patiënten met **<60 mg/kg** lumefantrine
  - 41% therapiefalen
- Patiënten  $\geq 70$  kg
  - 38.4 mg/kg lumefantrine

|                     | Number | Lumefantrine dose, mg/kg |            | Artemether dose, mg/kg |           |
|---------------------|--------|--------------------------|------------|------------------------|-----------|
|                     |        | Median (IQR)             | Range      | Median (IQR)           | Range     |
| Overall             | 14 327 | 68.6 (57.6–80.0)         | 26.2–144.0 | 11.4 (9.6–13.3)        | 4.4–24.0  |
| Age category, years |        |                          |            |                        |           |
| <1                  | 815    | 90.0 (81.8–102.9)        | 40–144     | 15.0 (13.6–17.1)       | 6.7–24    |
| 1 to <5             | 7333   | 68.6 (60.0–80.0)         | 37.9–144   | 11.4 (10–13.3)         | 6.3–24    |
| 5 to <12            | 2980   | 73.8 (65.5–83.1)         | 32–120     | 12.3 (10.9–13.8)       | 5.3–20    |
| $\geq 12$           | 3199   | 57.6 (49.7–65.5)         | 26.2–91.9  | 9.6 (8.3–10.9)         | 4.4–15.3  |
| Weight category, kg |        |                          |            |                        |           |
| 5 to <10            | 2074   | 85.7 (80.0–94.7)         | 37.9–144.0 | 14.3 (13.3–15.8)       | 6.3–24.0  |
| 10 to <15           | 4957   | 60.0 (55.4–67.3)         | 42.9–100.7 | 10.0 (9.2–11.2)        | 7.1–16.8  |
| 15 to <25           | 3396   | 80.0 (72.0–90.0)         | 39.6–105.0 | 13.3 (12.0–15.0)       | 6.6–17.5  |
| 25 to <35           | 963    | 74.5 (68.4–83.1)         | 42.4–96.9  | 12.4 (11.4–13.8)       | 7.1–16.2  |
| 35 to <70           | 2724   | 57.0 (50.5–64.0)         | 30.9–82.3  | 9.5 (8.4–10.7)         | 5.1–13.7  |
| $\geq 70$           | 213    | 38.4 (36.0–40.6)         | 26.2–41.1  | 6.4 (6.0–6.8)          | 4.4–6.9   |
| Region              |        |                          |            |                        |           |
| Asia                | 2359   | 61.3 (55.4–72.0)         | 30.9–120.0 | 10.2 (9.2–12.0)        | 5.1–20.0  |
| Africa              | 11 809 | 71.3 (60.0–80.9)         | 28.2–144.0 | 11.9 (10.0–13.5)       | 4.7–24.0  |
| South America       | 159    | 45.0 (40.6–53.3)         | 26.2–82.3  | 7.5 (6.8–8.9)          | 4.4–13.7  |
| Drug tradename      |        |                          |            |                        |           |
| Artrin              | 118    | 74.8 (60–90.0)           | 51.4–120.0 | 12.5 (10–15.0)         | 8.6–20.0  |
| Co-artesiane        | 134    | 71.1 (69.4–74.8)         | 60.7–79.2  | 11.8 (11.6–12.5)       | 10.1–13.2 |
| Coartem             | 14 075 | 68.4 (57.6–80.0)         | 26.2–144.0 | 11.4 (9.6–13.3)        | 4.4–24.0  |

Table 2: Total lumefantrine and artemether doses

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# Conclusie

- In non-immune volwassenen lijkt relatief veel therapiefalen te zijn na AL
  - Risicogroep: Europese mannen > ~70 kg
    - Nu ook in Nederland beschreven
    - Exacte oorzaak onbekend, meerdere factoren
      - Immuniteit
      - Gewicht
- Dosering AL lijkt in deze groep onvoldoende te zijn**

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# Discussie

Ongecompliceerde *P. falciparum* malaria in volwassenen

## SWAB Radboudumc

- Artemether-lumefantrine (Riamet®) po
  - Niet als patiënt mefloquine profylaxe heeft gebruikt
- Atavaquone-proguanil (Malarone®) po
  - Niet als patiënt atavaquone-proguanil profylaxe heeft gebruikt

## SWAB ErasmusMC

1. Atovaquone-proguanil po
2. Artemether-lumefantrine po

**Riamet® po, maar niet  
indien patiënt non-  
immuun, >70kg en man**

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# Dankwoord

- Lisa Meekes & Jaap van Hellemond



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**Radboudumc**

- Els van Nood



- Jean-Luc Murk

