Update on management of Malaria

Dr Owen Tsang

23 August 2022

IC forum

要聞港聞 2002年09月25日 國泰空姐瘧疾遲送院枉死

蚊叮奪命疑案專家作供 國泰空姐瘧疾遲送院枉死

2002

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熱帶病專家鍾世文醫生昨出庭作供。 梁家亮攝

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A 讚 熱帶病專家鍾世文醫生昨出庭作供。 梁家亮攝

【本報訊】三十二歲國泰日籍空姐出勤往南非疑遭瘧蚊叮，返港後不適及發燒，到診所求醫惟未見好轉，最後入院證實染上瘧疾死亡。熱帶病專家昨在死因庭作供指，若該名空姐能及早送院治理，獲救機會極高；由於瘧疾與感冒的病徵相若，醫生對持續發燒病者應詢問其旅遊經歷及進行驗血，專家意見認為機組人員甚至市民對瘧疾的知識明顯不足。

第二名替死者診斷的劉醫生表示，知道該空姐之前曾求醫但未見好轉，且連續發燒四天，他經診斷後認為病人患感冒，當時沒有詢問她的旅遊經歷及建議進行驗血，只開出感冒藥及建議兩日後覆診。

瘧疾似感冒易誤診

熱帶病專家鍾世文醫生供稱，該空姐知念明子於去年十二月十一日深夜被送往嘉勒撒醫院，由他負責診斷。病人當時神志不清，病況嚴重，其後證實患上一種名為（ Cerebral Malaria）的瘧疾，由於病人出現心律不正，曾替她進行換血

遊東非遇蚊叮 港婦瘧疾命危

今年七宗傳入個案 西貢兩公里揪媒蚊

本港錄得瘧疾個案 *截至8月16日

年份	宗數
2013	20
2014	23
2015*	7

今年7宗瘧疾傳入地點

印度	2	巴基斯坦	1
印尼	1	馬達加斯加	1
科特迪瓦	1	未能分類	1

資料來源：衞生防護中心

提高警覺

本港有市民到東非旅遊時被蚊叮感染瘧疾，目前情況危殆。該名居於西貢的女患者曾兩度到將軍澳醫院急症室求醫，第二次求診才獲入院治療。衞生防護中心昨表示，至今無發現同村居民出現感染，食物環境衞生署將在患者居所外方圓兩公里調查瘧疾媒蚊。有傳染病專家指出，本地瘧疾個案自九八年起絕迹，迄今發現的病例屬外地感染。殺傷力大的瘧原蟲可在人體內高速繁殖，經血液入侵器官，若及早知道患者旅遊史，可盡早以快速測試確診及作適切治療。

女患者四十四歲，過往健康良好，居於西貢南山村浪尾。她於七月廿一至三十一日與丈夫到訪東非馬達加斯加，返港後在八月九日開始出現發燒及腸嘔病徵，分別於十三日及十四日到將軍澳醫院急症室求醫，十四日入院，目前情況危殆，於深切治療部留醫。患者丈夫趙先生證實事件，他昨探訪太太，形容她病情已趨穩定。食環署表示，過去一年平均每星期到西貢南山村浪尾滅蚊一次。為審慎起見，將派員到患者處所調查，並向村民宣傳防蚊。

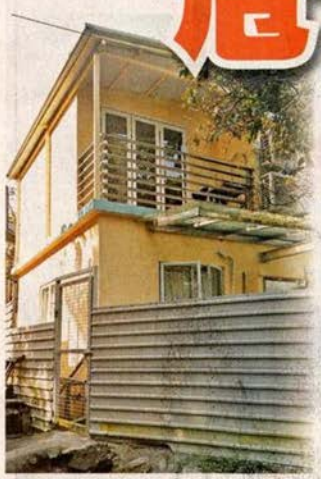
瘧原蟲經血液侵器官致衰竭

將軍澳醫院表示，女病人十三日求診時透露曾前往非洲國家，當天沒有發燒，醫生臨床診斷為腸胃炎並處方藥物。但翌日再求診時，病人發高燒及神志混亂，急症室醫生診斷為懷疑傳染病，並抽血化驗，其後病人情況轉差，十五日轉送深切治療部。

連同此個案，衞生防護中心今年至今共錄七宗瘧疾，當中六宗屬外地傳入，一宗未能分類。中文大學感染及傳染病學教授李禮舜指出，近年在港發現個案均由外地傳入，以印度、巴基斯坦及非洲國家傳入佔多。他解釋，瘧疾由按蚊將瘧原蟲傳人，瘧原蟲可分五種，殺傷力各有不同，以惡性瘧原蟲殺傷力最大。惡性瘧原蟲進入人體後，可在血液高速繁殖，再經血液入侵器官，導致多重器官衰竭，甚至死亡。

到高危地區前應先求醫配藥

李禮舜透露，上周他亦接獲一名南亞商人士自巴基斯坦回港後確診瘧疾，幸及時得知旅遊史，盡快進行緊急血液測試，確診後立即處方抗瘧疾藥物及支援性治療，病人現況穩定。他提醒，市民若準備到瘧疾高危國家，可於出發前求醫獲取預防藥物，出發前直至離開該地區後一至四周仍要服用。若返港後出現發燒、肌肉痛等徵狀，應盡快求醫，並清楚報告旅遊史。



■女患者位於浪尾的居所。（朱先儒攝）

瘧原蟲

2015

2017

初診未透露上月遊非洲加納

港女染瘧疾失知覺命危

一名40歲女子曾於上月到訪非洲加納，返港約兩周後因咳嗽、發燒及肌肉疼痛等到瑪麗醫院急症室求診，當時她未有向分流護士透露曾外遊，而醫生臨床診治為上呼吸道感染。三天後，她因上腹部疼痛、嘔吐、血尿等症狀再求醫，此時才向急症室醫生表明外遊紀錄，但病情已急轉直下，同日安排入院不久已失去知覺，出現腦水腫，需要急救及插喉協助呼吸，經血液化驗證實病人感染瘧疾，現情況危殆。瘧疾傳播途徑是被受感染的瘧蚊叮咬，不會在人傳人，但可透過血液傳播，而瘧疾亦可在懷孕或生產時經母體傳給胎兒或初生嬰兒。　本報港聞部報道

瘧疾是一種可致命的嚴重疾病，現時藥物可有效治療，但及早確診和治療對徹底治癒瘧疾尤為重要。根據瑪麗醫院昨天公布的資料，該名肇事女病人相信錯過治療的黃金時機。該病人仍在成人深切治療部留醫，情況危殆。院方會繼續跟進病人情況提供適切治療。

肝功能受損 出現腦水腫

瑪麗醫院發言人昨天公布一宗外地傳入病人感染罕見及嚴重瘧疾個案，患者一名40歲女子，她於上周三中午因咳嗽、發燒、喉嚨痛及肌肉疼痛到瑪麗醫院急症室求診。分流護士曾詢問病人最近十日的外遊紀錄，病人表示並無外遊，醫生診斷病人患上上呼吸道感染，病人獲處方治療上呼吸道感染的藥物後離開急症室。

該名病人於本月1日早上，因為上腹部疼痛、嘔吐、血尿等症狀再到該院急症室。急症室醫生於上午8時半左右為她診治，並安排抽血檢驗，初步血液報告顯示其肝功能受損，於是安排病人轉往內科病房作進一步治療，其間急症室醫生再次查詢病人的病歷，病人表示曾於3月8日至16日到訪非洲加納。

病人中午左右轉抵內科病房，但下午情況轉差，於下午2時十分失去知覺，需要急救及插喉協助呼吸。及後腦部掃描證實病人出現腦水腫，而血液報告亦證實病人感染瘧疾，病人隨即被轉往成人深切治療部，微生物學醫生亦到場會診，並於下午4時半左右展開瘧疾的藥物治療。

瘧疾屬於須呈報的傳染病，瘧疾常見於非洲、東南亞及南美洲等氣候溫暖的熱帶及亞熱帶地區，市民如須前往有關地區，應注意防蚊，並在出發前最少六個星期諮詢醫生意見，以便採取預防措施及於需要時獲取預防瘧疾的藥物。

潛伏期可達數月或更長

一般而言，瘧疾的潛伏期會因應不同的致病瘧原蟲種類而有所不同，通常在被受感染的瘧蚊叮咬七至三十日天後出現病徵，但潛伏期可達數月或更長。患者通常有間歇性發燒、發冷、冒汗、頭痛、疲倦、噁心、嘔吐及肌肉疼痛等徵狀，併發症包括貧血、肝臟及腎臟衰竭，嚴重個案可引致腦部水腫、誘發痙攣、神志不清及昏迷。如在外遊期間或回港後出現瘧疾徵狀，應立即求診並主動透露近期的外遊紀錄，以便盡快安排治療。

一宗嚴重瘧疾個案時序 資料來源：瑪麗醫院

3月8日至16日	一名40歲女子到訪非洲加納
3月29日中午	她因咳嗽、發燒、喉嚨痛及肌肉疼痛到瑪麗醫院急症室求診，當時病人無向分流護士提及曾外遊。醫生診斷病人患上呼吸道感染，獲處方治療藥物後離開
4月1日	
上午8時30分	該女子因上腹部疼痛、嘔吐、血尿等症狀再到瑪麗急症室求診，急症室醫生安排她抽血檢驗，初步血液報告顯示其肝功能受損，於是安排病人轉往內科病房作進一步治療。期間，急症室醫生再查詢病歷，病人表示曾外遊
中午12時半	轉抵內科病房
下午2時10分	情況轉差，失去知覺，需要急救及插喉協助呼吸，出現腦水腫。血液報告證實感染瘧疾
下午4時30分	轉往深切治療部，開始瘧疾的藥物治療，現仍留醫，情況危殆

August 2022

專家指從未見「身體咁多蟲」

瘧疾增1患者亡 港擬全球購藥

本報記者

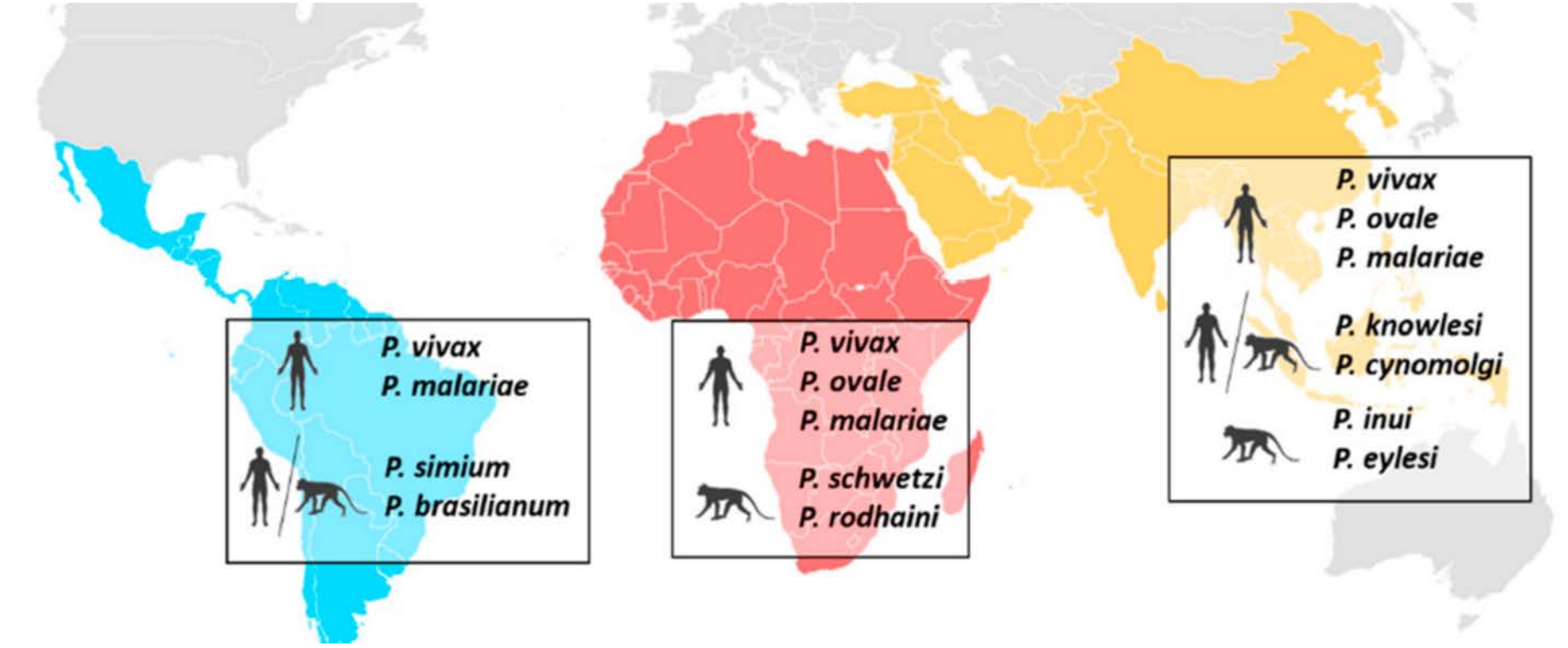
本港近月錄得三十宗瘧疾輸入個案，當中更有一人死亡。衞生防護中心指，三十名男子由非洲抵港，均在指定檢疫酒店確診瘧疾，一名男性在檢疫期間死亡，驗屍報告顯示他帶有瘧原蟲。專家更指「咁耐以來都無含瘧疾嘅種蟲咁多喺體內」。醫管局有需要時會在全球採購藥物。

篩查幾內亞抵港旅客

何栢良憂藥物不足

How many human strains of Plasmodium?

	P. vivax-like	*P. malariae*-like	*P. ovale*-like	*P. knowlesi*
Infects human	*P. vivax*	*P. malariae*	*P. ovale curtisi* *P. ovale wallikeri*	
Infects human and monkey	*P. cynomolgi* *P. simium*	*P. brasilianum*		*P. knowlesi*



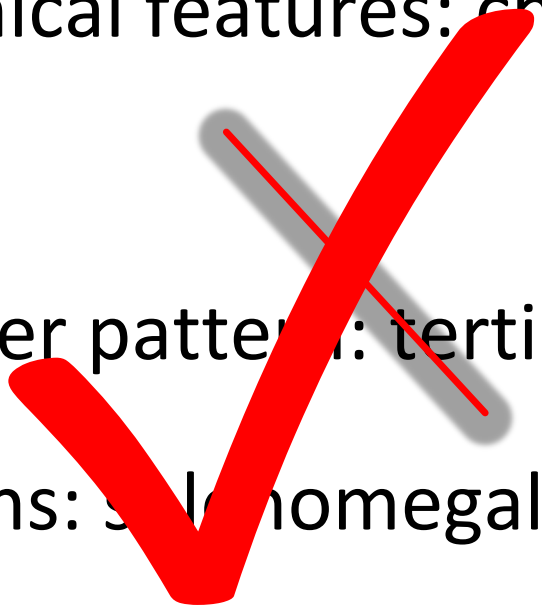
Hang JW, et al. ***Pathogens****. 2021 Jul 13;10(7):889.*

Difficult to make a diagnosis of malaria?

Yes or No

History and physical examination

- Typical clinical features: chill, headache, malaise…
- Typical fever pattern: tertian, Quantan
- Typical signs: splenomegaly, anemia
- Typical incubation period



SYMPTOMS OF MALARIA

Headache

Fever

Fatigue

Muscel pain

Back pain

Chills

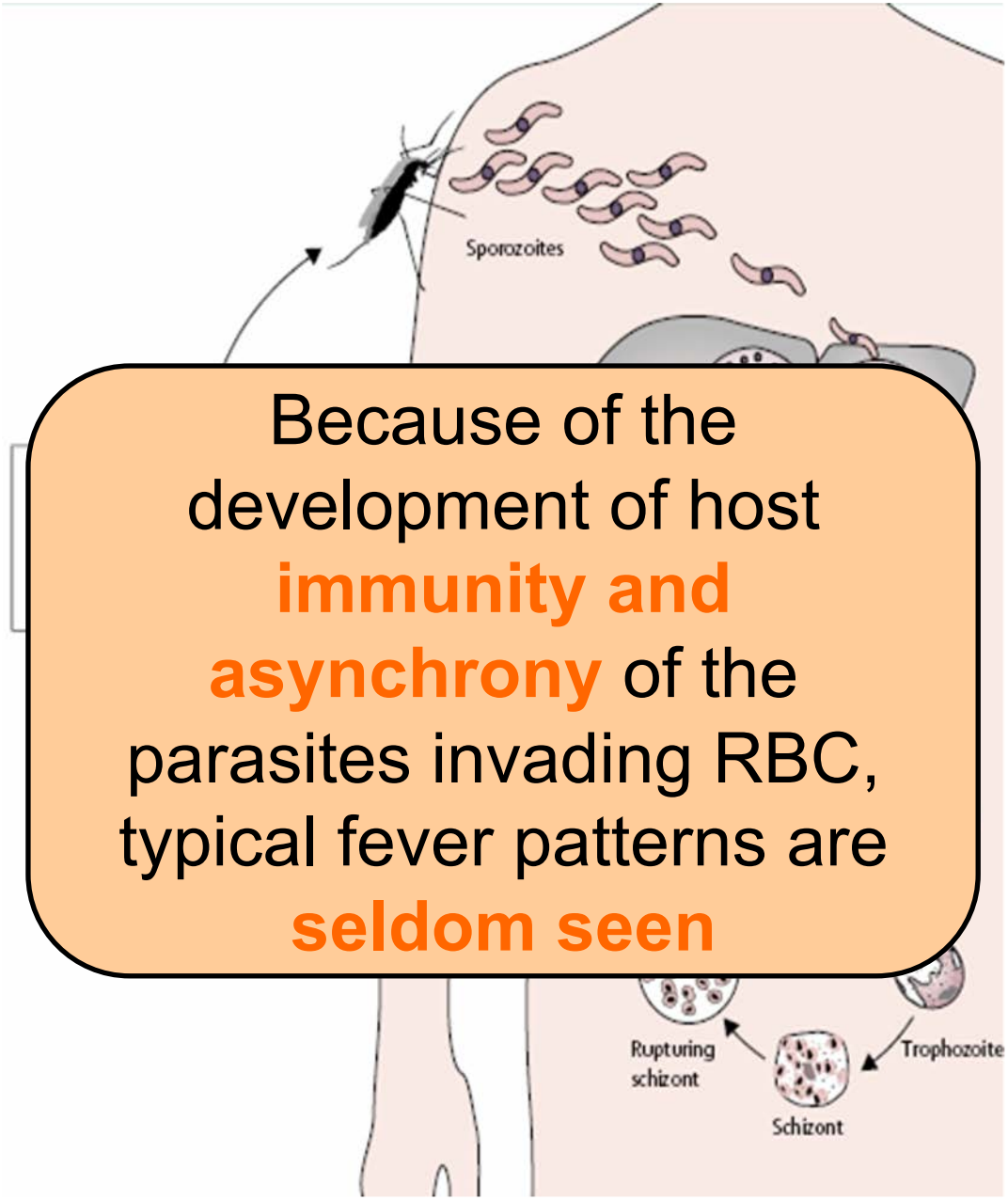
Sweating

Dry cough

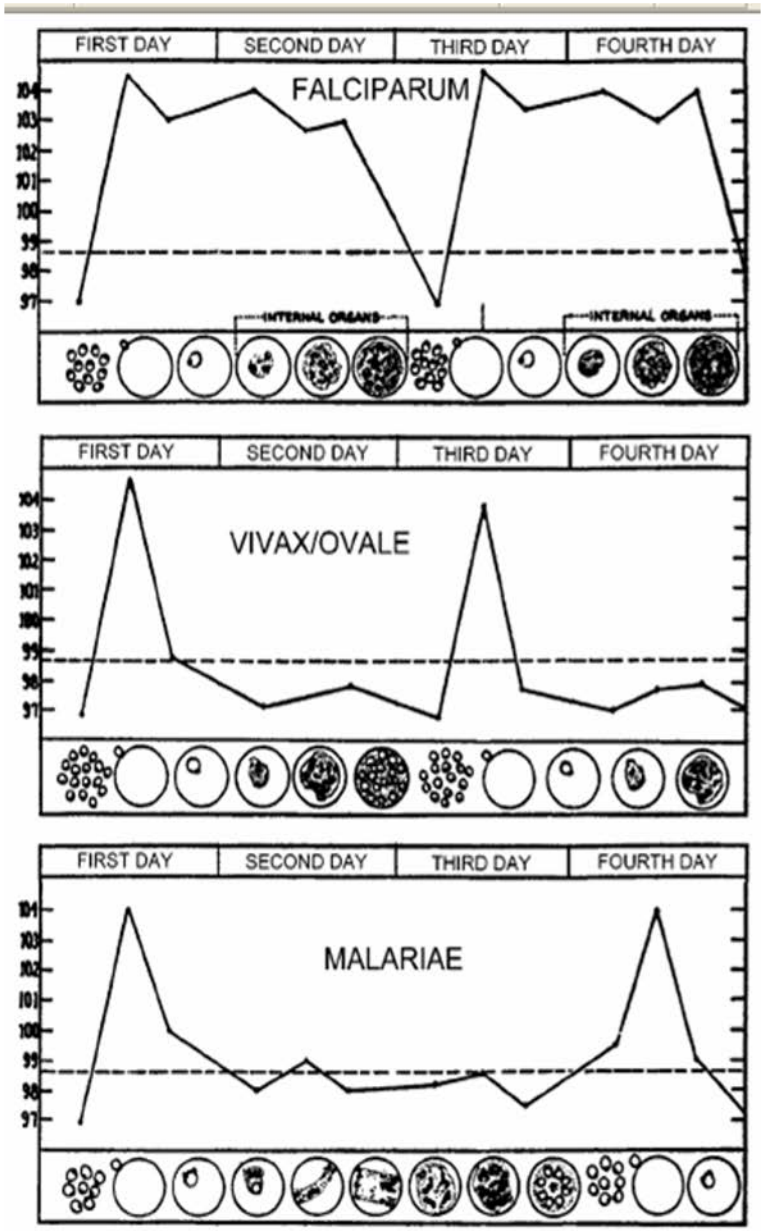
Enlarge-ment

Nausea

Vomiting



Because of the development of host **immunity and asynchrony** of the parasites invading RBC, typical fever patterns are **seldom seen**



Greenwood BM, et al. ***Lancet*** *2005; 365: 1487–98*

Disease Severity and Duration

	vivax	ovale	malariae	falciparum
Prepatent Period (days)	8-12	8-12	15-18	6-9
Incubation Period (days)	8-27	8-27	16->40	6-25
Severity of Initial Paroxysms	moderate to severe	mild	mild to moderate	severe
Average Parasitemia (per mm^3)	20,000	9,000	6,000	50,000-500,000
Maximum Parasitemia (per mm^3)	50,000	30,000	20,000	2,500,000
Typical Symptom Duration (untreated)	3-8 weeks	2-3 weeks	3-24 weeks	2-3 weeks
Maximum Infection Duration (untreated)	5-8 years*	12-20 months*	20-50 years	6-17 months
Anemia	++	+	++	++++
Other Complications			renal	cerebral

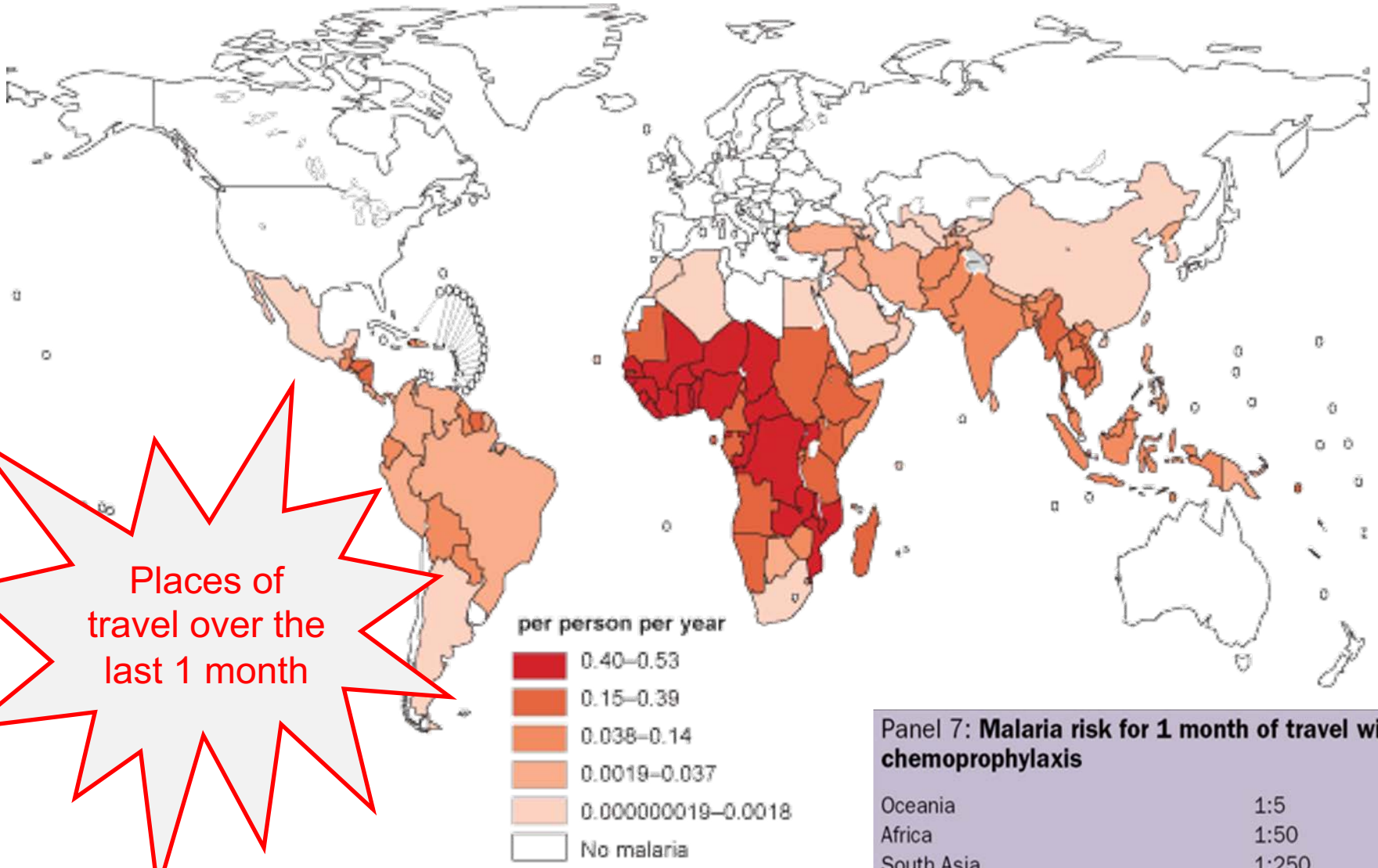
*Includes relapses

Difficult to predict malaria from the incubation period

Table 2
Incubation periods for diseases

Incubation Period	Diseases
<7 Days	Common: malaria, traveler's diarrhea, dengue, enteric fever, respiratory tract infection Others: rickettsioses, leptospirosis, meningitis, yellow fever, arbovirus, meningococcal
7–21 Days	Common: malaria, enteric fever Others: rickettsioses, viral hepatitis, leptospirosis, HIV, Q fever, brucellosis, African trypanosomiasis
>21 Days	Common: malaria, enteric fever Others: tuberculosis, hepatitis B virus, bacterial endocarditis, HIV, Q fever, brucellosis, amebic liver disease, melioidosis

Wattel C et al. ***Med Clin N Am 2012:****96;1225–1255*



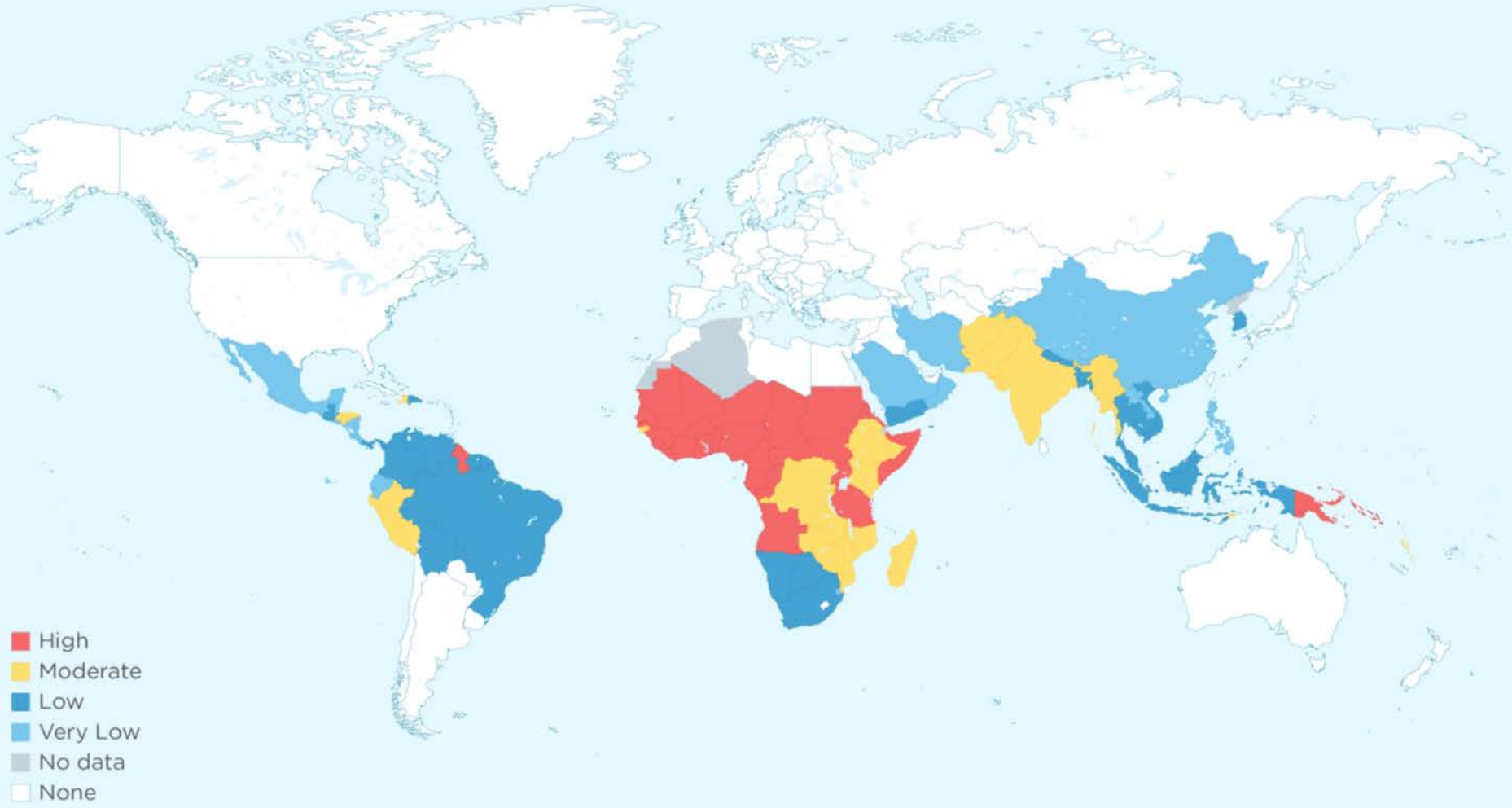
Places of travel over the last 1 month

Panel 7: **Malaria risk for 1 month of travel without chemoprophylaxis**

Oceania	1:5
Africa	1:50
South Asia	1:250
Southeast Asia	1:2500
South America	1:5000
Mexico and Central America	1:10 000

Spira AM. ***Lancet*** *2003;361:1459-69*

2018 Malaria Heat Map By CDC Estimated Risk



Data sourced from CDC, July 2018: https://www.cdc.gov/malaria/travelers/country_table/a.html

The message

Malaria can kill!

Everybody must know!

Travel history to endemic areas should be alert!

Symptoms can be vague!

Clinical

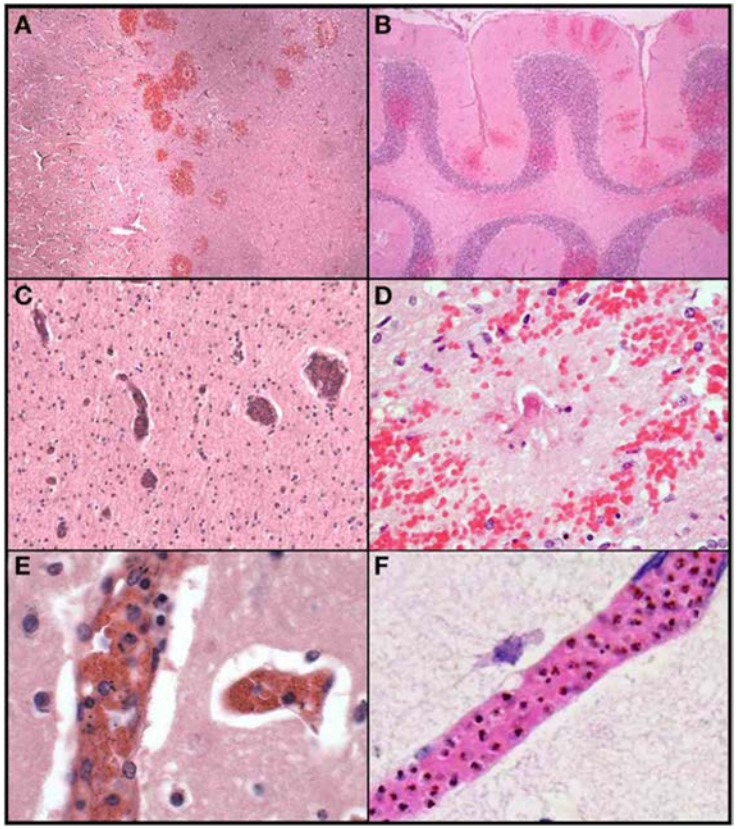
	Uncomplicated	Complicated
Species	Any	Falciparum mostly
Symptoms	Non-specific	Organs specific symptoms
P/E	Mild anemia, Mild splenomegaly	ARDS, circulatory collapse, renal failure, liver failure, metabolic acidosis, hypoglycemia, DIC, severe anemia
Parasitemia	< 5 parasites/ml of blood < 0.1% parasitized RBC	Hyperparasitemia: ≥ 1000 parasites/ml ≥ 5-10% parasitized RBC In Low transmission region: 5% In high transmission region: 10%
Cytoadherence	No	Yes
Cerebral malaria	Low risk	High risk
Mortality	Low	Severe anemia: 1% Metabolic acidosis: 15% Coma: 18%

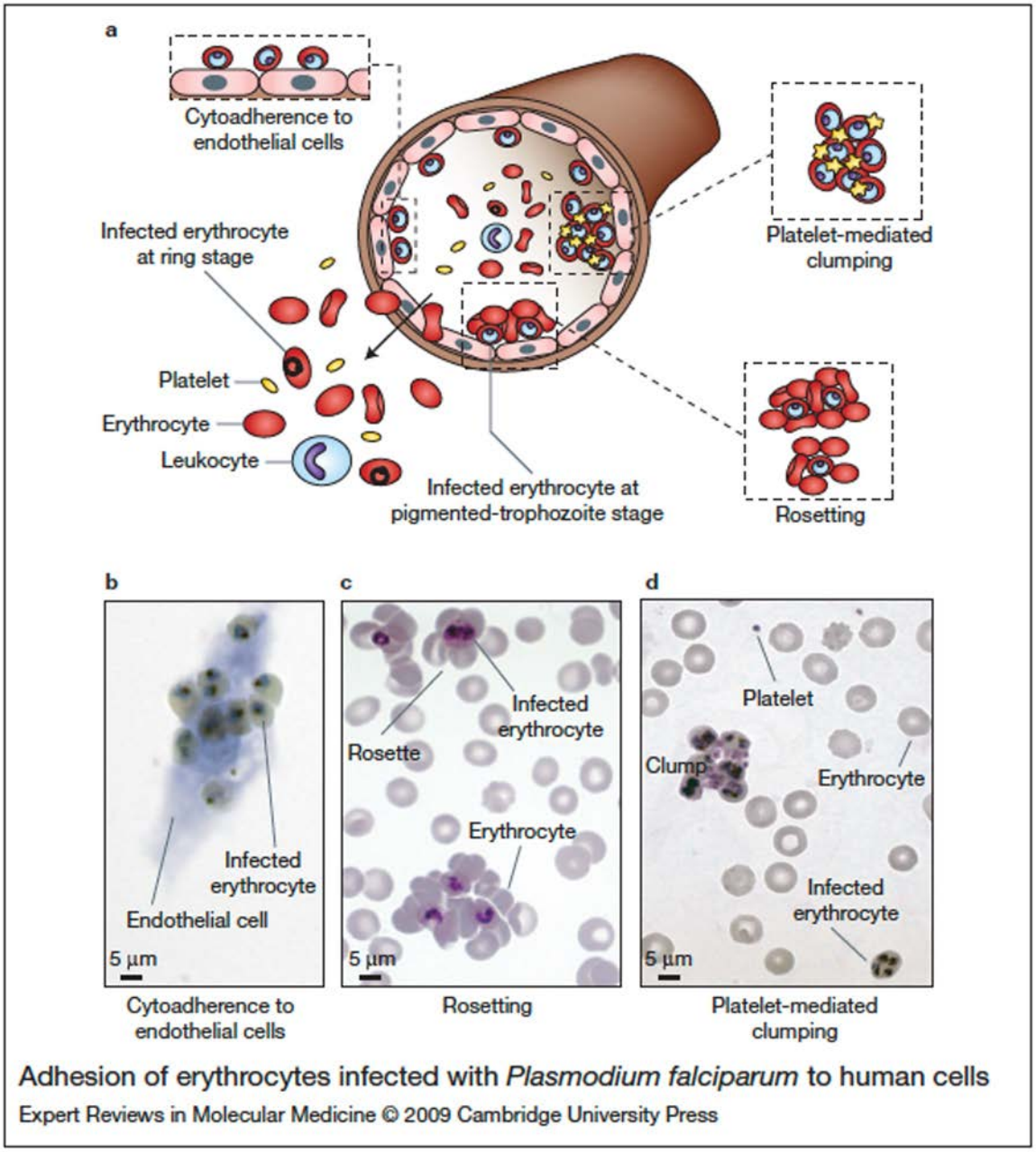
Severe Falciparum malaria

≥ 1 of the following, in the presence of P. falciparum asexual parasitaemia & after excluding other causes	
Impaired consciousness	GCS < 11 in adults or a Blantyre coma score < 3 in children
Prostration	unable to sit, stand or walk without assistance
Convulsions	> 2 episodes within 24 h
Acidosis	BE > 8 mEq/L, bicarbonate < 15 mmol/L or venous lactate ≥ 5 mmol/L.
Hypoglycaemia	Blood or plasma glucose < 2.2 mmol/L (< 40 mg/dL)
Severe anaemia	Hb ≤ 5 g/dL or a HCT ≤ 15% in children < 12 years of age (< 7 g/dL and < 20%, respectively, in adults) with a parasite count > 10 000/µL
Renal impairment	Cr > 265 µmol/L (3 mg/dL) or blood urea > 20 mmol/L
Jaundice	bilirubin > 50 µmol/L (3 mg/dL) with a parasite count > 100 000/ µL
Pulmonary oedema	Radiologically confirmed or SaO2 < 92% on RA with RR > 30/min
Significant bleeding	Recurrent or prolonged bleeding
Shock	Compensated shock: capillary refill ≥ 3 s or temperature gradient on leg (mid to proximal limb), but no hypotension. Decompensated shock: systolic BP < 70 mm Hg in children or < 80 mm Hg in adults, with evidence of impaired perfusion (cool peripheries or prolonged capillary refill).
Hyperparasitaemia	P. falciparum parasitaemia **> 10%**

WHO. Guideline for treatment of malaria

Pathogenesis of severe falciparum malaria





Adhesion of erythrocytes infected with *Plasmodium falciparum* to human cells

Milner DA Jr, et al. ***Front Cell Infect Microbiol****. 2014.*
Rowe JA, et al. ***Expert Rev Mol Med****. 2009.*

Treatment

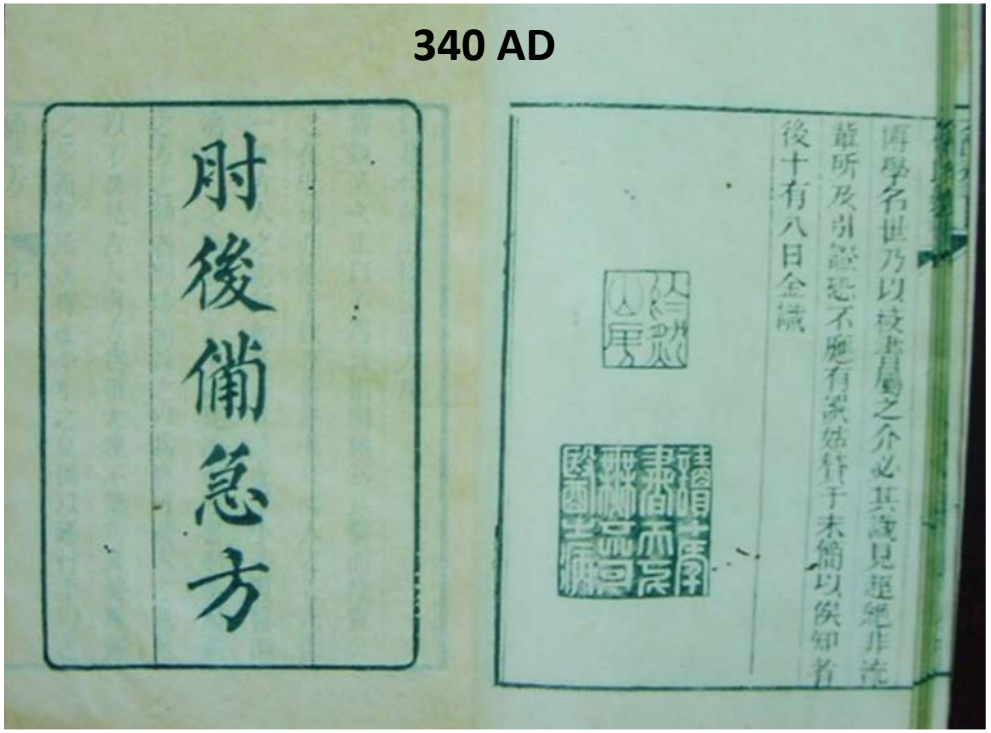
Management

- Objectives: to cure the infection as rapidly as possible and to prevent progression to severe disease
- Antimalarials ASAP even before the diagnosis if highly suspicious
- Supportive: Fluid, O2, monitoring of vital, GCS
- Consider LP for patients with impaired sensorium to R/O CNS infections
- Call ICU Dr Yung early for deterioration
- Watch out for hypoglycemia and clotting profile, especially in severe cases
- Monitor major organs: Liver, kidney, CNS, Resp and cardiac
- Empirical antibiotics for septic cases, especially in children

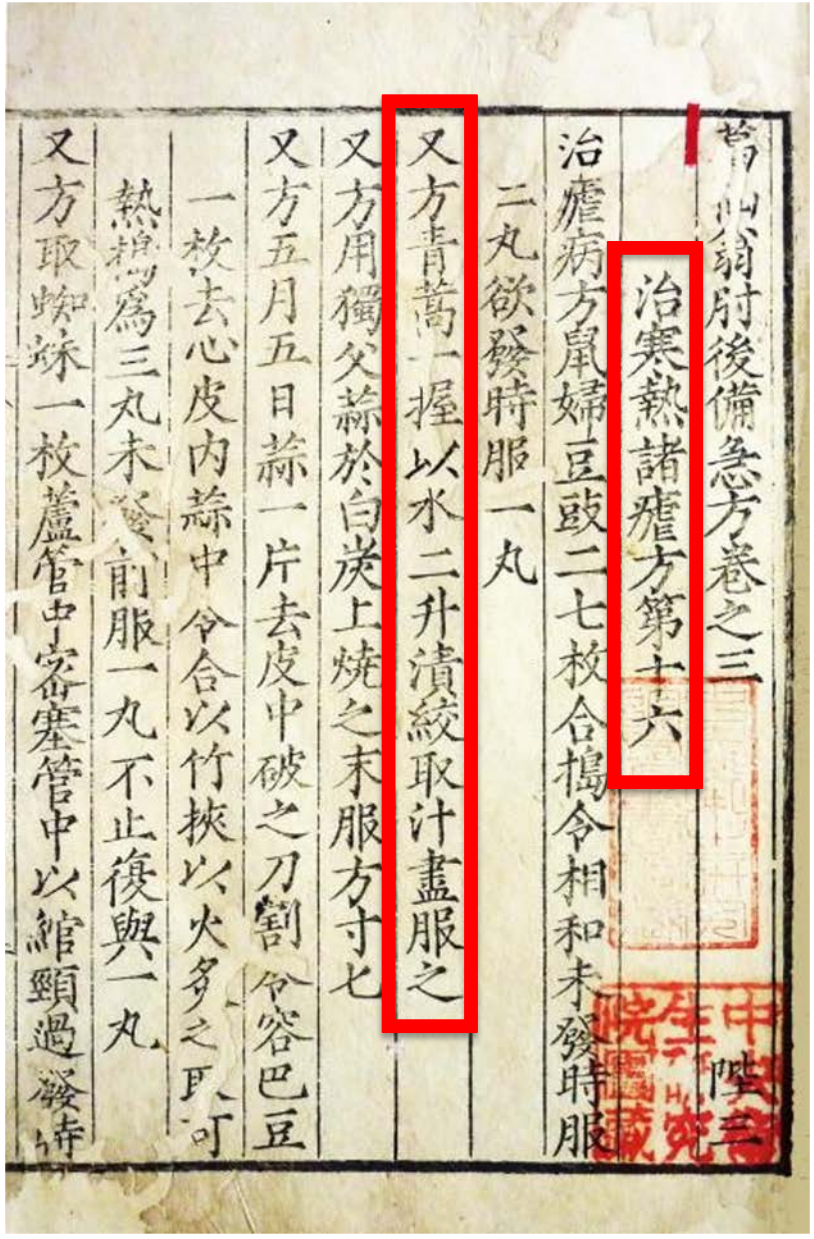
WHO guideline 2022

Manifestation or complication	Immediate management[a]
Coma (cerebral malaria)	Maintain airway, place patient on his or her side, exclude other treatable causes of coma (e.g. hypoglycaemia, bacterial meningitis); avoid harmful ancillary treatments, intubate if necessary.
Hyperpyrexia	Administer tepid sponging, fanning, a cooling blanket and paracetamol.
Convulsions	Maintain airways; treat promptly with intravenous or rectal diazepam, lorazepam, midazolam or intramuscular paraldehyde. Check blood glucose.
Hypoglycaemia	Check blood glucose, correct hypoglycaemia and maintain with glucose-containing infusion. Although hypoglycaemia is defined as glucose < 2.2 mmol/L, the threshold for intervention is < 3 mmol/L for children < 5 years and <2.2 mmol/L for older children and adults.
Severe anaemia	Transfuse with screened fresh whole blood.
Acute pulmonary oedemab	Prop patient up at an angle of 45o, give oxygen, give a diuretic, stop intravenous fluids, intubate and add positive end-expiratory pressure or continuous positive airway pressure in life-threatening hypoxaemia.
Acute kidney injury	Exclude pre-renal causes, check fluid balance and urinary sodium; if in established renal failure, add haemofiltration or haemodialysis, or, if not available, peritoneal dialysis.
Spontaneous bleeding and coagulopathy	Transfuse with screened fresh whole blood (cryoprecipitate, fresh frozen plasma and platelets, if available); give vitamin K injection.
Metabolic acidosis	Exclude or treat hypoglycaemia, hypovolaemia and septicaemia. If severe, add haemofiltration or haemodialysis.
Shock	Suspect septicaemia, take blood for cultures; give parenteral broad- spectrum antimicrobials, correct haemodynamic disturbances.

History of Artemisinin



Emergency medicine



肘後備急方卷之三

治寒熱諸瘧方第十六

治瘧病方鼠婦豆豉二七枚合搗令相和未發時服三丸欲發時服一丸

又方青蒿一握以水二升漬絞取汁盡服之

又方用獨父蒜於白炭上燒之末服方寸七

又方五月五日蒜一片去皮中破之刀割令容巴豆一枚去心皮內蒜中令合以竹挾以火炙之可熱搗爲三丸未發前服一丸不止復與一丸

又方取蜘蛛一枚盧管中密塞管中以綿頸過發時

2015 Nobel Prize winner Tu You You 屠呦呦

詩經: 小雅·鹿鳴

- 呦呦鹿鸣，食野之苹。
  .....
- 呦呦鹿鸣，食野之蒿。
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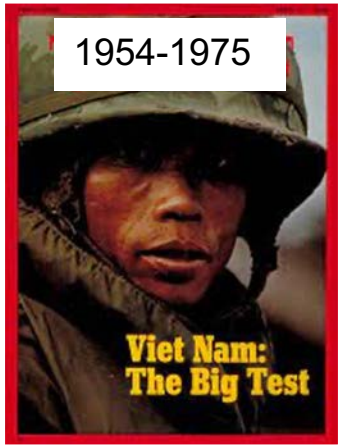
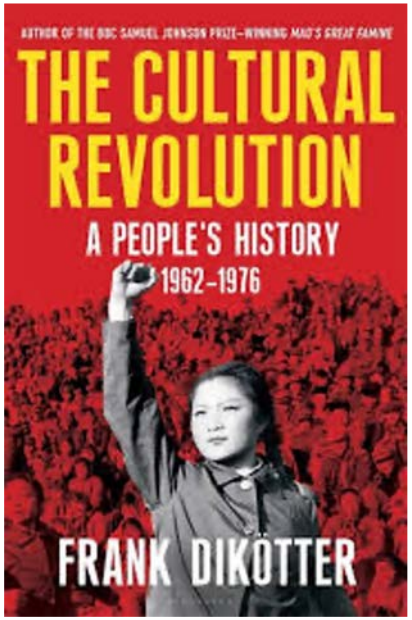
青蒿

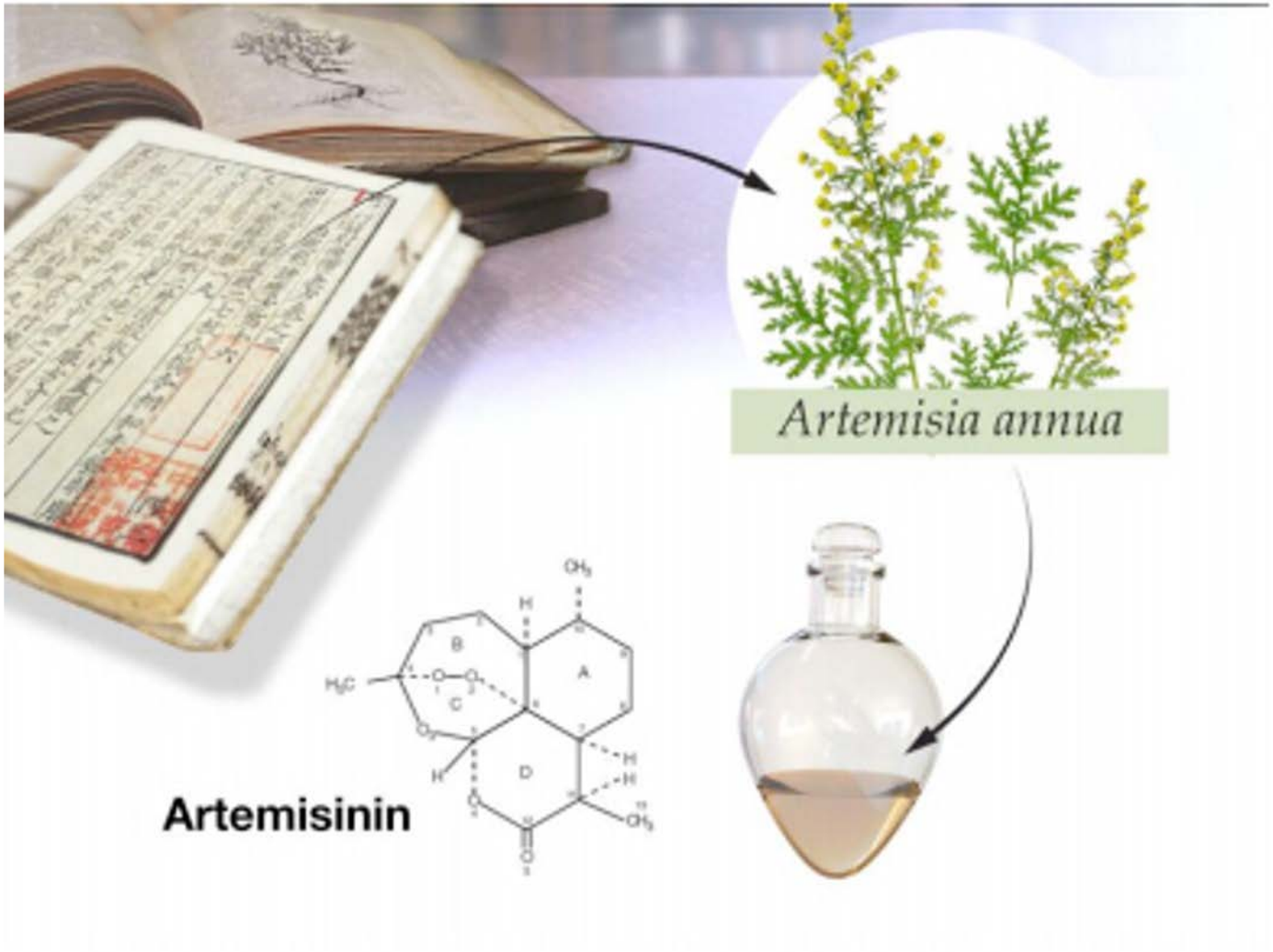
Discovery of Artemisinin

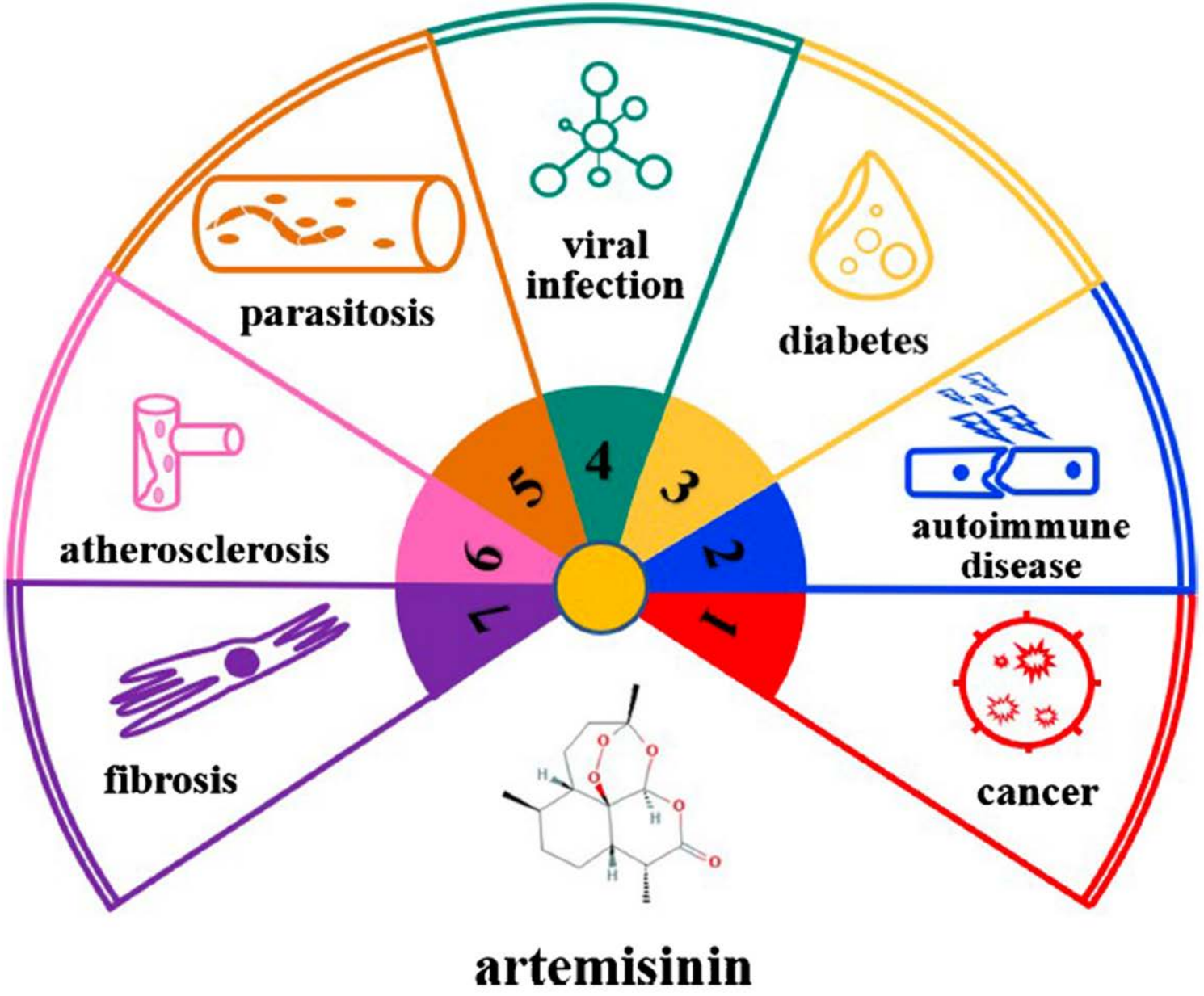


23 – 5 - 1967



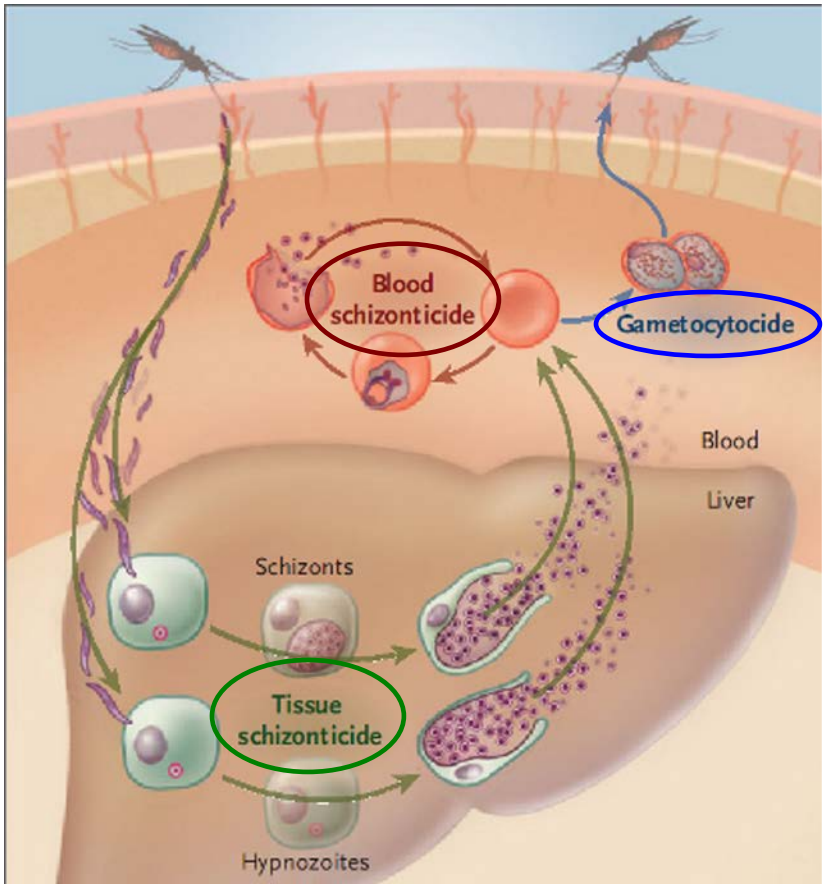
Extraction of Artemisinin





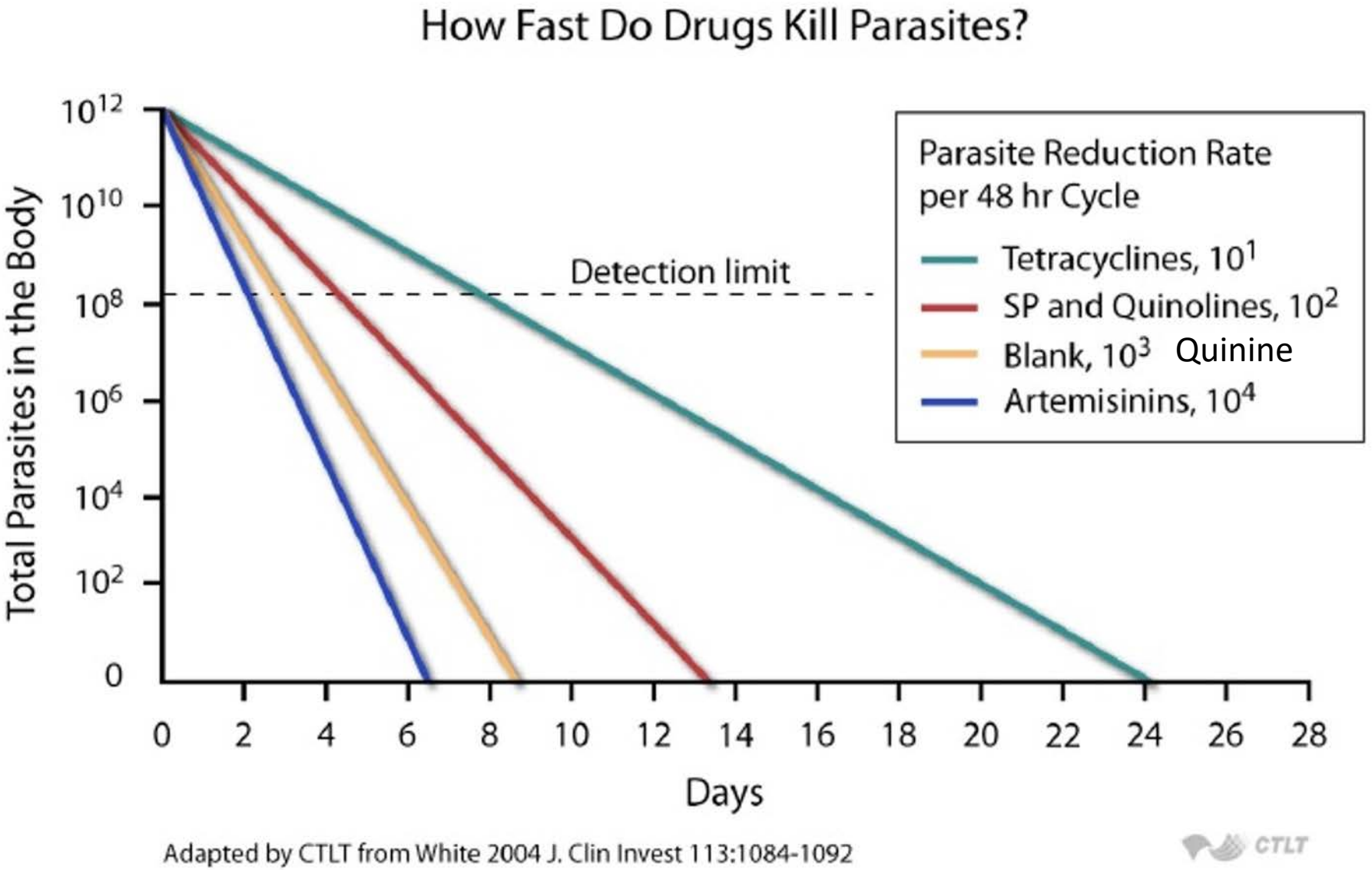
Wang Y, et al. ***Pharmacol Res.*** *2020 Jul;157:104829.*

Mechanism of actions of anti-malarials

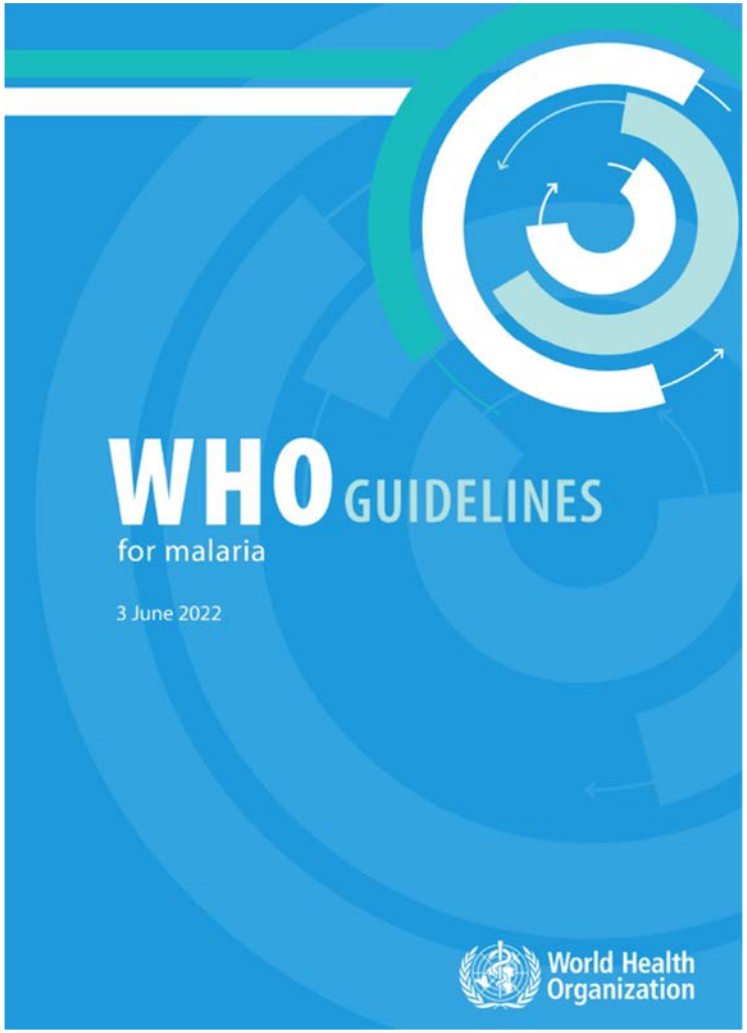


- Blood schizonticide:
  - Chloroquine,
  - Quinine,
  - Pyrimethamine/sulfadoxine,
  - Artemisinin,
  - Doxycycline
  - Mefloquine
  - Proguanil
  - Halofantrine
  - Lumefantrine
- Tissue schizonticide:
  - Primaquine
  - Proguanil
- Gametocytocide:
  - All species: Artemisinin, Primaquine
  - PV: Chloroquine, Quinine

Baird JK. ***N Engl J Med*** *2005;352:1565-77.*


How Fast Do Drugs Kill Parasites?
Total Parasites in the Body
10^{12}
10^{10}
10^{8}
10^{6}
10^{4}
10^{2}
0
Detection limit
Parasite Reduction Rate per 48 hr Cycle
Tetracyclines, 10^{1}
SP and Quinolines, 10^{2}
Blank, 10^{3} Quinine
Artemisinins, 10^{4}
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28
Days
Adapted by CTLT from White 2004 J. Clin Invest 113:1084-1092
CTLT

WHO recommendation June 2022



<u>Uncomplicated malaria:</u>

(Strong recommendation, High certainty evidence)

Treat children and adults with *P. falciparum* malaria (except pregnant women in their first trimester) with one of the following ACTs:

- **artemether + lumefantrine (Coartem)**
- artesunate + amodiaquine
- artesunate + mefloquine
- dihydroartemisinin + piperaquine
- artesunate + sulfadoxine–pyrimethamine (SP)
- artesunate + pyronaridine

WHO recommendation 2022

Condition	Treatment
Uncomplicated PF	**Artemisinin-based combination therapies (ACT)** x 3d + 1 dose of primaquine
Uncomplicated PF in Pregnancy	1st trimester: **Quinine + clindamycin** x 7d 2nd or 3rd trimester: **ACT**
Uncomplicated hyperparasitaemia (≥ 4% but no severe signs)	IV or IM **Artesunate** then **ACT** x 3d; longer course used before
Uncomplicated PV, PO, PM, PK	Chloroquine sensitive: **ACT or Chloroquine** Chloroquine resistant: **ACT** + **Primaquine**: ● 0.25 – 0.5mg/kg x 14d or ● 0.75mg/kg QW x 8w (G6PD deficiency)
Severe malaria (including 1st trimester pregnant women)	IV or IM **Artesunate** x at least 24h until PO is tolerated, then oral Rx x 3d

Duration of therapy

Rationale:

- A 3-day course of the artemisinin component of ACTs covers **two asexual cycles**,
- ensuring that only a **small fraction** of parasites remain for **clearance by the partner drug**,
- thus, **reducing the potential development of resistance** to the partner drug.

WHO guidelines for malaria 2022

Surge of malaria cases in HK in 6/2022

- Used to stock 2 patient courses of antimalarial drugs per cluster in HK
- HAHO liaised with China:
  - 3000 vials of **artesunate**
  - 400 tab of **Artequick (Artemisinin/piperaquine)**
- **Preparation**: one tab:
  - 62.5mg Artemisinin
  - 375mg Piperaquine
- **Original Dosage**: 2 tab daily for 2 days
- WHO worried about underdose
- HAHO recommendation after consideration of the safety and dose range:

Body Weight	Daily Tablets	Duration
< 45kg	2 tab	3 days
45-70kg	3 tab	
>70kg	4 tab	

ACT

Table 1 | **Plasma half-lives of drugs used in artemisinin-based combination therapies**

Antimalarial	$t_{1/2}$ of artemisinin derivative	$t_{1/2}$ of partner drug	Regions currently in use*
Artemether–lumefantrine	~3 hr	4–5 days	Africa, EM, SE Asia, WP and SA
Artesunate–mefloquine	<1 hr	14–21 days	Africa, SE Asia, WP and SA
Artesunate–amodiaquine	<1 hr	9–18 days‡	Africa and EM
Dihydroartemisinin–piperaquine	45 min	~5 weeks	SE Asia
Artesunate–pyronaridine§	<1 hr	16 days	NA
Chloroquine‖	NA	1–2 months	Africa, EM, SE Asia, WP and SA
Sulphadoxine–pyrimethamine‖	NA	~4 days (S) or ~8 days (P)	Africa, EM (IPT in Africa, EM and WP)

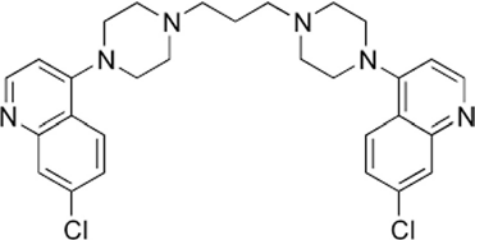
Activity of Dihydroartemisinin > artesunate > artemether

Eastman RD & Fidock DA. ***Nat Rev Microbiol*** *2009;7:864-74*

Mechanisms of action of antimalarials

Antimalarials	Classes	Mechanisms of action
Primaquine	Hypnozoiticidal Gametocytocidal	interferes with the **electron transport** in the parasite during respiration process
Chloroquine	Blood schizontocides	accumulate in the acidic **food vacuoles** of intraerythrocytic trophozoites and thereby **prevent haemoglobin degradation**
Artemisinin	Blood Schizontocides Gametocytocidal	heme-mediated decomposition of the peroxide bridge to produce carbon-centred **free radicals**
Lumefantrine	Blood schizontocides	Inhibits **nucleic** and formation of **hematin** by forming a complex with hemin
Piperaquine	Blood schizontocides	disrupting the **detoxification** of host heme

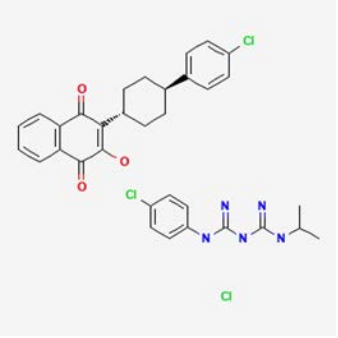
Mhlwatika Z, Aderibigbe BA. ***Molecules****. 2018 Oct 2;23(10):2527.*



Piperaquine

- Piperaquine is a bis-quinoline 1st synthesized in the 1960s
- Used extensively in China and Indochina as prophylaxis and treatment during 1960s to 1980s
- As effective as, and better tolerated than, chloroquine vs falciparum & vivax
- As ACT (**Dihydroartemisinin** or Artemisinin)
- Excellent efficacy of piperaquine-DHA combinations (**28-day cure rates >95**%)
- Good safety profile: not associated with significant cardiotoxicity or other adverse effects.
- Highly lipid-soluble drug with a large volume of distribution
- Long elimination half-life (20-30d)
- Low cost

Davis TME, et al. ***Drugs*** *2005; 65 (1): 75-87*

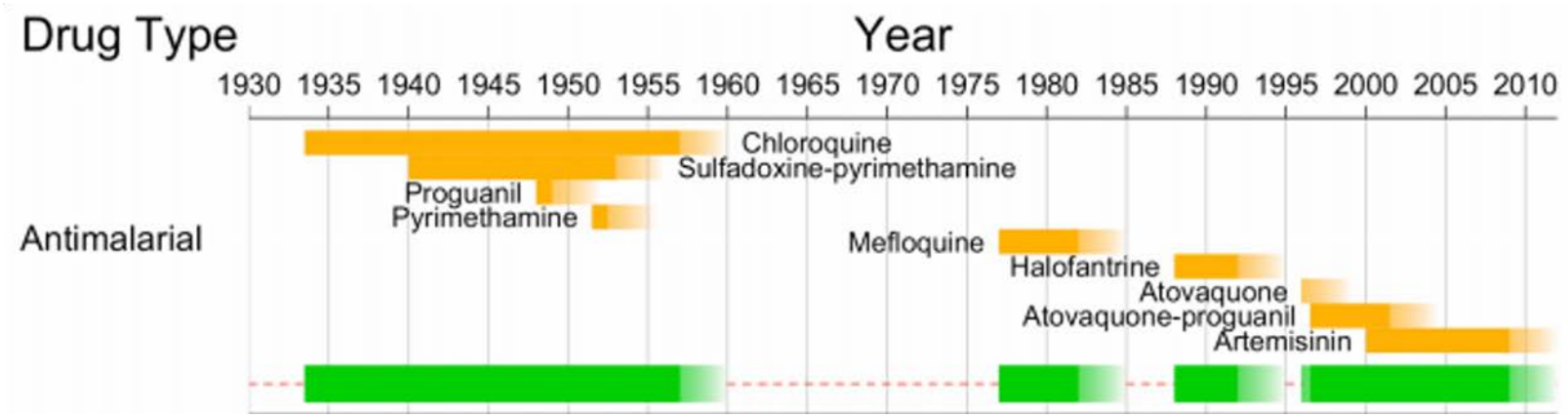


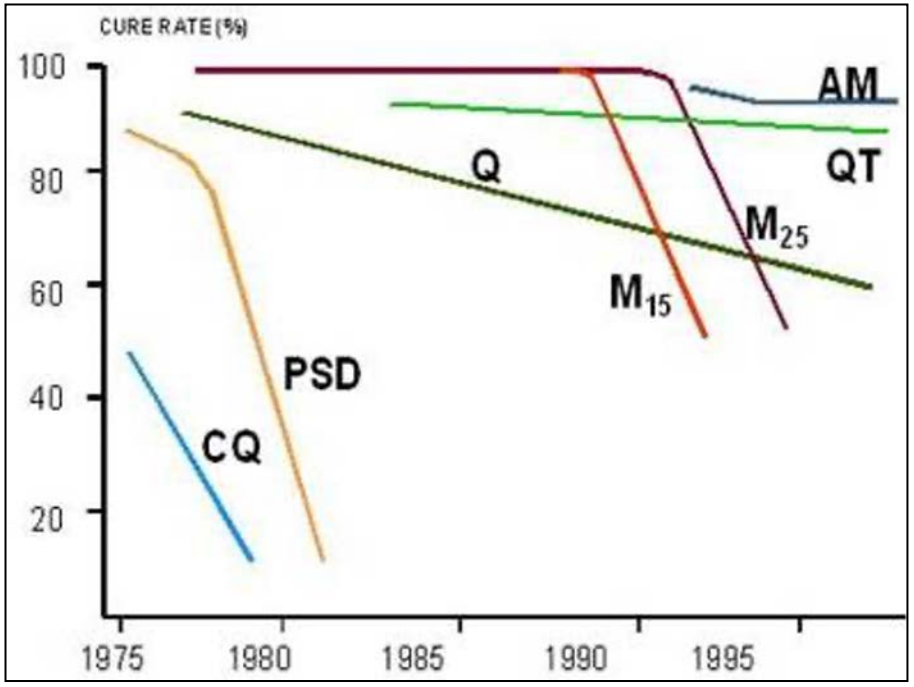
Atovaquone-Proguanil (Malarone)

- Fixed-dose combination for **uncomplicated malaria** only, including chloroquine-resistant malaria
- Atovaquone works by interfering with the function of **mitochondria** in malaria while proguanil by blocking **dihydrofolate reductase**
- Use as **prophylaxis** and **treatment**
- Approved for use in the US in 2000
- Common side effects: abdominal pain, vomiting, diarrhea, cough, and itchiness
- Serious side effects: anaphylaxis, Stevens–Johnson syndrome, hallucinations, and liver problems
- Long elimination half-life of 50–84 h.
- Elimination primarily via liver
- Not recommended in pregnancy except when benefit outweigh risk

Anti-malarial resistance

Antimalarials resistance





AM: Artemisinin + Mefloquine
QT: Quinine + tetracycline
M_{15}: Mefloquine 15mg/kg
M_{25}: Mefloquine 25mg/kg
PSD: Pyrimethamine + Sulfadoxine
CQ: Chloroquine

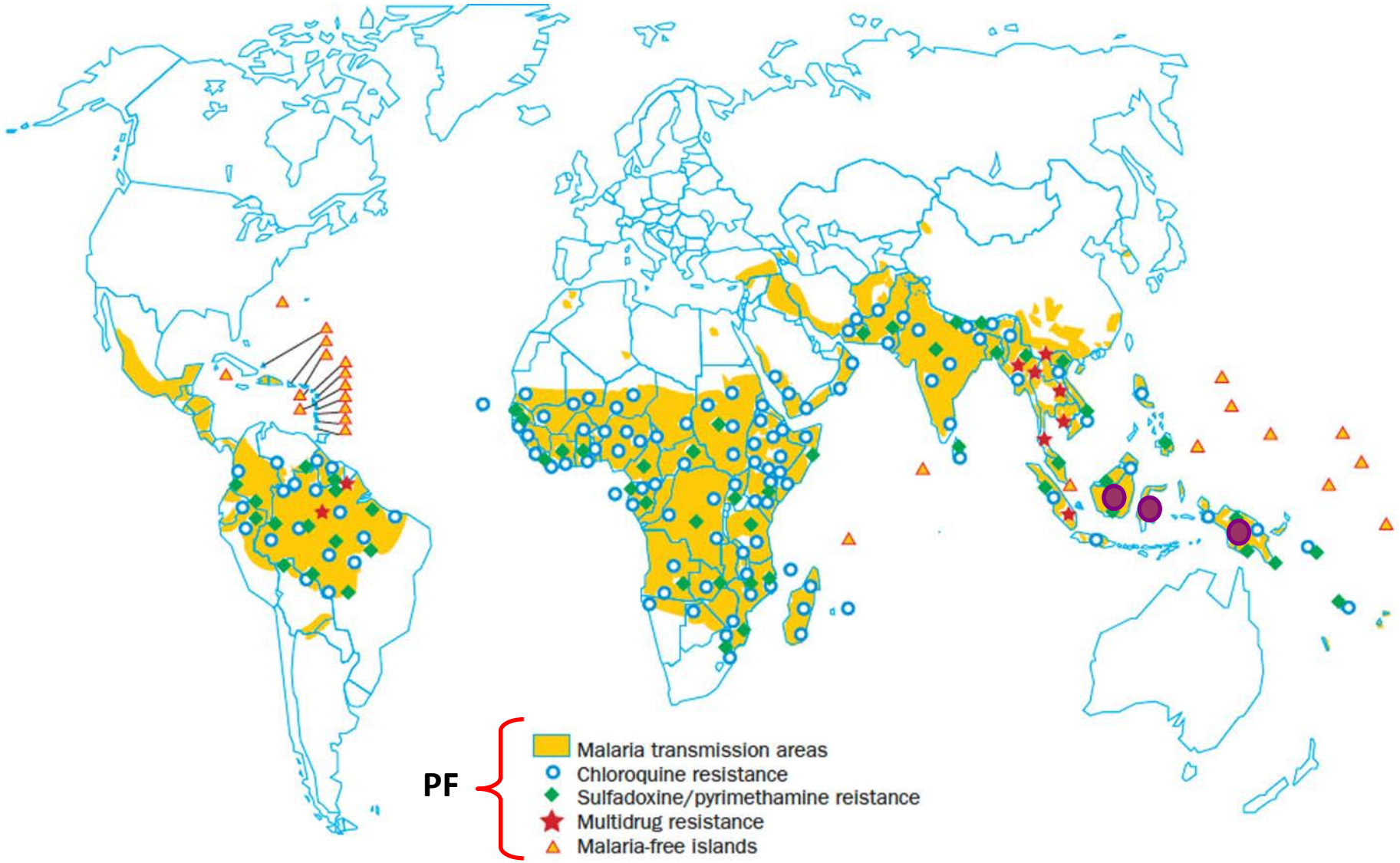
https://www.researchgate.net/figure/Drug-supply-timeline-for-antimalarials-and-anitbiotics-This-gives-the-time-of-drug_fig1_236456011

THE PATH OF CHLOROQUINE RESISTANCE

Malaria parasites resistant to chloroquine swept out of the Mekong region and spread around the world. So far, artemisinin hasn't followed that path, and researchers are debating the likelihood it will.

Roberts L. ***Science*** *21 April 2016*

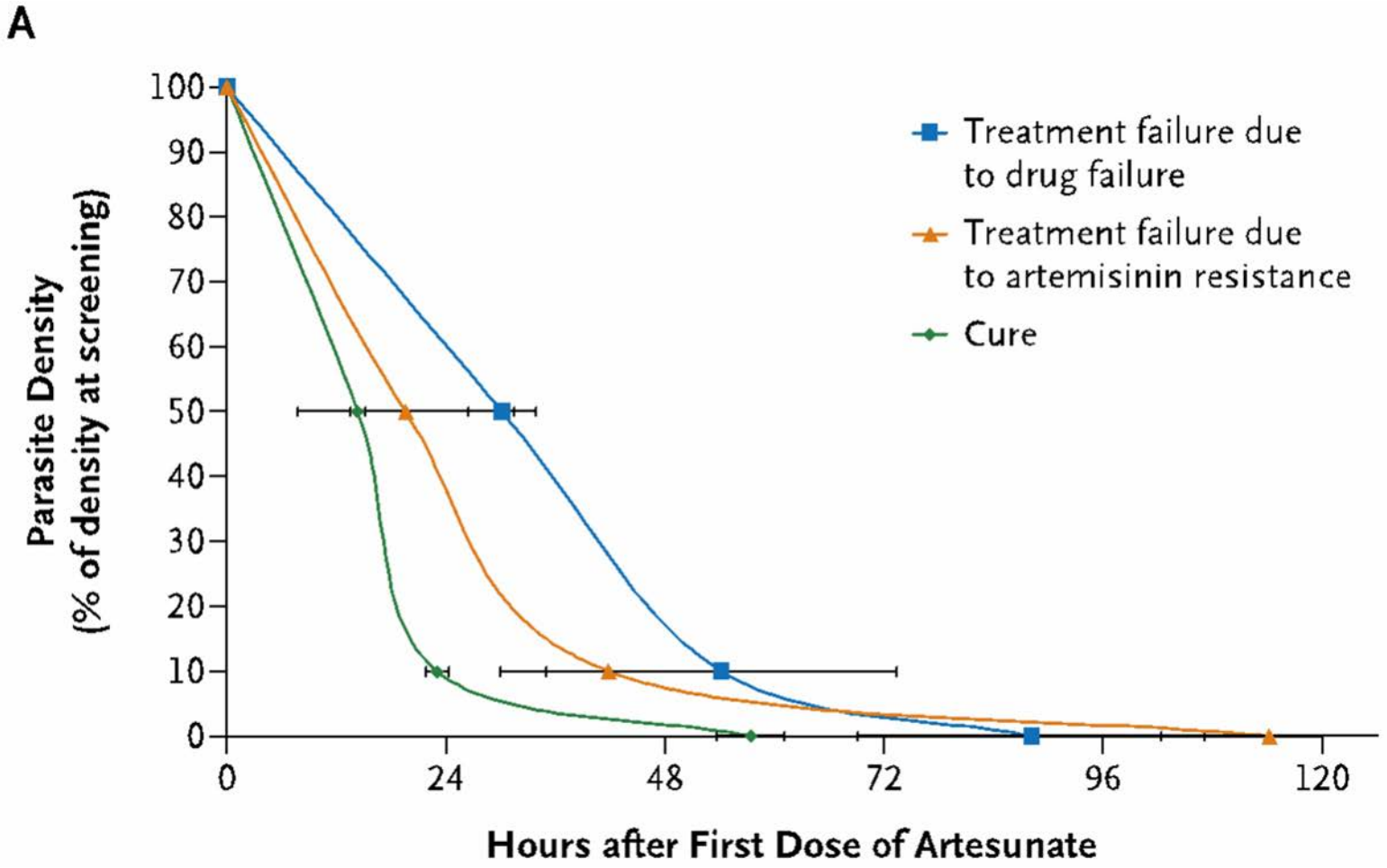
Malaria resistance



● **Chloroquine resistant PV**

Wongsrichanalai C, et al. ***Lancet Infect Dis*** *2002; 2: 209–18*

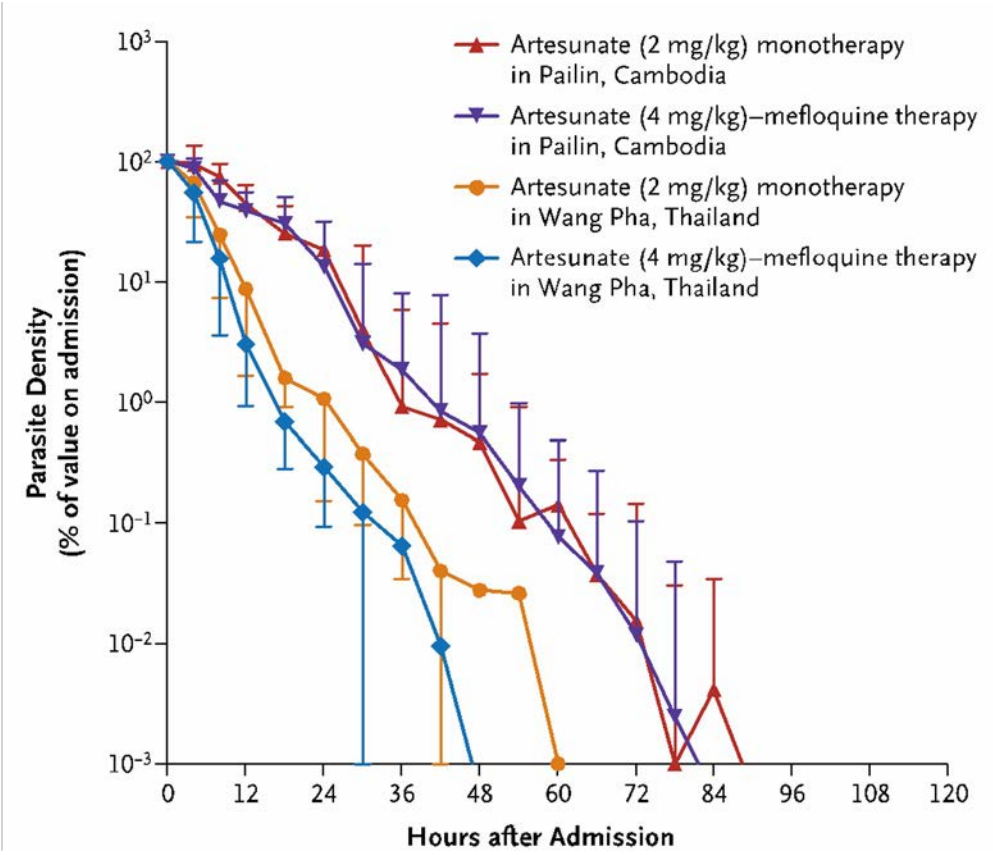
Artemisinin-Resistant PF in Western Cambodia in 2008

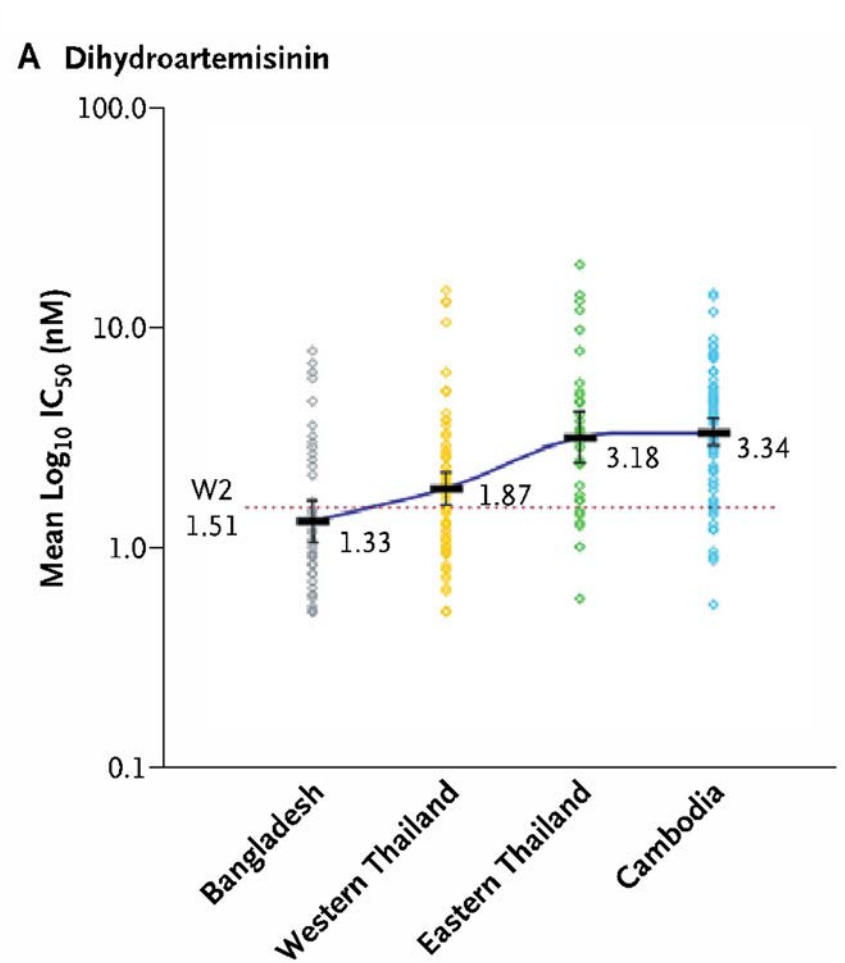


Irug level)

Noedl H, et al. ***N Eng J Med*** *2008;359:2619-20*

Artemisinin-Resistant in West Cambodia

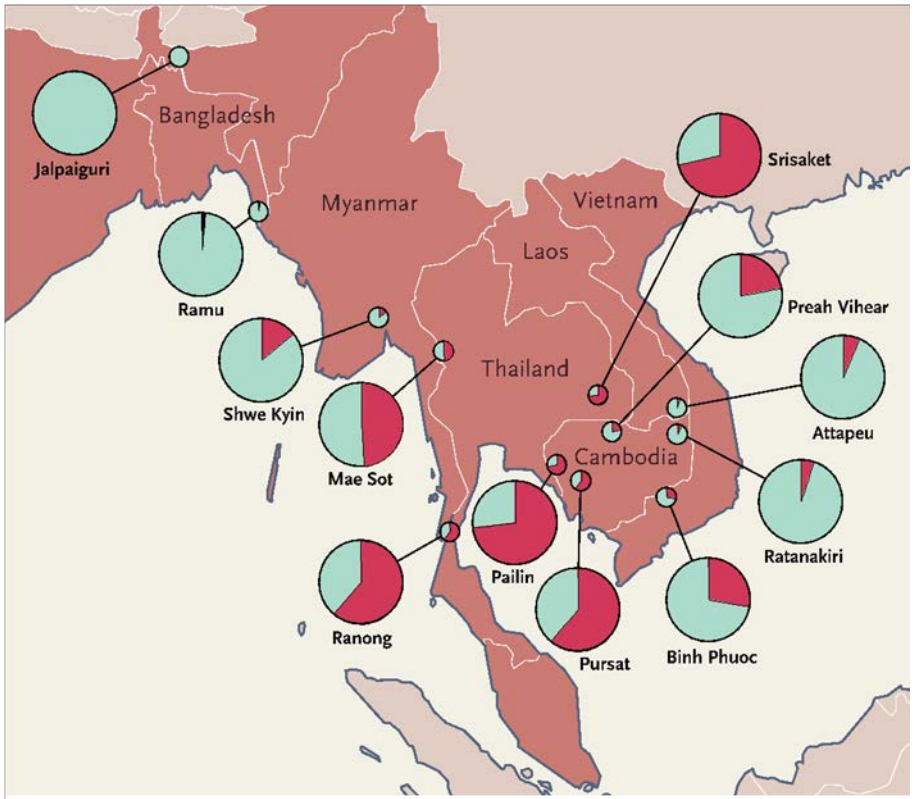


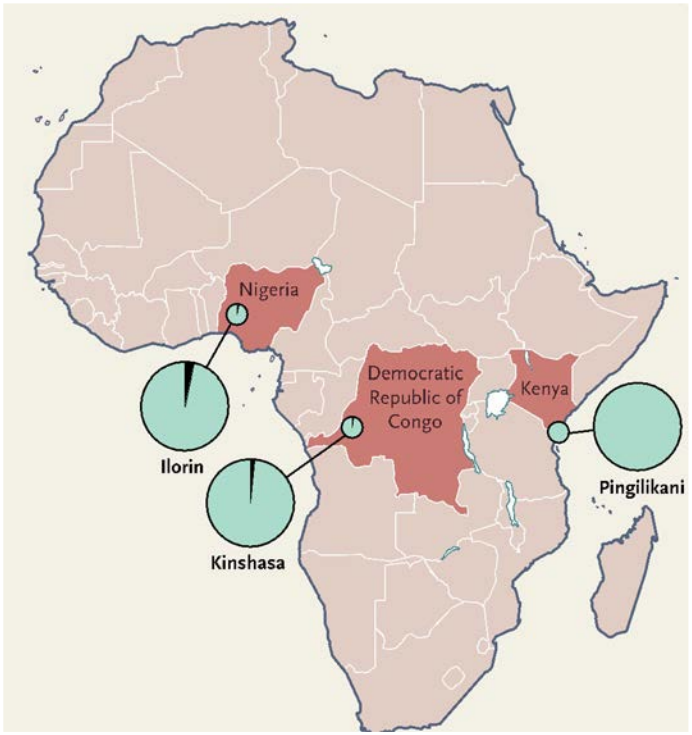


Dondorp AM, et al. ***N Engl J Med*** *2009;361:455-67.*

Noedl H, et al. ***N Eng J Med*** *2009;361:540-1*

Artemisinin resistance has spread in Mekong regions, but not yet in Africa in 2014



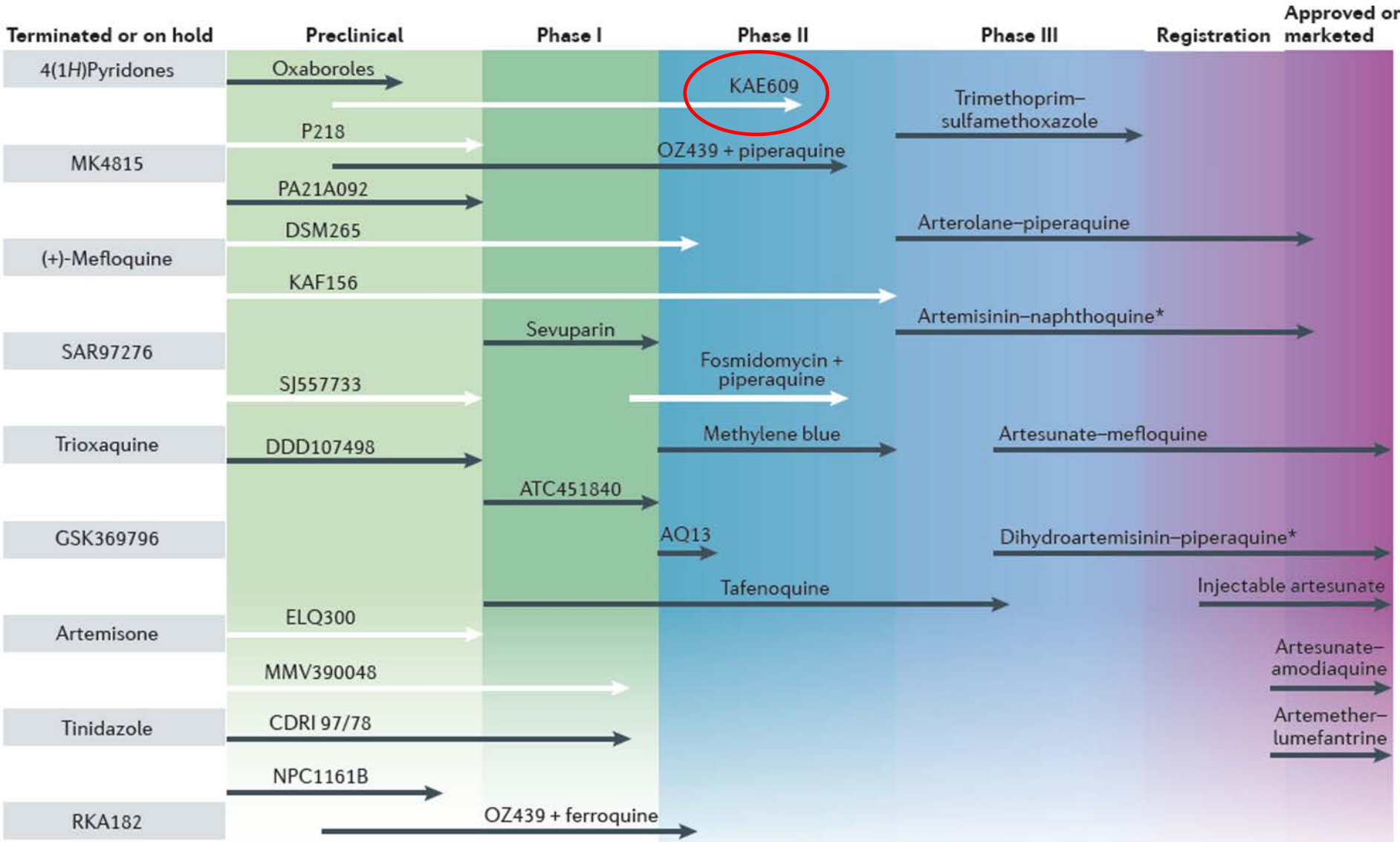


Note:

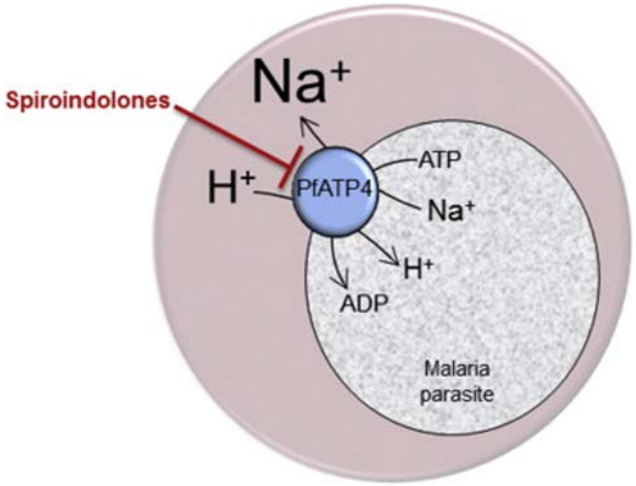
- Mutations in the **kelch 13** Propeller gene confers **resistance to artemisinin**
- The most common mutation is **C580Y** in Mekong region

Ashley EA, et al. ***N Engl J Med*** *2014;371:411-23.*

New medications for malaria



Wells TNC, et al. ***Nat Rev Drug Discov****. 2015 Jun;14(6):424-42*



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 31, 2014 VOL. 371 NO. 5

Spiroindolone KAE609 for Falciparum and Vivax Malaria

- Inhibit PfATP4, ie parasite membrane **NA-ATPase** that regulate Na & osmotic homeostasis
- Vs **both sexual & asexual** forms
- Parasite clearance t1/2 for both Pf & Pv **within an hour**, only < 1% of Pf treated with artesunate can achieve that within an hour
- Reliable absorption and **T1/2 of 20.8h**, allowing QD dose
- Main S/E: nausea & vomiting, but not leading to discontinuation

Table 1. Parasite Clearance in Cohorts of Patients with *Plasmodium vivax* or *P. falciparum* Infection.

End Point	*P. vivax* Cohort (N=10)	*P. falciparum* Cohort (N=11)
	hours	
Time to clearance of asexual parasitemia		
50% clearance	8	12
99% clearance	12	16
100% clearance	30	16
Time to parasite clearance		
Median	12	12
Interquartile range	8–16	10–16
Parasite clearance half-life		
Median*	0.95	0.90
Interquartile range	0.85–1.14	0.78–1.07
Range	0.68–2.01	0.68–1.64

Cipargamin (KAE609) Phase II Study in Adults in Sub-Saharan Africa With Uncomplicated falciparum Malaria

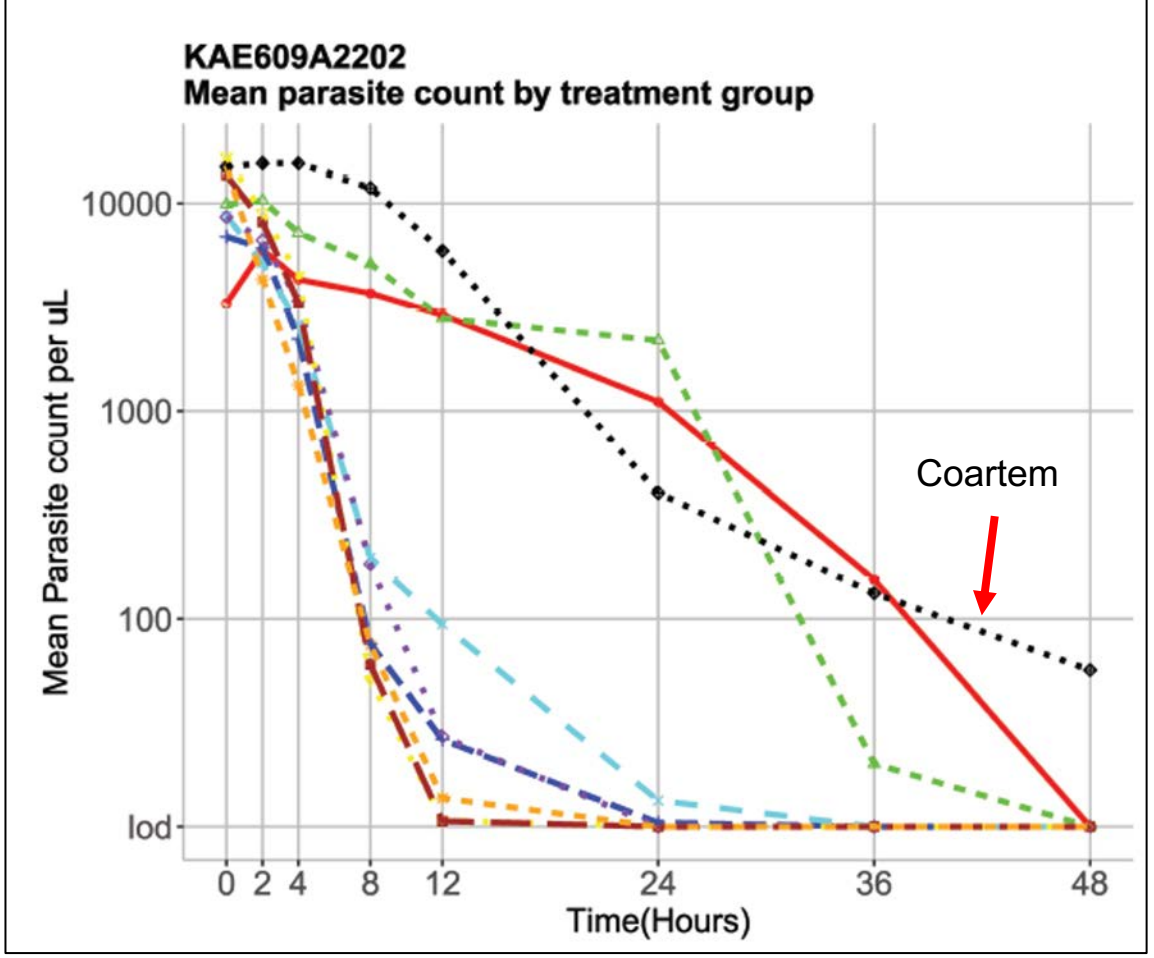


Table 1. Parasite Clearance Time (Hours) by Treatment Group

	Cipargamin Dose/Regimen								
	10 mg QD			25 mg QD		50 mg QD			
	10 mg SD (n = 10)	3 days (n = 10)	25 mg SD (n = 12)	3 days (n = 20)	50 mg SD (n = 21)	3 days (n = 19)	75 mg SD (n = 21)	150 mg SD (n = 22)	Artemether-lumefantrine (n = 51)
Median PCT	24.4	30.1	11.6	8.1	8.2	8.2	8.0	8.1	24.3
(2-sided 95% CI)	(8.0, 48.0)	(4.2, 36.7)	(8.0, 24.0)	(8.0, 12.2)	(8.0, 12.2)	(8.0, 12.0)	(8.0, 8.1)	(2.1, 9.2)	(24.1, 36.0)

Schmitt EK, et al. ***Clin Infect Dis.*** *2022;74(10):1831–9*

Cipargamin (KAE609) Phase II Study in Adults in Sub-Saharan Africa With Uncomplicated falciparum Malaria

Table 2. Occurrence of Recrudescence With *PfATP4* G358S Mutation, by Dose Regimen

Dose regimen	Number of Patients	Patients, n (%)	
		Late Treatment Failures	Recrudescences With G358S Mutation
Cipargamin 10 mg SD	9	1 (11)	0 (–)
Cipargamin 25 mg SD	12	4 (33)	0 (–)
Cipargamin 50 mg SD	21	4 (19)	4 (19)
Cipargamin 75 mg SD	20	5 (25)	3 (15)
Cipargamin 150 mg SD	22	9 (41)	5 (23)
Cipargamin 10 mg QD 3 days	10	1 (10)	1 (10)
Cipargamin 25 mg QD 3 days	20	4 (20)	3 (15)
Cipargamin 50 mg QD 3 days	19	6 (32)	6 (32)
Total	133	34 (26)	22 (17)

Abbreviations: QD, daily; *PfATP4*, Plasmodium falciparum ATPase 4; SD, single dose.

Cipargamin:

- **medium** risk for resistance
- All patients with recrudescence, including those with the **G358S mutation**, were successfully treated with Coartem.
- **Lack of cross-resistance** with artemisinins
- Resistance could be prevented by **combining with a long-acting partner** compound

Schmitt EK, et al. ***Clin Infect Dis.*** *2022;74(10):1831–9*

Summary

- No of cases locally is small but the severity is high
- Symptoms and signs are not specific
- Typical fever patterns are usually absent
- Incubation period variable and has to R/O other infections
- Place of travel is the most important consideration
- Artemisinin based combination therapy (ACT) is the recommended treatment in general
- 3 days treatment is recommended
- Dose of Artequick locally should be based on the body weight and the duration should be 3 days
- Resistance to Artemisinin is rising in Greater Mekong Subregion (GMS), but is still rare in Africa
- New drugs including Cipargamin are under investigation

Thanks