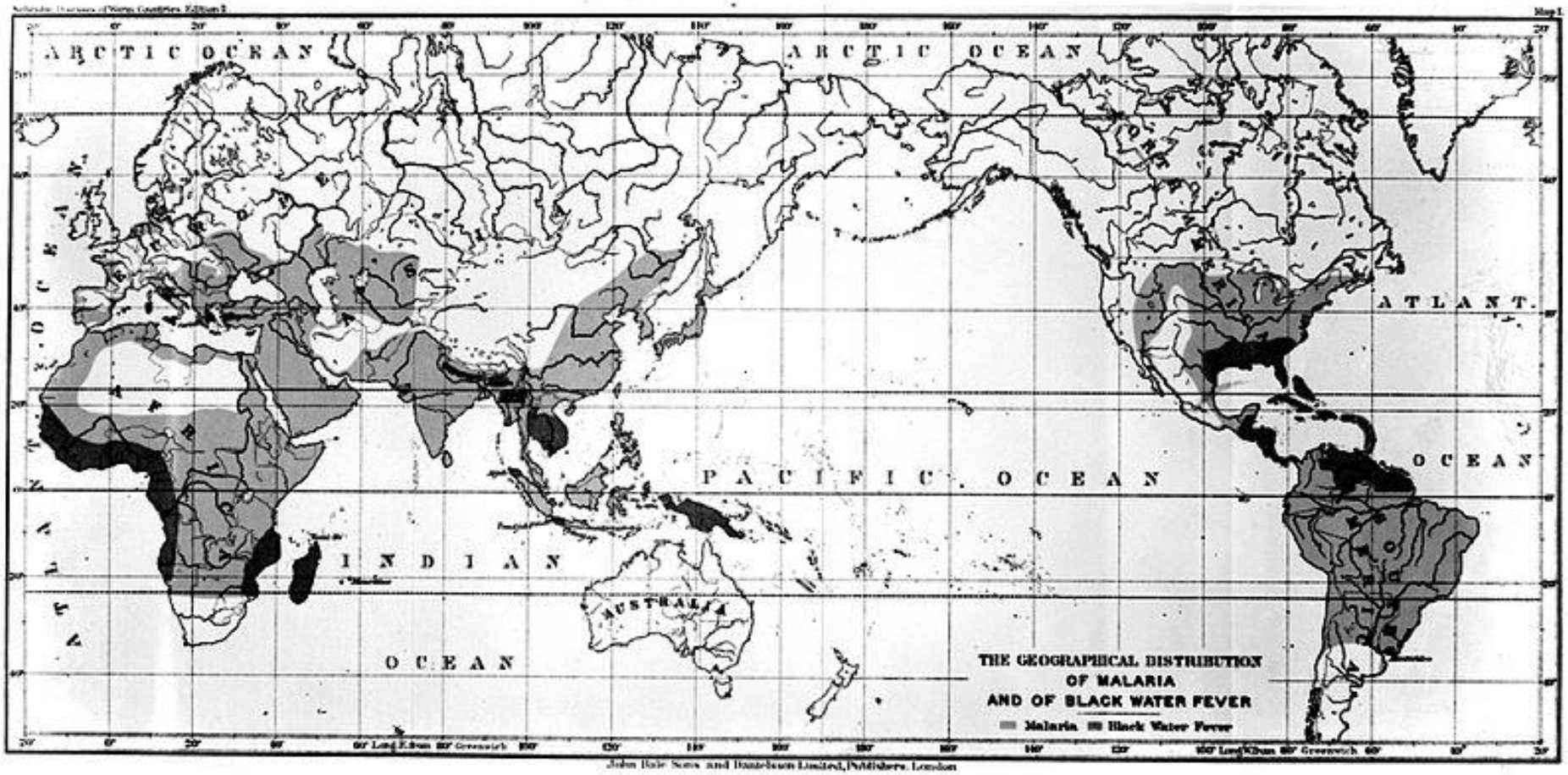
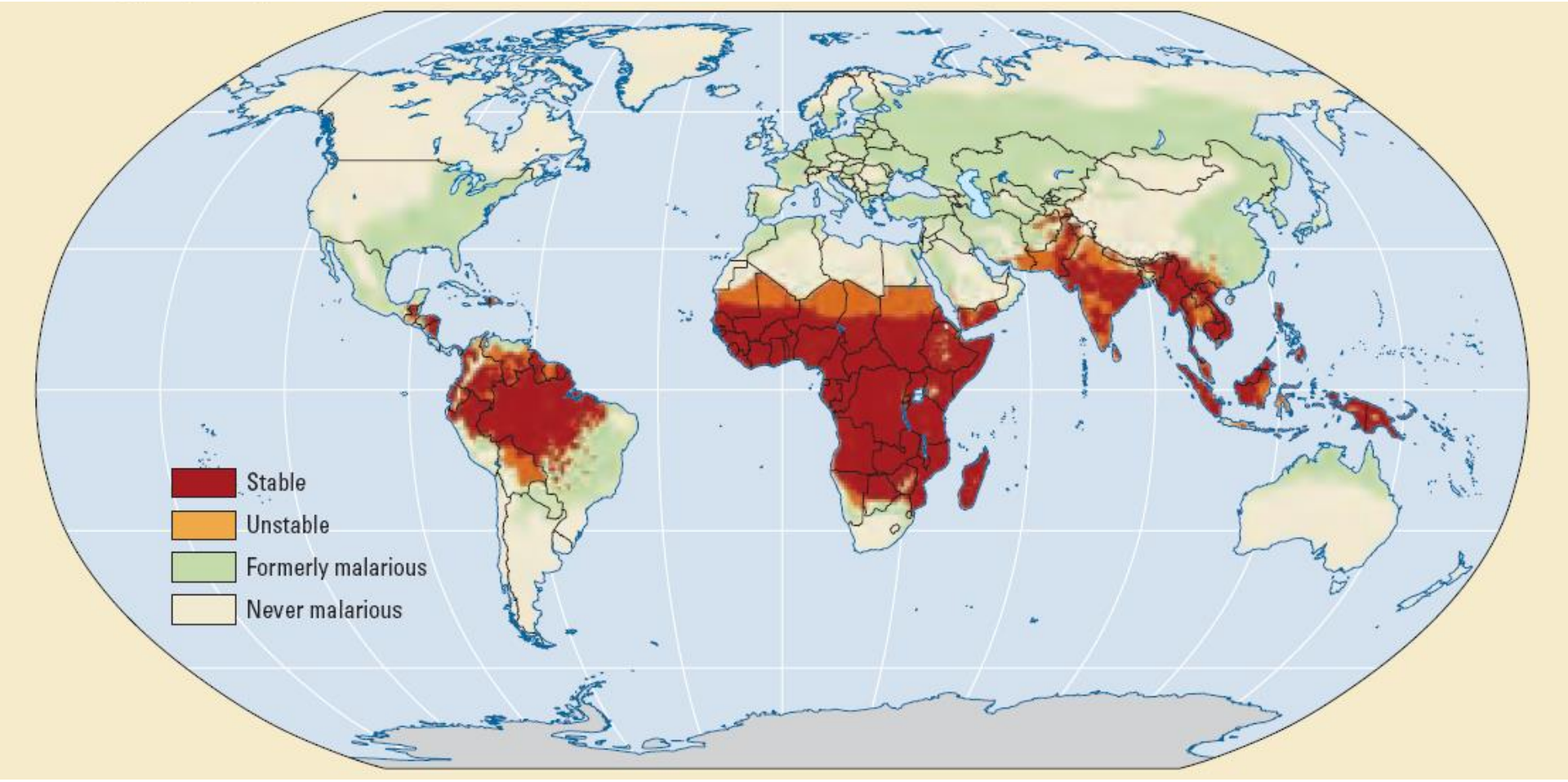

Plasmodium falciparum
Plasmodium vivax
Plasmodium malariae
Plasmodium ovale (2)
Plasmodium knowlesi

The past



John Bale Sons and Danielsson Limited, Publishers, London

Currently prosperous parts of the world were once malarious

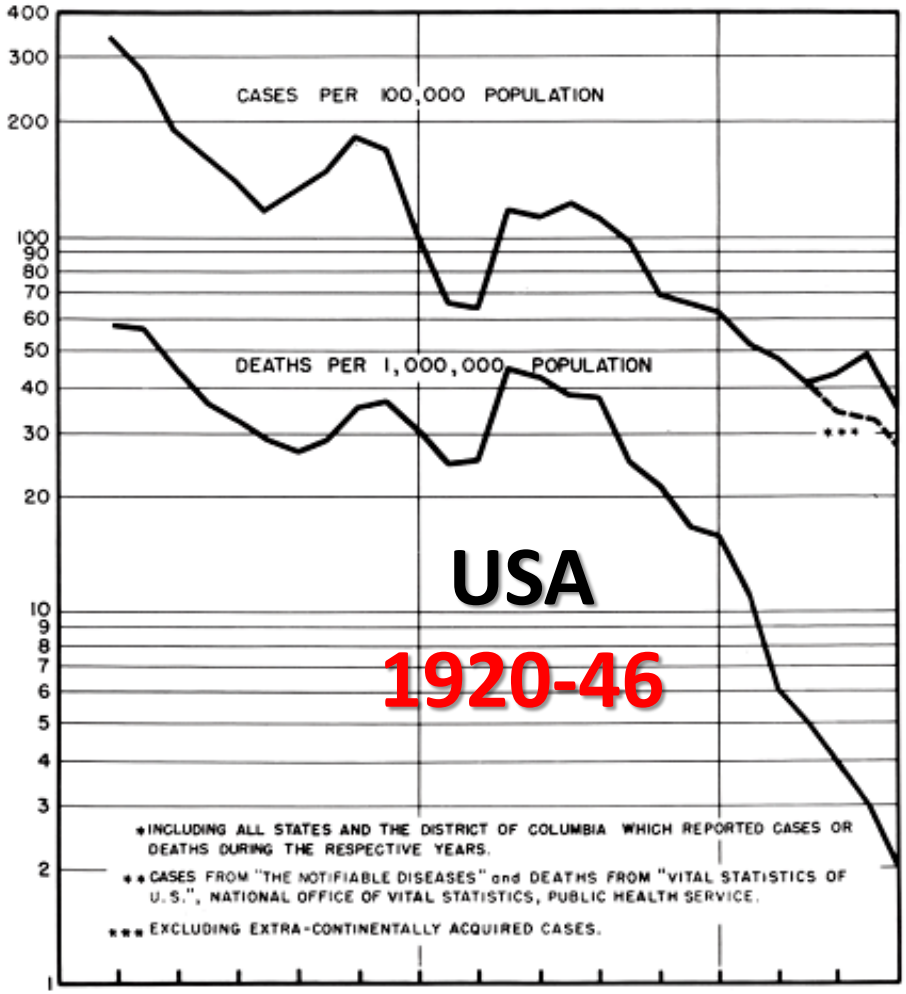


U. S. PUBLIC HEALTH SERVICE

COMMUNICABLE DISEASE CENTER

ATLANTA, GEORGIA

MALARIA MORBIDITY AND MORTALITY RATES IN ALL STATES* REPORTING CASES** AND DEATHS** DURING 1920-1946 INCLUSIVE



DHEW-PHS-CDC ATLANTA, GA. Rev. SEPT., 1954 AUG., 1947

70° N latitude

Arctic Circle

Kittilä

Tornedalen

FINLAND

Archangelsk

Helsinki

Stockholm

St. Petersburg

malaria study area

temperature series

northernmost malaria epidemics

[*October* 25, 1929.]

The Disappearance of Malaria from England.

S. P. JAMES, M.D., D.P.H., I.M.S. (retd.)

(*Adviser on Tropical Diseases to the Ministry of Health*).

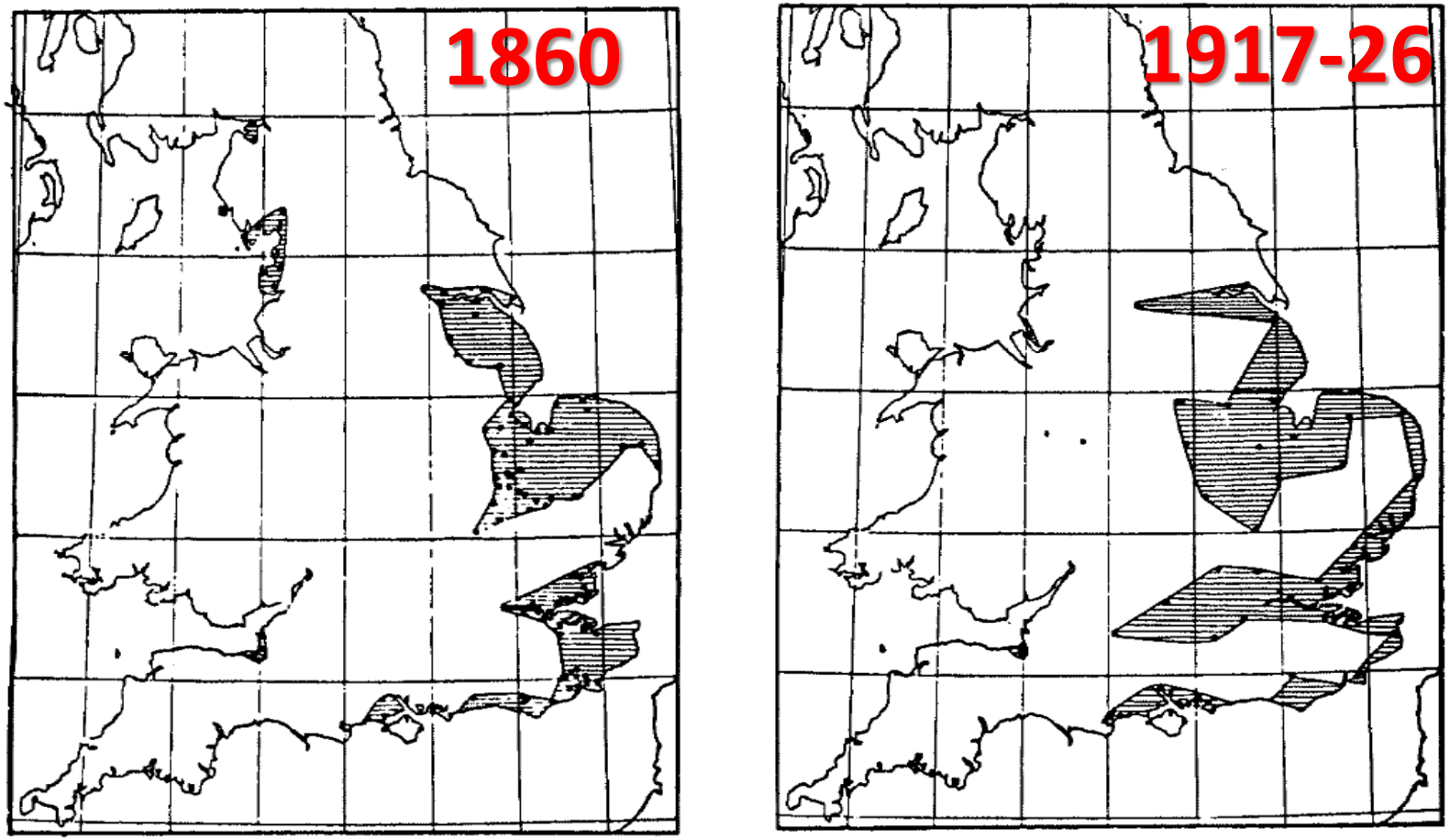


FIG. 1.—Geographical distribution of indigenous malaria.

About 1860. Between 1917 and 1926.

CHAPITRE VI.

Du Kinquina.

PLATE XXXVI.—*Cinchona calisaya* (Peruvian bark). (From Jackson: *Experimental Pharmacology and Materia Medica.*)

2 drachms = 7g at 5% alkaloid content = 350mg

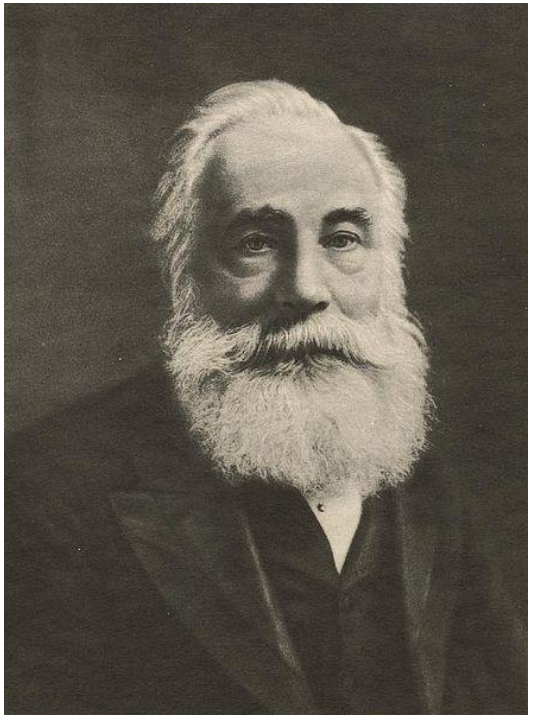
Quinine

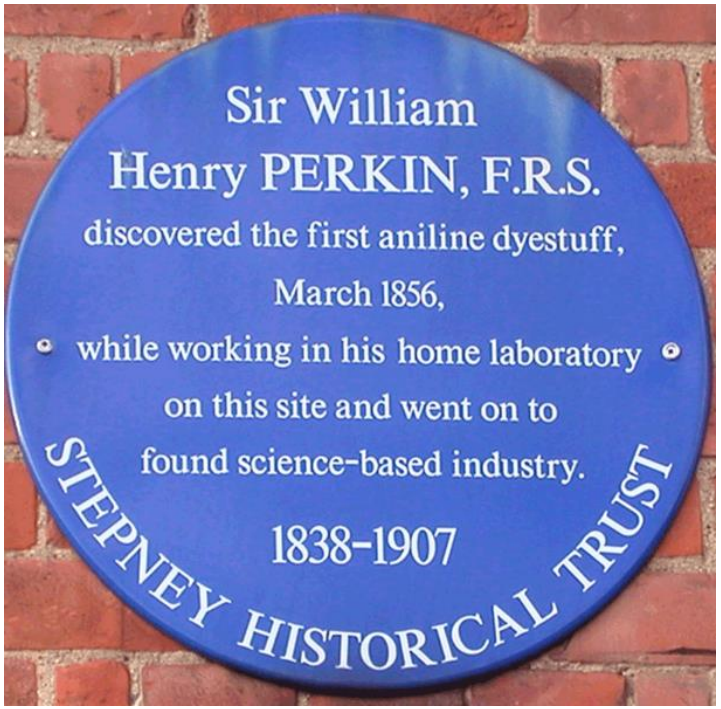
Quinidine

Cinchonine

Cinchonidine

CINCHONA. (GATHERING AND DRYING CINCHONA BARK IN A PERUVIAN FOREST.)



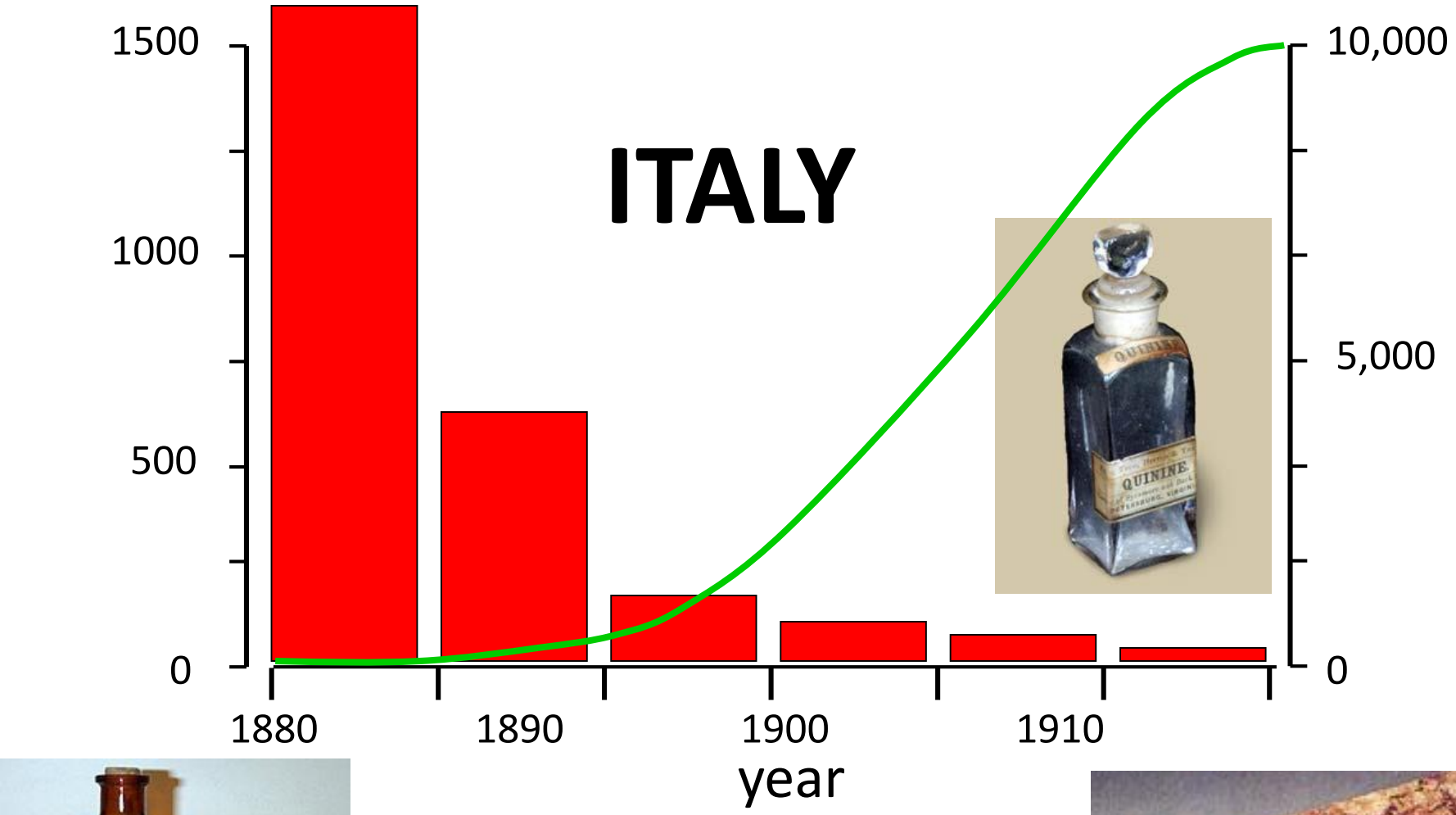


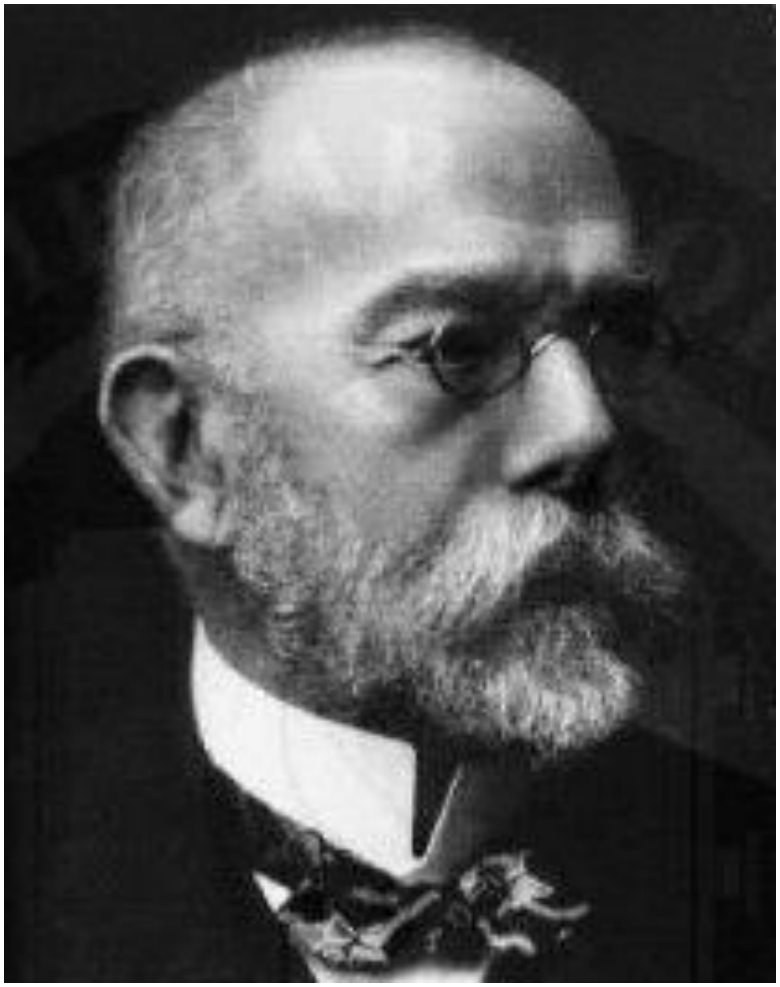
Cable St Stepney

William Henry Perkin 1838-1907

Quinine; price per kg ($ equivalent today)

Production (tonnes)





Robert Koch 1843 - 1910

Edwin Klebs 1834 - 1912

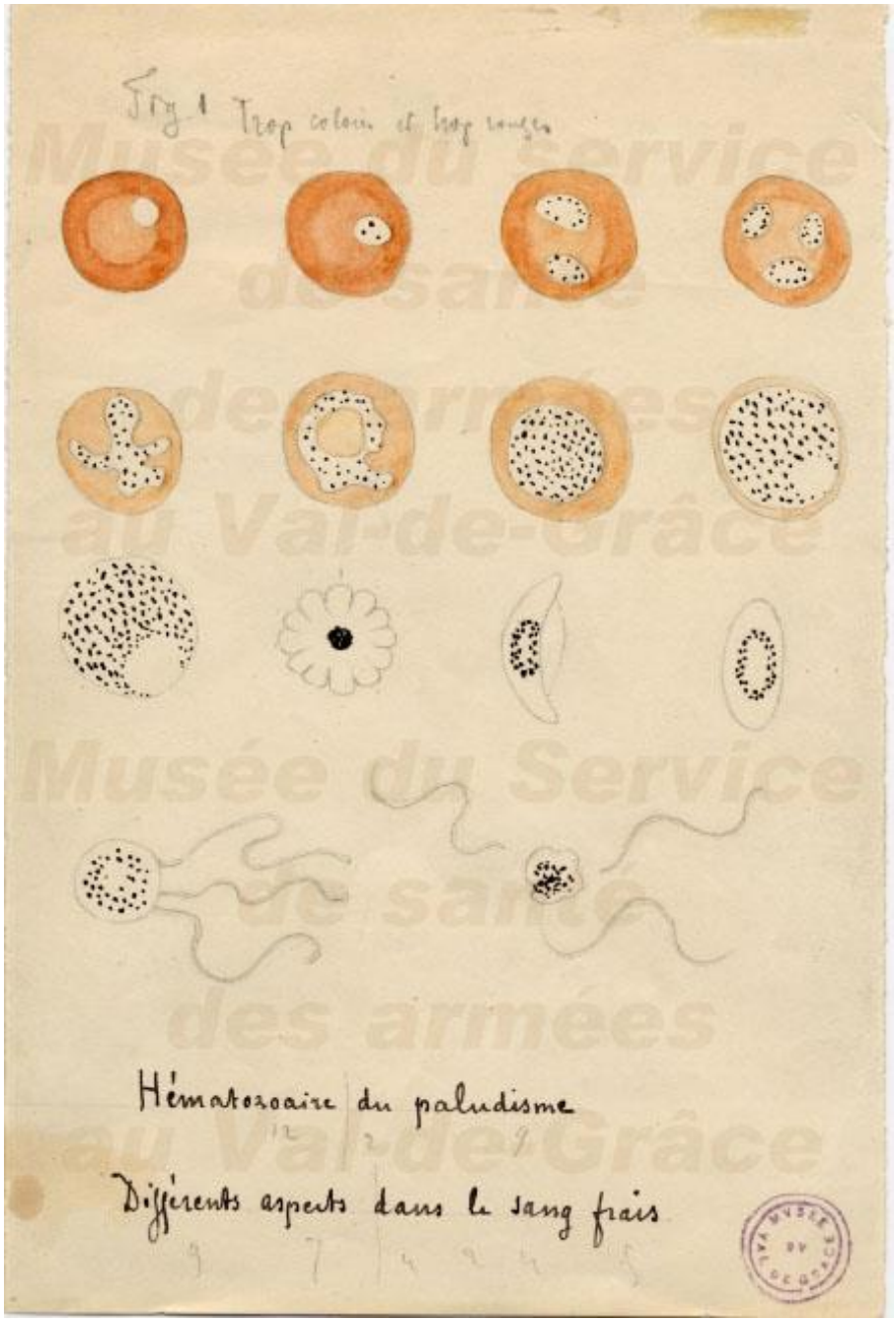
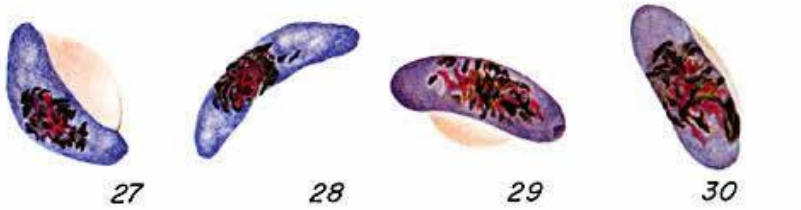
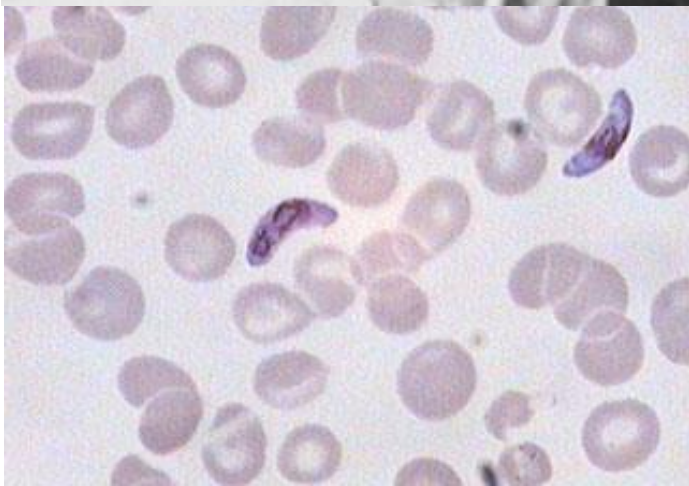


Fig. 1 Trop coloré et trop rouge
Hématozoaire du paludisme
Différents aspects dans le sang frais

That clear, luminous emblem of the Orient stares one in the face so that a mistake is impossible. One who fails to recognize a crescent when he sees it should wear a crown of thorns and bear a cross of gold.

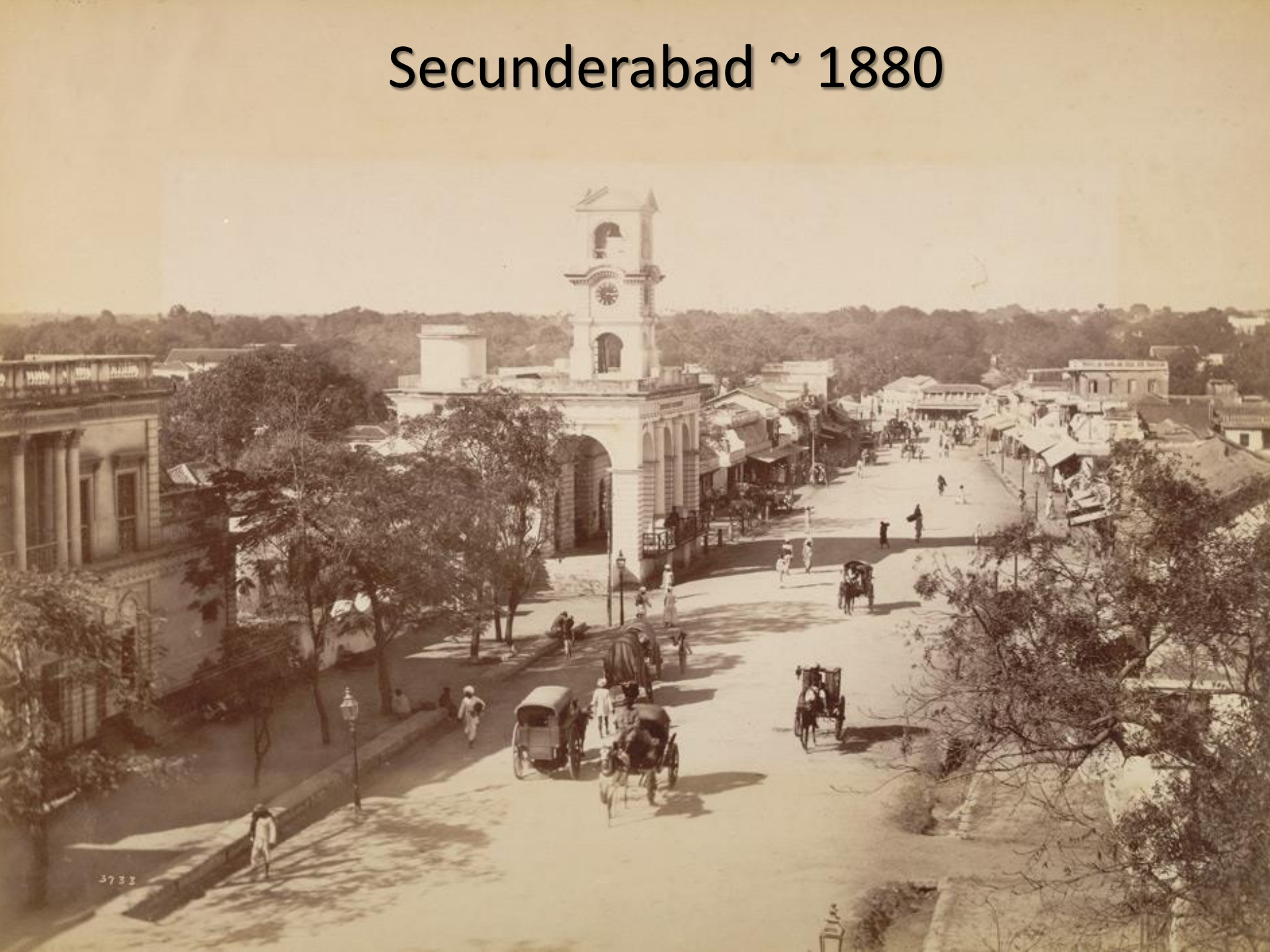


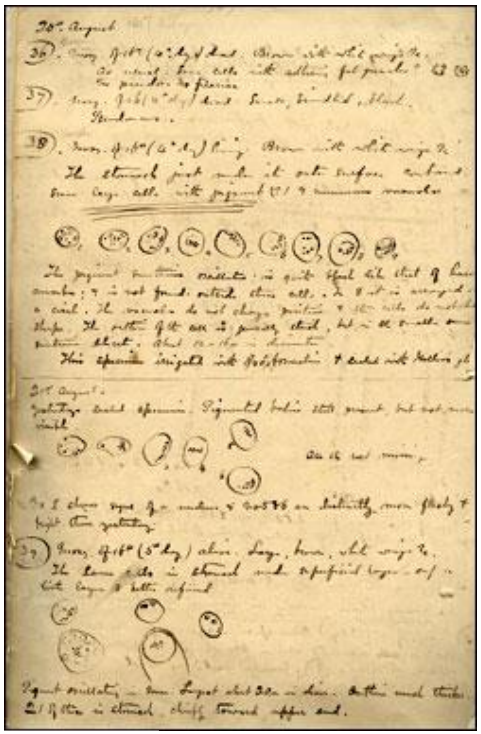


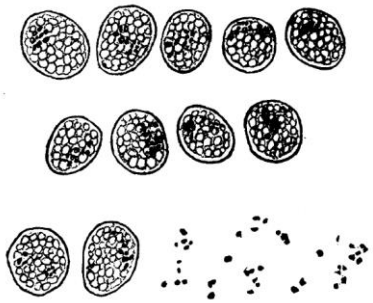
Patrick Manson 1844 - 1922

Ronald Ross 1857 - 1932

Secunderabad ~ 1880



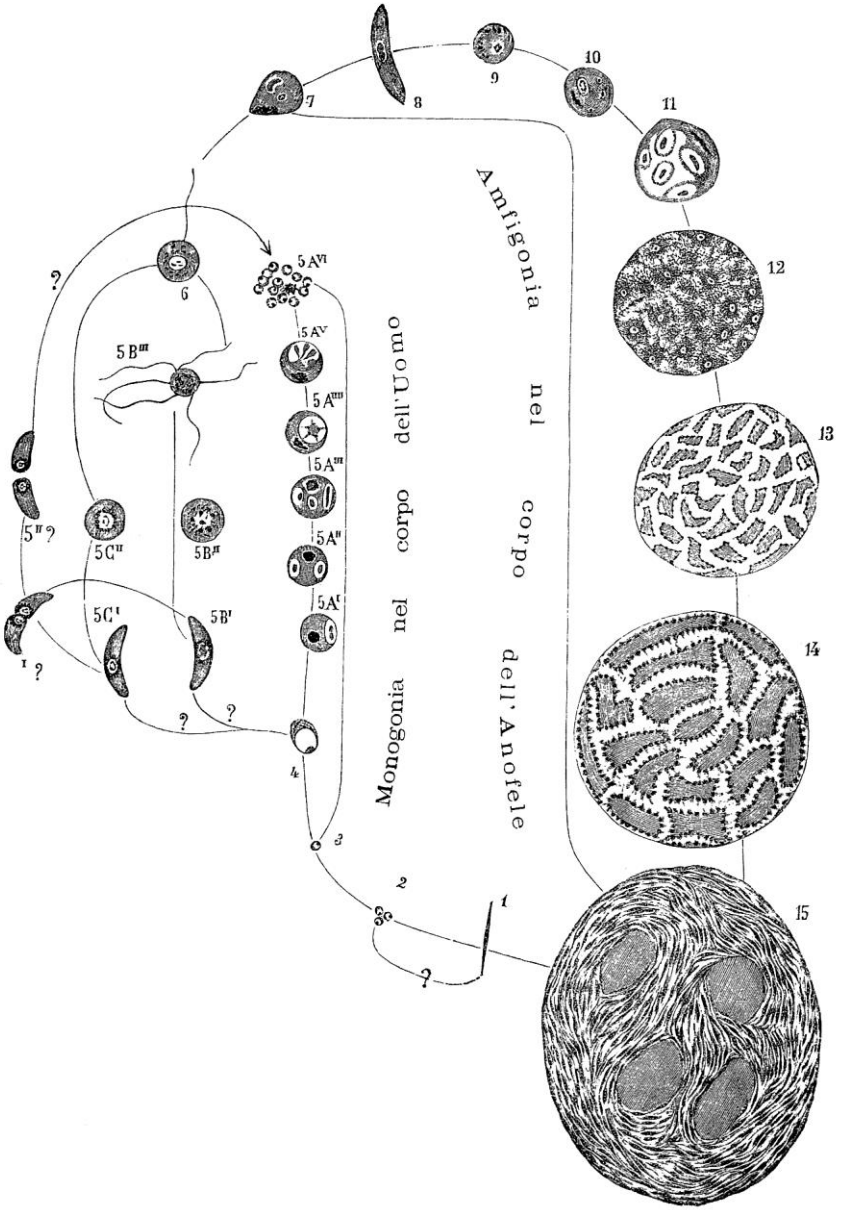




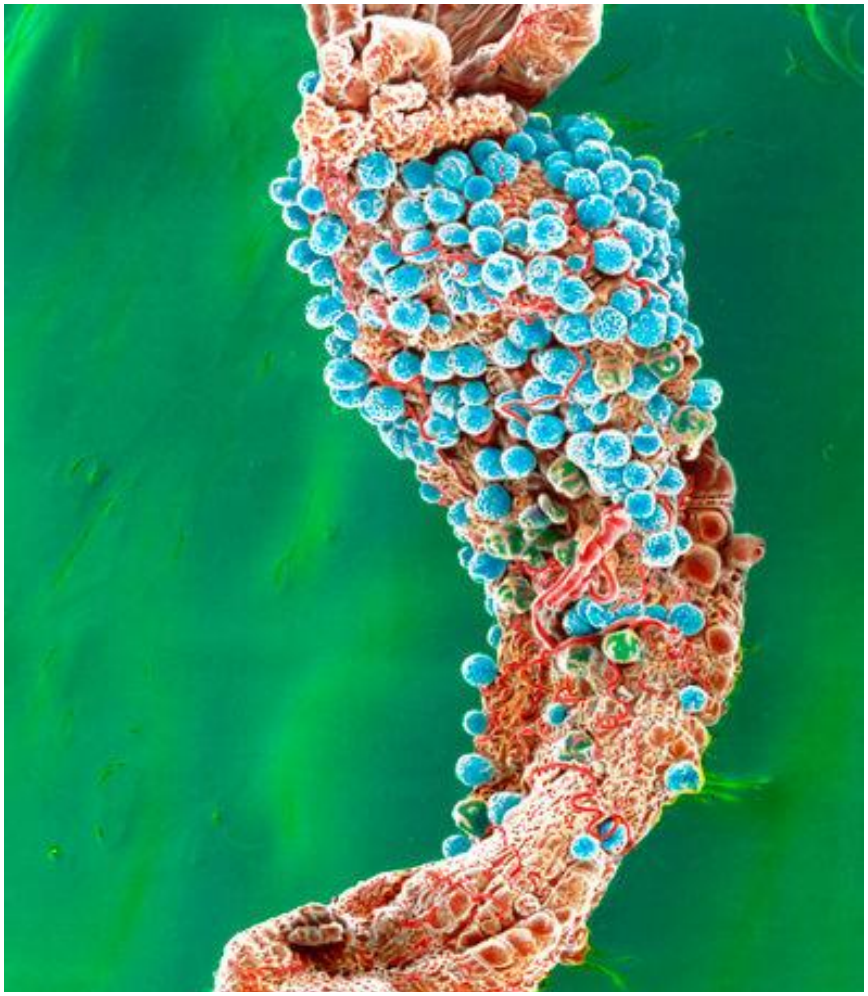
ON SOME PECULIAR PIGMENTED CELLS FOUND IN TWO MOSQUITOS FED ON MALARIAL BLOOD.

BY SURGEON-MAJOR RONALD ROSS, I.M.S.,
(With Note by Surgeon-Major SMYTH, M.D., I.M.S.)

gestion. Lately, however, on abandoning the brindled and grey mosquitos and commencing similar work on a new, brown species, of which I have as yet obtained very few individuals, I succeeded in finding in two of them certain remarkable and suspicious cells containing pigment identical in appearance to that of the parasite of malaria. As these cells



Malaria parasite cycle from Grassi (1900)



“An experiment that failed”

NEW SERIES.) No. 6.

SCIENTIFIC MEMOIRS

BY

OFFICERS OF THE MEDICAL AND SANITARY DEPARTMENTS

OF THE

GOVERNMENT OF INDIA.

FIRST REPORT OF THE ANTI-MALARIAL OPERATIONS AT MIAN-MIR, 1901-1903.

BY

CAPTAIN S. P. JAMES, M.B. (LOND.), I.M.S.

(On Special Duty.)

ISSUED UNDER THE AUTHORITY OF THE GOVERNMENT OF INDIA BY THE SANITARY COMMISSIONER WITH THE GOVERNMENT OF INDIA, SIMLA.

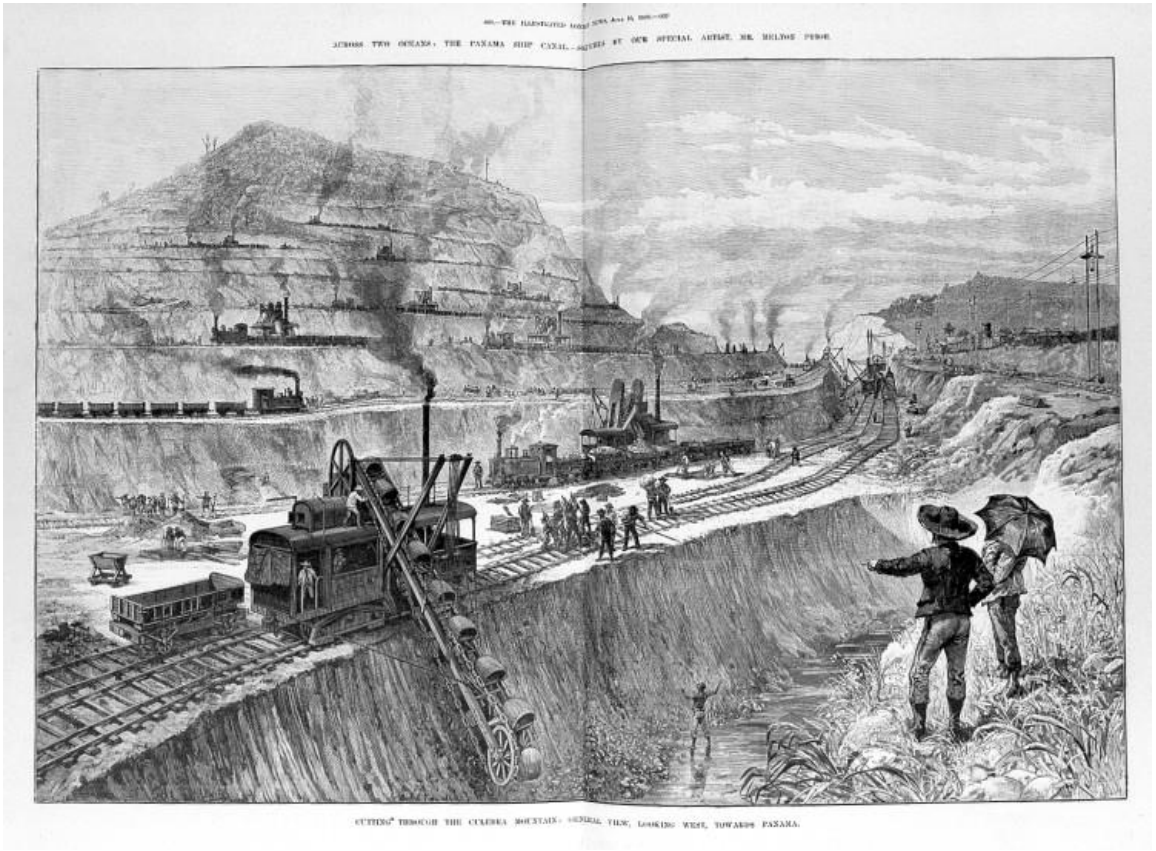
CALCUTTA:

OFFICE OF THE SUPERINTENDENT OF GOVERNMENT PRINTING, INDIA.

1903.

Price 12 Annas or 1s. 2d.

CONSTRUCTION OF THE PANAMA CANAL

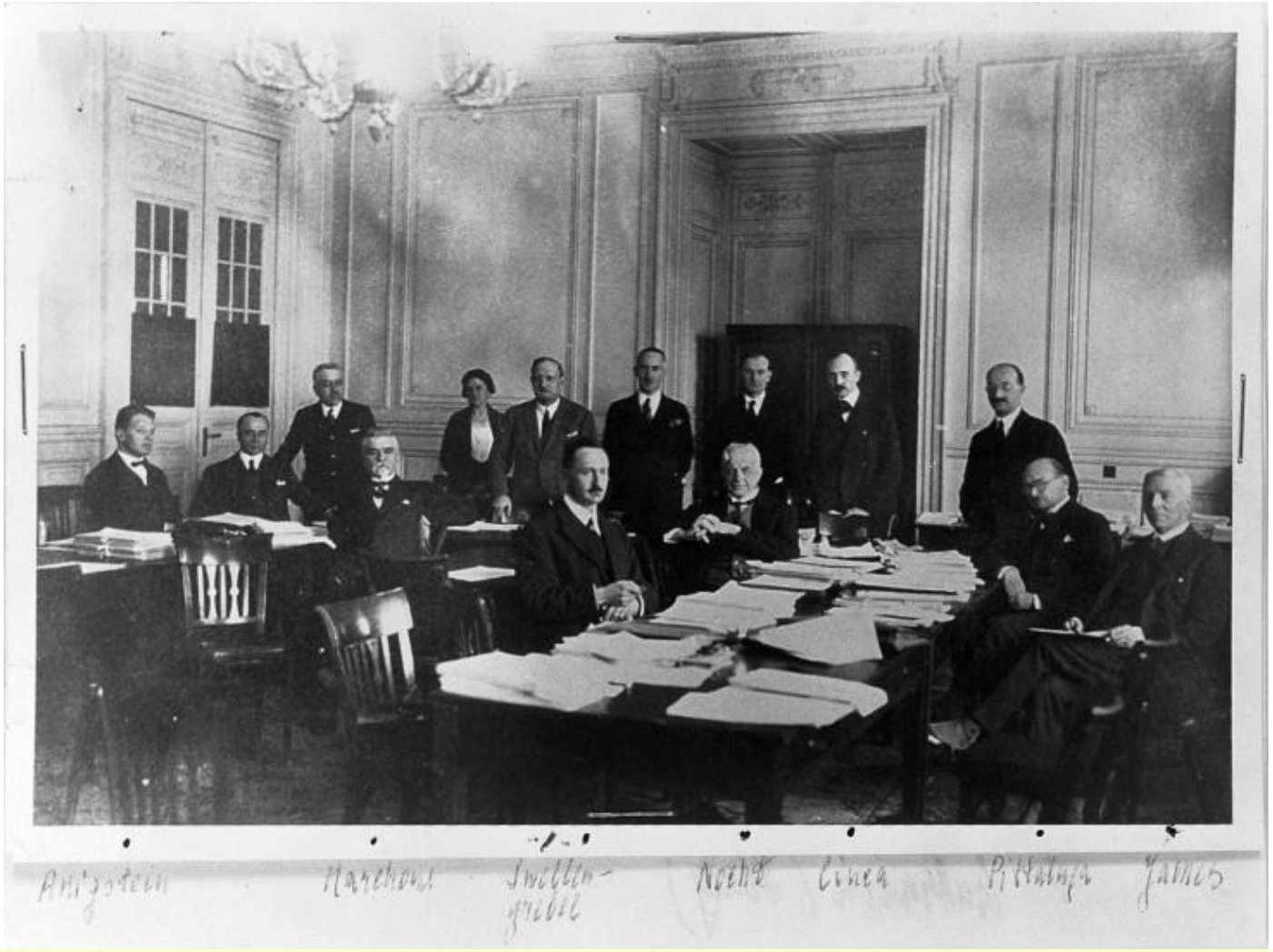


Gorgas 1906- 1916

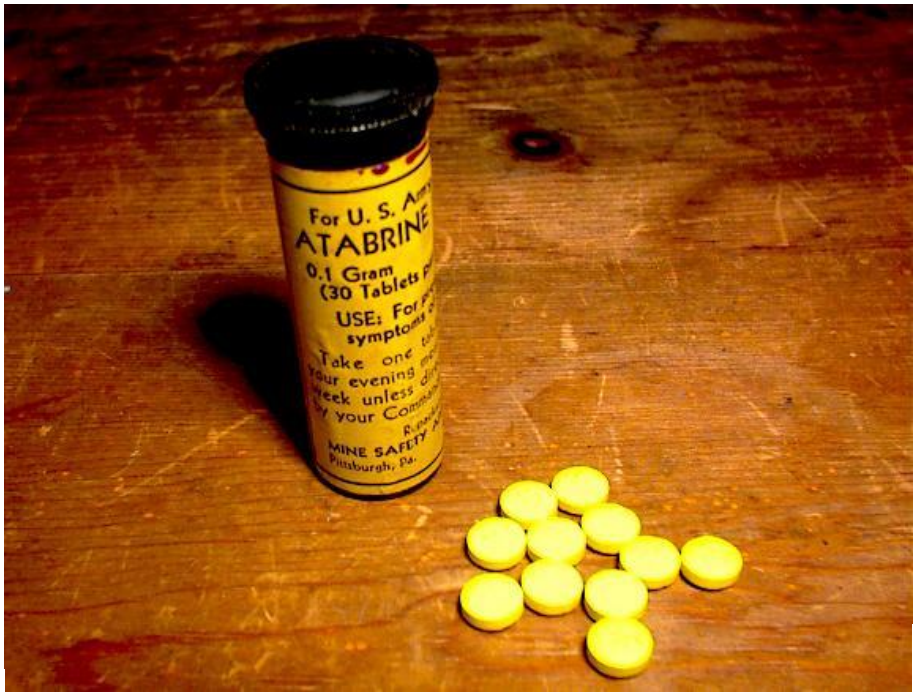
Attack on breeding sites

Reduction of man /vector contact

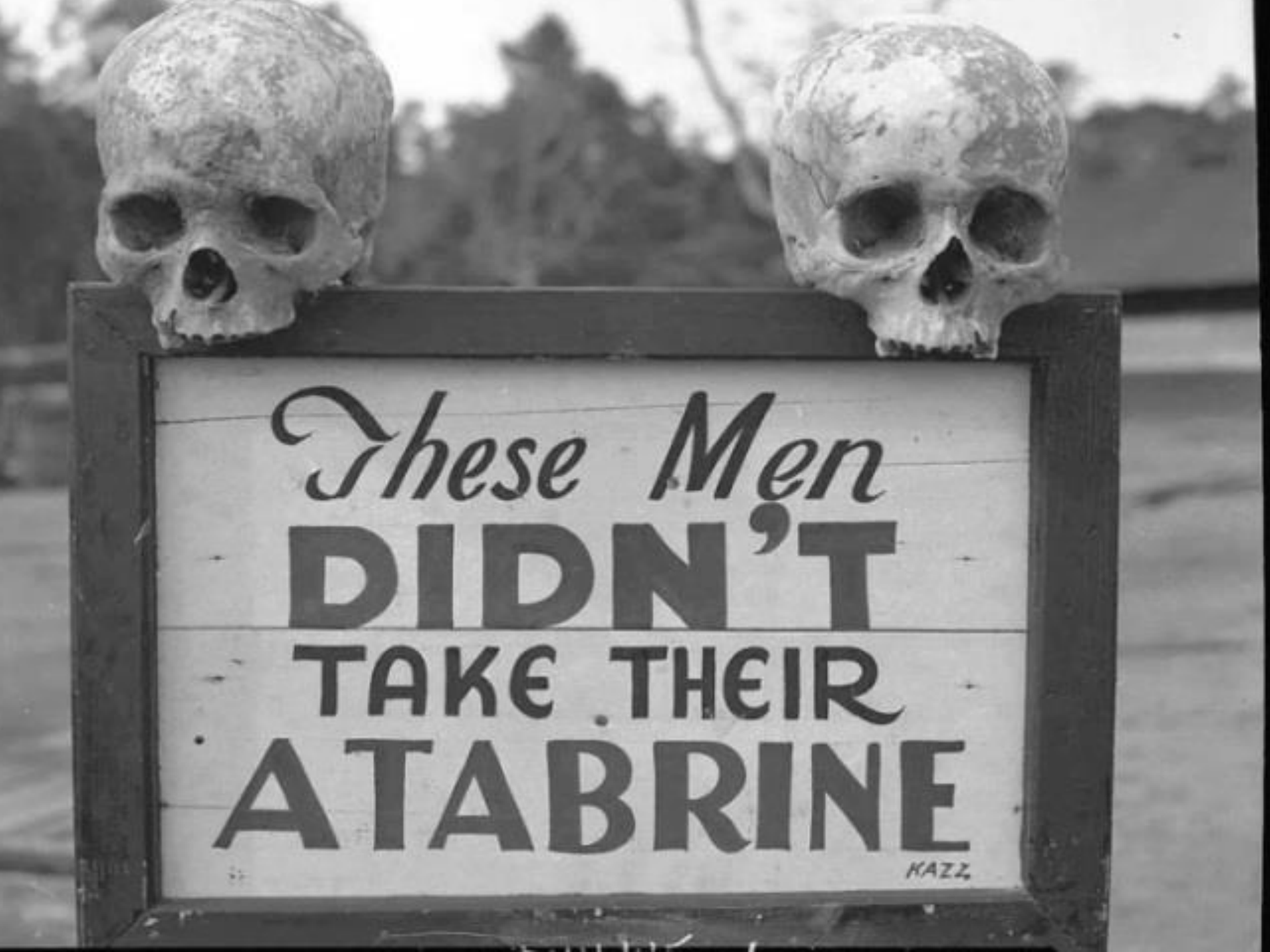
Mass Drug Administration (quinine)



Malaria Commission; League of Nations 1924, Geneva


For U. S.
ATABRINE
0.1 Gram
USE:
MINE SAFETY
Pittsburgh, Pa.


U. S. S. R.
MONGOLIA
MANCHURIA
Kurile Is.
N
CHINA
KOREA
JAPAN
PACIFIC
OCEAN
INDIA
Okinawa
FORMOSA
BURMA
Wake I.
SIAM
FRENCH INDO-CHINA
PHILIPPINES
Guam
Marshall Is.
MALAYA
Gilbert Is.
Sumatra
Borneo
New Guinea
New Britain
Ellice Is.
Solomon Is
Java
Japan 1928
Furthest extent of Japanese occupation 1942
AUSTRALIA
0
500 km
0
500 miles


These Men
DIDN'T
TAKE THEIR
ATABRINE
KAZZ

MALARIA CONTROL IN ITALY

1900- 1960

- Socio-economic improvement
- Education
- Improving health services
- Changing agricultural practices
- Vector control
- Antimalarial drug affordability
- Mass Drug Administration

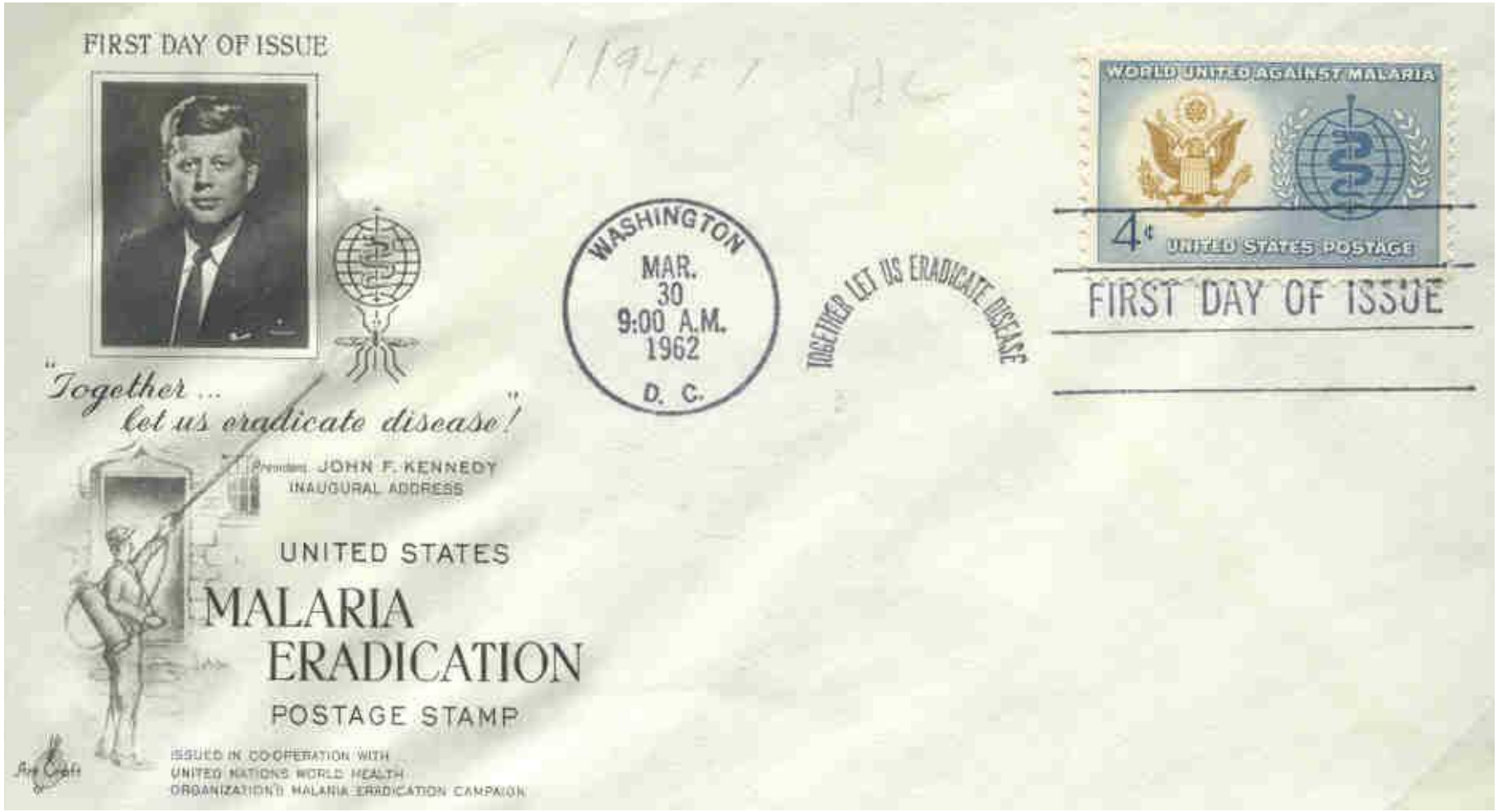
The Conquest of Malaria in Italy 1900 – 1962
Frank Snowden

WHO Interim committee on malaria 1947

Kampala 1950

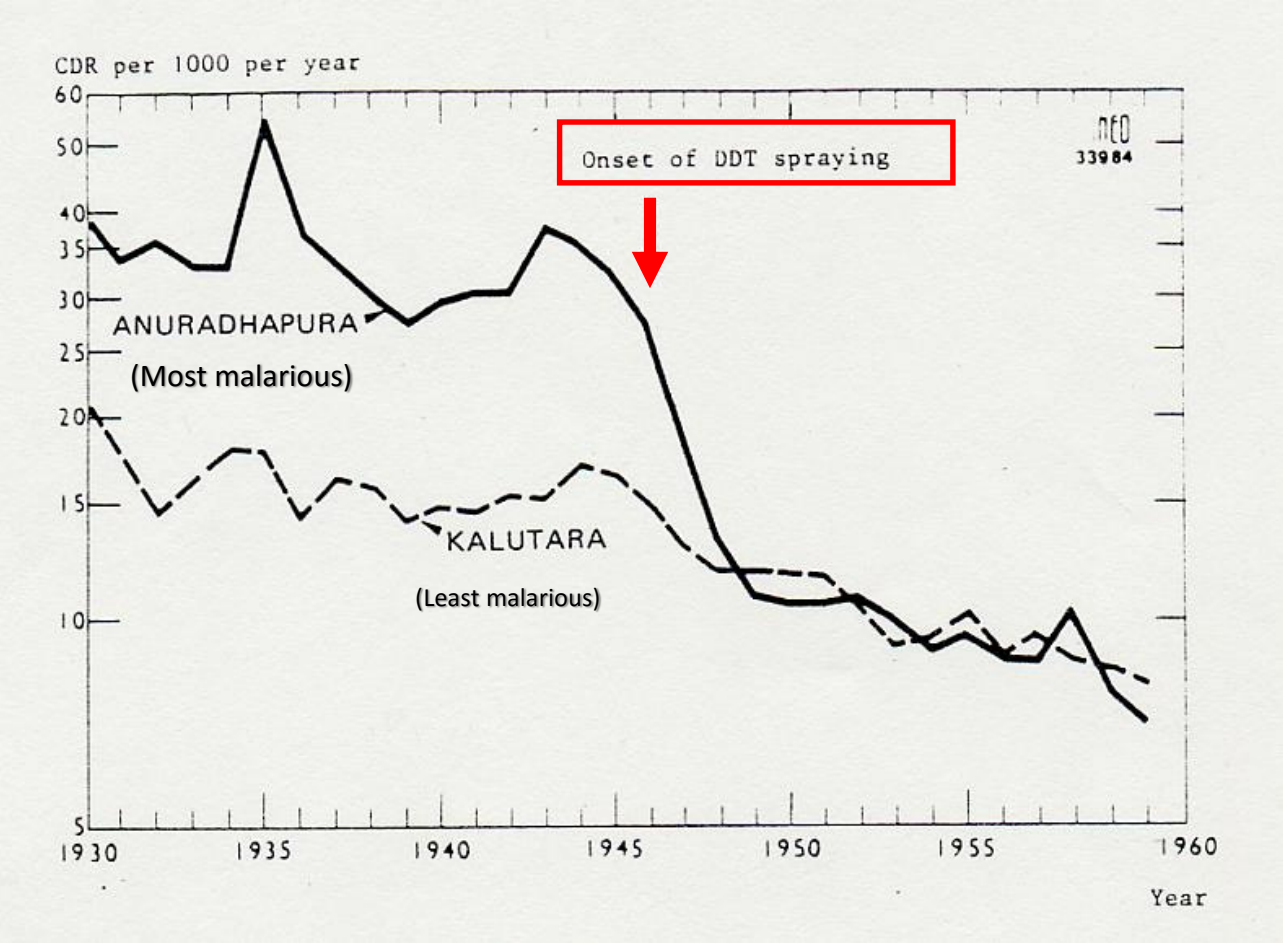
Eradication

Was this a failure or a success?



MALARIA ERADICATION IN SRI LANKA

1930-1960



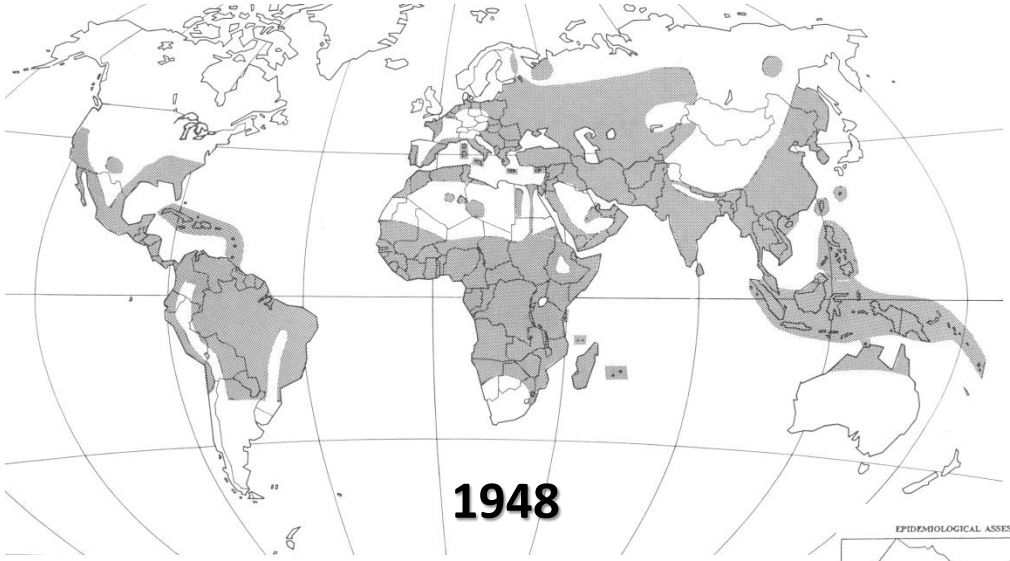
1966

18 cases!

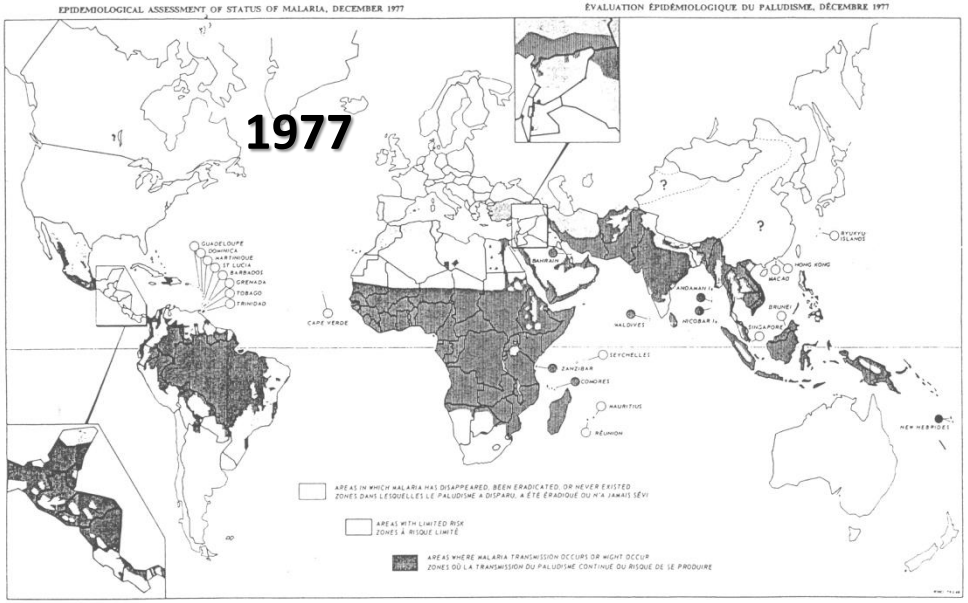
(IUSSP Seminar. Edited by Vallin & Lopez Paris, 1983).

THE MALARIA ERADICATION CAMPAIGN

1955 - 1969



1948

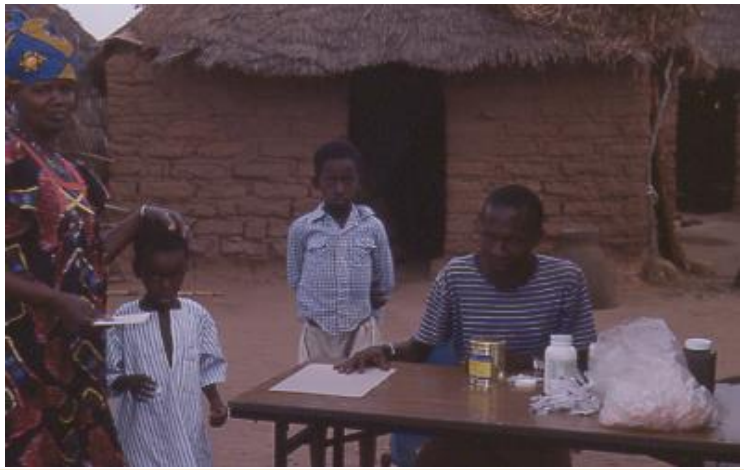


1977

Containment

MALARIA CONTROL 1969 - 1998

Control through treatment



TDR's Dr David Davidson inspecting production facilities for artemisinin-derivative anti-malarial drugs in China (CHINA • 1991 • WHO/TDR).

Little attention and inadequate funding

Reliance on treatment with dying drugs

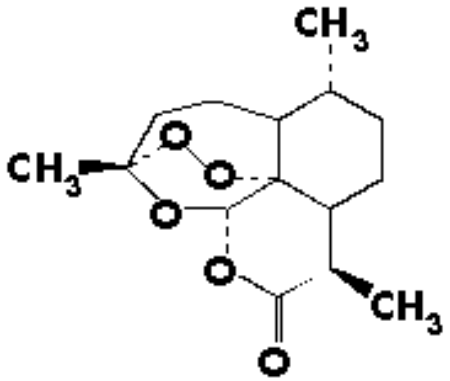
Failing vector control

No attempts at prevention

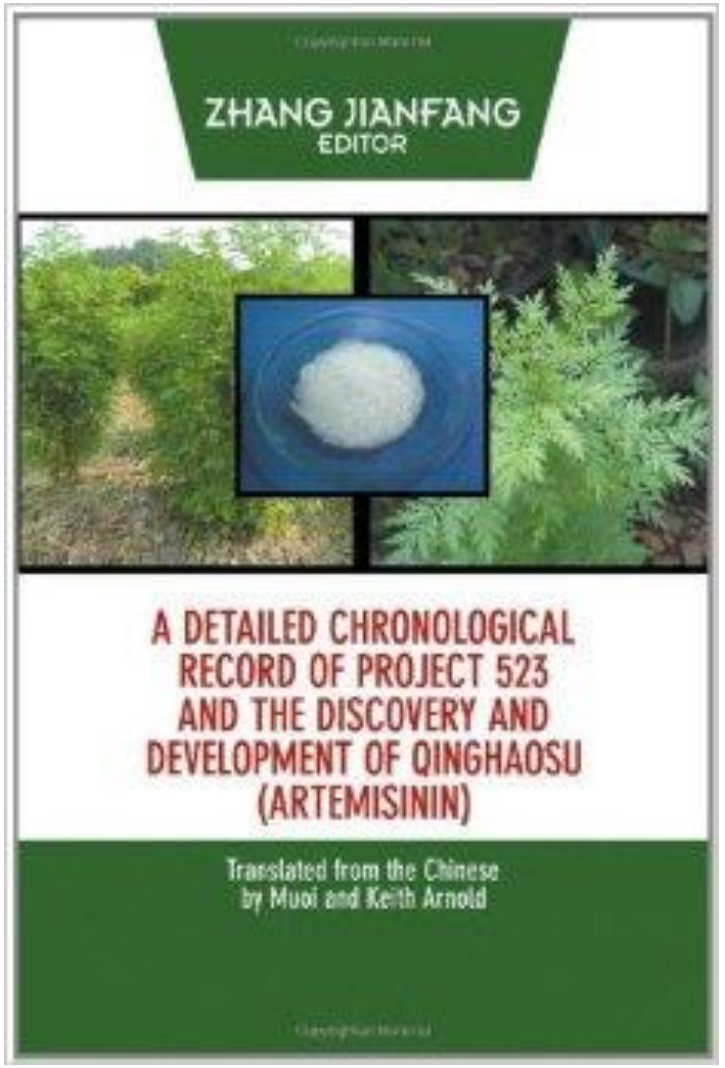
Institutional and donor reluctance to endorse artemisinins

Viet Nam

青 蒿 素




青蒿素


ZHANG JIANFANG
EDITOR
A DETAILED CHRONOLOGICAL RECORD OF PROJECT 523 AND THE DISCOVERY AND DEVELOPMENT OF QINGHAOSU (ARTEMISININ)
Translated from the Chinese by Muoi and Keith Arnold

CHINESE MEDICAL JOURNAL
中华医学杂志英文版
Volume 92 Monthly, December 1979 Number 12

ANTIMALARIA STUDIES ON QINGHAOSU

*Qinghaosu Antimalaria Coordinating Research Group**

An effective antimalaria constituent was extracted from a traditional Chinese medicinal herb — Qinghao (Artemisia annua L) 青蒿 in 1972. It was named Qinghaosu 青蒿素. According to the data from spectral analysis, X-ray diffraction analysis and chemical reaction it is a new type sesquiterpene lactone with a peroxy-group. Pharmacologic studies and clinical observations in every type of malarial infection show that Qinghaosu is a new type antimalaria drug with rapid action and low toxicity. It has direct parasiticidal action on plasmodium in the erythrocytic stage. The parasites in *plasmodium vivax* and *plasmodium falciparum* (including cerebral malaria and chloroquine-resistant falciparum malaria) especially in the areas of chloroquine-resistant falciparum malaria were cleared more rapidly than that with chloroquine and quinine etc, it is ineffective in the tissue stage. In general the short term recurrence rate is higher with Qinghaosu than with chloroquine.

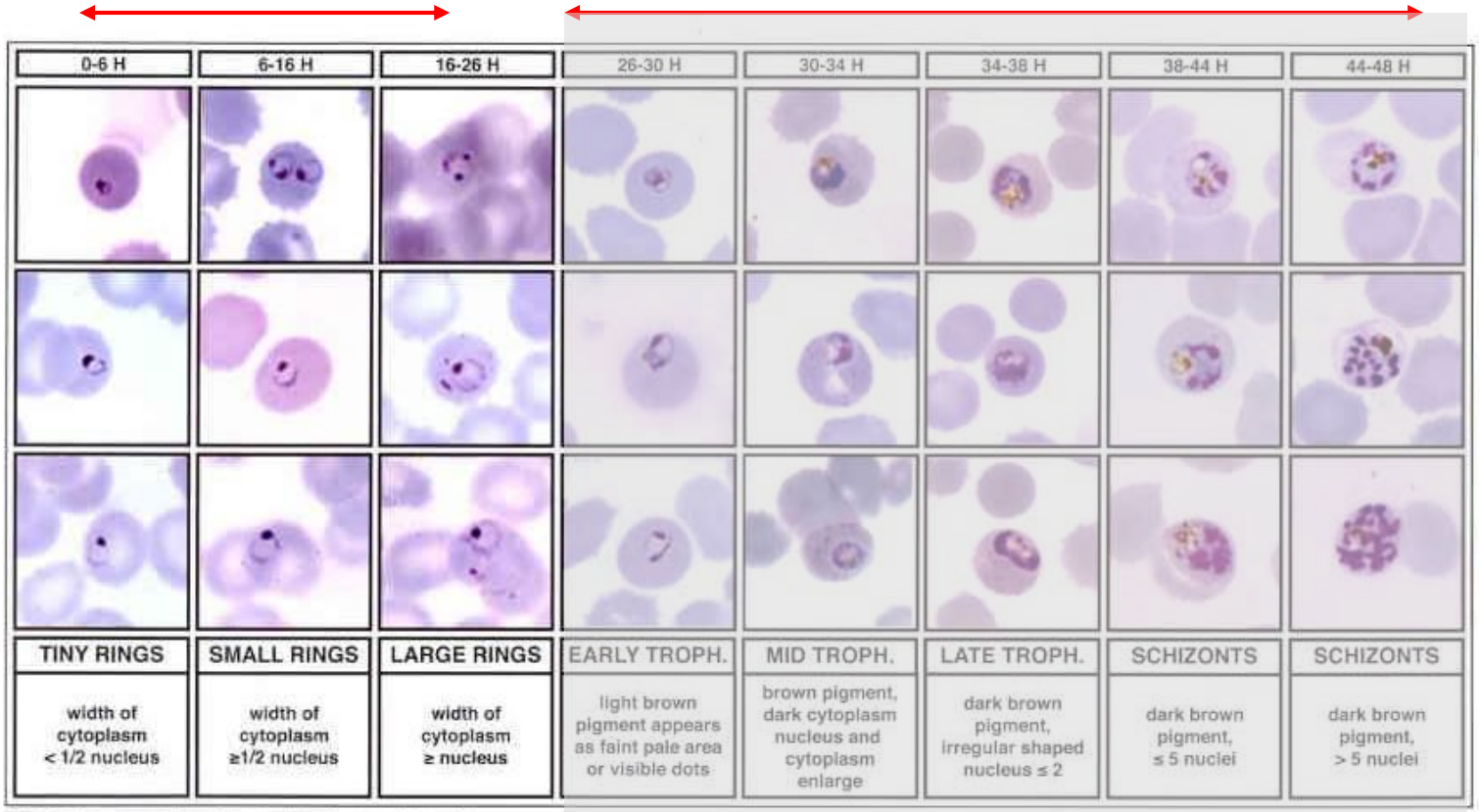
Qinghaosu is a new type antimalaria drug with rapid action and low toxicity.

The parasites…..were cleared more rapidly than that with chloroquine and quinine etc

Chin Med J. 1979; 92: 811-6.

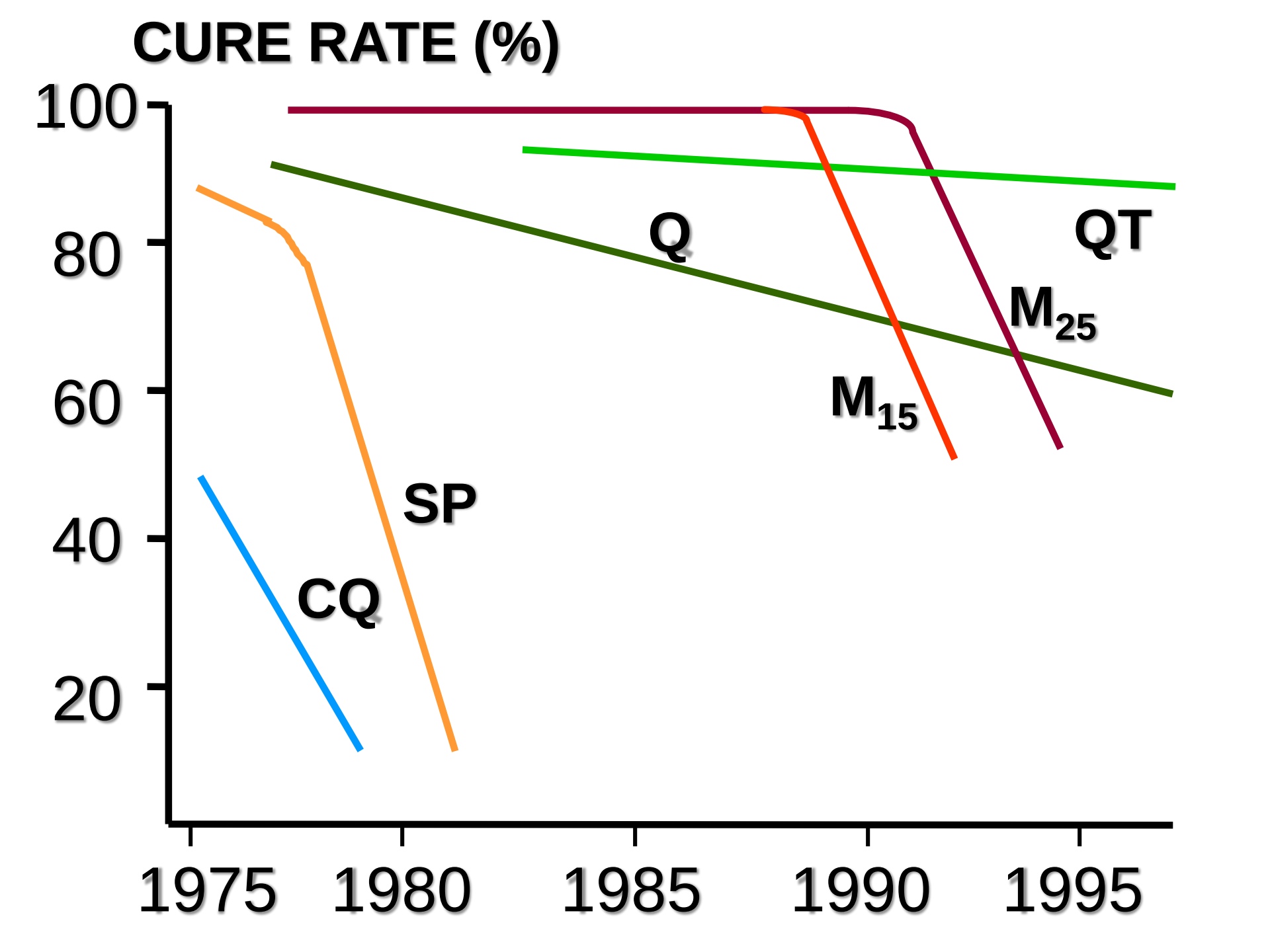
Plasmodium falciparum

Circulating Sequestered



P.falciparum staging (*in vitro* culture)

Wellcome unit, Bangkok 2000


CURE RATE (%)
100
80
60
40
20
1975
1980
1985
1990
1995
Q
QT
M25
M15
SP
CQ


Artemisinin combination treatment

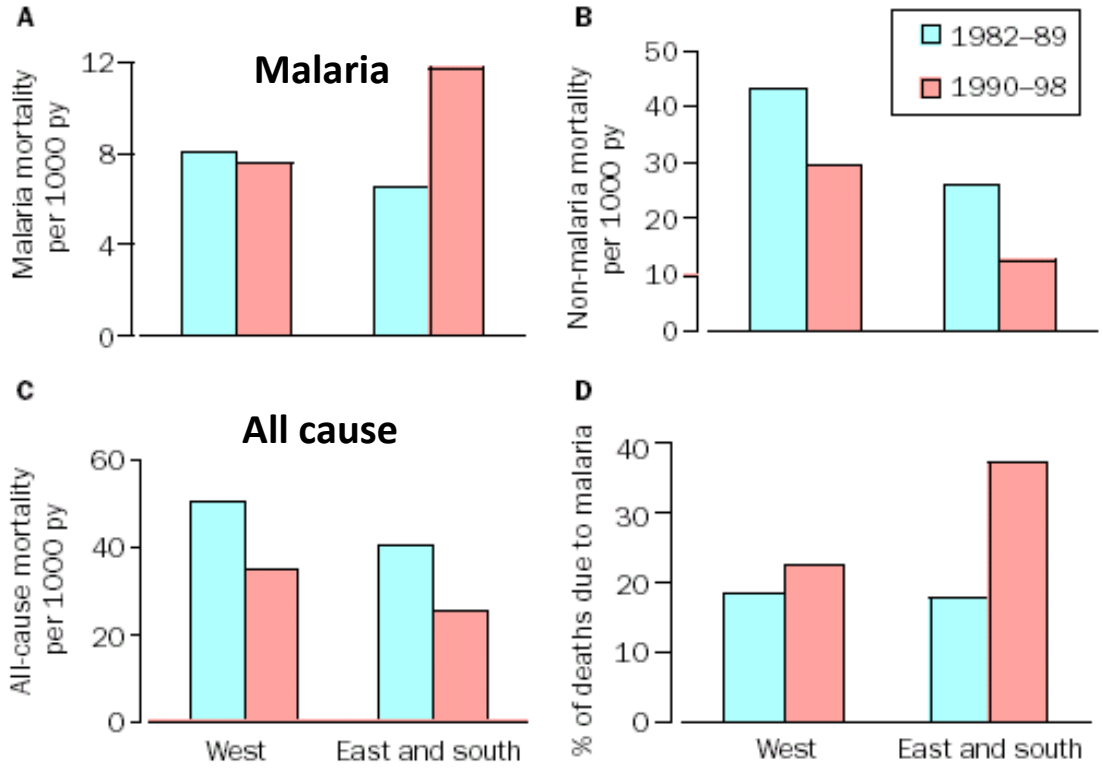
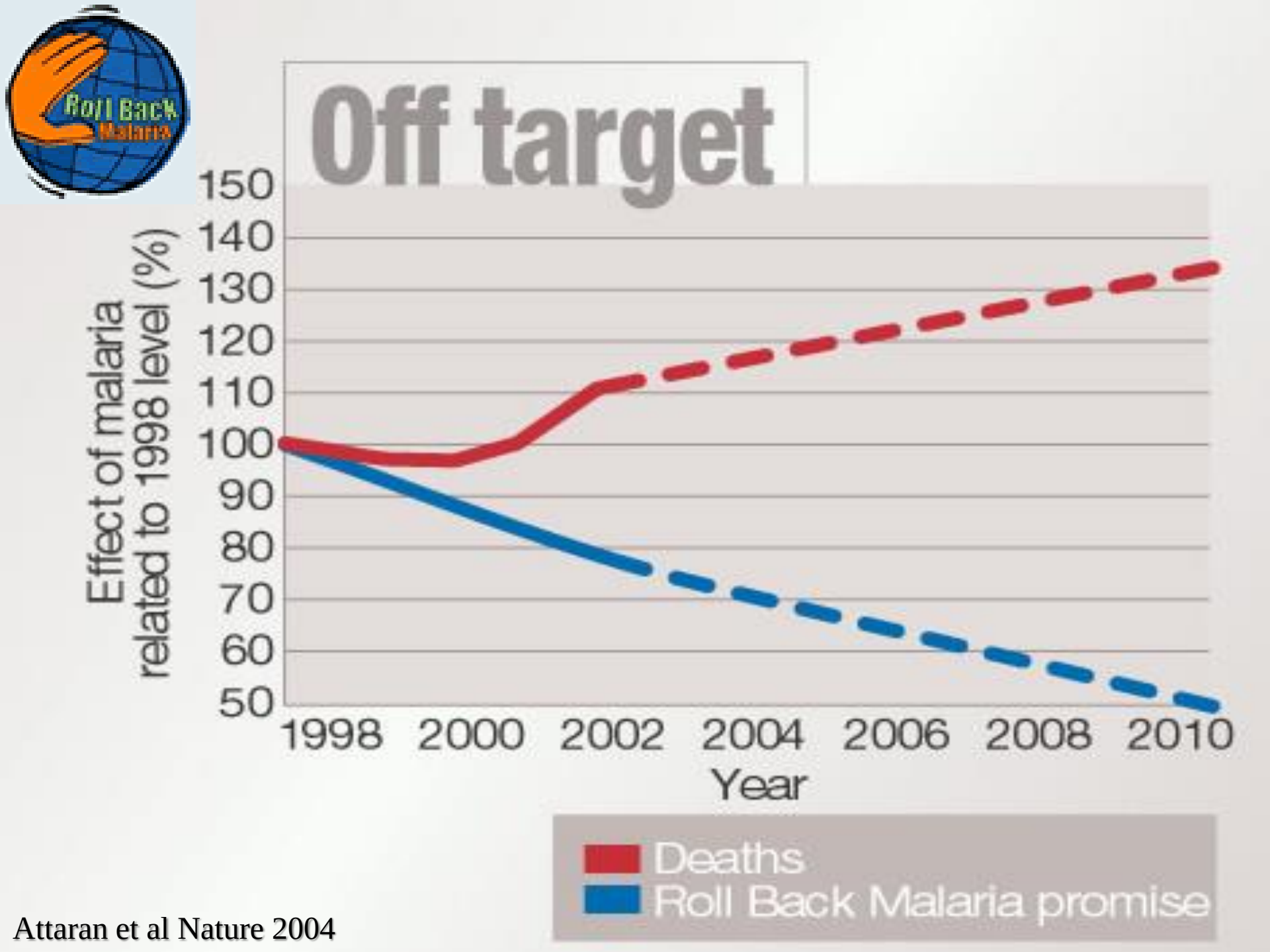


Figure 2. VA-adjusted mortality outcomes in children under 5 years estimated by multivariate regression on African DSS data, for average parasite prevalences of 63% in west Africa and 38·5% in east and southern Africa (difference p=0·03; parasite prevalence did not significantly change over time in either region, p=0·13). The predicted non-malaria and malaria mortality rates do not add exactly to the predicted all-cause rate because the models weighted the different studies differently (depending on the respective influences on both outcomes of VA and sampling error). Note that scales differ. Significance of differences: malaria mortality rate—period p=0·106, region p=0·006, interaction time X region p=0·055; non-malaria mortality rate—period p=0·013, region p=0·002, no interaction; all-cause mortality rate—period p=0·003, region not significant; proportional malaria mortality—period p=0·004, region p=0·002, interaction time X region p=0·043. For further statistics see table 3.

Malaria mortality in <5s in Eastern and Southern Africa was <u>rising</u> while deaths from other causes were <u>falling</u>

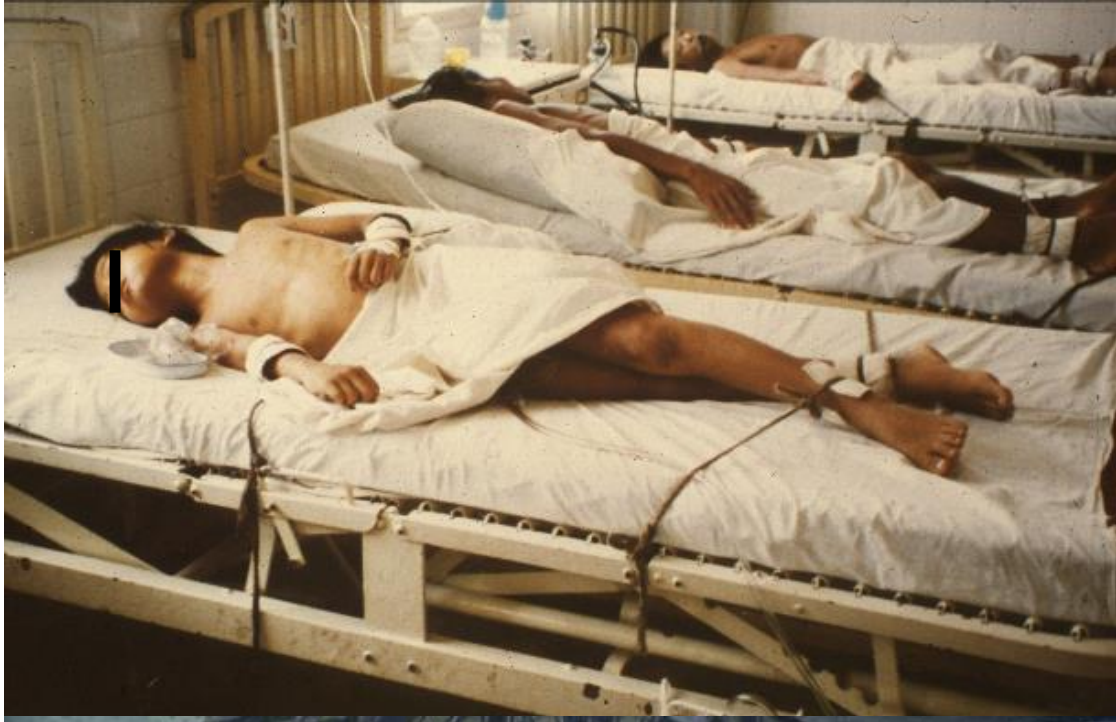
Korenromp et al. Lancet Infect Dis 2003; 3: 349-357



Attaran et al Nature 2004

Rising global malaria mortality

Most malaria affected countries had as National treatment recommendations, antimalarial drugs which were partially or totally ineffective



$2-24 per DALY

Cost-benefit ratios for major health care interventions

Health care intervention	Cost per DALY averted ($)	Burden (in M of DALYs)
Childhood immunization	1 - 5	Not assessed
Malaria prevention[a]	*2 - 24*	*35.4*
Surgical services & emergency care	7 - 215	25 - 134.2
Childhood illnesses	9 - 218	9.6 - 45.1
Cardiovascular disease	9 - 273	4.6
HIV/AIDS (prevention)	6 - 377	56.8
Maternal / neonatal care	82 - 409	29.8 - 37.7
HIV/AIDS (treatment)	673 - 1,494	56.8
Tuberculosis (treatment)	4,129 - 5,506	*8.1*


THE
SANITARY CONDITION
OF
WASHINGTON, D.C.
REPORT
MALARIA,
IS A
FASHIONABLE
DISEASE,
HEATH OFFICER
TOWNSEND,

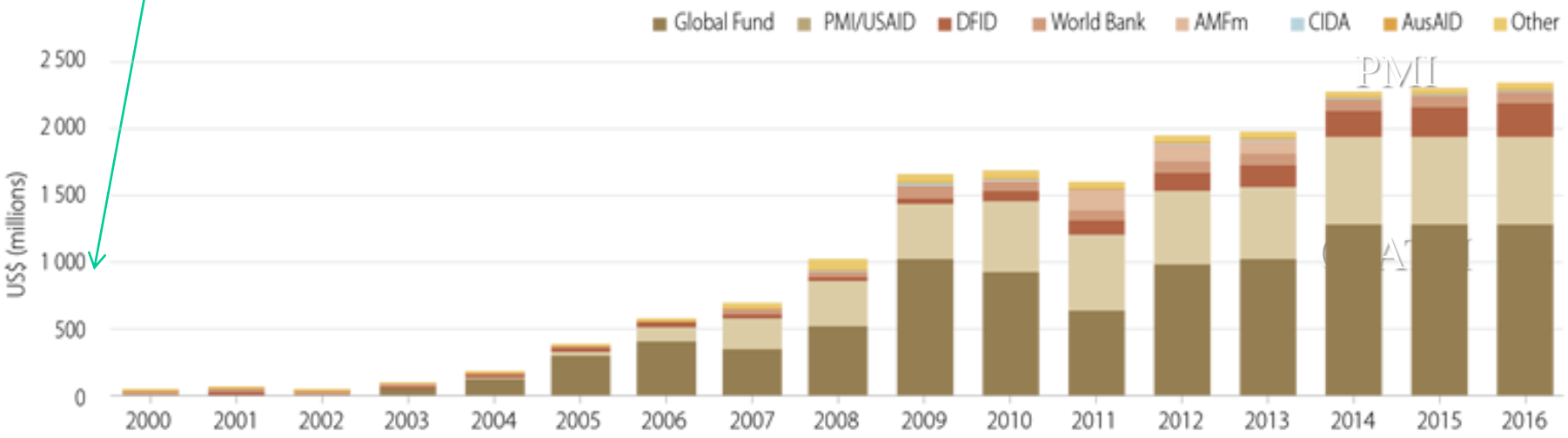
War on malaria

Elimination

2007

Evolution of international funding disbursements for malaria

Past and projected international funding for malaria control, 2000-2016



AMFm, Affordable Medicines Facility – malaria; AusAID, Australian Agency for International Development; CIDA, Canadian International Development Agency; DFID, Department for International Development; GF, Global Fund; PMI, President's Malaria Initiative; USAID, United States Agency for International Development; WB, World Bank

For the GF and PMI/USAID, funds from the last quarter of 2013 onwards are projected; for other agencies, funds from 2012 onwards are projected.

Source: *See Box 3.1*

MVT
MALARIA
VACCINE TRIALS

enter site

African Malaria Network Trust
AMANET

mvi
malaria vaccine initiative

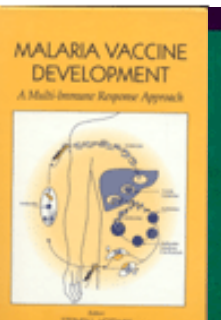
Vaccine?

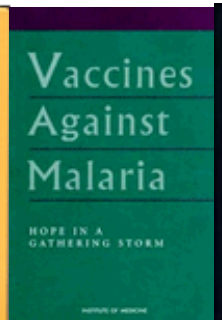
University of Oxford

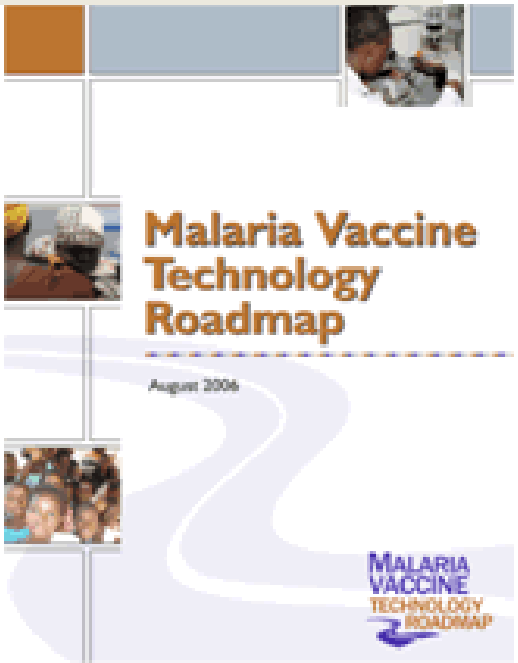
MALARIA VACCINE INITIATIVE
path

wellcome trust

MALARIA VACCINE TECHNOLOGY ROADMAP







EMVI

European Malaria Vaccine Initiative

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 17, 2011 VOL. 365 NO. 20

2011

50%

First Results of Phase 3 Trial of RTS,S/AS01 Malaria Vaccine in African Children

The RTS,S Clinical Trials Partnership*

The NEW ENGLAND JOURNAL of MEDICINE

2012

31%

ORIGINAL ARTICLE

A Phase 3 Trial of RTS,S/AS01 Malaria Vaccine in African Infants

The RTS,S Clinical Trials Partnership

November 2012


18/10/2015

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 30, 2016 VOL. 374 NO. 26

Seven-Year Efficacy of RTS,S/AS01 Malaria Vaccine among Young African Children

Ally Olotu, Ph.D., Gregory Fegan, Ph.D., Juliana Wambua, M.Sc., George Nyangweso, B.Sc., Amanda Leach, M.R.C.P.C.H., Marc Lievens, M.Sc., David C. Kaslow, M.D., Patricia Njuguna, M.Med., Kevin Marsh, F.R.C.P., and Philip Bejon, Ph.D.

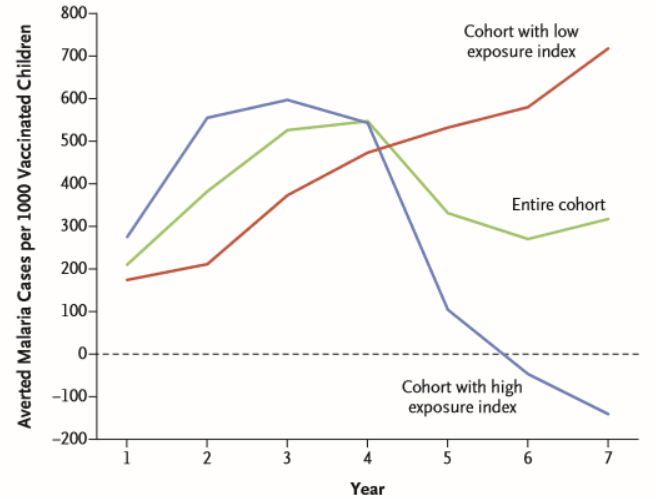


Figure 3. Malaria Cases Averted during Follow-up in the Intention-to-Treat Population.

Shown are the cumulative numbers of malaria cases averted, according to year of follow-up and exposure index of the cohort. We calculated cases averted in each year by subtracting the measured incidence per person-year among participants in the RTS,S/AS01 group from the incidence per person-year among participants in the control group and then multiplying by 1000 to express the result as the number of cases averted per 1000 children vaccinated with RTS,S/AS01. We calculated cumulative cases by summing the cases averted up to and including the year under consideration.

4.4%

Global Malaria Programme

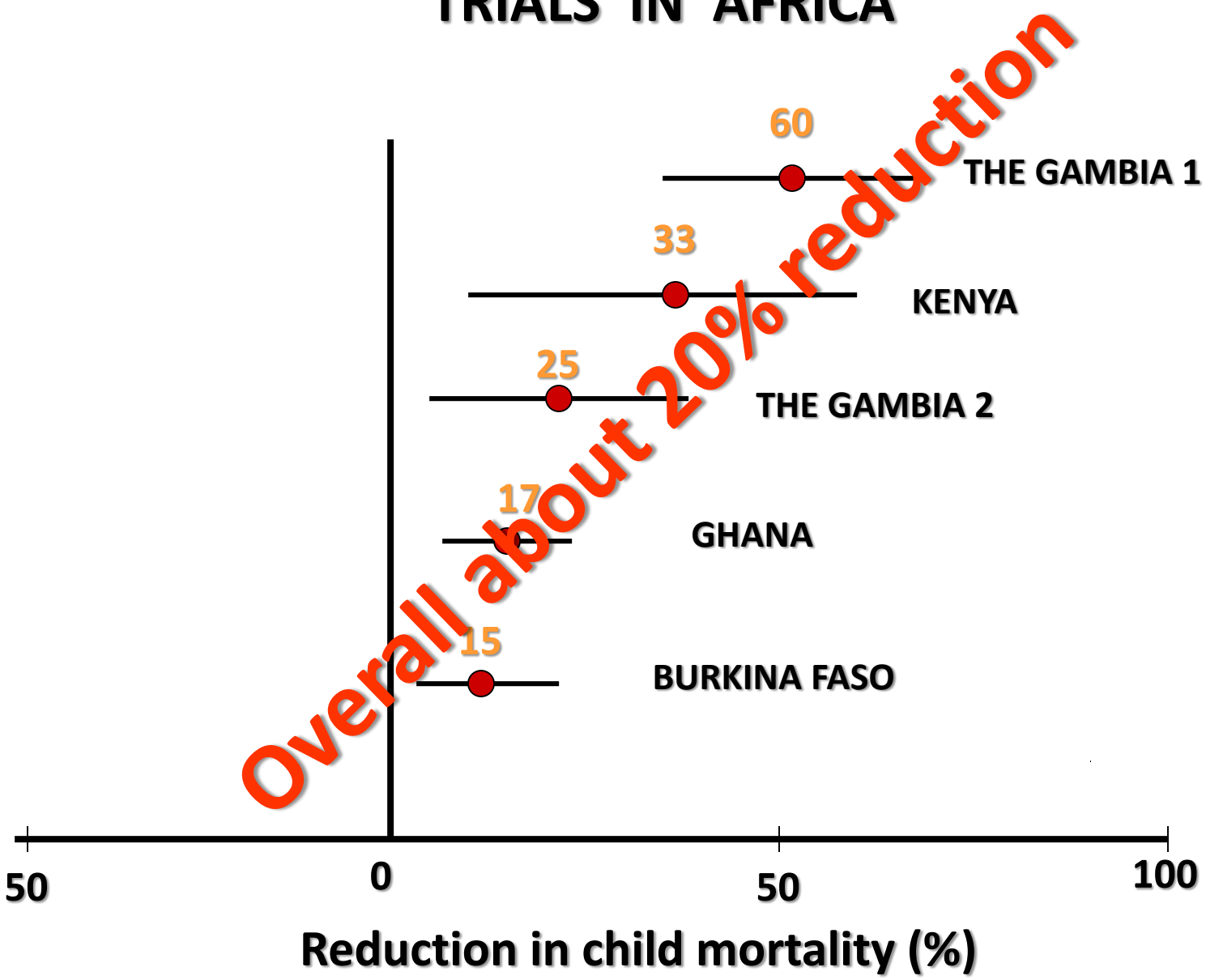
Indoor residual spraying

Use of indoor residual spraying for scaling up global malaria control and elimination

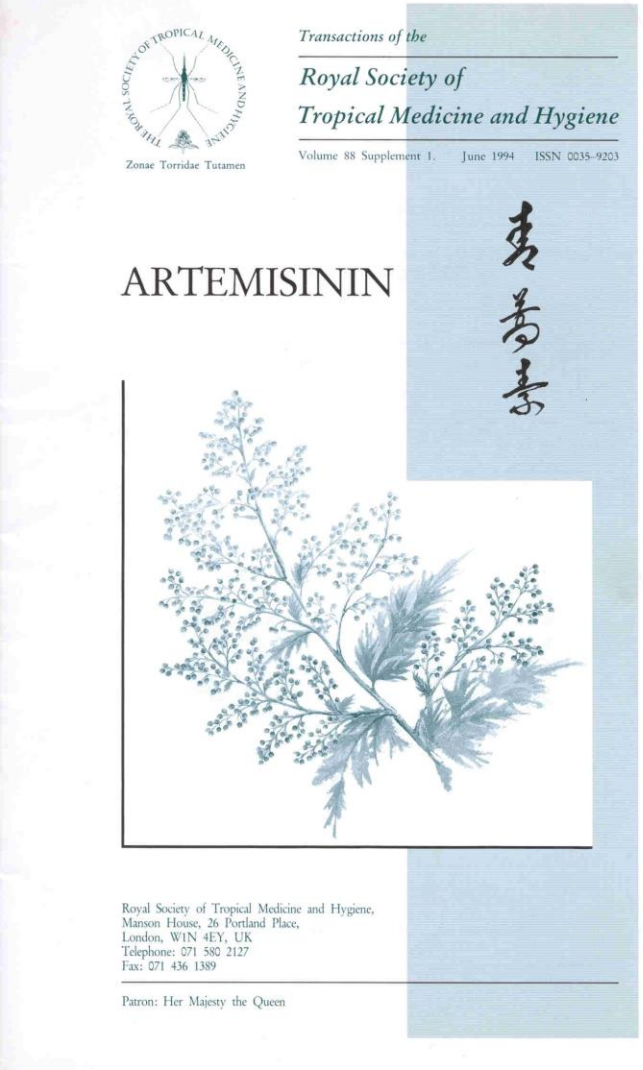
World Health Organization

ITNs

INSECTICIDE TREATED BEDNETS / CURTAINS TRIALS IN AFRICA



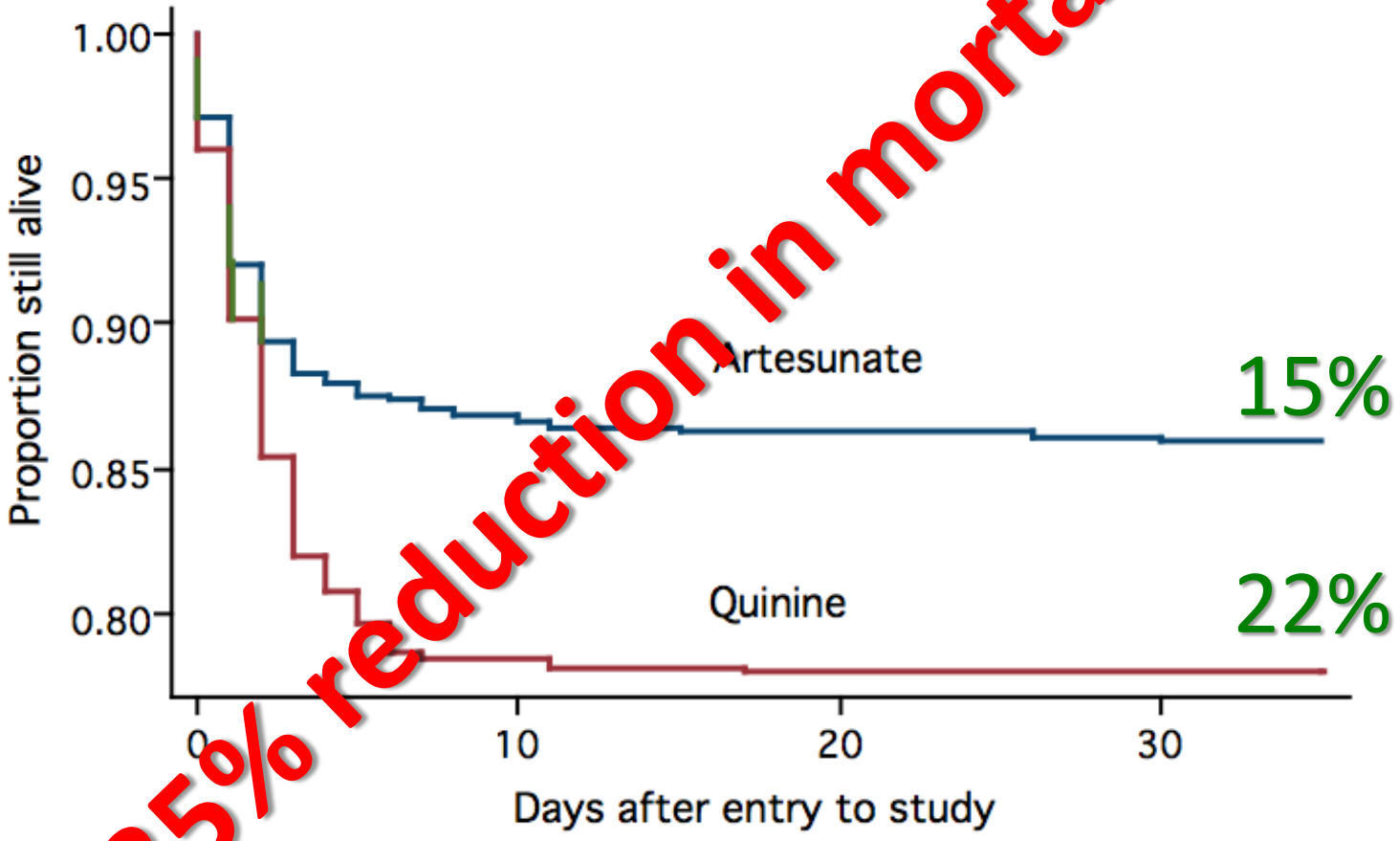
Drugs


Transactions of the
Royal Society of
Tropical Medicine and Hygiene
Volume 88 Supplement 1. June 1994 ISSN 0035-9203
Zonae Torridae Tutamen
ARTEMISININ
青蒿素
Royal Society of Tropical Medicine and Hygiene,
Manson House, 26 Portland Place,
London, W1N 4EY, UK
Telephone: 071 580 2127
Fax: 071 436 1389
Patron: Her Majesty the Queen

Qinghaosu

SEAQUAMAT study

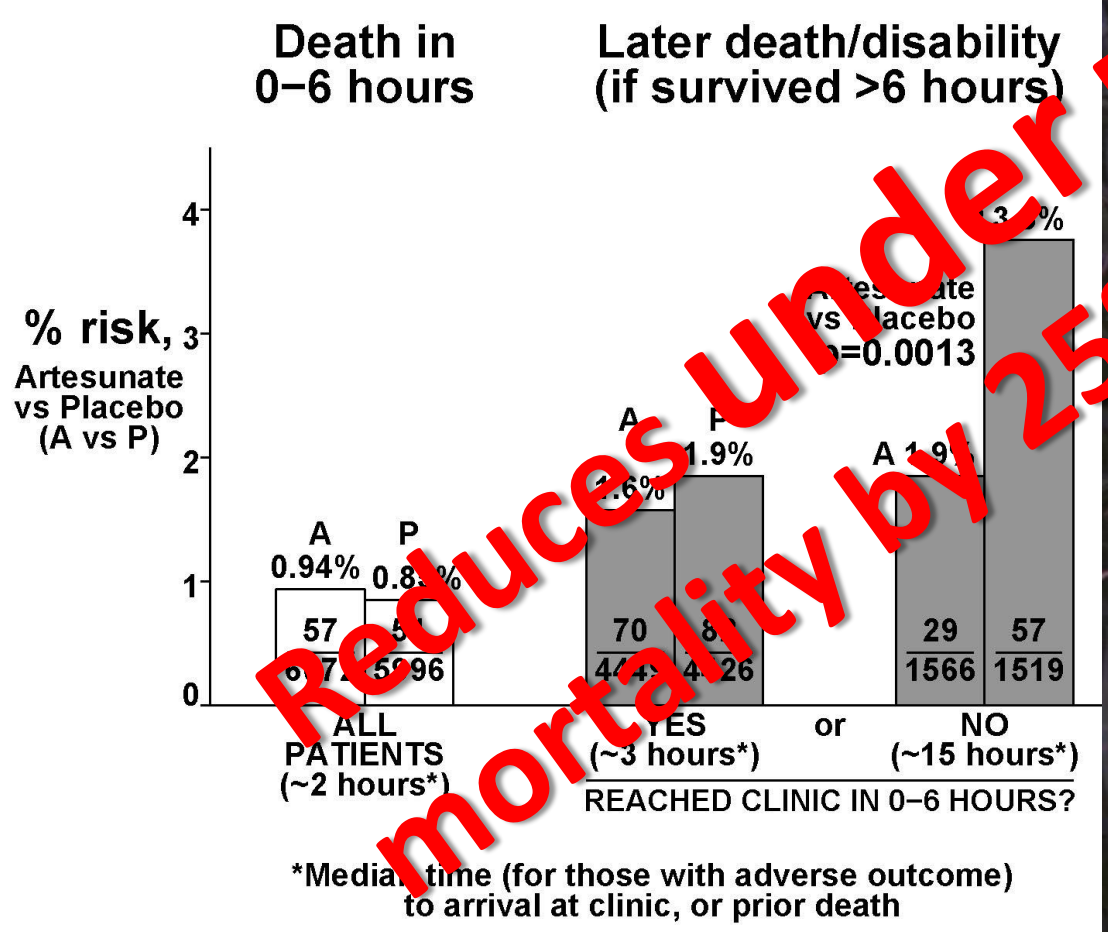
Trial stopped on advice of DSMB after recruitment of 1461 patients



35% reduction in mortality

Dondorp et al , Lancet 2005; **366**: 717 – 725.

Lethal delays in receiving antimalarial drugs



Reduces under 5 mortality by 25%

Gomes et al, Lancet, 2008

AQUAMAT ITT

In-hospital Mortality

- **Quinine:** 297/2713 (10.9%) *p=0.002*
- **Artesunate:** 230/2712 (8.5%)

Relative difference 22.5%

(95%CI: 8.1% to 36.9%)

Dondorp et al. Lancet. 2010 ;376:1647-57.

青蒿素

Artemisinin combination treatment

Viewpoint

2004

WHO, the Global Fund, and medical malpractice in malaria treatment

INTERNATIONAL
Herald Tribune
PUBLISHED BY THE NEW YORK TIMES

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Malaria on the rise

Malaria, a disease forgotten in developed countries, is advancing, killing a million people or more a year, at least 700,000 of them African children. In many nations, some people spend several months a year ill from malaria, a toll that cripples African economies. One reason for malaria's resurgence is that it has evolved to resist the two standard treatments. In East Africa, chloroquine, the most widely used drug, fails two-thirds of the time, and a newer treatment is useless in nearly half of the cases.

A better treatment exists, but the world is adopting it far too slowly. It is a two-drug therapy that includes artemisinin, a Chinese plant used against malaria in herbal form for thousands of years. The combination therapy works 95 percent of the time, prevents disease transmission to others and is slow to provoke resistance.

Yet only six of the 42 African nations with endemic malaria — whose decisions are heavily constrained by outsiders — have changed drugs. For two years, the aid agency Médecins sans Frontières has been arguing that the global malaria establishment, especially influential donors like the U.S. Agency for International Development, has been dragging its feet. An article published last week in the medical journal The Lancet provides evidence that international health organizations are pushing countries to continue to use drugs they know do not work.

The main reason is cost. A chloroquine dose costs a few pennies. The best price available for the artemisinin-based combination therapy is 40 cents for a child's treatment and $1.50 for an adult's. That may not sound like much. But until recently, poor countries bore the cost of drugs themselves. Many sick people cannot pay 40 cents.

Wealthy countries are going to have to pay for the more expensive drugs. The Global Fund to Fight AIDS, Tuberculosis and Malaria is now doing this, but the fund has very little money. Changing drugs requires countries to adapt health care services and find ways to get people to finish a three-day treatment. Countries will not switch unless they are sure of steady financing for the new drugs.

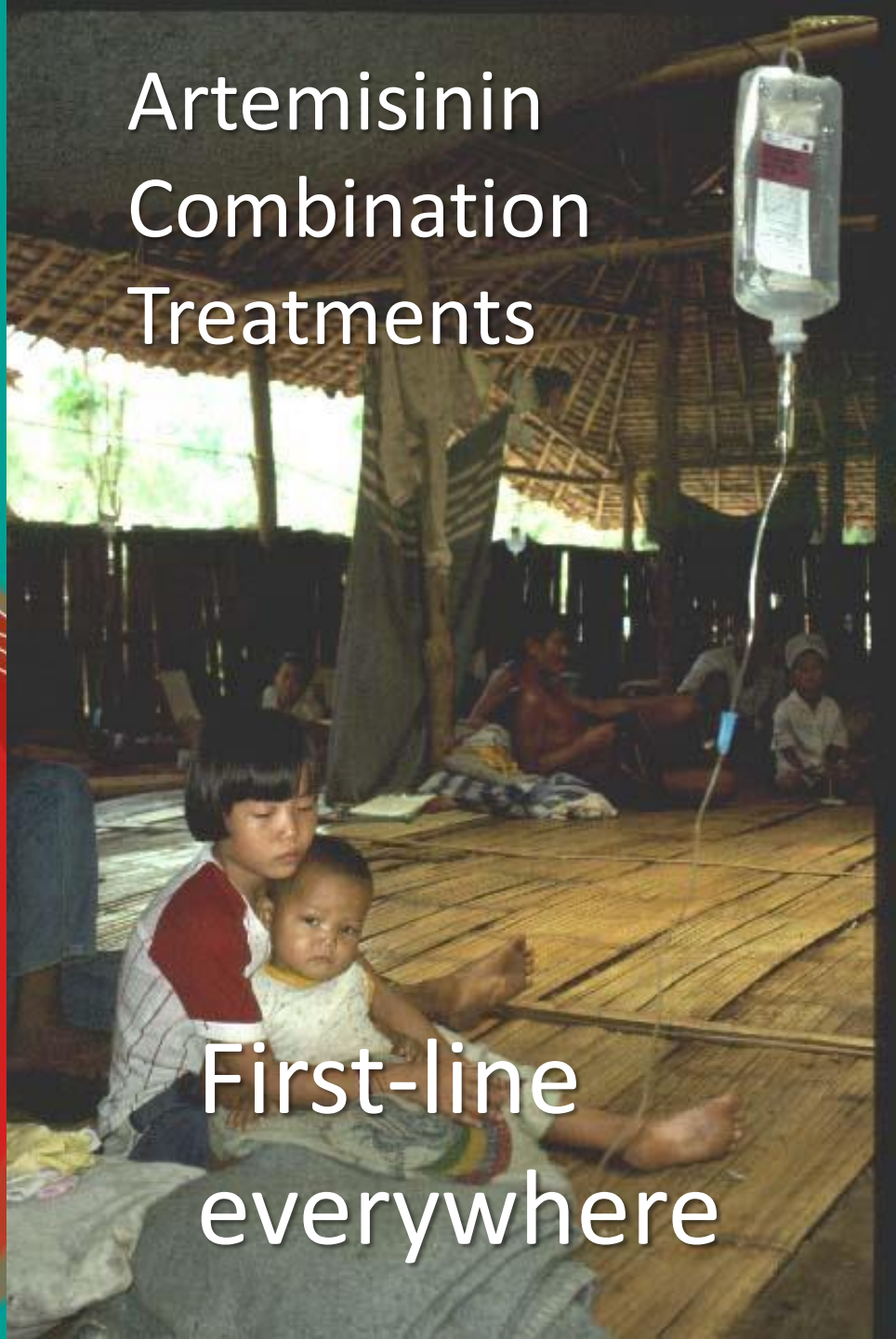
The underlying problem is that most people who die of malaria are poor rural children, and the disease has been eradicated in most wealthy nations. The lack of a global lobby against malaria has brought the world to the sad, absurd point where organizations dedicated to saving lives are pushing drugs that they know will allow children to die.

The underlying problem is that most people who die of malaria are poor rural children, and the disease has been eradicated in most wealthy nations. The lack of a global lobby against malaria has brought the world to the sad, absurd point where organizations dedicated to saving lives are pushing drugs that they know will allow children to die.

World Health Organization

GUIDELINES FOR THE TREATMENT OF MALARIA

2006



Artemisinin Combination Treatments

First-line everywhere

FDCs

Artesunate + mefloquine

Artemether + lumefantrine

Artesunate + amodiaquine

Dihydroartemisinin + Piperaquine

Not ; Artesunate +SP

Seized counterfeit artesunate in Yunnan

Fake artemisinin derivatives in Africa

"TAKING THE ELIMINATION AGENDA FORWARD"

Investing in our future
The Global Fund
To Fight AIDS, Tuberculosis and Malaria

ROLL BACK MALARIA

PMI
President's Malaria Initiative
SAVING LIVES IN AFRICA

The World Bank
IBRD & IDA: Working for a World Free of Poverty

The Malaria Elimination Group (MEG)

UCSF

malaria consortium
disease control, better health

MADNESS AGAINST MALARIA

WORLD SWIM AGAINST MALARIA

Kicking Malaria
Find out how soccer superstars FC Barcelona are teaming up with MNM

UNITAID

TOGETHER TO HEAL

BUY-A-NET

unicef

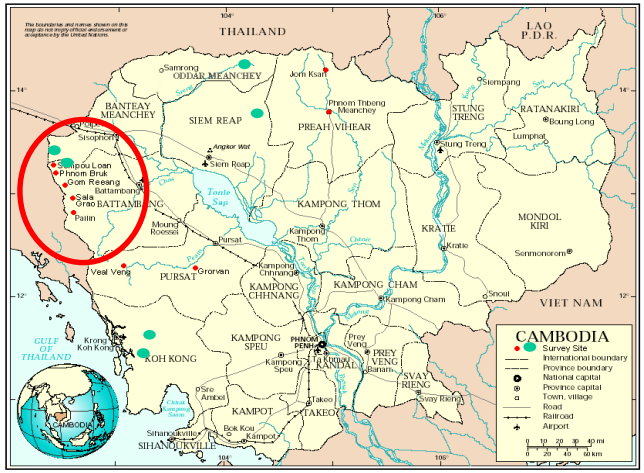
malaria NO MORE

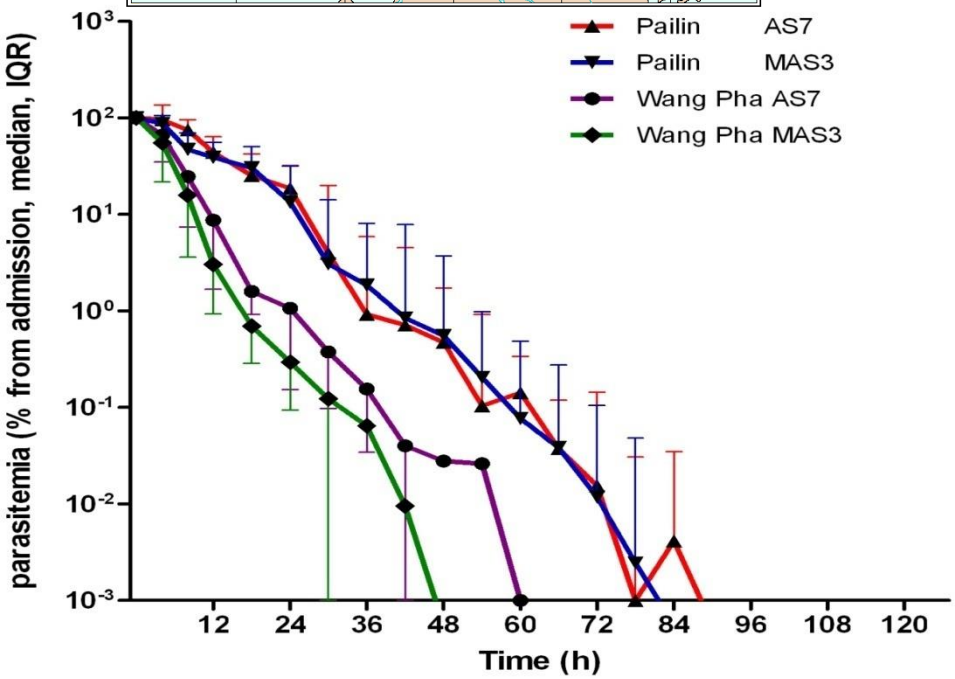
malERA
Malaria Eradication Research Agenda

Rotarians Eliminating Malaria
a Rotarian Action Group

Linked To End Malaria

Artemisinin resistance





The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Artemisinin Resistance in *Plasmodium falciparum* Malaria

Arjen M. Dondorp, M.D., François Nosten, M.D., Poravuth Yi, M.D., Debashish Das, M.D., Aung Phae Phyo, M.D., Joel Tarning, Ph.D., Khin Maung Lwin, M.D., Frederic Ariey, M.D., Warunee Hanpithakpong, Ph.D., Sue J. Lee, Ph.D., Pascal Ringwald, M.D., Kamolrat Silamut, Ph.D., Mallika Imwong, Ph.D., Kesinee Chotivanich, Ph.D., Pharath Lim, M.D., Trent Herdman, Ph.D., Sen Sam An, Shunmay Yeung, Ph.D., Pratap Singhasivanon, M.D., Nicholas P.J. Day, D.M., Niklas Lindegardh, Ph.D., Duong Socheat, M.D., and Nicholas J. White, F.R.S.

THE LANCET
Volume 374 · Number 9686 · Pages 265-356 · July 25-31, 2009 www.thelancet.com

"If malaria parasites develop full-blown resistance to artemisinin derivatives...there will be nothing in the malarial drug pipeline to replace these compounds for 5 years, or possibly more."

See Special Report page 277

The spread of chloroquine resistance

<u>Millions</u> died as a result

Wooton et al, Nature 2002

SP resistance followed *exactly* the same route

Intercontinental Spread of Pyrimethamine-Resistant Malaria

Cally Roper,[1]* Richard Pearce,[1] Shalini Nair,[2] Brian Sharp,[3]
François Nosten,[4] Tim Anderson[2]

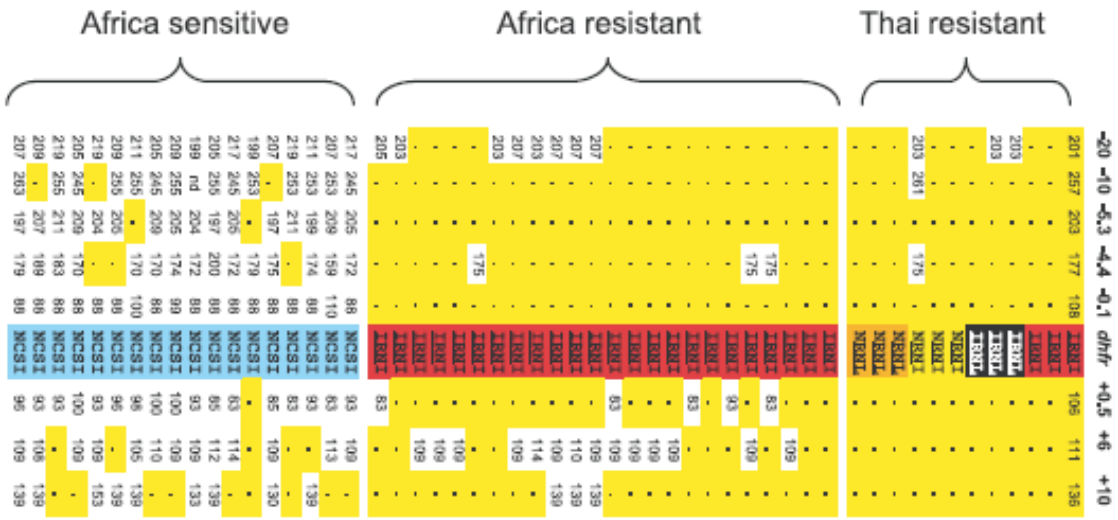


Fig. 1. *dhfr* alleles and flanking microsatellites of parasites from Africa and Thailand. The figure comprises data from 12 Thai parasites with two to four resistance mutations, 24 African parasites with triple-mutant alleles, and 18 African parasites with sensitive *dhfr* alleles. The four-letter codes describe amino acids present at positions 51, 59, 108, and 164 in the predicted *dhfr* protein (*10*). Amino acids conferring resistance are underlined, and *dhfr* alleles are shaded yellow, orange, red, and black in order of increasing resistance. Sensitive alleles are shaded turquoise. Allele lengths are shown for eight microsatellites positioned at −0.1, −4.4, −5.3, −10, and −20 kb upstream and +0.5, +6, and +10 kb downstream of *dhfr*. Dots and yellow shading indicate identical allele size to the predominant resistant haplotype (shown at right).

The flanking sequence around the successful “triple” DHFR mutant that spread in Africa came from the Thailand-Cambodia border

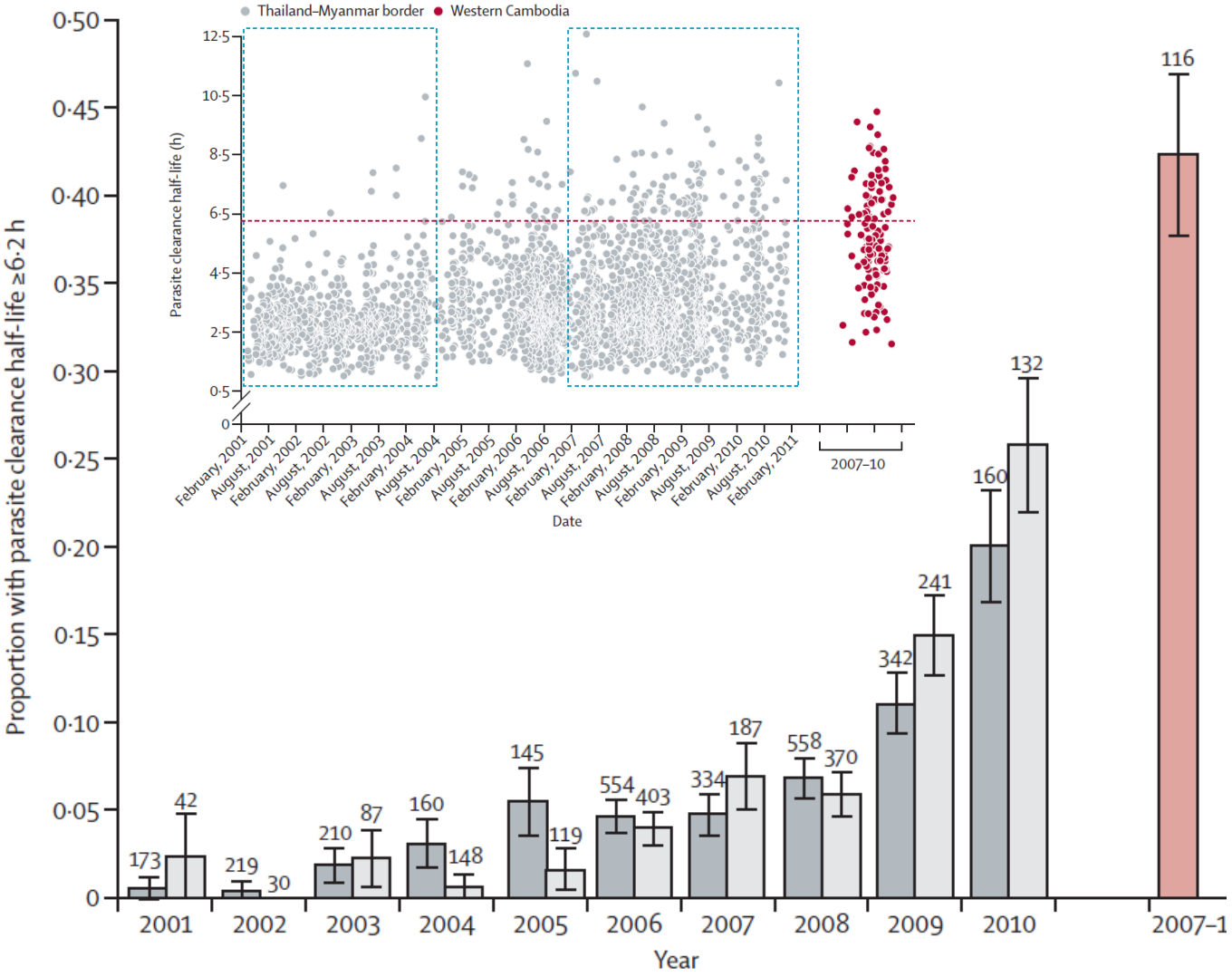
Science 2004

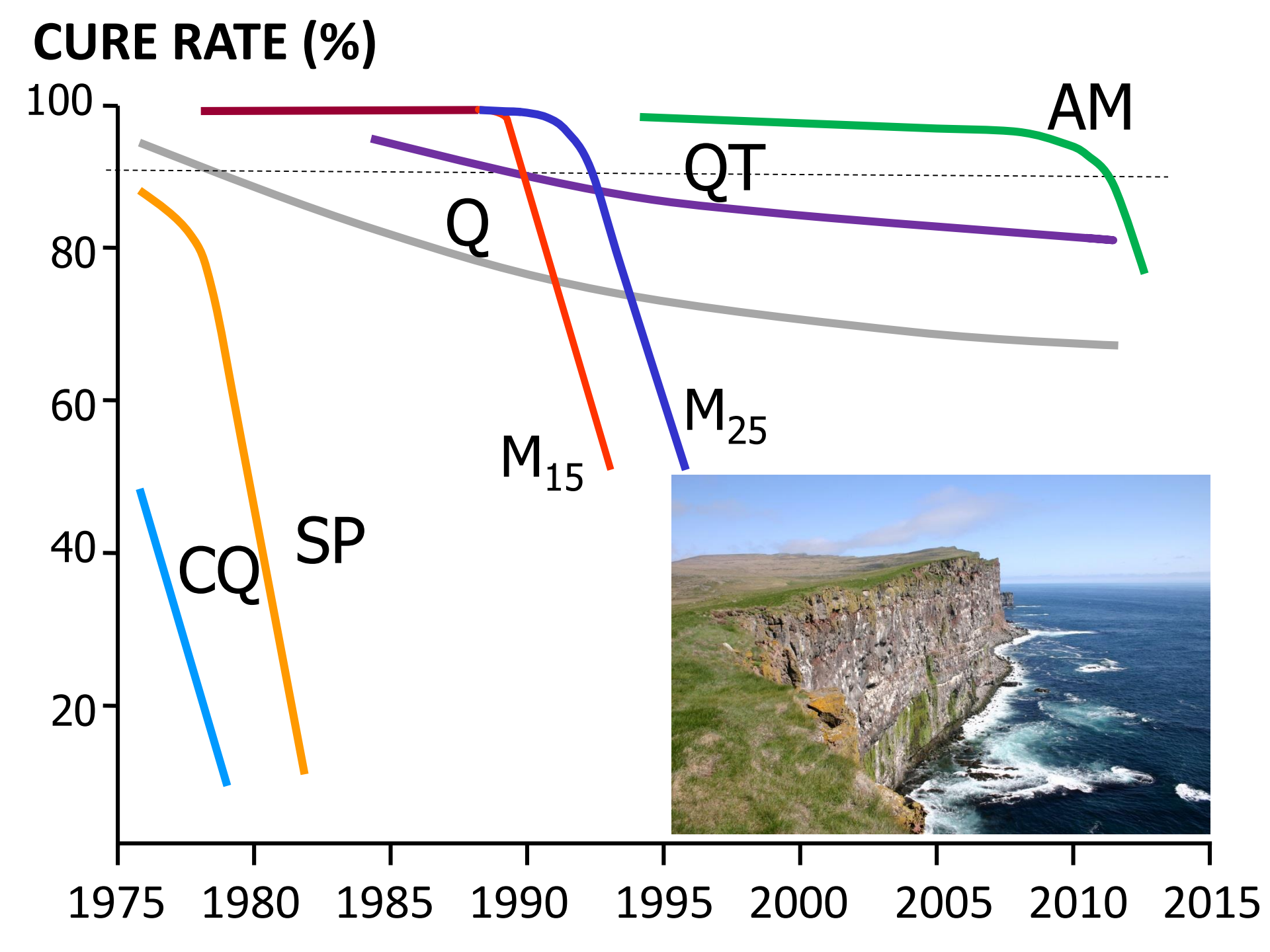

Antimalarial drug resistance
CHINA
Xi'an
Nanjing
Shanghai
Fukuoka
Chengdu
Wuhan
Hangzhou
Chongqing
Changsha
Nanchang
East China Sea
Guiyang
Kunming
Taipei
Guangzhou
Nanning
Taiwan
Hong Kong S.A.R.
Macau S.A.R.
Luzon Strait
Philippine Sea
New Delhi
NEPAL
Kathmandu
Lhasa
BHUTAN
Thimphu
Jaipur
Lucknow
Kānpur
BANGLADESH
Dhaka
Kolkata (Calcutta)
Ahmadābād
Nāgpur
INDIA
Pune
Hyderābād
Bangalore
Chennai (Madras)
BURMA
Hanoi
LAOS
Vientiane
Gulf of Tonkin
Hainan Dao
Chiang Mai
Rangoon
Bay of Bengal
THAILAND
Bangkok
VIETNAM
PARACEL ISLANDS
Hue
CAMBODIA
Phnom Penh
Ho Chi Minh City
Gulf of Thailand
South China Sea
Andaman Sea
ANDAMAN ISLANDS (INDIA)
SPRATLY ISLANDS
Manila
PHILIPPINES
Cebu
Davao
Northern Mariana Islands (U.S.)
Koror
PALAU
Laccadive Sea
Colombo
SRI LANKA
Male
NICOBAR ISLANDS (INDIA)
Bandar Seri Begawan
BRUNEI
Kuala Lumpur
MALAYSIA
Medan
Singapore
SINGAPORE
Celebes Sea
Pontianak
Palembang
INDONESIA
Makassar
Jakarta
Java Sea
Banda Sea
Semarang
Surabaya
Bandung
Timor Sea
Darwin
Cocos (Keeling) Islands
Ashmore and Cartier Islands

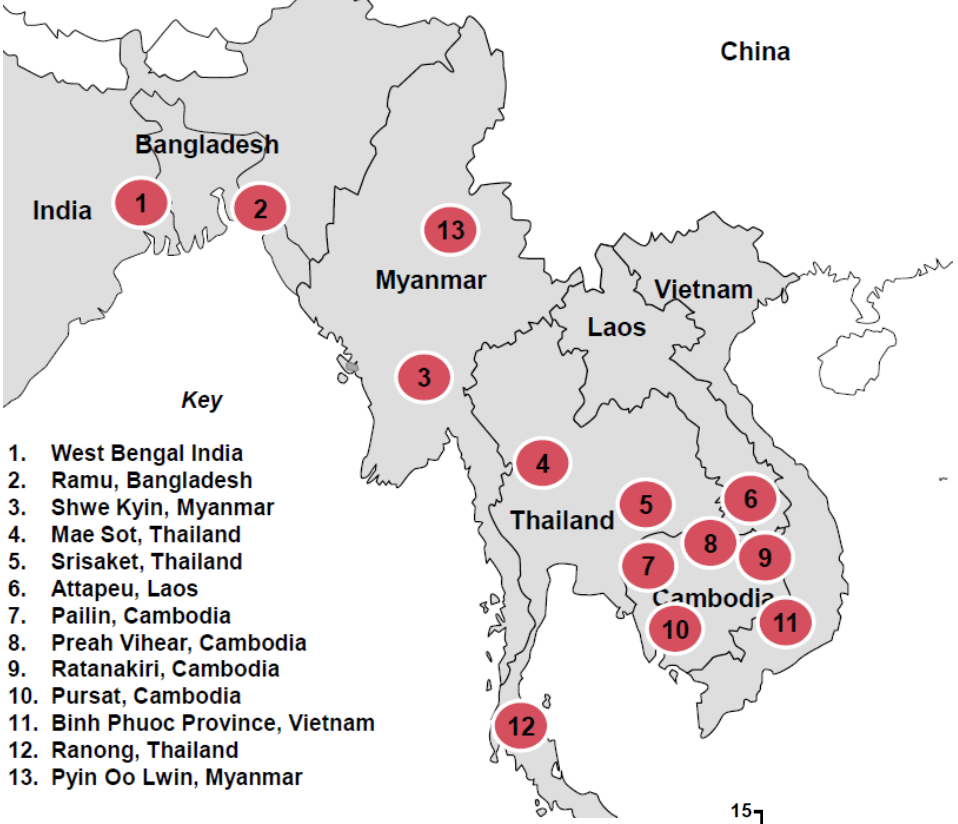
Confined to Western Cambodia?

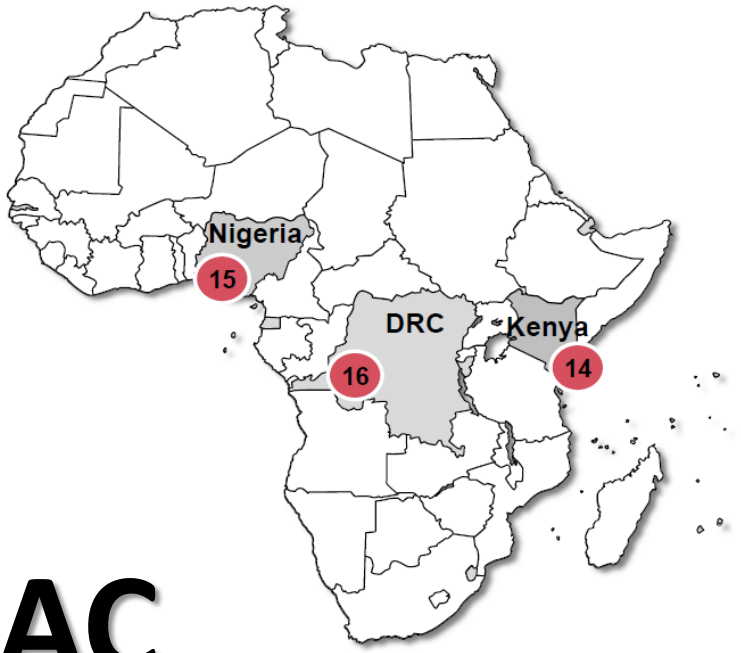
Emergence of artemisinin-resistant malaria on the western border of Thailand: a longitudinal study

Aung Pyae Phyo, Standwell Nkhoma, Kasia Stepniewska, Elizabeth A Ashley, Shalini Nair, Rose McGready, Carit Ier Moo, Salma Al-Saai, Arjen M Dondorp, Khin Maung Lwin, Pratap Singhasivanon, Nicholas P J Day, Nicholas J White, Tim J C Anderson, François Nosten




CURE RATE (%)
100
80
60
40
20
AM
QT
Q
M25
M15
CQ
SP
1975
1980
1985
1990
1995
2000
2005
2010
2015





TRAC

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Spread of Artemisinin Resistance in *Plasmodium falciparum* Malaria

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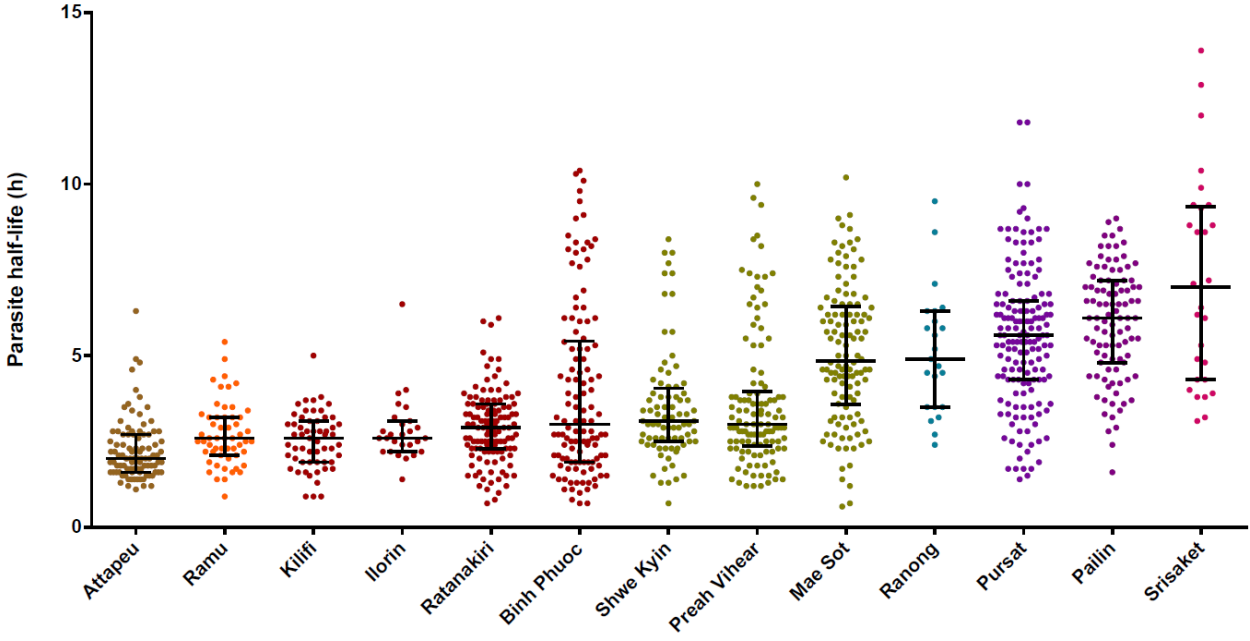

ARTICLE

doi:10.1038/nature12876

A molecular marker of artemisinin-resistant *Plasmodium falciparum* malaria

Frédéric Ariey[1,2]†, Benoit Witkowski[3], Chanaki Amaratunga[4], Johann Beghain[1,2]†, Anne-Claire Langlois[1,2], Nimol Khim[3], Saorin Kim[3], Valentine Duru[3], Christiane Bouchier[5], Laurence Ma[5], Pharath Lim[3,4,6], Rithea Leang[6], Socheat Duong[6], Sokunthea Sreng[6], Seila Suon[6], Char Meng Chuor[6], Denis Mey Bout[7], Sandie Ménard[8]†, William O. Rogers[9], Blaise Genton[10], Thierry Fandeur[1,3], Olivo Miotto[11,12,13], Pascal Ringwald[14], Jacques Le Bras[15], Antoine Berry[8]†, Jean-Christophe Barale[1,2]†, Rick M. Fairhurst[4]*, Françoise Benoit-Vical[16,17]*, Odile Mercereau-Puijalon[1,2]* & Didier Ménard[3]*

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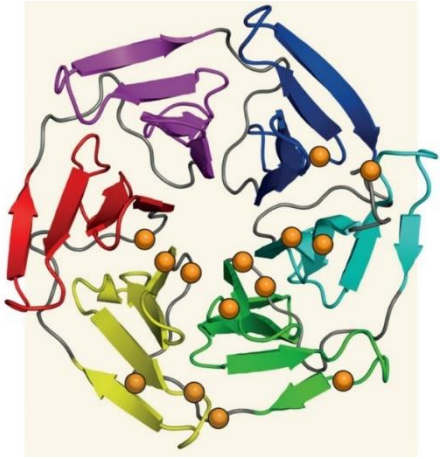

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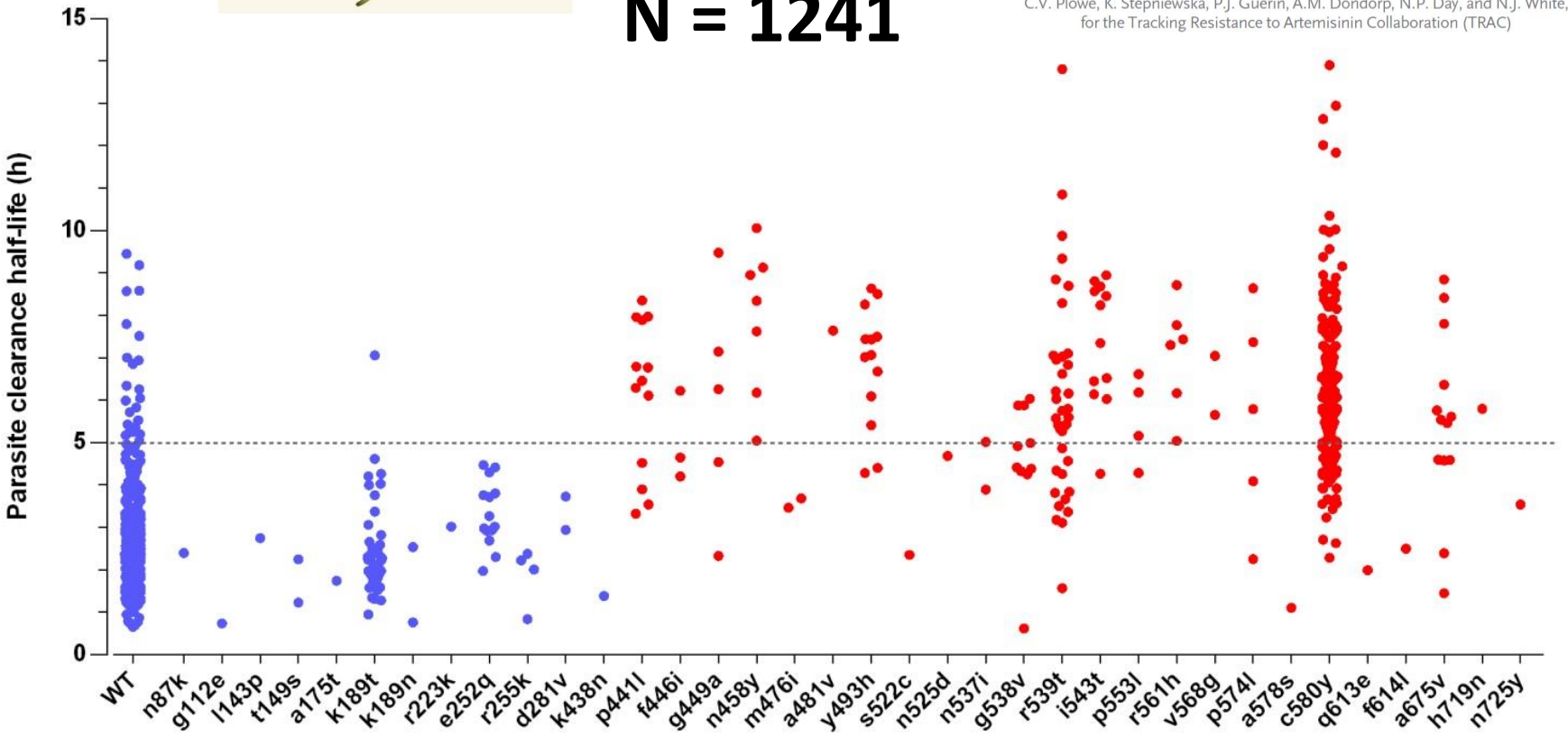
N = 1241



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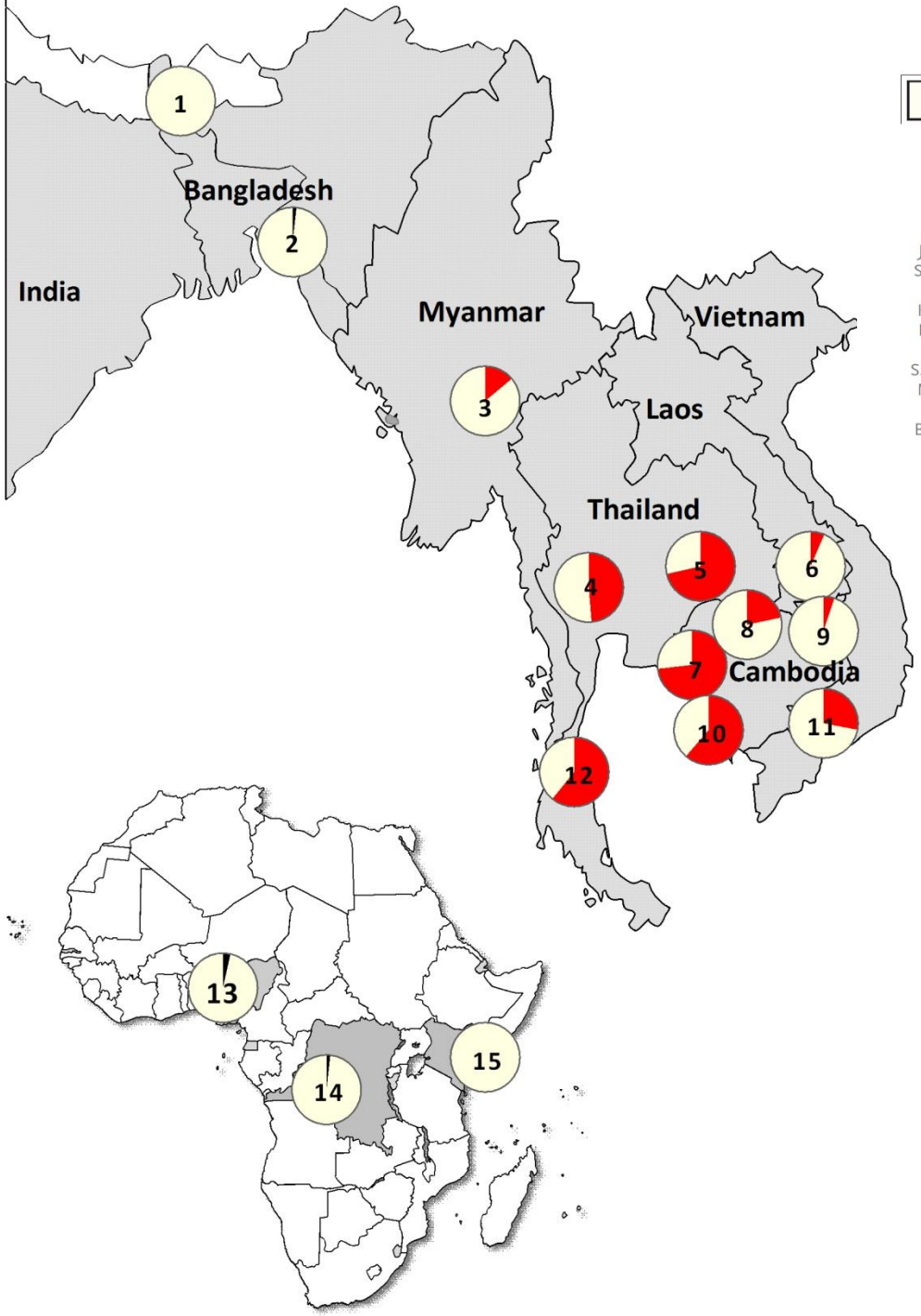
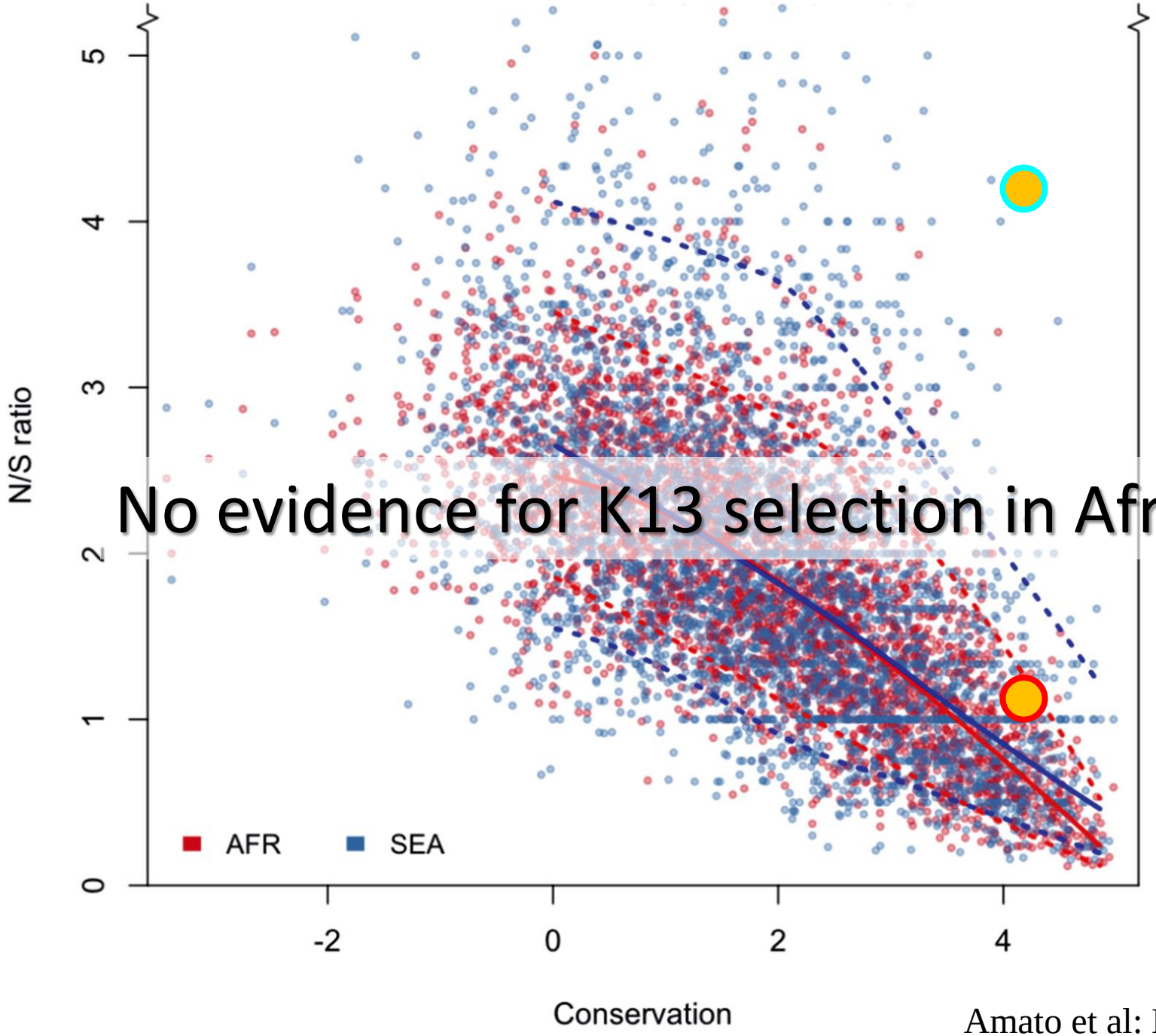


1. West Bengal,India
2. Ramu, Bangladesh
3. Shwe Kyin, Myanmar
4. Mae Sot, Thailand
5. Srisaket, Thailand
6. Attapeu, Laos
7. Pailin, Cambodia
8. Preah Vihear, Cambodia
9. Ratanakiri, Cambodia
10. Pursat, Cambodia
11. Binh Phuoc, Vietnam
12. Ranong,Thailand
13. Ilorin, Nigeria
14. Kinshasa, DRC
15. Pingilikani, Kenya



No evidence for K13 selection in Africa

Amato et al: E-life 2016

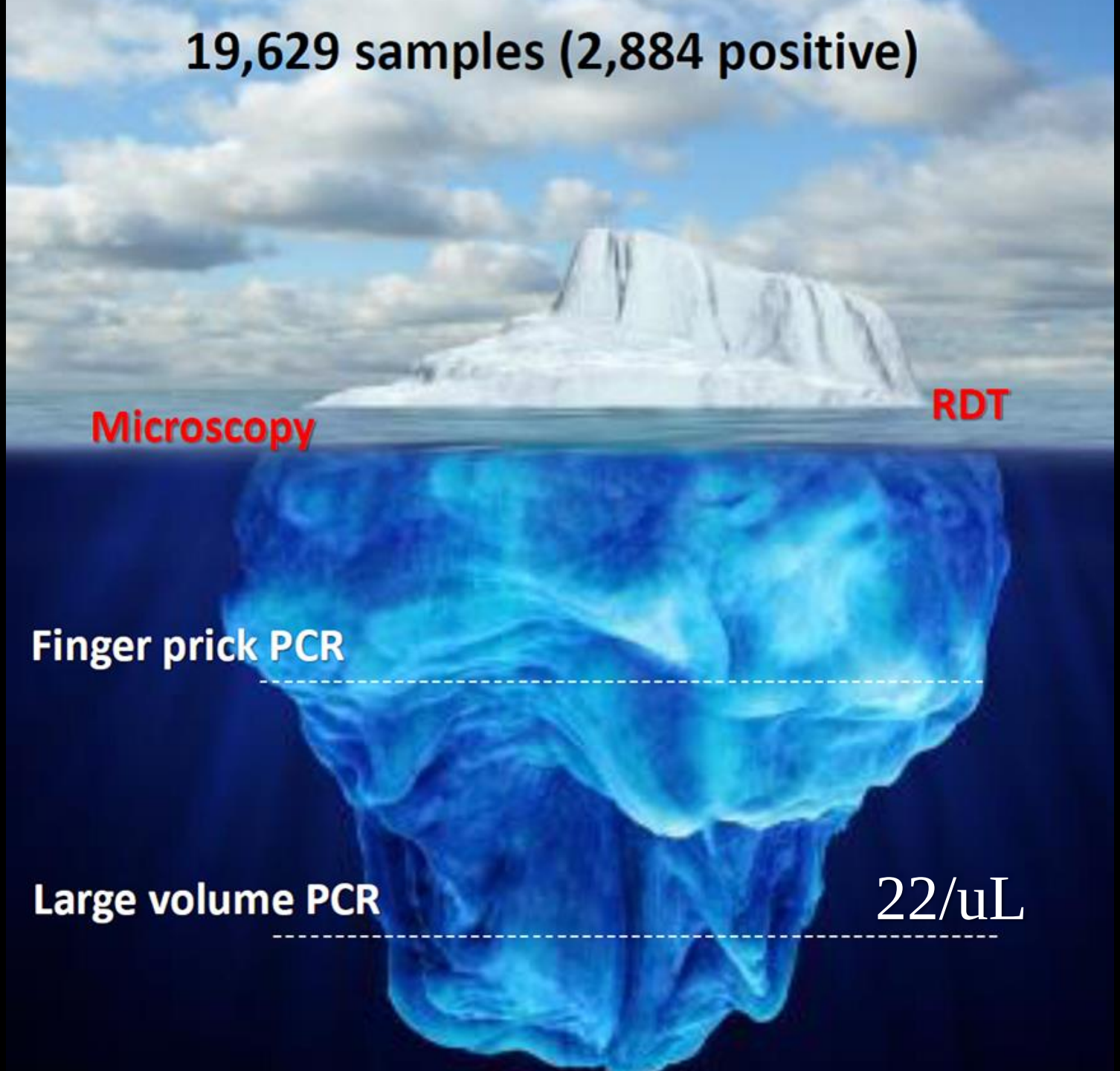
WORLD MALARIA REPORT 2012

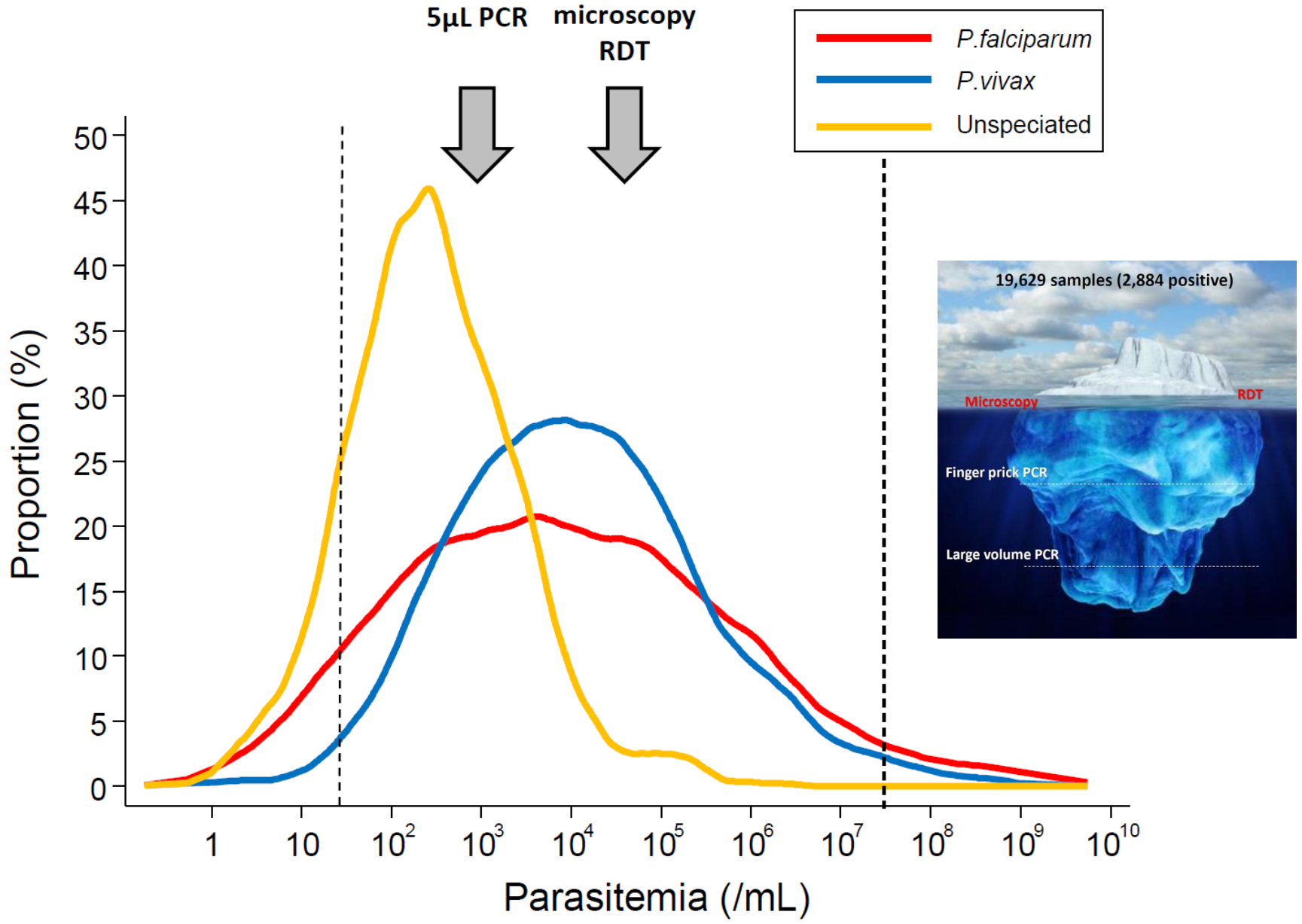
In addition, while our current tools remain remarkably effective in most settings, resistance to artemisinins – the key compounds in artemisinin-based combination therapies – has been detected in four countries of South-East Asia, while mosquito resistance to insecticides has been found in 64 countries around the world. While such resistance has not yet led to operational failure of malaria control programmes, urgent and intensified efforts are required to prevent a future public health disaster.

Mlehan

1. Stop the spread of resistant parasites. In areas for which there is evidence of artemisinin resistance, an immediate comprehensive response using a combination of malaria control and elimination measures is needed to stop the survival and spread of resistant parasites.

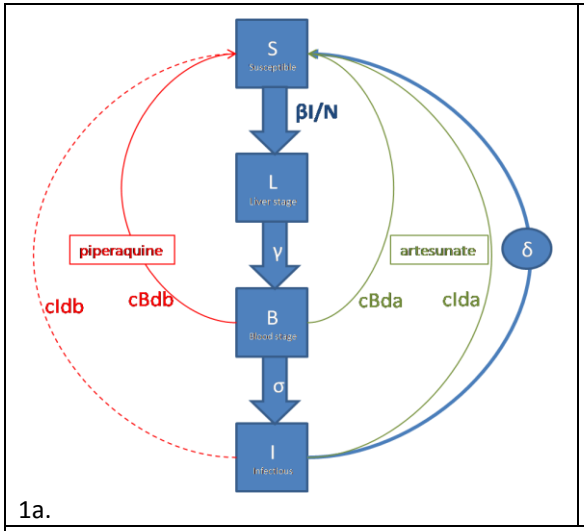
How?


19,629 samples (2,884 positive)
Microscopy
RDT
Finger prick PCR
Large volume PCR
22/uL

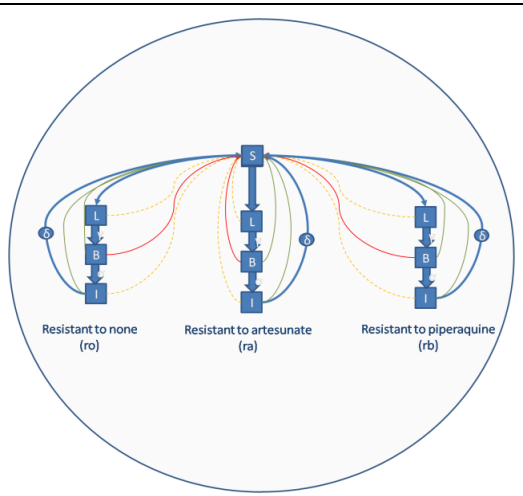

5µL PCR
microscopy
RDT
P.falciparum
P.vivax
Unspeciated
Proportion (%)
50
45
40
35
30
25
20
15
10
5
0
1
10
10^2
10^3
10^4
10^5
10^6
10^7
10^8
10^9
10^10
Parasitemia (/mL)
19,629 samples (2,884 positive)
Microscopy
RDT
Finger prick PCR
Large volume PCR

Stop the spread of resistant parasites. In areas for which there is evidence of artemisinin resistance, an immediate comprehensive response using a combination of malaria control and elimination measures is needed to stop the survival and spread of resistant parasites.

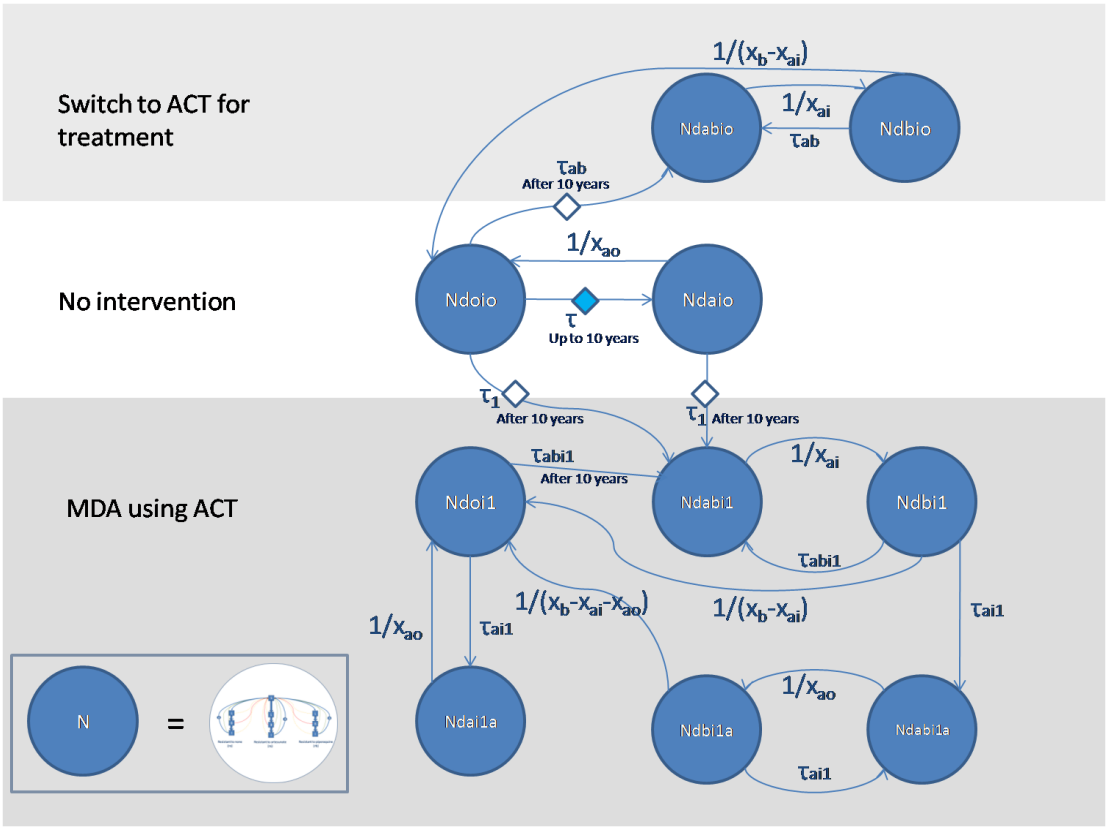
Can artemisinin resistant falciparum malaria be eliminated rapidly without treating all people in the endemic area who are infected?



1a.

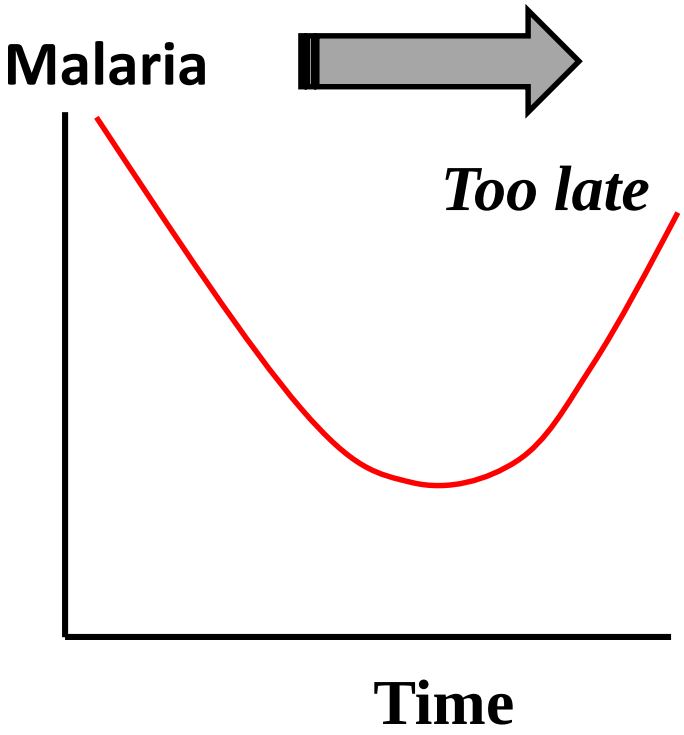


1b.



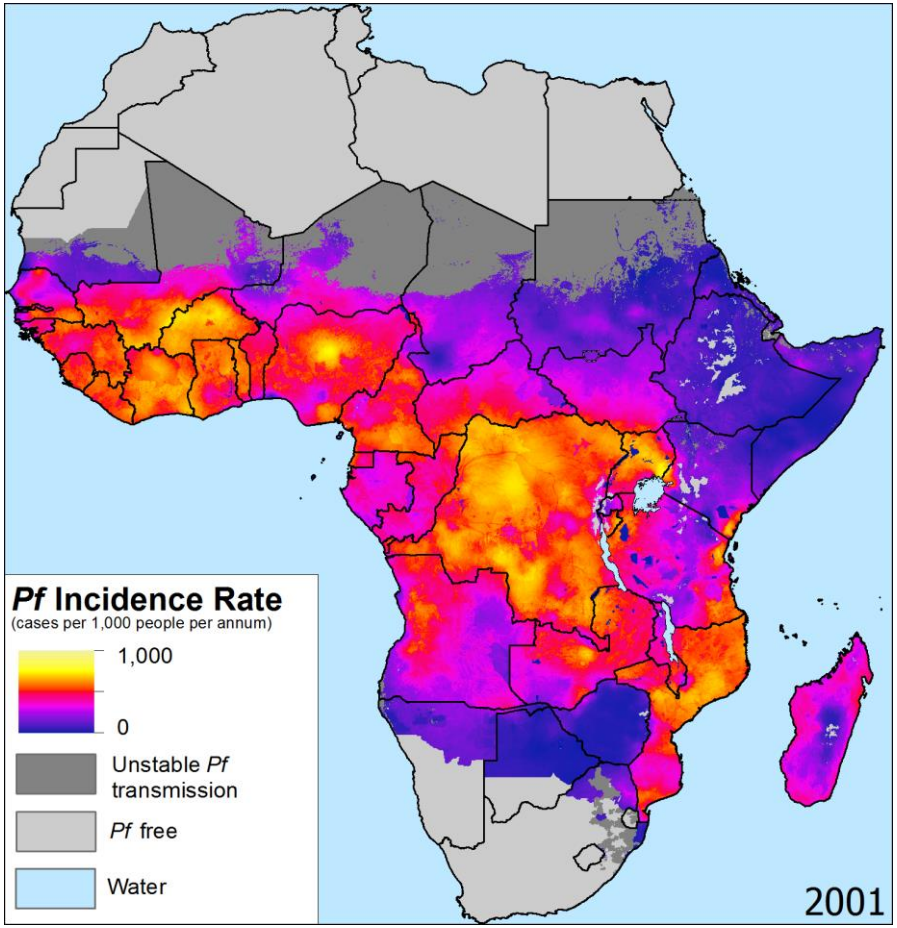
1c.

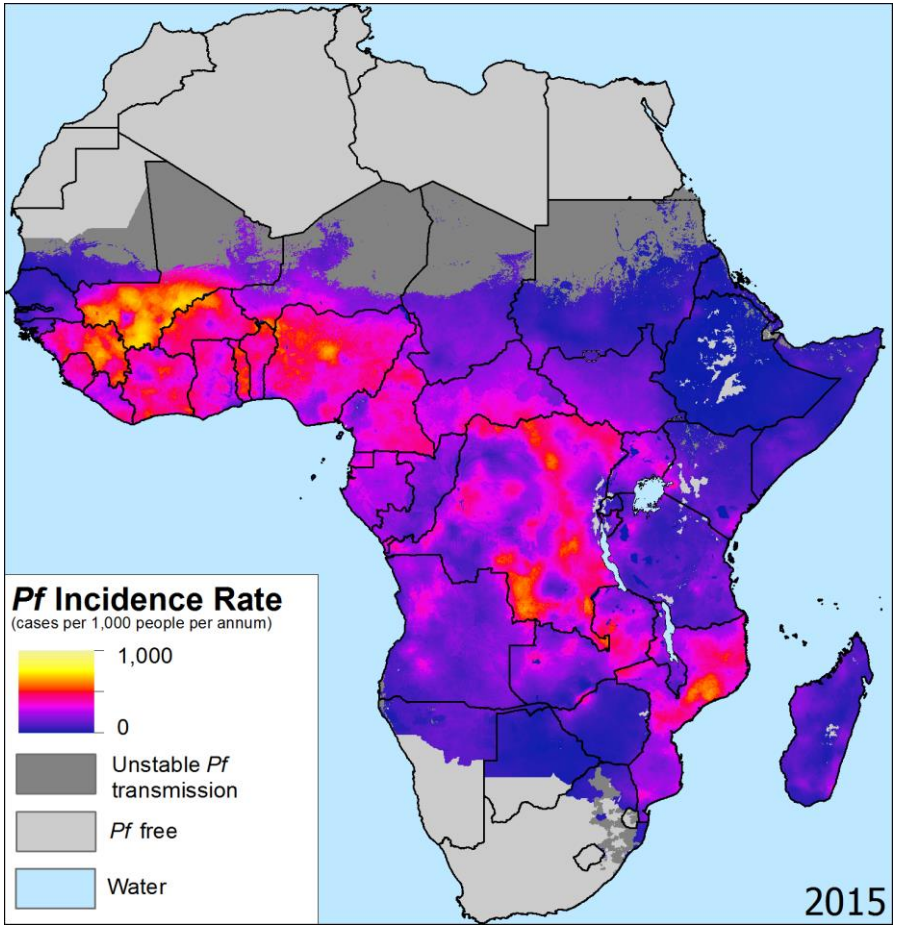
The last man standing is the most resistant



Maude et al, Malaria J, 2009

Declining malaria incidence in Africa





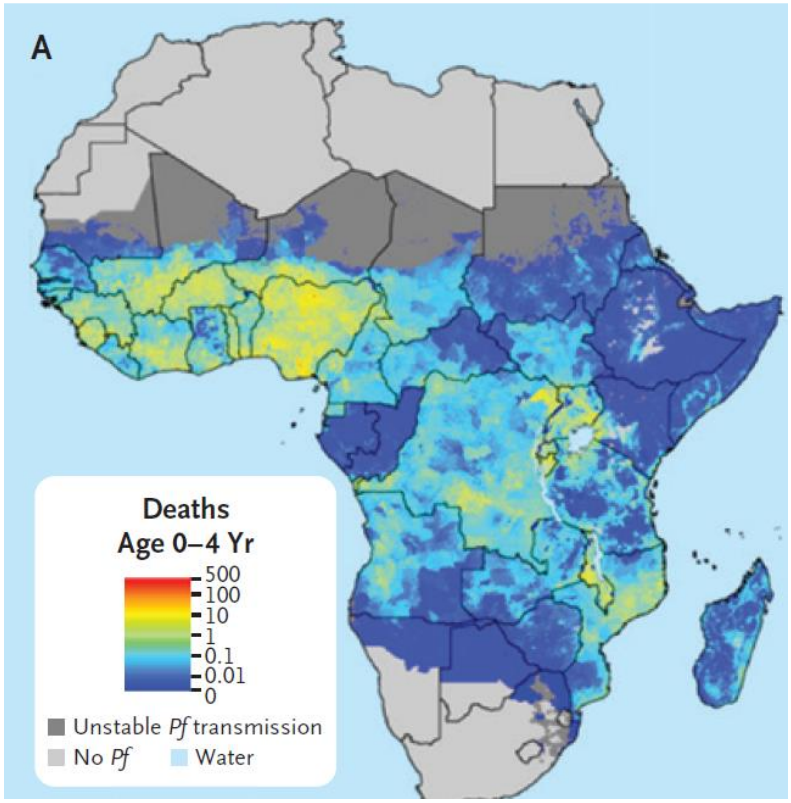
The NEW ENGLAND JOURNAL of MEDICINE

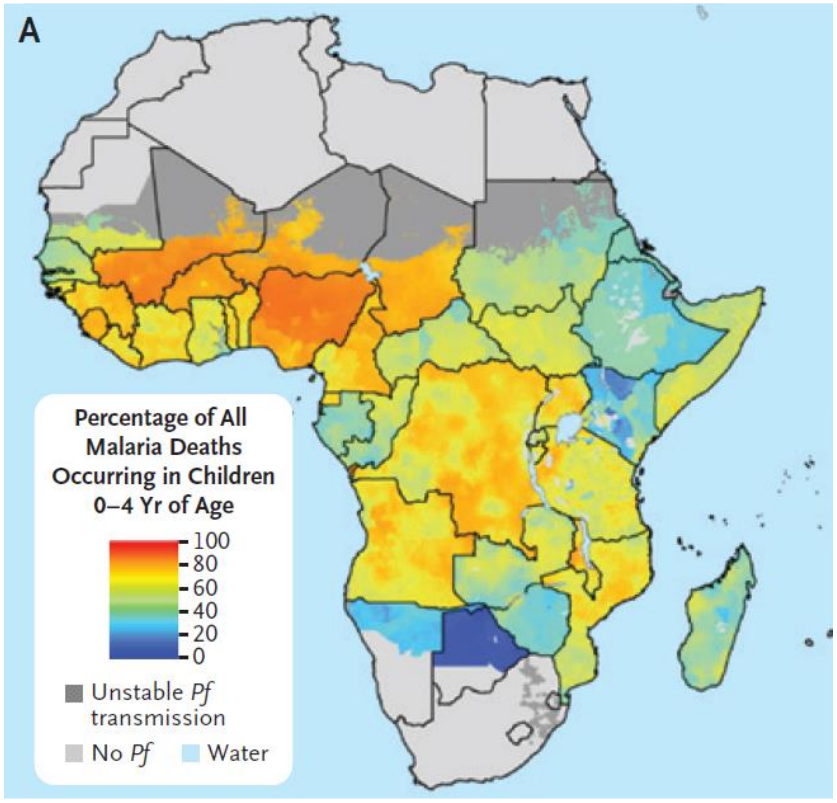
ORIGINAL ARTICLE

Mapping *Plasmodium falciparum* Mortality in Africa between 1990 and 2015

Peter W. Gething, Ph.D., Daniel C. Casey, B.A., Daniel J. Weiss, Ph.D., Donal Bisanzio, Ph.D., Samir Bhatt, D.Phil., Ewan Cameron, Ph.D., Katherine E. Battle, D.Phil., M.P.H., Ursula Dalrymple, B.Sc., Jennifer Rozier, M.Sc., Puja C. Rao, M.P.H., Michael J. Kutz, B.S., Ryan M. Barber, B.S., Chantal Huynh, B.A., Katya A. Shackelford, B.A., Matthew M. Coates, B.S., Grant Nguyen, B.A., Maya S. Fraser, B.A., Rachel Kulikoff, B.A., Haidong Wang, Ph.D., Mohsen Naghavi, M.D., M.P.H., Ph.D., David L. Smith, Ph.D., Christopher J.L. Murray, M.D., D.Phil., Simon I. Hay, D.Sc., and Stephen S. Lim, Ph.D.

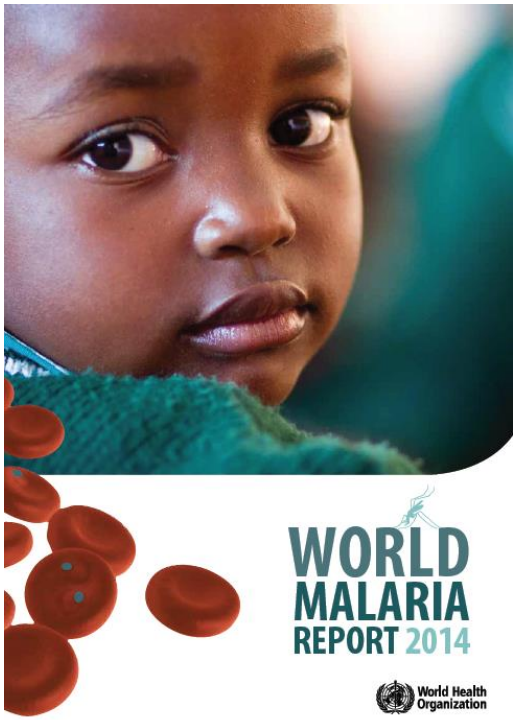
Verbal autopsy





Worldwide, between 2000 and 2012, estimated malaria mortality rates fell by 42% in all age groups and by 48% in children under 5 years of age. If the annual rate of decrease that has occurred over the past 12 years is maintained, then malaria mortality rates are projected to decrease by 52% in all ages, and by 60% in children under 5 years of age by 2015; this represents substantial progress towards the World Health Assembly target of reducing malaria mortality rates by 75% by 2015.

3.3 million deaths averted



WORLD MALARIA REPORT 2015

World Health Organization

To address remaining and emerging challenges, WHO developed a *Global technical strategy for malaria 2016–2030.* The strategy was developed under the guidance of a Steering Committee that comprised leading malaria technical experts, scientists and country representatives. Oversight was provided by the MPAC. During the strategy development process,

The GTS

Malaria cases. The number of malaria cases globally fell from an estimated 262 million in 2000 (range: 205–316 million), to 214 million in 2015 (range: 149–303 million), a decline of 18%. Most cases in 2015 are estimated to have occurred in the WHO African Region (88%), followed by the WHO South-East Asia Region (10%) and the WHO Eastern Mediterranean Region (2%). The incidence of malaria, which takes into account population growth, is estimated to have decreased by 37% between 2000 and 2015. In total, 57 of 106 countries that had ongoing transmission in 2000 have reduced malaria incidence by >75%. A further 18 countries are estimated to have reduced malaria incidence by 50–75%. Thus, the target of Millennium Development Goal (MDG) 6 "to have halted and begun to reverse the incidence of malaria" (Target 6C) has been achieved.

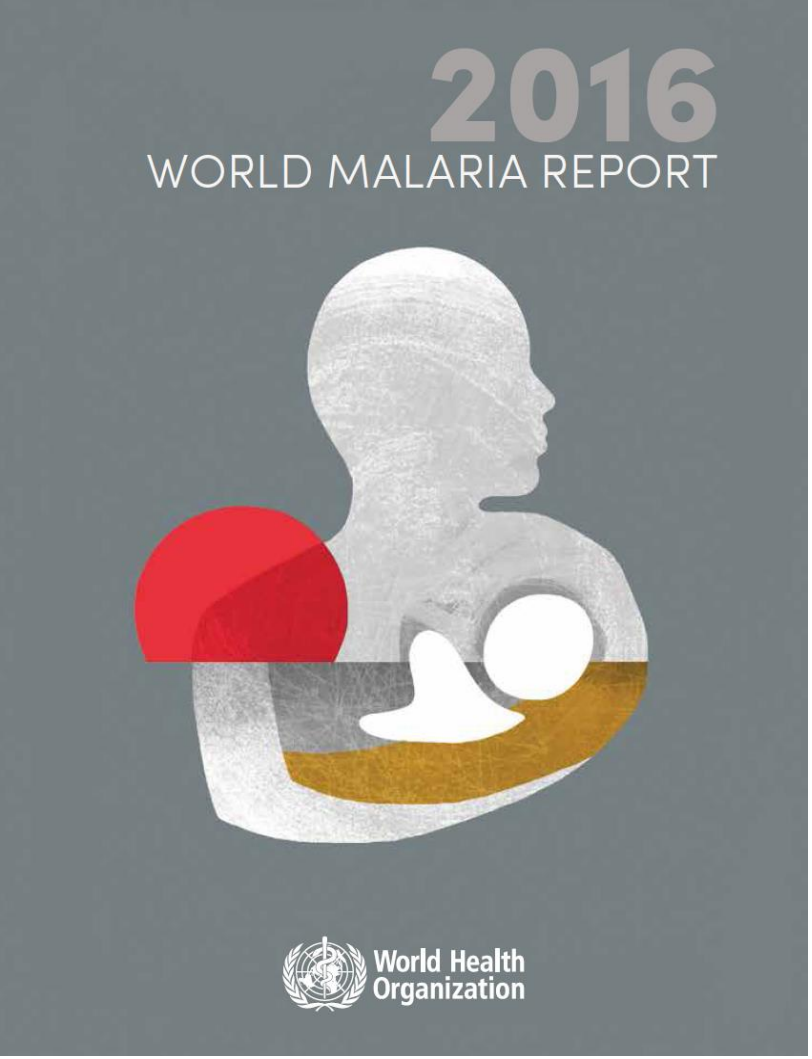
Cases down from 262M to **214M**

MDG on track

Malaria deaths in all ages. The number of malaria deaths globally fell from an estimated 839 000 in 2000 (range: 653 000–1.1 million), to 438 000 in 2015 (range: 236 000–635 000), a decline of 48%. Most deaths in 2015 were in the WHO African Region (90%), followed by the WHO South-East Asia Region (7%) and the WHO Eastern Mediterranean Region (2%). The malaria mortality rate, which takes into account population growth, is estimated to have decreased by 60% globally between 2000 and 2015. Thus, substantial progress has been made towards the World Health Assembly target of reducing the malaria burden by 75% by 2015, and the Roll Back Malaria (RBM) Partnership target of reducing deaths to near zero.

Deaths down from 839,000 to 438,000

6.2 million deaths averted



In 2015, an estimated 212 million cases of malaria occurred worldwide (UI: 148–304 million).

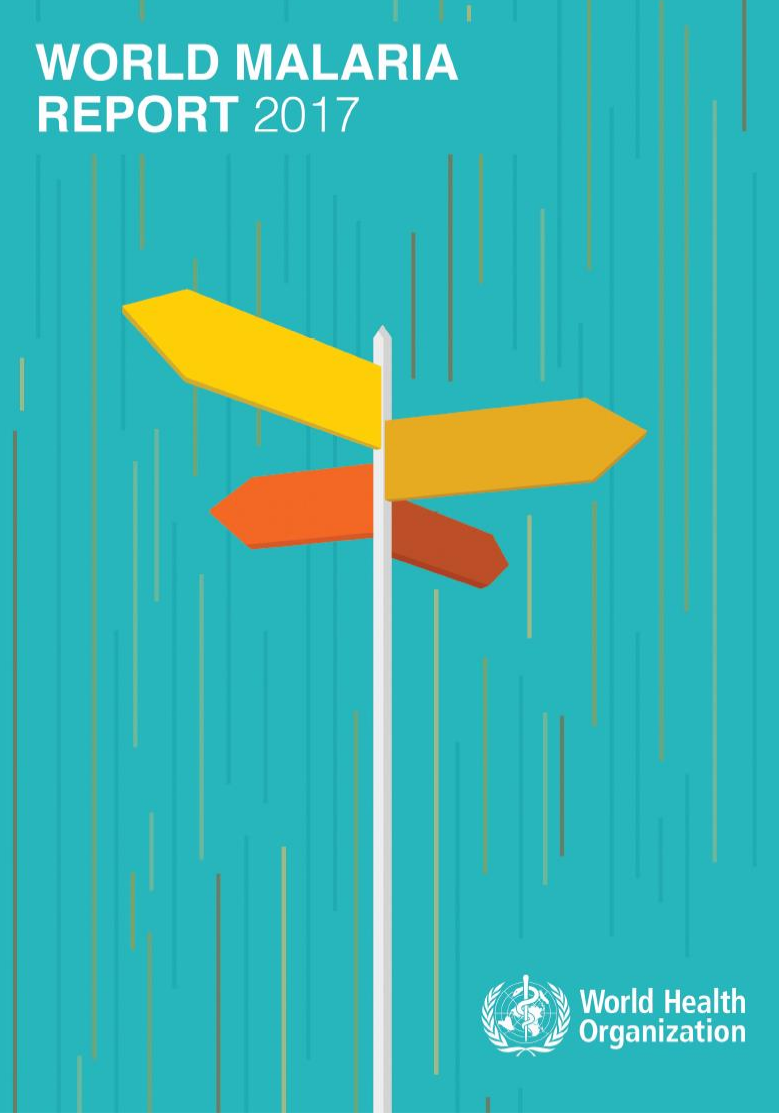
Cases **212M** (214M previous year)

In 2015, it was estimated that there were 429 000 deaths from malaria globally (UI: 235 000–639 000).

Deaths **429,000**
(438,000 previous year)

Key points

1. The targets of the *Global Technical Strategy for Malaria 2016–2030* (GTS) are, by 2030: to reduce malaria incidence and mortality rates globally by at least 90% compared with 2015 levels; to eliminate malaria from at least 35 countries in which malaria was transmitted in 2015; and to prevent re-establishment of malaria in all countries that are malaria free.



Malaria cases

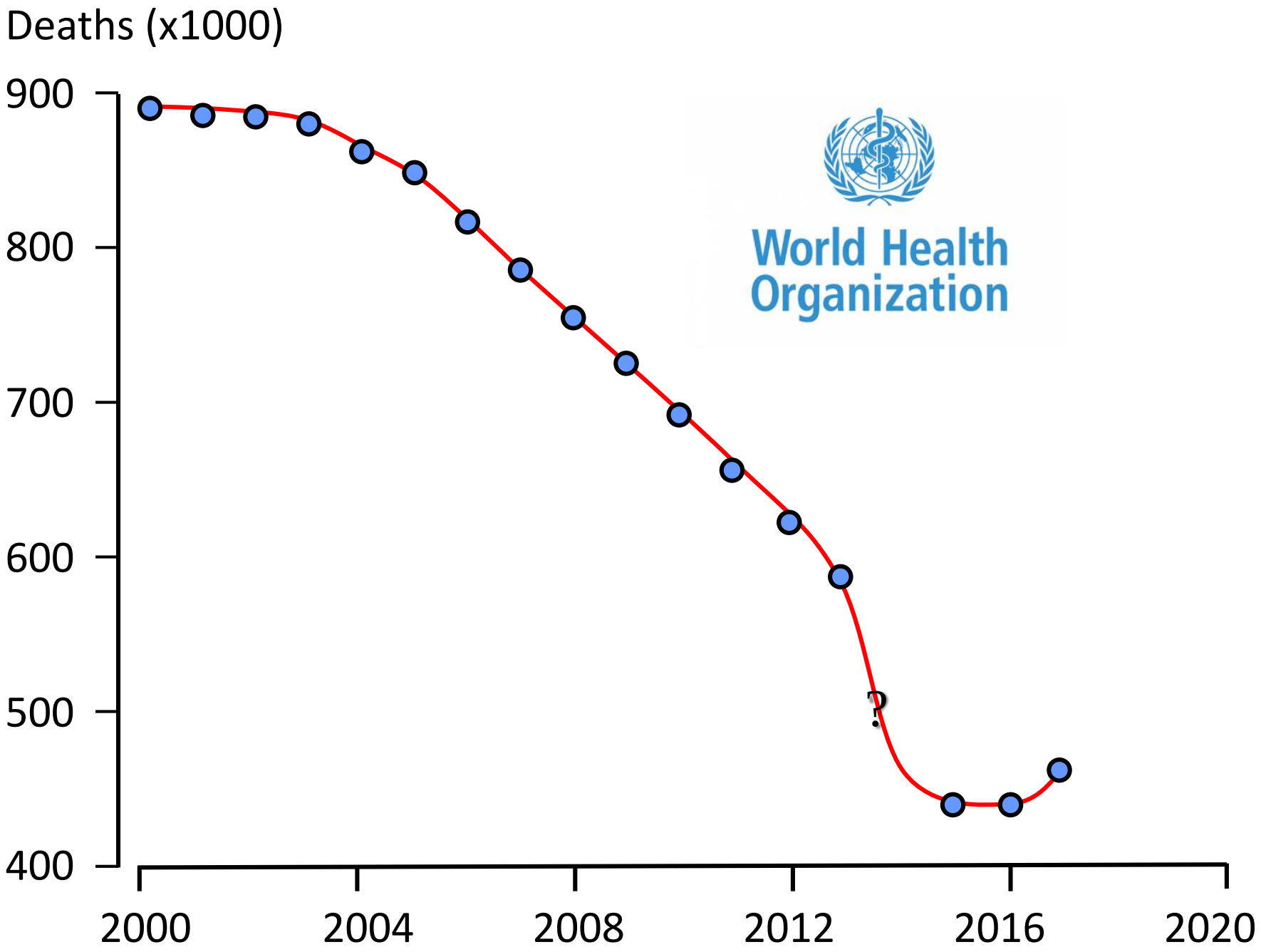
- In 2016, an estimated 216 million cases of malaria occurred worldwide (95% confidence interval [CI]: 196–263 million), compared with 237 million cases in 2010 (95% CI: 218–278 million) and 211 million cases in 2015 (95% CI: 192–257 million).

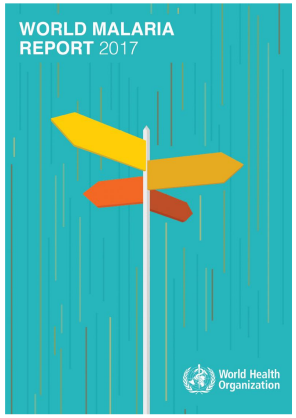
Cases **216M** ↑ (212M previous year)

Malaria deaths

- In 2016, there were an estimated 445 000 deaths from malaria globally, compared to 446 000 estimated deaths in 2015.

Deaths **445,000** ↑
(429,000 previous year)


Deaths (x1000)
900
800
700
600
500
400
2000
2004
2008
2012
2016
2020
?
World Health Organization



World Health Organization

“In recent years, we have made major gains in the fight against malaria,” said Dr Tedros Adhanom Ghebreyesus, Director-General of WHO.
“**We are now at a turning point**. Without urgent action, we risk going backwards, and missing the global malaria targets for 2020 and beyond.”

The WHO Global Technical Strategy for Malaria calls for reductions of at least 40% in malaria case incidence and mortality rates by the year 2020. According to WHO’s latest malaria report, the world is not on track to reach these critical milestones.

A **major problem is insufficient funding** at both domestic and international levels, resulting in major gaps in coverage of insecticide-treated nets, medicines, and other life-saving tools.

Countries certified malaria-free

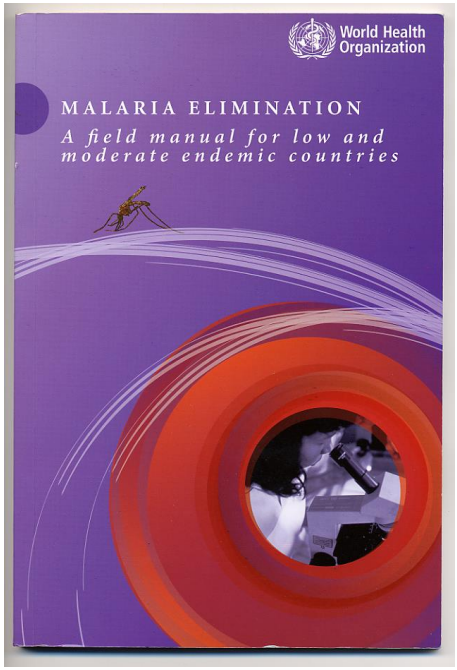
Armenia
Turkmenistan
Kyrgyzstan
Morocco
United Arab Emirates
Sri Lanka
Algeria

Countries in the prevention of reintroduction phase

Georgia
Iraq
Syria
Oman
Egypt
Uzbekistan
Turkey
Kazakhstan
Argentina
Paraguay
Azerbaijan

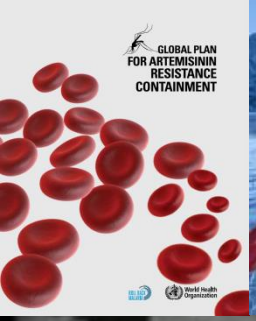
Countries in the elimination phase

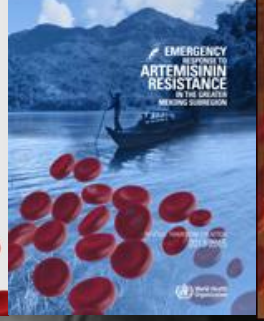
Tajikistan
Iran
Saudi Arabia
Republic of Korea

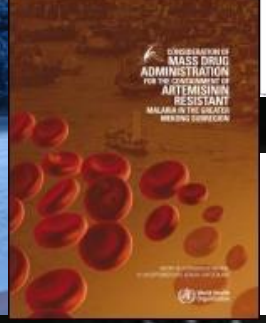


Countries in the pre-elimination phase

Cabo Verde
Belize
Costa Rica
El Salvador
Ecuador
Mexico
Malaysia
Bhutan
DPR Korea







World Health Organization

Strategic framework for Artemisinin resistance containment in Myanmar (MARC) 2011-2015

Emergency Response to Artemisinin Resistance in the Greater Mekong Sub-region

Action Plan to Improve Access of Malaria Interventions to Mobile and Migrant Populations, Develop Malaria Surveillance, Monitoring & Evaluation Strategy, and Behavior Change Communication Strategy

Report of an informal consultation
19–23 August, 2014
Phuket, Thailand

World Health Organization

Strategy for Malaria Eliminatio
in the Greater Mekong Subregi
(2015–2030)

Present

WORLD MALARIA REPORT

2018

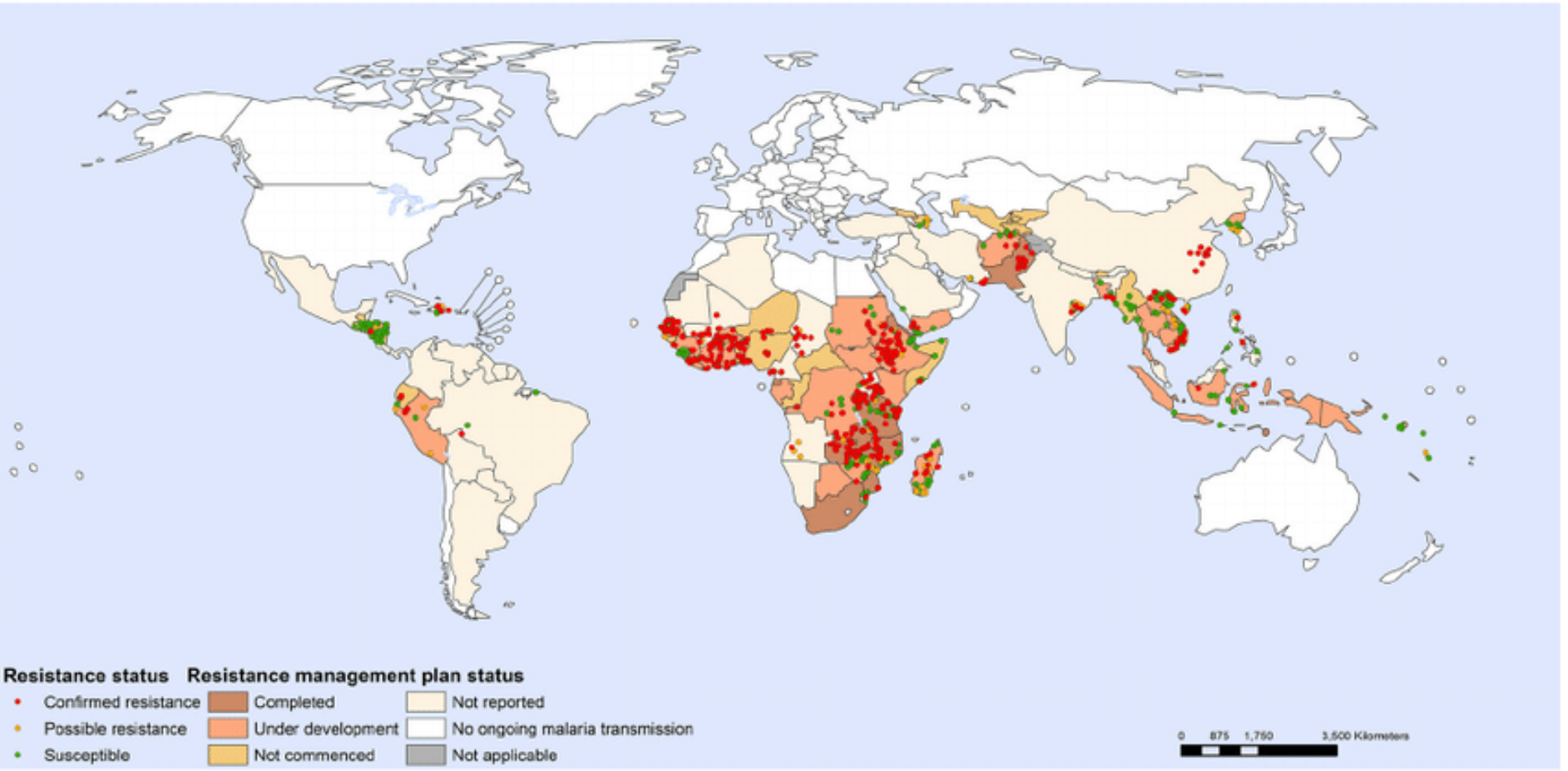
World Health Organization

No significant progress

Malaria cases

- In 2017, an estimated 219 million cases of malaria occurred worldwide (95% confidence interval [CI]: 203–262 million), compared with 239 million cases in 2010 (95% CI: 219–285 million) and 217 million cases in 2016 (95% CI: 200–259 million).
- Although there were an estimated 20 million fewer malaria cases in 2017 than in 2010, data for the period 2015–2017 highlight that no significant progress in reducing global malaria cases was made in this timeframe.

Reported pyrethroid susceptibility status for malaria vectors (2010-2014) and status of national insecticide resistance monitoring and management plan (2014)



Where multiple insecticide classes or types, mosquito species or time points were tested, the highest resistance status is shown.

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: World Malaria Report 2014
Map Production: Global Malaria Programme
World Health Organization

World Health Organization

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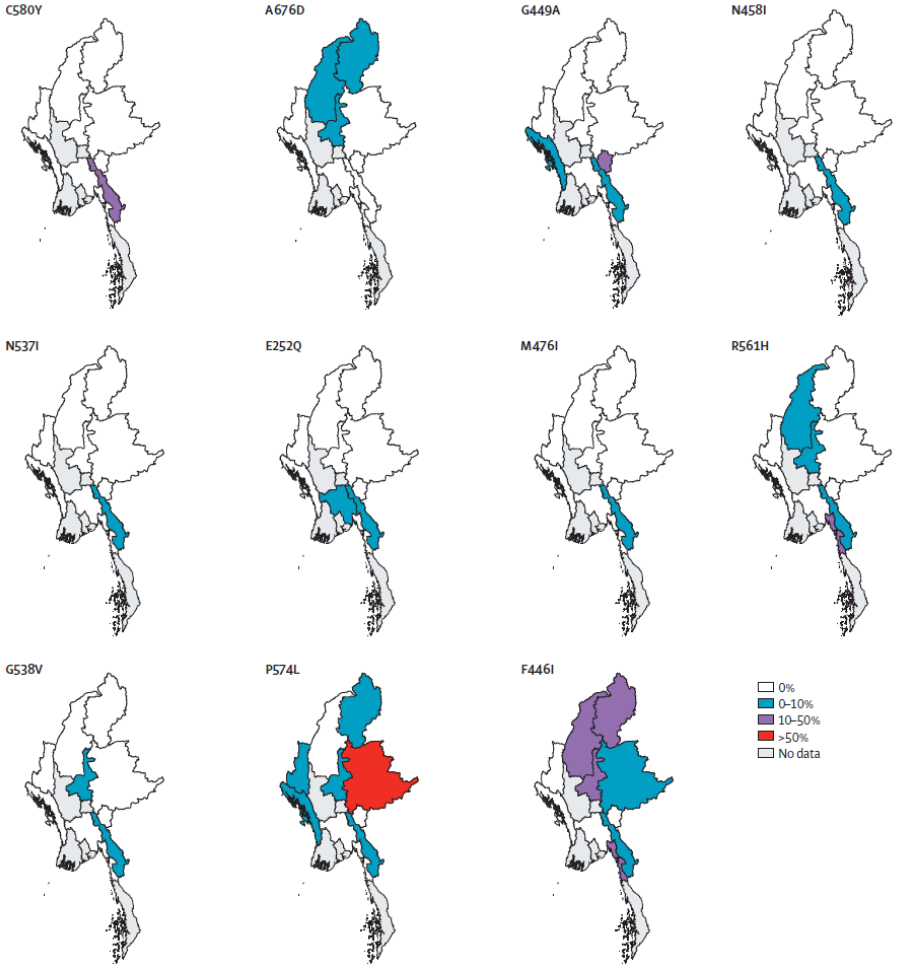
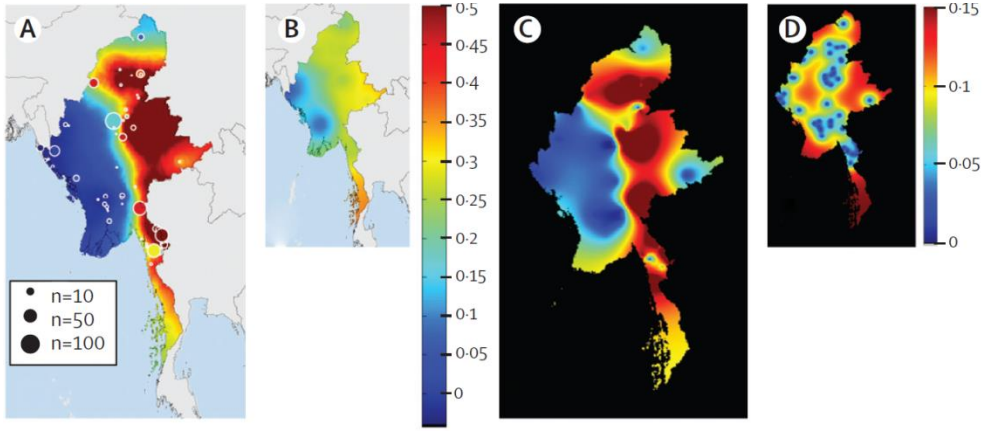
Spread of artemisinin-resistant *Plasmodium falciparum* in Myanmar: a cross-sectional survey of the K13 molecular marker

Kyaw M Tun, Mallika Imwong, Khin M Lwin, Aye A Win, Tin M Hlaing, Thaung Hlaing, Khin Lin, Myat P Kyaw, Katherine Plewes, M Abul Faiz, Mehul Dhorda, Phaik Yeong Cheah, Sasithon Pukrittayakamee, Elizabeth A Ashley, Tim J C Anderson, Shalini Nair, Marina McDew-White, Jennifer A Flegg, Eric P M Grist, Philippe Guerin, Richard J Maude, Frank Smithuis, Arjen M Dondorp, Nicholas P J Day, François Nosten, Nicholas J White, Charles J Woodrow

Lancet Infect Dis 2015; 15: 415–21

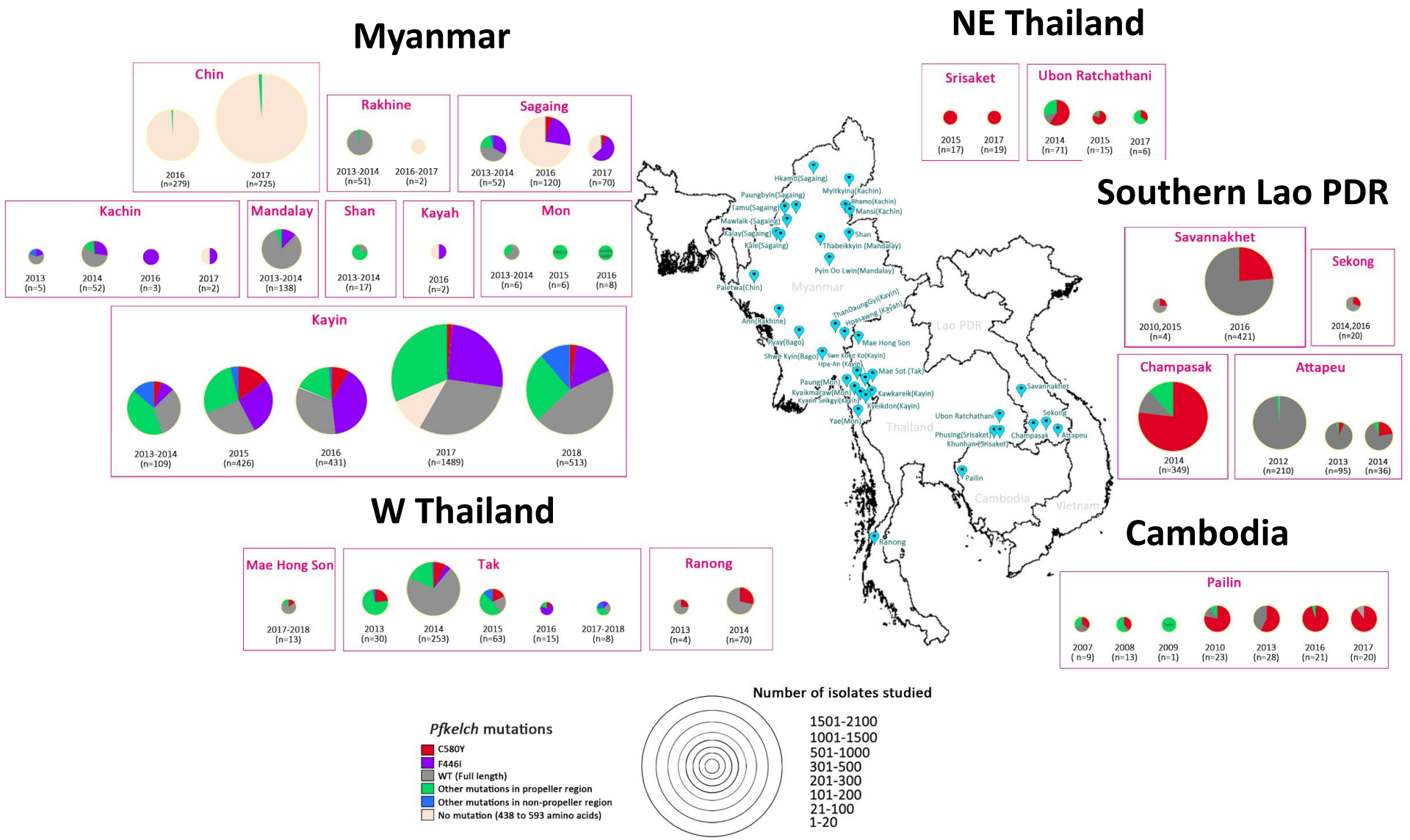


Very close to India

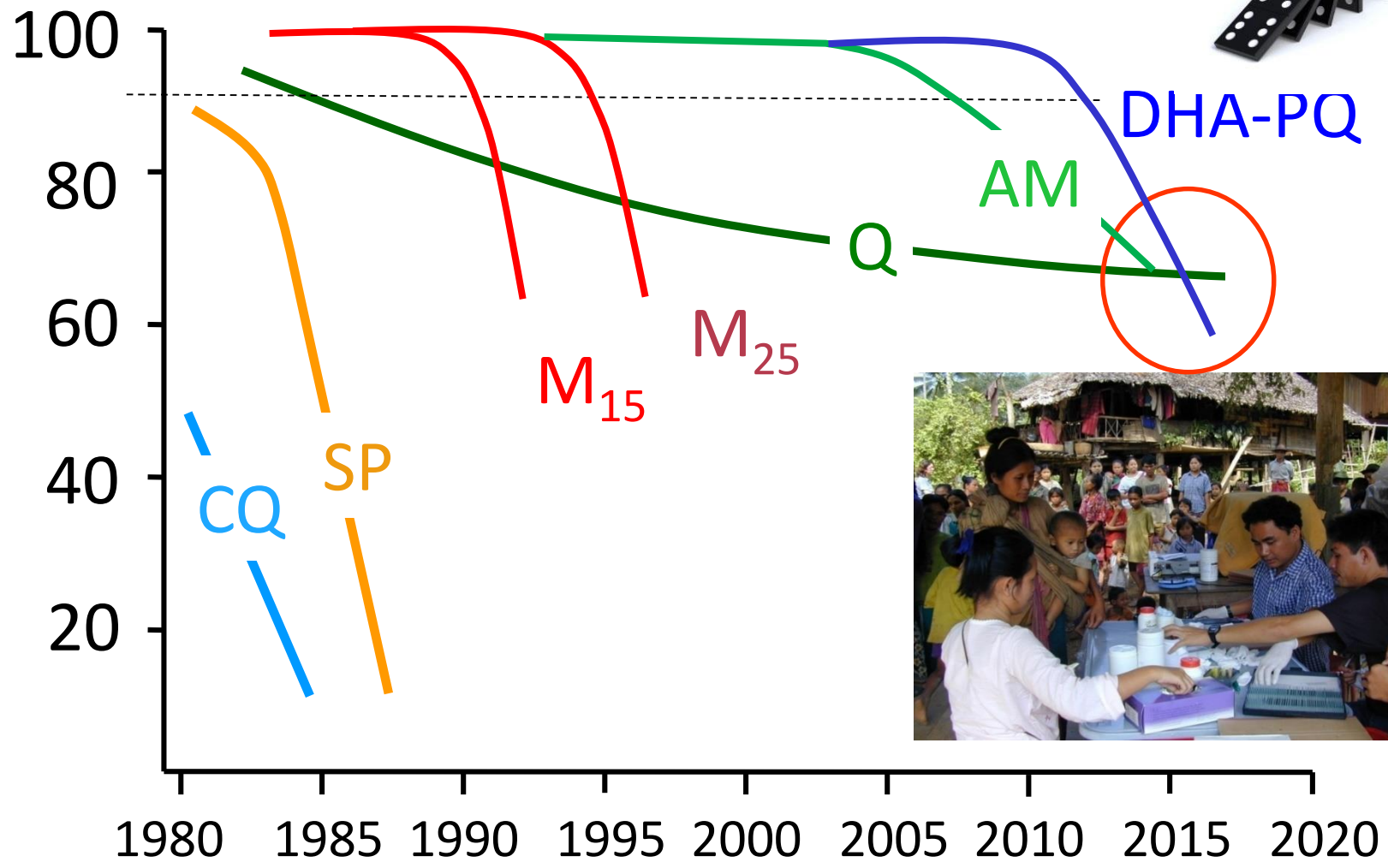


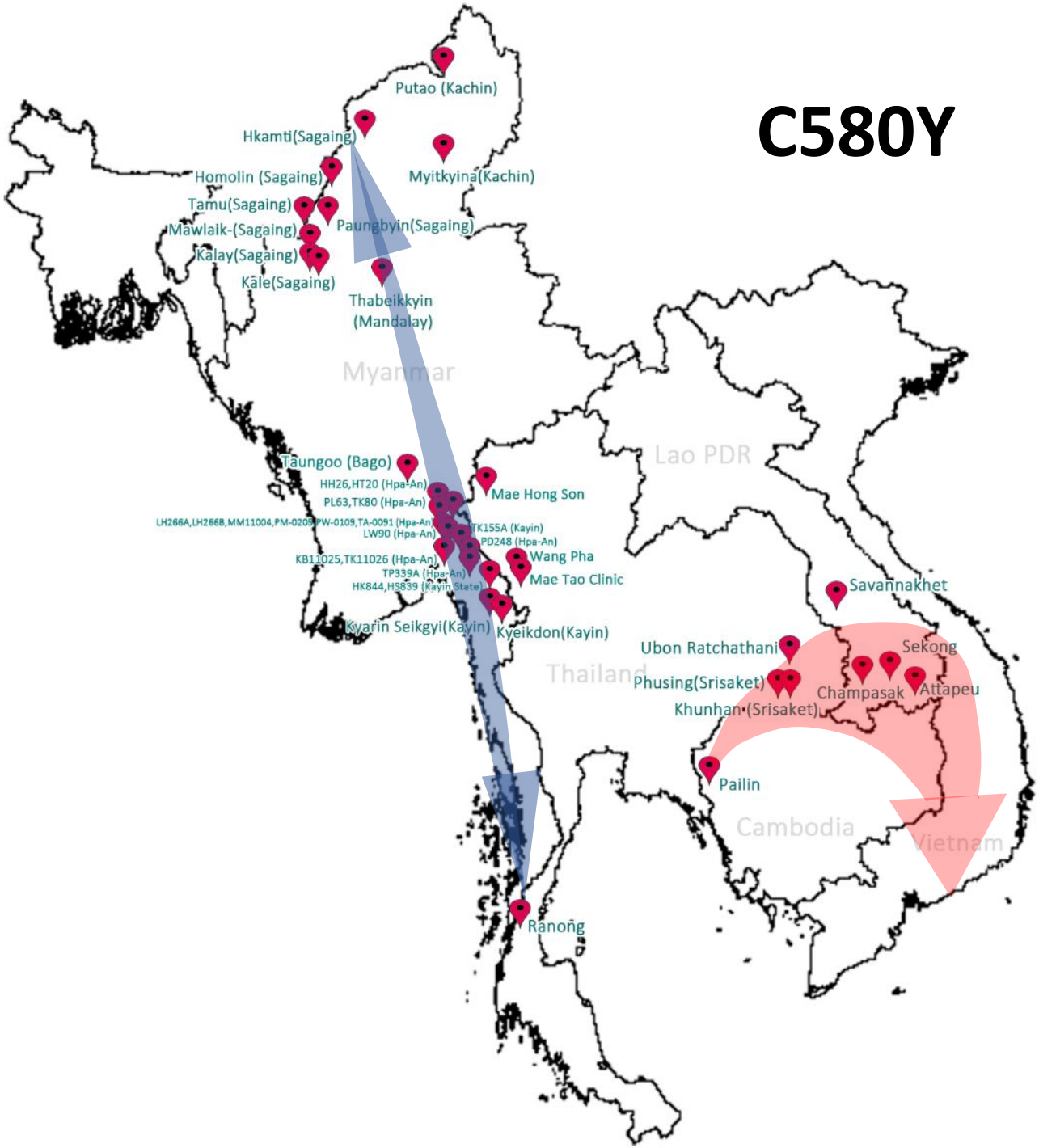

Zika virus
1 February 2016
WHO declares a Public Health Emergency of International Concern

Pf kelch


Myanmar
Chin
2016 (n=279)
2017 (n=725)
Rakhine
2013-2014 (n=51)
2016-2017 (n=2)
Sagaing
2013-2014 (n=52)
2016 (n=120)
2017 (n=70)
Kachin
2013 (n=5)
2014 (n=52)
2016 (n=3)
2017 (n=2)
Mandalay
2013-2014 (n=138)
Shan
2013-2014 (n=17)
Kayah
2016 (n=2)
Mon
2013-2014 (n=6)
2015 (n=6)
2016 (n=8)
Kayin
2013-2014 (n=109)
2015 (n=426)
2016 (n=431)
2017 (n=1489)
2018 (n=513)
NE Thailand
Srisaket
2015 (n=17)
2017 (n=19)
Ubon Ratchathani
2014 (n=71)
2015 (n=15)
2017 (n=6)
Southern Lao PDR
Savannakhet
2010,2015 (n=4)
2016 (n=421)
Sekong
2014,2016 (n=20)
Champasak
2014 (n=349)
Attapeu
2012 (n=210)
2013 (n=95)
2014 (n=36)
W Thailand
Mae Hong Son
2017-2018 (n=13)
Tak
2013 (n=30)
2014 (n=253)
2015 (n=63)
2016 (n=15)
2017-2018 (n=8)
Ranong
2013 (n=4)
2014 (n=70)
Cambodia
Pailin
2007 (n=9)
2008 (n=13)
2009 (n=1)
2010 (n=23)
2013 (n=28)
2016 (n=21)
2017 (n=20)
Hkamti(Sagaing)
Myitkyina(Kachin)
Paungbyin(Sagaing)
Bhamo(Kachin)
Tamu(Sagaing)
Mansi(Kachin)
Mawlaik-(Sagaing)
Kalay(Sagaing)
Shan
Kale(Sagaing)
Thabeikkyin (Mandalay)
Pyin Oo Lwin(Mandalay)
Paletwa(Chin)
Myanmar
Ann(Rakhine)
ThanDaungGyi(Kayin)
Hpasawng (Kayah)
Lao PDR
Pyay(Bago)
Mae Hong Son
Shwe Kyin(Bago)
Swe Kote Ko(Kayin)
Hpa-An (Kayin)
Mae Sot (Tak)
Paung(Mon)
Savannakhet
Kyaikmaraw(Mon)
Kawkareik(Kayin)
Kyain Seikgyi(Kayin)
Kyeikdon(Kayin)
Ubon Ratchathani
Sekong
Yae(Mon)
Thailand
Phusing(Srisaket)
Champasak
Attapeu
Khunhan (Srisaket)
Pailin
Cambodia
Vietnam
Ranong
Pfkelch mutations
C580Y
F446I
WT (Full length)
Other mutations in propeller region
Other mutations in non-propeller region
No mutation (438 to 593 amino acids)
Number of isolates studied
1501-2100
1001-1500
501-1000
301-500
201-300
101-200
21-100
1-20

Antimalarial drug efficacy in the Mekong region




C580Y
Putao (Kachin)
Hkamti(Sagaing)
Myitkyina(Kachin)
Homolin (Sagaing)
Tamu(Sagaing)
Paungbyin(Sagaing)
Mawlaik-(Sagaing)
Kalay(Sagaing)
Kale(Sagaing)
Thabeikkyin
(Mandalay)
Myanmar
Lao PDR
Taungoo (Bago)
HH26,HT20 (Hpa-An)
PL63,TK80 (Hpa-An)
LH266A,LH266B,MM11004,PM-0209,PW-0109,TA-0091 (Hpa-An)
LW90 (Hpa-An)
TK155A (Kayin)
PD248 (Hpa-An)
KB11025,TK11026 (Hpa-An)
TP339A (Hpa-An)
HK844,HS839 (Kayin State)
Mae Hong Son
Wang Pha
Mae Tao Clinic
Kyarin Seikgyi(Kayin)
Kyeikdon(Kayin)
Thailand
Savannakhet
Ubon Ratchathani
Sekong
Phusing(Srisaket)
Champasak
Attapeu
Khunhan (Srisaket)
Pailin
Cambodia
Vietnam
Ranong

World Health Organization
Western Pacific Region

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Cambodia addresses increase of reported Malaria cases

Share Print

2018

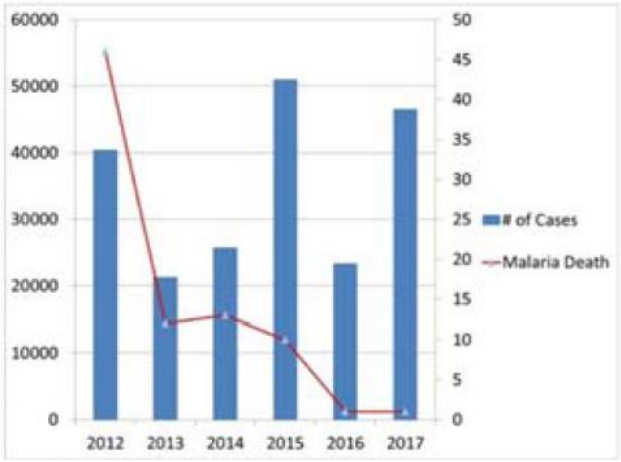
PHNOM PENH, CAMBODIA, 9 March 2018 – The National Center for Parasitology, Entomology and Malaria Control (CNM) has confirmed an increase of malaria cases which started mid 2017, at the National Malaria Conference on 22 February.

The Minister of Health and WHO representative to Cambodia visiting the exhibition of the National Malaria Conference, accompanied by Director General for Health and Deputy Director of CNM

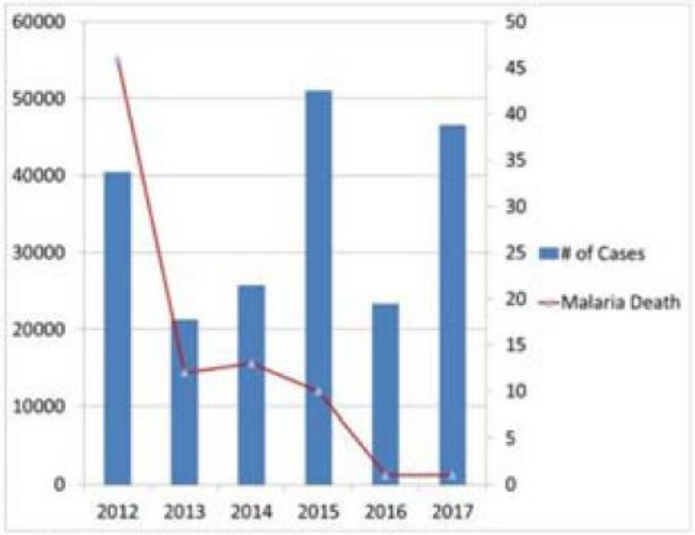
Joining the efforts of countries in the Greater Mekong Subregion, Cambodia has made significant progress in reducing its total number of malaria cases by 42%, between 2012 and 2016. Furthermore, there has been an impressive decrease of deaths due to malaria, from 46 in 2012 to 1 death in 2017.

Since the middle of last year, reported number of cases started to show an increase largely in 10 districts from 8 provinces in the north-east region of the country. The CNM has attributed this increase to a series of possible reasons, including:

- Interruption of Village Malaria Workers program for two years
- Low use of mosquito nets, distributed in 2015
- Increased movement to and from forest areas
- Abnormal early and heavy rainfalls in 2017



- Interruption of Village Malaria Workers program for two years
- Low use of mosquito nets, distributed in 2015
- Increased movement to and from forest areas
- Abnormal early and heavy rainfalls in 2017



Cambodia confirmed malaria cases from health centers (HC)

In response to the increase number of malaria cases, more than 20,000 cases compared to 2016, an emergency response was organized by CNM with the support of WHO and other partners through six combined interventions implemented in 8 most affected provinces:

- Emergency Supply of rapid diagnostic test and treatment for 6 months
- Monthly support of 2 CNM teams to provincial and district health levels
- Distribution of 241,669 mosquito nets
- Emergency monthly meeting with Village Malaria Workers
- Mass screening and treatment carried out in 2 most affected villages
- Collection of blood spots for resistance marker/genotyping

It is important to notice that the results from therapeutic efficacy studies (TES) last year shows full efficacy of the first line treatment artesunate-mefloquine, which means that the increase of reported malaria cases is probably not linked to drug resistance. In addition WHO has supported the collection of filter papers in the affected area, which will allow to confirm this assumption and to better understand the resistance background of these parasites.

The Ministry of Health is strongly committed to ensure full implementation of the emergency response plan and to reach elimination goal with the other fives countries of the Greater Mekong Subregion.

"With all the partners, we must continue to work together and even accelerate our efforts. WHO continues to support the Ministry of Health in his efforts towards this outbreak response and the implementation of the National Malarial Elimination Plan by 2025," said Dr Liu Yungo, WHO representative in Cambodia.

2018

"The increase of reported malaria cases is probably not linked to drug resistance"

Antimalarial drug resistance in the Greater Mekong Subregion: How concerned should we be?

Q&A with Dr Pedro Alonso, Director of the Global Malaria Programme

29 September 2017

World Health Organization

WHO is leading the elimination effort in the GMS with the support of a number of partners, including the Global Fund to Fight AIDS, Tuberculosis & Malaria, the Bill & Melinda Gates Foundation, USAID, and the Australian Department of Foreign Affairs and Trade.

We are winning the battle. We are on the right track. The massive reductions in disease and death reported in GMS countries are a testament to the sustained progress that has been achieved along the path toward elimination in this subregion. It is only through eliminating this parasite that we will do away – once and for all – with the problem of drug resistance in this subregion.

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

Evidence of Artemisinin-Resistant *Plasmodium falciparum* Malaria in Eastern India

Sabyasachi Das, Ph.D.
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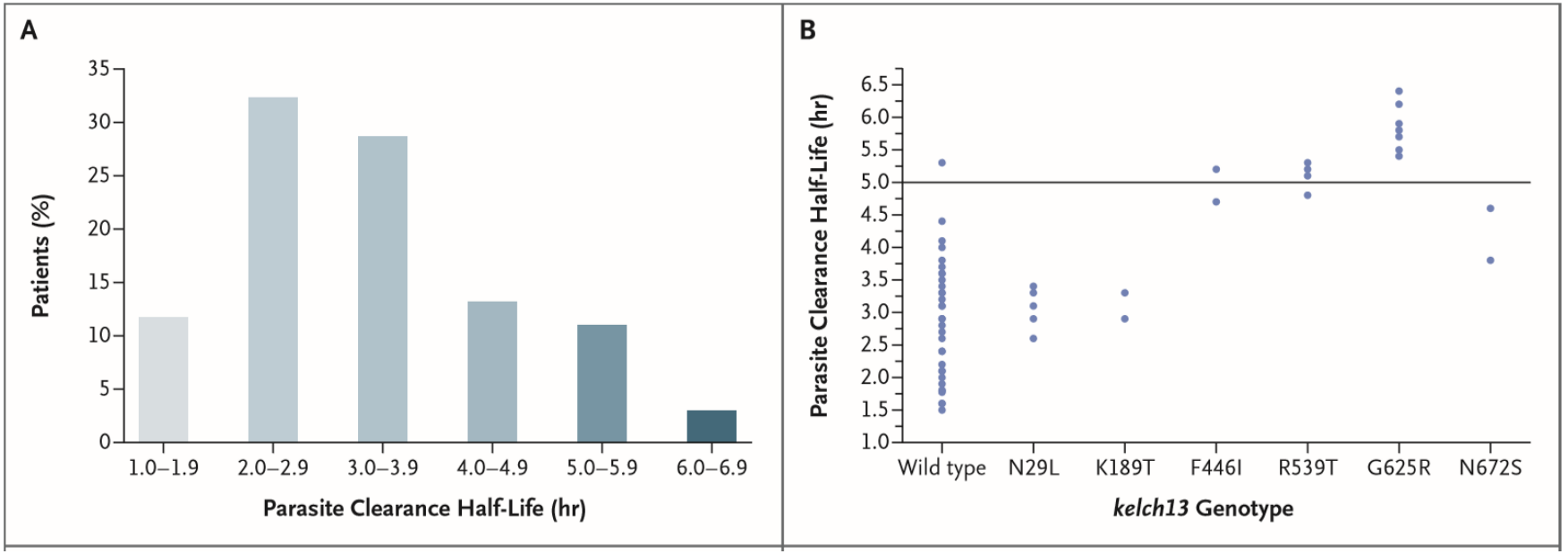


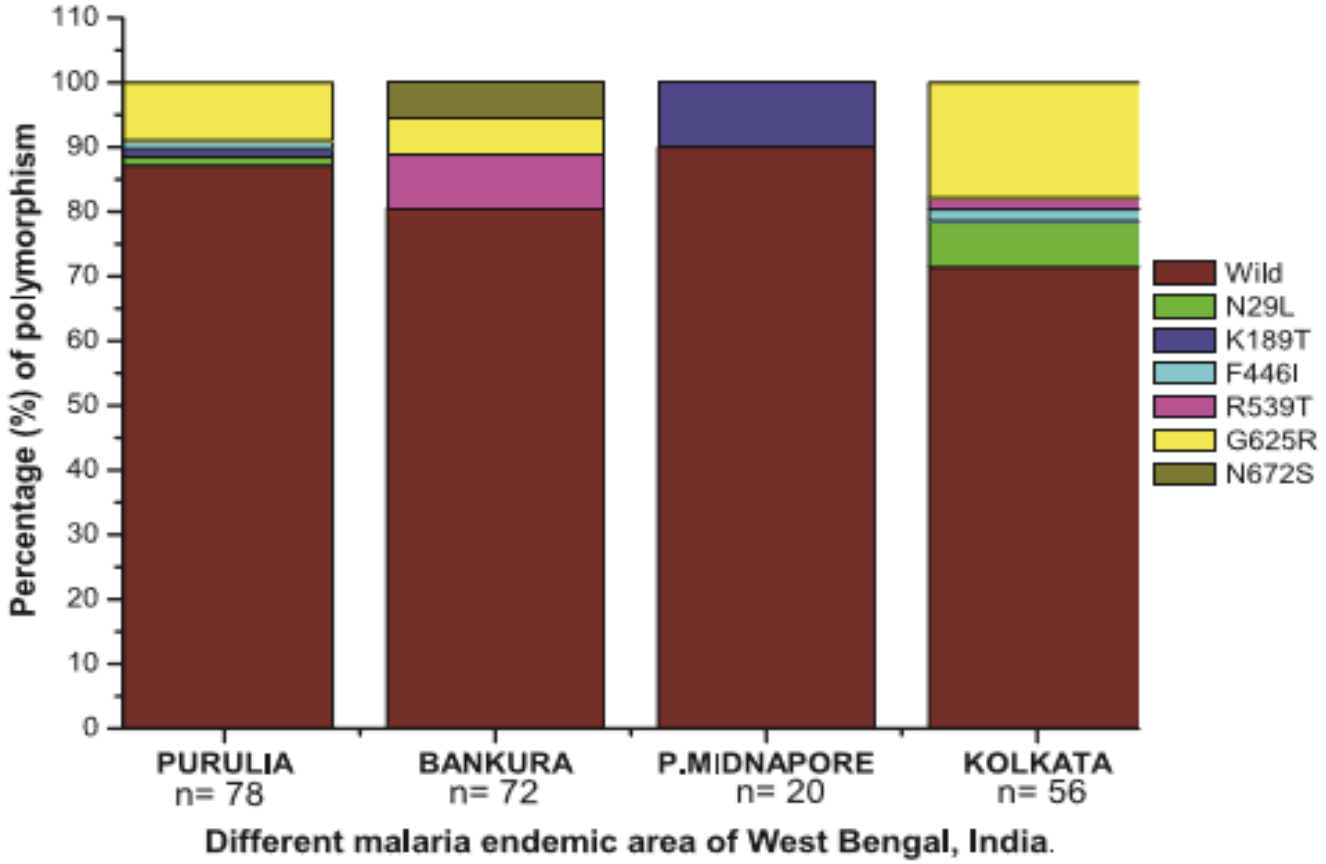
Clinical Infectious Diseases

MAJOR ARTICLE

Novel *pfkelch13* Gene Polymorphism Associates With Artemisinin Resistance in Eastern India

Sabyasachi Das,[1] Subhankar Manna,[1] Bhaskar Saha,[2] Amiya Kumar Hati,[3] and Somenath Roy[1]

[1]Immunology and Microbiology Laboratory, Department of Human Physiology with Community Health, Vidyasagar University, Midnapore, West Bengal, [2]National Centre for Cell Science, Ganeshkhind, Pune, and [3]Calcutta School of Tropical Medicine, Kolkata, West Bengal, India



Clinical Infectious Diseases

CORRESPONDENCE

Lack of Convincing Evidence of Artemisinin Resistance in India

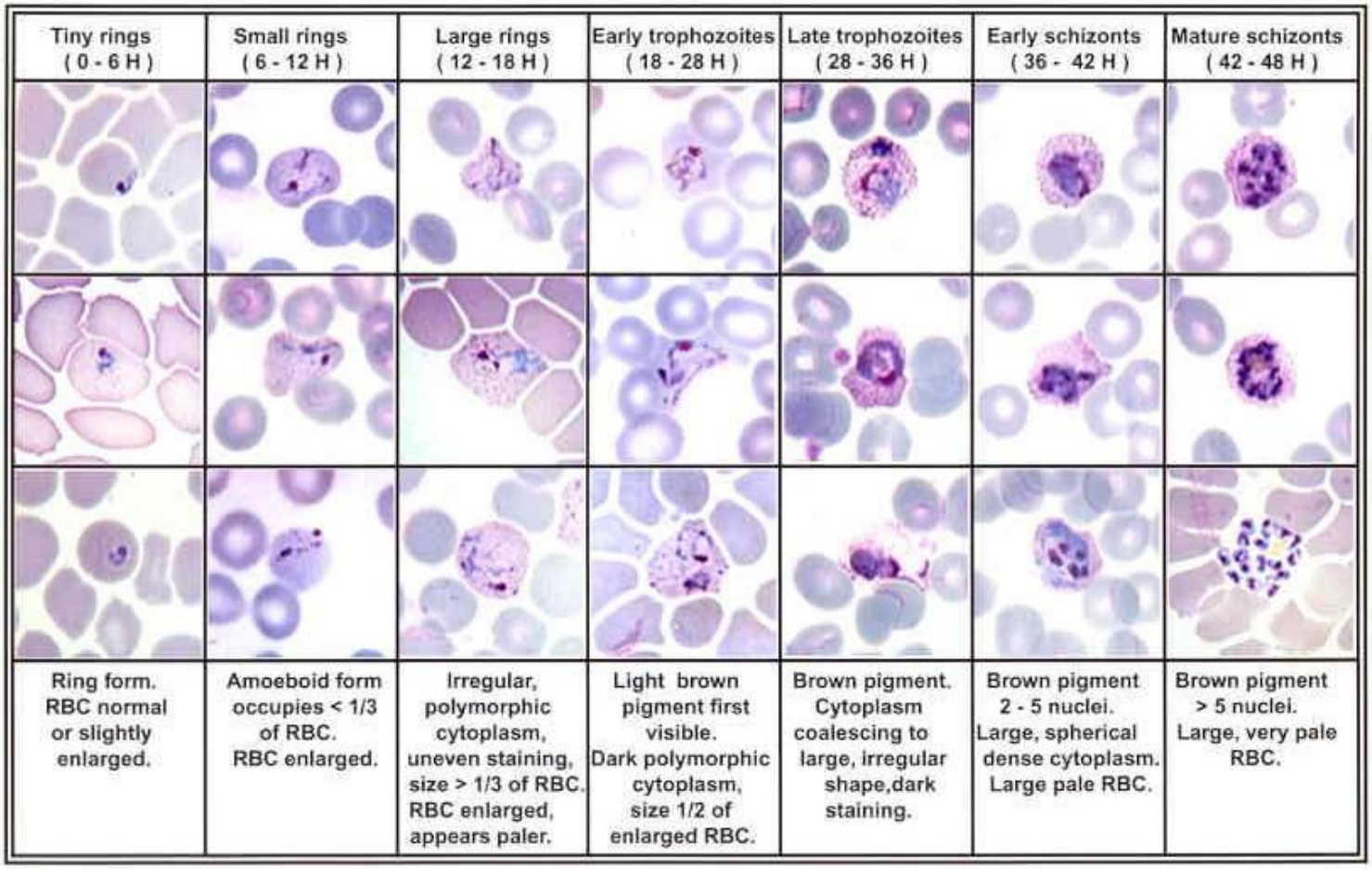
Charlotte Rasmussen,[1] Neena Valecha,[2] and Pascal Ringwald[1]

[1]Drug Efficacy and Response Unit, Global Malaria Programme, World Health Organization, Geneva, Switzerland; and [2]National Institute of Medical Research, New Delhi, India

Reply to Rasmussen, Valecha, and Ringwald

With all the responses being easily addressable and some being self-contradictory/unnecessary, it seems that the authors' claim to change our interpretations voices a nonscientific emphasis that cannot be entertained. For the experiments suggested, we admit that it is the way science perpetuates itself. Given the present situation and information, we do not see any justification to reinterpret our data.

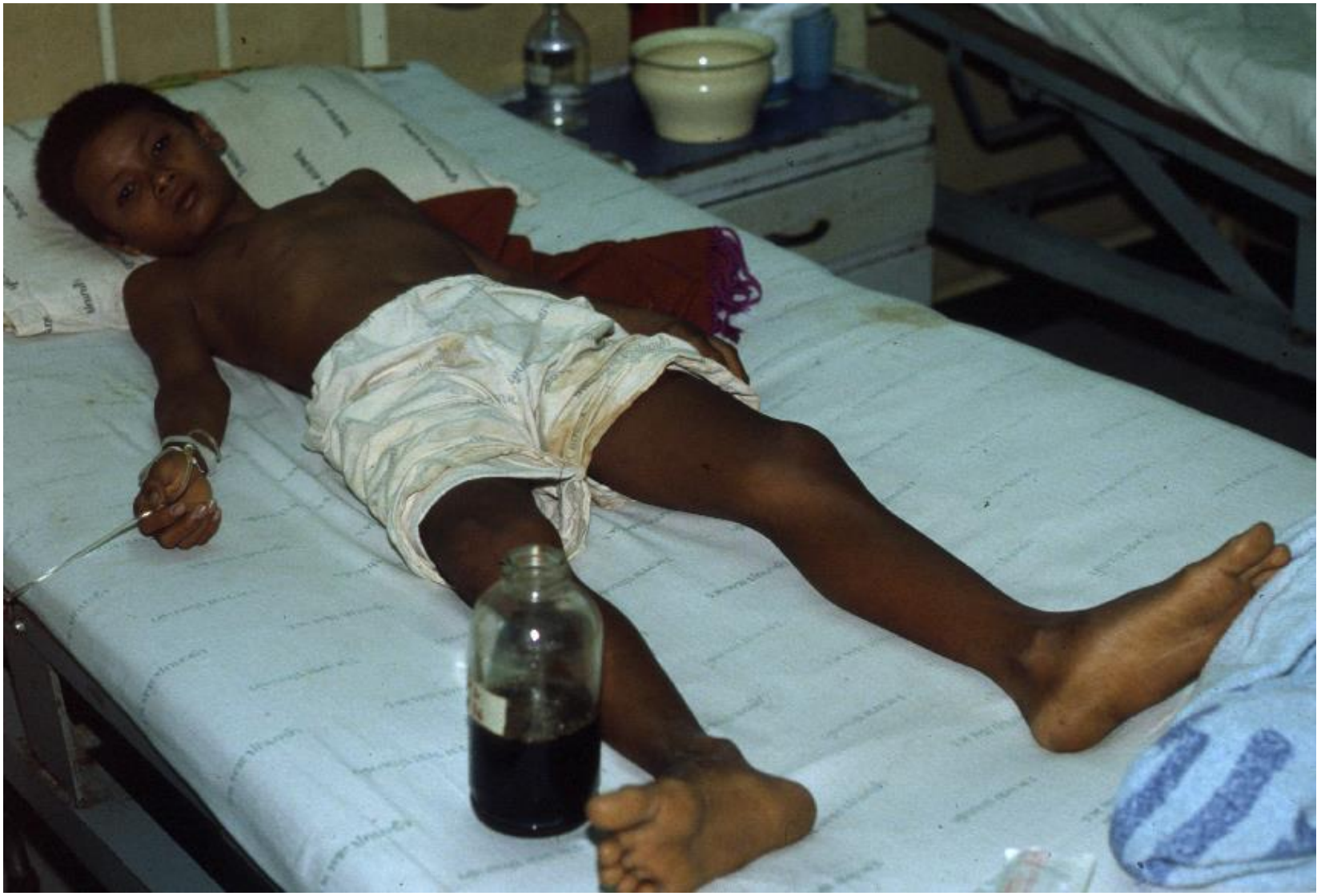
Plasmodium vivax



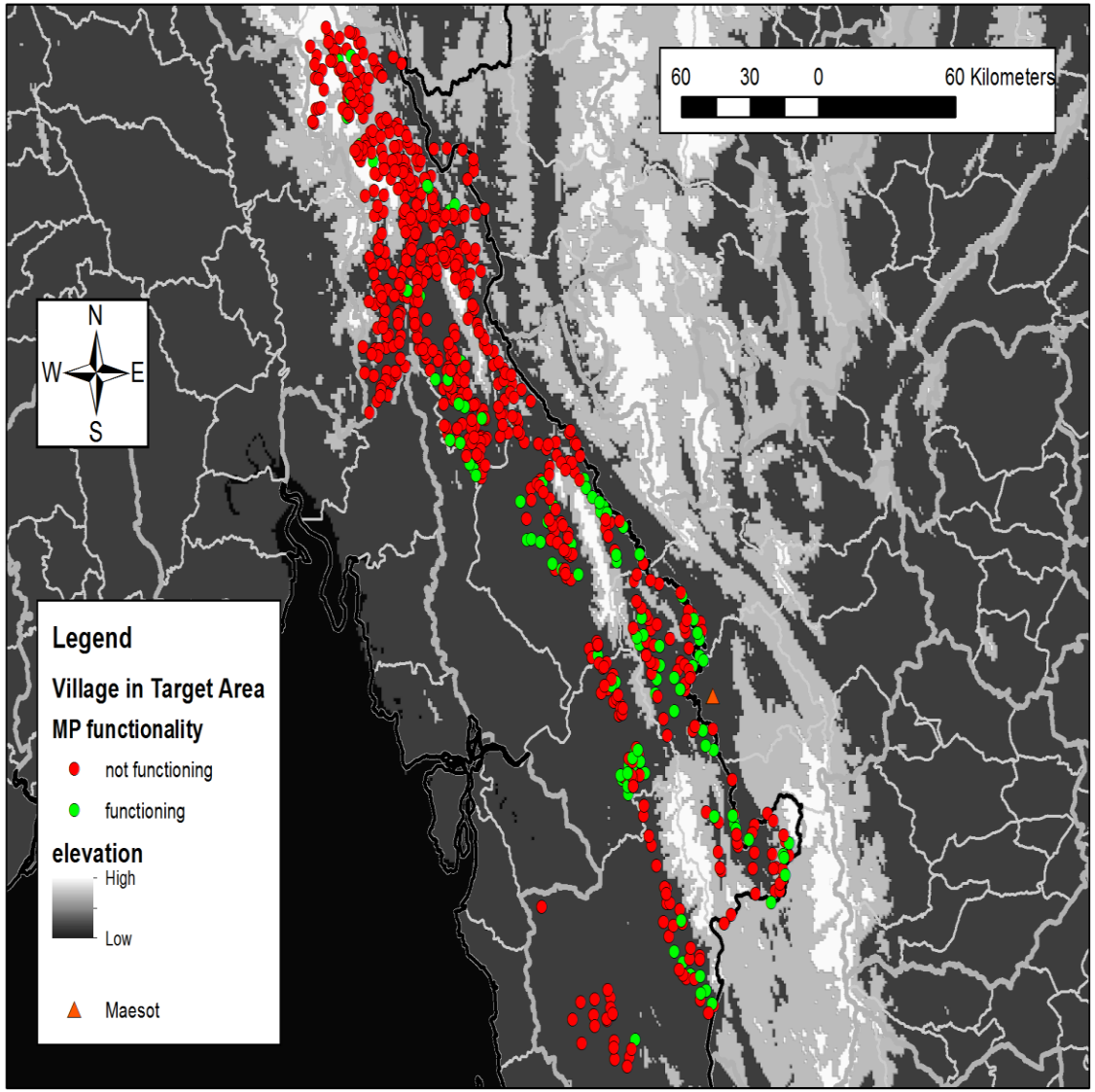
***Plasmodium vivax in vitro* culture**

Wellcome Unit, Bangkok 2000

Primaquine

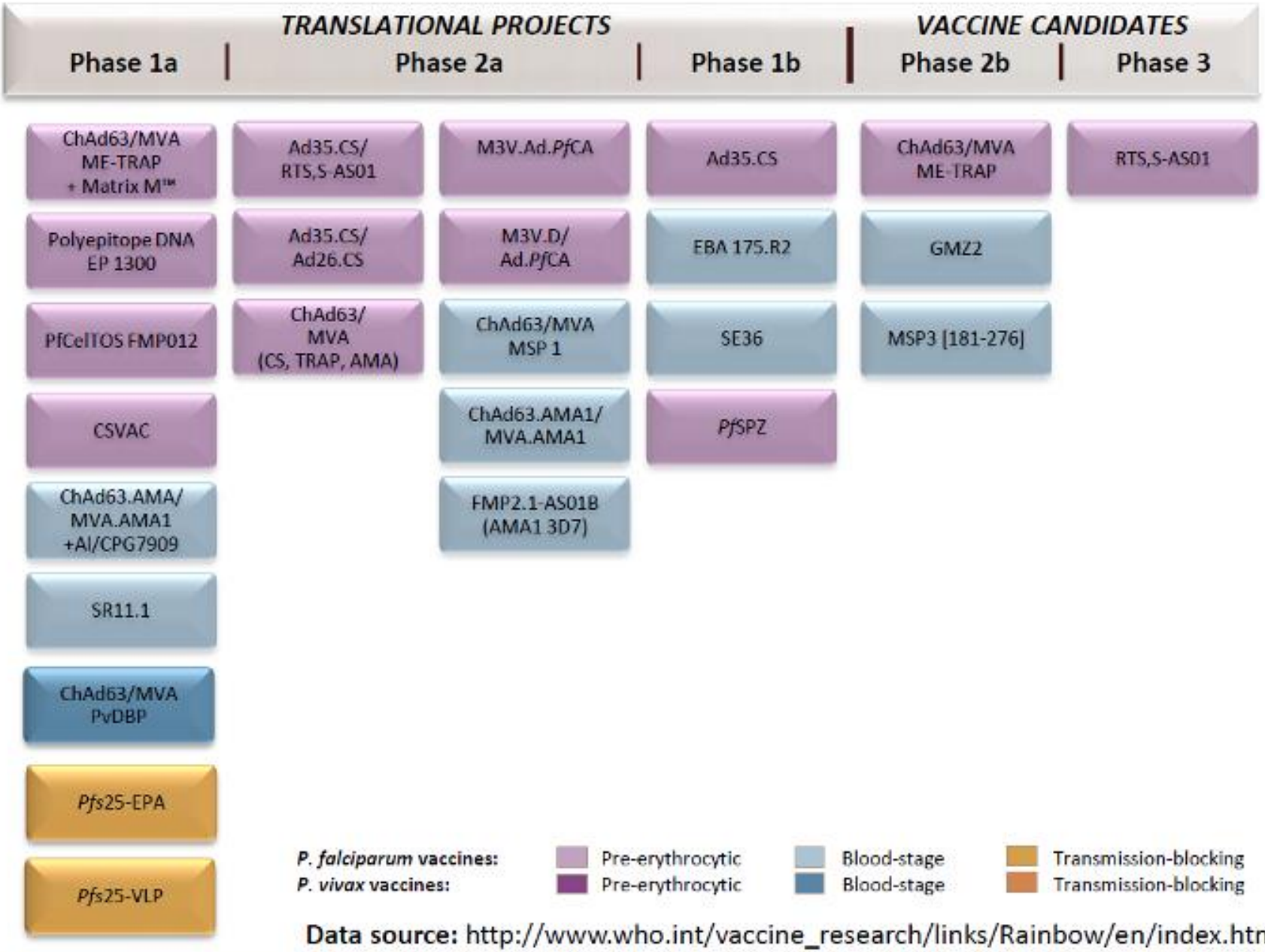



The only way to eliminate artemisinin resistant falciparum malaria is to eliminate all falciparum malaria from the region



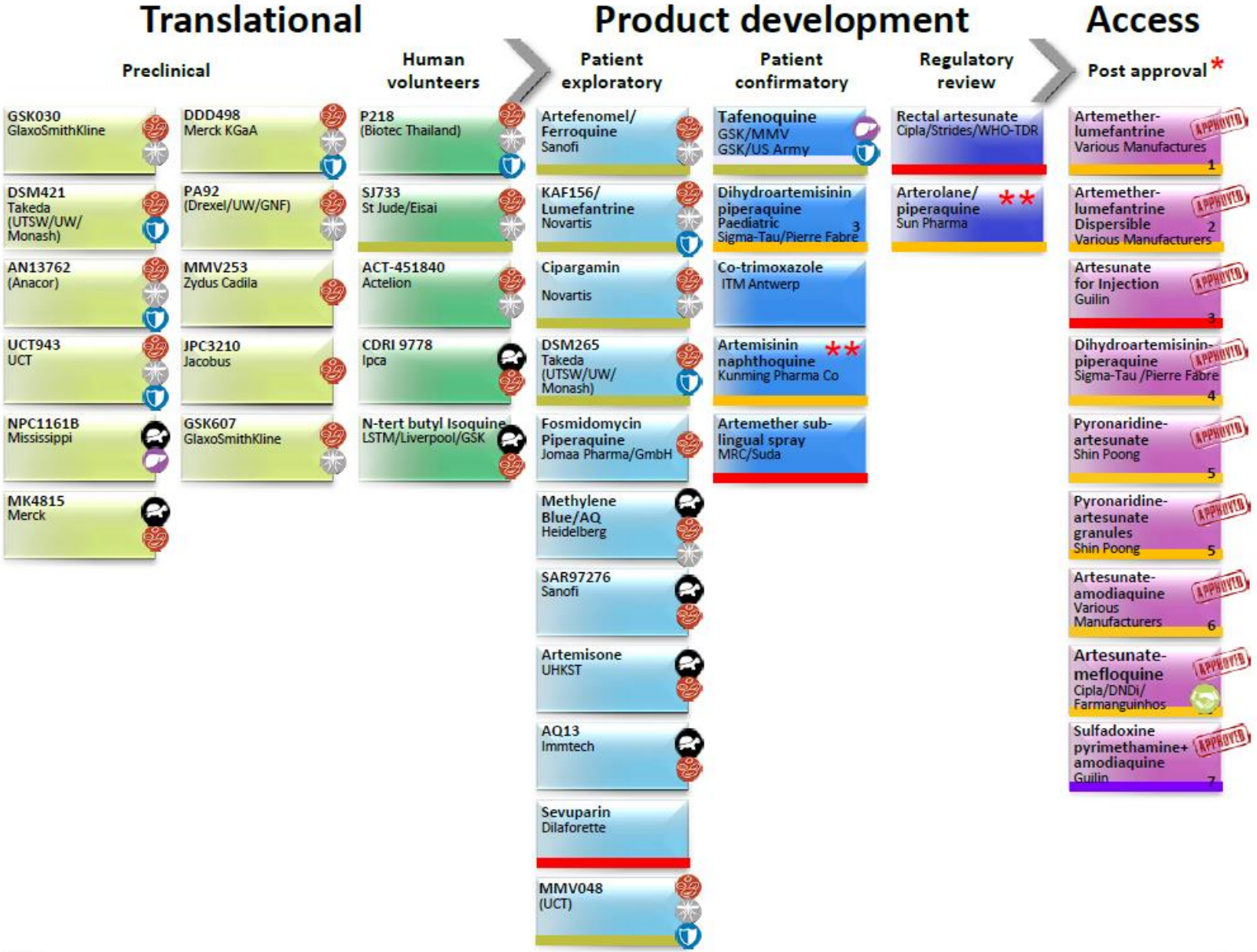
Targeted Malaria Elimination

Global malaria vaccine pipeline



Data source: http://www.who.int/vaccine_research/links/Rainbow/en/index.html

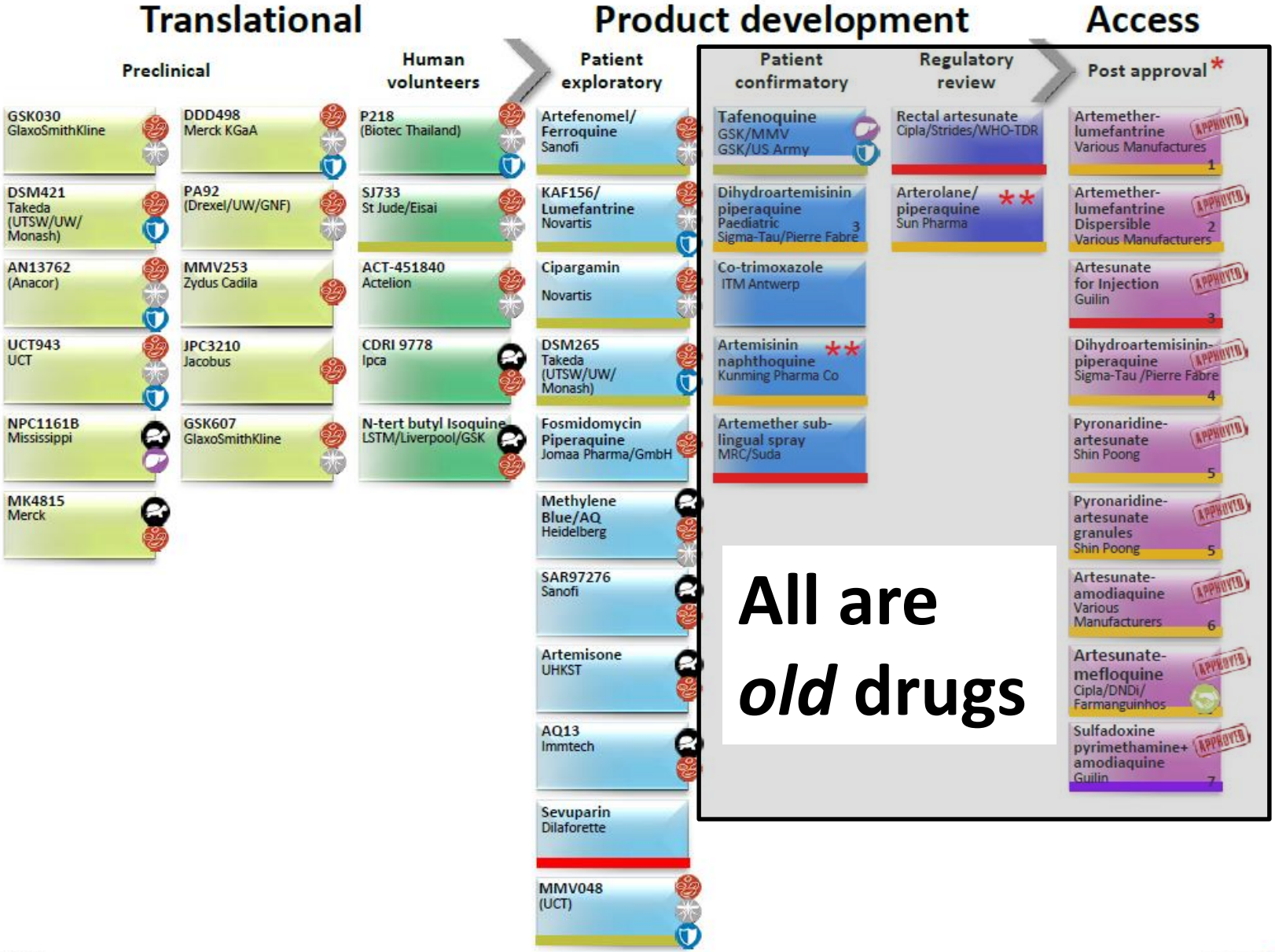
Global Portfolio of Antimalarial Medicines



31 Dec 2016

MMV
Medicines for Malaria Venture

Global Portfolio of Antimalarial Medicines

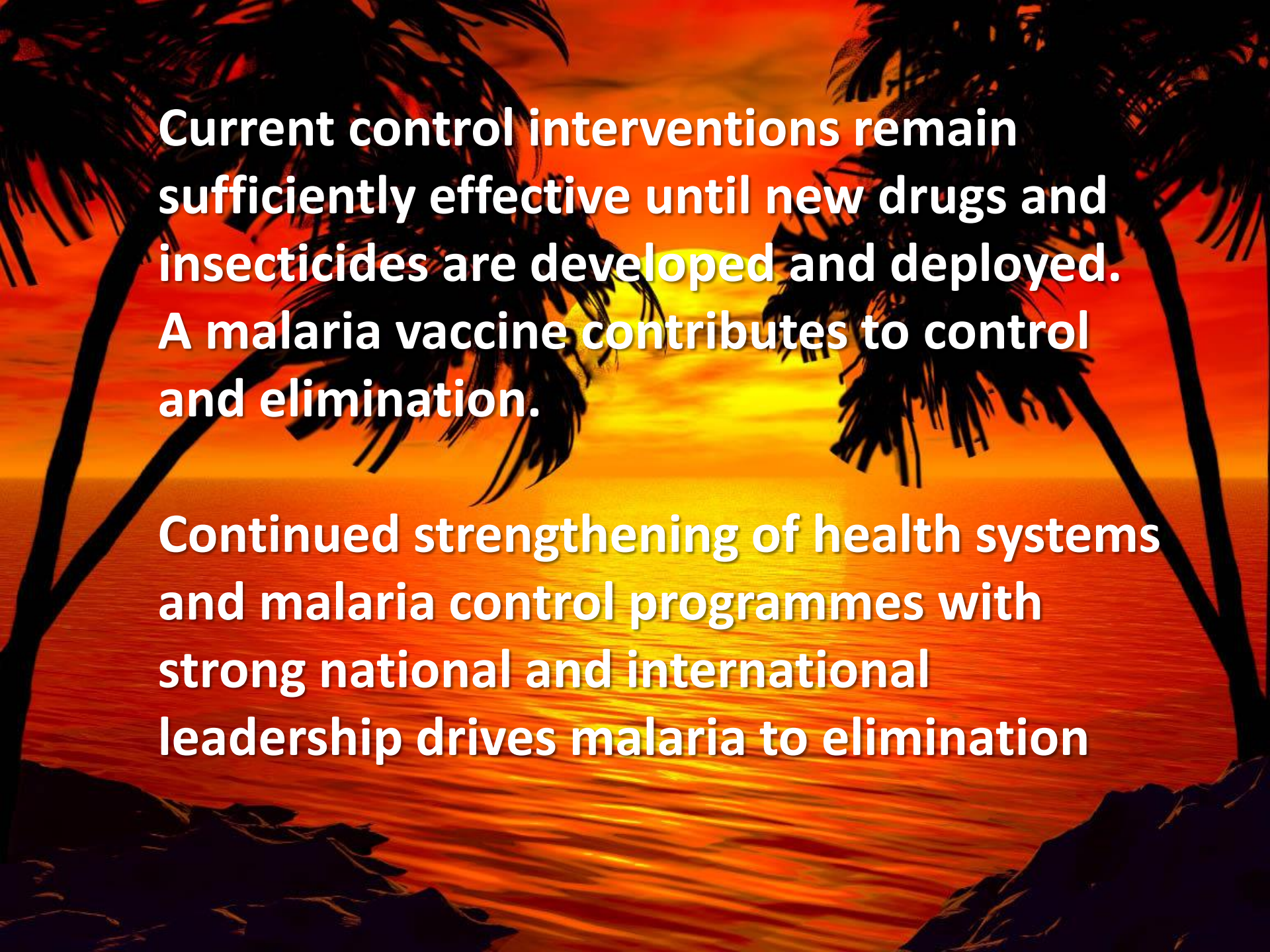


31 Dec 2016

MMV Medicines for Malaria Venture


Future


DOOM
GLOOM


Current control interventions remain sufficiently effective until new drugs and insecticides are developed and deployed. A malaria vaccine contributes to control and elimination.
Continued strengthening of health systems and malaria control programmes with strong national and international leadership drives malaria to elimination

Current control interventions do not remain sufficiently effective. New drugs and insecticides are deployed eventually but fall to resistance rapidly. Malaria increases again. The malaria vaccine is not cost-effective. All the recent gains are reversed.

Artemisinin resistance spreads to Africa and partner drug resistance follows.

Health systems and malaria control programmes remain weak and international agencies remain ineffective.