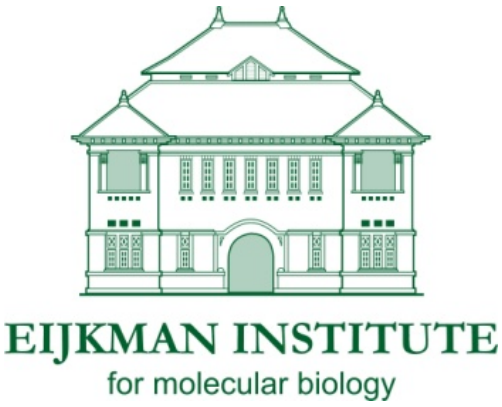
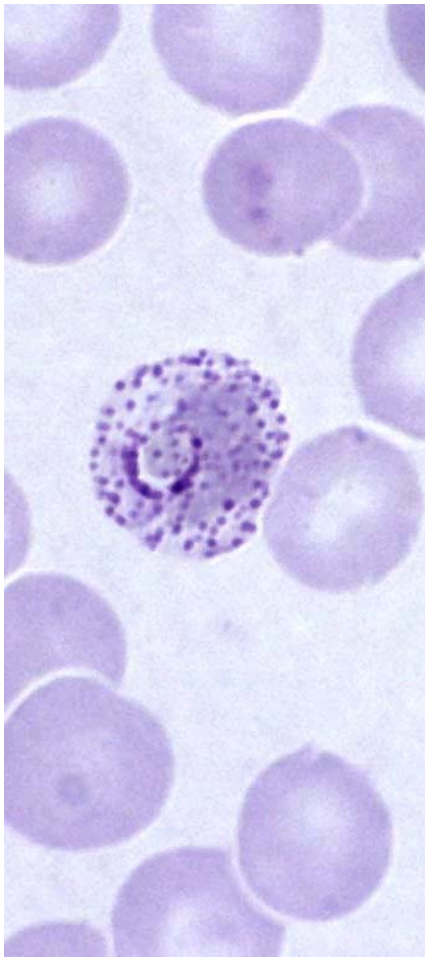
Obstacles to Elimination of *Plasmodium vivax :* Chemotherapeutic Unknowns

J. Kevin Baird, Ph.D.
Eijkman-Oxford Clinical Research Unit
Jakarta, Indonesia



P. vivax Dogma



- Limited burden
- Benign infection
- Primaquine effective
- Chloroquine effective

Plasmodium vivax *is a benign infection affecting relatively few people and is effectively treated with widely available & affordable drugs.* = **NEGLECT**

This may be the largest obstacle of them all!

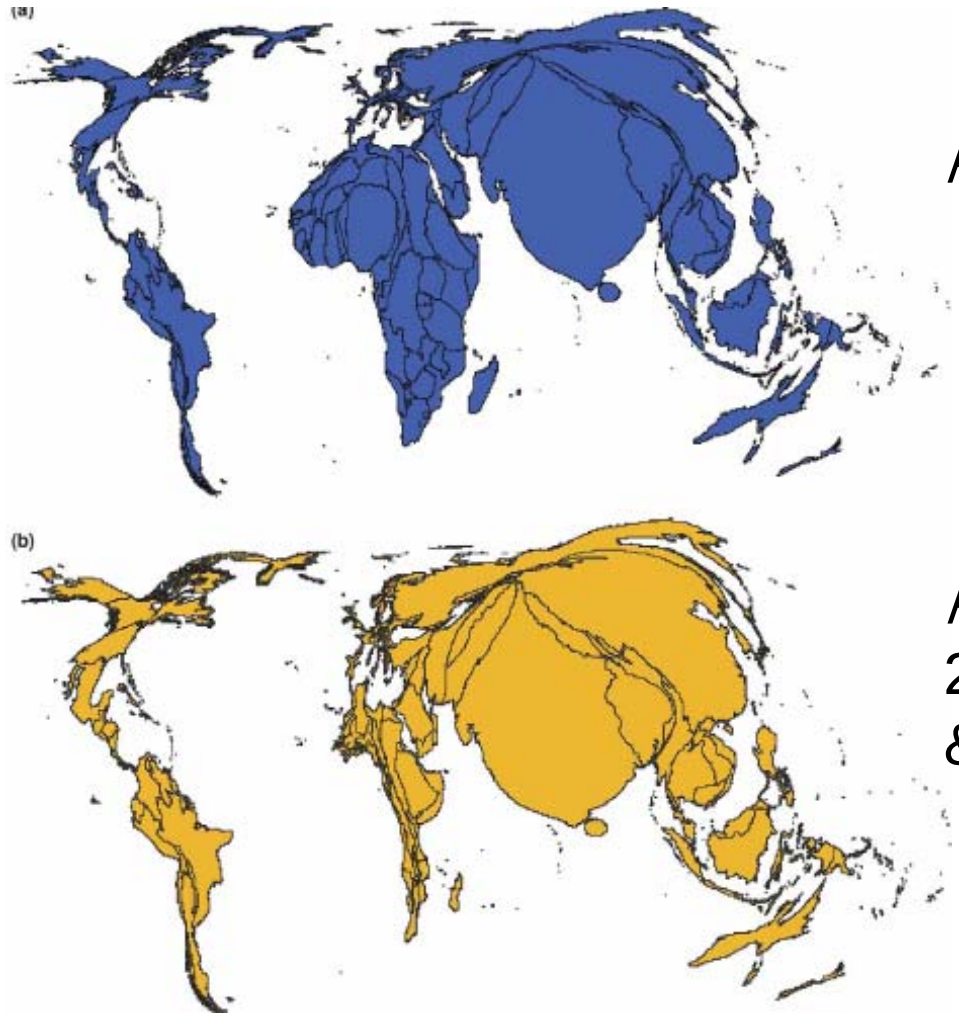
Neglect Barometer: Chemotherapeutics

- First-line therapies fielded 60 years ago
- Failing for 20 years and today:
  - We do not know how the therapies work
  - We do not know how to detect resistance
  - We do not know if therapies work
  - We do not know replacement therapies
- No drug discovery for vivax malaria since WWII

What if?

- The number of infections by *P. vivax* were 5 times higher than we thought
- *P. vivax* threatened life with the same spectrum of severe disease syndromes historically considered domain of *P. falciparum* alone
- Resistance to chloroquine and to primaquine by *P. vivax* rendered these therapies no longer useful?

Burden of Risk



P. falciparum

P. vivax
2.9 billion at risk
& 100-400 million/yr

Opinion TRENDS in Parasitology Vol.22 No.8 August 2006

Mapping the global extent of malaria in 2005

Carlos A. Guerra[1,2], Robert W. Snow[2,3] and Simon I. Hay[1,2]

OPEN ACCESS Freely available online PLoS NEGLECTED TROPICAL DISEASES

The International Limits and Population at Risk of *Plasmodium vivax* Transmission in 2009

Carlos A. Guerra[1]*, Rosalind E. Howes[1], Anand P. Patil[1], Peter W. Gething[1], Thomas P. Van Boeckel[1,2], William H. Temperley[1], Caroline W. Kabaria[3], Andrew J. Tatem[4,5], Bui H. Manh[6], Iqbal R. F. Elyazar[7], J. Kevin Baird[7,8], Robert W. Snow[3,9], Simon I. Hay[1]*

Benign Tertian Malaria?

- 3 deaths “directly traceable to malaria” among 68 patients treated with *P. vivax* in Washington, DC (Eldridge, *JAMA* 1925)
- Krauss (*Southern Med J* 1932) reviewed 8,354 inoculated with *P. vivax* in USA and found 448 deaths (5.4% case fatality).
- 17 patients treated with *P. vivax* autopsied and 11 found to be caused directly by malaria (Fong, *Southern Med J* 1937)
- 62 of 807 Dutch syphilis patients treated with Madagascar strain *P. vivax* died (8% case fatality rate; with no deaths caused by a Dutch strain)
  - Jan Peter Verhave, personal communication

Benign Tertian Malaria?

- Mississippi 1935: Antemortem microscopic diagnosis of malaria reported on approx. 1/3 of all deaths caused by malaria.
  - Among Caucasians: 33% *P. falciparum*; 15% *P. vivax*, 4% *P. malariae*
  - Among African-Americans: 21% *P. falciparum*; 13% *P. vivax*, 2% *P. malariae*
- Florida 1935: Deaths caused by *P. falciparum* was 40% of reported total, 21% *P. vivax*, 2% *P. malariae* (remainder not confirmed).

Dauer & Faust, *Southern Med J* 1937; 30: 939-943

Am. J. Trop. Med. Hyg., 77(5), 2007, pp. 984–991

Demographic Risk Factors for Severe and Fatal Vivax and Falciparum Malaria Among Hospital Admissions in Northeastern Indonesian Papua

Mazie J. Barcus,* Hasan Basri, Helena Picarima, C. Manyakori, Sekartuti, Iqbal Elyazar, Michael J. Bangs, Jason D. Maguire, and J. Kevin Baird

OPEN ACCESS Freely available online

PLOS MEDICINE

Plasmodium vivax and Mixed Infections Are Associated with Severe Malaria in Children: A Prospective Cohort Study from Papua New Guinea

Blaise Genton[1*¤], Valérie D'Acremont[1], Lawrence Rare[2], Kay Baea[2], John C. Reeder[2], Michael P. Alpers[2], Ivo Müller[2]

Am. J. Trop. Med. Hyg., 80(2), 2009, pp. 194–198

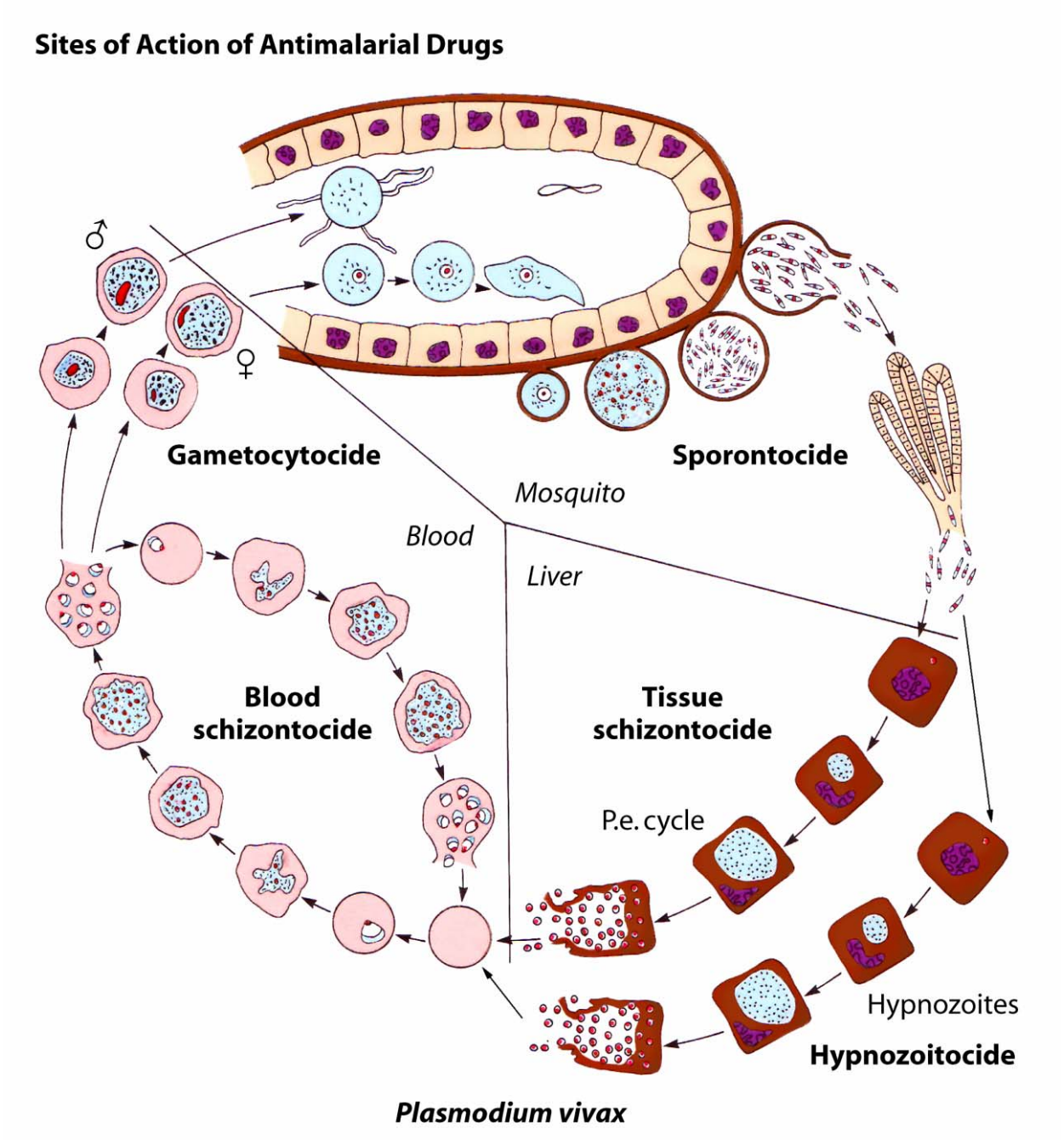
Severe *Plasmodium vivax* Malaria: A Report on Serial Cases from Bikaner in Northwestern India

Dhanpat K. Kochar,* Ashish Das, Sanjay K. Kochar, Vishal Saxena, Parmendra Sirohi, Shilpi Garg, Abhishek Kochar, Mahesh P. Khatri, and Vikas Gupta

Vivax Reality Check

- Very many at risk and very many infections!
- Infection can lead to life-threatening severe illness

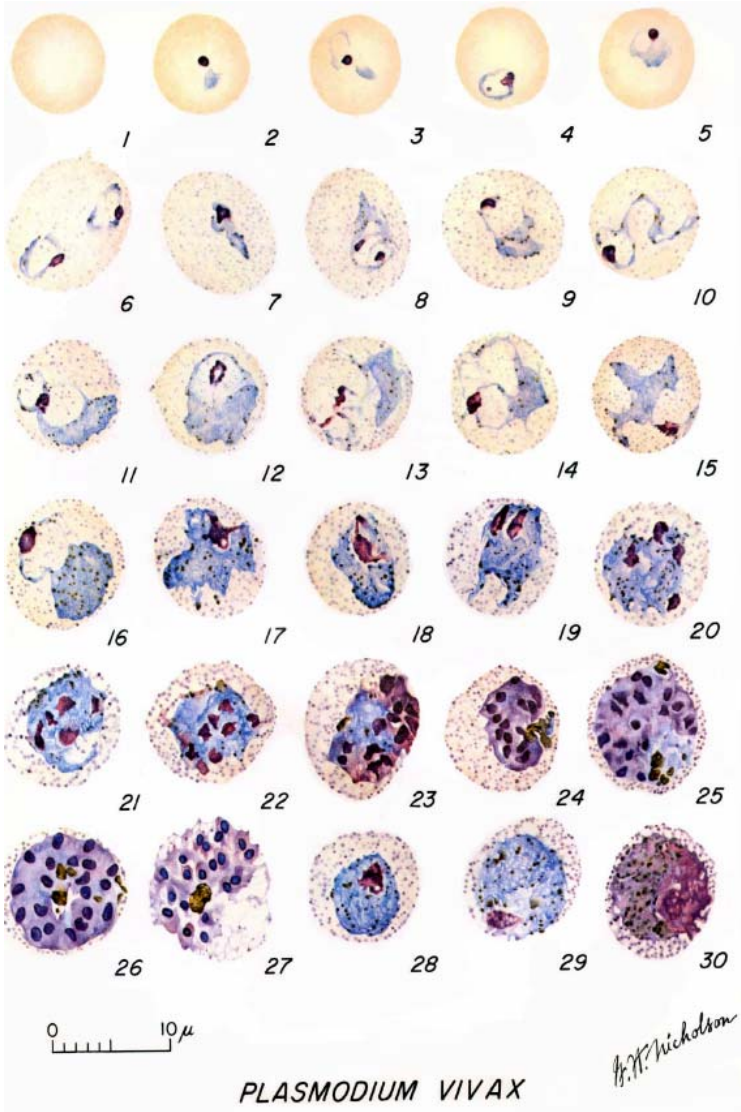
So how are our drugs for dealing with this threat doing?

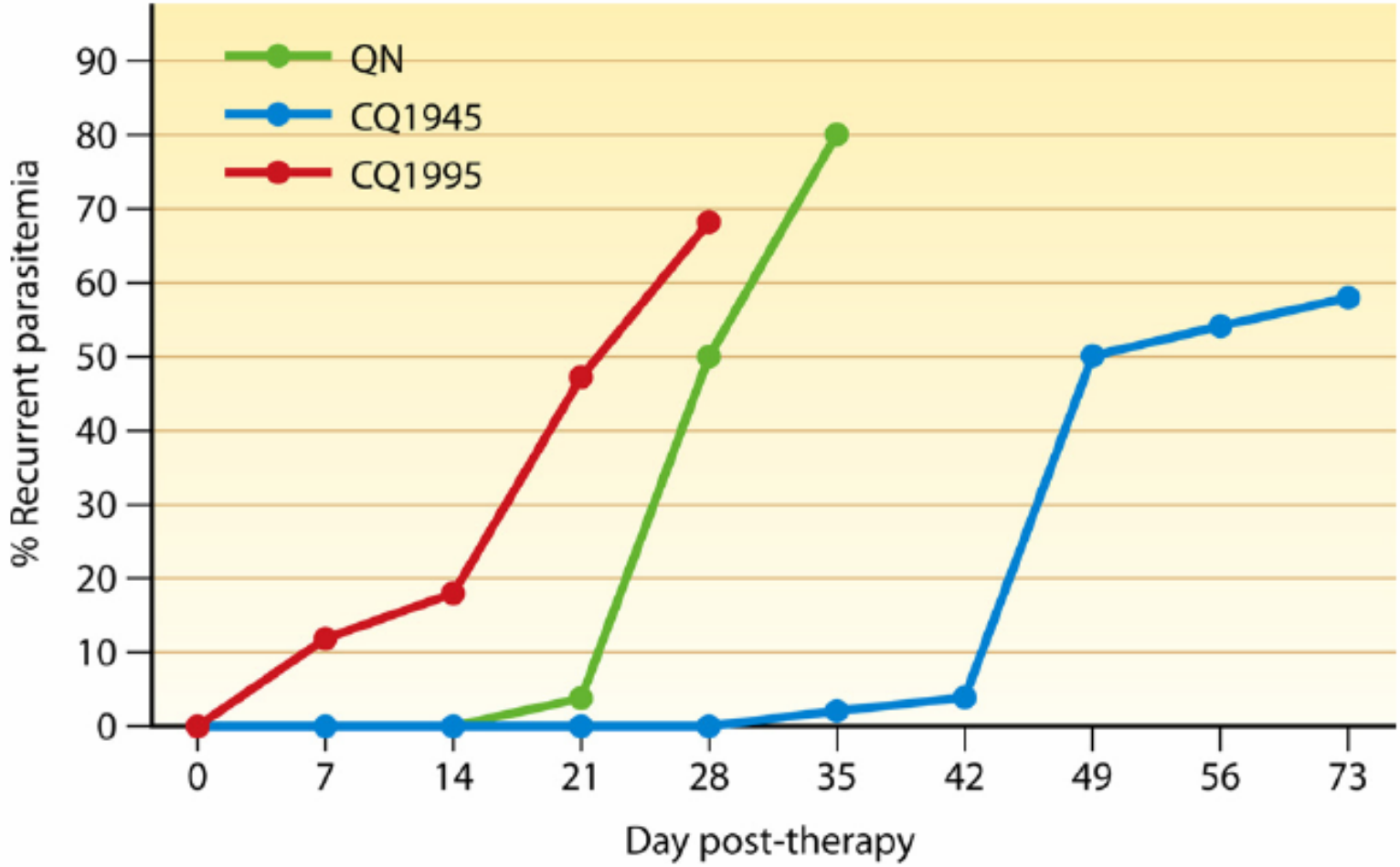


Courtesy of Prof. Wallace Peters. Art by Andrea Darlow

Treatment of Vivax Malaria

- Resolving acute disease requires blood schizontocide (**chloroquine**)
- Preventing relapse requires a hypnozoitocide (**primaquine**)
- These therapies together are called **radical cure**





CLINICAL MICROBIOLOGY REVIEWS, July 2009, p. 508–534 Vol. 22, No. 3
0893-8512/09/$08.00+0 doi:10.1128/CMR.00008-09

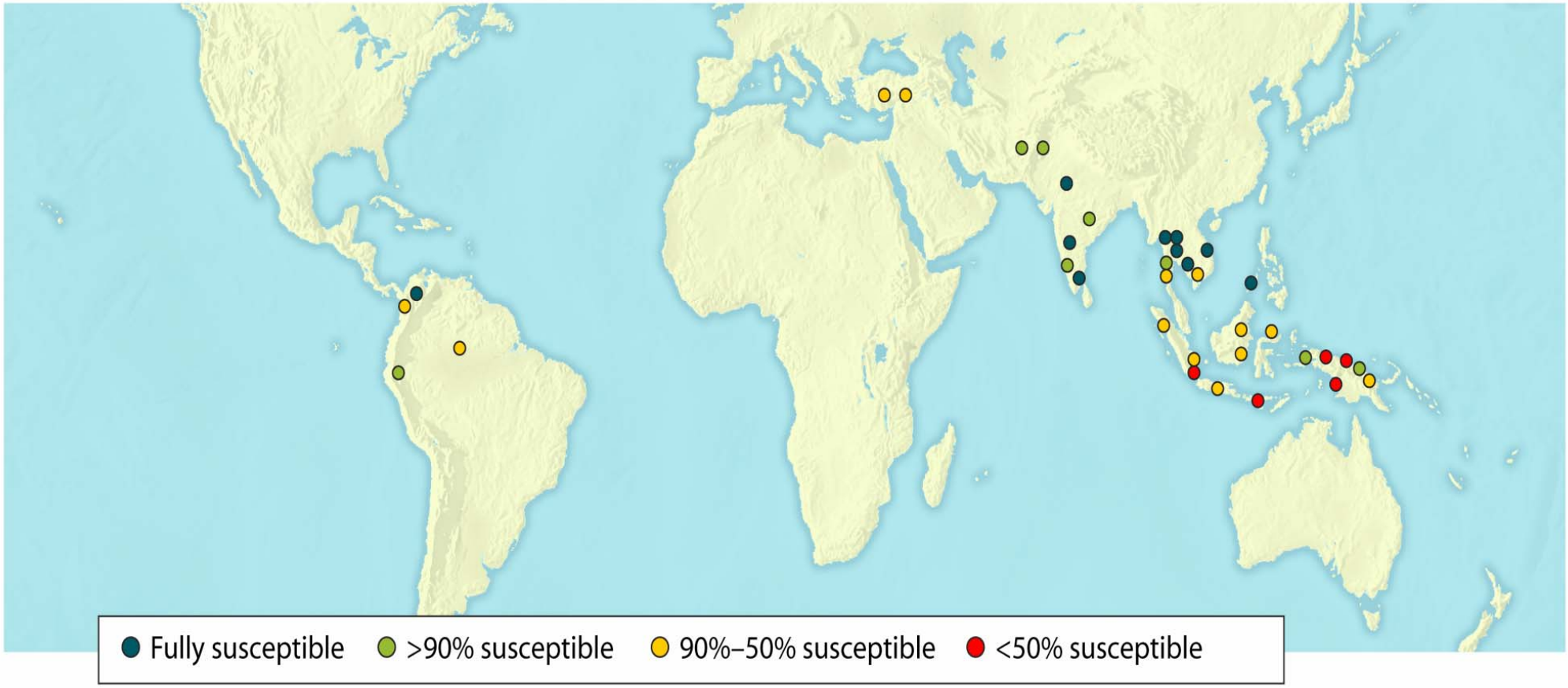
Resistance to Therapies for Infection by *Plasmodium vivax*

J. Kevin Baird*

Eijkman-Oxford Clinical Research Unit, Jakarta, Indonesia, and the Centre for Tropical Medicine, Nuffield Department of Clinical Medicine, Oxford University, Oxford, United Kingdom

Chloroquine-resistant *P. vivax*

Survey of Resistance to Chloroquine in Plasmodium vivax : 1998–2008



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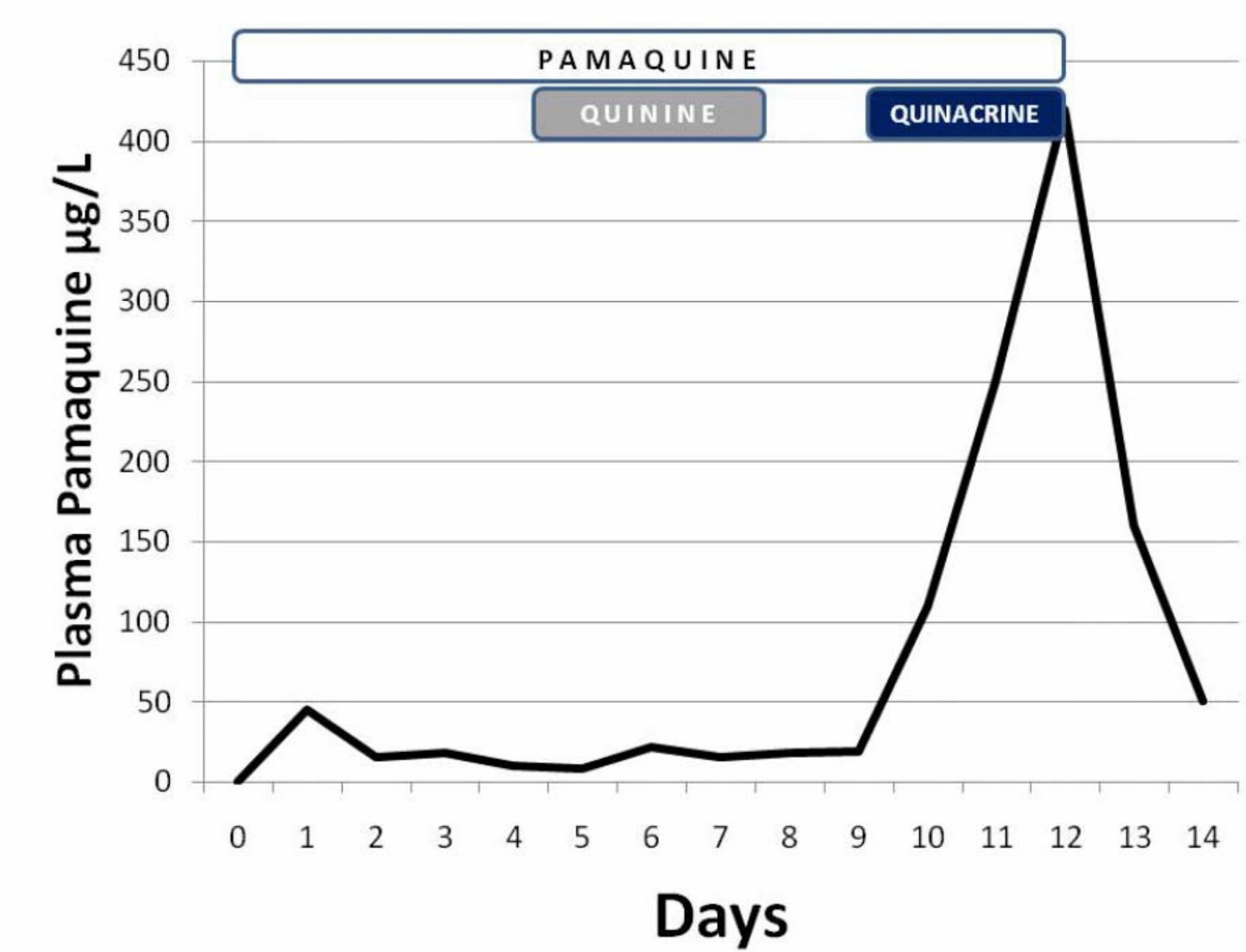
Relapse Behaviors

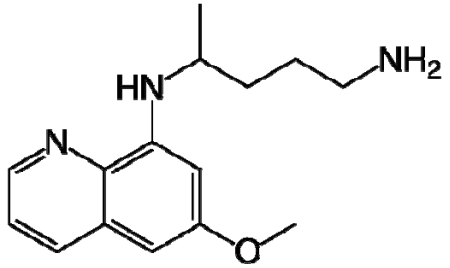
Location	Number Observed	% Relapsing
Southeast Asia	342	63%
Southeast Asia	562	72%
Southwest Pacific	213	99%
Southwest Pacific	54	100%
India	264	19%
India	5528	9%
Korea	1021	32%
Korea	433	28%

War & Malaria

- Americans at Guadalcanal 1942 suffer 1.8 attacks/man-year
- Vivax relapse attack rate is 3.7 cases /man-yr
- 5 of 6 malaria cases are vivax malaria
- Japanese occupation of Java makes quinine unavailable
- Allies field quinacrine (also called atabrin or mepacrine) for use in radical cure of vivax malaria with **pamaquine**

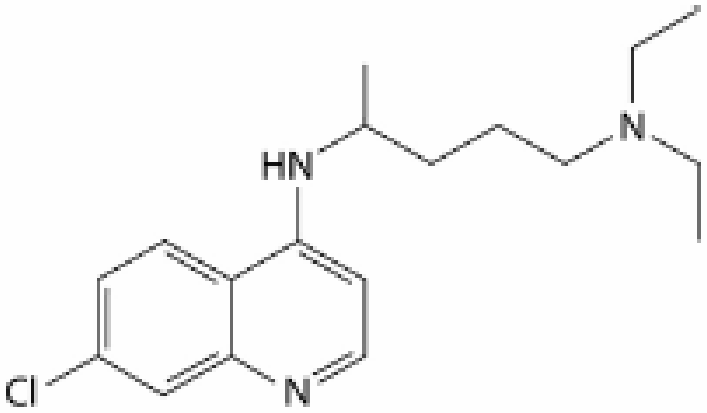


Classified US Army report, 1942

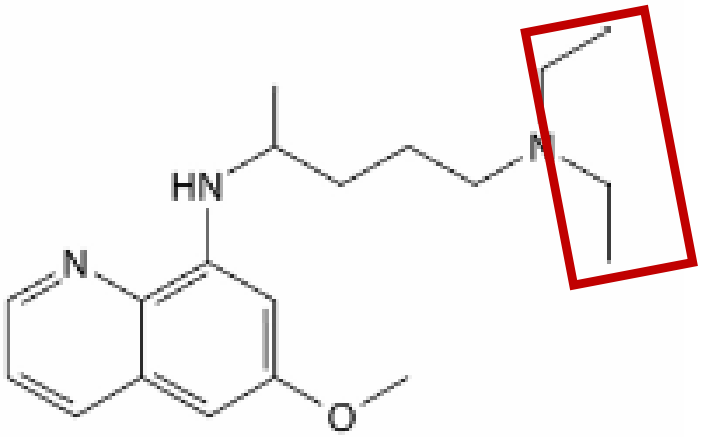


Primaquine Discovery

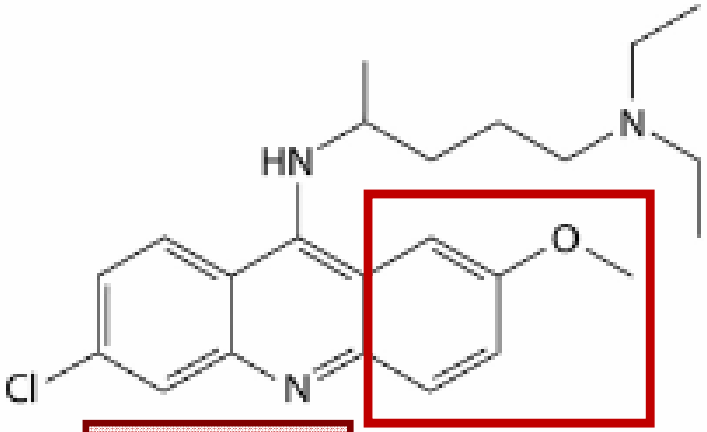
- US military launch desperate search for a solution to the pamaquine/quinacrine problem
- Only 8-aminoquinolines considered
- Screening of thousands of candidates based largely on safety data in rats & monkeys
- 22 candidates advanced to clinical trials
- Primaquine emerged as safer option
- Combined with newly discovered chloroquine, was safe & effective.



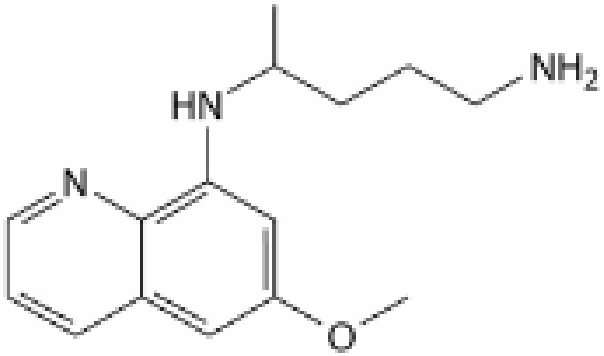
Chloroquine



Pamaquine



Mepacrine



Primaquine

Companion Blood Schizontocide

- Quinine or chloroquine have no effect on hypnozoites
- Primaquine widely presumed active against hypnozoites independently of companion drug
- We conveniently segregate the blood and liver therapeutic compartments
- So, if CQ fails, ***we simply plug in another blood schizontocide***

THE CLINICAL TRIAL OF EIGHTEEN ANALOGUES OF PAMAQUIN (PLASMOCHIN) IN *VIVAX* MALARIA (CHESSON STRAIN) [1]

By ALF S. ALVING, THEODORE N. PULLMAN,[2] BRANCH CRAIGE, JR.,[2] RALPH JONES, JR.,[2] C. MERRILL WHORTON,[2] AND LILLIAN EICHELBERGER

(*From the Malarial Research Unit, Department of Medicine, University of Chicago*)

(Received for publication February 14, 1947)

Administration of drugs. The drugs were administered over a 14-day period in equal doses every four hours to insure fairly constant concentrations in the body fluids. Quinine was administered concurrently with the drugs for two reasons: (*1*) the synergistic effect of quinine on pamaquin may also extend to pamaquin analogues, and (*2*) if it is assumed that a curative agent may prevent relapse by action chiefly on hypothetical exo-erythrocytic stages of the parasite with little or no action on the erythrocytic stages, the concurrent administration of an anti-trophozoite agent is indicated. Qui-

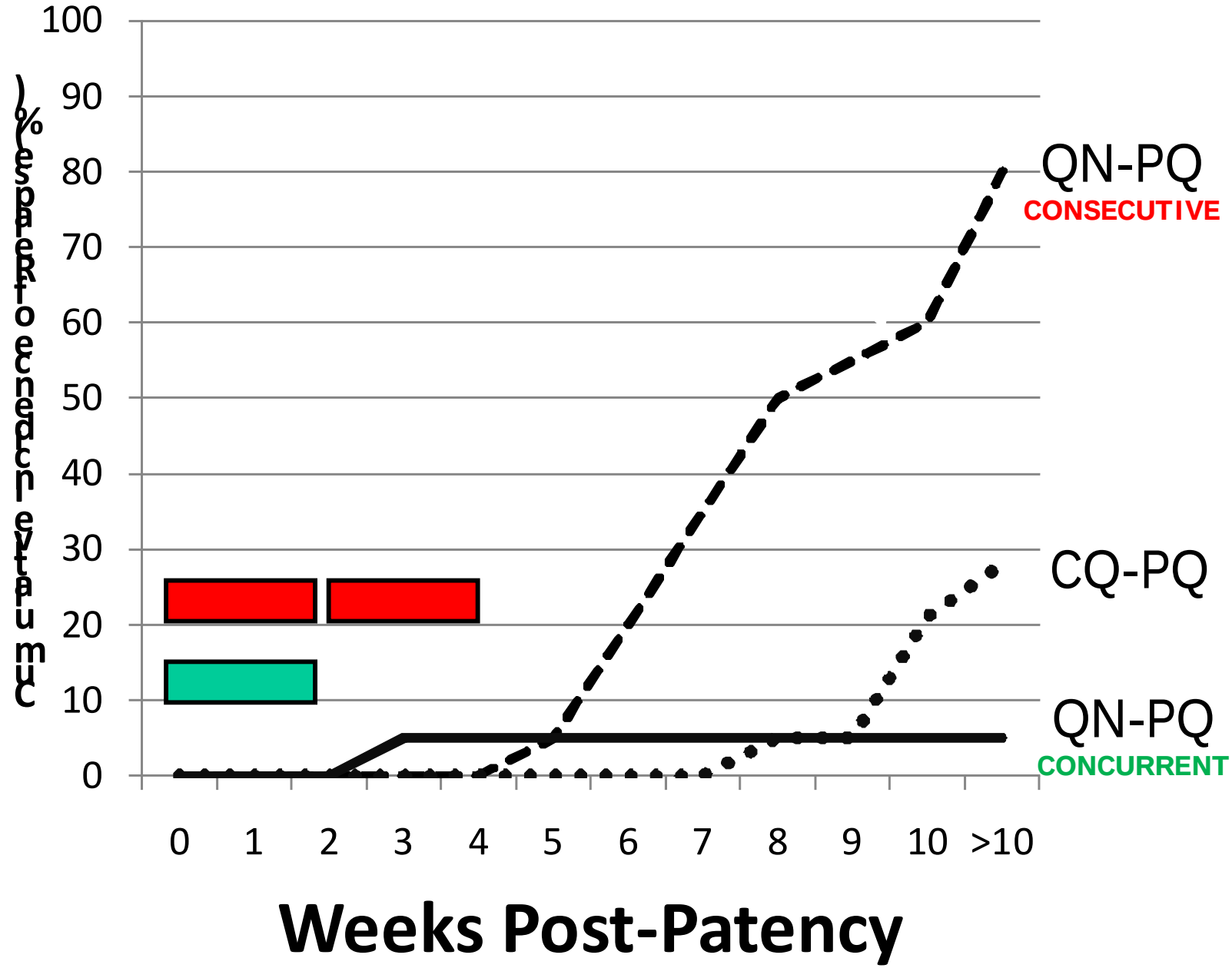
J Clin Invest. 1948 May;27(3 Pt1):34-45.

POTENTIATION OF THE CURATIVE ACTION OF PRIMAQUINE IN VIVAX MALARIA BY QUININE AND CHLOROQUINE

ALF S. ALVING, M.D., JOHN ARNOLD, M.D.,* ROBERT S. HOCKWALD, M.D.,**
CHARLES B. CLAYMAN, M.D.,** RAYMOND J. DERN, M.D.,***
ERNEST BEUTLER, M.D.,**** AND C. LARKIN FLANAGAN, M.D.
CHICAGO, ILL.

pharmacologic action of pamaquine and primaquine. A few experiments conducted in nonendemic areas under controlled hospital observation suggest potentiation of pamaquine by quinine. These experiments, however, cannot be considered definitive because the individual groups treated were either small or the different test groups lacked adequate controls.[14–16] The possibility of pontentiation of the action of any 8-aminoquinoline against tissue stages by concurrent administration of quinine, therefore, still remains a matter of uncertainty.

Alving's Experiment



Implications

- Primaquine requires an appropriate companion drug to kill hypnozoites
- Primaquine toxicity may be exacerbated by some companion drugs

Replacing chloroquine in radical cure will require re-establishing the safety & efficacy of **primaquine** when used with that new drug

Vivax Reality

- 2.9 billion people at risk
- >100 million clinical cases
- Risk of life-threatening syndromes
- Chloroquine failed in Indonesia & failing in Myanmar & Cambodia
- Limited ability to establish safety & efficacy of primaquine when combined with any given drug intended to replace chloroquine
- ACT + primaquine has unproven efficacy as radical cure

Obstacle to Elimination

- CQ resistance strongly emergent
- New partner to PQ may exacerbate its toxicity or fail to synergize its efficacy
- New radical cure means re-establishing safety & efficacy of primaquine with each new partner blood schizontocide.

We are losing our only proven therapy for cure of vivax malaria & replacing it is far more complex and difficult than with P. falciparum*.*

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