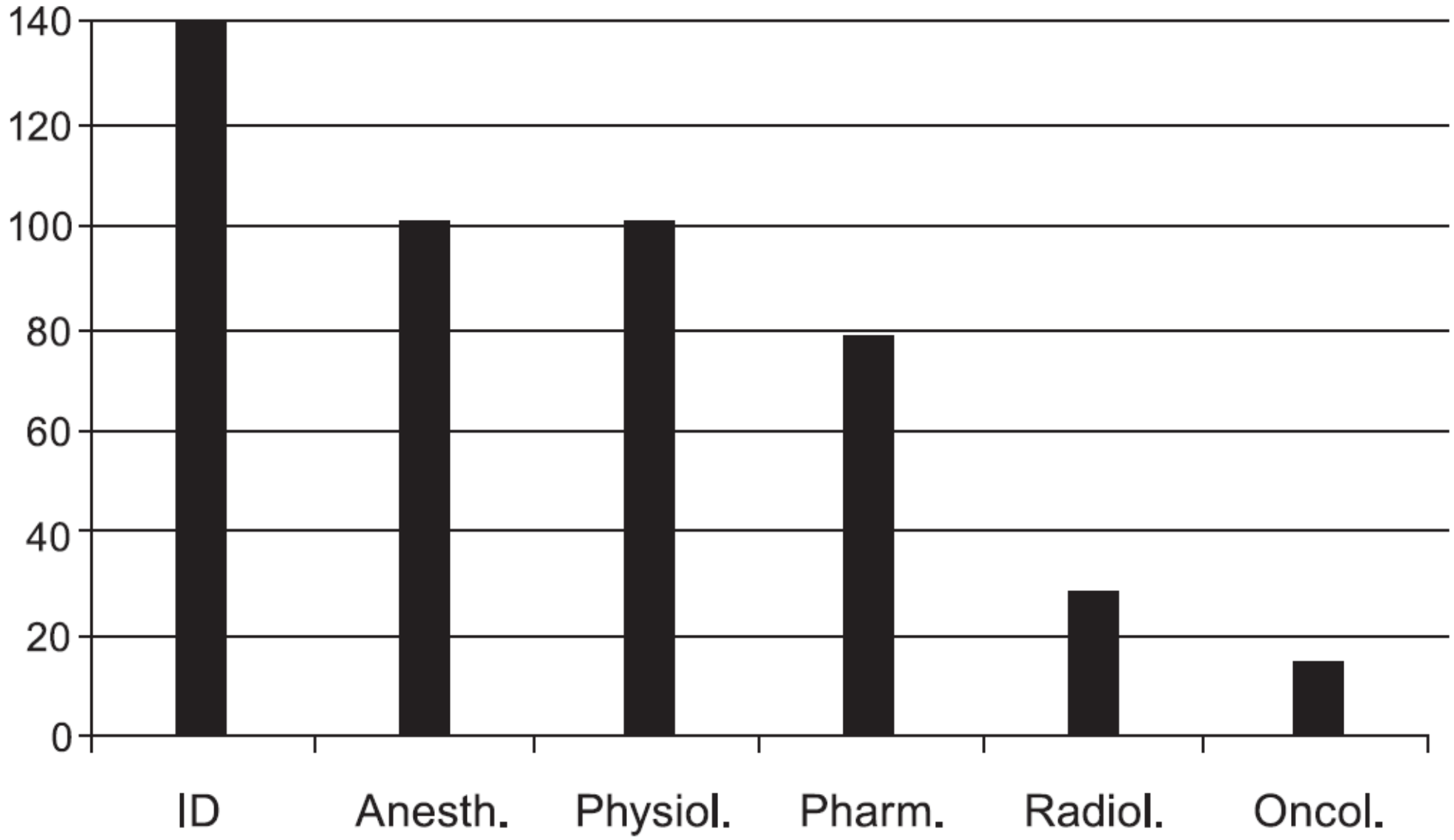
Daniel Alcides Carrión García (August 12, 1857 – October 5, 1885)

Human self experimentation 1800-1999



N= 465

Weisse A 2012

Nobel prizes awarded to self experimenters

Year	Recipient	Research Area	
1903	Niels Finsen	Phototherapy	
1904	William Ramsay	Discovery of inert elements*	Inhaled different gases to investigate anaesthetic effects
1908	Elic Metchnikoff	Phagocytes*	
1923	Frederick Banting	Insulin	
1928	Charles Nicolle	Cause of typhus	
1930	Karl Landsteiner	Blood types	Injected himself with spirochaetes
1936	Victor Hess	Discovery of cosmic rays	
1939	Gerhard Domagk	Sulfa drugs	
1939	Ernest Lawrence	Cyclotron*	Drank solution containing radioactive sodium
1943	George de Hevesy	Polarography*	Drank heavy water to study elimination
1952	Albert Schweitzer	Humanitarianism*	Injected unproven yellow fever vaccine to study side effects
1956	Werner Forssmann	Cardiac catheterization	
2005	Barry Marshall	*Helicobacter pylori*	

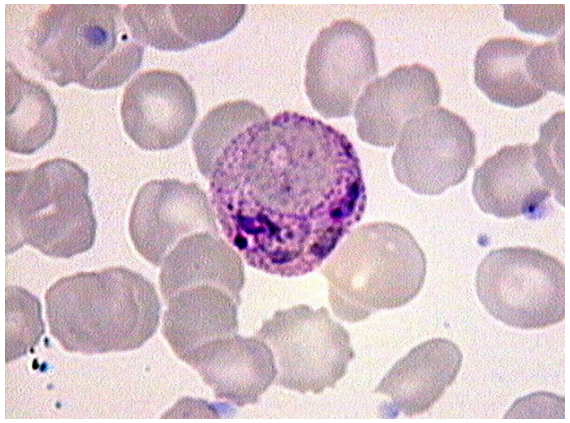
*Nobel prize awarded for work unrelated to self-experimentation.

Death from self experimentation 1800-1999

Year of Death	Person (Country)	Cause of Death
1817	Alois Rosenfeld (Austria)	Bubonic plague (?)
1849	Anthony White (United Kingdom)	Plague
1873	Otto Obermeier (Germany)	Cholera vaccine
1874	Joseph von Lindwurm (Germany)	Secondary syphilis
1885	Daniel Carrion (Peru)	Oroyo fever
1900	Jesse Lazear (United States)	Yellow fever
1920	Arthur Bacot (United Kingdom)	Typhus
1928	Alexander Bogdanov (Russia)	Multiple blood transfusions

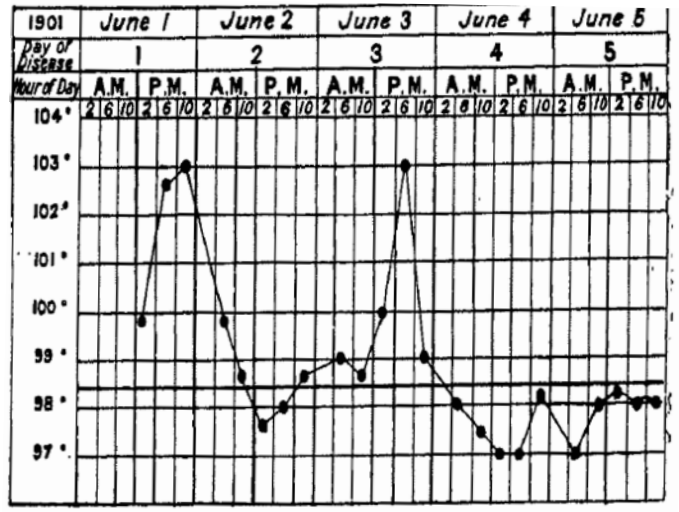
EXPERIMENTAL MALARIA: RECURRENCE AFTER NINE MONTHS.

BY P. THURBURN MANSON, M.B.LOND.,
Aberdeen.



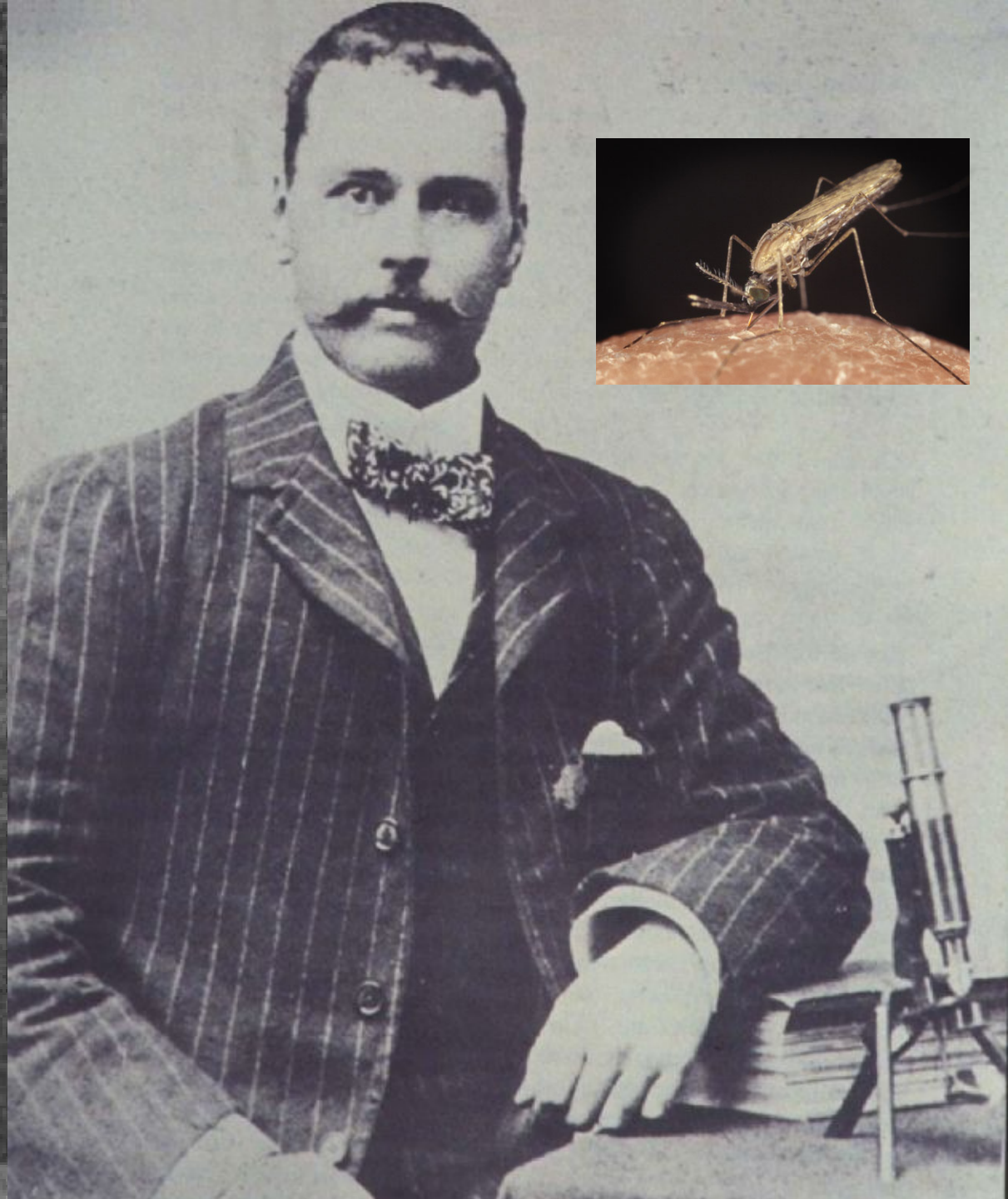
A SUCCESSFUL experiment, of which I was the subject, on the production of malarial infection by mosquito bite, is recorded in the BRITISH MEDICAL JOURNAL of September 29th, 1900. The sequel is of interest.

As a result of the bites of mosquitos fed in Rome on a case of benign tertian ague, I developed a double tertian fever. The first symptoms appeared on September 13th, 1900, after an incubation period of between ten and sixteen days. The illness lasted from September 13th to September 17th, when.

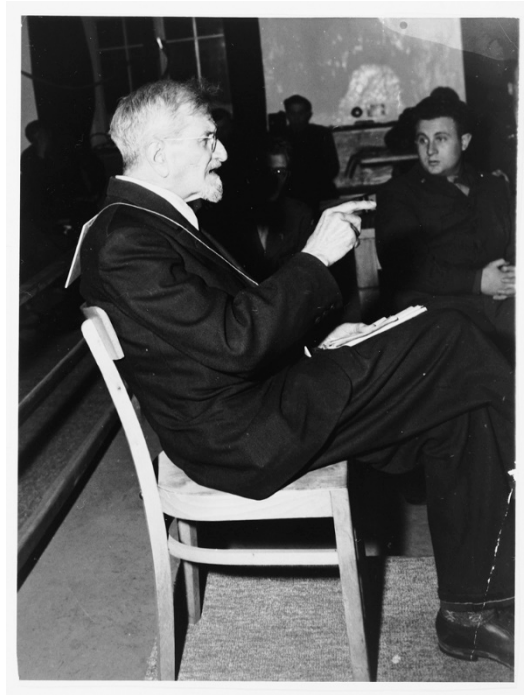


On May 30th, 1901, I commenced without obvious reason to have prodromal symptoms of illness; these were *malaise* and pain in the splenic region. Two days later—on June 1st—a definite malarial paroxysm occurred. The following are the notes of my case:

September 17 –May 30 = 8.5 months



1928



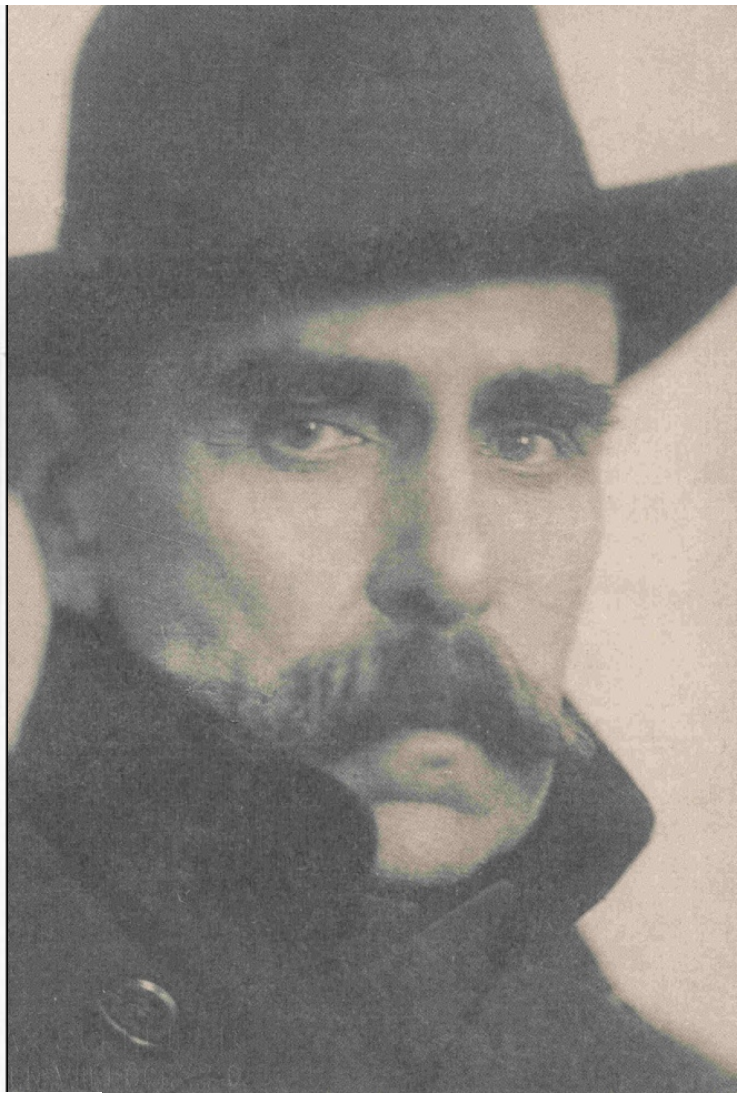
1946

The Nuremberg Code (1947)

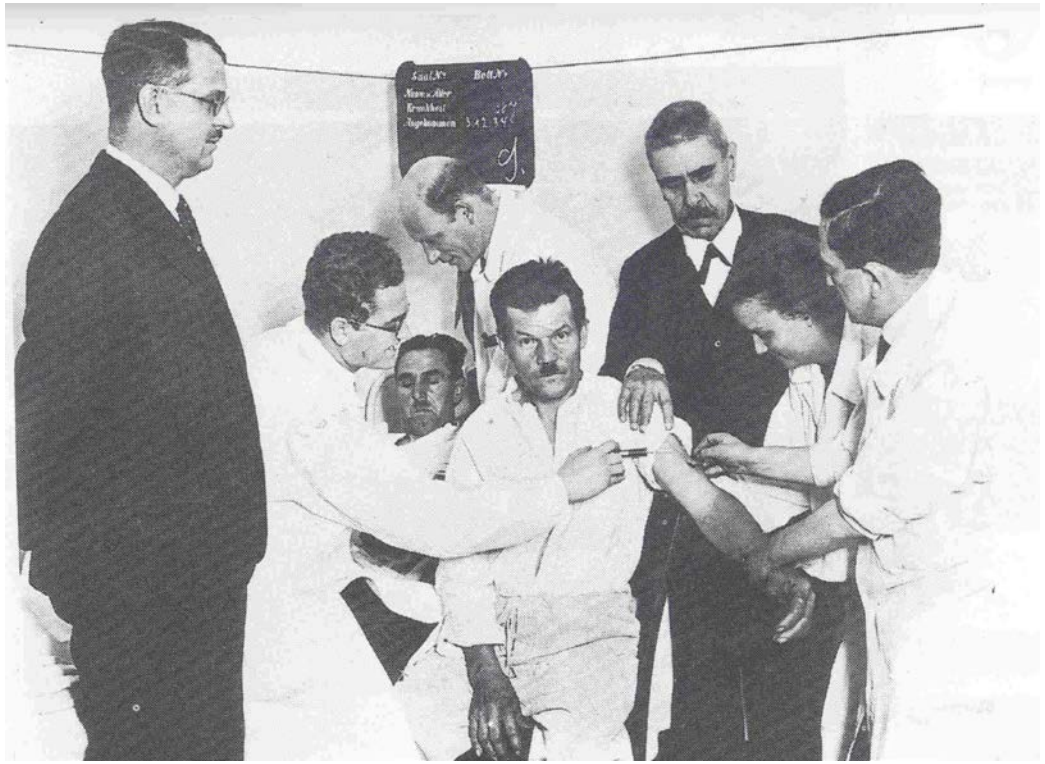
1.Required is the voluntary, well-informed, understanding consent of the human subject in a full legal capacity.
2.The experiment should aim at positive results for society that cannot be procured in some other way.
3.It should be based on previous knowledge (e.g., an expectation derived from animal experiments) that justifies the experiment.
4.The experiment should be set up in a way that avoids unnecessary physical and mental suffering and injuries.
5.It should not be conducted when there is any reason to believe that it implies a risk of death or disabling injury.
6.The risks of the experiment should be in proportion to (that is, not exceed) the expected humanitarian benefits.
7.Preparations and facilities must be provided that adequately protect the subjects against the experiment's risks.
8.The staff who conduct or take part in the experiment must be fully trained and scientifically qualified.
9.The human subjects must be free to immediately quit the experiment at any point when they feel physically or mentally unable to go on.
10.Likewise, the medical staff must stop the experiment at any point when they observe that continuation would be dangerous

The Declaration of Helsinki (1964-2013)

On 1 January 1913, of 103,842 patients suffering from mental disorder in 95 public mental hospitals in England, 6380 (5352 men and 1028 women) were diagnosed as suffering from general paralysis of the insane (GPI). In the mental hospitals administered by the London County Council (LCC) at that time more than 8% of new admissions were found to be suffering from the same dread disease – a late syphilitic invasion of the brain and central nervous system – most of whom were doomed to die a wretched, lingering death. There was no known cure. There was no hope.



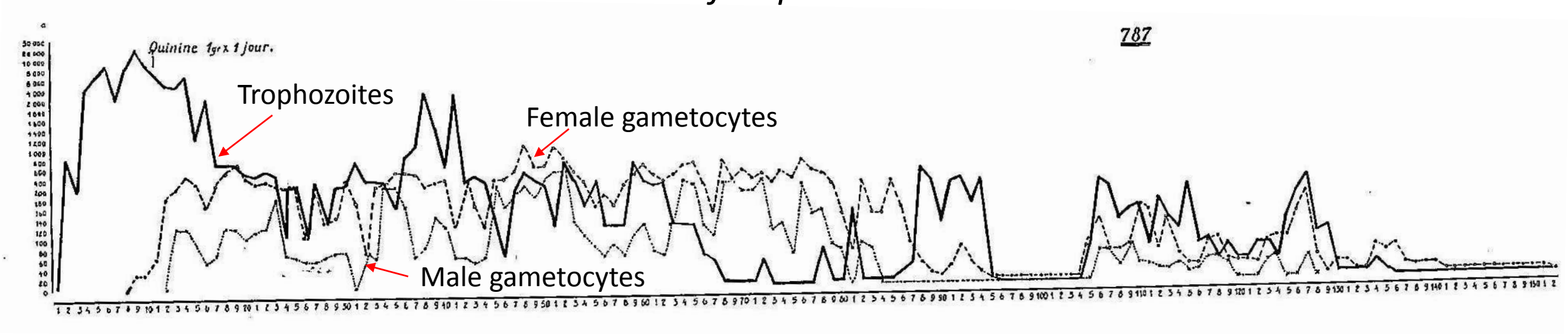
MALARIATHERAPY



Nobel laureates who studied malaria

1902. Ronald Ross
1905. Robert Koch
1906. Camillo Golgi, Santiago Ramón y Cajal
1907. Alphonse Laveran
1908. Ilya Mechnikov, Paul Ehrlich
1927. Julius Wagner-Jauregg
2015. Tu Youyou

P. falciparum



6 months

Ciuca et al 1936

Proceedings of a Meeting of the Society held on Thursday, 15th May, 1924, at 8.15 p.m., at 11, Chandos Street, Cavendish Square, W. 1, Dr. A. G. BAGSHAWE, C.M.G. *(Vice-President)*, in the Chair.

The CHAIRMAN said he had received a letter from the President, Sir PERCY BASSETT-SMITH, who wished the meeting to be informed how sorry he was he could not occupy the Chair, but he hoped to be able to do so at the next meeting.

OBSERVATIONS ON MALARIA MADE DURING TREATMENT OF GENERAL PARALYSIS.

BY

WARRINGTON YORKE, M.D., AND J. W. S. MACFIE, D.Sc., M.B., CH.B.

Malignant Tertian Malaria.—At the very beginning of our work one case was inoculated with the blood from a patient suffering from malignant tertian malaria. The infection which resulted was of a fulminating character and the disease terminated fatally.

Pijper & Russell 1924

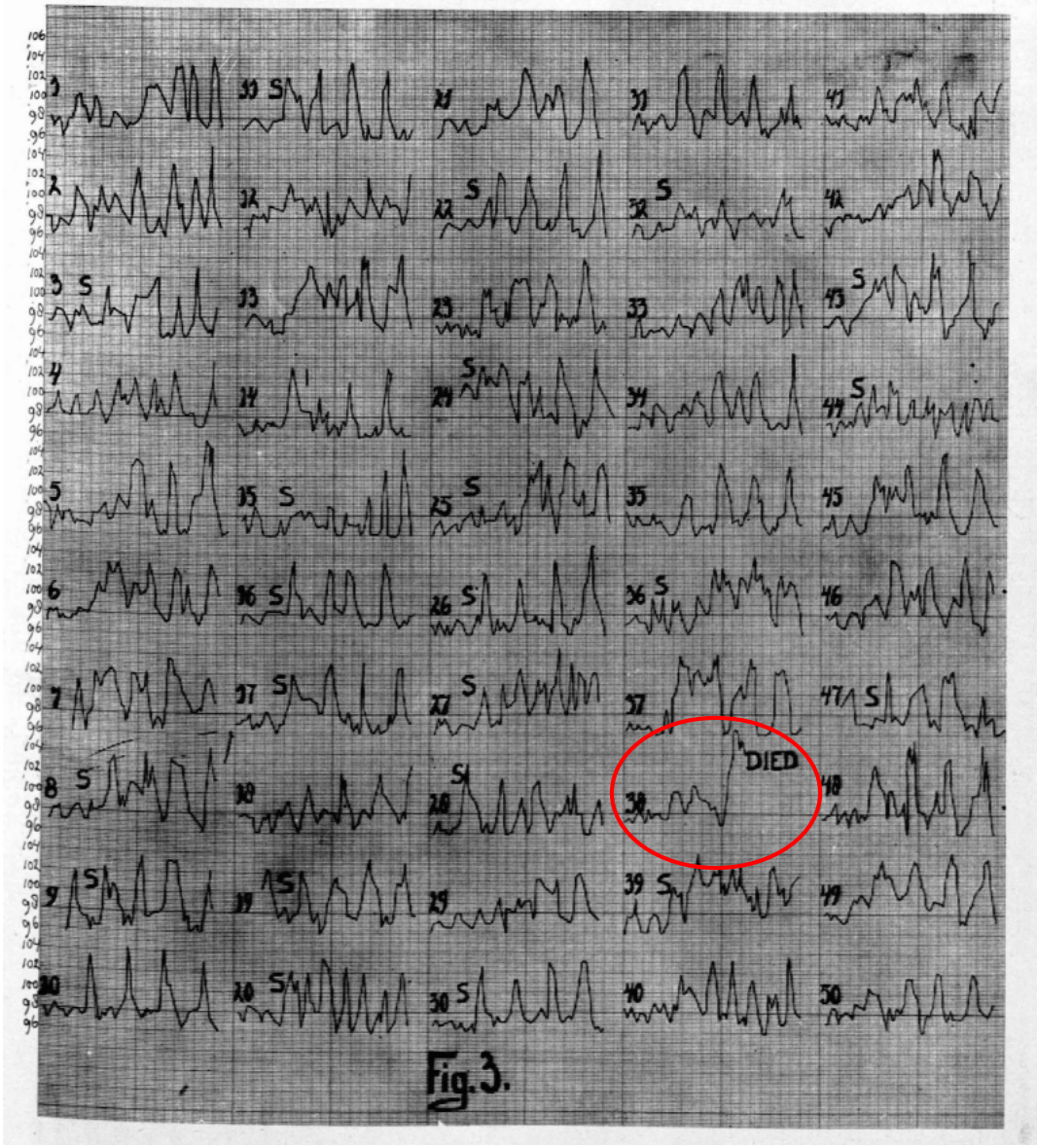


Fig. 3.

1931

TRANSACTIONS

OF THE

ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE.

VOL. XXIV. No. 5.

Proceedings of an **Ordinary Meeting** of the Society, held at 11, Chandos Street, Cavendish Square, London, on Thursday, 15th January, 1931.

Dr. G. CARMICHAEL LOW, F.R.C.P. (*President*), in the Chair.

PAPER.

SOME GENERAL RESULTS OF A STUDY OF INDUCED MALARIA IN ENGLAND.

BY

Lieut.-Colonel S. P. JAMES, M.D., I.M.S. (Retired).

Adviser on Tropical Diseases to the Ministry of Health.

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OBSERVATIONS ON MALARIA MADE DURING TREATMENT OF GENERAL PARALYSIS.

BY

WARRINGTON YORKE, M.D., AND J. W. S. MACFIE, D.Sc., M.B., Ch.B.

Blood inoculation:

4-18 months follow up following quinine treatment

1/61 recrudescence

(XXX grains/day 2-4 days)

Mosquito inoculation

2-6 months follow up following quinine treatment

4/31 relapsed; Intervals (days)

1. 24, 19
2. 24,31
3. 11,18, 33, 40
4. 25, 42

1924

FURTHER OBSERVATIONS ON MALARIA MADE DURING TREATMENT OF GENERAL PARALYSIS.

BY

PROFESSOR WARRINGTON YORKE, M.D.

Blood inoculation

18-24 months follow up following quinine treatment

2/100 recrudescence

(XXX grains/day 2-4 days)

Mosquito inoculation

21/34 relapsed! : median 168 (range)20-331 days

Long latency *P. vivax*

1925

MALARIA IN THE NETHERLANDS

by

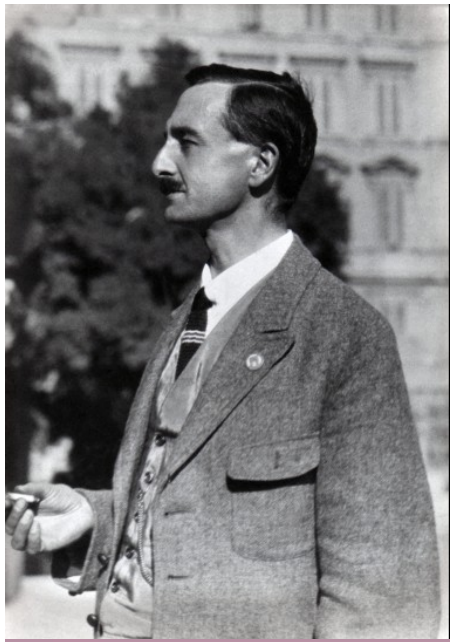
N. H. SWELLENGREBEL

and

A. DE BUCK

AMSTERDAM

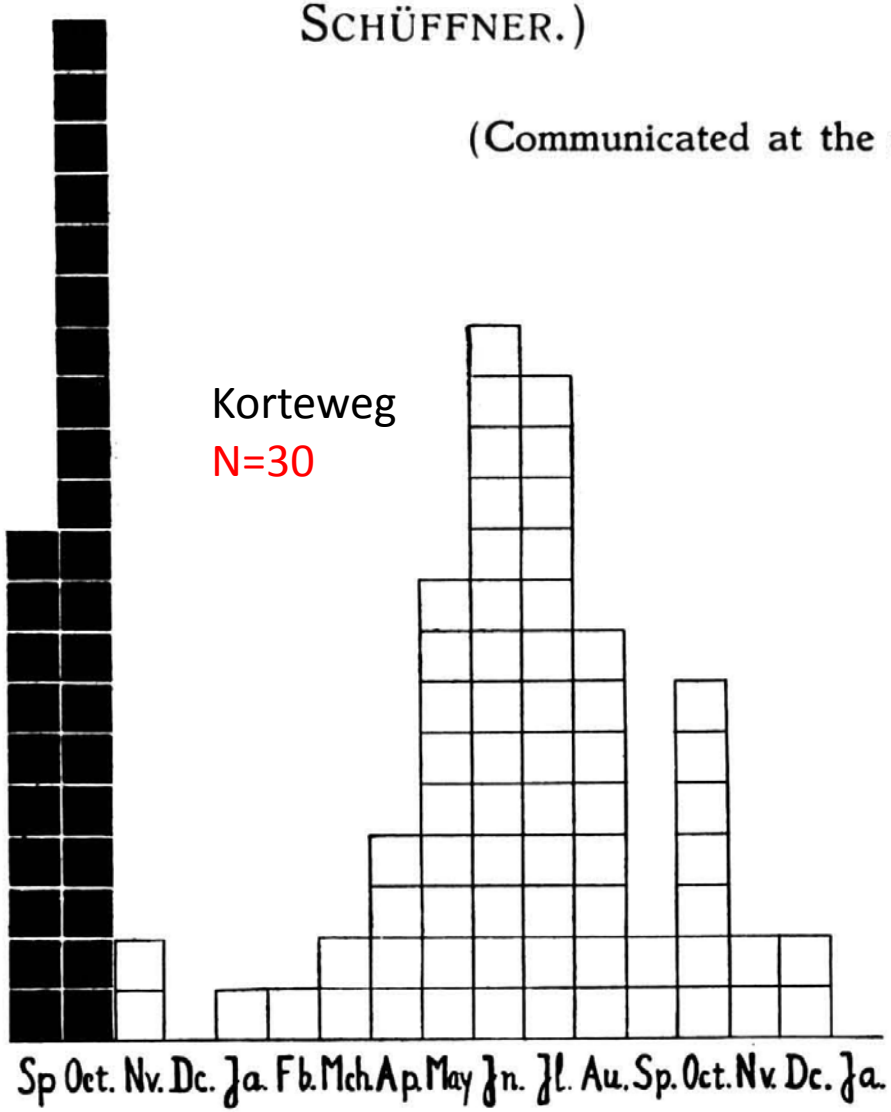
SCHELTEMA & HOLKEMA Ltd.



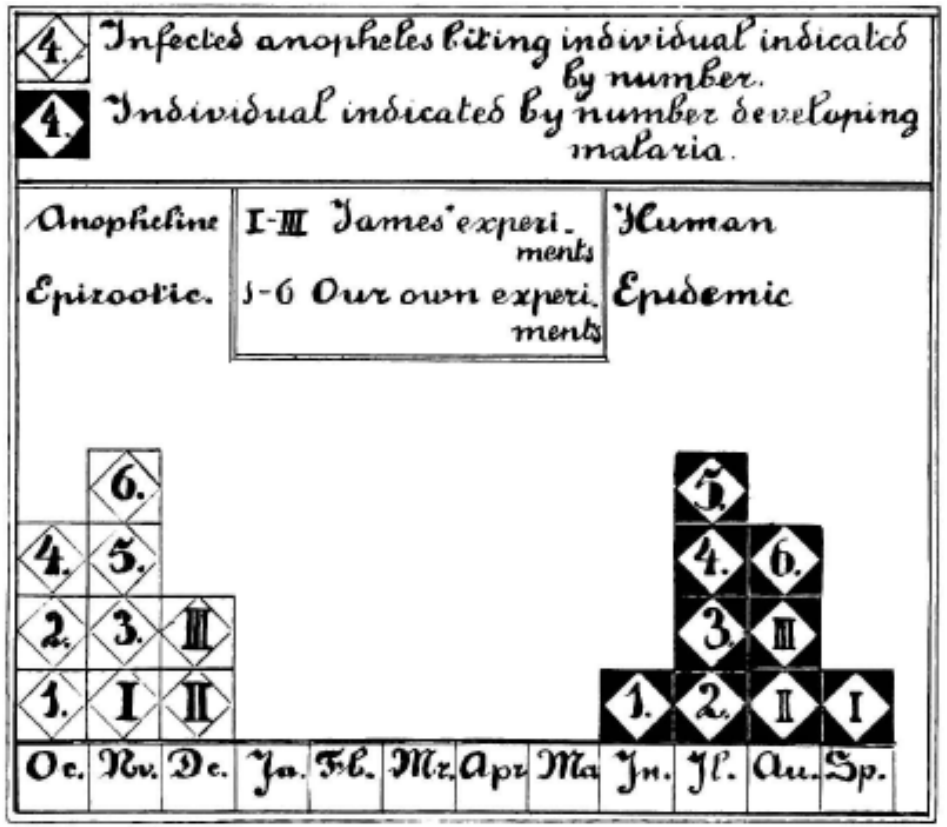
THE MOSES OF MALARIA

Medicine. — *Report on a small experimental epidemic of benign tertian malaria started in September 1931 and followed up till January 1933.* By N. H. SWELLENGREBEL. (Communicated by Prof. W. A. SCHÜFFNER.)

(Communicated at the meeting of February 25, 1933.)



Korteweg
N=30



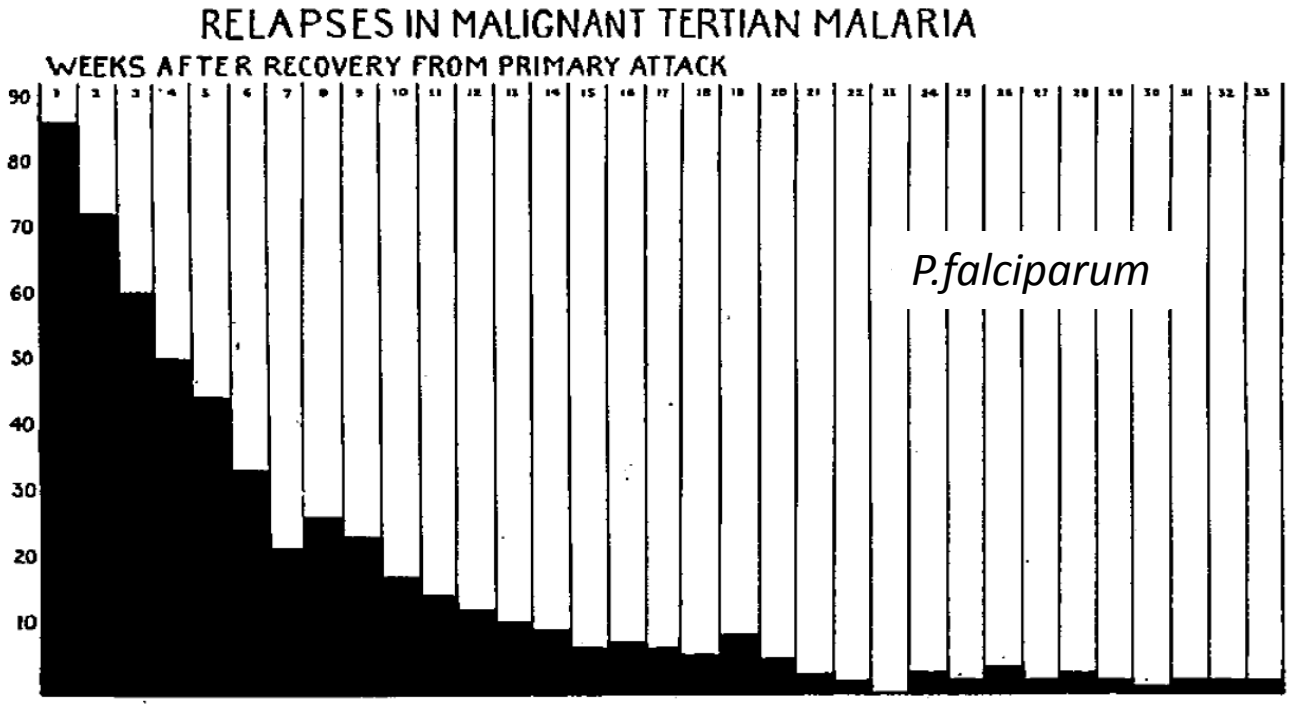


FIG. 1. The two charts display the recrudescence and relapse patterns of *P. falciparum* on the one hand and those of the long term relapse Madagascar strain of *P. vivax* on the other. (From James, S. P., Nicol, W. D. and Shute, P. G., 1936. *Proc. Roy. Soc. Med.*, 29, 879.)

[*May* 5, 1932.]

A Study of Induced Malignant Tertian Malaria.

By S. P. JAMES, W. D. NICOL and P. G. SHUTE.

Arch. Inst. Pasteur Madagascar 1978 (1979), 47, 173-183.

THE MADAGASCAR STRAIN OF PLASMODIUM VIVAX

by

the late P.-G. SHUTE, P.-C.-C. GARNHAM and Mary MARYON

In a series of cases, James, Nicol and Shute (1936) recorded the time of the relapse and showed that the relapses occured between 189 and 273 days after the primary attack.

1925-1933

Total number of patients infected 1,739

Total number of mosquitoes infected 24,361

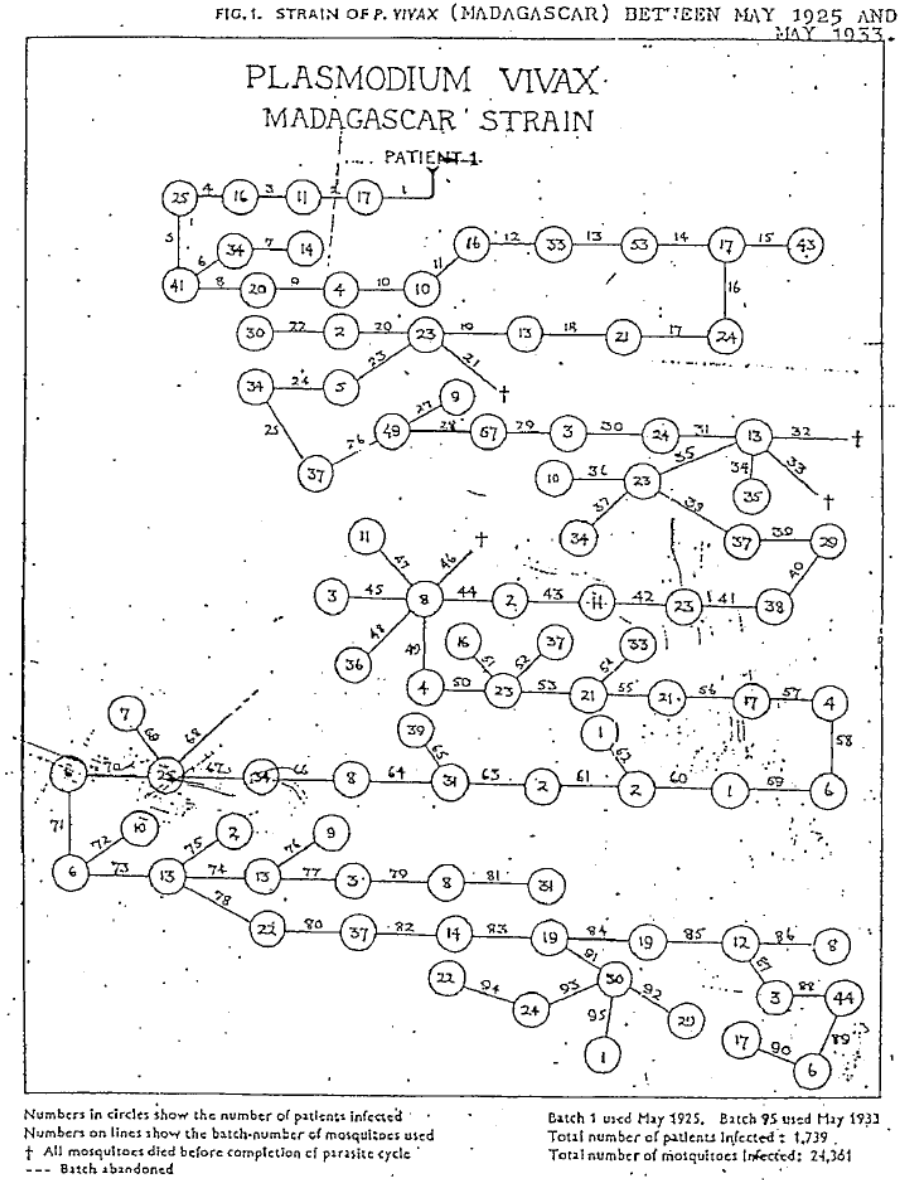


FIG. 1. STRAIN OF P. VIVAX (MADAGASCAR) BETWEEN MAY 1925 AND MAY 1933.

Numbers in circles show the number of patients infected
Numbers on lines show the batch-number of mosquitoes used
† All mosquitoes died before completion of parasite cycle
--- Batch abandoned

Batch 1 used May 1925. Batch 95 used May 1933
Total number of patients infected: 1,739
Total number of mosquitoes infected: 24,361

Whorton et al 1947 JID; 80: 237-249

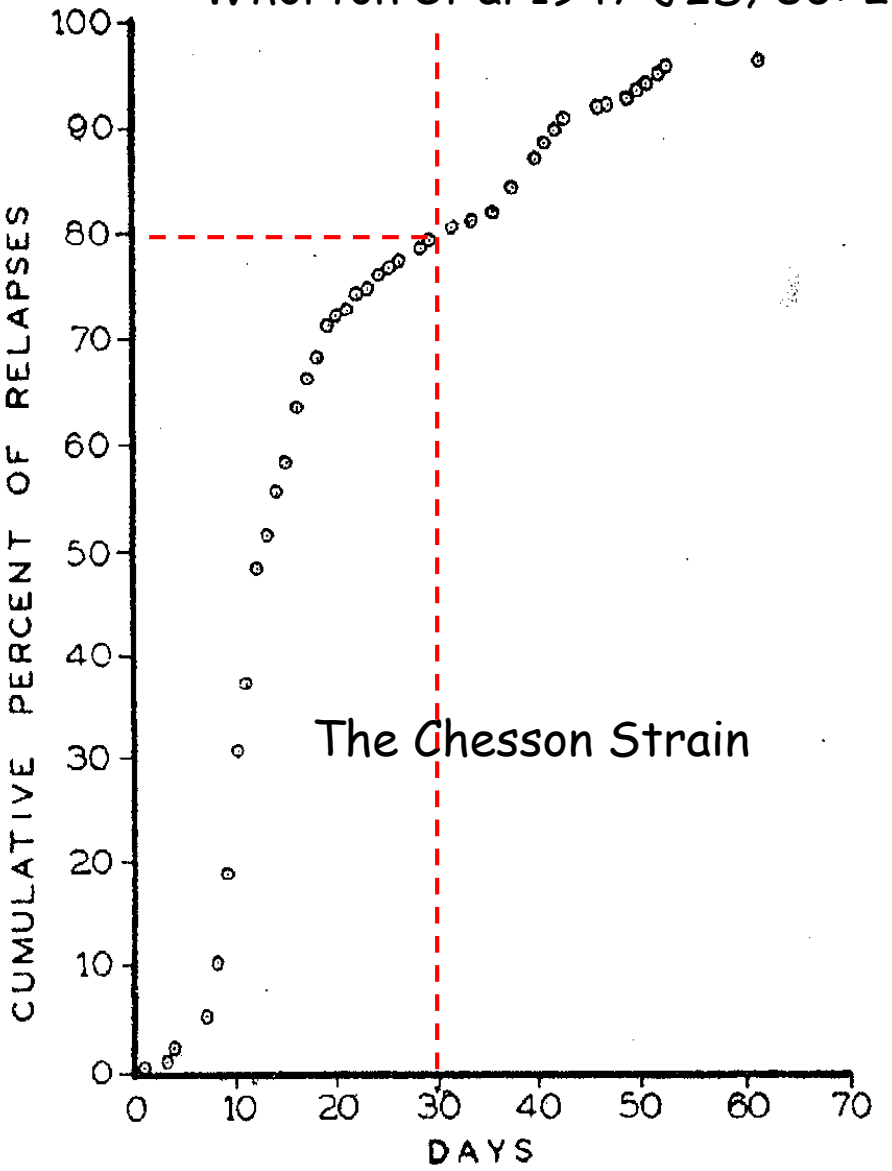


FIG. 4.—Duration of latent period after 151 malarial attacks† in patients who subsequently relapsed.

Whorton et al 1947 JID; 80: 237-249

The Chesson Strain

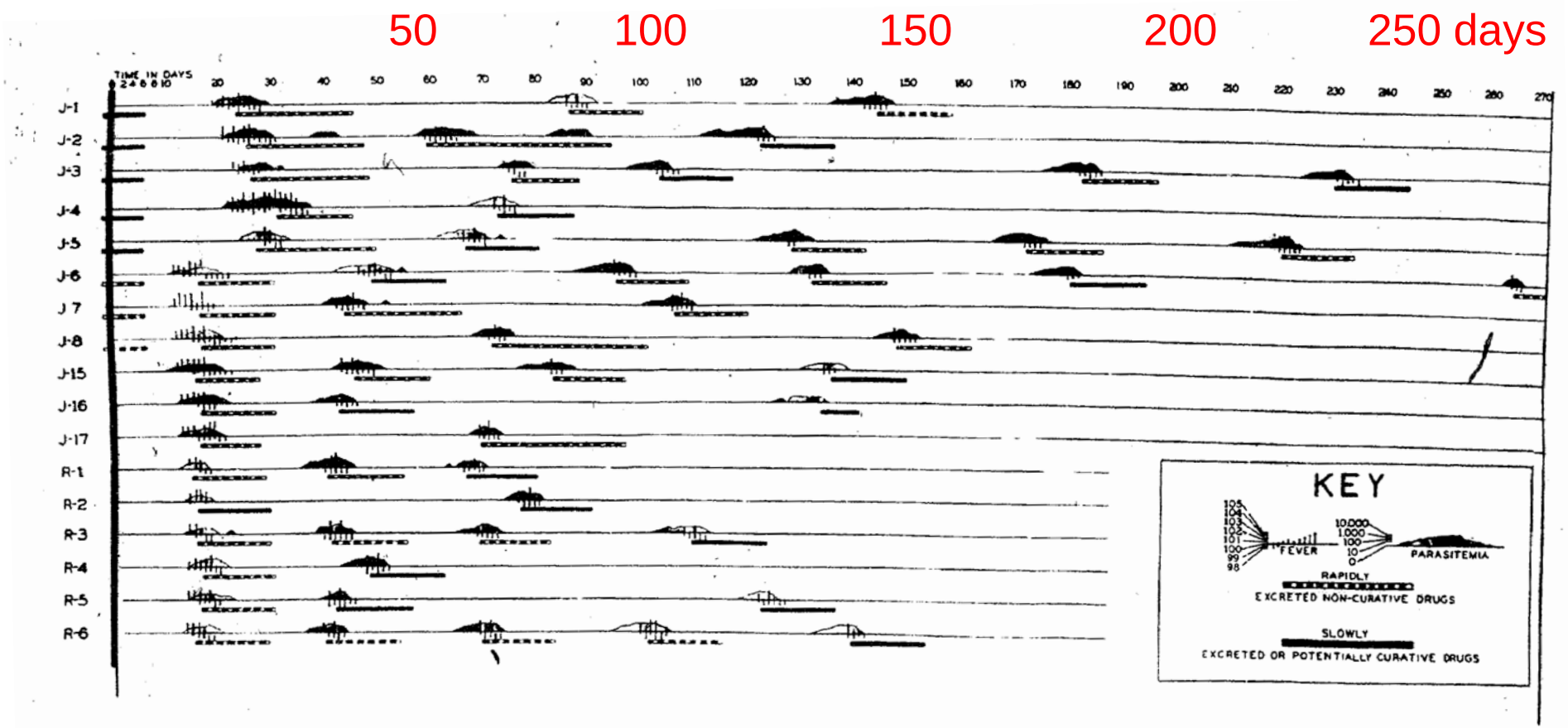


FIG. 5.—Malarial attacks and latent periods of a selected group of sporozoite-induced (Chesson) infections. Note absence of delayed primary attacks after prophylactic therapy and absence of long latent intervals after treatment of primary attacks. This relapse pattern is in sharp contrast to that of the St. Elizabeth strain of *vivax* malaria. (Time indicates days after inoculation.)

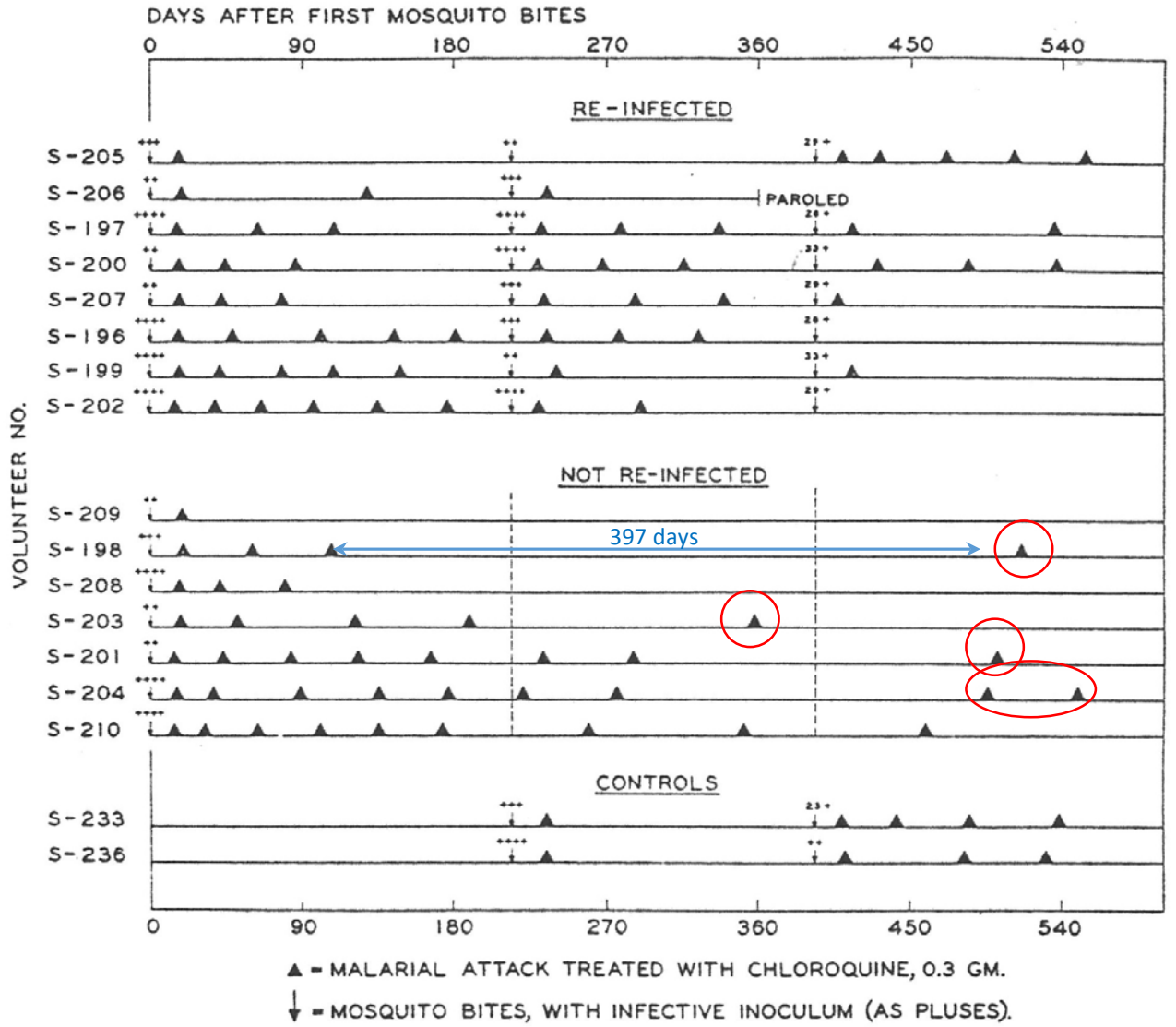
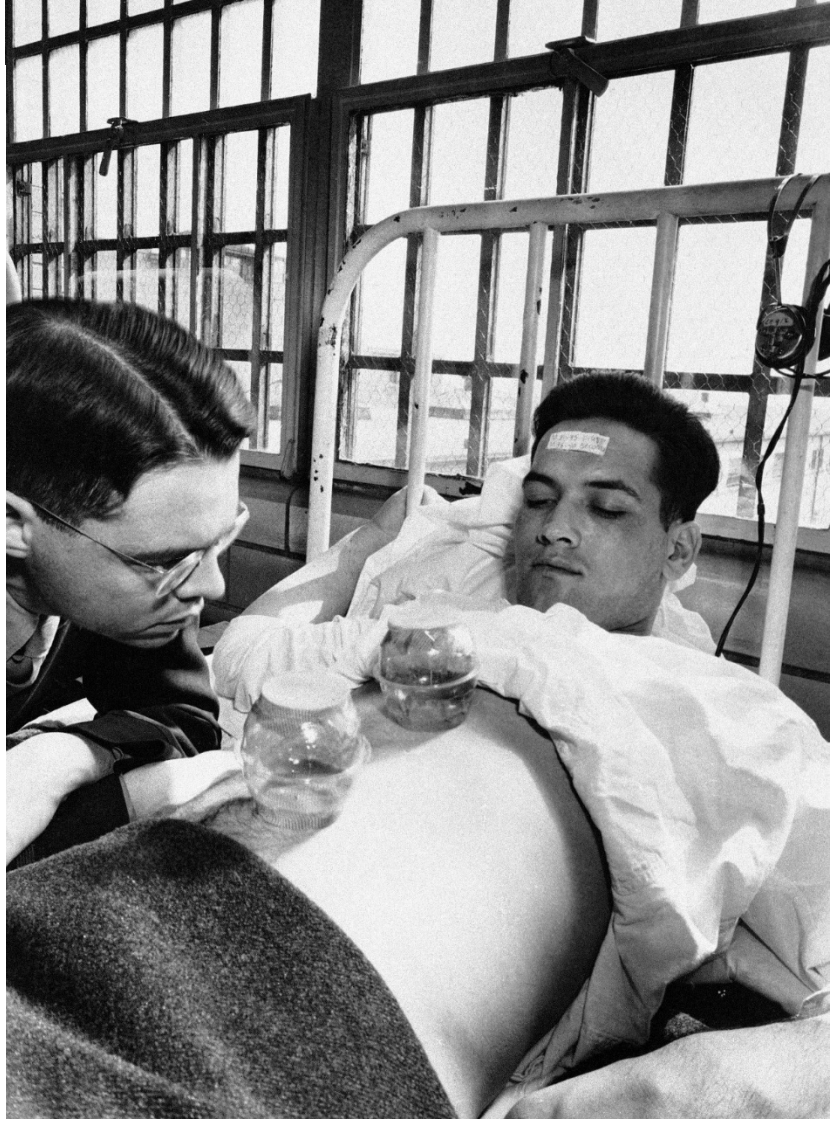


FIG. 2. Pattern of attacks of Chesson strain *vivax* malaria in subjects bitten by one infected mosquito each. (Presentation of attacks is diagrammatic). Selected individuals were reinfected as indicated.



Coatney GR et al J Nat Mal Soc 1948

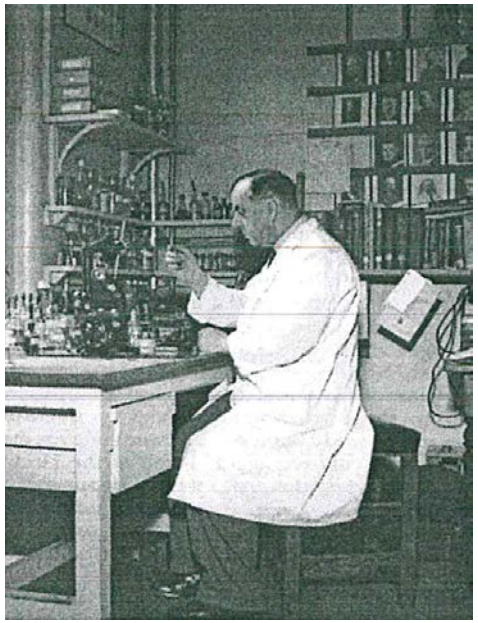
A CONTRIBUTION TO THE PROBLEM OF STRAINS OF HUMAN PLASMODIUM

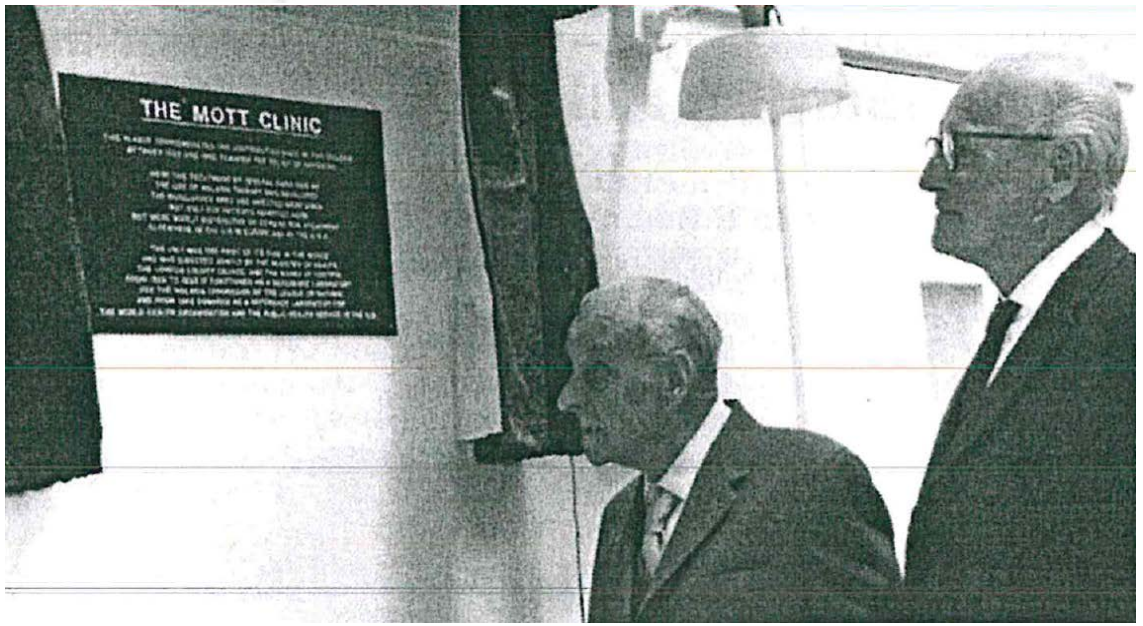
by

P. G. SHUTE and M. MARYON
Medical Research Council Malaria Reference Laboratory, Horton Hospital, Epsom, Surrey.

Estratto dalla «*Rivista di Malariologia*» - Vol. XXXIII, nn. 1-3, 1954

P. falciparum from Europe required ten times more quinine for cure than *P. falciparum* from India





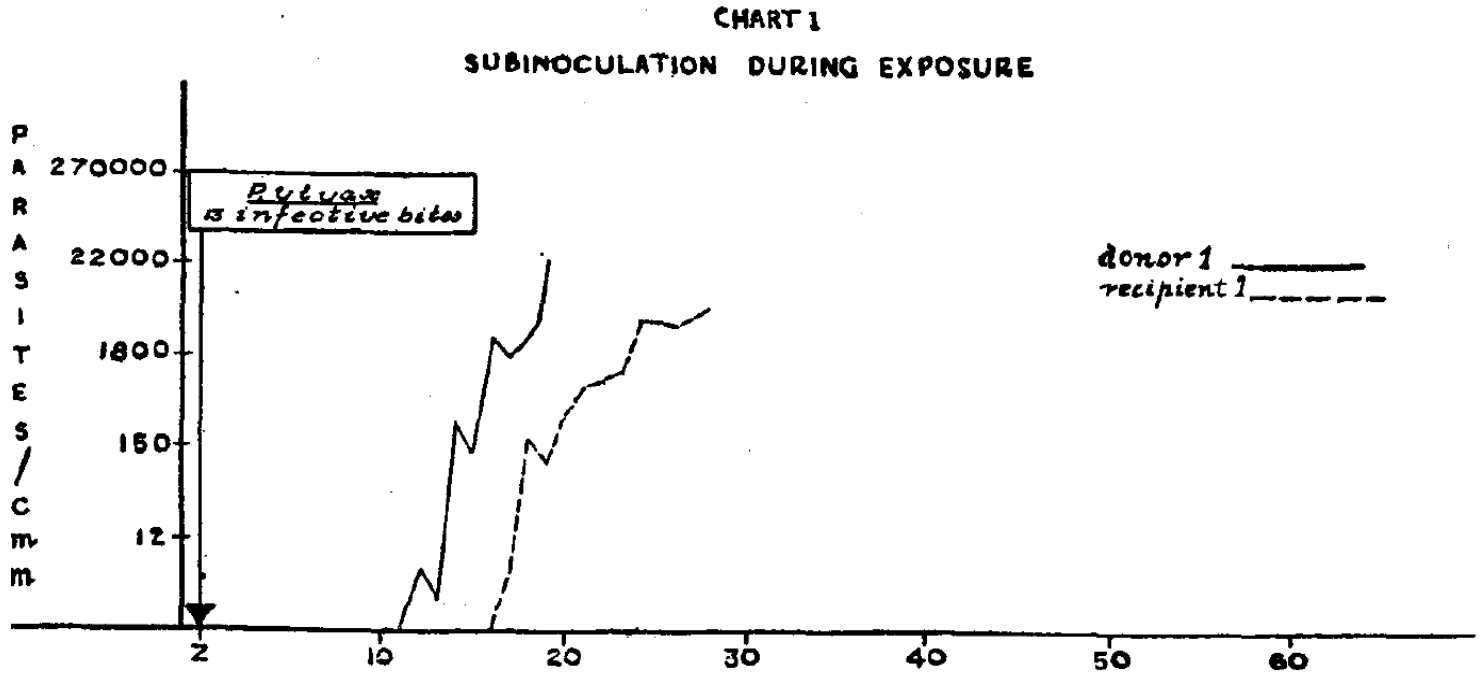
TRANSACTIONS OF THE ROYAL SOCIETY OF
TROPICAL MEDICINE AND HYGIENE.
Vol. 40. No. 5. May, 1947.

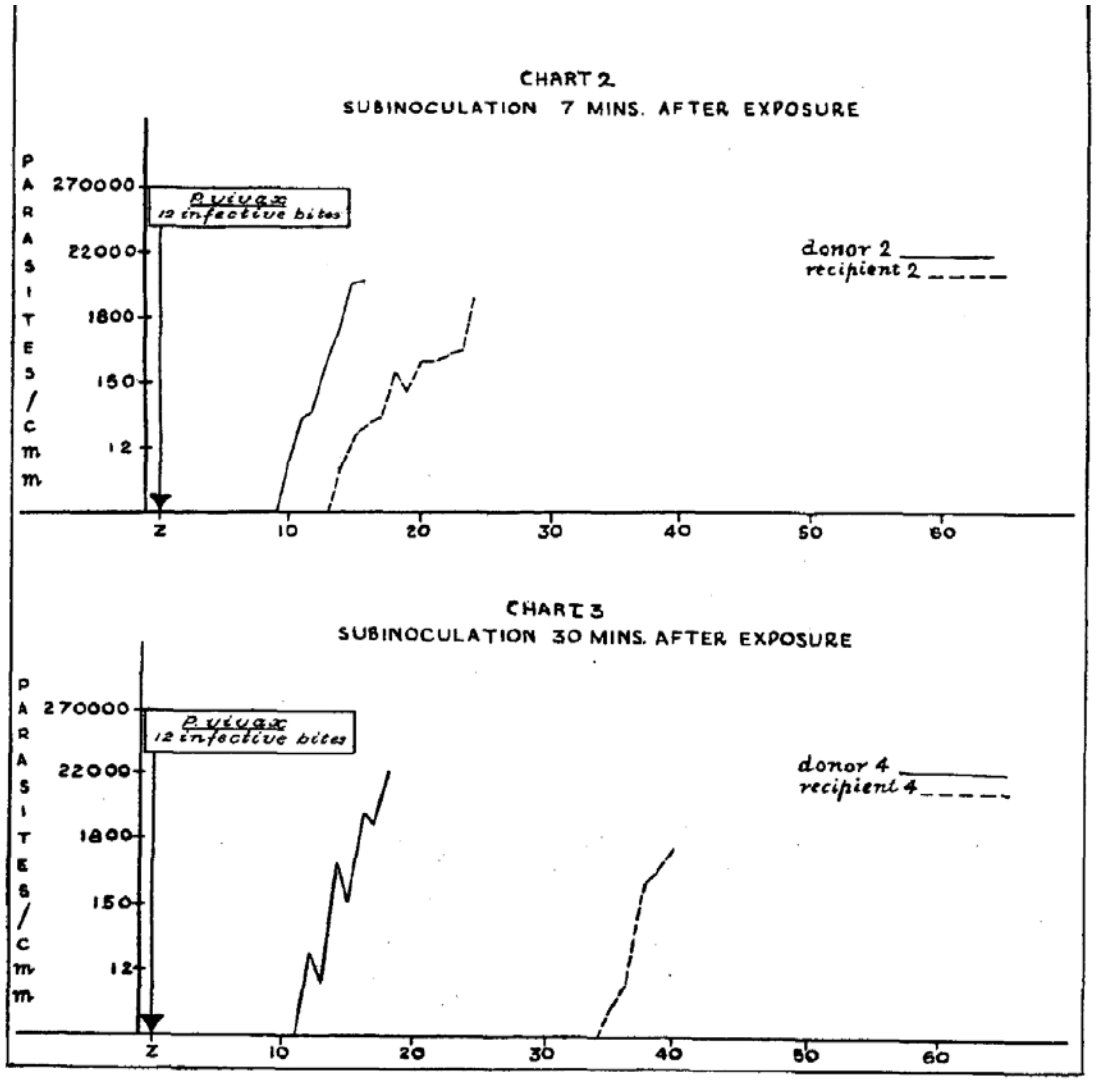
SIDELIGHTS ON MALARIA IN MAN OBTAINED BY SUBINOCULATION EXPERIMENTS.

BY

Brigadier N. HAMILTON FAIRLEY, C.B.E., F.R.S., *et al.**

(*From the Land Headquarters. Medical Research Unit (A.I.F.), Cairns, Australia*).





SIDELIGHTS ON MALARIA IN MAN OBTAINED BY SUBINOCULATION EXPERIMENTS.

BY

Brigadier N. HAMILTON FAIRLEY, C.B.E., F.R.S., *et al.**

(*From the Land Headquarters. Medical Research Unit (A.I.F.), Cairns, Australia*).

(*a*) The initial invasion stage when viable sporozoites may be demonstrated in the circulating blood for short periods ($\frac{1}{2}$ to 1 hour) after inoculation of sporozoites by anopheline mosquitoes into the tissues or directly into the blood vessels.

(*b*) The negative blood phase or prepatent period when pre-erythrocytic or early e.e. forms are presumably undergoing schizogony in reticulo-endothelial cells; this lasts approximately 6 days in *P. falciparum* and 8 days in *P. vivax* during which time massive subinoculations of blood from heavily infected volunteers uniformly fail to induce malaria in recipients.

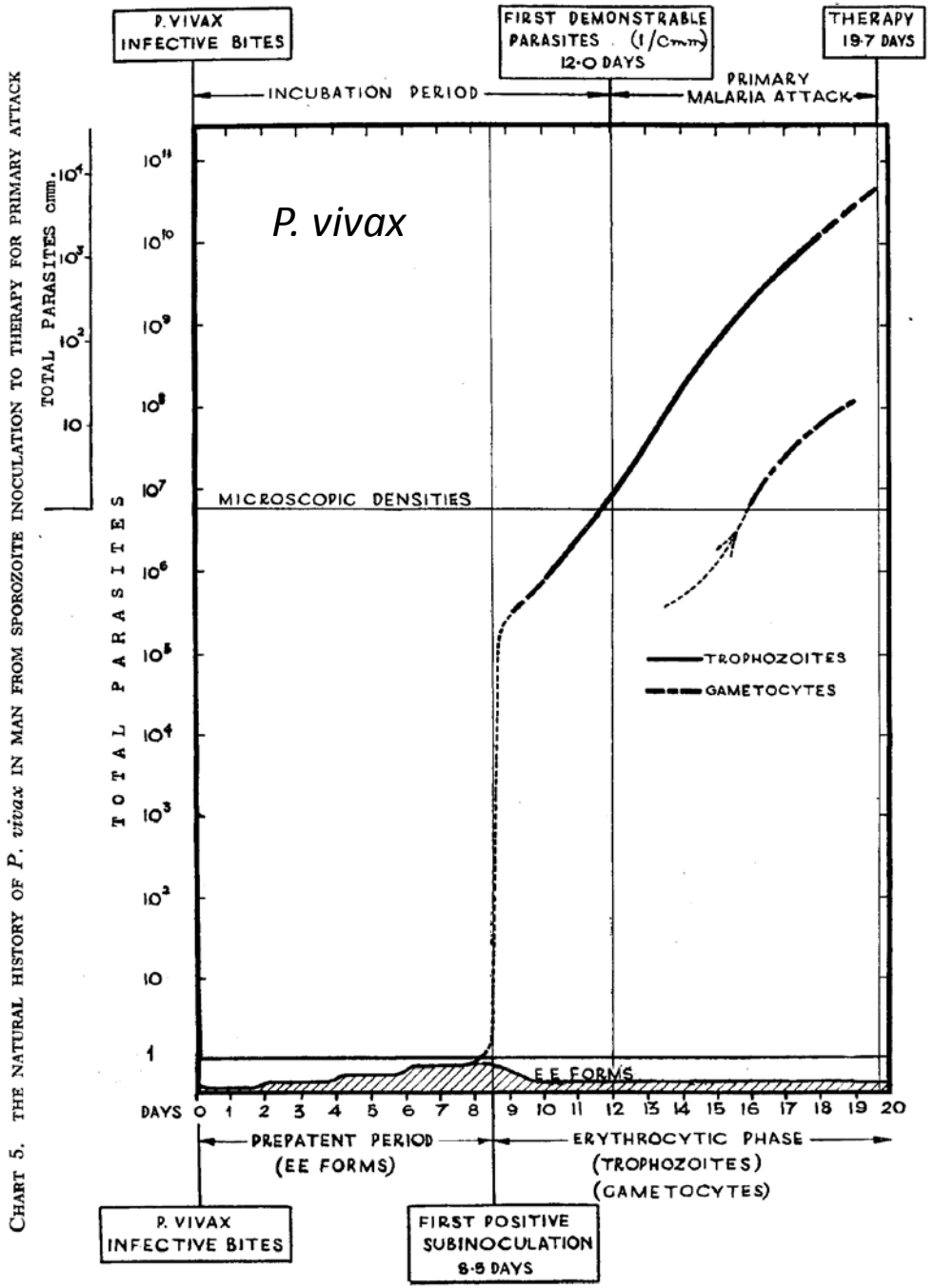


CHART 5. THE NATURAL HISTORY OF *P. vivax* IN MAN FROM SPOROZOITE INOCULATION TO THERAPY FOR PRIMARY ATTACK

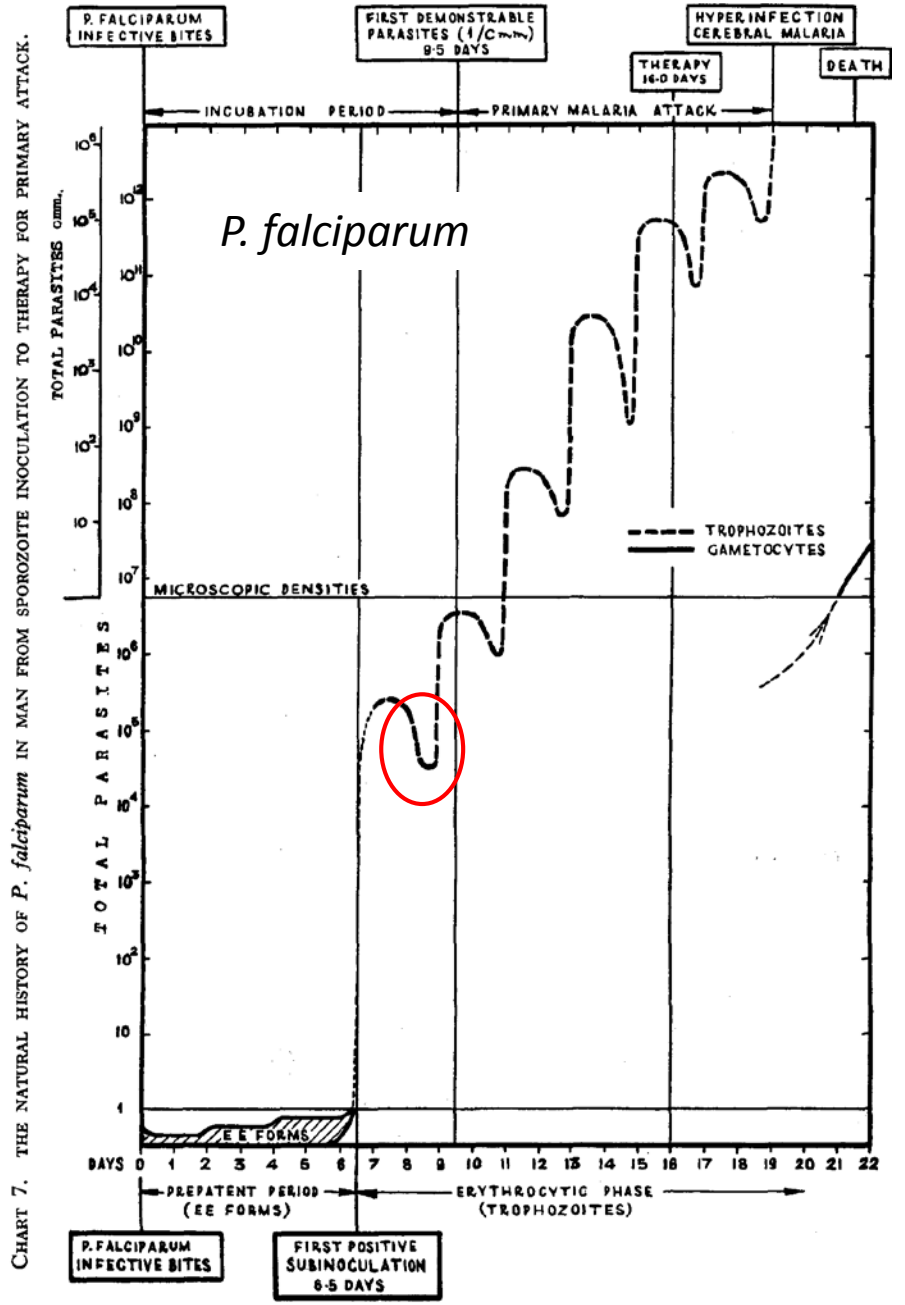
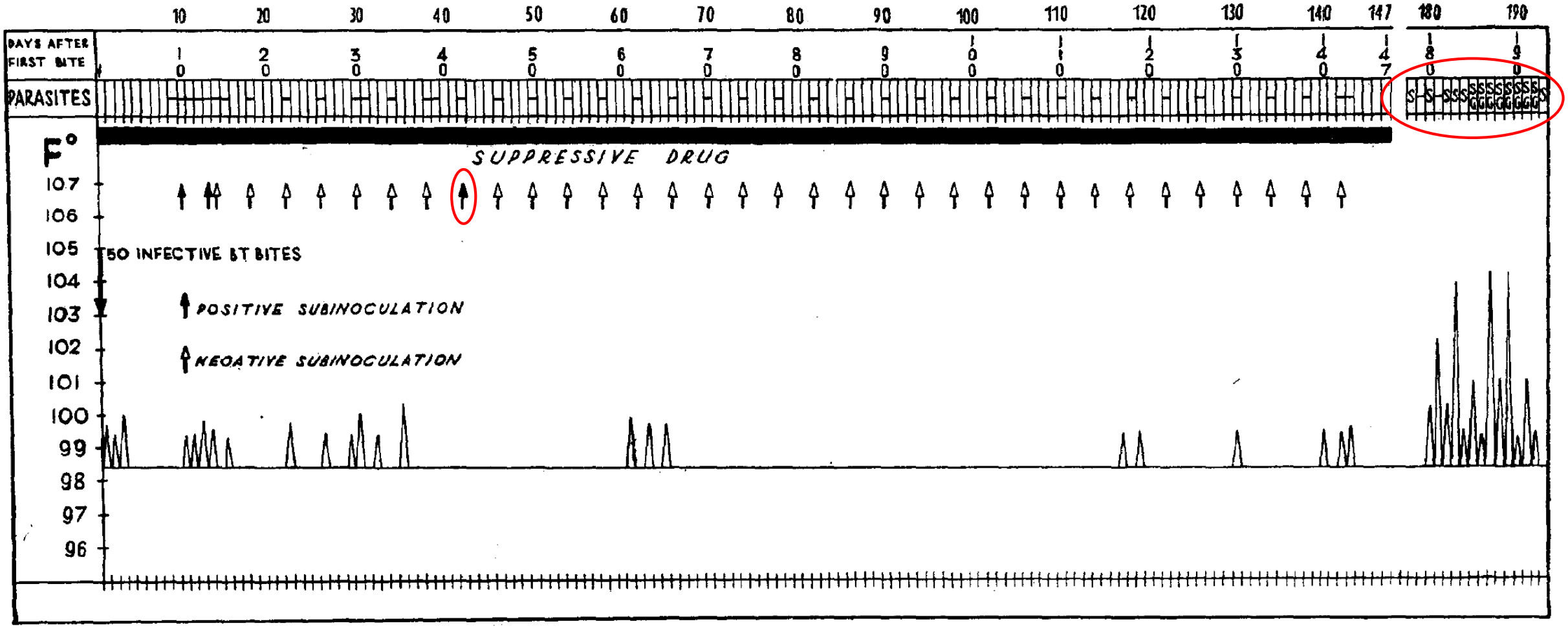
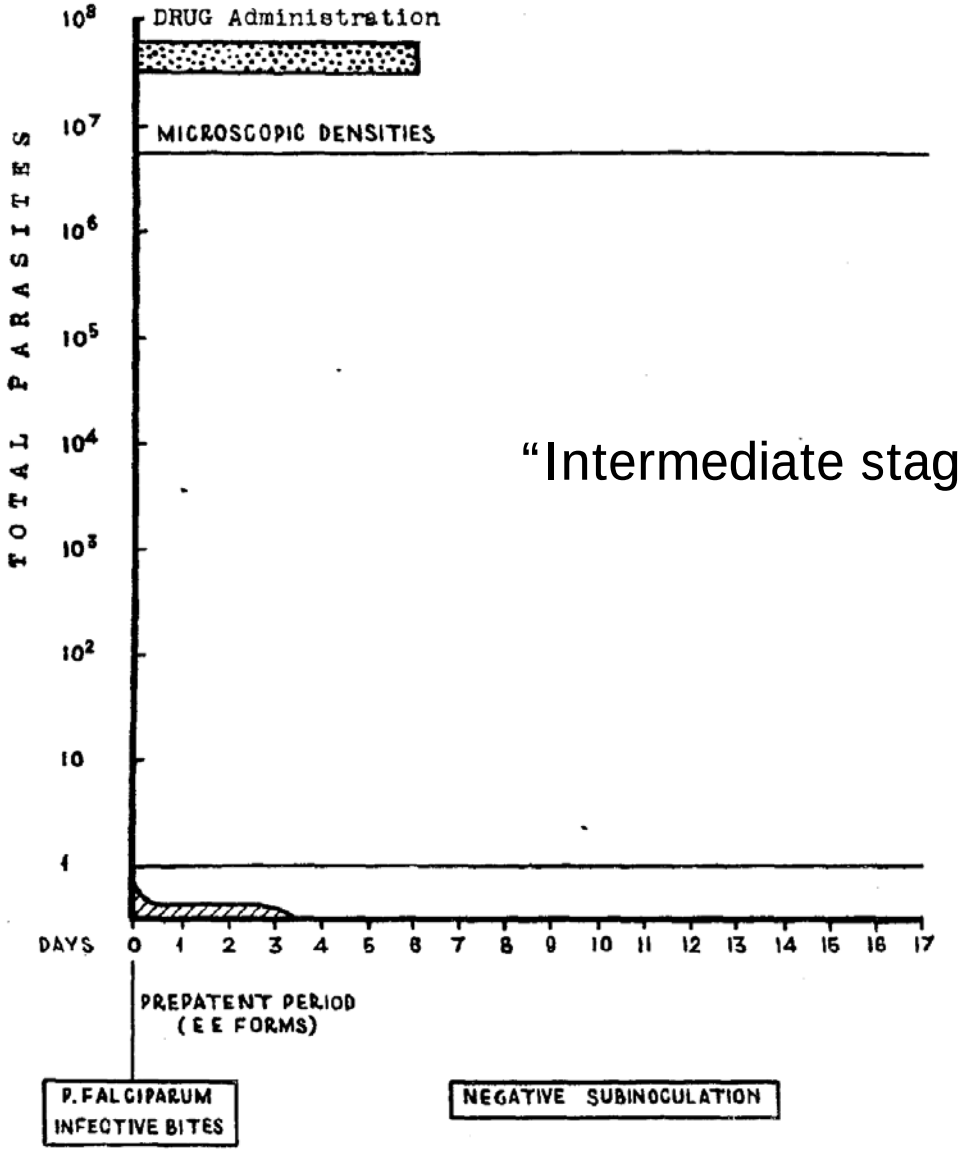


CHART 7. THE NATURAL HISTORY OF *P. falciparum* IN MAN FROM SPOROZOITE INOCULATION TO THERAPY FOR PRIMARY ATTACK.

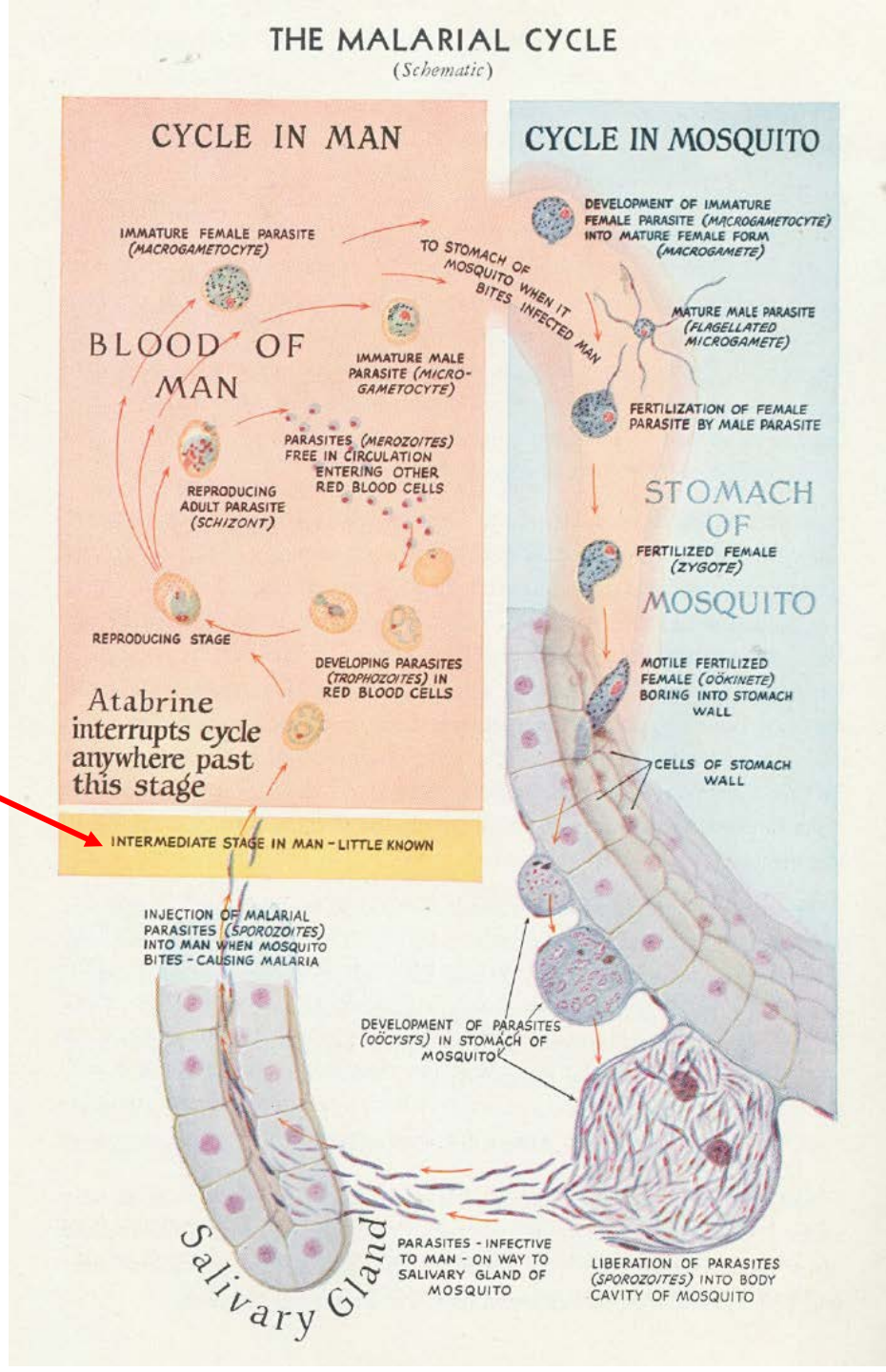

DAYS AFTER FIRST BITE
PARASITES
F°
SUPPRESSIVE DRUG
50 INFECTIVE BT BITES
POSITIVE SUBINOCULATION
NEGATIVE SUBINOCULATION

ACTION OF CAUSAL PROPHYLACTIC DRUGS IN SPOROZOITE-INDUCED MALARIA
(*P. falciparum*) IN MAN. (PALUDRINE. PLASMOQUINE.)



Diagrammatic representation of effects of causal prophylactics on pre-erythrocytic forms. Note that these drugs rapidly destroy the pre-erythrocytic or early e.e. forms. Blood smears fail to show parasites and subinoculations from the 7th day onwards prove that asexual parasites never appear in the blood.

"Intermediate stage in man-little known"



PENICILLIN IN THE TREATMENT OF NEUROSYPHILIS*

BY

W. D. NICOL and M. WHELEN

From the Mott Clinic, Horton Hospital, Epsom, Surrey

1945-1947

Therapy	Males	Females	Total
Penicillin only	19	12	31
Penicillin plus Malaria ..	109	43	152
Malaria only	207	73	280

Conclusion

It is our view that, in spite of the divergent opinions quoted above, it would be unwise to eliminate malaria altogether, but at the same time we feel that penicillin has usurped the role played by malaria. Penicillin is now the main line of treatment and malaria the supplementary, at any rate in the more severe forms of parenchymatous neurosyphilis.


INDONESIA
LAOS
MALAYSIA
PHILIPPINES
Mahidol University
Faculty of Tropical Medicine

INFECTION-RATES OF MALARIAL PARASITES IN RED BLOOD-CELLS WITH NORMAL AND DEFICIENT GLUCOSE-6-PHOSPHATE-DEHYDROGENASE

MONGKOL KRUATRACHUE
M.B. Bangkok, D.T.M. & H.

KOSSOM KLONGKUMNUANHARA
B.SC. Bangkok

CHAMLONG HARINASUTA
M.D. Bangkok, PH.D. Lpool, D.T.M. & H.

Faculty of Tropical Medicine, University of Medical Sciences, Bangkok, Thailand

PATIENTS AND METHODS

6 adults (3 male and 3 female) deficient in G.-6-P.D. as measured by the brilliant-cresyl-blue dye test were studied. All had natural *P. falciparum* infections except in case 2 in which infection was induced therapeutically for cerebral syphilis by intravenous injection of approximately 0·5 million trophozoites. Thin films were made from blood.

CHANGES IN BLOOD VOLUME IN *FALCIPARUM* MALARIA†

TAN CHONGSUPHAJAISIDDHI, RATANAPORN KASEMSUTH, SIRIVAN TEJAVANIJA and TRANAKCHIT HARINASUTA

Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand.

MATERIALS AND METHODS

The study was made on 5 Thai male patients who had been transferred from a mental hospital to the Hospital for Tropical Diseases, Faculty of Tropical Medicine, Bangkok. *Plasmodium falciparum* trophozoites 5-10 million, from a donor of the same blood group was given intravenously to each of the subjects, except case 2 who was infected by mosquito.

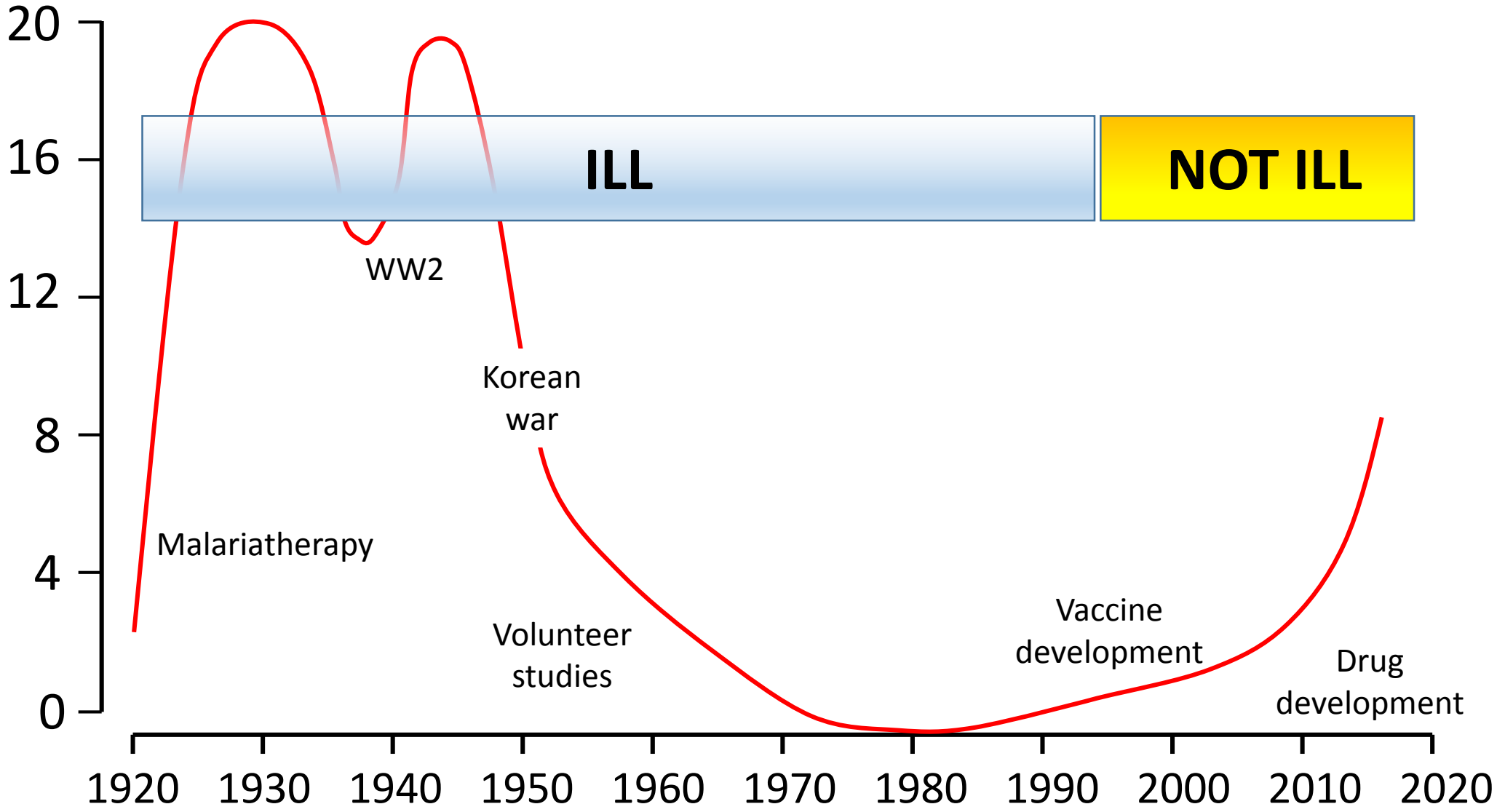
Malariatherapy

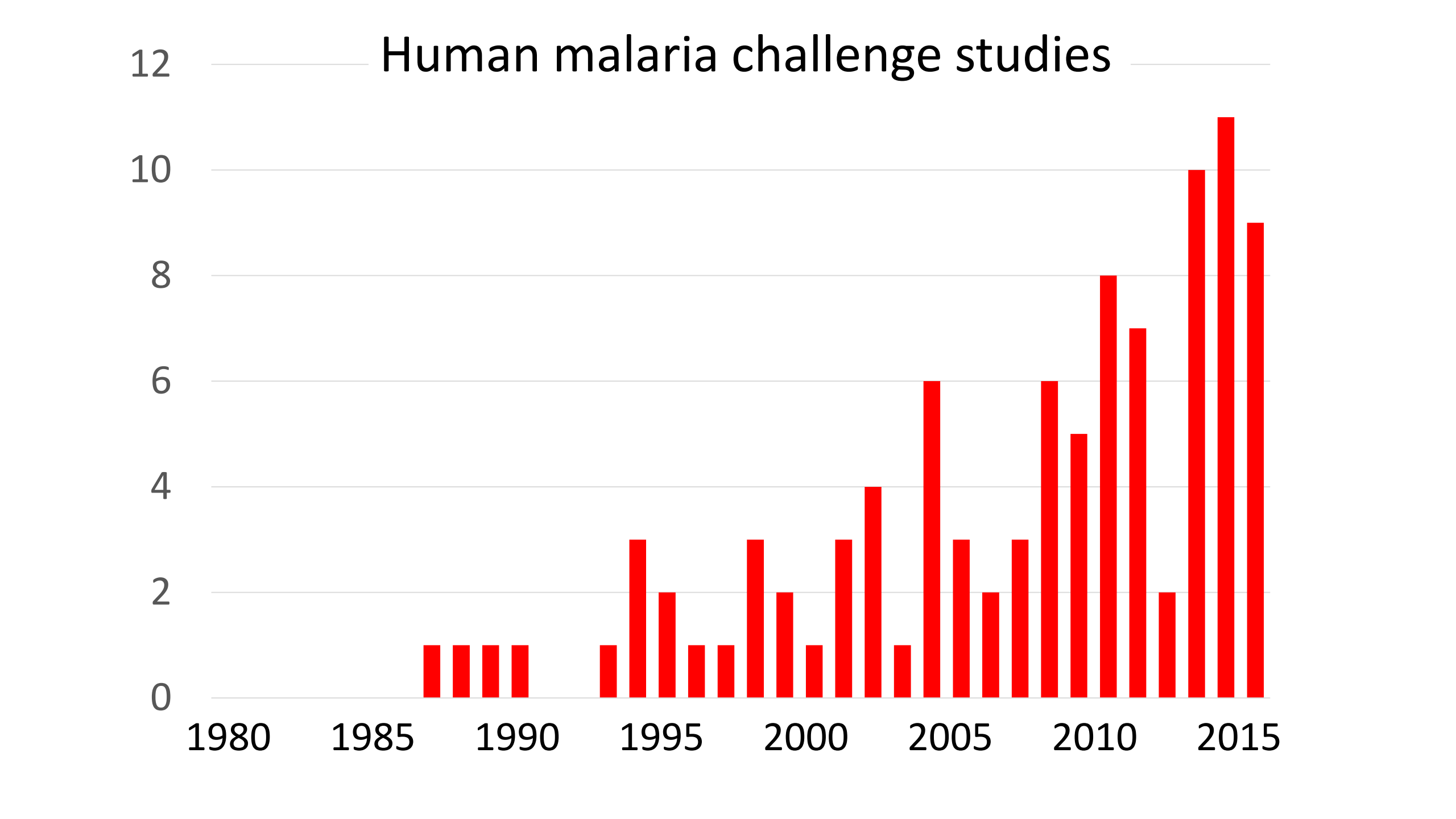
1. A major therapeutic advance in a common, previously incurable and devastating disease.
2. Tens of thousands of patients treated –over half benefited.
3. Revealed the complex biology of malaria in quantitative detail.
4. Facilitated safe human challenge studies in volunteers

Human volunteer studies (pre 1980s)

5. First detailed PK-PD and dose finding studies
   (quinine, mepacrine, chloroquine, primaquine, proguanil, pyrimethamine)
6. Detailed safety assessment of primaquine in G6PD A- variant

Human malaria challenge studies




Human malaria challenge studies
12
10
8
6
4
2
0
1980
1985
1990
1995
2000
2005
2010
2015

Walk et al. Malar J (2016) 15:398
DOI 10.1186/s12936-016-1434-z

Malaria Journal

RESEARCH Open Access

Diagnosis and treatment based on quantitative PCR after controlled human malaria infection

Jona Walk[1†], Remko Schats[2†], Marijke C. C. Langenberg[2], Isaie J. Reuling[1], Karina Teelen[1], Meta Roestenberg[1], Cornelus C. Hermsen[1], Leo G. Visser[2] and Robert W. Sauerwein[1*]

Vaccine 33 (2015) 5316–5320

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Profiling the host response to malaria vaccination and malaria challenge

Susanna Dunachie[a,b,c,*], Adrian V.S. Hill[a], Helen A. Fletcher[d,a]

[a] The Jenner Institute, Nuffield Department of Medicine, University of Oxford, Churchill Hospital, Oxford OX3 7LJ, UK
[b] Mahidol-Oxford Tropical Medicine Research Unit, 3rd Floor, 60th Anniversary Chalermprakiat Building, 420/6 Ratchawithi Road, Bangkok 10400, Thailand
[c] Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine Research Building, University of Oxford, Old Road Campus, Roosevelt Drive, Oxford OX3 7FZ, UK
[d] London School of Hygiene & Tropical Medicine, London, W1CE 7HT, UK

Review

Cell PRESS

Breaking barriers: a leap ahead in Plasmodium biology

Experimentally induced blood stage malaria infection as a tool for clinical research

Christian R. Engwerda[1,2], Gabriela Minigo[3], Fiona H. Amante[1], and James S. McCarthy[1,2]

Hodgson et al. Malaria Journal (2015) 14:182
DOI 10.1186/s12936-015-0671-x

MALARIA JOURNAL

CASE STUDY Open Access

Lessons learnt from the first controlled human malaria infection study conducted in Nairobi, Kenya

Susanne H Hodgson[1*], Elizabeth Juma[2,3], Amina Salim[4], Charles Magiri[2], Daniel Njenga[2], Sassy Molyneux[4], Patricia Njuguna[4], Ken Awuondo[4], Brett Lowe[4], Peter F Billingsley[5], Andrew O Cole[2,3], Caroline Ogwang[4], Faith Osier[4], Roma Chilengi[6], Stephen L Hoffman[5], Simon J Draper[1], Bernhards Ogutu[2,3] and Kevin Marsh[4]

Human malaria challenge studies

Experimental human challenge infections can accelerate clinical malaria vaccine development

Robert W. Sauerwein, Meta Roestenberg and Vasee S. Moorthy

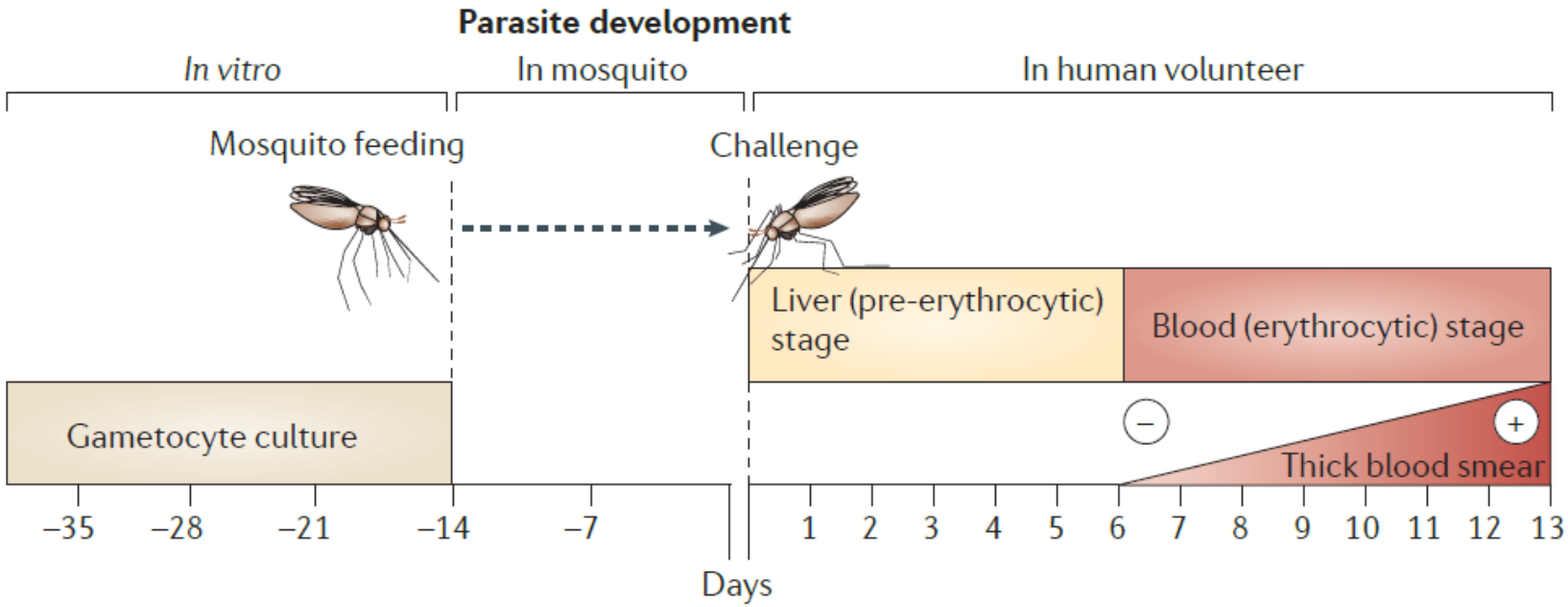


Figure 2 | **Timeline of *Plasmodium falciparum* sporozoite challenge infection in humans.** Gametocytes are derived from *in vitro* parasite culture in donor blood and are fed to laboratory-reared *Anopheles stephensi* mosquitoes. After 14–21 days, five infectious mosquitoes are allowed to feed on malaria-naive human volunteers for 5–10 minutes. Subsequent development of liver-stage parasites is subclinical and takes approximately 6 days. Parasites can be detected in the blood of unprotected volunteers by microscopy (using a thick blood smear) on average 11 days (range 7–15 days) after challenge.

Hodgson *et al. Malaria Journal* (2015) 14:182
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MALARIA JOURNAL

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Lessons learnt from the first controlled human malaria infection study conducted in Nairobi, Kenya

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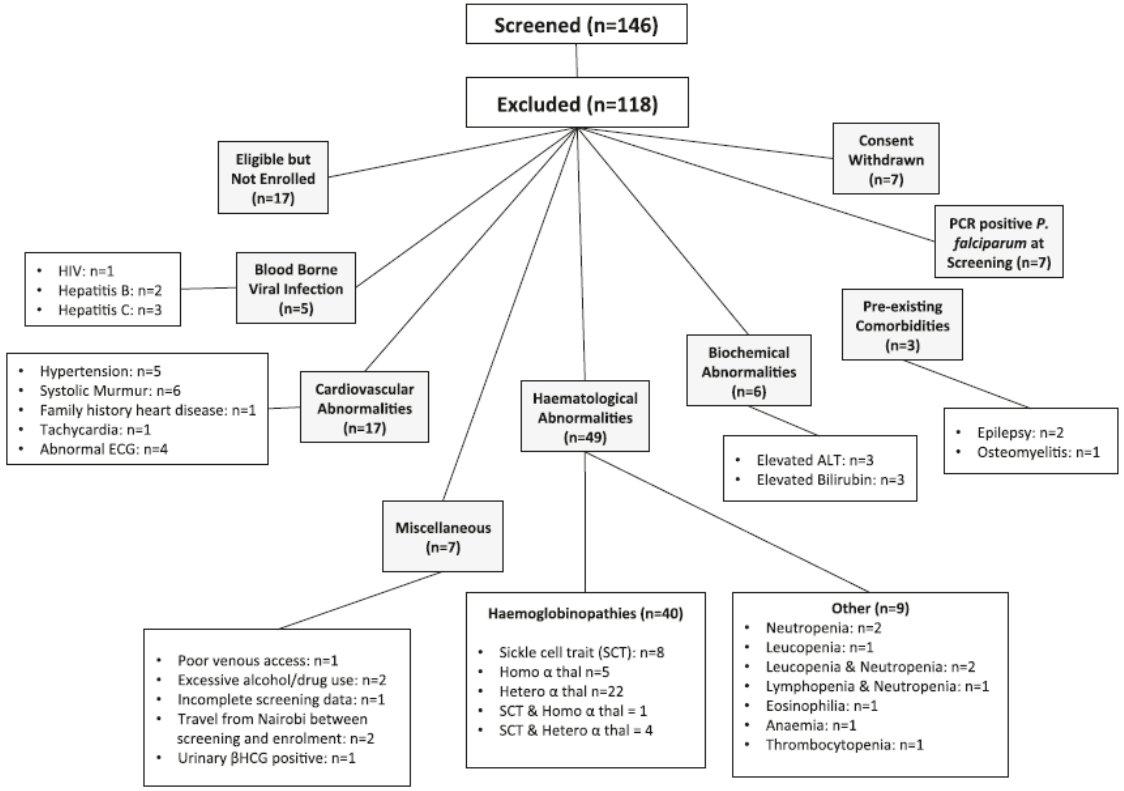


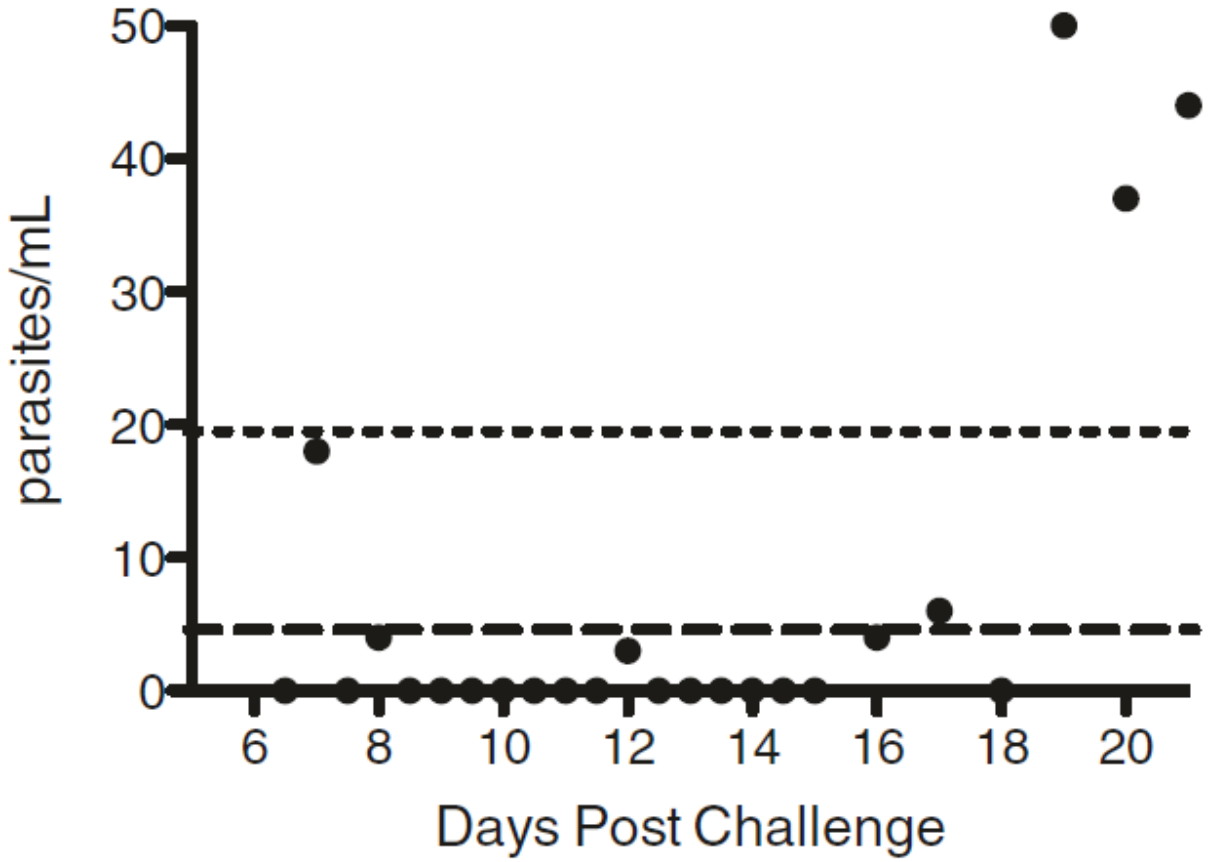


Figure 4 qPCR results post-challenge for Volunteer 110, Group 2. Long dashed line = lower limit of detection (i.e., a probability of > 50% of ≥ 1 positive result among three replicate PCR reactions) for qPCR assay (5 parasites/mL). Short dashed line = lower limit of quantification (defined as %CV < 20%) for qPCR assay (20 parasites/mL).

Why is controlled human malaria infection “coming back”?

1. Accelerates malaria vaccine assessment

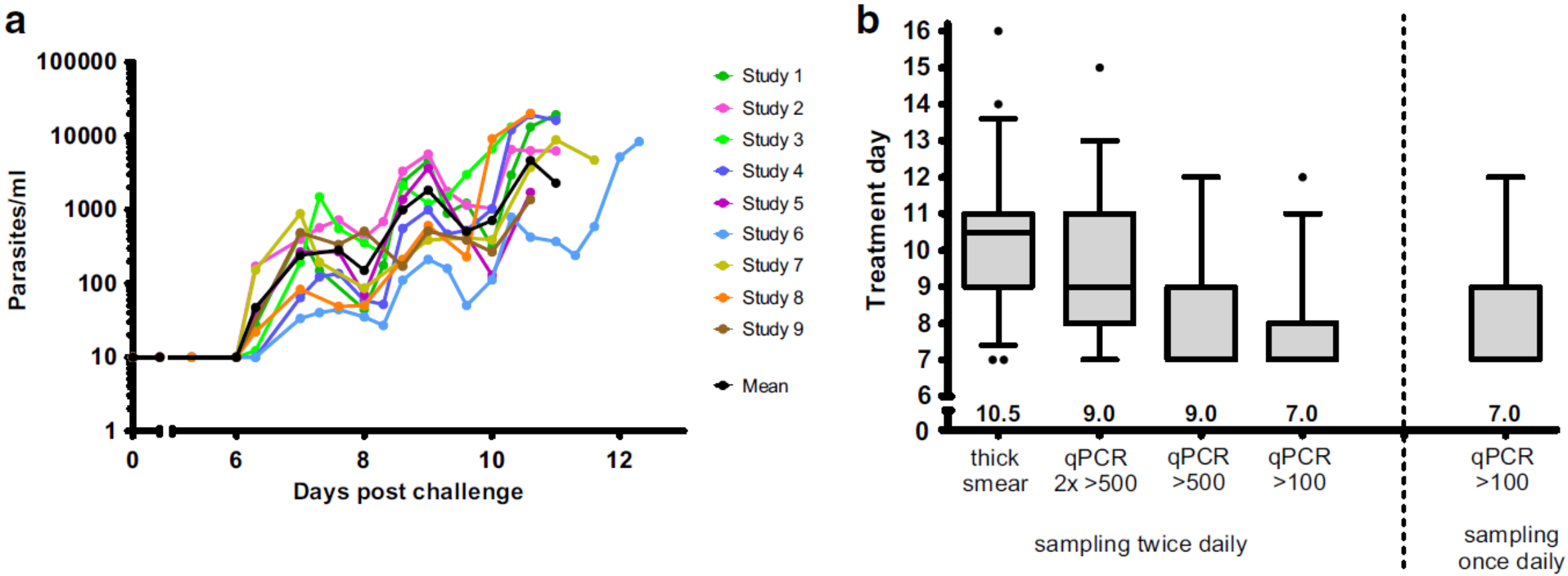
2. Accelerates antimalarial drug development

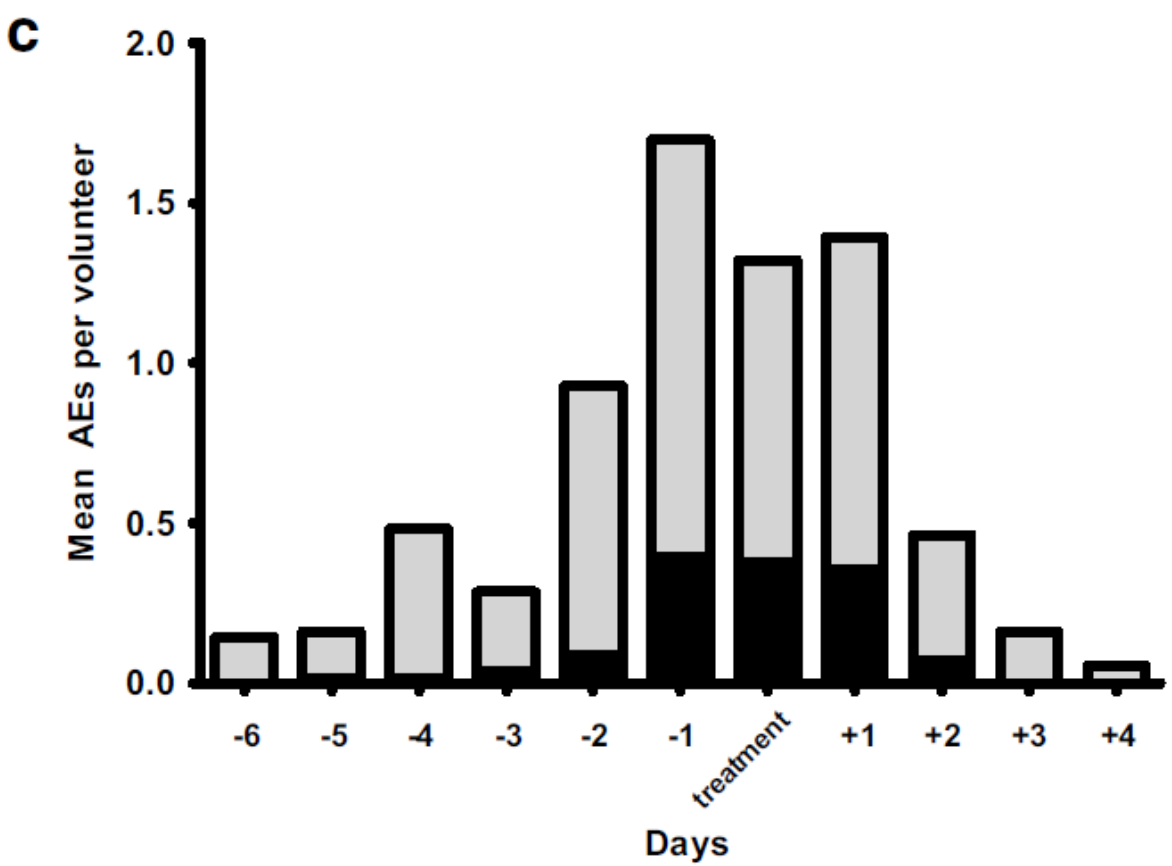
3. uPCR allows all information to be obtained “sub-clinically”

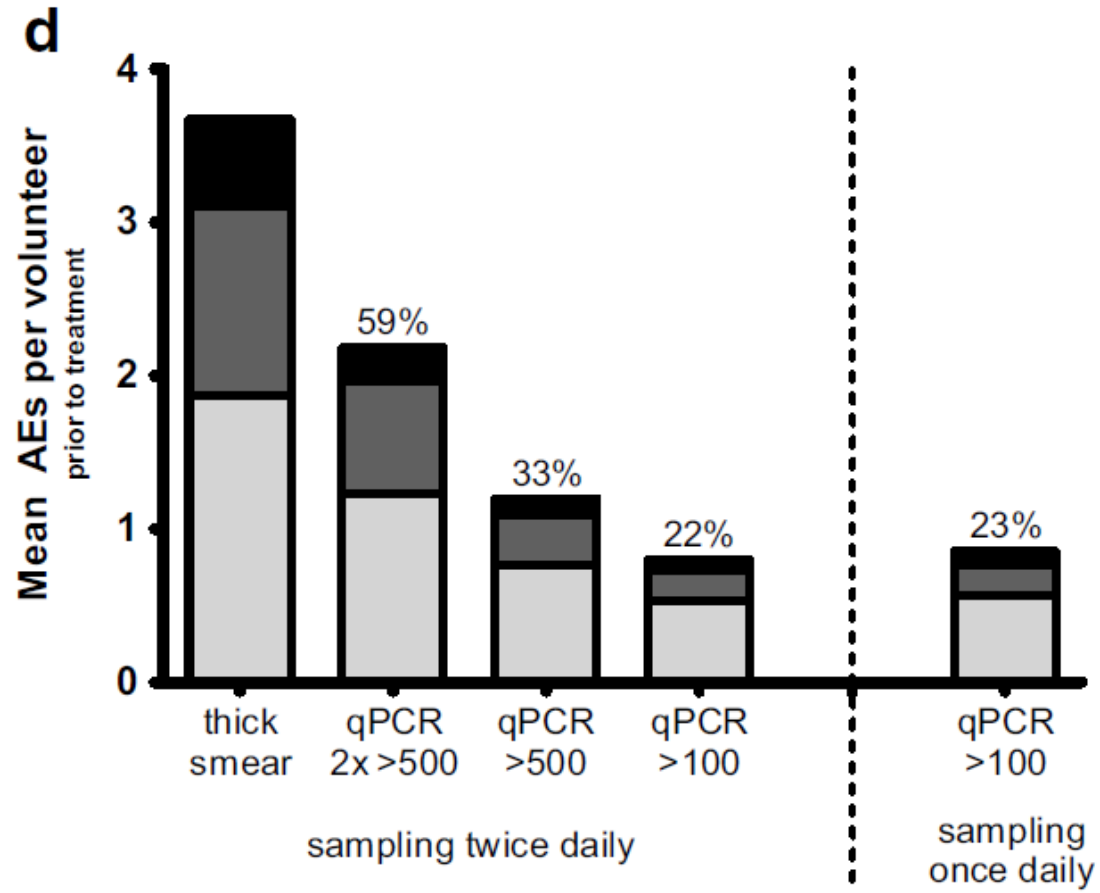
4. Minimal risk

Pyrogenic density = 50,000 parasites/mL
Limit of quantitation ~ 20 parasites/mL

Therefore there are ~ 3 asexual cycles between LOQ and illness


a
100000
10000
1000
100
10
1
Parasites/ml
0
6
8
10
12
Days post challenge
Study 1
Study 2
Study 3
Study 4
Study 5
Study 6
Study 7
Study 8
Study 9
Mean
b
Treatment day
16
15
14
13
12
11
10
9
8
7
6
0
10.5
9.0
9.0
7.0
7.0
thick smear
qPCR 2x >500
qPCR >500
qPCR >100
qPCR >100
sampling twice daily
sampling once daily


c
Mean AEs per volunteer
2.0
1.5
1.0
0.5
0.0
-6
-5
-4
-3
-2
-1
treatment
+1
+2
+3
+4
Days


d
Mean AEs per volunteer
prior to treatment
4
3
2
1
0
59%
33%
22%
23%
thick smear
qPCR 2x >500
qPCR >500
qPCR >100
qPCR >100
sampling twice daily
sampling once daily

Box 1. Relative merits of approaches to undertake CHMI

Parameter	SIM	IBSM
Safety record	>1500	>100
Risk of introduction of adventitious agents	Minimal	Possible
Ability to vary size of inoculum	+	+++
Knowledge of size of inoculum	+/–	+++
Logistical ease	Need for insectary	Cryopreserved blood
Availability	Widespread	Limited
Life cycle stages amenable to study	All human stages	Limited to erythrocytic and gametocytes

Sporozoite induced malaria infection

Induced blood stage malaria infection

Engwerde et al TiP 2012

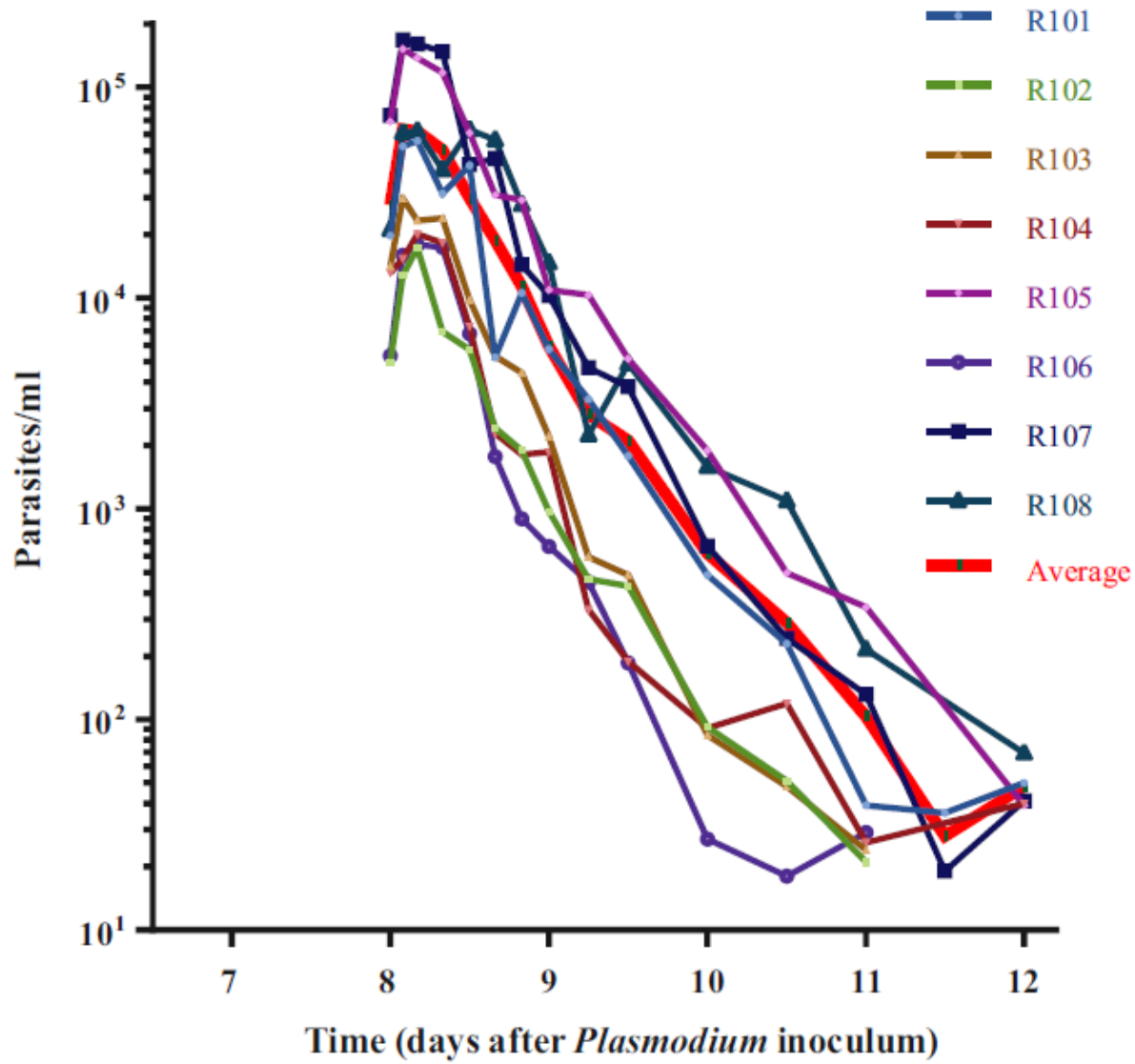
McCarthy *et al. Malar J (2016) 15:469*
DOI 10.1186/s12936-016-1511-3

Malaria Journal

RESEARCH Open Access

A Phase II pilot trial to evaluate safety and efficacy of ferroquine against early *Plasmodium falciparum* in an induced blood-stage malaria infection study

James S. McCarthy[1,2], Thomas Rückle[3], Elhadj Djeriou[4], Cathy Cantalloube[8], Daniel Ter-Minassian[4], Mark Baker[3,7], Peter O'Rourke[1], Paul Griffin[1,2,5,6], Louise Marquart[1], Rob Hooft van Huijsduijnen[3] and Jörg J. Möhrle[3*]



Trends in Parasitology 2017 CellPress

Review

Plasmodium vivax Controlled Human Malaria Infection – Progress and Prospects

Ruth O. Payne,[1,2,*] Paul M. Griffin,[3,4,5,6] James S. McCarthy,[3,6] and Simon J. Draper[1,*]

Table 1. Overview of Published *Plasmodium vivax* CHMI Studies

Trial site	Number of volunteers	Pre-patent period (days)[a]	Number of infected mosquitoes OR infective inoculum	Number of volunteers with patent parasitemia	Refs
Sporozoite (mosquito-bite) CHMI studies					
Cali, Columbia	18	9–13	2–10	17/18[b]	[26]
Cali, Columbia	17 Duffy positive 5 Duffy negative	9–16	2–4	17/17 (Duffy positive) 0/5 (Duffy negative)	[27]
Cali, Columbia	7 malaria-naïve 9 semi-immune	11–13	2–4	16/16[c]	[28]
Cali, Columbia	12 Duffy -positive vaccinees 2 Duffy-positive controls 5 Duffy-negative controls	12–13	2–4	7/12 vaccinees 2/2 Duffy-positive controls 0/5 Duffy-negative controls	[31]
WRAIR, USA	27 vaccinees 6 infectivity controls	10–13 10–11	5	27/27 vaccinees 6/6 controls	[32]
Blood-stage CHMI studies (IBSM)					
QIMRB, Australia	2	8–9	13 000 genome equivalents	2/2	[35]
QIMRB, Australia	6	8–9	31 786 (± 11 947) as determined by qPCR (= 15 ± 5 viable *P. vivax* parasites)	6/6	[37]

Conclusion:

1. Controlled human malaria infections (CHMI) can be performed safely and reliably in hospitalized volunteers with little or no symptomatology provided there is close monitoring and real-time quantitative uPCR is available.

2. CHMI can accelerate both vaccine and drug development.

3. It may be particularly useful in the evaluation of new treatments for artemisinin resistant falciparum malaria and for assessment of radical cure in vivax malaria.