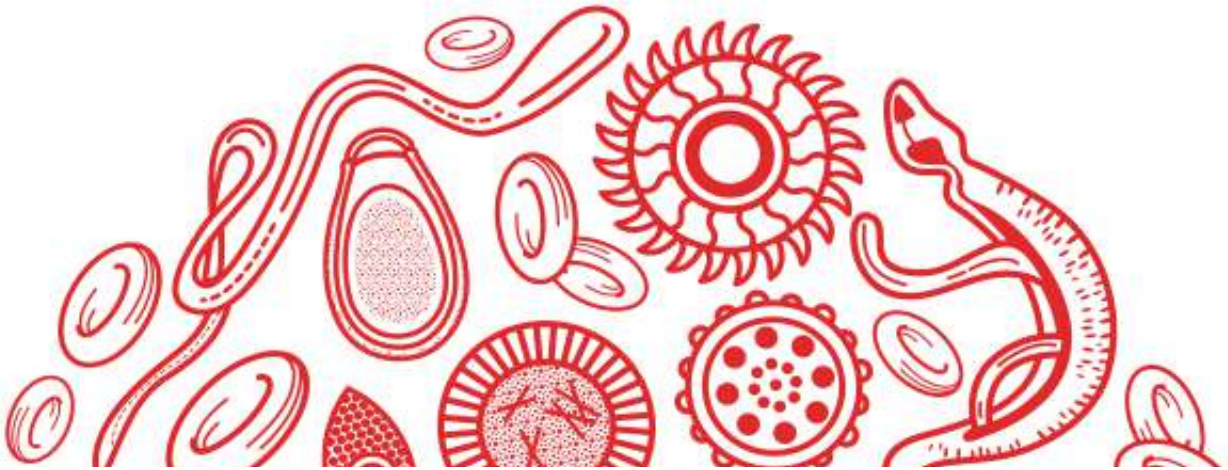


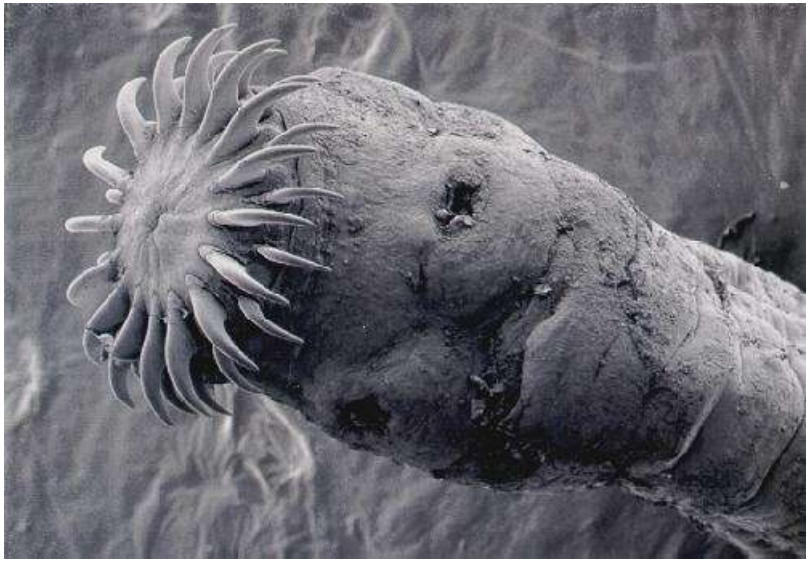
Parasites : Far , Near and in the Future

The General Rule

Wealth,
Development

=

Parasitological
Health burden



Parasitology in a Quickly Changing Society: The Past, Present and Future of Parasitology in Korea

Seung-Yull Cho, Korean Journal of Parasitology Vol 28, Supp 1-121990

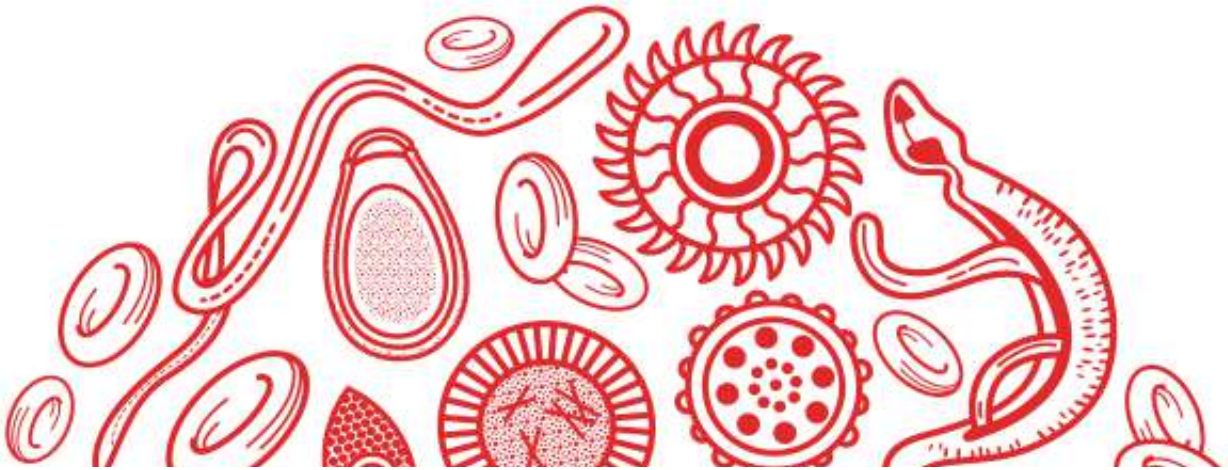
Seoul, Cheonggyecheon River

1955

Parasite Paradise

Today

Parasite Hell



Parasites : Far , Near and in the Future

3.4
Billion people live in areas at risk of malaria transmission

91
Affected countries & territories

UNIVERSITY of OTAGO
Te Whare Wānanga o Otāgo
NEW ZEALAND

216
Million cases estimated in 2016

445K
Deaths estimated in 2016

CASES	90%
DEATHS	91%

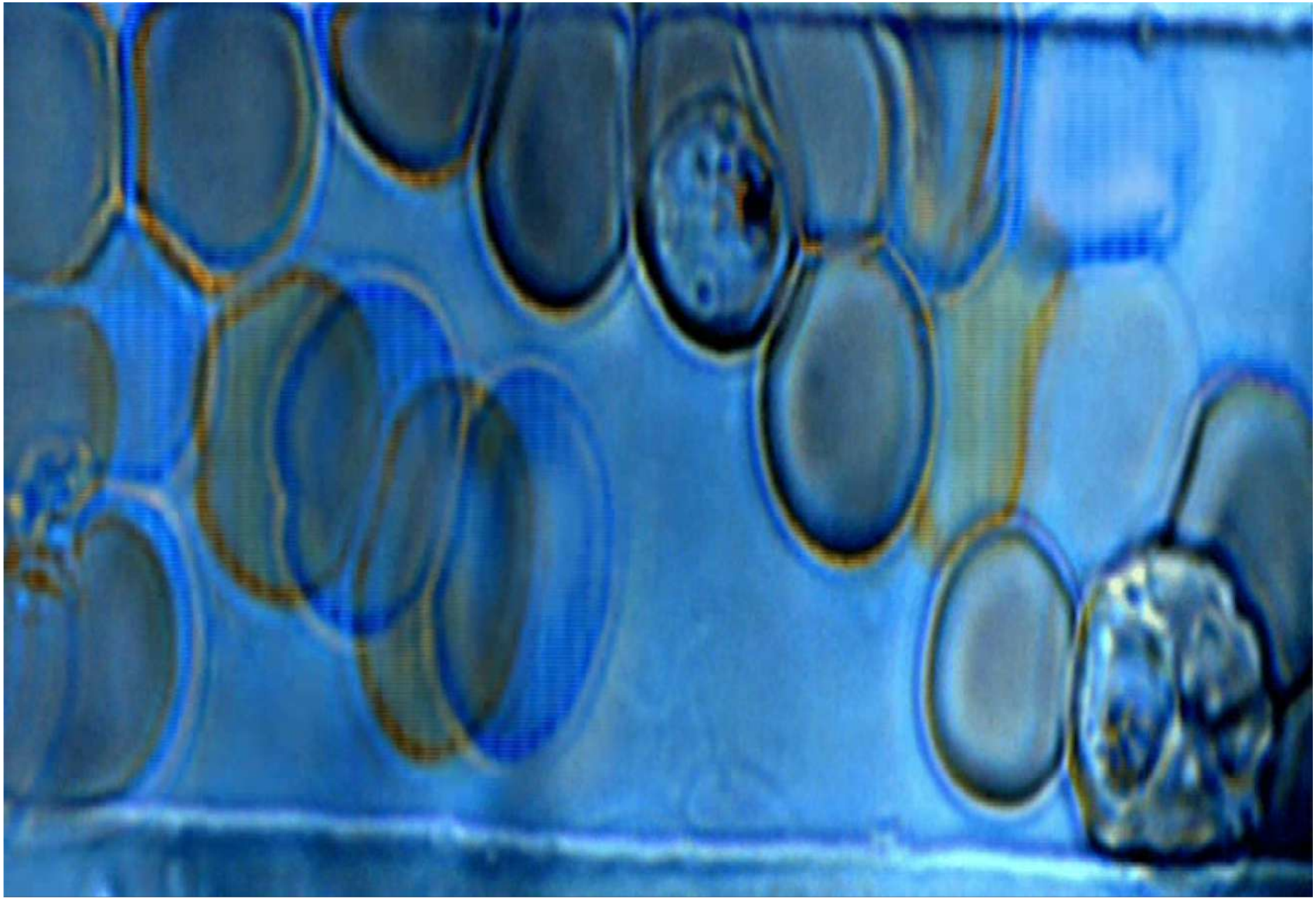
WHO African Region (2016)

Nigeria accounts for the highest proportions in the world

MOST VULNERABLE?

Young children

Pregnant women

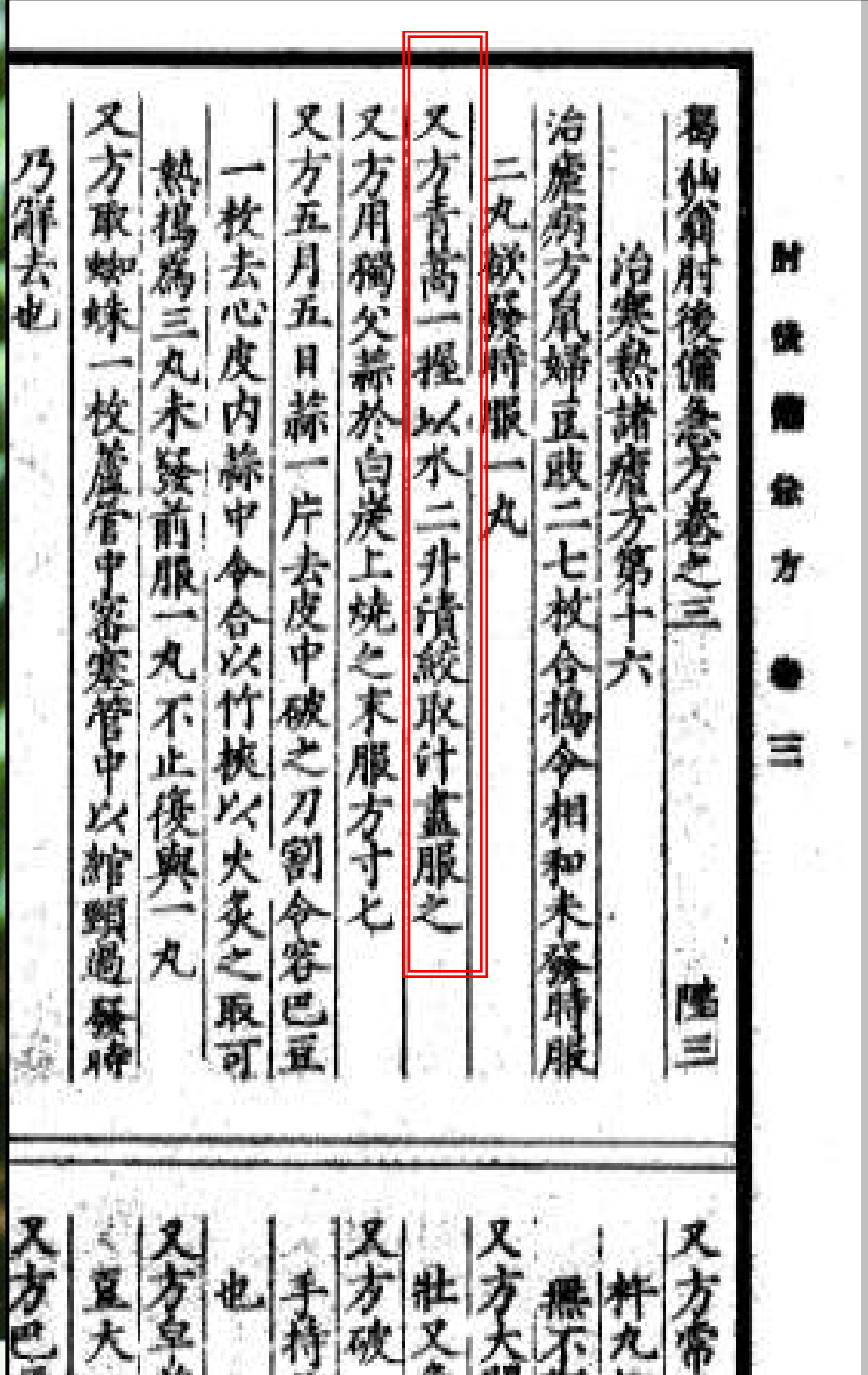


黃花蒿

Artemisia annua L.

青蒿素

Qinghaosu, Artemisinin



肘後備急方 卷三

陸三

葛仙翁肘後備急方卷之三

治寒熱諸瘧方第十六

治瘧病方鼠婦五枚二七枚合搗令相和未發時服二丸欲發時服一丸

又方青蒿一握以水二升漬絞取汁盡服之

又方用獨父蒜於白炭上燒之末服方寸七

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

又方取蜘蛛一枚盧管中密塞管中以綿裹過發時乃解去也

又方常

丸

不

又方大

壯又

又方破

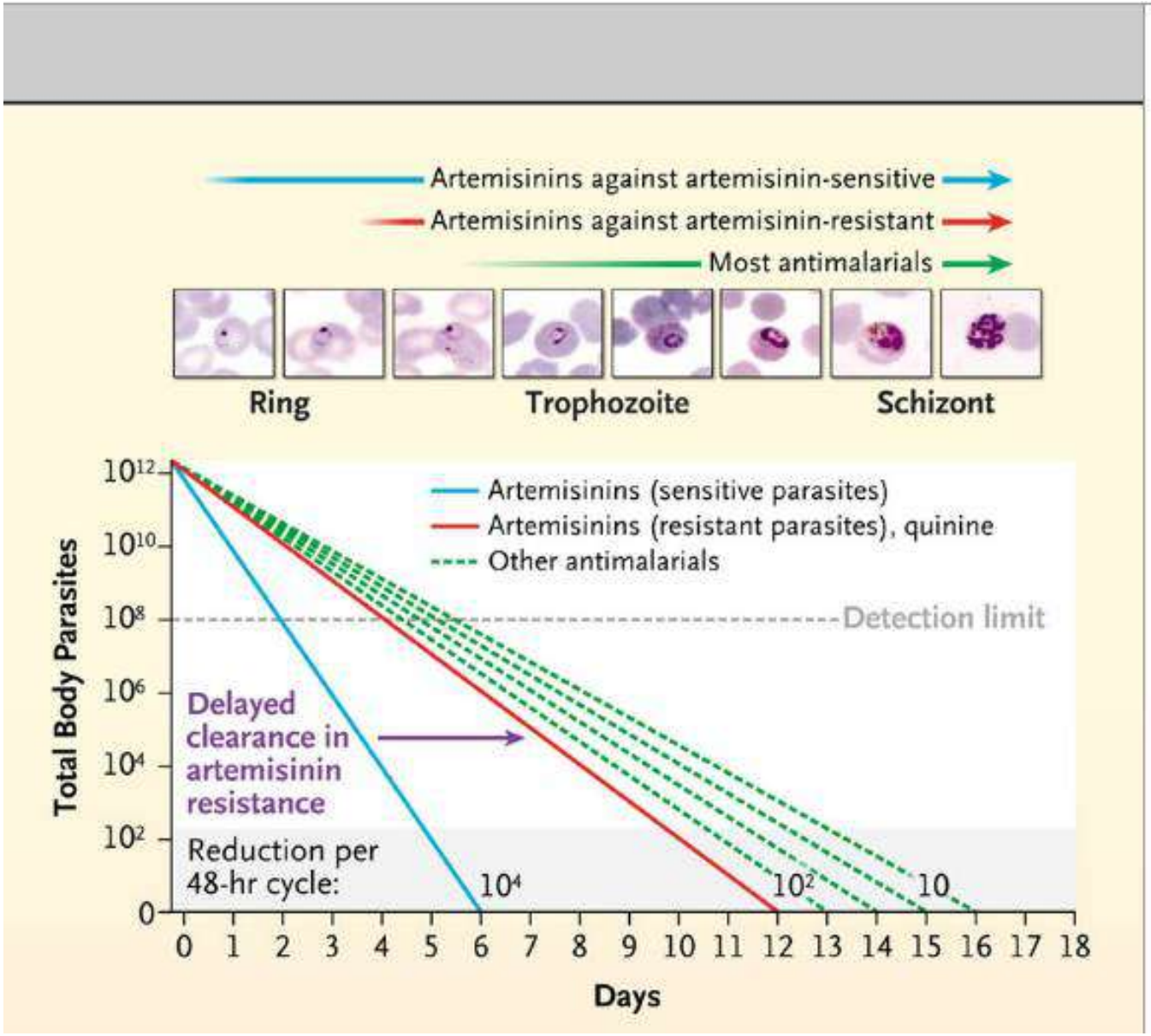
手持

也

又方皂

豆大

又方巴



Dynamics of Parasite-Killing Activity of Artemisinins and Other Antimalarial Drugs.

Against sensitive *P. falciparum* infection, the fast-acting and rapidly cleared artemisinins are the most potent antimalarial drugs known, reducing the parasite load by a factor of 10,000 per 48-hour asexual-stage parasite cycle. In the partially resistant strains of *P. falciparum* that are commonly found on the Cambodia–Thailand border, the parasite load is now reduced only by a factor of 100 per cycle — an effect similar to that of slower-acting drugs such as quinine (bottom of figure). Another unique and advantageous feature of the artemisinins is their broad stage-specificity, but this seems to be compromised in the resistant Southeast Asian parasites (top). Parasites that are at the ring stage during the brief period of exposure to rapidly eliminated artemisinins have reduced susceptibility, which results in delayed parasite clearance following treatment.

N Engl J Med 2011; 365:1073-1075September 22, 2011DOI

ANTIMALARIAL DRUGS IN THE PAST 50 YEARS

1979 Artemisinin

1982 Artesunate

1975 Mefloquine

1987 Pyronaridine

1982 Halofantrine

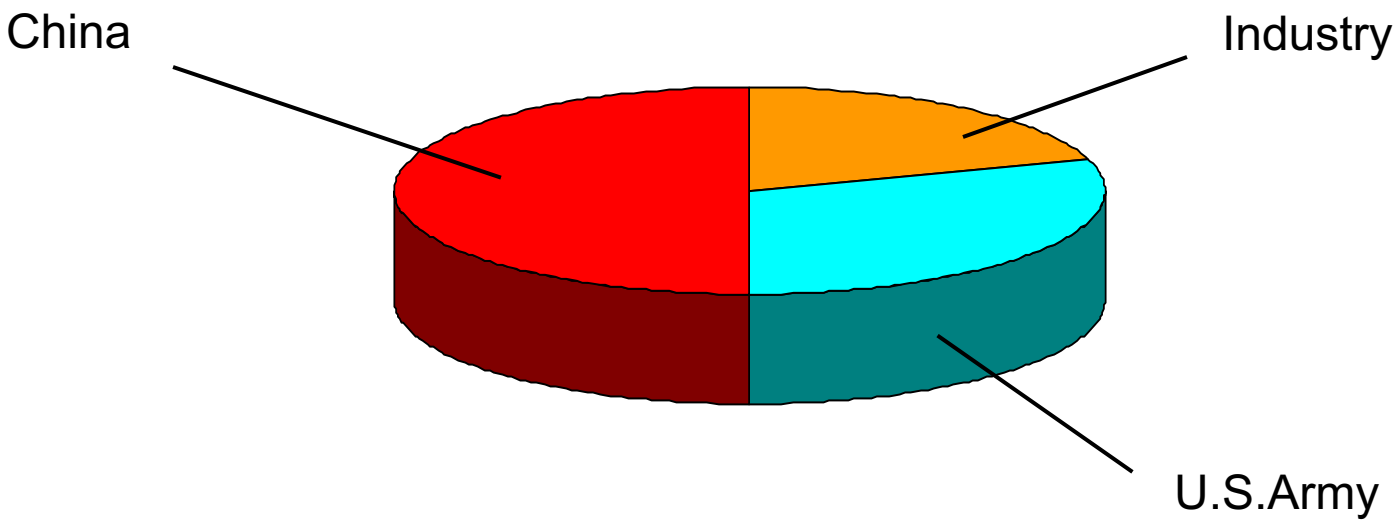
1988 Chlorproguanil-dapsone

1990 Atovaquone proguanil

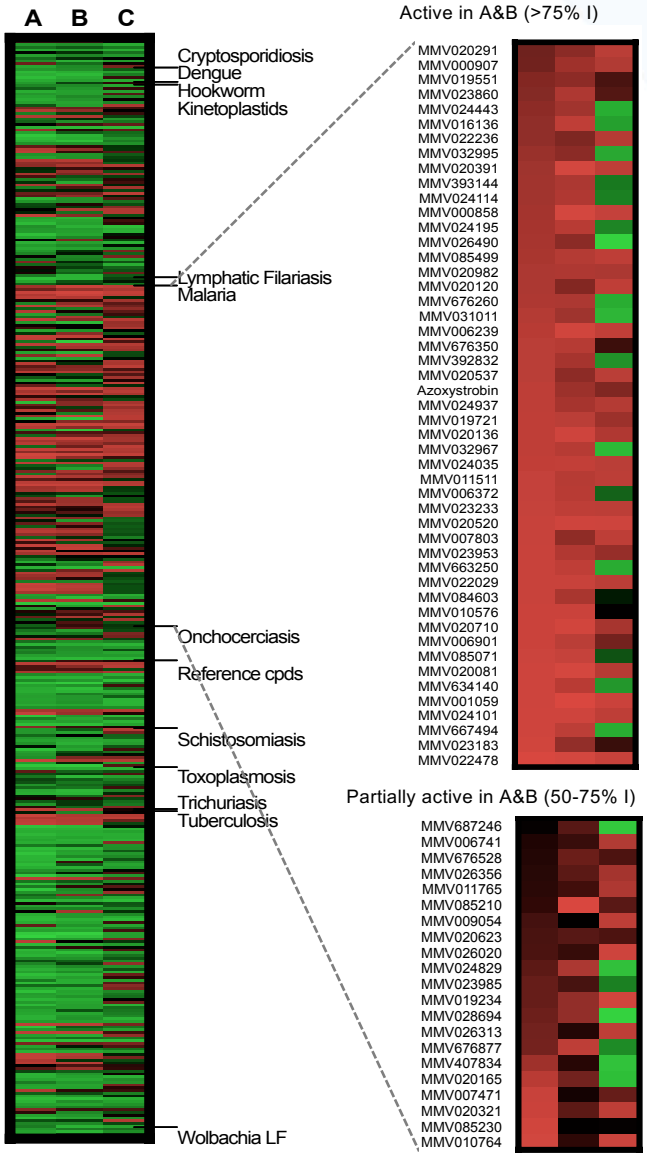
1994 Artemether-lumefantrine

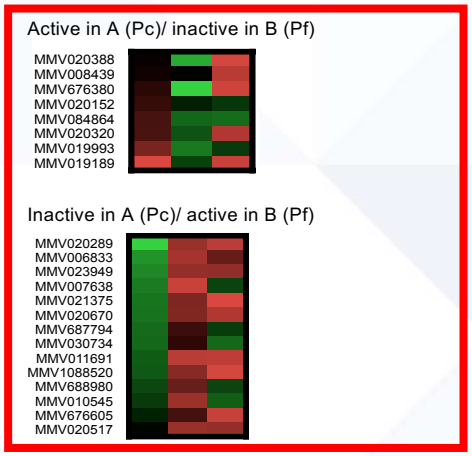
1998 Tafenoquine

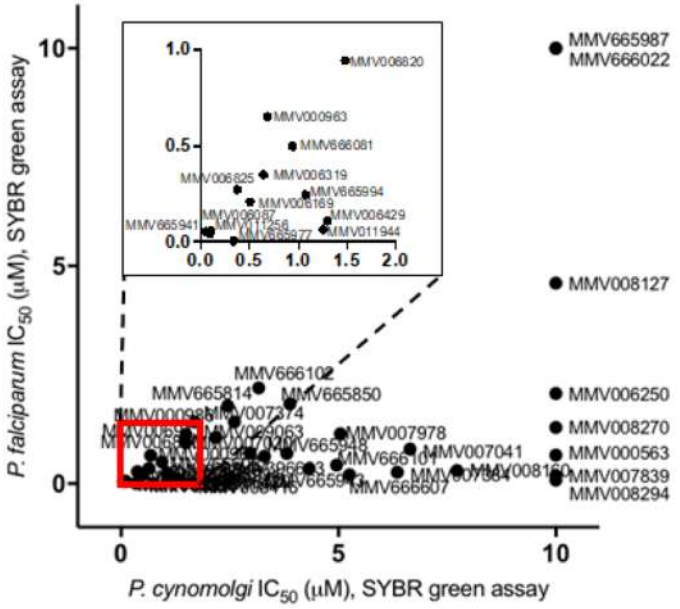
1998 Artekin(DHA-Piperaquine)



Drug Screening Platform

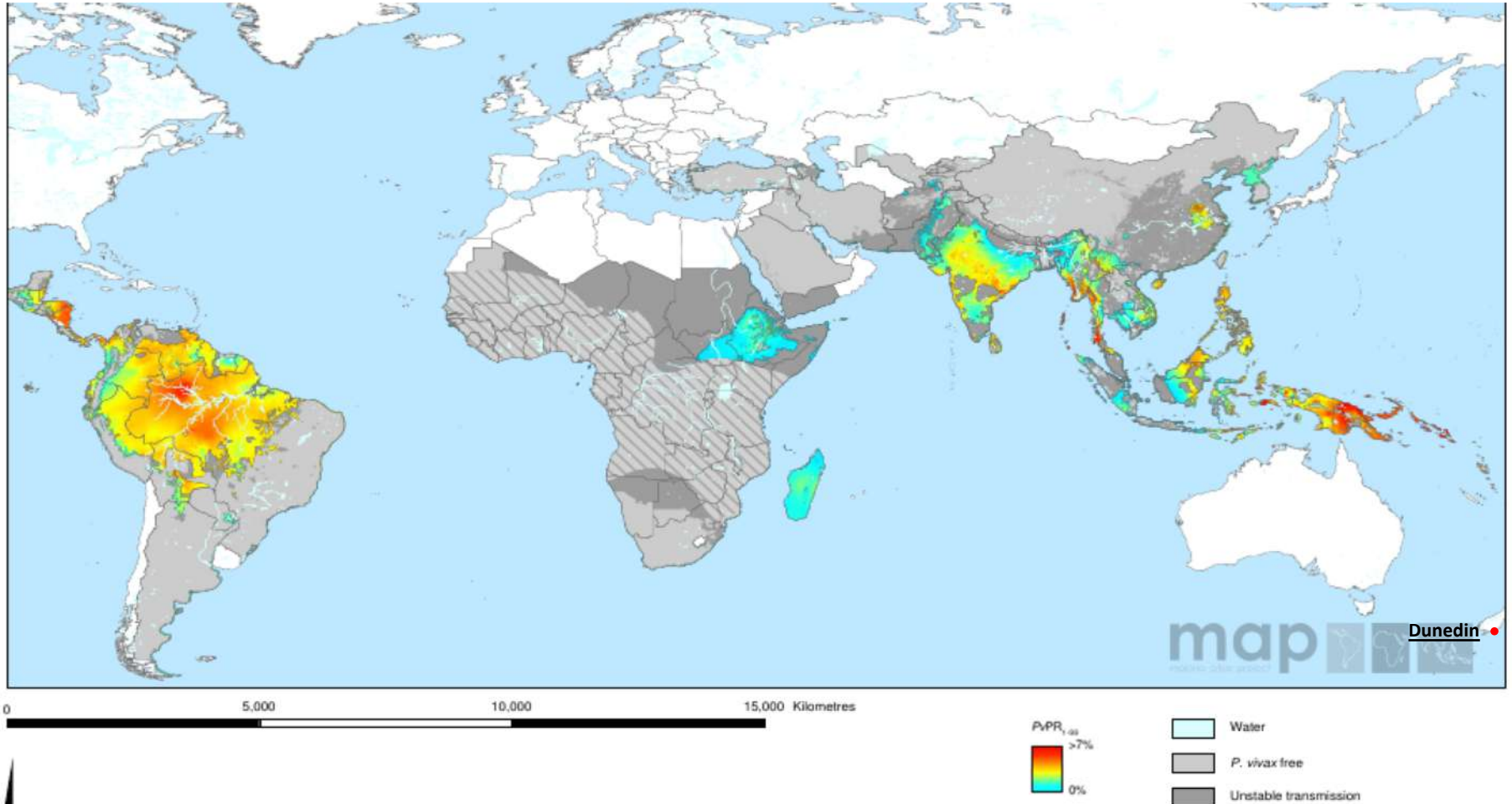






The Distribution of Malaria Post `Elimination' = Vivax Malaria Distribution!!

1. NO EFFECTIVE POC DIAGNOSTICS
2. CURRENT MOLECULAR DETECTION INSENSITIVE
3. RESISTANCE VIVAX MALARIA TREAMENTS (BLOOD STAGES)
4. RADICAL CURE NOT PRACTICAL AND DANGEROUS (LIVER STAGE)
5. BED NETS INEFFECTIVE AND CURRENT VECTOR CONTROL INADEQUATE
6. NO VACCINE



Gething, P.W., …Baird, J.K. and Hay, S.I. (2012). **A long neglected world malaria map: *Plasmodium vivax* endemicity in 2010.** *Public Library of Science Neglected Tropical Diseases*, **6**(9): e1814.

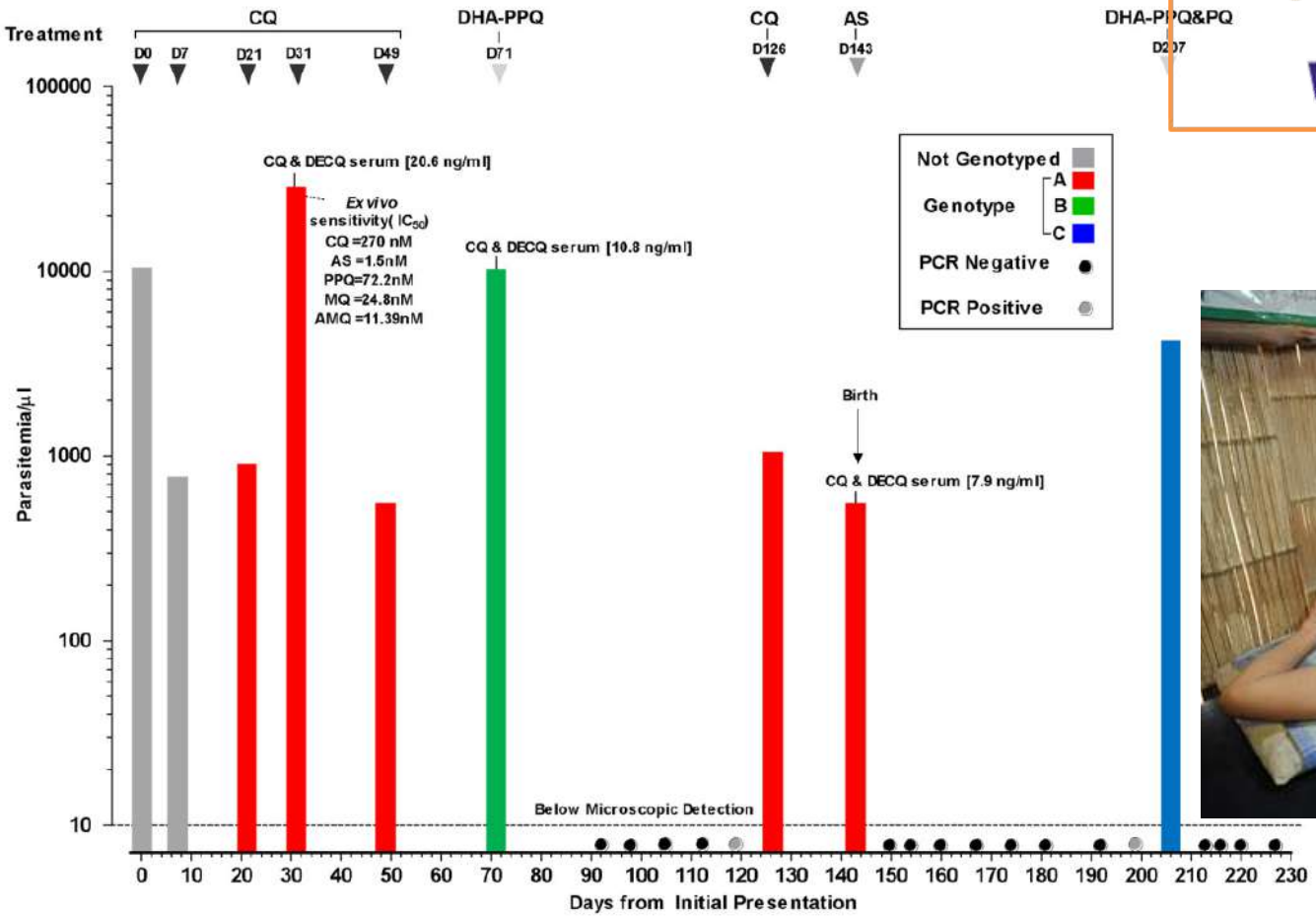
VIVAX MALARIA: SEVERITY IS NOT THE POINT

Rijken *et al. Malaria Journal* 2011, **10**:113
http://www.malariajournal.com/content/10/1/113

MALARIA JOURNAL

CASE REPORT **Open Access**

Chloroquine resistant vivax malaria in a pregnant woman on the western border of Thailand



Prof. Francois Nosten

Smru Shoklo Malaria Research Unit

Mahidol Oxford MORU
WELLCOME TRUST - MAHIDOL UNIVERSITY-OXFORD TROPICAL MEDICINE RESEARCH PROGRAMME

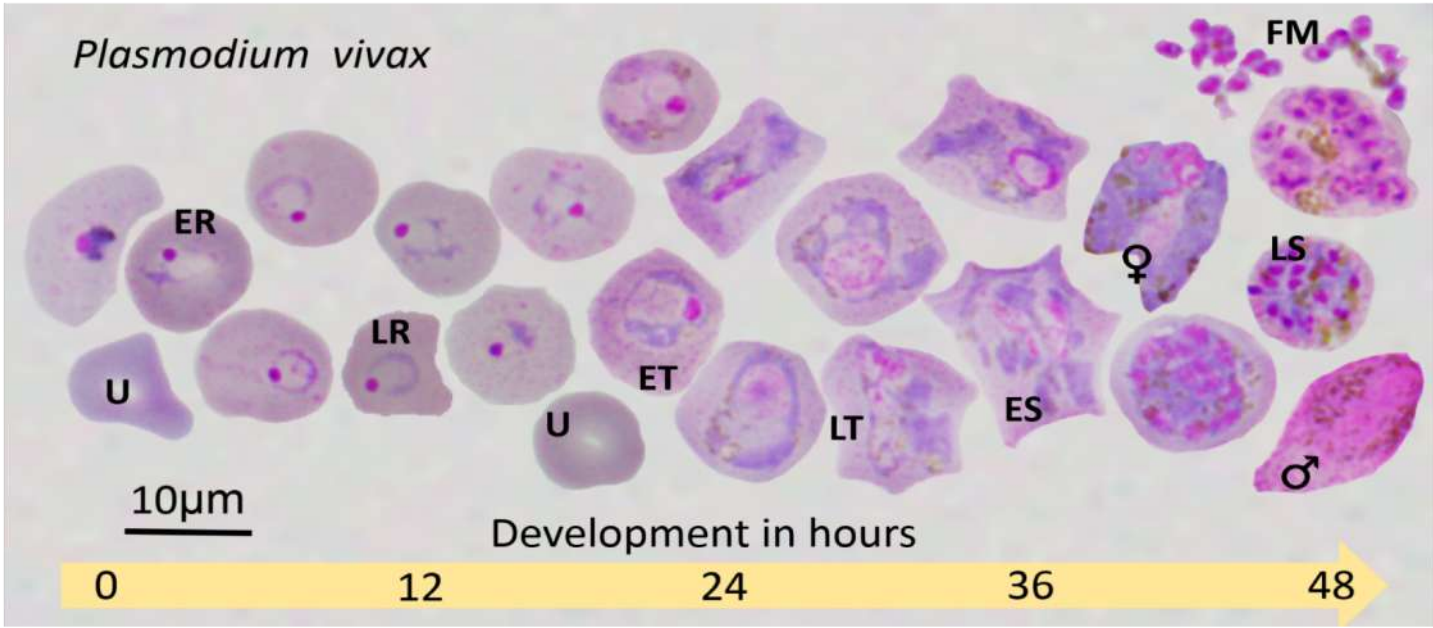
wellcome trust

Elimination of vivax needs <u>new long half life drugs</u> and possibly a <u>vaccine</u>

NO CONTINUOUS CULTURE

Vivax malaria research is mostly limited

Ex vivo studies?



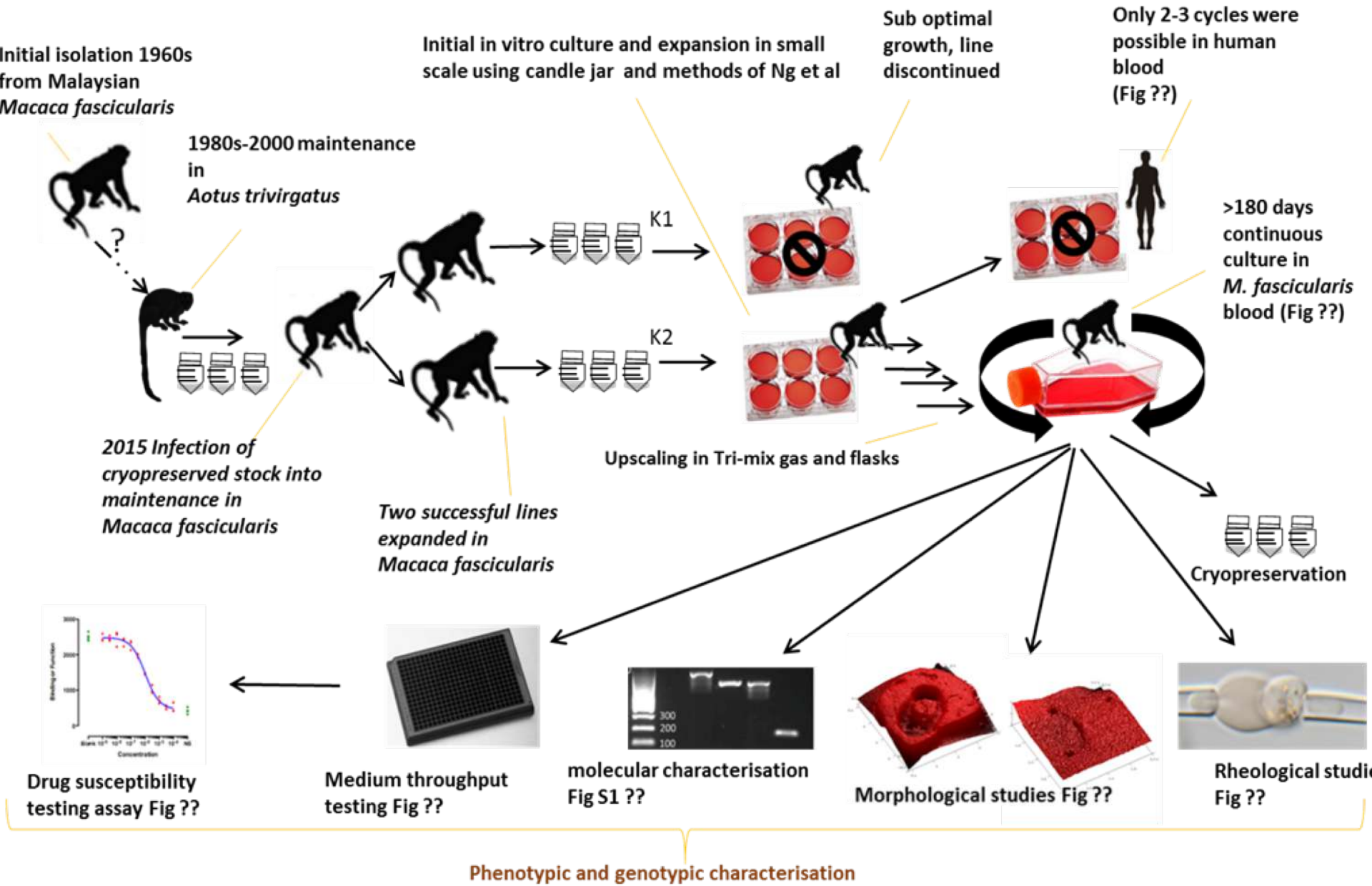
Human cynomolgi malaria in humans is relatively mild and uncomplicated

NEWS · 16 APRIL 2018

Rare human outbreak of monkey malaria detected in Malaysia

Handful of people diagnosed with parasite found in macaques has scientists worried about increasing contact between monkeys and humans.

Yao-Hua Law


Initial isolation 1960s from Malaysian *Macaca fascicularis*
1980s-2000 maintenance in *Aotus trivirgatus*
?
2015 Infection of cryopreserved stock into maintenance in Macaca fascicularis
Initial in vitro culture and expansion in small scale using candle jar and methods of Ng et al
K1
K2
Two successful lines expanded in Macaca fascicularis
Sub optimal growth, line discontinued
Only 2-3 cycles were possible in human blood (Fig ??)
>180 days continuous culture in *M. fascicularis* blood (Fig ??)
Upscaling in Tri-mix gas and flasks
Cryopreservation
Drug susceptibility testing assay Fig ??
Medium throughput testing Fig ??
300
200
100
molecular characterisation Fig S1 ??
Morphological studies Fig ??
Rheological studi
Fig ??
Phenotypic and genotypic characterisation

Parasite Threats Near

NEW ZEALAND

Public Health Surveillance Report

March 2018: Covering October to December 2017

CONTENTS AND HIGHLIGHTS

1. Editorial

- Increase in *Neisseria meningitidis* group W invasive disease

2. Notifiable disease surveillance

Significant increases in 12-monthly notification rate

- Cryptosporidiosis
- Hepatitis A
- Leptospirosis
- Malaria
- Meningococcal disease
- Mumps
- Pertussis
- Shigellosis
- Typhoid fever
- VTEC/STEC infection

Significant decreases in 12-monthly notification rate

- Campylobacteriosis
- Chikungunya fever
- Gastroenteritis (acute)
- Listeriosis
- Measles
- Zika virus infection

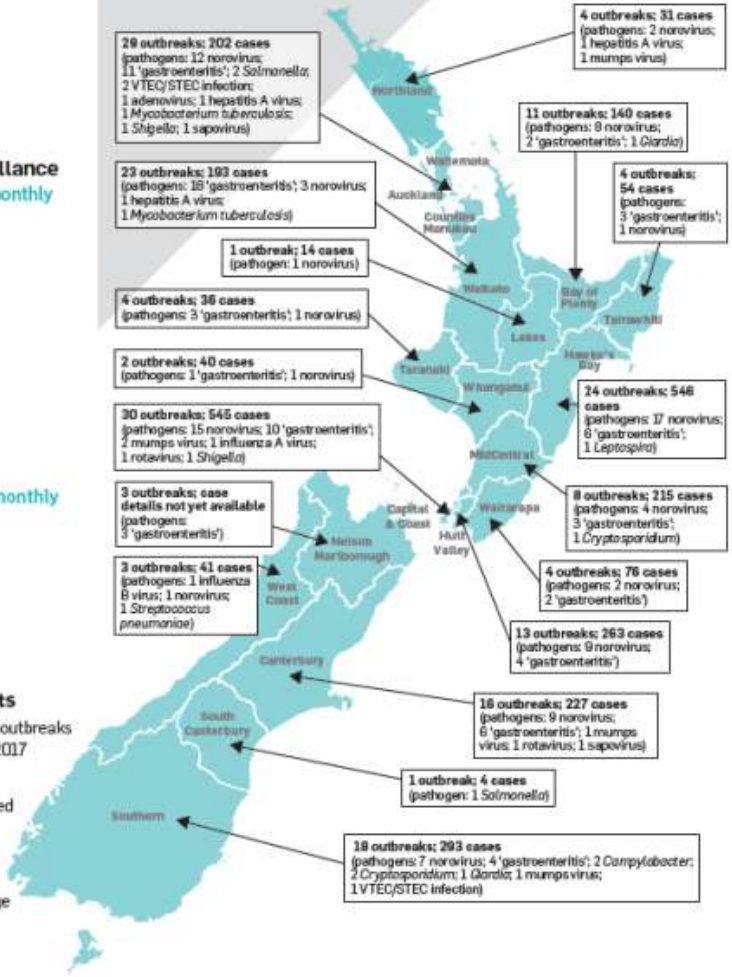
3. Other surveillance reports

- Increase in institutional norovirus outbreaks in the greater Wellington region, 2017

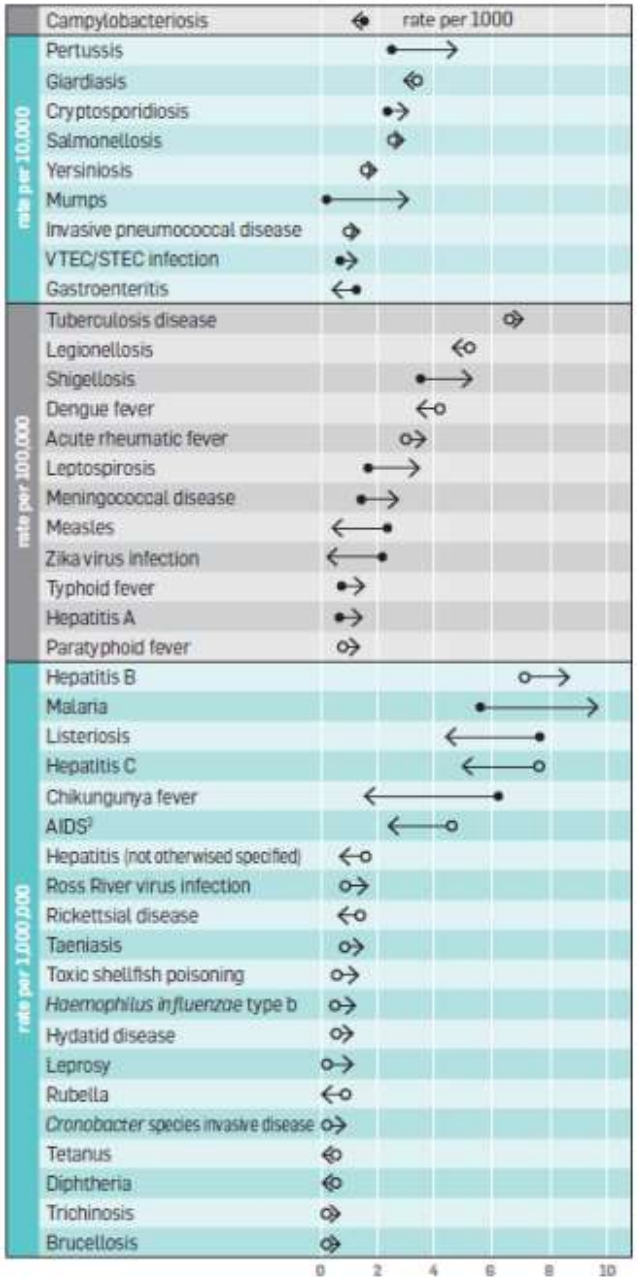
4. Outbreak surveillance

- 198 outbreaks (2924 cases) notified in this quarter
- 134 final reports (2420 cases); 64 interim reports (504 cases)
- 18.1 cases per outbreak on average
- 38 hospitalisations, 5 deaths

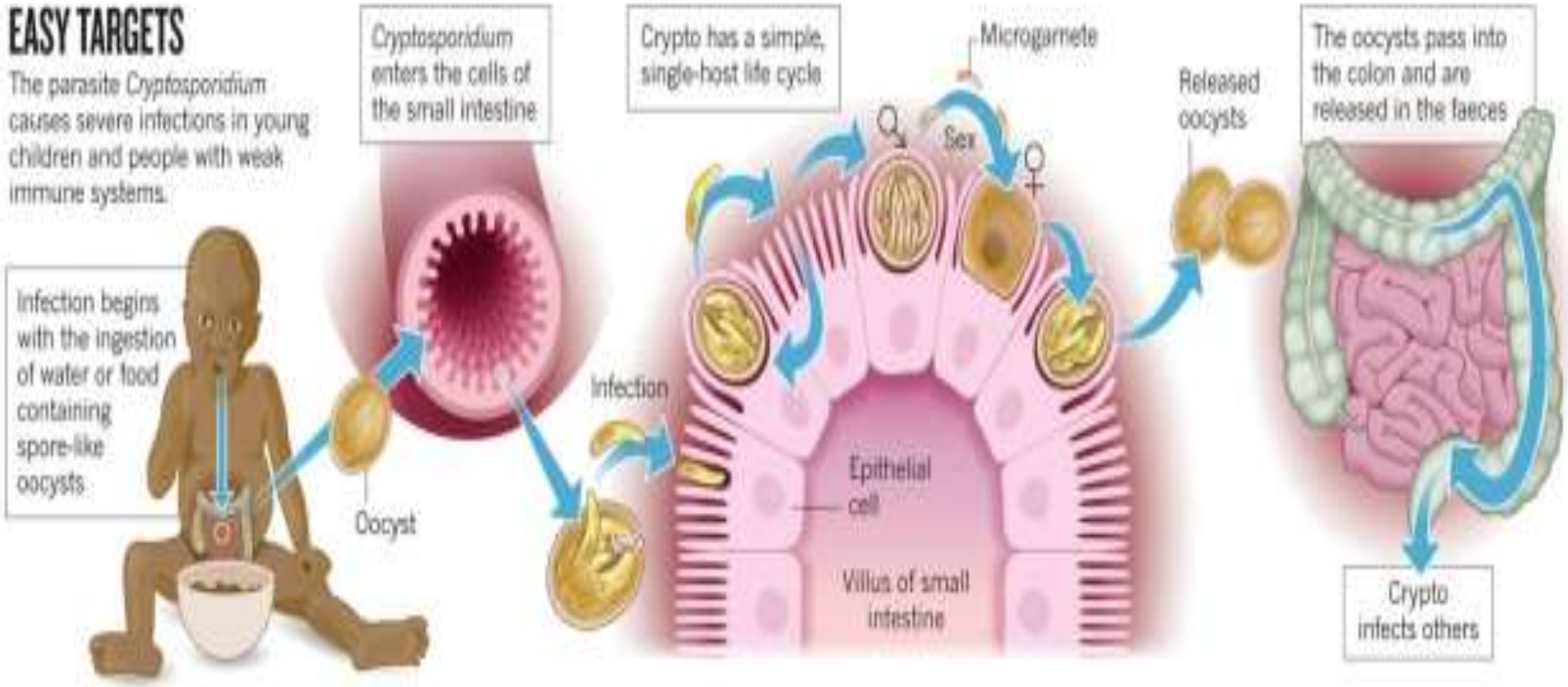
5. Outbreak case reports



National surveillance data 12-monthly notification rate changes[1]

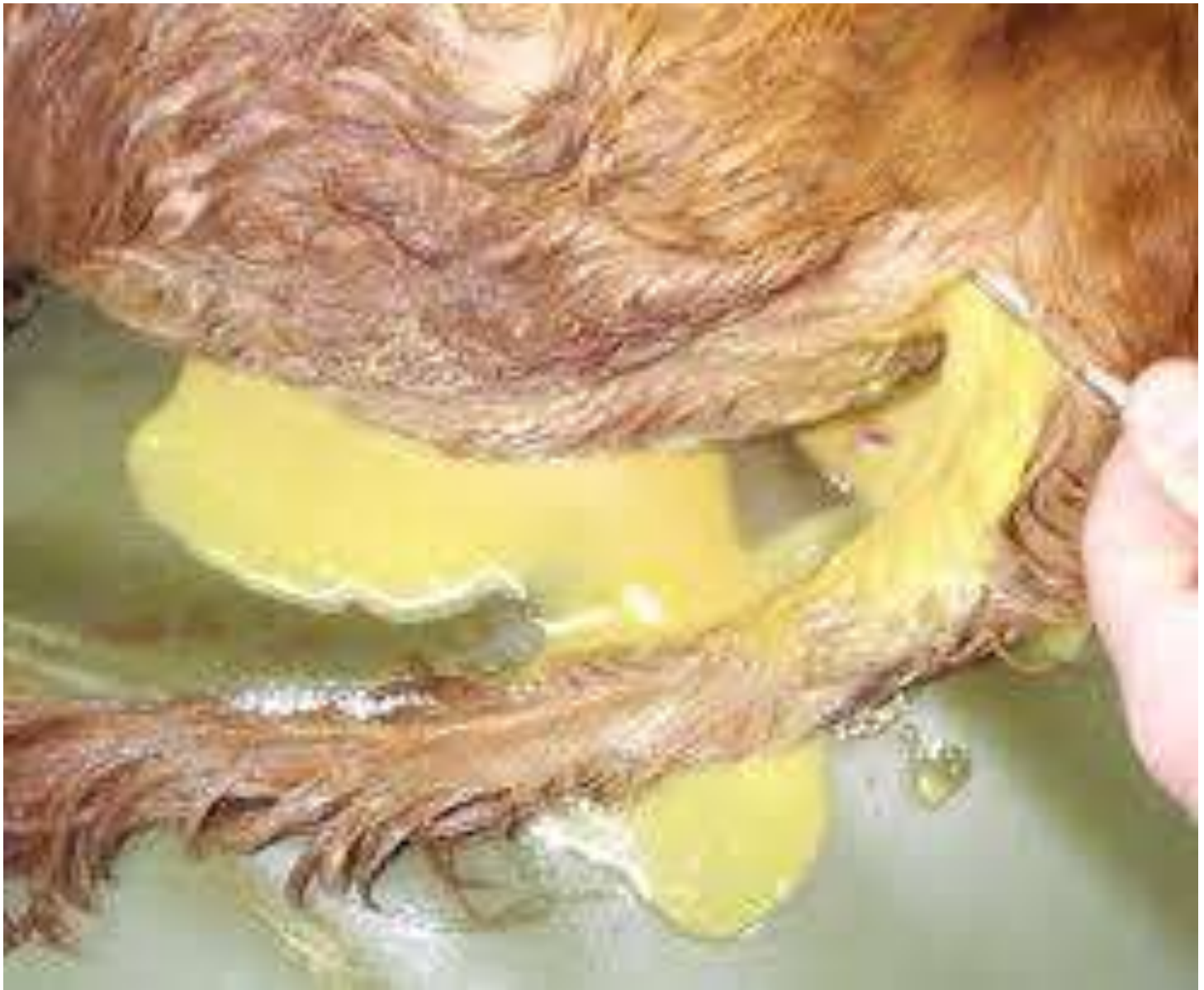


Cryptosporidium life cycle



Nitazoxanide is not enough

Drug Development



ARTICLE

doi:10.1038/nature22337

A *Cryptosporidium* PI(4)K inhibitor is a drug candidate for cryptosporidiosis

Ujjini H. Manjunatha[1]*, Sumiti Vinayak[2]*, Jennifer A. Zambriski[3]*, Alexander T. Chao[1], Tracy Sy[3], Christian G. Noble[1], Ghislain M. C. Bonamy[1], Ravinder R. Kondreddi[1], Bin Zou[1], Peter Gedeck[1], Carrie F. Brooks[2], Gillian T. Herbert[2], Adam Sateriale[2], Jayesh Tandel[4], Susan Noh[3,5,6], Suresh B. Lakshminarayana[1], Siau H. Lim[1], Laura B. Goodman[7], Christophe Bodenreider[1], Gu Feng[1], Lijun Zhang[8], Francesca Blasco[1], Juergen Wagner[1], F. Joel Leong[1], Boris Striepen[2,4] & Thierry T. Diagana[1]

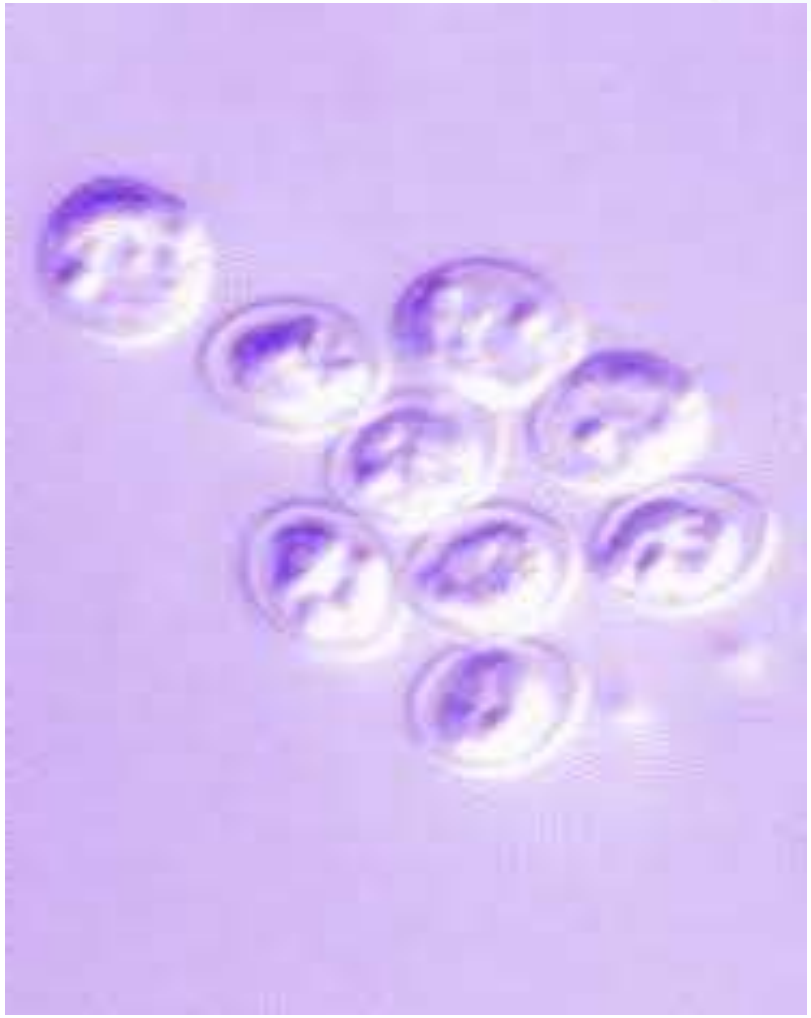
Diarrhoeal disease is responsible for 8.6% of global child mortality. Recent epidemiological studies found the protozoan parasite *Cryptosporidium* to be a leading cause of paediatric diarrhoea, with particularly grave impact on infants and immunocompromised individuals. There is neither a vaccine nor an effective treatment. Here we establish a drug discovery process built on scalable phenotypic assays and mouse models that take advantage of transgenic parasites. Screening a library of compounds with anti-parasitic activity, we identify pyrazolopyridines as inhibitors of *Cryptosporidium parvum* and *Cryptosporidium hominis*. Oral treatment with the pyrazolopyridine KDU731 results in a potent reduction in intestinal infection of immunocompromised mice. Treatment also leads to rapid resolution of diarrhoea and dehydration in neonatal calves, a clinical model of cryptosporidiosis that closely resembles human infection. Our results suggest that the *Cryptosporidium* lipid kinase PI(4)K (phosphatidylinositol-4-OH kinase) is a target for pyrazolopyridines and that KDU731 warrants further preclinical evaluation as a drug candidate for the treatment of cryptosporidiosis.

Biotech

UPDATED: Novartis to move R&D tropical disease base out of Singapore, cut Zurich, Shanghai jobs

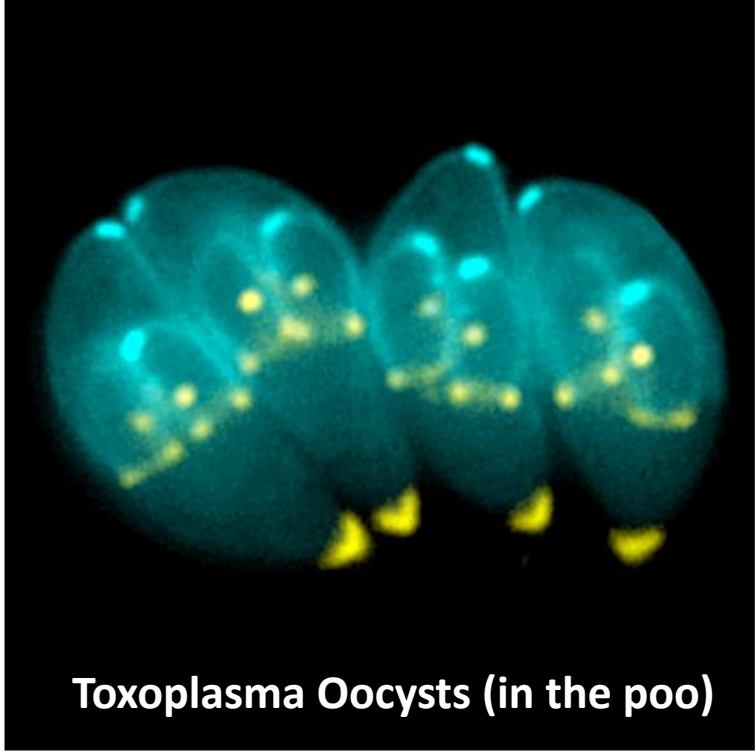
by *Ben Adams* | Oct 5, 2016 8:57am

Crypto Platform

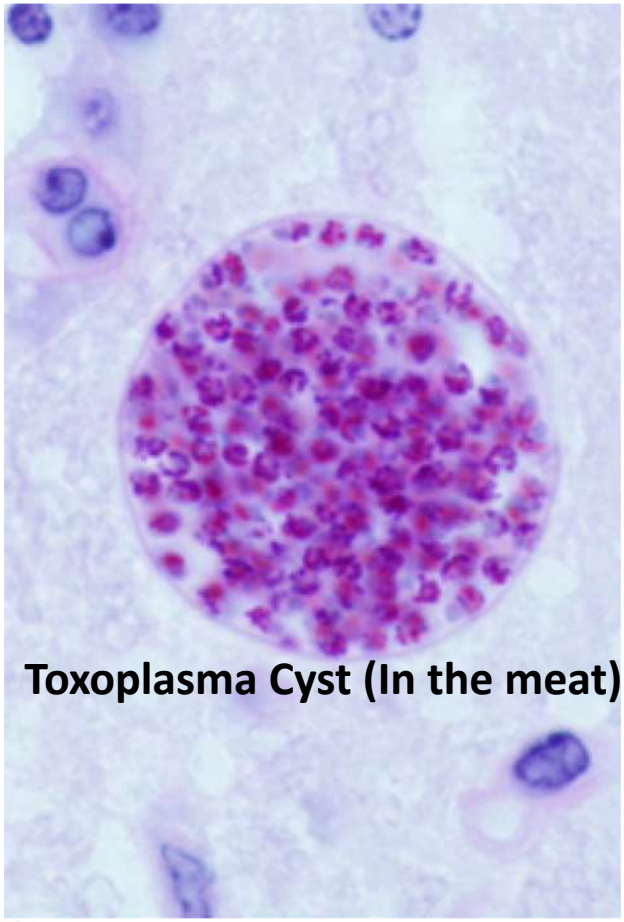


Parasites and the Future

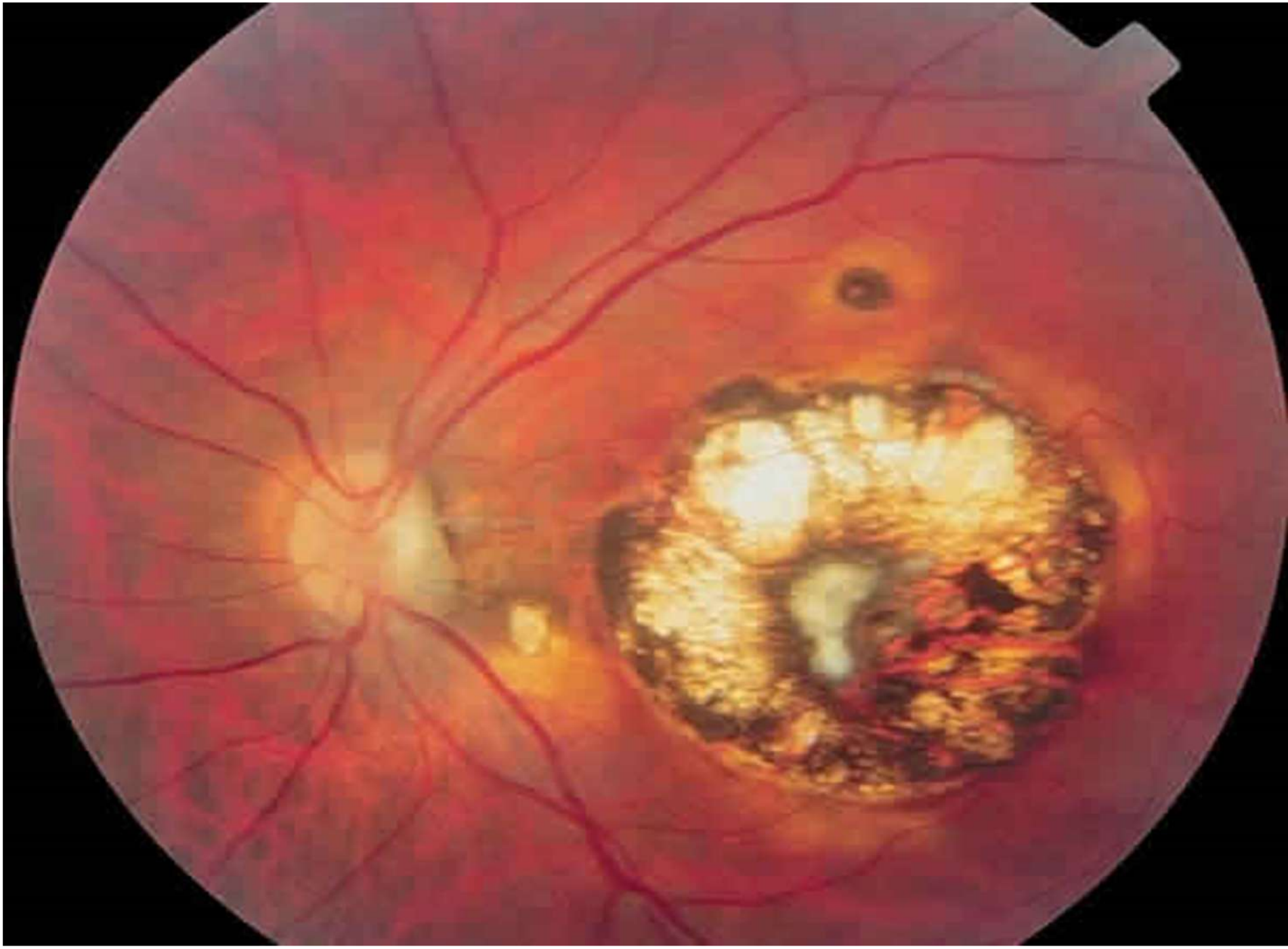
Toxoplasma gondii causative agent of Toxoplasmosis



Toxoplasma Oocysts (in the poo)



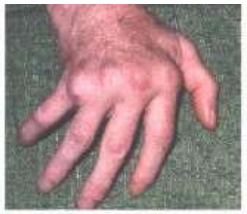
Toxoplasma Cyst (In the meat)

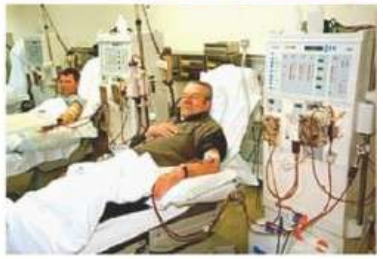


The Good Worm!
Immunological therapies derived from parasites

The General Rule

Wealth, Development = Parasitological Health burden + Autoimmune Diseases





Parasitic helminths: a pharmacopeia of anti-inflammatory molecules

JOHNSTON et al Parasitology (2009), 136, 125–147.

~40 products identified so far

Species	Worm product	Bioactivity	Reference
Schistosoma japonicum	900 kDa ECF-SjE from homogenized eggs; pronase and heat insensitive glycoprotein; destroyed by periodate oxidation	*In vitro* eosinophil chemotaxis	Owhashi and Ishii (1982)
	440 kDa JAE-H and <440 kDa JAE-L glycoproteins from adult ES products	Eosinophil chemotactic factors; JAE-L also induces neutrophil chemotaxis	Horii *et al.* (1984)
Schistosoma mansoni	Analogues of adrenocorticotrophin (ACTH) and α-melanotrophin (α-MSH)	ACTH converts to α-MSH by polymorphonuclear cells via neutral endopeptidase; αMSH inhibits leukocyte adherence and immunosuppressive	Duvaux-Miret *et al.* (1992)
	Various surface glycans	Fucose and Galactose linked to bovine serum albumin reduced ERK and PKC phosphorylation and phagocytosis in *Lymnaea stagnalis* haemocytes	Plows *et al.* (2005)
	25 kDa glutathione S-transferase in ES products	Detoxification of peroxides involved in oxidative stress	Guillou *et al.* (2007)
Fasciola hepatica	ES products contain metal ion dependent glycosidases (β-galactosidase, β-N-acetylhexosaminidase and β-glucosidase)	May degrade host mucins rich in galactose, N-acetylglucosamine and N-acetylgalactosamine	Irwin *et al.* (2004)
	ES products	Prevent superoxide production by PMA-activated sheep and human neutrophils *in vitro* (a heat resistant ES component from the related species, *F. gigantica*, does the same)	Jefferies *et al.* (1997) El-Ghaysh *et al.* (1999)
Diplostomum pseudopathaceum	22–24 kDa lectin with homology to β1,3 glucan binding protein localizes to the cercarial penetration glands	Agglutinates murine red blood cells and may facilitate tissue recognition and penetration	Mikes and Horak (2001)
Paragonimus westermani	27 kDa cysteine protease in ES products	Induces superoxide production and human eosinophil degranulation	Chung *et al.* (2008)
Opisthorchis viverrini	24 kDa thioredoxin peroxidase (TPx) isolated by genomic probing; also exists in ES products	Protects worm from reactive oxygen metabolites and may have other roles similar to *F. hepatica* TPx	Suttiprapa *et al.* (2008)

Immunomonitoring
Novel Therapies