

Tafenoquine For Malaria Elimination?

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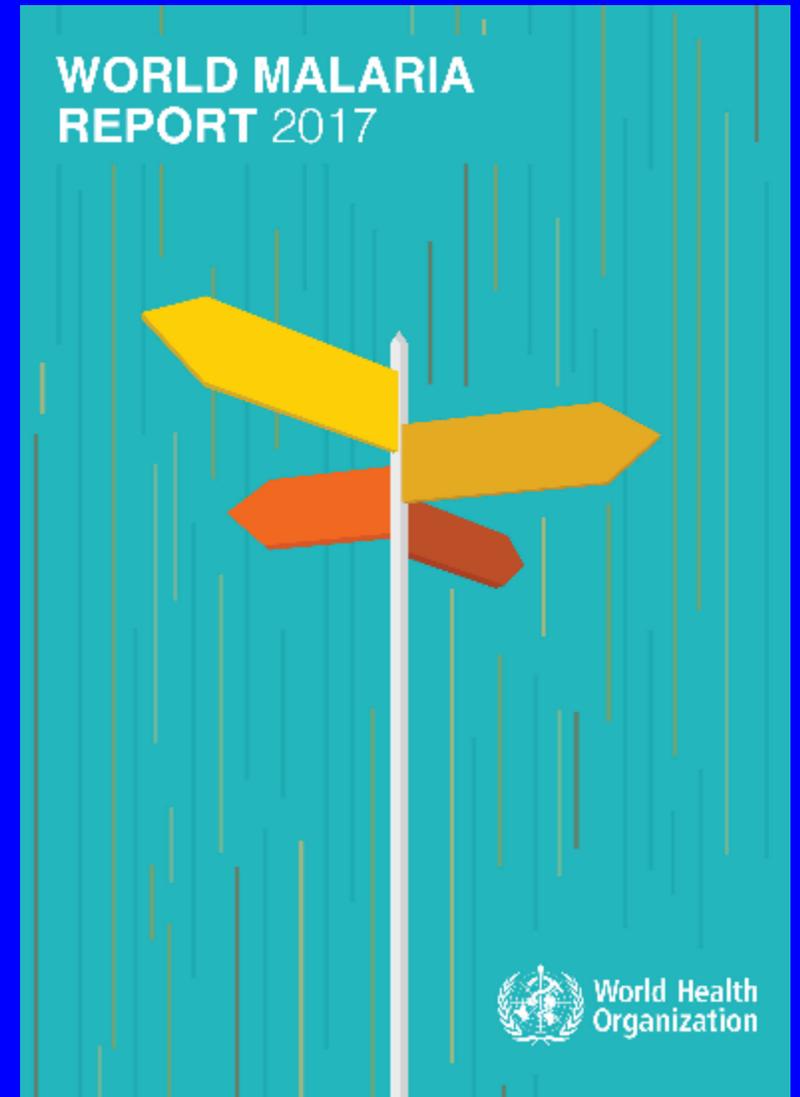
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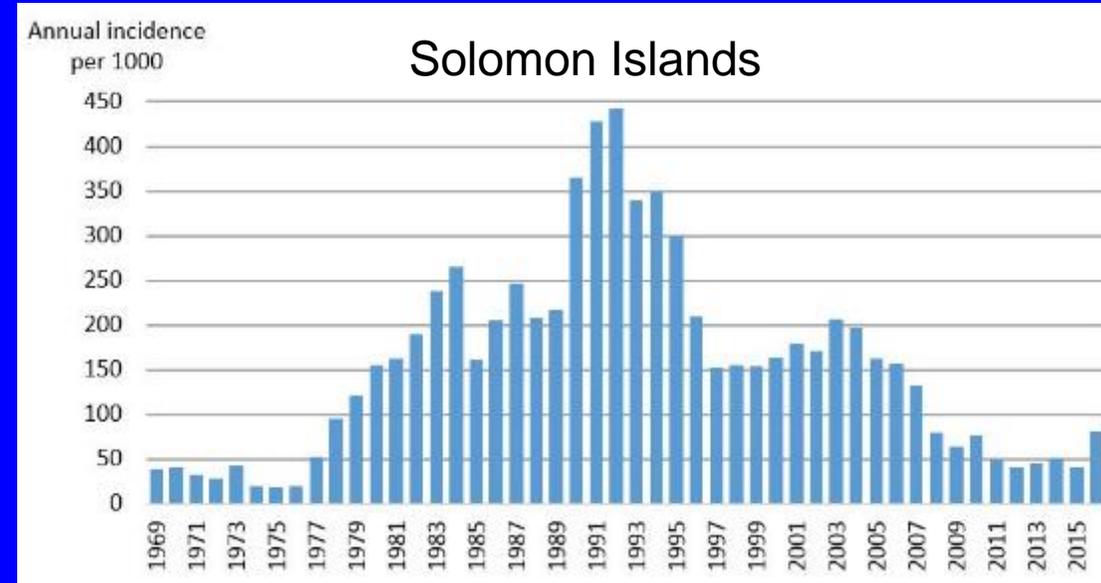
Are We Winning the War Against Malaria?

- **Gains in morbidity mortality reduction in Melanesia from rapid diagnostic tests, artemisinin combination therapy and insecticide treated bed nets**
- **This progress is fragile and there is evidence of negative developments when external resources are limited**



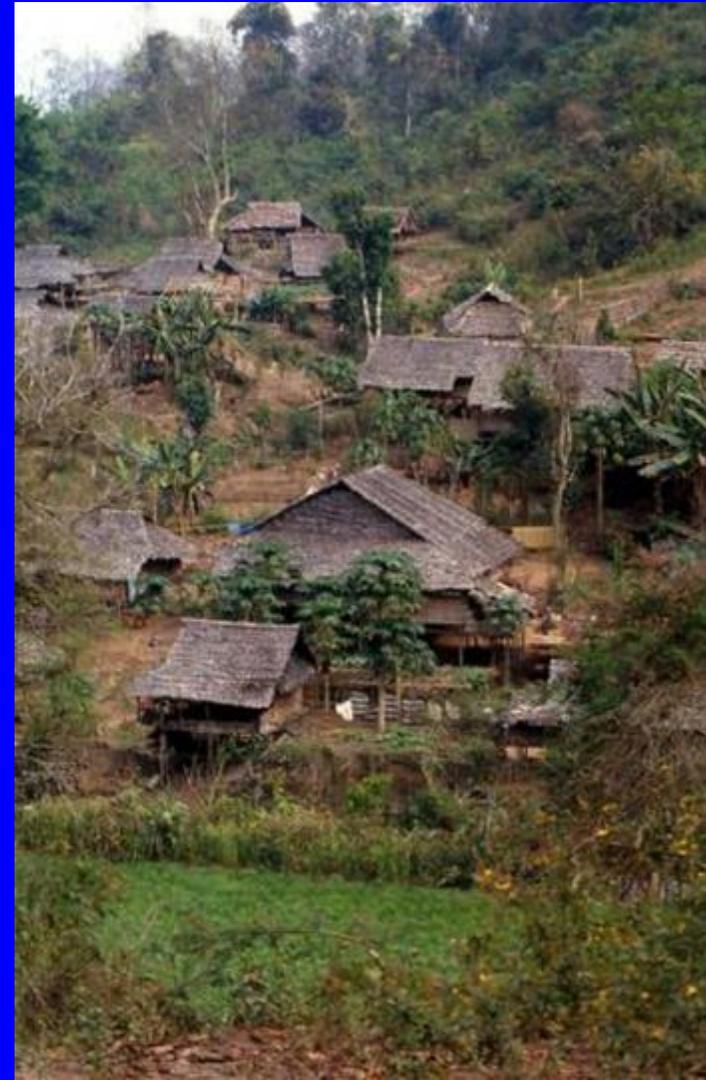
Cycle of Malaria Control Followed by Epidemics

- Malaria control requires consistency; malaria elimination requires perfection
- Melanesian countries have gone through cycles of control / failure when cases drop to point that donors are no longer interested
- Vivax is now a large proportion of malaria cases in Solomon Islands



Not Much Malaria in SE Asia, but It Is Ugly

- **Falciparum malaria left in small pockets of highly drug resistant parasites**
- **Residual transmission in SE Asia is not found in the usual tourist destinations**
- **Rural areas of Cambodia and Myanmar are problematic**



Low Risk Is Not the Same as No Risk

- What level of risk is tolerable?
- When do drug adverse events become greater than disease risk?
- Very hard to get malaria in Latin America, SE Asia, India if you are not living like a local (visiting friends and relatives)



Algorithm for Malaria Elimination in Melanesia

- Relapsing malaria (vivax) will be much harder to eliminate than falciparum
- Drugs that cure relapsing malaria are required
- Use of primaquine (and now tafenoquine) is not optional if we intend to eliminate malaria



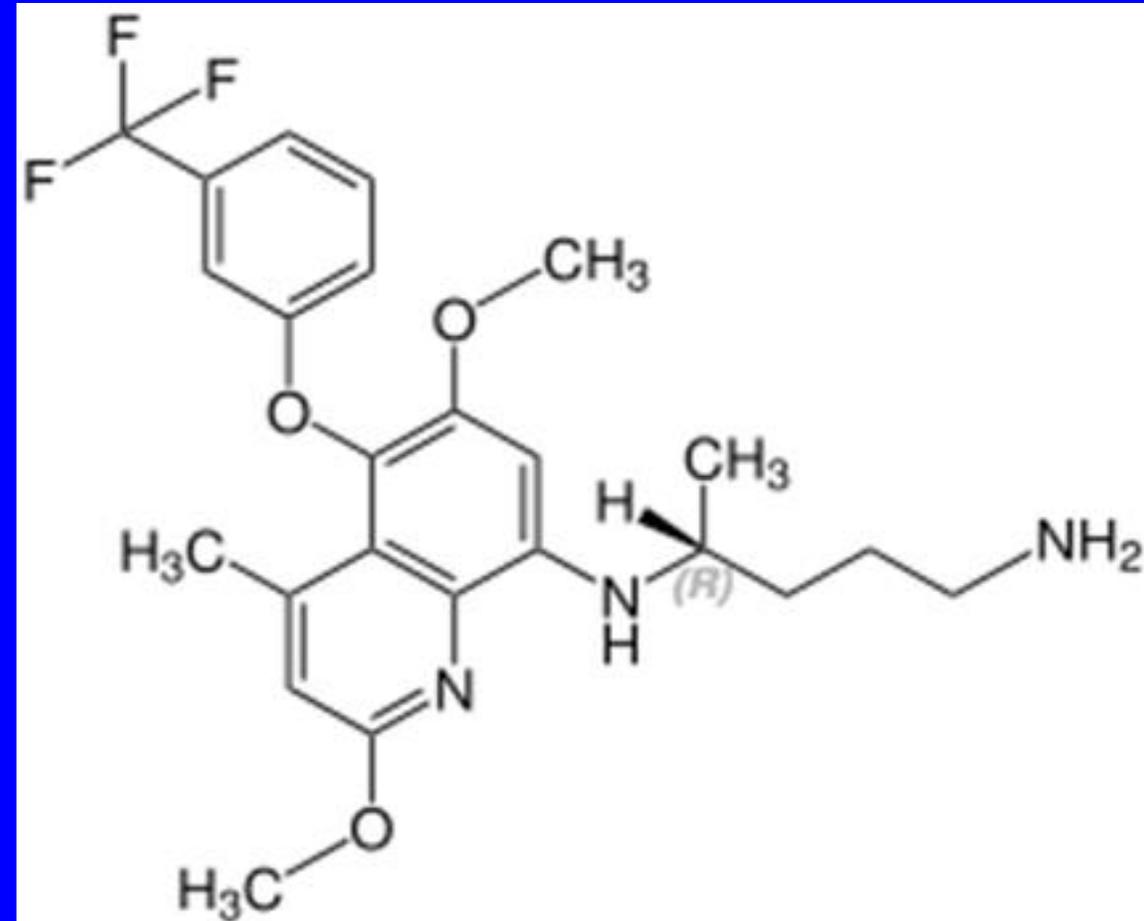
China Eliminated Vivax Malaria with Primaquine

- Mass campaigns of 1970-90s distributed >100M primaquine in areas with epidemic vivax
- Surveillance with focal MDA then used to finish remaining areas of transmission
- Estimated severe adverse events (hemolysis) at 1:10,000 despite no G6PD screening



Tafenoquine: A 'New' 8-aminoquinoline

- Tafenoquine (TQ) is a long-acting ($T_{1/2}$ 14 days) primaquine analogue
- TQ kills all stages of parasite including liver but is relatively slow acting against blood parasites
- Approved by US FDA and Australian TGA for both single dose treatment and weekly malaria chemoprophylaxis in G6PD tested



Long History of Tafenoquine

- **First synthesized in 1978**
- **First in humans at WRAIR, Washington DC in 1996**
- **Phase 2 chemoprophylaxis field trial in Kenya 1998**
- **Phase 3 chemoprophylaxis trial Australian Army 2000-01**
- **Phase 2 relapsing malaria treatment multi-center 2010-12**
- **Phase 3 relapsing malaria treatment multi-center 2013-16**

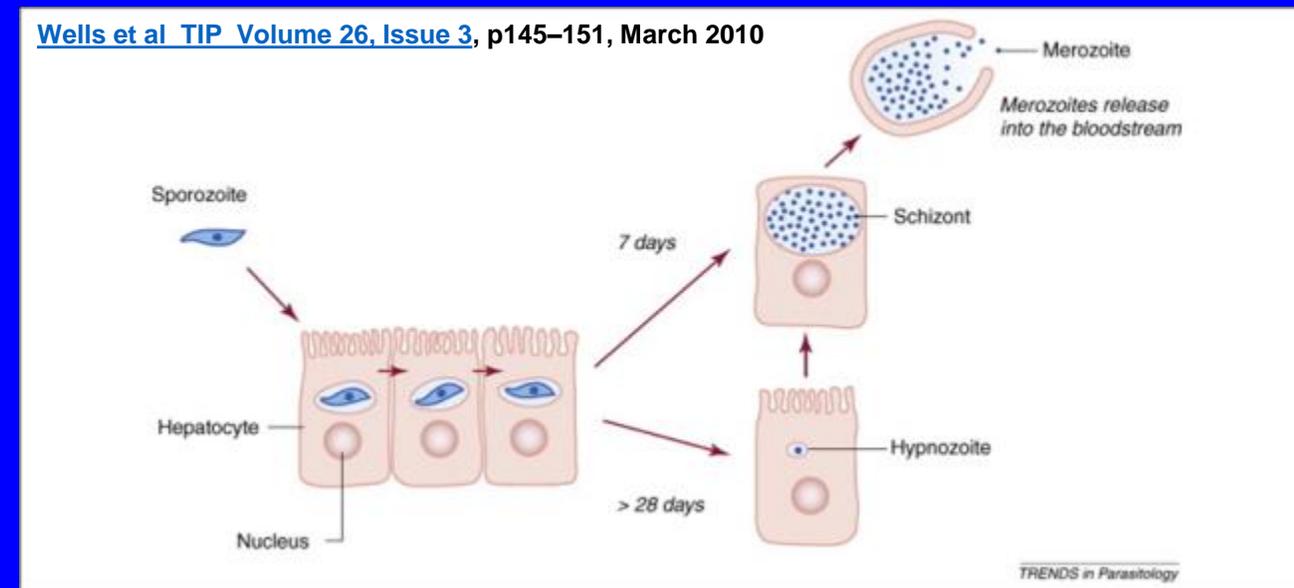
Tafenoquine: Long-Acting Primaquine-Like Drug

- Weekly dosing likely to partially fix compliance problems
- Has same G6PD liability as primaquine so need to have measured G6PD status once
- Other wise well tolerated and most appropriate for very high risk travellers



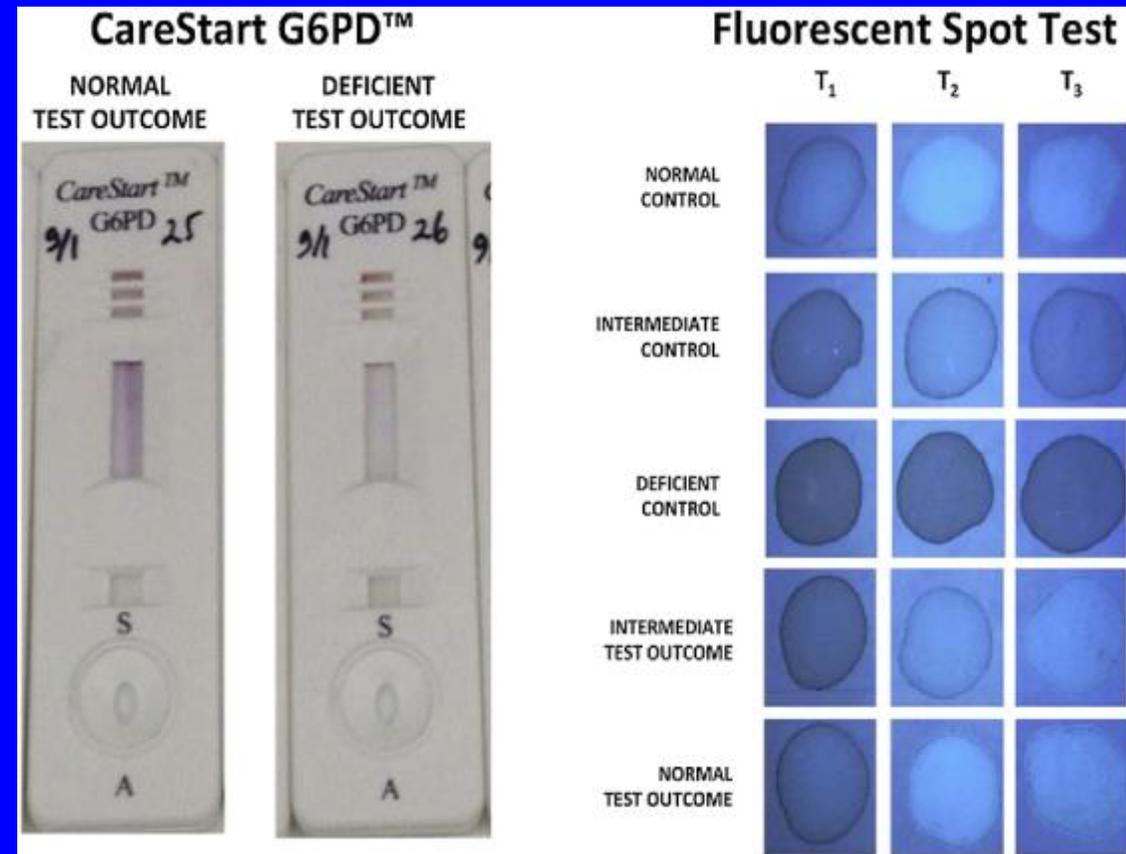
Killing Residual Hepatic Parasites (Hypnozoites)

- Quiescent post-sporozoite parasite in hepatocyte able to reactivate months after infection
- 8-aminoquinolines only class of drug known to kill hypnozoites; primaquine only drug currently available for clinical use
- Destruction of hypnozoites necessary for malaria elimination



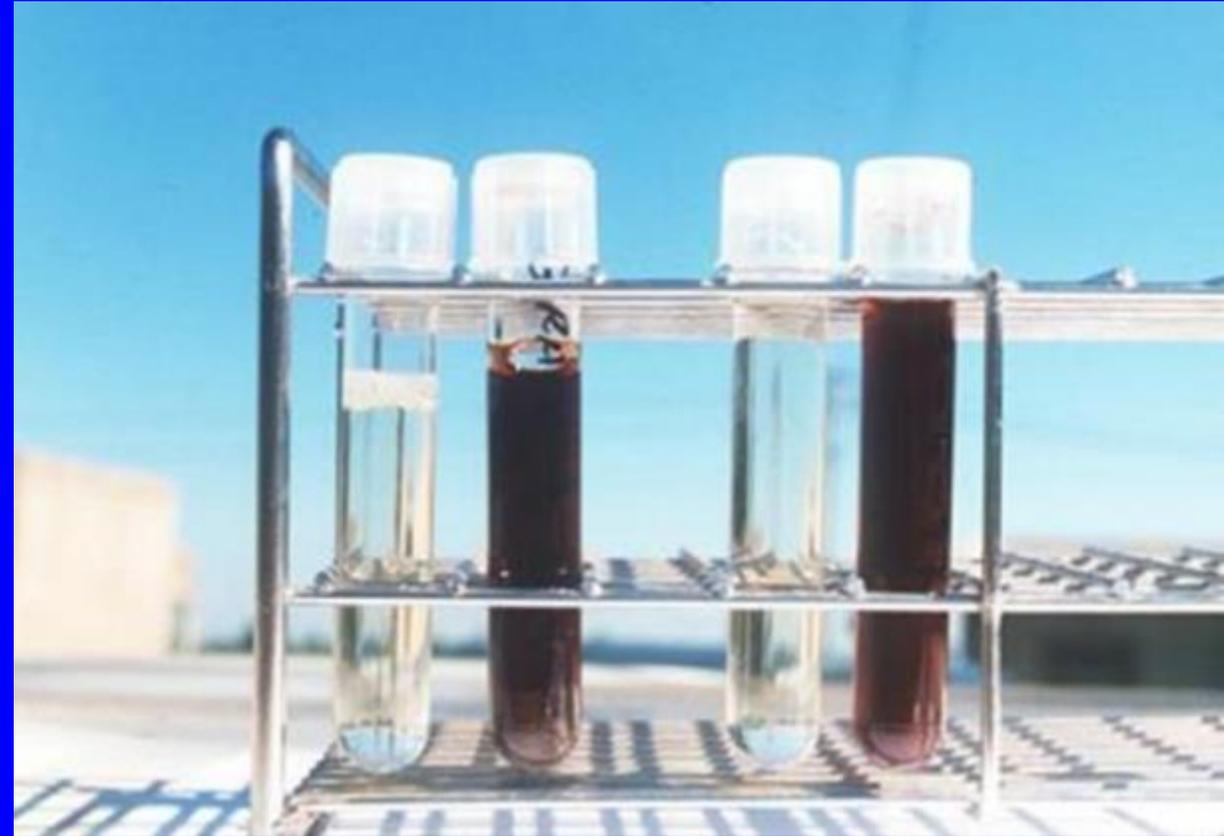
Getting Around Genetic Polymorphisms?

- **G6PD: Extremely common (10%) in some male populations in malaria endemic areas; difficult to evaluate females**
- **Rapid tests G6PD becoming available but add greatly to cost**
- **Cytochrome P450 metabolism: 2D6 null individuals do not clear hypnozoites with primaquine**



Problems with G6PD Testing in Australia

- Males are easy as G6PD measurements are unambiguous for X linked gene
- Female heterozygotes may test normal but still be liable to hemolysis in half their erythrocytes
- Currently one does not get a quantitative G6PD value



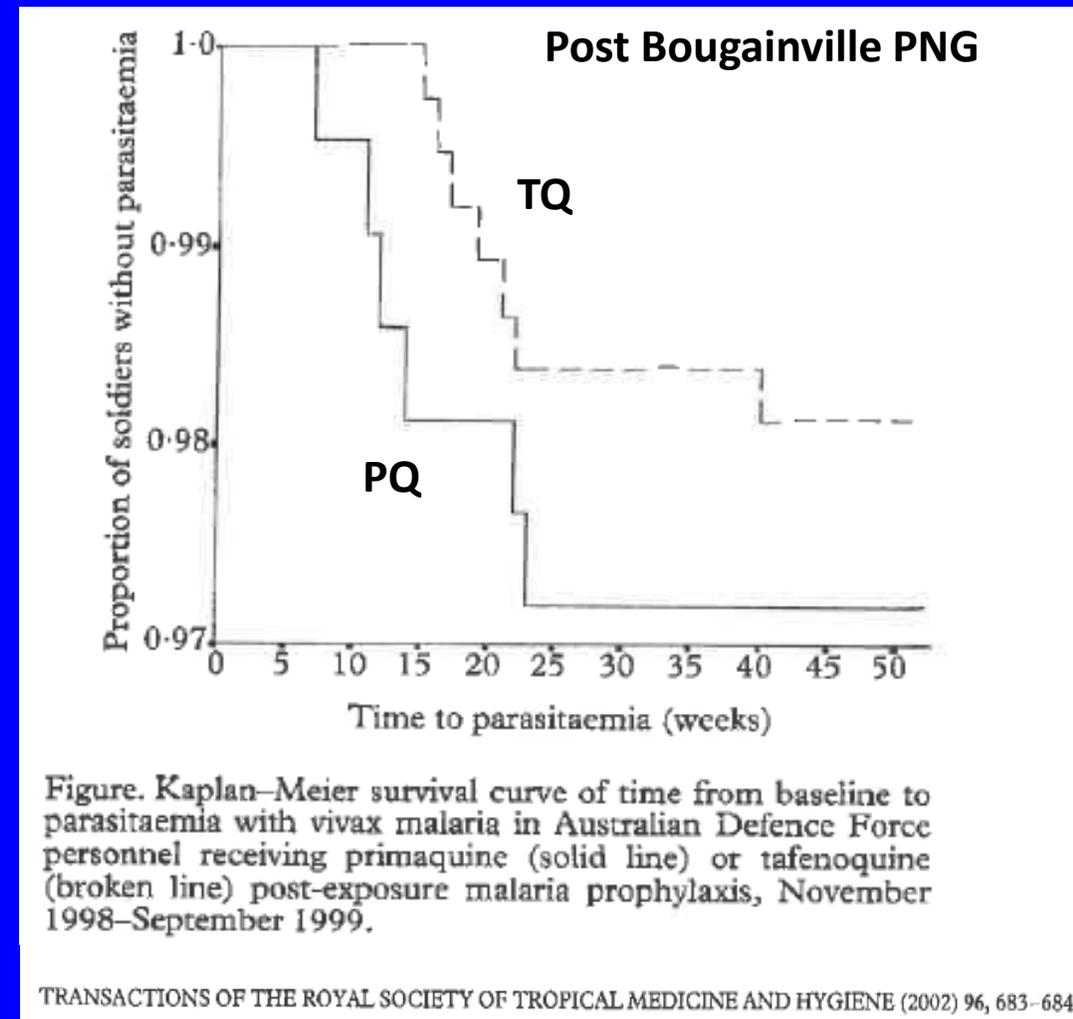
Tafenoquine Chemoprophylaxis in East Timor

- Soldiers received either weekly tafenoquine 200 mg (n=492) or mefloquine 250 mg (n=162) for 6 months
- No failures during prophylaxis followed by late vivax relapses 16-20 weeks later in 4 TQ and 1 MQ despite PQ 30mg x14
- Treatment related adverse events were 13.4 % TQ and 11.7 % MQ; vortex keratopathy noted in >90% of TQ which spontaneously resolved over 1 year



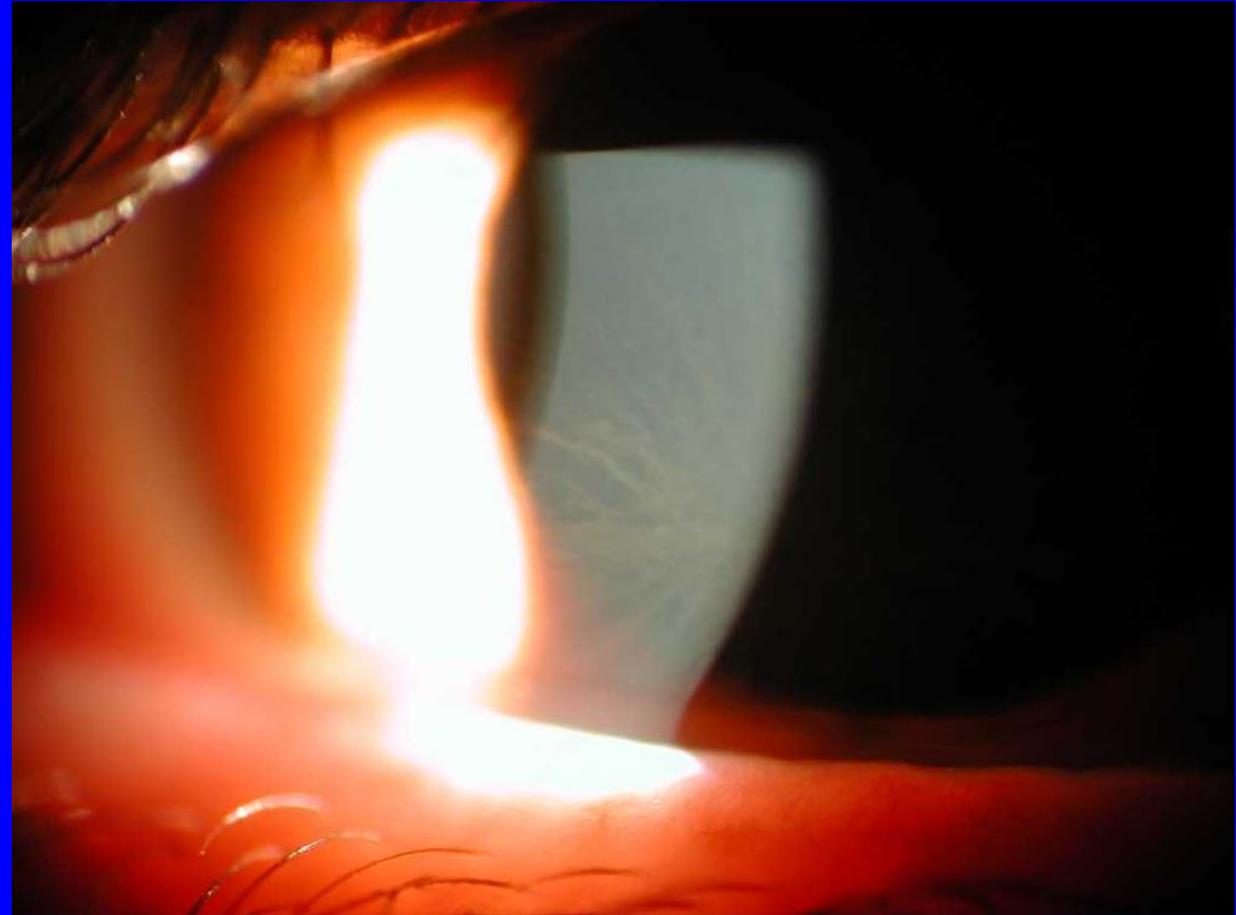
Tafenoquine Eradication after East Timor

- >400 malaria episodes during East Timor intervention from 1999-2004 most of them late vivax relapses while in Australia
- Australian soldiers received TQ (n=636) 200mg x3 as eradication therapy vs. PQ (n=289) with 4.9% vs. 10% relapses median 106 d (68-332) after return to Australia
- Most frequent adverse events for single course of TQ (600mg) were GI similar to that seen with primaquine



Should We Worry About the Eye Findings with TQ?

- Phospholipidosis was a known risk from animal toxicology
- All corneal findings were asymptomatic and spontaneously resolved
- Currently being tested out to 12 months continuous weekly use



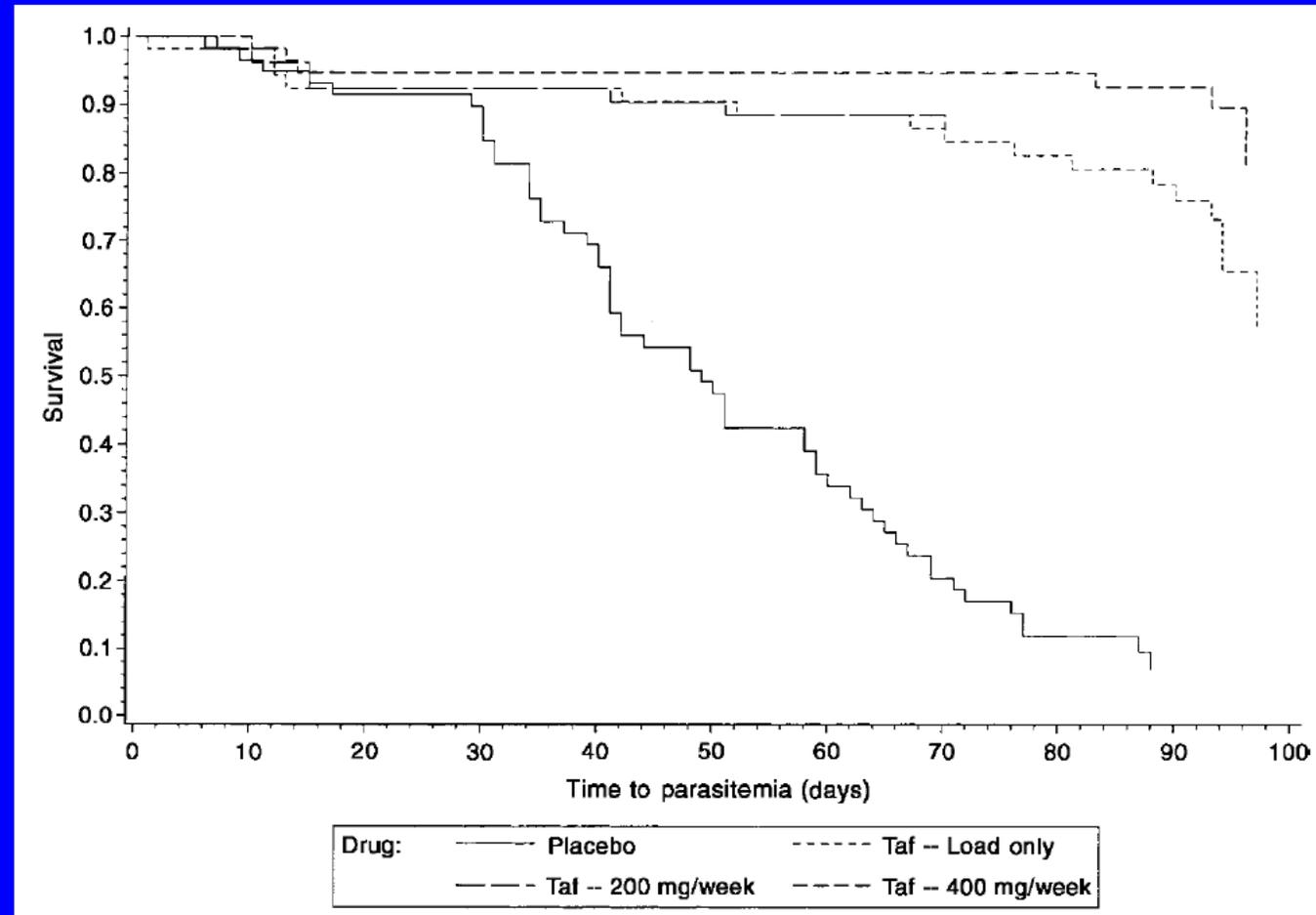
Directions to Use Prophylactic Tafenoquine

- Loading regimen of 200mg x3 OD followed by 200mg weekly for adults
- Best taken with food for improved absorption
- Working on pediatric formulation / indication



Large Doses Tafenoquine Protect for 10 Weeks

- Loading dose of 1200 mg TQ given during field trials in Kenya
- Loading dose remained as effective as weekly medication out to 10 weeks post drug (about 7 half lives)
- Likely that doses < 200 mg still have good antimalarial effect lasting at least 2 weeks



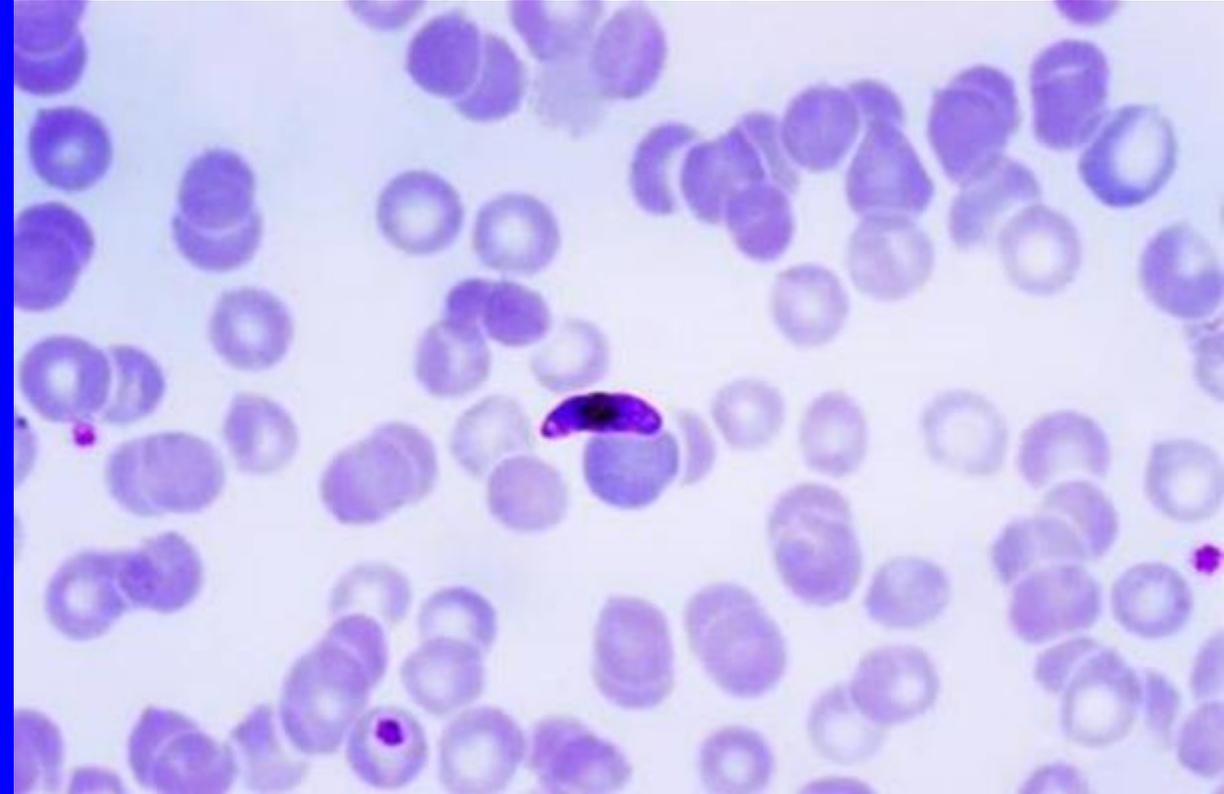
Possible Tafenoquine Scenario for Elimination?

- **Pulse of drug into a defined area to stop transmission**
- **Mass drug administration in order to eliminate relapses**
- **Stopping an on-going epidemic with tafenoquine**



Other Aspects of Tafenoquine Being Tested

- Extend from 6m to 12m for prevention
- Monthly dosing regimens or single dose short-term protection
- Presumptive treatment (post travel eradication)



Public Health Indications for Tafenoquine?

- Tafenoquine kills gametocytes thus blocking transmission
- Destroy the hypnozoite reservoir to stop source of relapsing malaria
- Unlikely to be used for mass drug administration until G6PD problem is better worked out



Conclusions for Traveller's Malaria

- Most important function of travel medicine practitioner is to accurately evaluate risk
- Menu of chemoprophylaxis choices now includes a safe weekly drug: tafenoquine
- Still are good reasons to use atovaquone / proguanil or doxycycline in some travellers



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