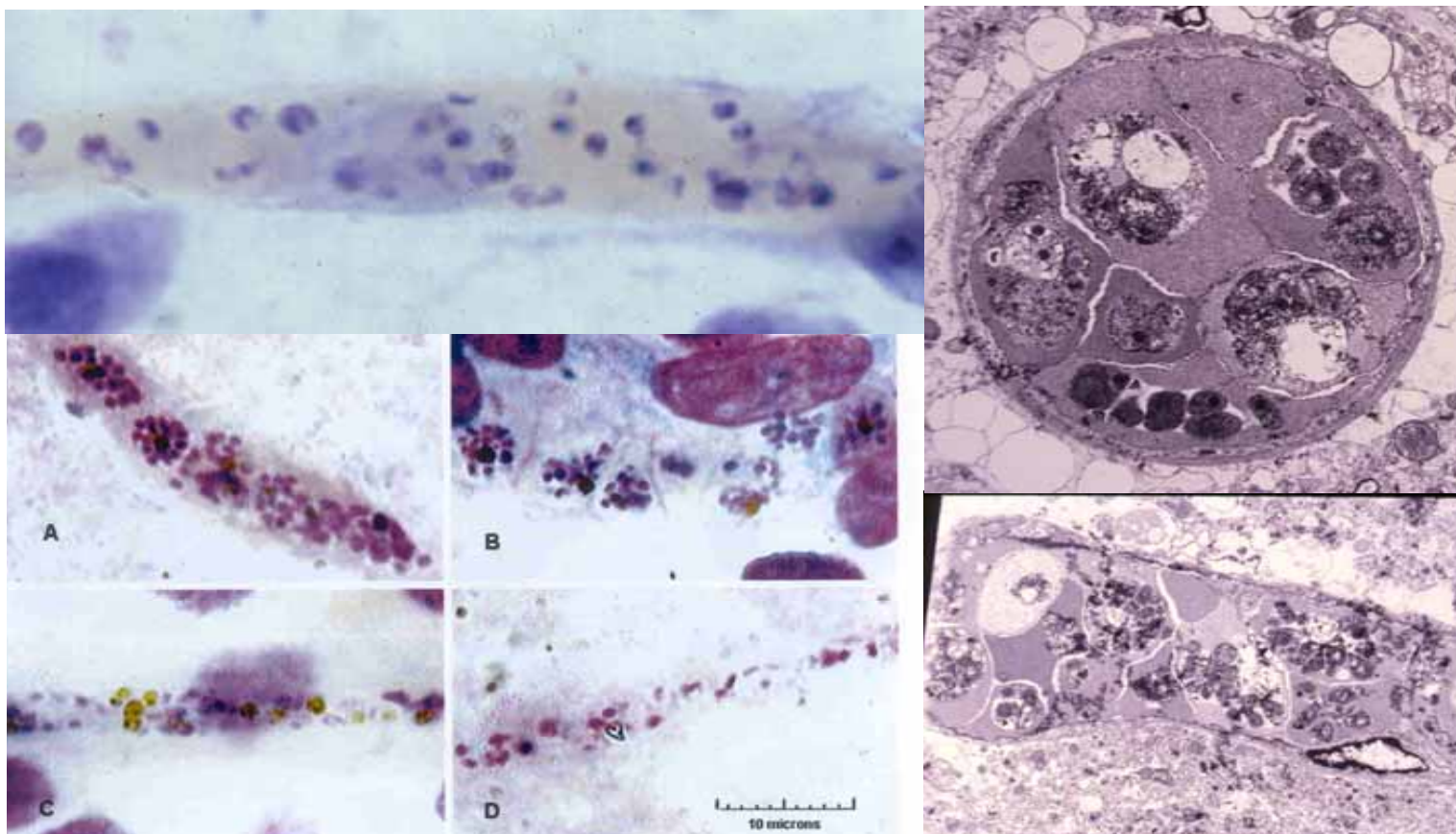


IV Artesunate Access in South Africa

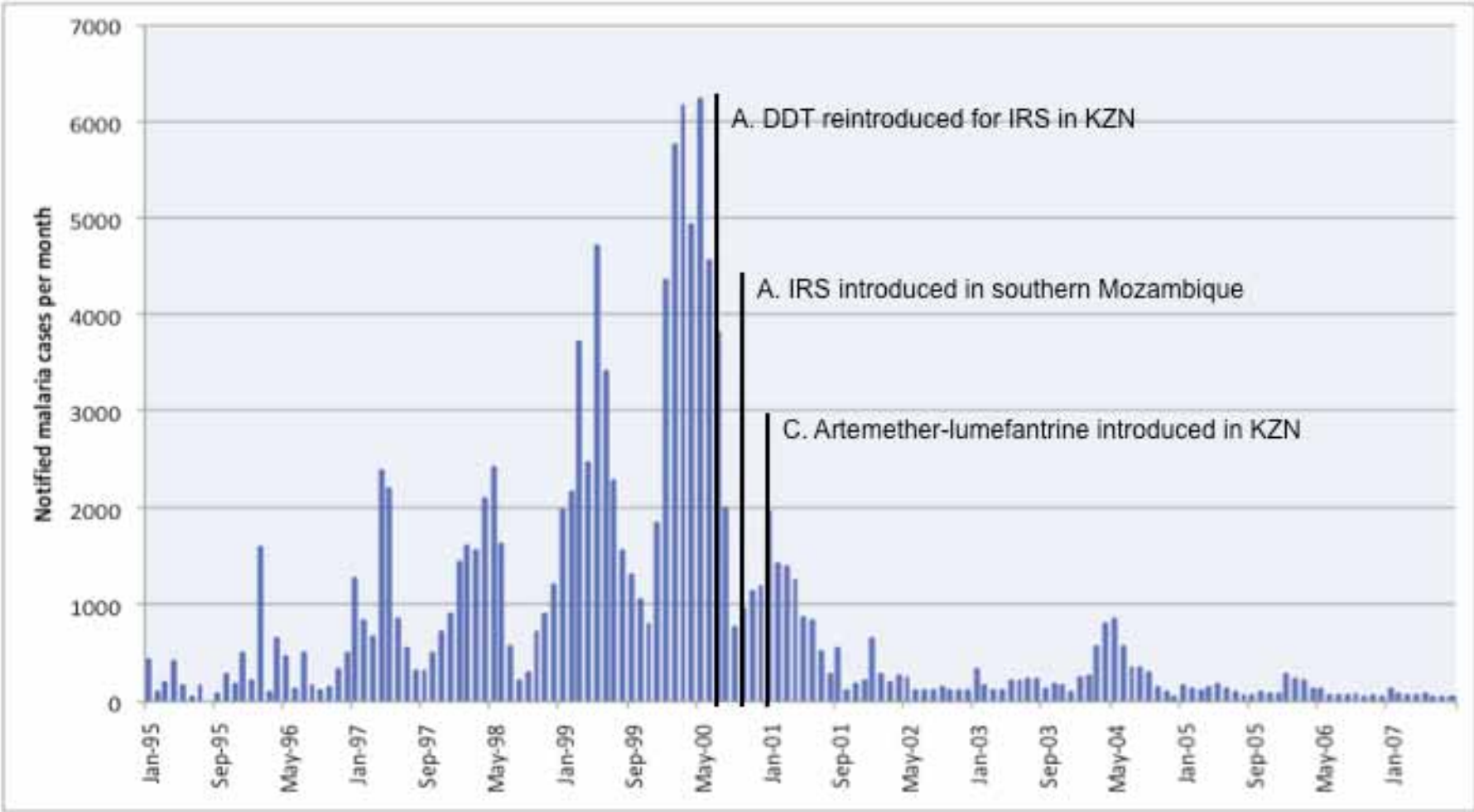
For adult patients with severe malaria

Karen I Barnes, UCT Division of Clinical Pharmacology



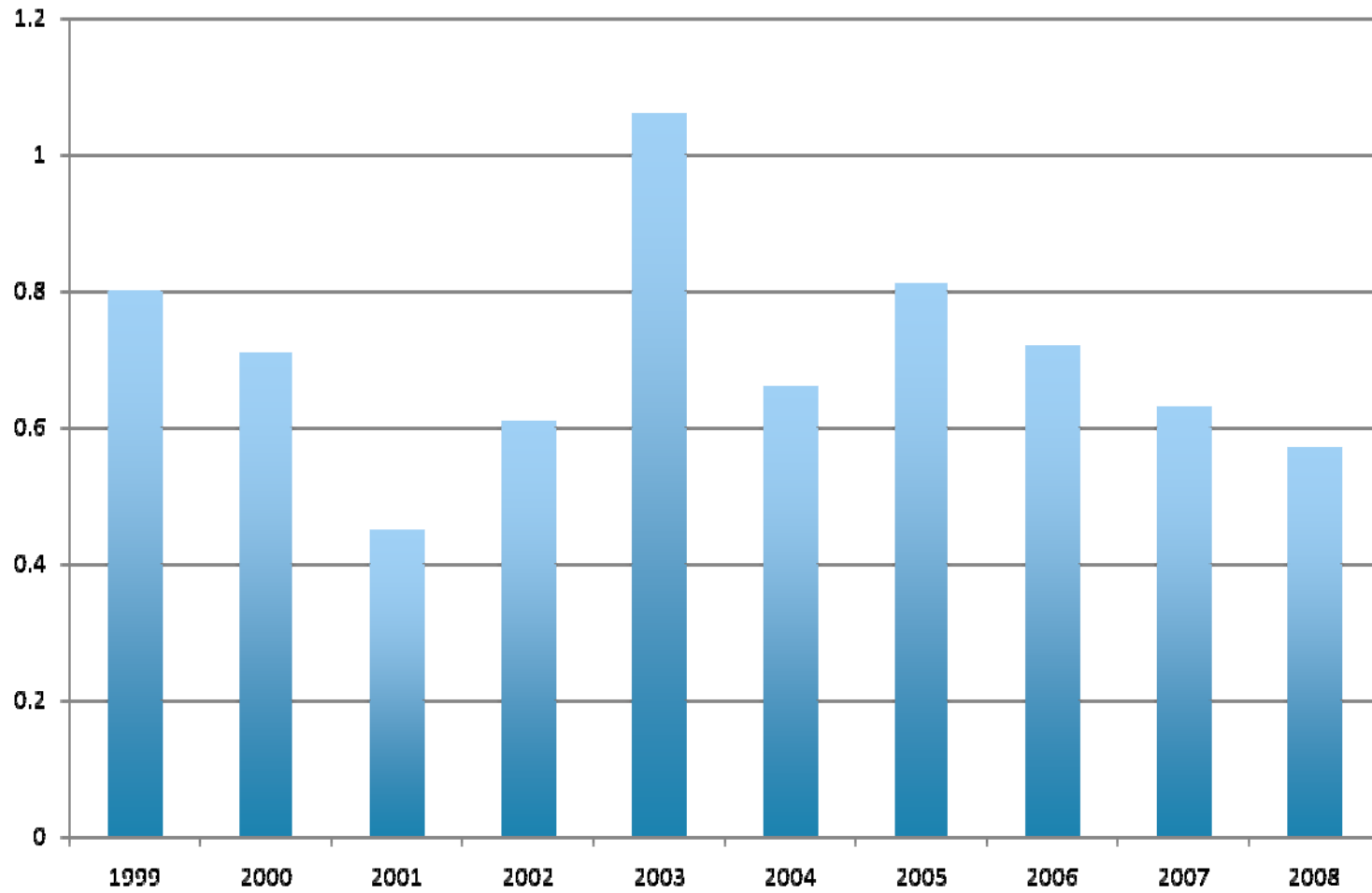
Pongponratn et al. *Am J Trop Med Hyg* 1991; 44: 168-75

Notified malaria cases in KwaZulu Natal



Source: South African Department of Health

Malaria Case Fatality Rate



Source: SA Department of Health

Why is the Malaria Case Fatality Rate not decreasing?

Malaria no longer major concern of community in South Africa:

- Delay in treatment seeking

Healthcare workers have a lower index of suspicion of malaria

- Delay in diagnosis

HIV co-infection increases malaria case fatality rates in hospitalised severe malaria cases increased by up to 8.8 –fold.

Non-malaria areas probably have more cases than any of the malaria risk provinces.

- 22% severe malaria
- 2.1% Case Fatality Rate

Problems associated with quinine use

Malaria deaths as sentinel events to monitor healthcare delivery and antimalarial drug safety

U. Mehta¹, D. N. Durrheim², L. Blumberg³, S. Donohue⁴, F. Hansford⁵, A. Mabuza⁶, P. Kruger⁵, J. K. Gumedde⁷, E. Immelman⁸, A. Sánchez Canal⁹, J. J. Hugo¹⁰, G. Swart¹⁰ and K. I. Barnes¹

Problems identified with quinine use:

- Quinine **loading dose not administered** in 36% (61/166) of fatal malaria cases.
- **Loading dose repeated** in 4 patients already on quinine, following clinical deterioration.
- Quinine was **administered very rapidly** in five patients, one of whom died within minutes of bolus quinine dose.
- **Severe hypoglycaemia** (glucose < 2.2 mol/L) developed or was exacerbated in 14% (23/161) of patients.

Reducing malaria mortality in South Africa

- Ensure early treatment seeking among patients & high index of suspicion among healthcare workers
- Sustain excellent malaria control in KwaZulu Natal, Mpumalanga and Limpopo.
- Extend malaria control further in Mozambique (and ideally Zimbabwe).
- Improve treatment of malaria in non-malaria areas
 - Increased awareness of malaria
 - Access to artemether-lumefantrine for uncomplicated malaria and completion of treatment of severe malaria
 - **Access to intravenous artesunate for severe malaria**

Mortality: an absolute risk reduction of 34.7%

Articles

Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial



South East Asian Quinine Artesunate Malaria Trial (SEAQUAMAT) group*

Summary

Background In the treatment of severe malaria, intravenous artesunate is more rapidly acting than intravenous quinine in terms of parasite clearance, is safer, and is simpler to administer, but whether it can reduce mortality is uncertain.

Methods We did an open-label randomised controlled trial in patients admitted to hospital with severe falciparum malaria in Bangladesh, India, Indonesia, and Myanmar. We assigned individuals intravenous artesunate 2.4 mg/kg bodyweight given as a bolus (n=730) at 0, 12, and 24 h, and then daily, or intravenous quinine (20 mg salt per kg loading dose infused over 4 h then 10 mg/kg infused over 2–8 h three times a day; n=731). Oral medication was substituted when possible to complete treatment. Our primary endpoint was death from severe malaria, and analysis was by intention to treat.

Findings We assessed all patients randomised for the primary endpoint. Mortality in artesunate recipients was 15% (107 of 730) compared with 22% (164 of 731) in quinine recipients; an absolute reduction of 34.7% (95% CI 18.5–47.6%; p=0.0002). Treatment with artesunate was well tolerated, whereas quinine was associated with hypoglycaemia (relative risk 3.2, 1.3–7.8; p=0.009).

Interpretation Artesunate should become the treatment of choice for severe falciparum malaria in adults.

Lancet 2005; 366: 717–25

*Members listed at end of paper

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Thailand
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WHO Malaria Treatment Guidelines 2009 (Sneak preview)

Recommendation

Intravenous artesunate should be used in preference to quinine for the treatment of severe *P. falciparum* malaria in adults (STRONG recommendation, HIGH quality evidence).

GRADE evaluation

- Intravenous artesunate has been shown to significantly reduce the risk of death from severe malaria compared to intravenous quinine (6 trials, 1938 participants; RR 0.62, 95% CI 0.51 to 0.75; high quality evidence).
- Intravenous artesunate was associated with a lower risk of hypoglycaemia.
- No difference has been shown in the risk of serious neurological sequelae.

Other considerations

Artesunate offers a number of programmatic advantages over quinine in terms of not requiring rate-controlled infusion nor cardiac monitoring.

The panel considers there to be insufficient evidence from trials to date involving children to recommend artesunate in preference to quinine in this group.

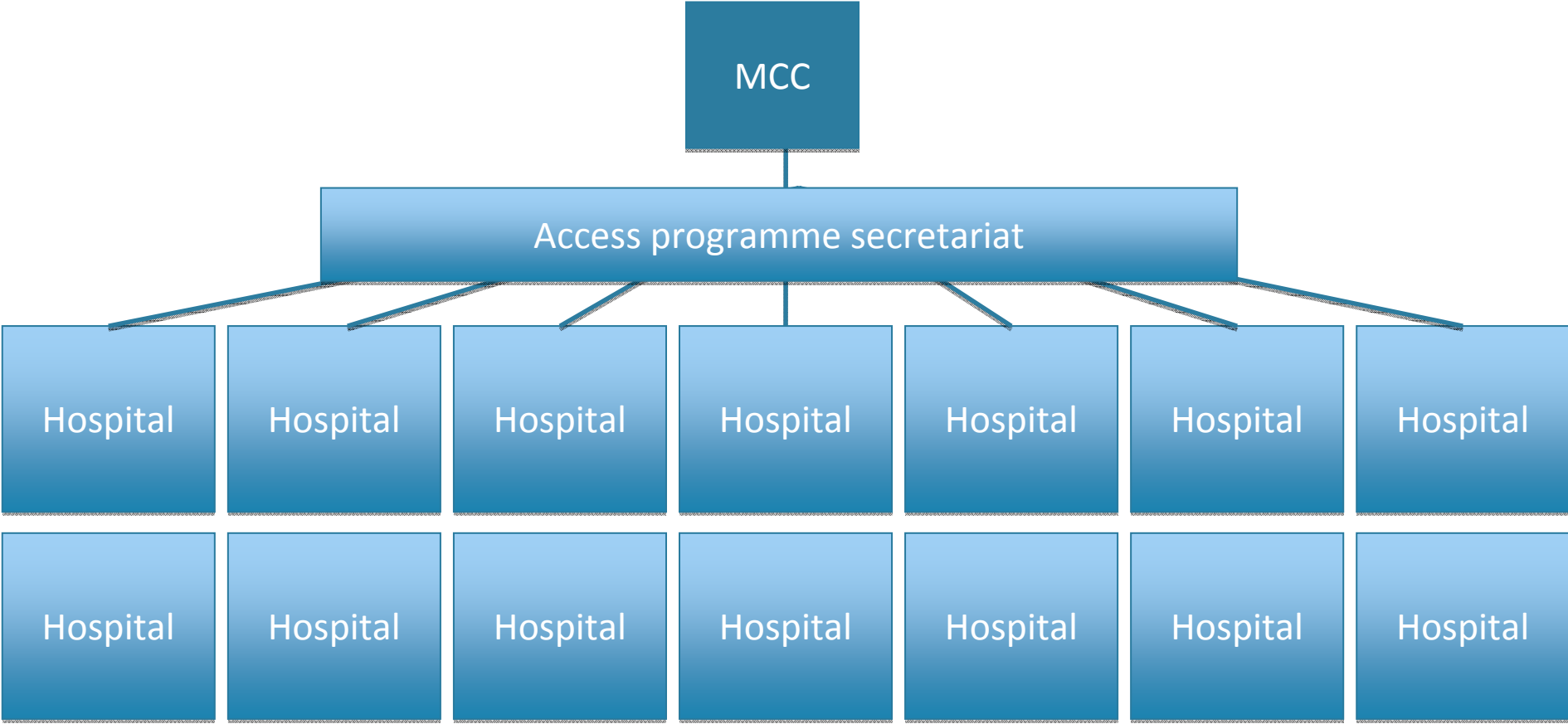
Way forward

- Multi-centre RCTs are currently being conducted to compare IV quinine and artesunate in **African children** with severe malaria.
- IV artesunate **registered** for use in many Asian and African countries
- Australia, UK, USA and Canada have released IV artesunate for use on a “special access scheme” on a **named facility basis**.
- **Approval for Section 21** release on named patient basis obtained from South African Medicines Control Council in June 2009.

3 step plan

1. Procure, QC and distribute to 16+ sentinel hospital sites by 1 Dec 2009
 - 10 treatment courses per hospital (150 packages)
 - When down to 50 packages, will arrange repletion of stock from central storage
2. Support case management (training; informed consent; monitoring chart; drug accountability)
 1. Named-patient authorisation and reporting via secretariat

Access Programme



Administration

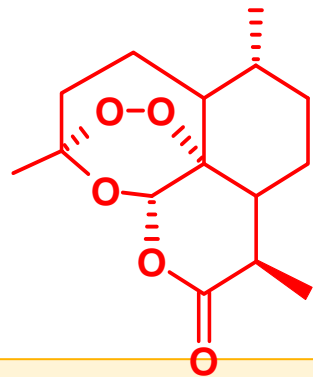
- Dose: 2.4mg/kg at 0, 12, 24 hours and daily until oral meds can safely be taken
- Store at room temperature (15-30°C). Keep out of light.
- Dilute in 1 ml 5% bicarbonate (it has poor stability in aqueous solutions at neutral or acid pH)
- Shake gently, then dilute the reconstituted solution in 5% dextrose.
- Once reconstituted, use within 30 minutes.
- Administration is by slow (over 2 minutes) intravenous injection.
- Complete course of artemether-lumefantrine once able to tolerate oral treatment.

Support structures

- IV Artesunate Access Programme Secretariat
 - Marilyn Solomons 021 406 6779
 - Dr Tamara Kredo 021 406 6355
- Drug information centres
 - UCT Medicines Information Centre (0800 212 506)
 - Amayeza Info Centre (0861 669 943).
- SA Medicines Formulary 9th edition
- Medicines Control Council

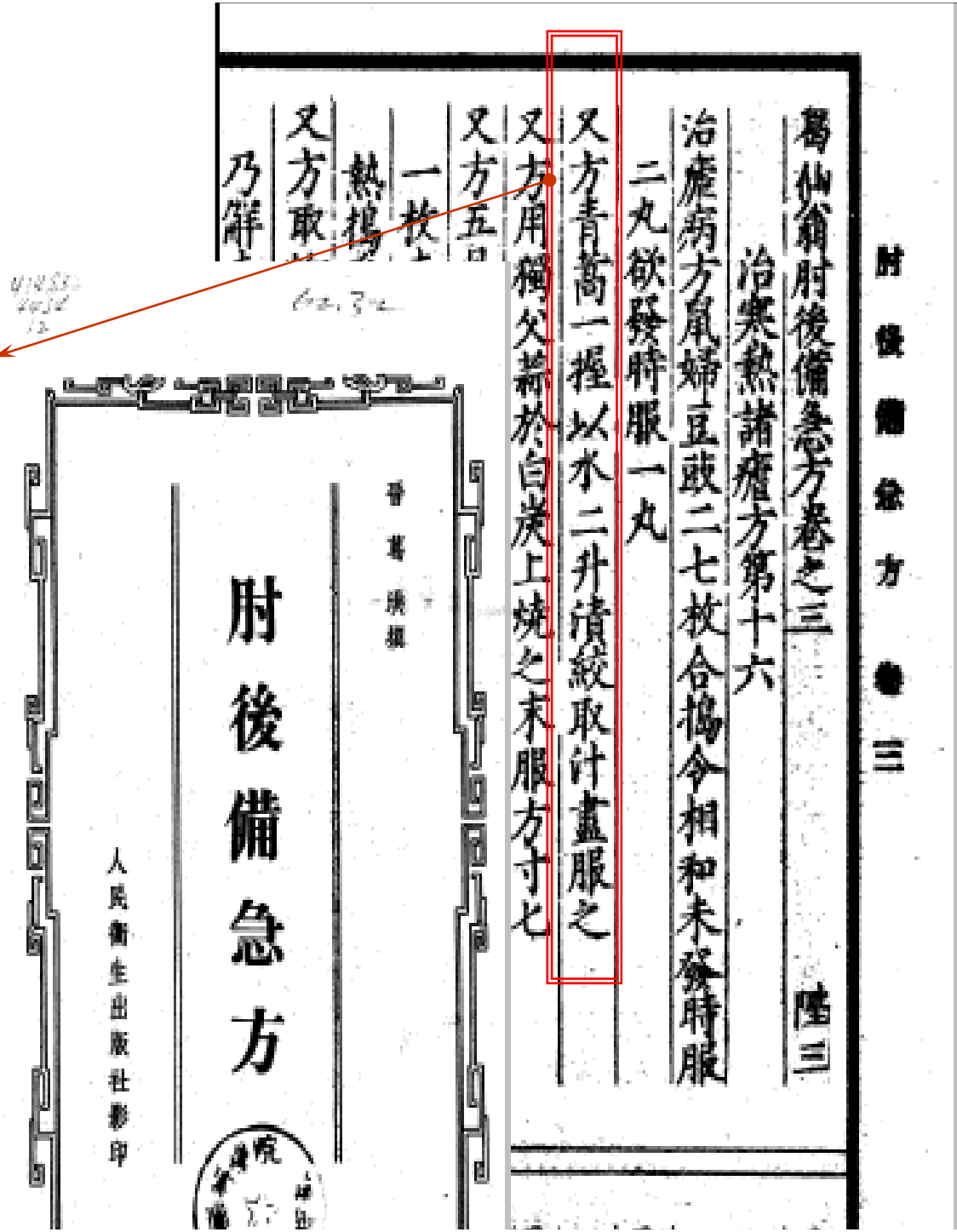
Conclusions

- IV artesunate access programme is being launched with the objective of reducing malaria related mortality
- Strict section 21 documentation needed to assure safety of unregistered product and longevity of the access programme
- The project will be reviewed annually by MCC and any nonconformities could result in closure.



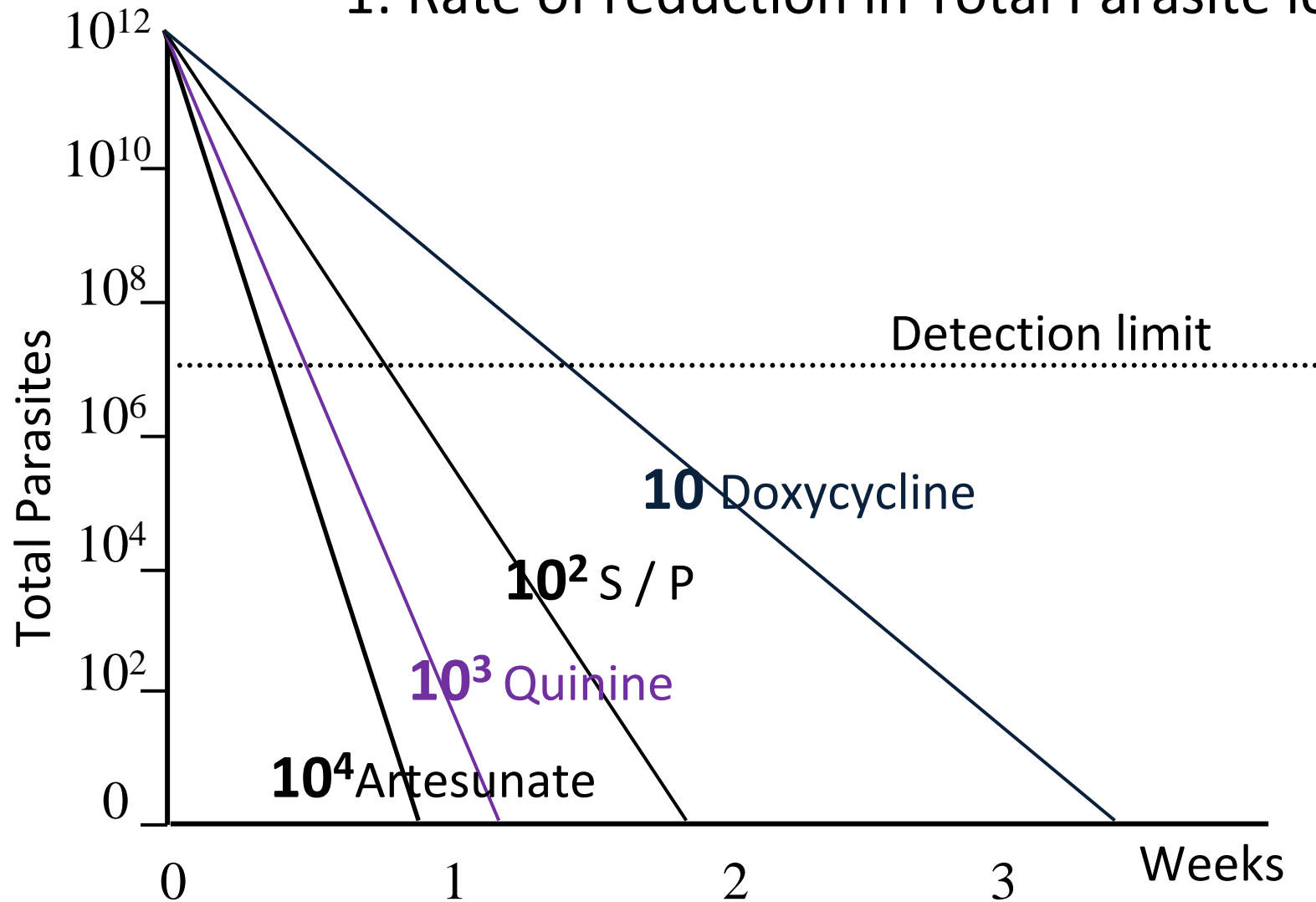
The treatment of malaria with qinghao was first recorded in 肘后备急方 (Handbook of Prescriptions for Emergency Treatment) by 葛洪 (Ge Hong, 281-340 AD)

a handful of qinghao immersed with 2 liters of water, get juice and drink it.



Why is artesunate better than quinine?

1: Rate of reduction in Total Parasite load



Why is artesunate better than quinine?

2: Stage specificity

