DEPARTMENT OF PRIMARY HEALTH CARE

UNIVERSITY OF OXFORD

Clinical Research on Traditional Medicines

Dr Merlin Willcox
Clinical Researcher

SEVENTH FRAMEWORK PROGRAMME

Plan

- Why traditional medicine?
- Innovative methods for clinical research on TMs
- Research capacity strengthening

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Why study traditional herbal medicine?

- Has been the source of many of our most effective medicines
- Africa has a “competitive advantage”
  - Very rich traditions of herbal medicine
- Available and affordable locally
- Can generate income for farmers and producers
- Preferred by many patients
- Is in widespread use

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What is different about traditional medicine?

- People are using it already
  - observational studies can be done before any laboratory work
- History of traditional use, with no observed adverse effects, reduces the need for pre-clinical toxicology
- Less funding available
  - approaches need to be more cost-effective
- Multidisciplinary teams are essential:
  - Clinicians
  - Statisticians
  - Traditional healers
  - Botanists, anthropologists
  - Pharmacologists, Chemists

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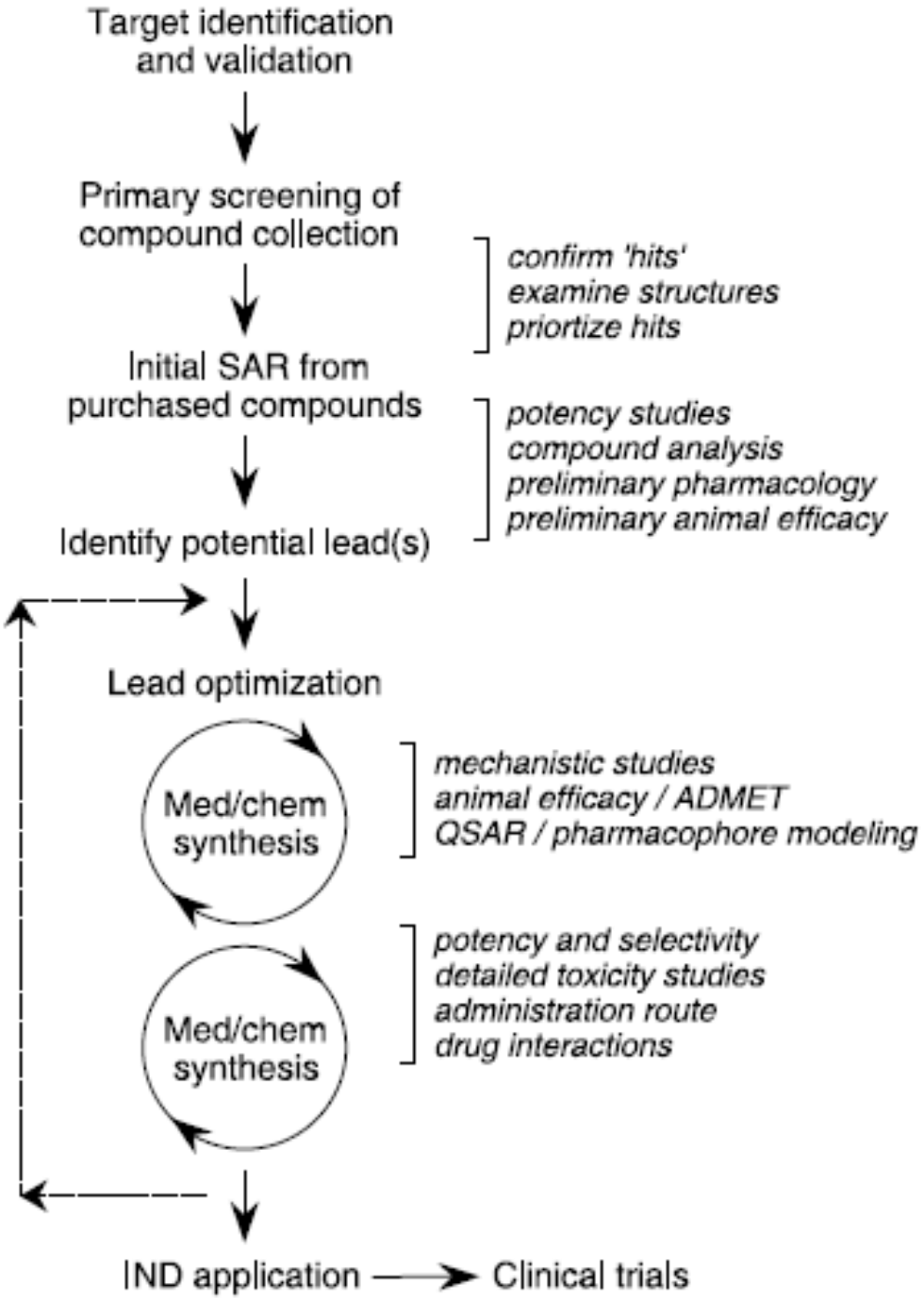
How to research and develop traditional medicines?

Conventional Drug Discovery

Conventional Drug Discovery

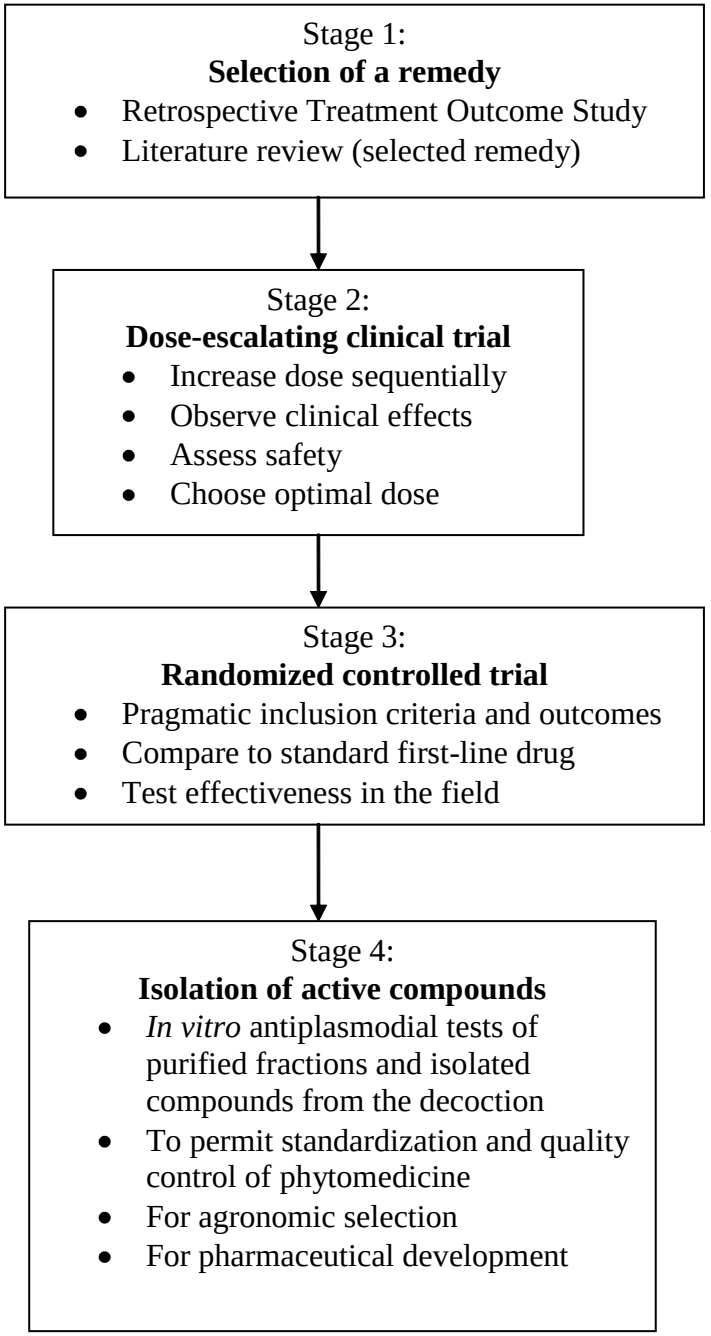
- Takes 15 years
- Costs up to $800m
- End product is often unaffordable and unavailable to the poor



But there are other approaches…

Reverse Pharmacology

- Took 6 years to develop an “improved traditional phytomedicine” in Mali
- Cost about 0.4m Euros
- End product is easily affordable and available

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DEPARTEMENT MEDECINE TRADITIONNELLE
INRSP
B.P. 1746

Aim

- To develop a new cost-effective antimalarial phytomedicine for Mali
- For production as an “Improved Traditional Medicine”
- And for local cultivation and production at the village level

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Stage 1: Selection of a remedy

Retrospective Treatment Outcome Study

- Household heads interviewed at end of rainy season
- “Has anyone in your household had malaria / fever in the last 2 weeks?”
- “If so, what treatment(s) did they take?”
- “What was their outcome?”

Graz et al (2005), J Ethnopharm

RTO in Mali

- Studied case histories of 952 children with recent “malaria”
  - 87% treated at home
  - 40% with modern medicine alone
  - 33% with modern + trad medicine
  - 27% with trad medicine alone
- 66 plants used traditionally for treatment of malaria

Diallo et al (2006) Trans Roy Soc Trop Med Hyg

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RTO: analysis

Table 1 Sample results from the RTO study for the three most promising plants (the full table included 66 plants in total)

Plant	Preparation	No of cases reporting use	No of cases reporting clinical recovery	No of treatment failures	Correlation with clinical recovery	(95% CI)	P (Fisher) *
Argemone mexicana (Papaveraceae)	Aerial parts decoction	30	30	0	100%	(88-100)	NA (best results)
Carica papaya	Leaves decoction	33	28	5	85%	(68-95)	0.05
Anogeissus leiocarpus	Leaves	33	27	6	82%	(64-93)	0.03

*(Number with and without clinical recovery compared to the plant with best results.

- Adjust for confounding factors
- Select traditional medicines which
  - are systematically associated with rapid and complete cure,
  - with no failures

Selection of a plant

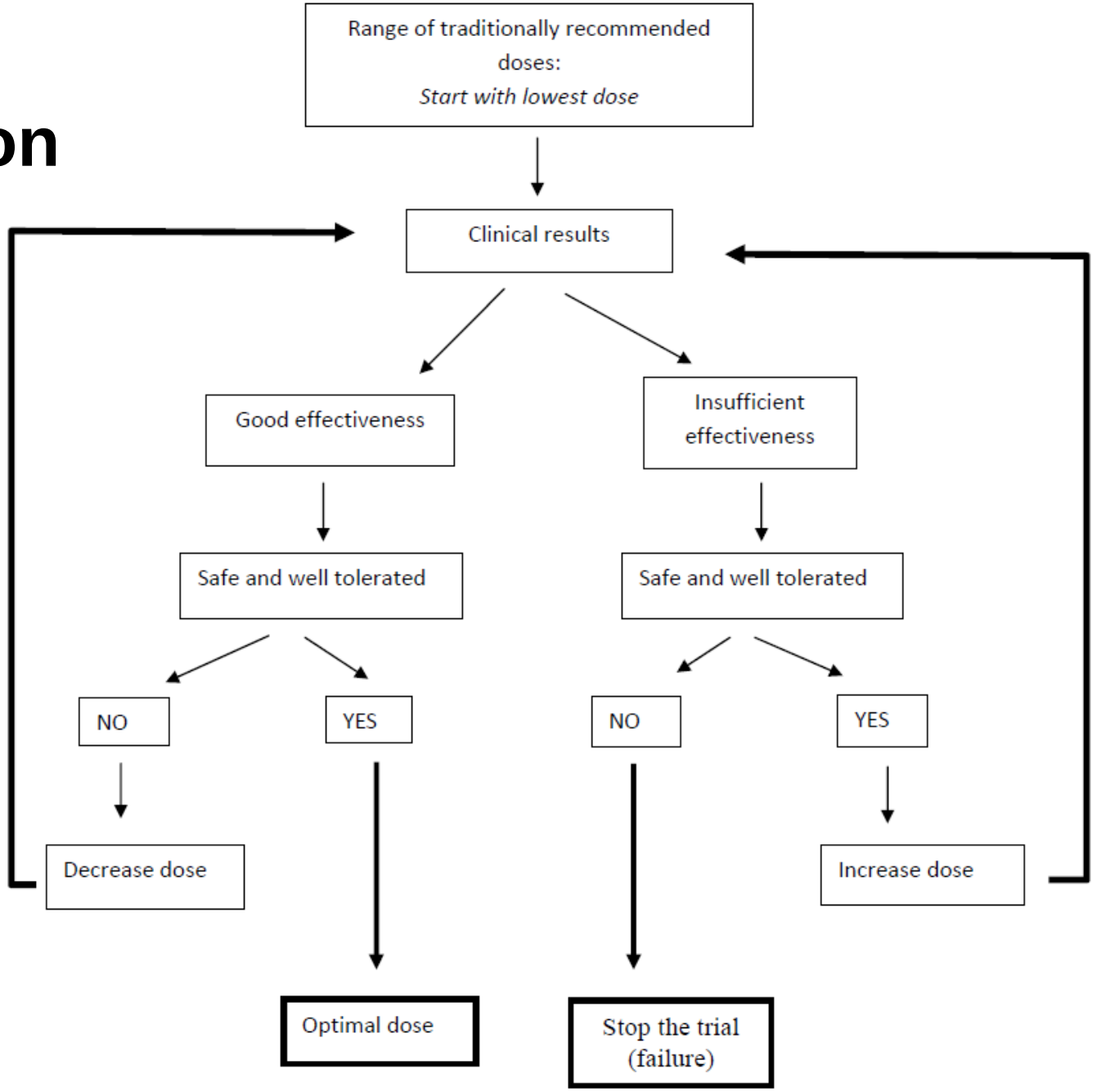
- *Argemone mexicana* associated with clinical recovery in all cases.
- Four crude extracts had IC_{50} <5mcg/ml:
  - *Spondias mombin*,
  - *Opilia celtidifolia*,
  - *Securinega virosa*,
  - *Argemone mexicana*.

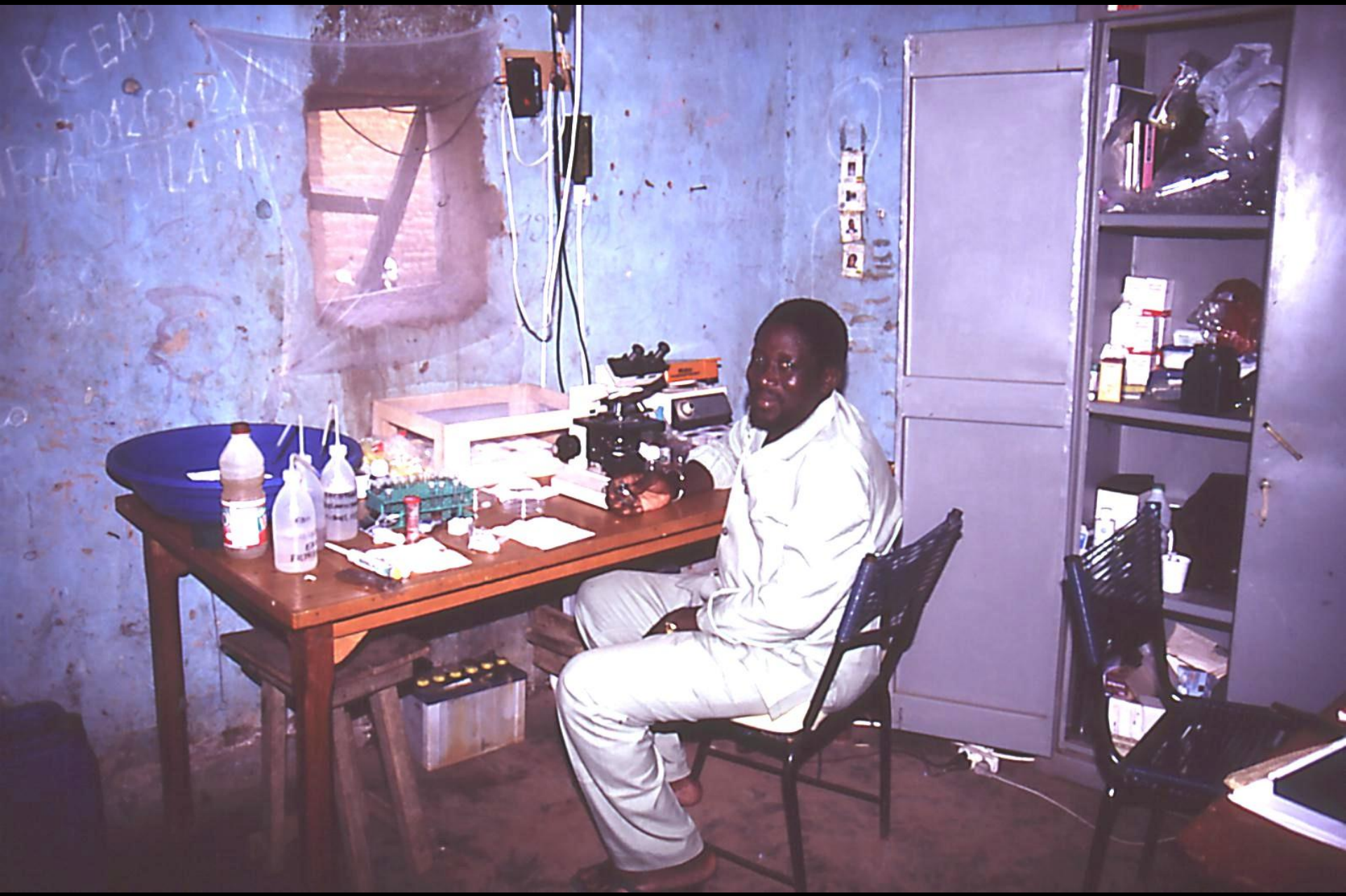
Diallo et al (2006) Trans Roy Soc Trop Med Hyg

Stage 2: Dose-escalating clinical study

- Observation of patients who chose to take the remedy
- Diagnosis of malaria confirmed (microscopy)
- Starting at lowest dose traditionally used
- Increasing dose according to response

Dose Optimisation





Inclusion criteria

- Traditional healer decided to treat with “AM”
- Clinical diagnosis of malaria
- Parasitaemia >2000 / mcl
- No other obvious cause of fever
- No signs of severe malaria
- Informed consent

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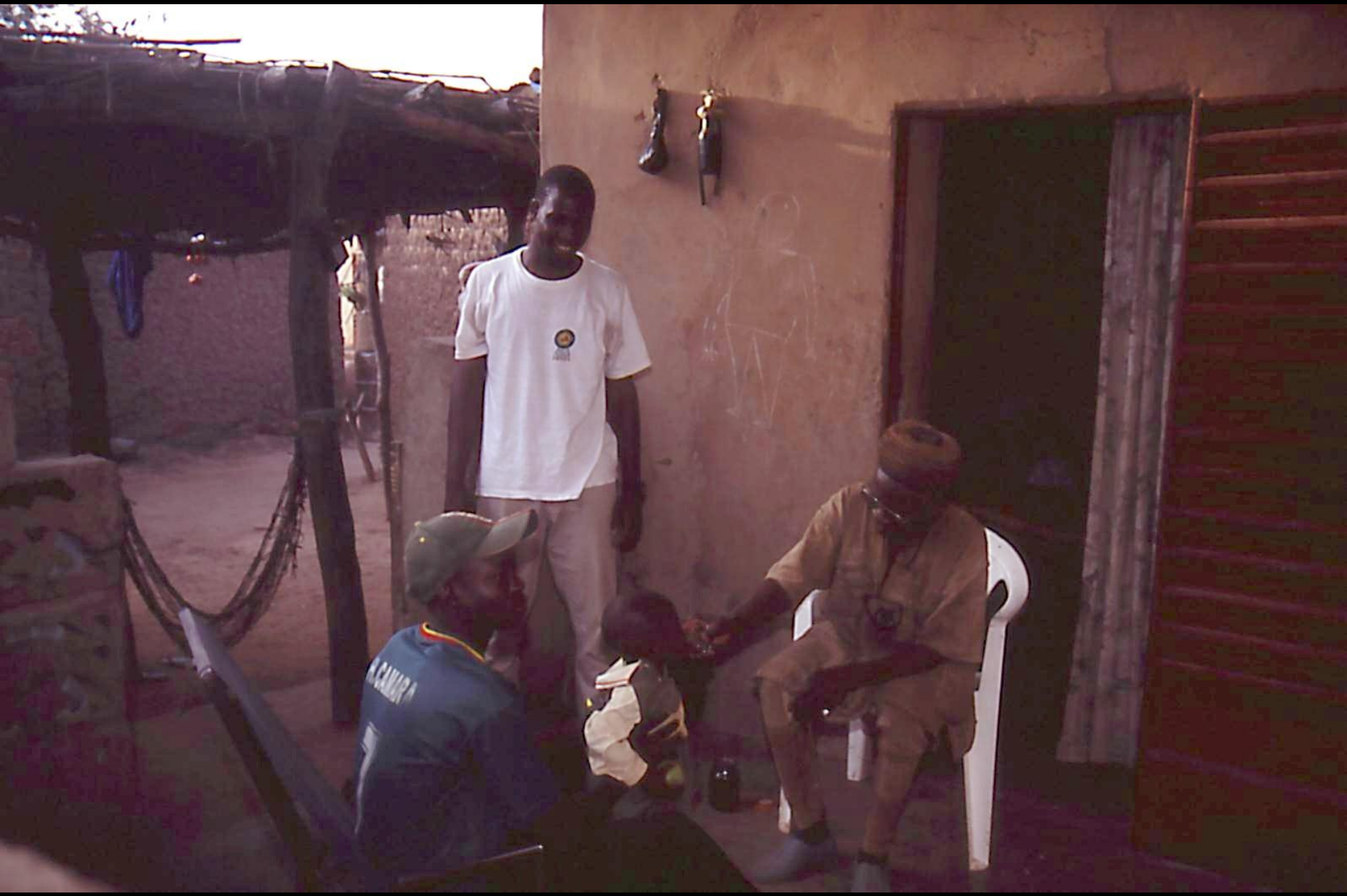

Clinical follow-up

- Days 1,2,3,7,14,28
- Additional consultations as necessary
- At each follow-up: history, temperature, clinical examination
- Laboratory analyses: parasitaemia, haematocrit, platelets, WCC, Creatinine, AST, ALT, ECGs.

Dose escalation

- Dose of remedy in 3 groups:
  - A: Low range = od for 3 days
  - B: Mid range = bd for 7 days
  - C: High range = qds for 4 days, then bd for 3 days

Baseline characteristics

Group	A	B	C
N	23	40	17
% males	48%	50%	47%
Mean age (years)	3.69	4.74	3.25

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D14 efficacy by intention to treat

Dose group:	A	B	C	P=
N	23	40	17	
Adequate Clinical Response	**39%**	**72.5%**	64.7%	0.03
Lost to Follow-Up	9%	0	0	

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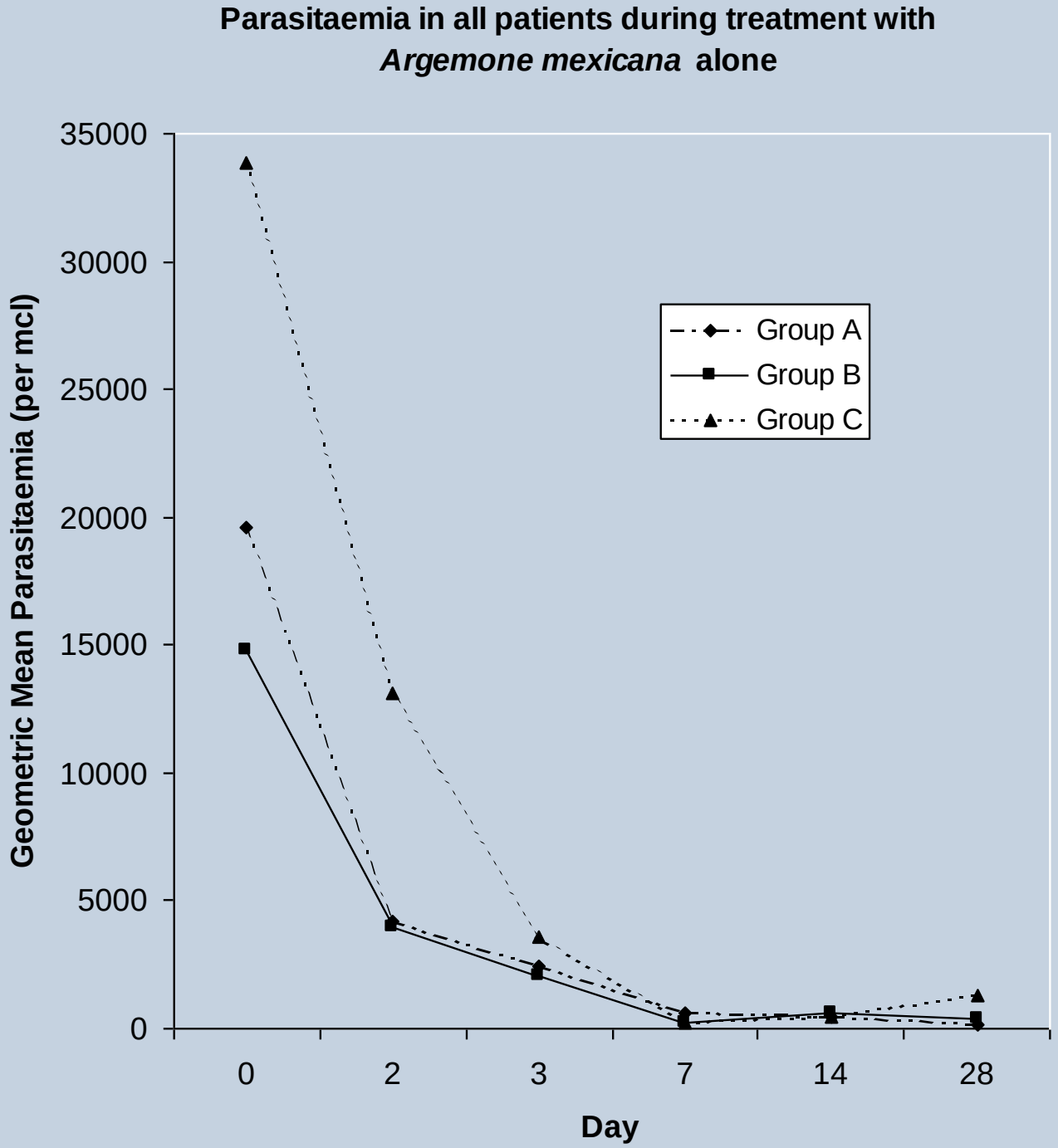
Parasitaemia in all patients during treatment with
Argemone mexicana alone
Geometric Mean Parasitaemia (per mcl)
35000
30000
25000
20000
15000
10000
5000
0
0
2
3
7
14
28
Day
Group A
Group B
Group C

Adverse effects

- Diarrhoea / cough in 17-25% of patients (all doses)
- Transitory elevation of AST/ALT in 7 patients
- At highest dose, prolonged QTc interval in 2 patients.
- No serious adverse effects

Further Toxicology

- Chemical analysis: no sanguinarine detected in decoction.
- Animal tests: no evidence of acute toxicity at doses up to 3.2g/kg of the freeze-dried tea (equivalent to 35g/kg of plant powder)

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Conclusions:

- AM decoction appears effective in a dose-escalating study
- The optimal dosage is bd for 1 week
- This dosage is safe and well tolerated

Willcox et al (2007), Trans Roy Soc Trop Med Hyg

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Stage 3: Randomised Controlled Trial

- P: patients with presumed uncomplicated malaria, all ages
- I: *Argemone mexicana* decoction twice daily for 7-14 days
- C: Artesunate-amodiaquine
- O: outcomes:
  - Clinical recovery (no need for 2nd line Rx)
  - incidence of new clinical episodes of malaria;
  - incidence of severe malaria

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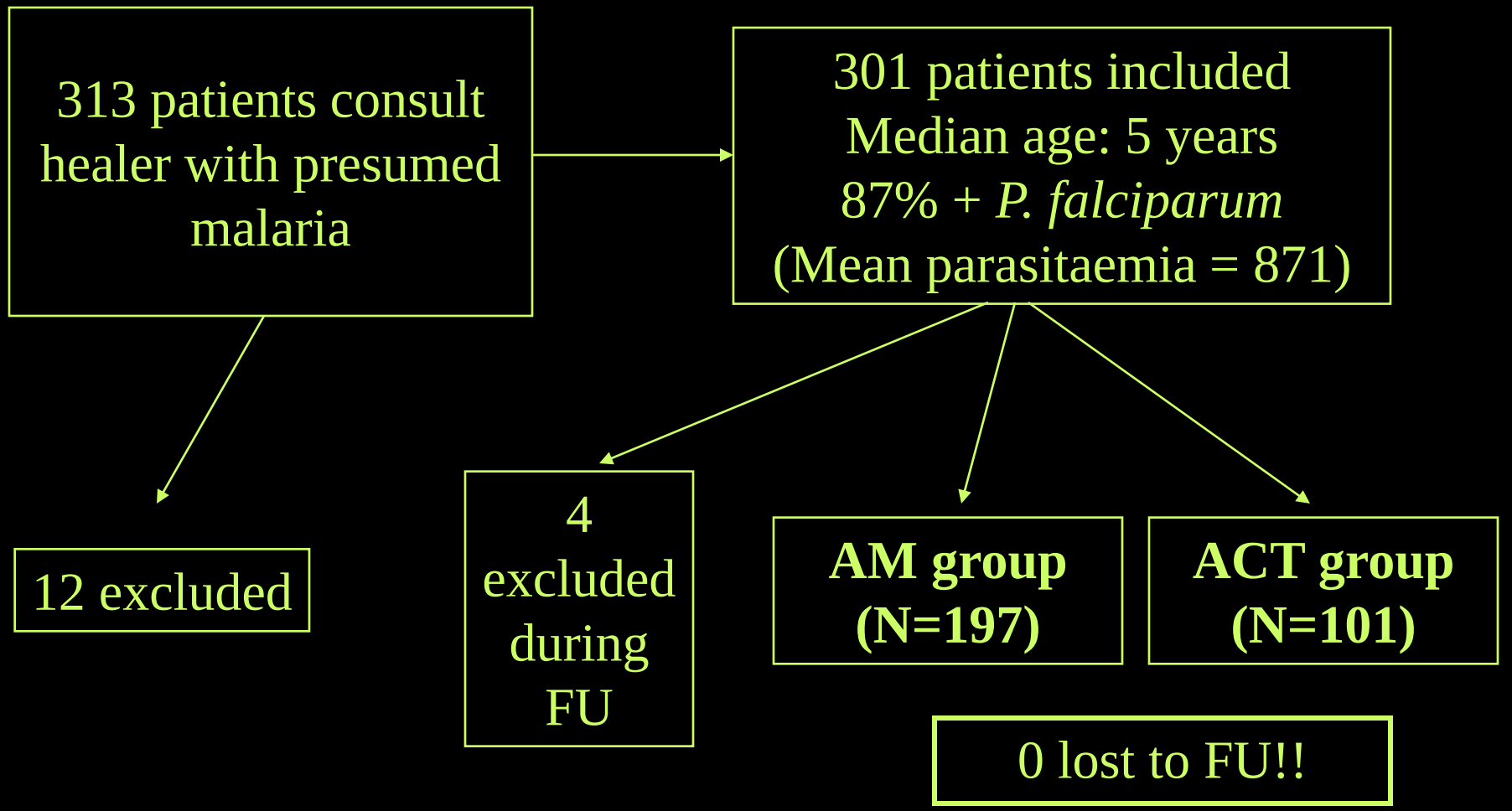
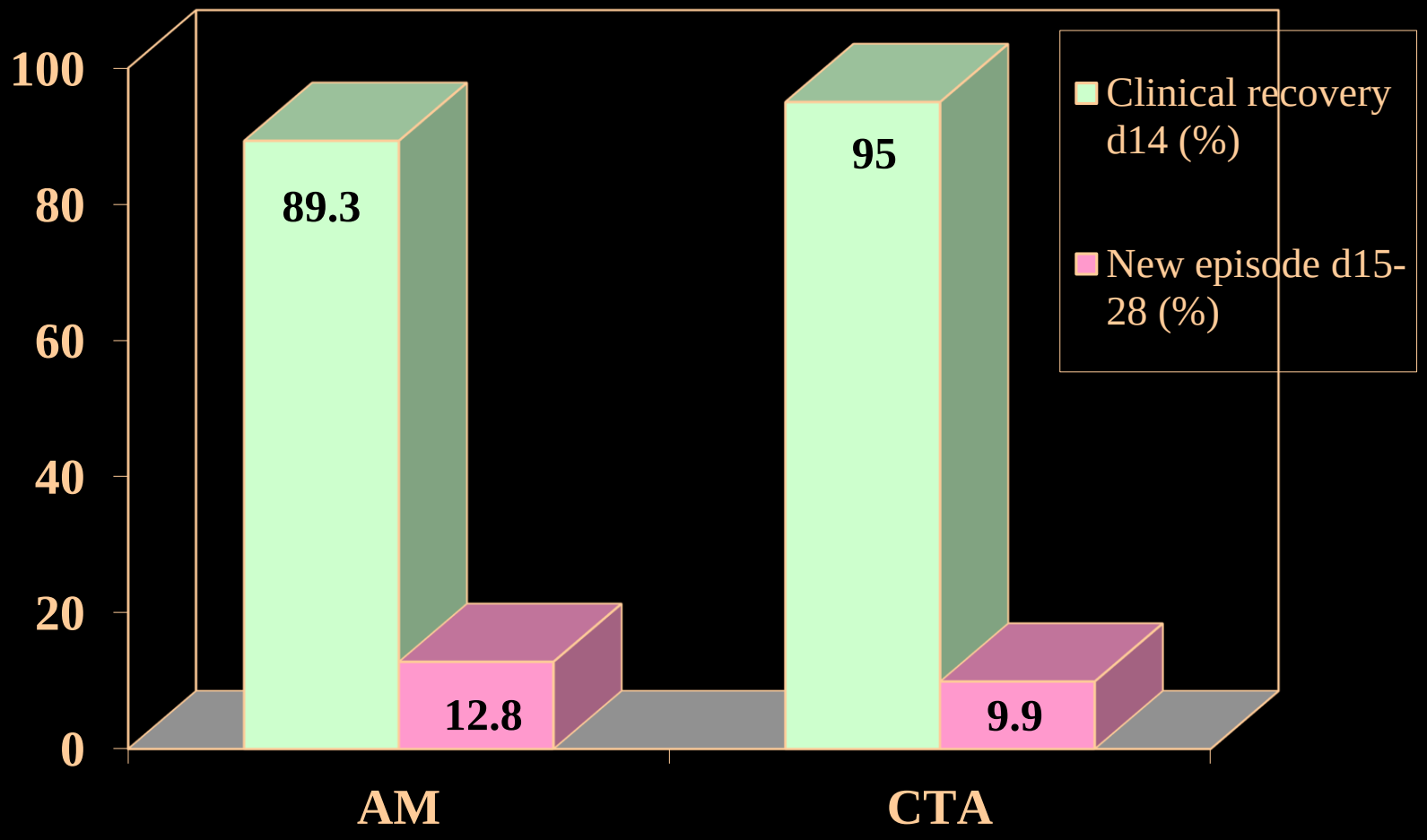
Consultation with village health worker


Informed
Consent

RCT: AM vs ACT


313 patients consult healer with presumed malaria
301 patients included
Median age: 5 years
87% + *P. falciparum*
(Mean parasitaemia = 871)
12 excluded
4 excluded during FU
AM group (N=197)
ACT group (N=101)
0 lost to FU!!

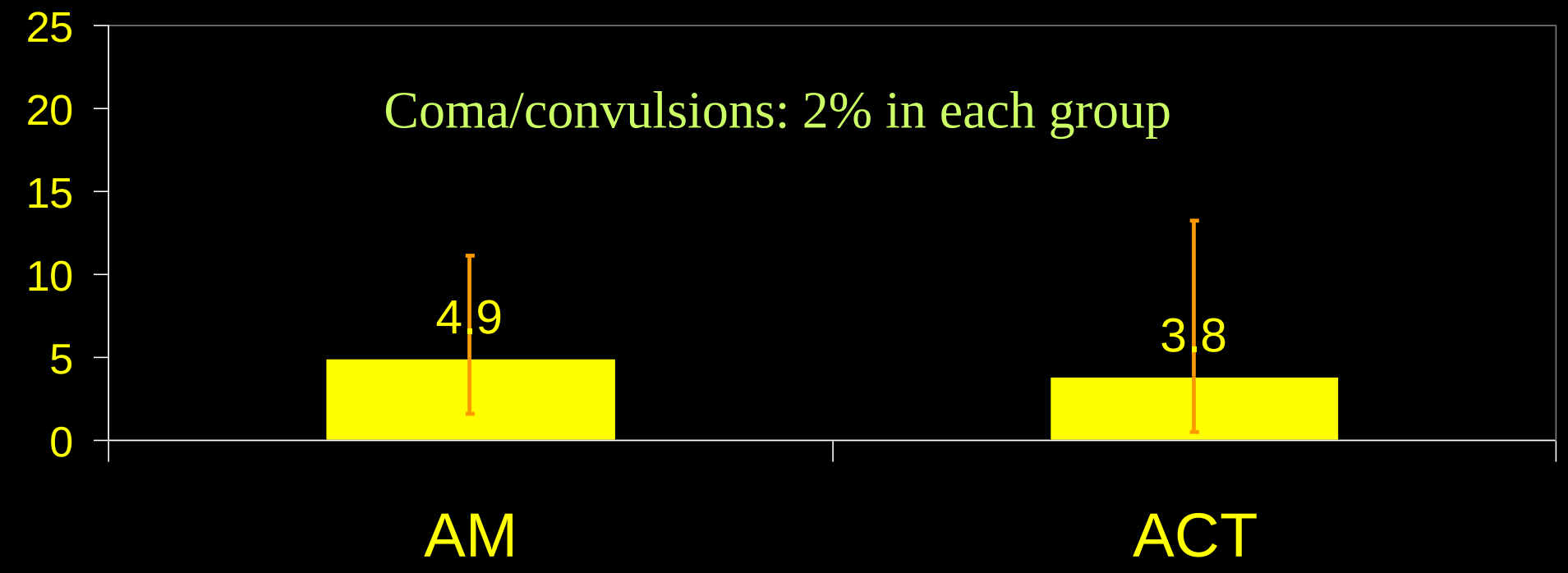
Clinical recovery and new episodes



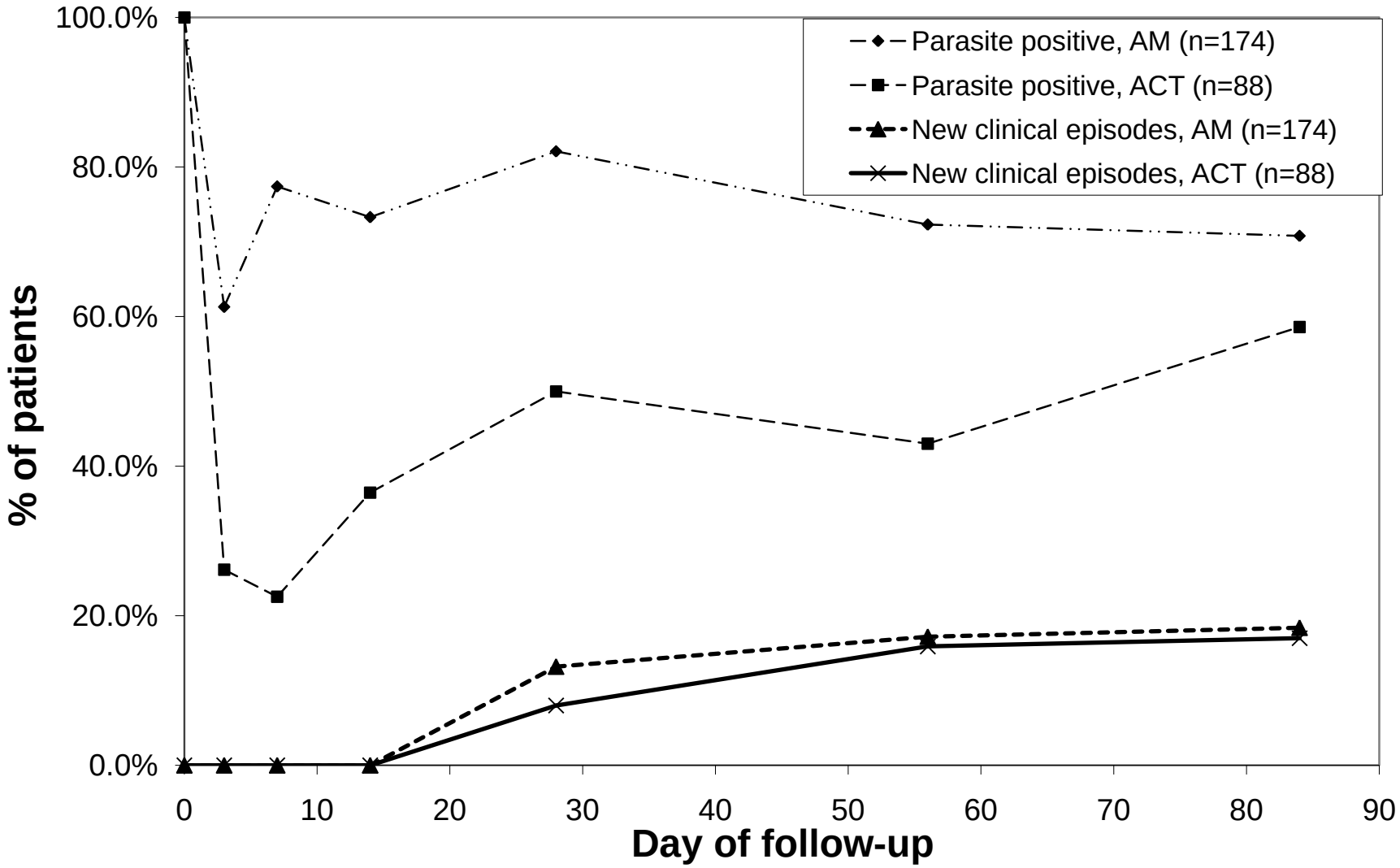
Follow-up of first 28 days

	AM group	ACT group
Mortality	0	0
Severe mal >5yo	0	0
Severe mal (0-5 yo)	1.0% (0.02 – 5.3)	1.9% (0.05 – 10.3)
Coma / convulsions	0	0
Adverse effects	14% (cough, diarrhoea)	19% (vomiting)

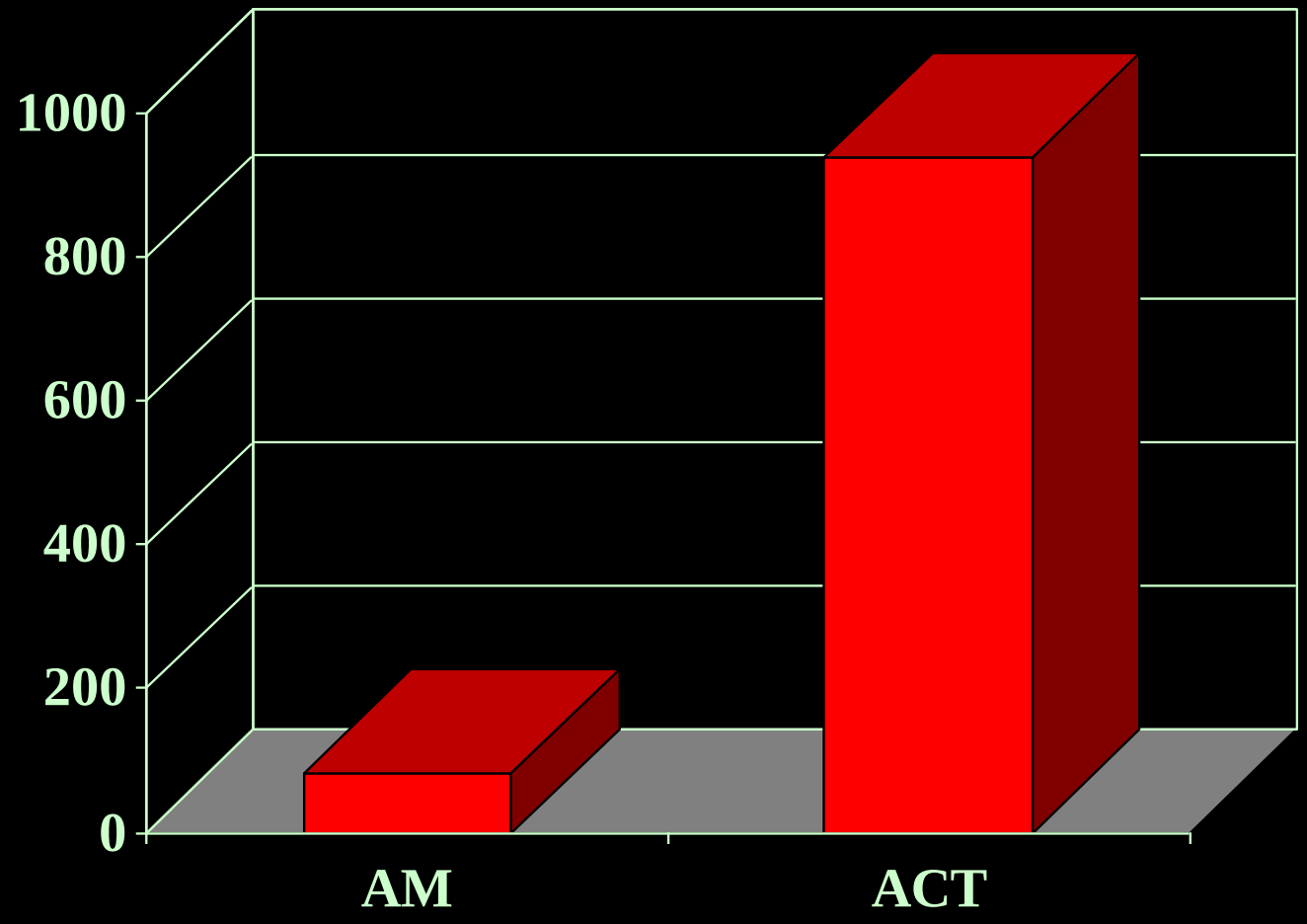
Incidence of severe malaria over 3 months (% children aged 0-5y)



Presence of parasites and incidence of new episodes of malaria



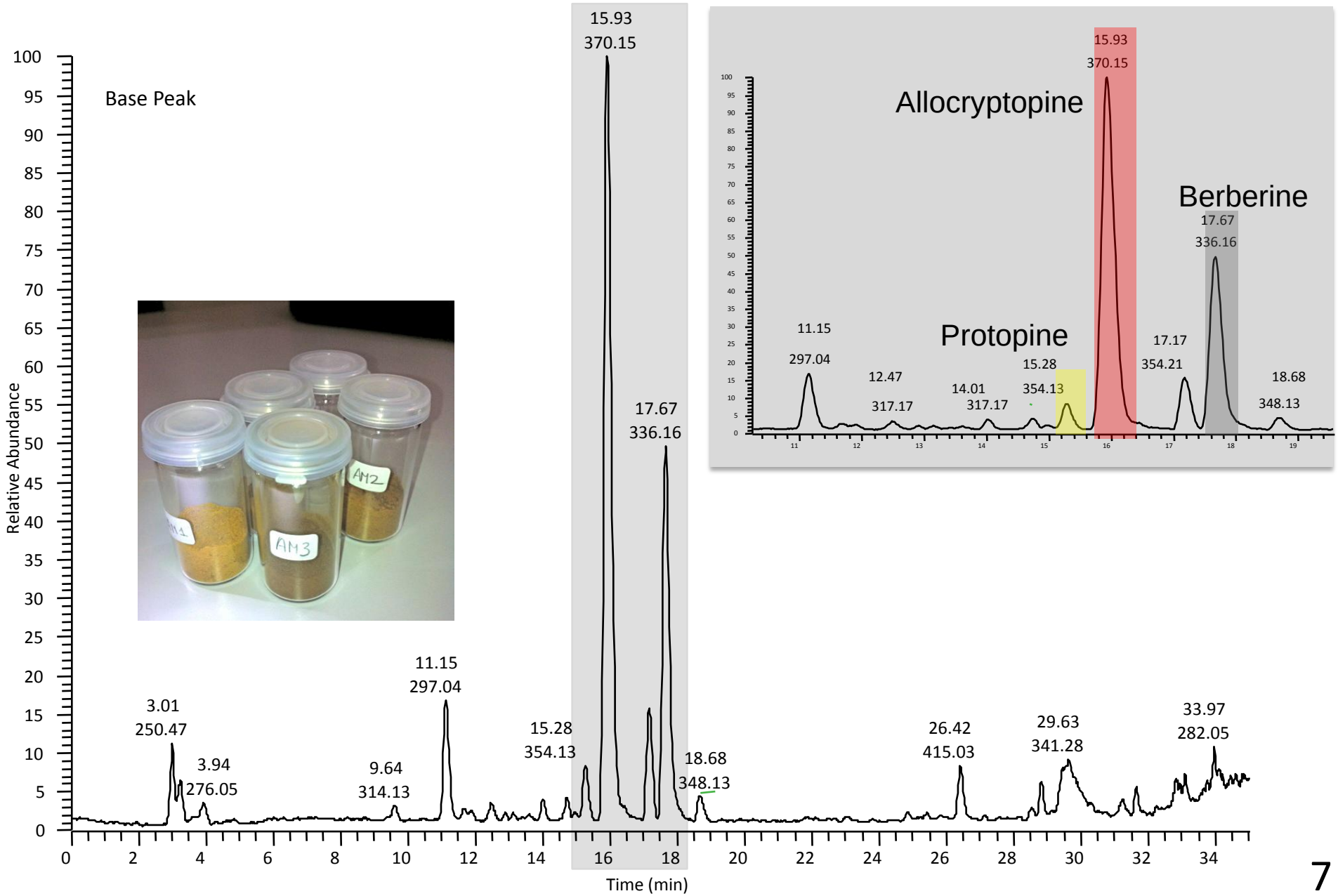
Comparison of AM and ACT strategies: cost per episode (FCFA)



Stage 4:
Isolation of “active compounds”

- For agricultural selection of best plants
- For standardisation
- For quality control
- What is an “active compound”?

LC-MS analysis of *Argemone* decoction



Argemone alkaloids - activity

	P. falciparum*	*T. cruzi*	*T. b. brucei*	Cytotoxicity**
		IC_{50} (µg/mL)		
protopine (**A1**)	0.32	>32.00	10.75	>32.00
allocryptopine (**A2**)	1.46	>32.00	10.49	>32.00
berberine (**A3**)	0.32	0.32	1.66	3.20
A4	8.58	7.85	>32.00	24.78
sanguinarine	7.02	7.42	>32.00	16.26

*IC_{50} < 2.0 µg/mL: highly active

** On human fibroblasts (MRC-5). IC_{50} < 10 µg/mL: highly toxic

Pharmacokinetic study

- Healthy adult volunteers with / without asymptomatic malaria
- Samples of blood at different time intervals after ingestion of *A. mexicana* decoction
- Analysis of blood

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Lessons Learned

- “Reverse pharmacology” is a viable method for the development of phytomedicines
- It is becoming the PREFERABLE method
- Phytomedicines can be developed in parallel with conventional drug development
- Dose escalation is a crucial step

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What would have happened in a conventional approach?

- *Argemone mexicana* screened and active in vitro
- Bioguided fractionation reveals berberine as the “active compound”
- NOT effective in animal models (poor bioavailability)
- Dustbin

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Conventional Drug Discovery

Willcox et al. Malaria Journal 2011, 10(Suppl 1):S8
http://www.malariajournal.com/content/10/S1/S8

MALARIA JOURNAL

REVIEWS Open Access

A "reverse pharmacology" approach for developing an anti-malarial phytomedicine

Merlin L Willcox[1,2*], Bertrand Graz[3], Jacques Falquet[2], Chiaka Diakite[4], Sergio Giani[5], Drissa Diallo[4]

Abstract

A "reverse pharmacology" approach to developing an anti-malarial phytomedicine was designed and implemented in Mali, resulting in a new standardized herbal anti-malarial after six years of research. The first step was to select a remedy for development, through a retrospective treatment-outcome study. The second step was a dose-escalating clinical trial that showed a dose-response phenomenon and helped select the safest and most efficacious dose. The third step was a randomized controlled trial to compare the phytomedicine to the standard first-line treatment. The last step was to identify active compounds which can be used as markers for standardization and quality control. This example of "reverse pharmacology" shows that a standardized phytomedicine can be developed faster and more cheaply than conventional drugs. Even if both approaches are not fully comparable, their efficiency in terms of public health and their complementarity should be thoroughly

Multi-disciplinary University Traditional Health Initiative: Building Sustainable Research Capacity on Plants for Better Public Health in Africa

EU 7th Research Framework Programme – Theme HEALTH, Coordination and support action

Grant Agreement No.: 266005


MANAGEMENT RESERVES
RIGHT OF ADMISSION
GUEST HOUSE
BUSINESS HOURS
08:30HRS - 22.00HRS
OWN FOOD & DRINKS
NOT ALLOWED

MUTHI workpackages

- 1: Medical Anthropology and Ethnobotany
- 2: Quality Control of phytomedicines and nutraceuticals
- 3: Bioactivity and safety of phytomedicines and nutraceuticals
- 4: Observational and Clinical trials
- 5: Intellectual Property Rights
- 6: Management

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Training needs assessment

- 58 responded by the deadline (response rate = 63%).

Country	No of institutions	No of respondents
Uganda	11	18
Nigeria	6	12
Cameroon	5	5
Mali	2	5
Sudan	2	3
South Africa	1	3
Burkina Faso	1	3
Democratic Republic of Congo	1	2
Tanzania	1	2
Gabon	1	1
Kenya	1	1
Madagascar	1	1
Mozambique	1	1
Zambia	1	1

Experience in clinical trials of herbal medicines

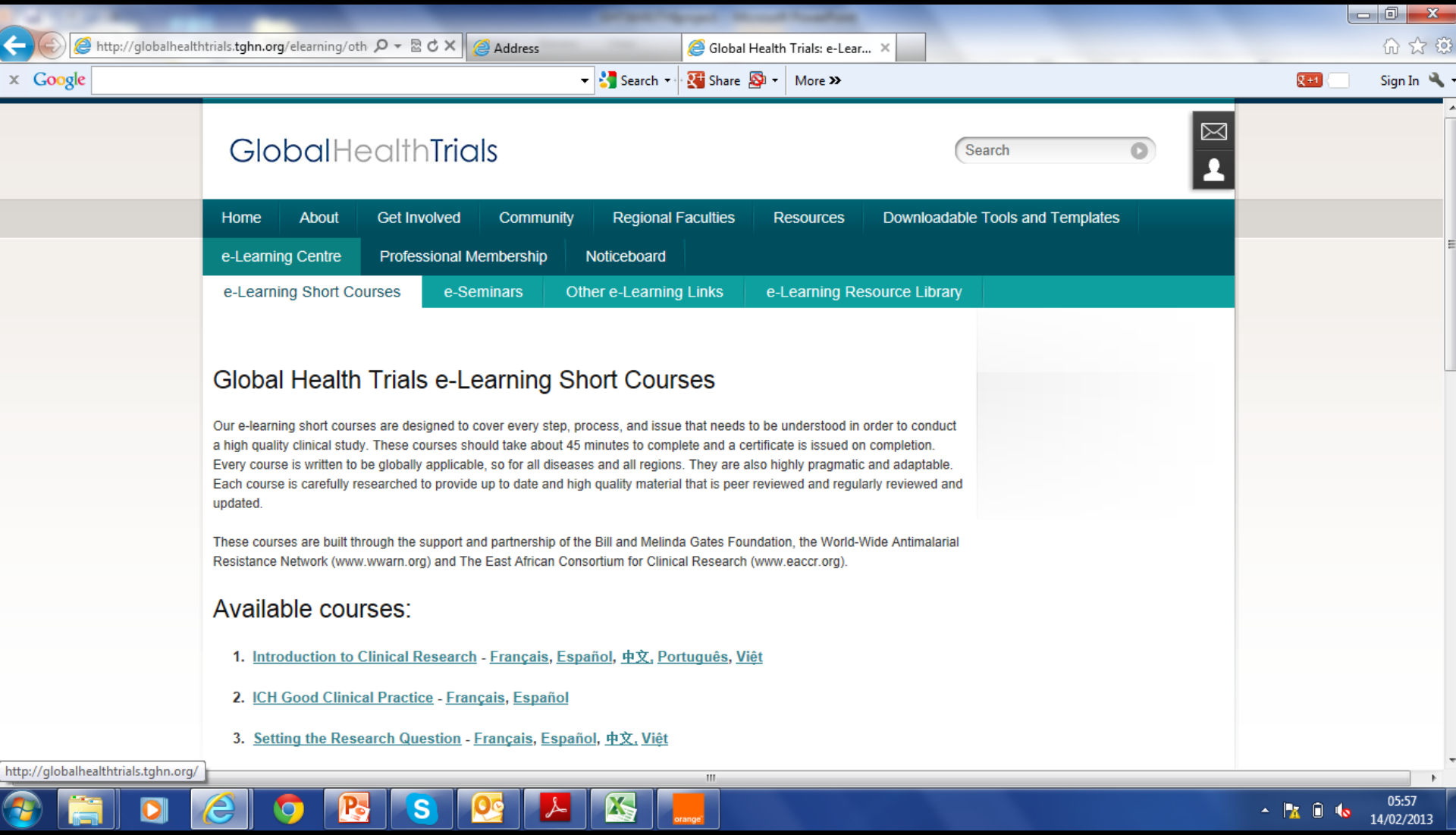
- Thirty-two (57%) of the respondents had already been involved in conducting a clinical trial of a herbal medicine.
  - 23 completed
  - 5 ongoing
- Commonest conditions studied were
  - malaria (9 trials)
  - HIV/AIDS (6 trials)
- Fifty-four (96%) of the researchers were planning future clinical trials of herbal medicines

Publish or Perish!

- 5 trials (21%) had been published
  - Three of these in a peer-reviewed, Medline-listed journal.
- One had resulted in a product with an official marketing authorisation: NIPRISAN for the prevention of crises in patients with sickle cell disorder
- Another product (FARADIN, also for sickle cell disease) had been licensed although the trial had not been published.

Difficulties encountered

Frequency in completed / ongoing trials (n=28)	Frequency anticipated in future trials (n=54)	Broad category	Examples
19	35	Resource constraints	Lack of funding; lack of equipment; lack of human resources
18	25	Social acceptance of the clinical trials	Rapport with traditional healers, willingness of healers to cooperate; difficulty involving biomedical doctors; patient recruitment; patient compliance
9	8	Logistical constraints	Loss to follow-up of patients; distance to study sites; trial management
9	19	Herbal medicine supply	Cultivation, sustainable harvesting and production of herbal medicine; formulation and quality control
6	12	Need for training or support	Lack of trained staff
3	3	Trial design	Protocol design, blinding, data management and analysis
2	5	Ethics	Obtaining ethical approval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Global Health Trials e-Learning Short Courses
Our e-learning short courses are designed to cover every step, process, and issue that needs to be understood in order to conduct a high quality clinical study. These courses should take about 45 minutes to complete and a certificate is issued on completion. Every course is written to be globally applicable, so for all diseases and all regions. They are also highly pragmatic and adaptable. Each course is carefully researched to provide up to date and high quality material that is peer reviewed and regularly reviewed and updated.
These courses are built through the support and partnership of the Bill and Melinda Gates Foundation, the World-Wide Antimalarial Resistance Network (www.wwarn.org) and The East African Consortium for Clinical Research (www.eaccr.org).
Available courses:
1. Introduction to Clinical Research - Français, Español, 中文, Português, Việt
2. ICH Good Clinical Practice - Français, Español
3. Setting the Research Question - Français, Español, 中文, Việt
http://globalhealthtrials.tghn.org/
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14/02/2013

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3. Setting the Research Question - Français, Español, 中文, Việt
4. The Research Protocol: Part one - Français
5. The Research Protocol: Part two - Français
6. Data Safety Monitoring Boards for Clinical Trials - Français
7. Introduction to Consent
8. Introduction to Data Management For Clinical Research Studies
9. Introduction to Collecting and Reporting Adverse Events in Clinical Research
10. Introduction to Reviewing Genomic Research **(New!)**
11. Basic Malaria Microscopy **(New!)**
12. The Retrospective Treatment Outcome Study **(New!)**

We will continue to extend this list of courses so tell us if you need to learn about something that you do not see listed here. Please also get in touch if you currently teach a course that we have not listed. All of our courses are continuously updated and are peer reviewed. Therefore please do let us know if you have comments or remarks as we can incorporate these into the courses.

The Retrospective Treatment Outcome Study (RTO)

This module is designed for researchers interested in selecting traditional medicinal plants for further research (including pre-clinical, and clinical trials).

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www.phc.ox.ac.uk

Funding:

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http://www.mn.uio.no/farmasi/english/research/projects/muthi/
It was funded by the European Union Research Directorate through the MUTHI project, FP7 Grant Agreement No.: 266005.

Reviewers:

This course is currently under review

MUTHI clinical research course
Makerere University, 7-13 Feb 2014

- 25 participants (clinicians, pharmacologists, chemists, botanists, traditional healers)
- Syllabus:
  - Clinical trial design
  - Writing a protocol and ethical approval
  - Statistics: sample size and analysis
  - Data management and monitoring
  - Reporting and publication
  - Critical appraisal and systematic reviews

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Ethnobotanical survey of plants used by traditional healers for the treatment of schizophrenia in Bandiagara district, Mali, West Africa


medicinal plants in the tropics


Bushenyi
ical & Traditional Healers
Association (BUMETHA)
Rukararwe Partnership Workshop
for Rural Development
Save our Herbs
0774025002
Pharmacy


SESAMUM INDICUM
SAGE
BLOOD TONIC (ROSELLA)
KIGALAMGA
CHILLI POWDER
EUCALYPTUS GLOB
URINE RETENSION
TEPHROSIA VOGEL
OREGANA
MELIA

Plans for ongoing support after the workshop

- Mentoring to help participants
  - develop their protocols,
  - apply for funding and ethical approval,
  - carry out the research
  - publish it.
- Online training materials
- Cascading of training

Our goal: high quality, standardised, safe, effective, evidence-based “improved traditional medicines”