Intervention Study (Clinical Trial)

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GFMER - WHO - UNFPA - LAO PDR

Training Course in Reproductive Health Research

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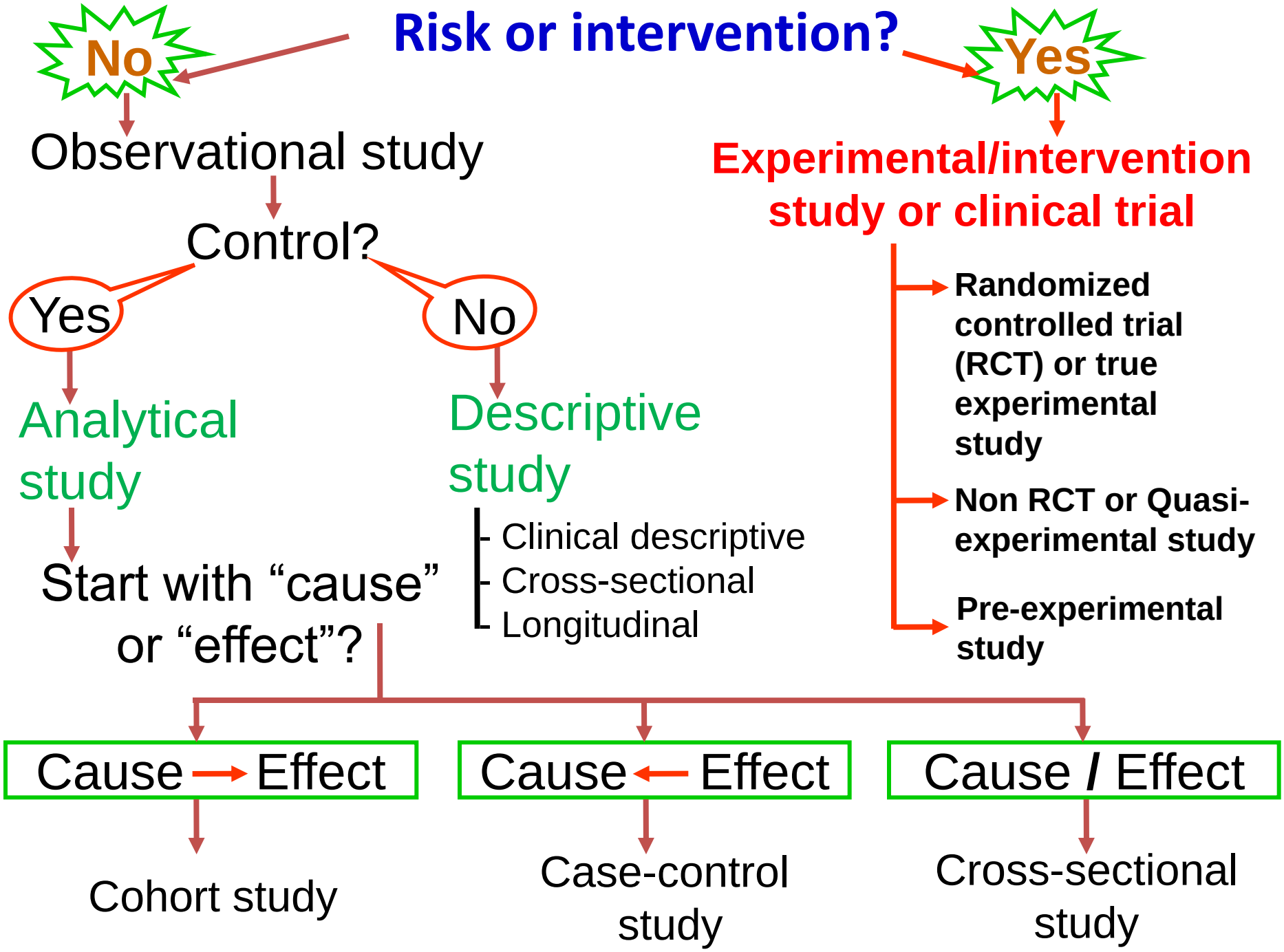

Risk or intervention?
No
Yes
Observational study
Control?
Yes
No
Analytical study
Descriptive study
Clinical descriptive
Cross-sectional
Longitudinal
Start with "cause" or "effect"?
Experimental/intervention study or clinical trial
Randomized controlled trial (RCT) or true experimental study
Non RCT or Quasi-experimental study
Pre-experimental study
Cause → Effect
Cause ← Effect
Cause / Effect
Cohort study
Case-control study
Cross-sectional study

What Are Clinical Trials?

- Research studies involving people
- Try to answer scientific questions and find better ways to prevent, diagnose, or treat disease
- Follow somewhat the pattern of observational studies

Why Are Clinical Trials Important?

- Clinical trials translate results of basic scientific research into better ways to prevent, diagnose, or treat disease
- The more people take part, the faster we can:
  - Answer critical research questions
  - Find better treatments and ways to prevent disease

Intervention Study/Clinical Trial

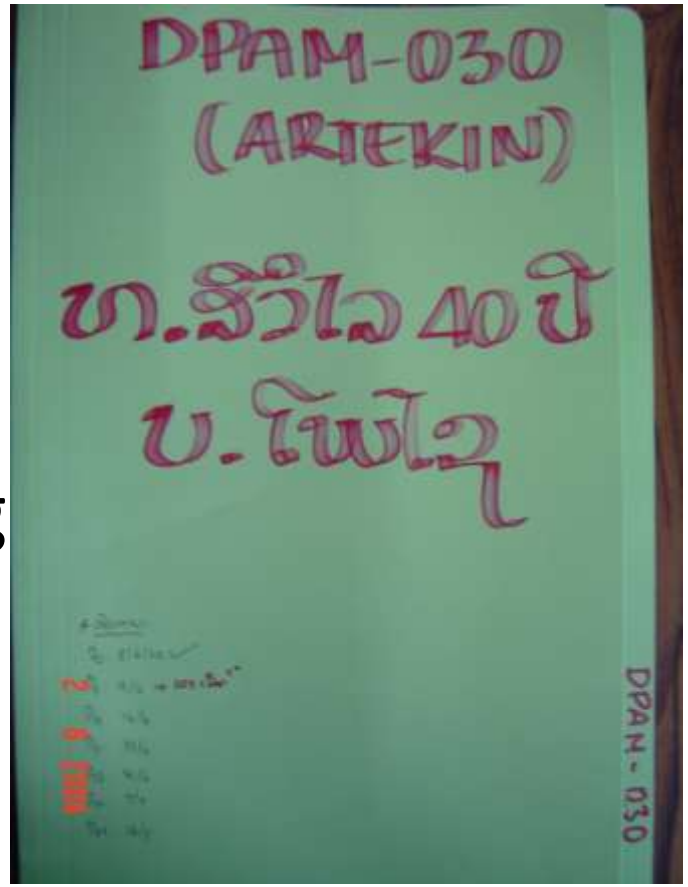
- Cohort
- Intervention /manipulation
- Follow up
- Measurement of intervention

3 sub-types:

  - Randomized controlled trial (RCT)
  - Non RCT
  - Pre-experimental

Randomized controlled trial (RCT)

- Randomization
- Intervention
- Control
- Gold standard for studying intervention in a clinical setting



Non-randomized controlled trial (NRCT)

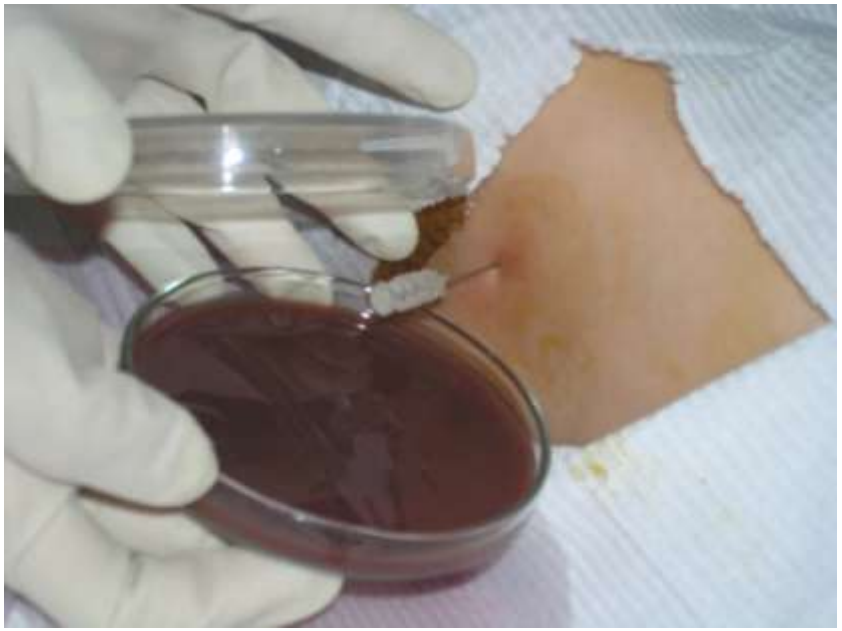
- No randomization (patients can select)
- Intervention
- Control

Pre-experimental study

- Intervention
- No control
- No randomization

What Are the Different Types of Clinical Trials?

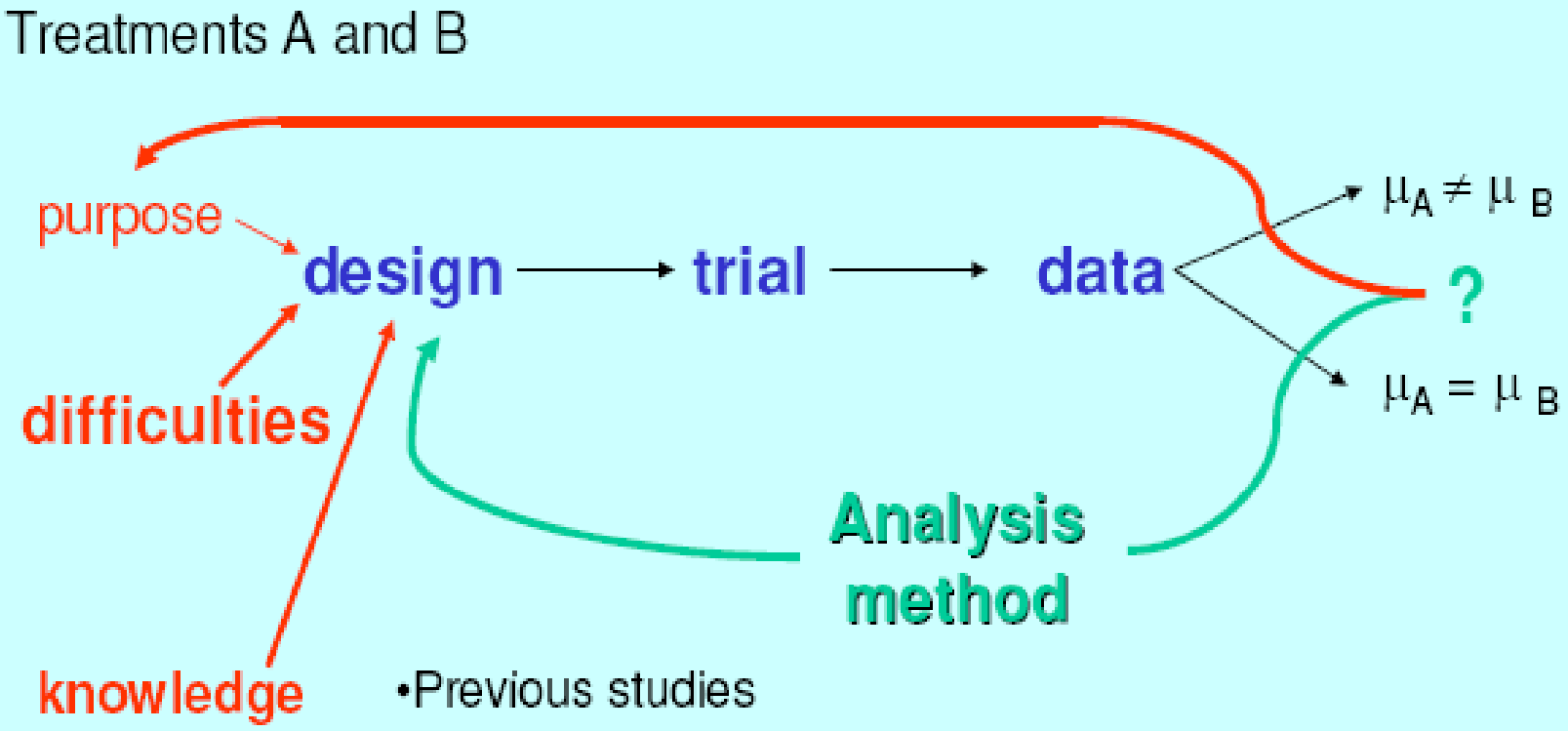
- Treatment
- Prevention
- Early detection/screening
- Diagnostic
- Quality of life/supportive care



Treatment Trials

- What new treatments can help people with a particular disease?
- What is the most effective treatment for people with that disease?

Clinical trials To determine whether or not there are differences between the effects of treatments



Clinical Trial Phases

Phase 1 trials

- How does the agent (drug) affect the human body?
- What dosage is safe?

Phase 2 trials

Does the agent or intervention have an effect on the disease?

Phase 3 trials

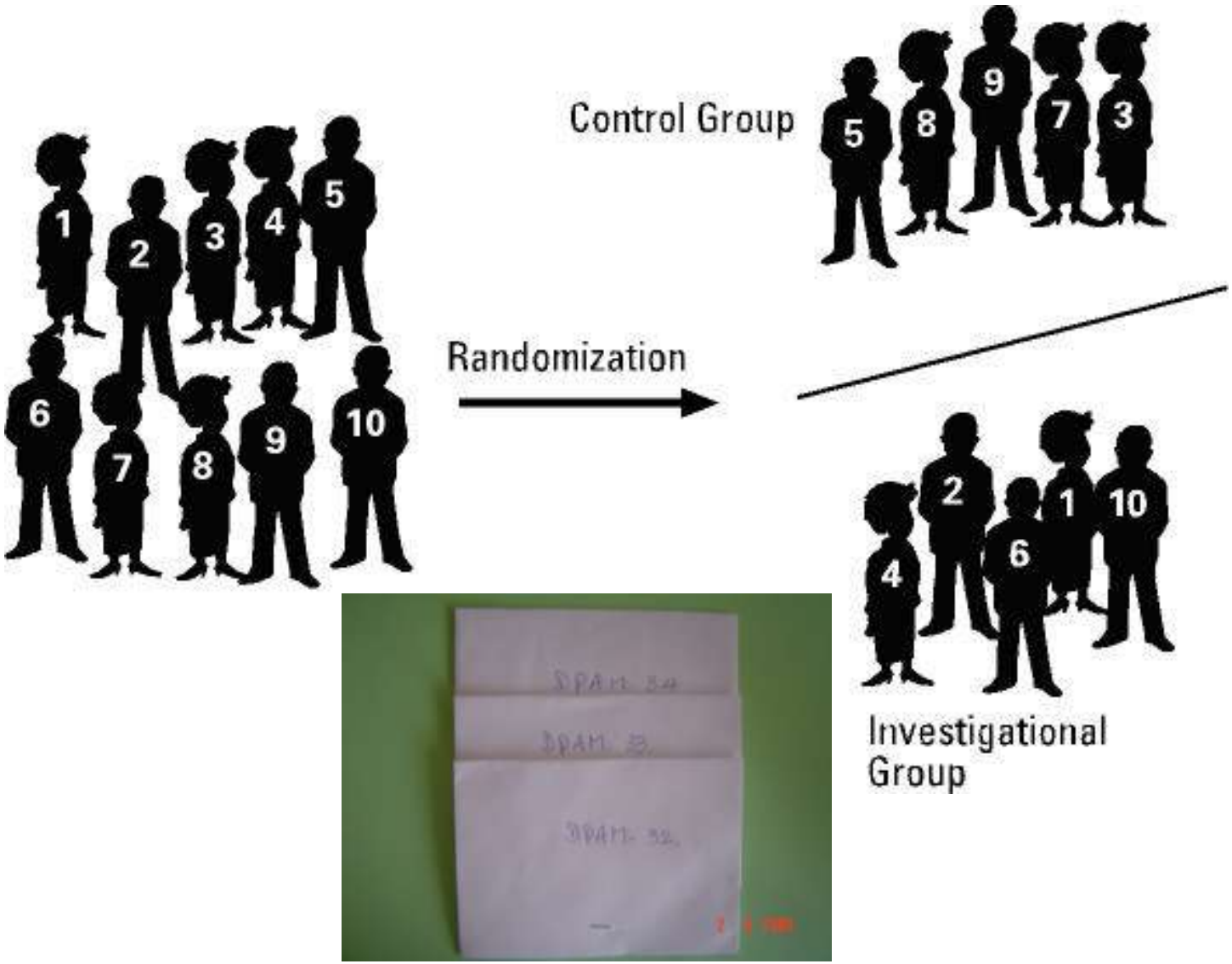
- Is the new agent or intervention (or new use of a treatment) better than the standard?
- Participants have an equal chance to be assigned to one of two or more groups

Randomized Trials

Participants have an equal chance to be assigned to one of two or more groups:

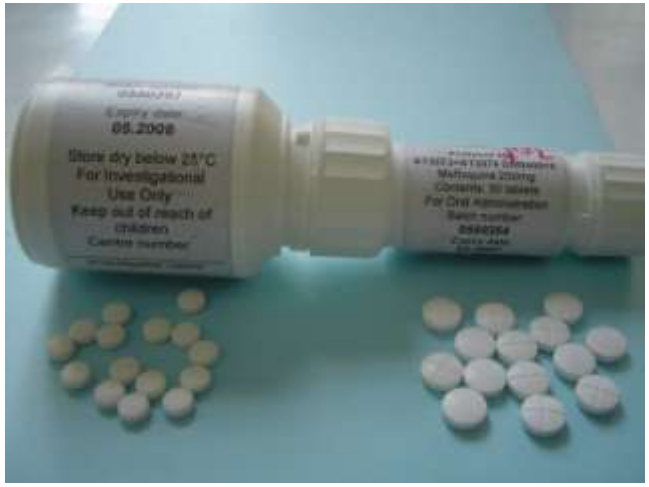
- One gets the most widely accepted treatment (standard treatment)
- The other gets the new treatment being tested, which researchers hope and have reason to believe will be better than the standard treatment

Randomization



Why is Randomization Important?

- So all groups are as alike as possible
- Provides the best way to prove the effectiveness of a new agent or intervention



Control (Placebo) vs Drug

Placebos are almost never used:

- Placebos are used only when no standard treatment exists
- Patients are told of this possibility before deciding to take part

Difficulties and ethics:

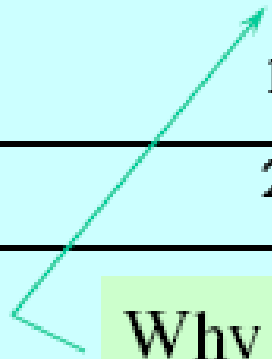
- Patients
  - availability
  - inclusion and exclusion criteria
  - willingness to participate
  - presentation rates
  - compliance
  - how many?
- Data
  - measures of effects
  - adverse effects
  - influence of other factors
  - random variation of effects between people
  - bias
    - allocation bias
    - assessment bias
    - analysis
- Cost

Is treatment A better than treatment B?

	Treatment **A**	*Treatment* **B**	*total*
Recovered	17	8	25
No better	3	12	15
total	20	20	40

If treatment A is better than treatment B . . .

	Treatment **A**	*Treatment* **B**	*total*
Recovered	**17**	**8**	**25**
No better	**3**	**12**	**15**
total	**20**	**20**	**40**

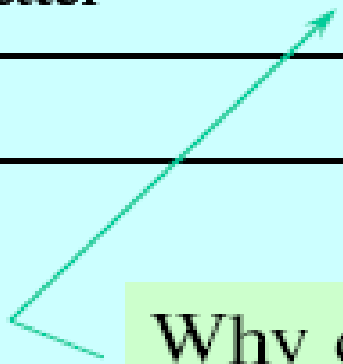


Why did these eight recover?

Were they younger, stronger, or in a better condition than those who did not recover?

If treatment A is better than treatment B . . .

	Treatment **A**	*Treatment* **B**	*total*
Recovered	**17**	**8**	**25**
No better	**3**	**12**	**15**
total	**20**	**20**	**40**



Why didn't these three recover?

Were they older, more feeble, or in a worse condition than those who did?

Perhaps treatment A is <u>not</u> better than treatment B? So . . .

	Treatment **A**	*Treatment* **B**	*total*
Recovered	17	8	25
No better	3	12	15
total	20	20	40

Could there have been an allocation bias?

Perhaps treatment A is <u>not</u> better than treatment B? So . . .

	Treatment **A**	*Treatment* **B**	*total*
Recovered	**17**	**8**	**25**
No better	**3**	**12**	**15**
total	**20**	**20**	**40**

Could there have been an assessment bias?

Perhaps treatment A is not better than treatment B? So . . .

	Treatment **A**	*Treatment* **B**	*total*
Recovered	**17**	**8**	**25**
No better	**3**	**12**	**15**
total	**20**	**20**	**40**

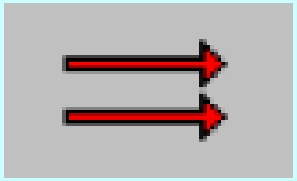
Could the results have occurred by chance?

The efficiency and effectiveness and **cost** of a clinical trial depend on:

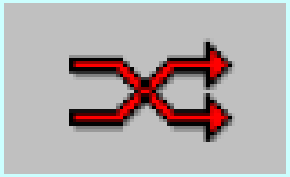
- response to each treatment
- influence of other factors such as age, gender or life style
- number of patients
- how patients are selected for the trial
- how patients are allocated to treatments
- type of trial: parallel or crossover
- compliance of patients to treatments
- how data are recorded, analysed and interpreted

Type of trial:

- **Parallel**

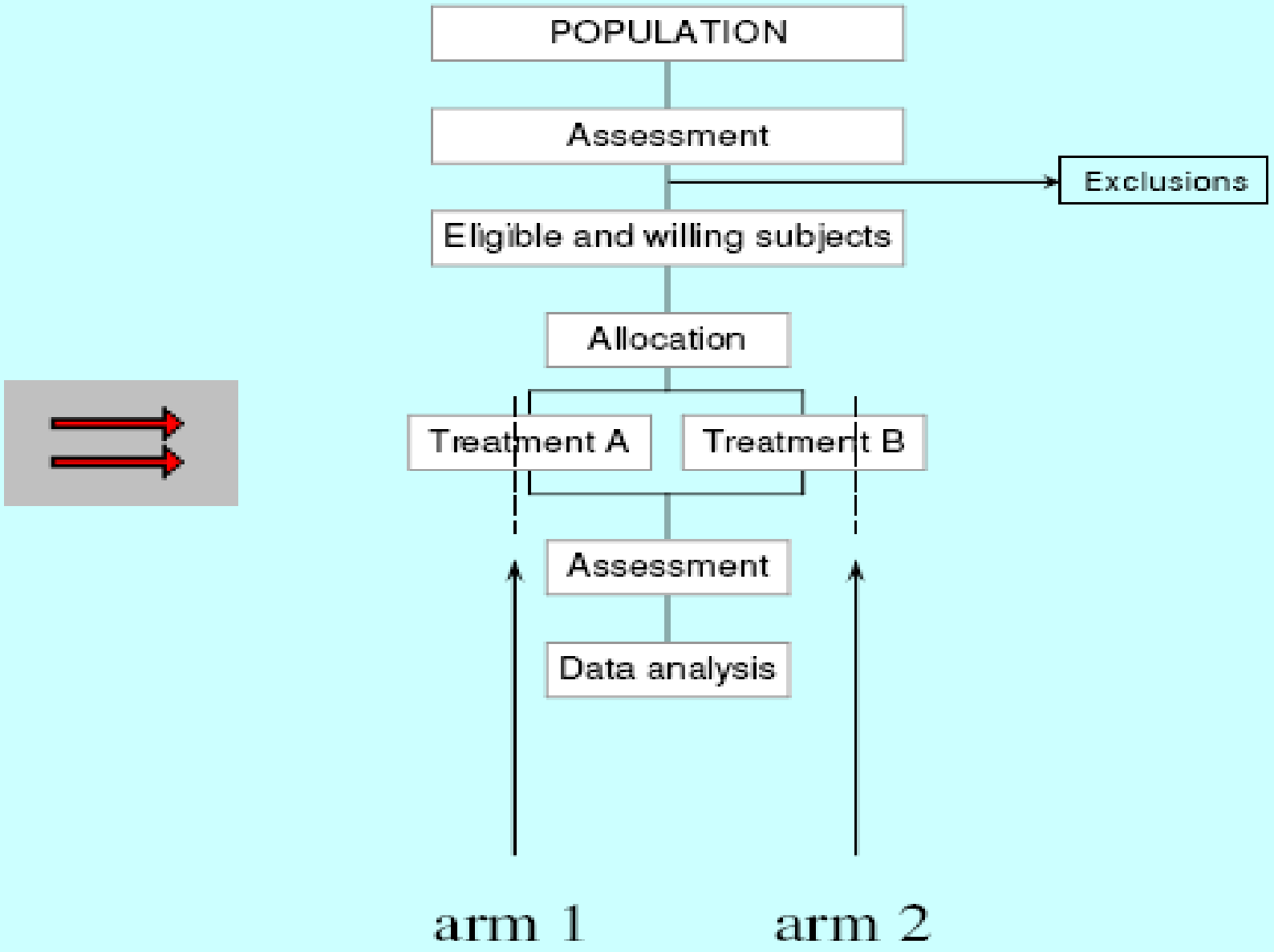


- **Cross-over**

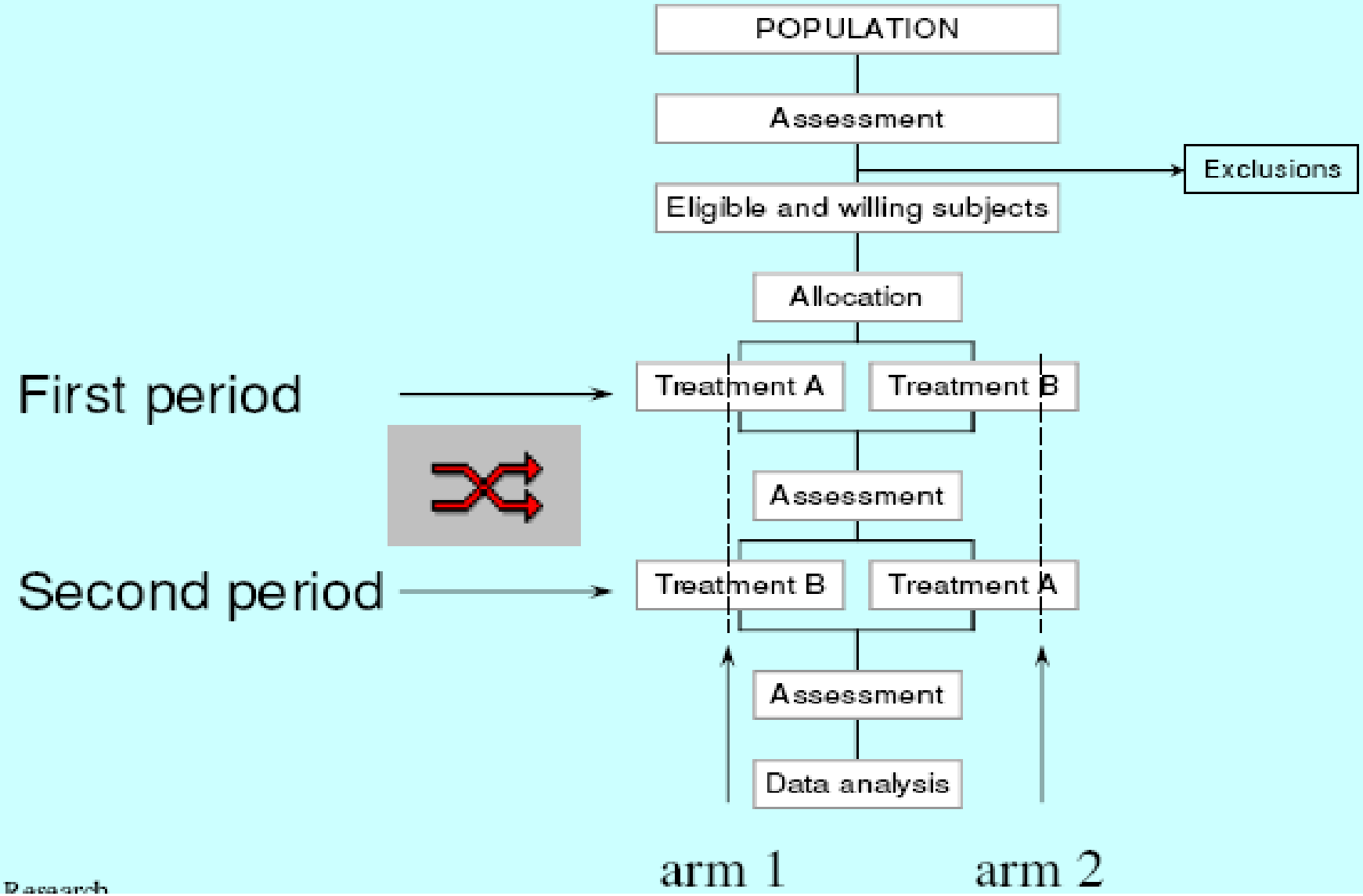


- Sequential
- Group sequential
- Factorial

Parallel Designs



Two-period Cross-over designs



Prevention Trials

- Evaluate the effectiveness of ways to reduce the risk of a particular disease
- Enroll healthy people at high risk for developing that disease

- **Action studies** ("doing something")
- **Agent studies** ("taking something")—also called "chemoprevention studies"

Chemoprevention Trials

- Phase 3 chemoprevention trials compare a promising new agent with either a:

  -- Standard agent

  -- Placebo

Clinical Trial Protocol

- A recipe or blueprint
- Strict scientific guidelines:
  -- Purpose of study
  -- How many people will participate
  -- Who is eligible to participate
  -- How the study will be carried out
  -- What information will be gathered about participants
  -- Endpoints

Benefits of Participation

Possible benefits:

- Patients will receive, at a minimum, the best standard treatment (if one exists)
- If the new treatment or intervention is proven to work, patients may be among the first to benefit
- Patients have a chance to help others and improve patient care

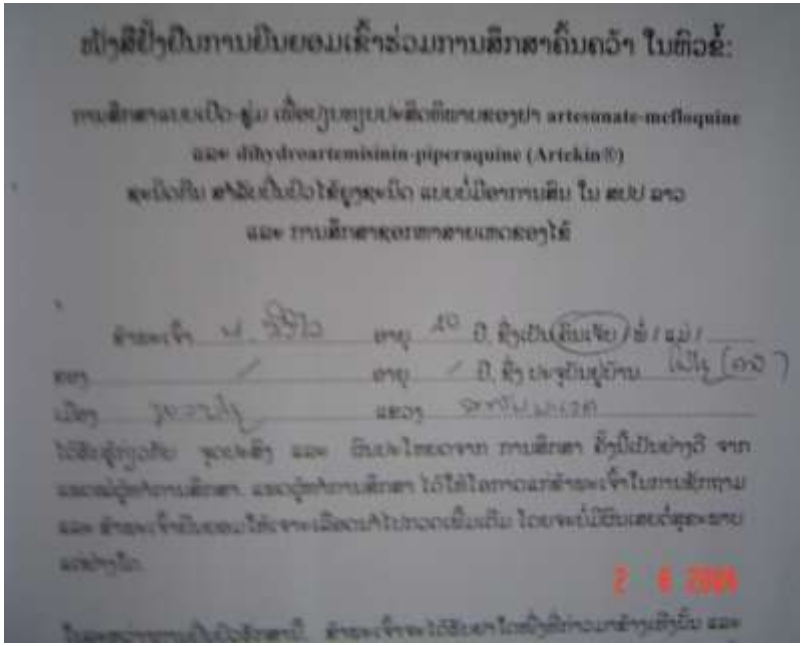
Risks of Participation

Possible risks:

- New treatments or interventions under study are not always better than, or even as good as, standard care
- Even if a new treatment has benefits, it may not work for every patient
- Health insurance and managed care providers do not always cover clinical trials

Patient Protection

- There have, unfortunately, been past abuses in patient protection
- Federal regulations ensure that people are told about the benefits, risks, and purpose of research before they agree to participate



How Are Patients' Rights Protected?

- Informed consent
- Scientific review
- Institutional review boards (IRBs)
- Data safety and monitoring boards (DSMBs)

RCT: unethical if the intervention is strongly believed to be the best available, whether or not that has been established scientifically by careful design and control studies

Advantages & Disadvantages of Clinical Trial

- **Advantages:**

  - Bias & systematic error can be controlled

  - Intervention, samples, outcome can be controlled

- **Disadvantages:**

  - Ethical problem

  - Very expensive & time consuming

  - Problems related to therapy changes & dropped outs

  - Limited in the possibility to generalize results

An Example of RCT in Laos

A Randomized Clinical Trial of

ORAL ARTESUNATE + MEFLOQUINE (AM)

VERSUS

ORAL DIHYDROARTEMISININ - PIPERAQUINE (ARTEKIN®) (DP)

in the treatment of uncomplicated falciparum malaria in Laos

Why / What study ?

* Chloroquine (CQ) & Fansidar (SP): not longer effective in Laos

* In 2000 - 01: Clinical trials of CQ vs SP with 42 days of follow up:

Treatment failure rate of CQ = 35 – 80 %
Treatment failure rate of SP = 18 – 40 %

(Mayxay *et al*., 2003; Schwobel *et al*., 2003; Guthmann *et al*., 2002)

* In 2002 - 03: Clinical trial of 3 combination treatments with 42 days of follow up:

		Cure rate
CQ + SP	=	92 %
Artesunate + mefloquine	=	100 %
Artemether - lumefantrine	=	94 - 97 %

(Mayxay *et al*., 2004; Stohrer *et al*., 2004)

COSTS PER 3 DAYS-TREATMENT COURSE IN ADULTS (in $US)

* Artesunate + mefloquine ~ 3.5

* Artemether - lumefantrine (Coartem®) ~ 2.4

* Dihydroartemisinin - piperaquine (Artekin ®) (DP) ~ 1.2

QUESTION TO ANSWER

What combination treatment

will be appropriate for Laos ?

STUDY PLAN

- What regimen to compare ?

  → Artesunate + mefloquine

- How many cases ?

  Cure rate for AM ~ 97%

  Power of 80%, Alpha error of 5%

  Significant difference in the treatment success rate of 10%.

  = 200 cases. but ~ 10% lost to follow up = 220 cases !

- Definition to measure end-point ?

This must be defined before the trial

- Is the trial ethical ?
- Can the trial be compared with other studies ?
- When and where ?

Ethical Considerations

- Blood Volume
- Safety monitoring of the patients
- Change of treatment in case of treatment failure
- Informed consent and information sheet
- The patients can withdraw from the trial at any time without negative impact on their treatment
- What to do when the patients develop severe disease ?
- Patient information must be kept confidential
- Conflict of interest ?
- Ethical review by the external people who are not involved in the trial (Approval from 2 ethical committees are preferable)
- Must be published

RANDOMISATION AND BLINDNESS

- Those who are in the study team must not know the treatment allocation before the patient recruitment
- Randomization: done by people who will not enroll the patients
- Patients are randomized in block of 10
- Treatment code in the envelops (thick paper)
- The envelops will be open only when the patients sign informed consents
- Blinded vs Open / Placebo vs Non-placebo?

ARTESUNATE + MEFLOQUINE (AM)

VERSUS

DIHYDROARTEMISININ - PIPERAQUINE (ARTEKIN®) (DP)

FOR

THE TREATMENT OF UNCOMPLICATED FALCIPARUM MALARIA IN LAOS:

AN OPEN, RANDOMIZED CLINICAL TRIAL

OBJECTIVES

To determine the efficacy & tolerability of dihydro-artemisinin - piperaquine (Artekin®) in comparison with artesunate + mefloquine in Lao patients with uncomplicated falciparum malaria

All patients were admitted to the clinic

Study site - Phalanxay, Savannakhet Province

Study site ~ 605 Km southeast of Vientiane

Phalanxay District Clinic with 10 beds

Study duration: May 20 – Sept 28, 2004

Criteria:


Going out for patient follow up at home

* Informed written consent
* Age ≥ 1 years & not pregnant
* *P.falciparum* parasitemia ~ 1,000 - 200,000/µL
* Temperature ≥ 37.5 ^{0}C, or fever in previous 3 days
* Likely to complete 42-day follow up
* Did not take full course of antimalarials in previous 3 days
* No signs of severe malaria (WHO; 2000)
* No contraindication or allergy to study drugs

Procedure

Patients' details, medical history, physical examination

Urine test: CQ, Q, Pyr Finger prick: parasite count, Hct, PCR

Randomised to:

AM **DP**

Follow up daily until parasite clearance, then weekly for 42 days

Assessment using

WHO (2002) guidelines: ETF, LTF, ACR

Follow up of patient at home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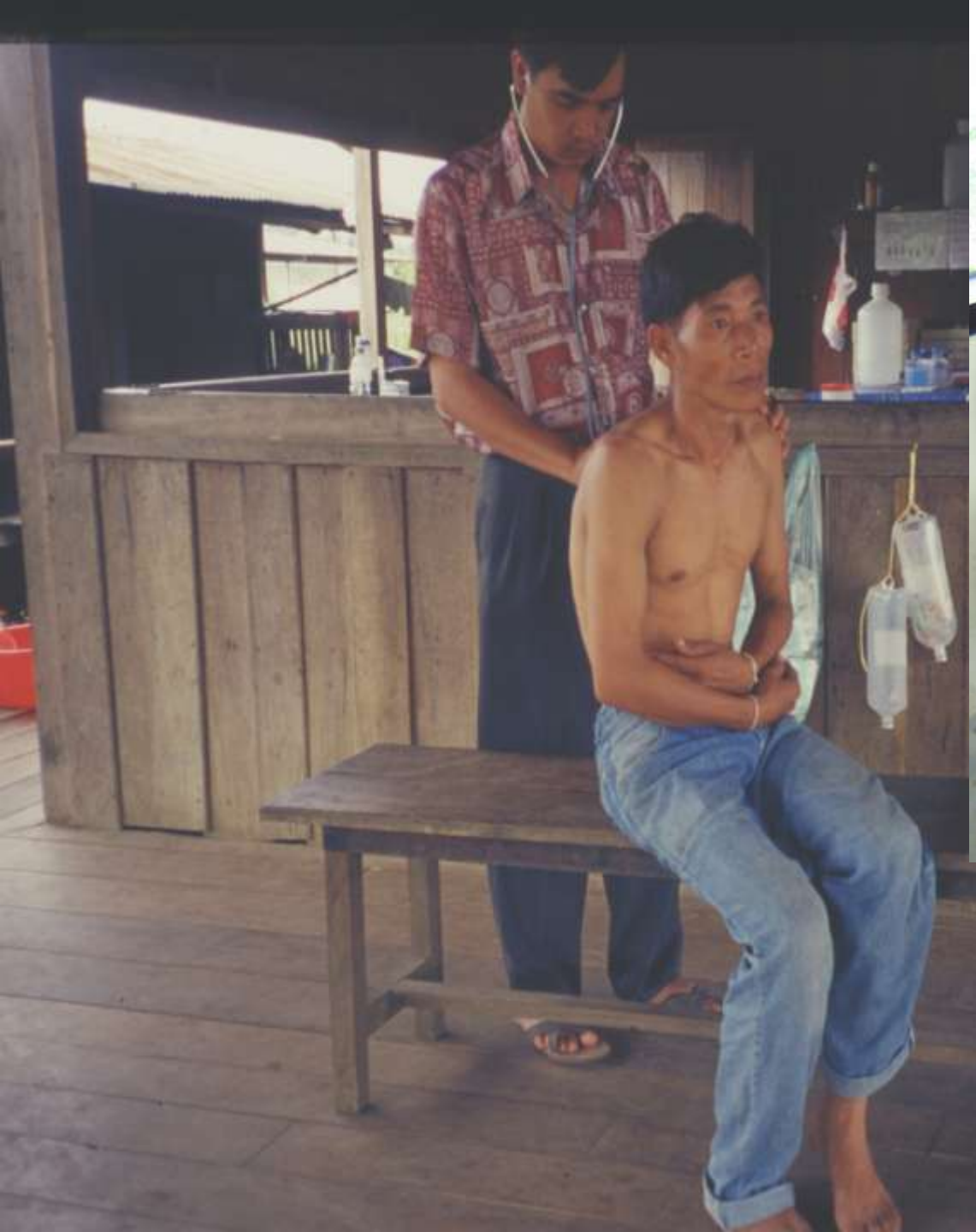


FRAGILE
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DPAM. 32.
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DPAM. 34
DPAM. 33.
DPAM. 32.
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TREATMENTS

1. AM: D0 = Artesunate 4 mg/kg

D1 = Artesunate 4 mg/kg + Mefloquine 15 mg/kg

D2 = Artesunate 4 mg/kg + Mefloquine 10 mg/kg

2. DP: (dihydroartemisinin/ piperaquine)

2.1/16.8 mg/kg/day

once daily at hour 0, 24, 48

Drug administration in children

RE-TREATMENT

1. Failure of AM → DP

2. Failure of DP → AM

3. Second failure or severe → ARTESUNATE

IV ~ 7 days


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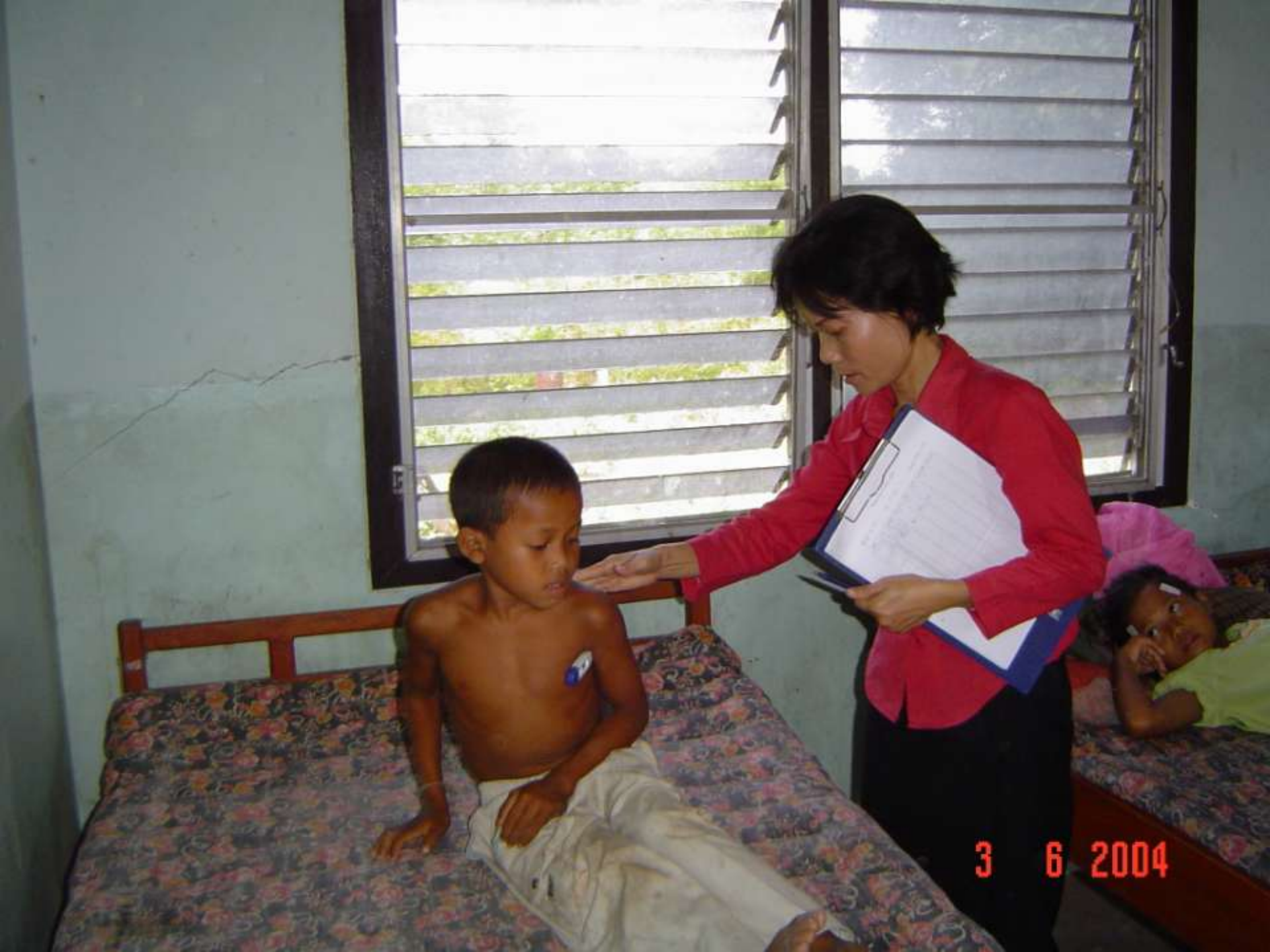
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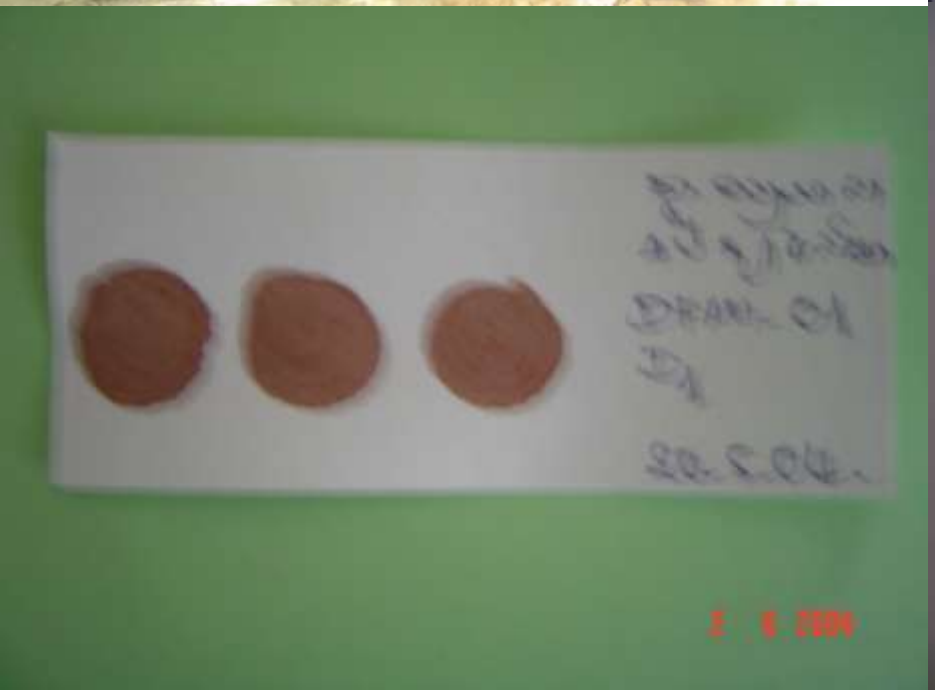
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Outcome measures

Directly observed therapy

Primary

* Cure rate: clinical responses

Secondary

* Parasite clearance time (PCT)

‘interval in days between the first treatment dose and the first thick film negative for *P. falciparum* parasites after checking > 200 oil fields ”

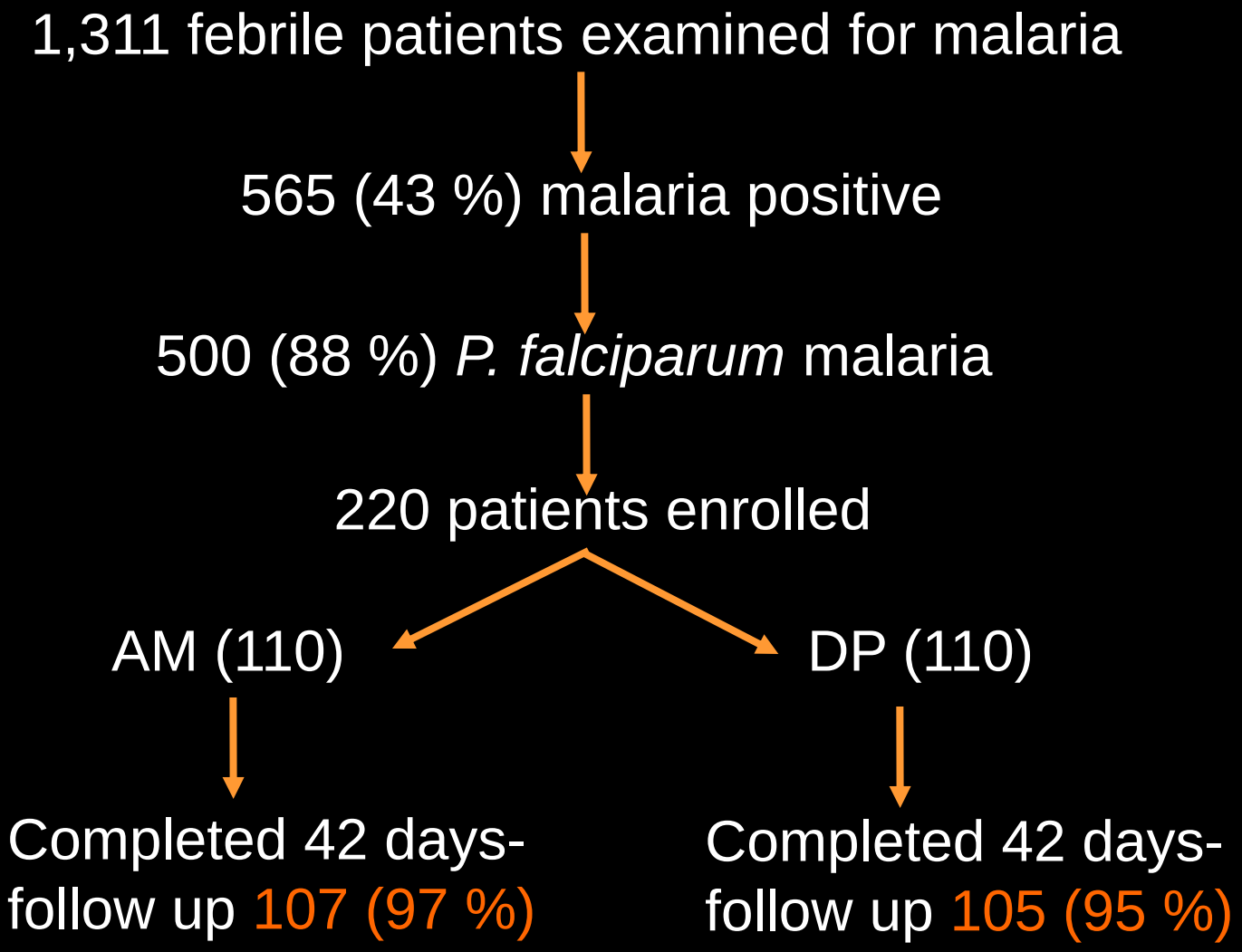
* Fever clearance time (FCT)

‘the time, from onset of treatment, to the first time axillary temperature fell below 37.5 ^{0}C and remained below 37.5 ^{0}C for 48 hours ‘

* Gametocytaemia after treatment

* Adverse effects

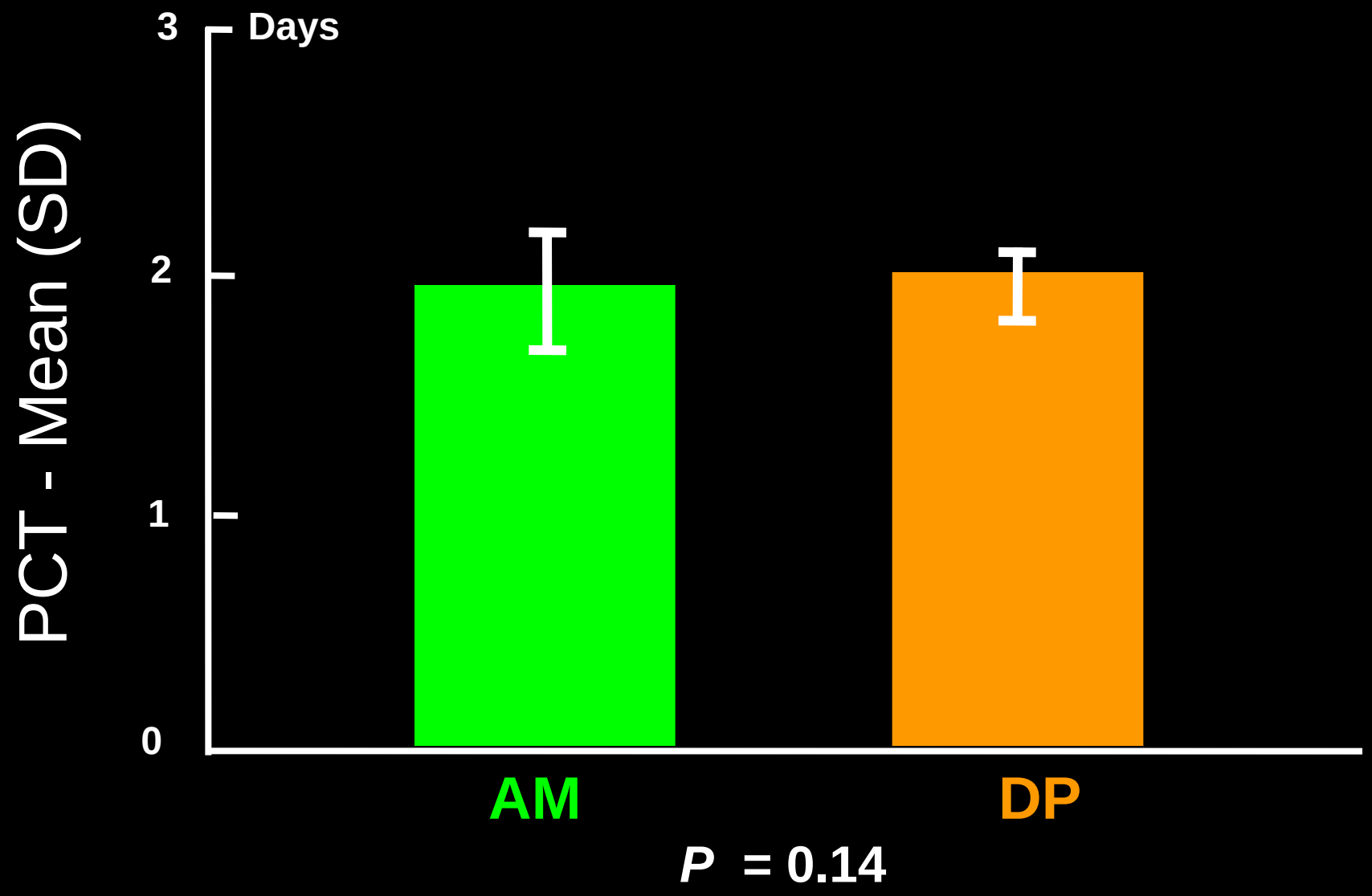
RESULTS


1,311 febrile patients examined for malaria
565 (43 %) malaria positive
500 (88 %) P. falciparum malaria
220 patients enrolled
AM (110)
DP (110)
Completed 42 days-follow up 107 (97 %)
Completed 42 days-follow up 105 (95 %)

OUTCOMES (Adjusted for re-infection)

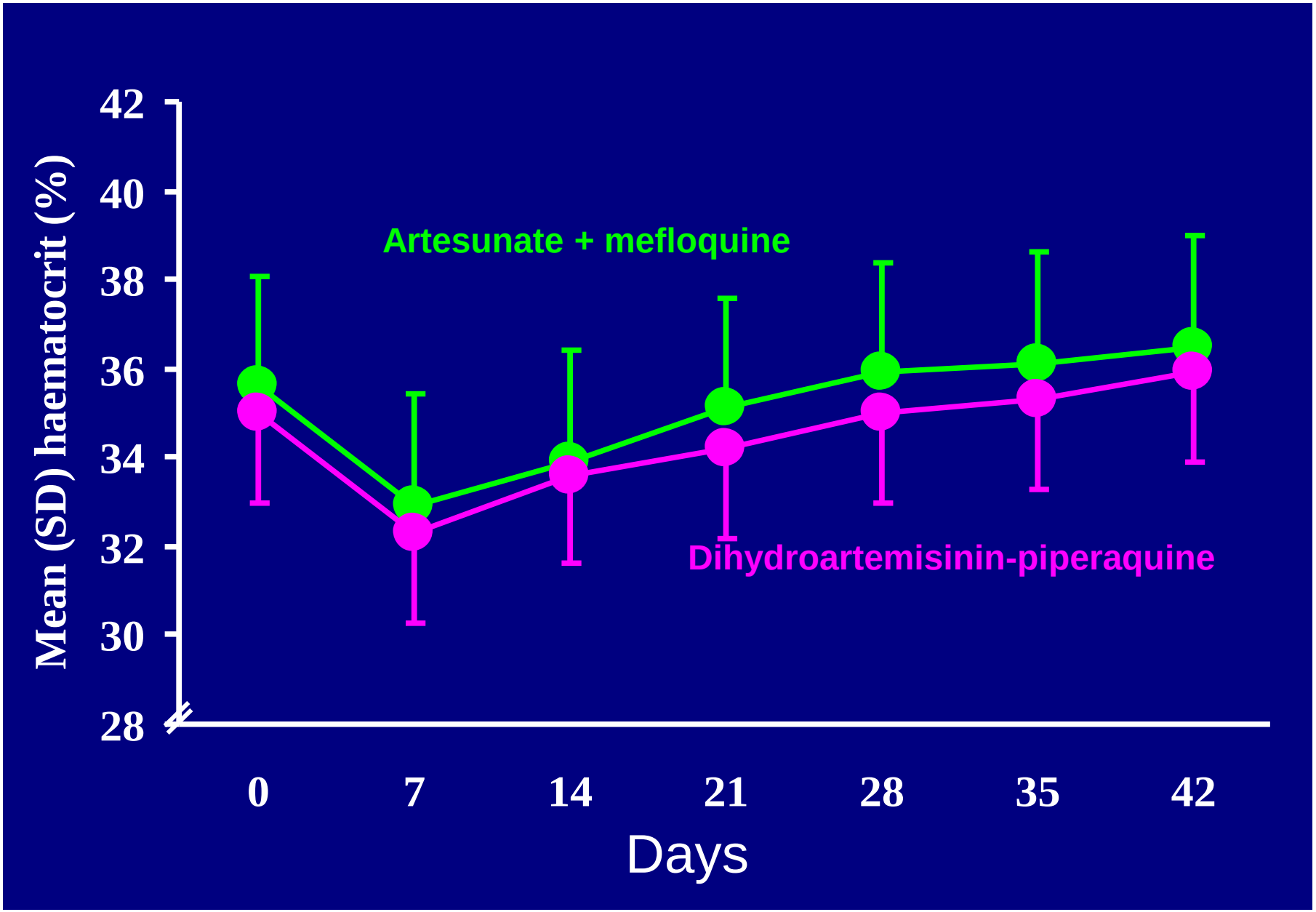
	AM = 110	DP = 110
42-day cure rate (%) (95% CI)	99 (94 - 100)	100 (100 - 100)
Recrudescence	0	0
New infection	3	3
P. vivax appearance	1 (1%)	3 (3%)

COMPARISON OF PARASITE CLEARANCE TIMES



COMPARISON OF FEVER CLEARANCE TIMES

HAEMATOCRIT CHANGE AFTER TREATMENT

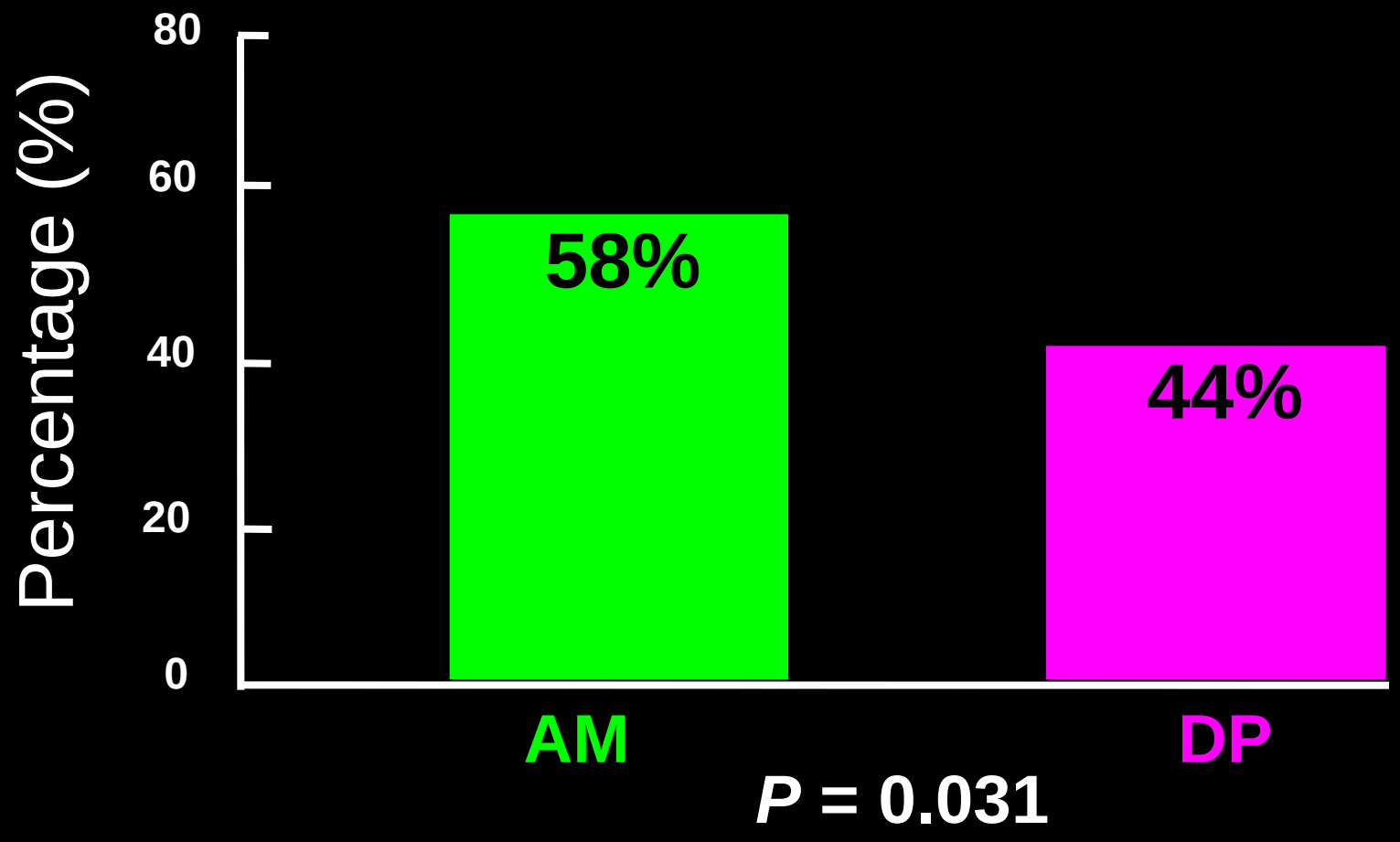


COMPARISON BETWEEN CHILDREN AND ADULTS

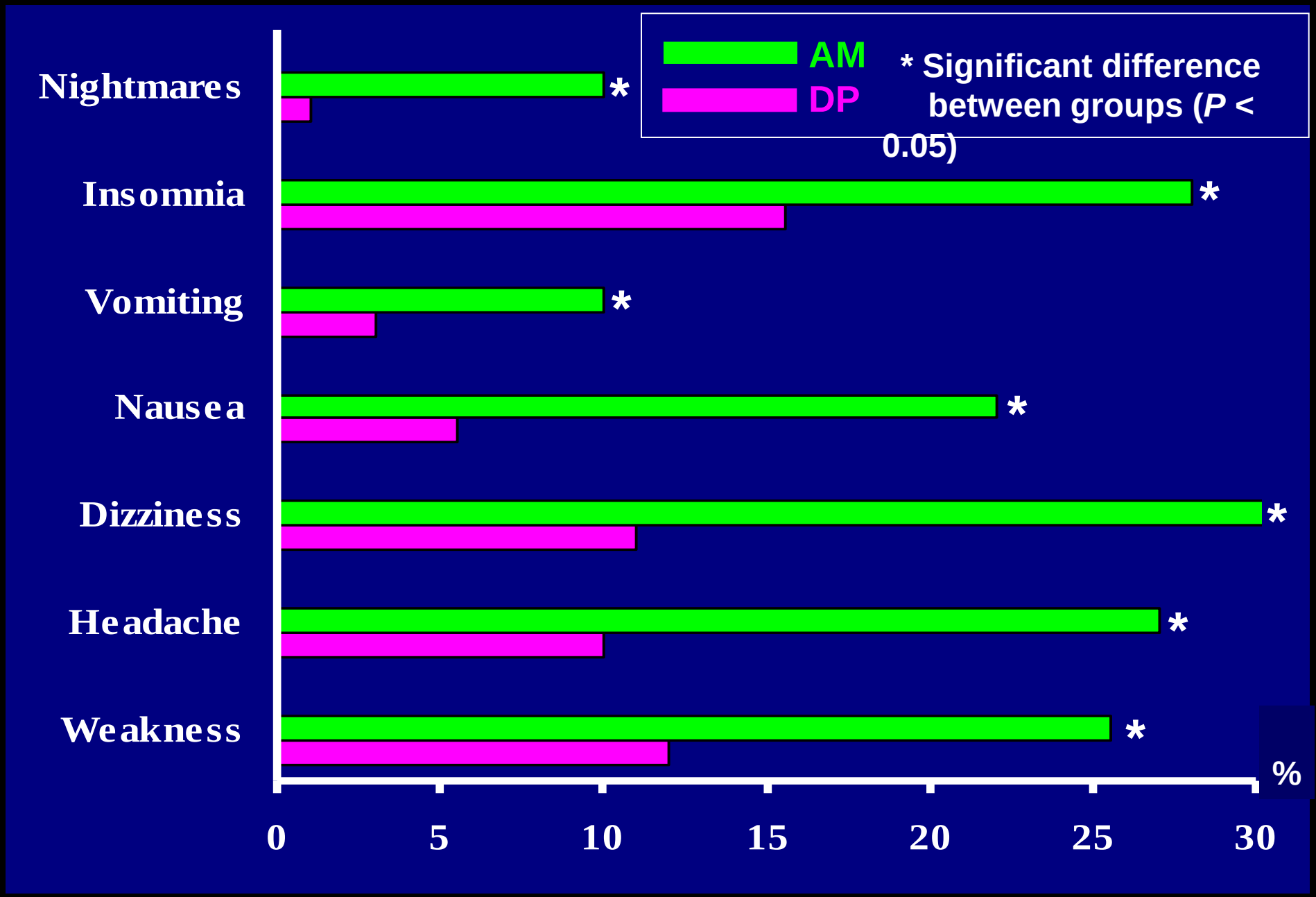
[*Data shown as mean (95% CI) unless indicated]

Variables	Children (≤15 yr) n = 151 (69%)	Adults (> 15 yr) n = 69 (31%)	*P*-value
Adm temp (^{0}C)*	38.4 (38.2 - 38.6)	37.9 (37.5 - 38.2)	0.006
Adm Hct (%)*	33.3 (32.4 - 34.3)	39.4 (37.9 - 41.0)	< 0.001
PCT (days)*	2.07 (2.01 – 2.12)	1.90 (1.80 – 1.90)	< 0.001
FCT (hours)*	24.3 (22.1 – 26.5)	20.2 (17.6 – 22.7)	0.031
Gametocytaemia after treatment No. (%)	11/151 (7 %)	1/69 (1 %)	0.1

PROPORTION OF PATIENTS WITH AT LEAST ONE PROBABLE RECORDED SIDE-EFFECT



PROBABLE SIDE EFFECTS AFTER TREATMENT



CONCLUSION

DP did not have superior efficacy to AM for the treatment of uncomplicated falciparum malaria in Laos but was associated with fewer adverse effects

Children after malaria treatment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