Quantifying Primaquine efficacy & effectiveness

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Radical cure of *P. vivax*

Schizonticide plus Hypnozoiticide
Schizonticidal Efficacy

- Therapeutic efficacy studies
- 28/42 day follow up

- Endpoints:
  - Early treatment failure, late treatment failures or cure
  - Parasite clearance time/ rate

- CQ concentration at time of recurrence
  - Growth through MIC ➔ Resistance
Schizonticidal Efficacy

Analyses:
Kaplan Meier (time to first event)
Radical Cure Efficacy

- Efficacy of the drug to prevent relapse
  - Long enough follow up to the main period of relapses
  - Depends on natural relapse pattern

- No reliable method to distinguish relapses, recrudesences and reinfections:
  - PCR ➔ heterologous and homologous infections
  - Control arm - without PQ allows background reinfection / relapse rates
Outcome measures:

- Symptomatic *P. vivax* -> Passive FU
- Asymptomatic *P. vivax* -> Active FU
- Any recurrence
- Other – cumulative anaemia
- ...

Follow up depends on chosen outcome measure and preferred metric
**Hypnozoitocidal Efficacy**

**Incidence Risk:** Time to first event analyses. Survival analyses

**Incidence Rate:** number of malaria episodes divided by the number of person-years of observation (PYO) in the study population.
Antimalarial Effectiveness

- **Effectiveness** - the extent to which a drug regimen achieves its intended effect in the real world

= Efficacy Plus...

**Host Factors**
- Treatment seeking behaviour
- Access to healthcare
- Education and information
- Severity of disease / Perception of need
- Adherence
- Cost to the patient and carers

**Drug Factors**
- Tolerability
- Complexity of regimen
- Concomitant treatments
- Formulation / packaging

**Health Systems**
- Prescribing habits
- Perception of need
- Concerns over safety
- Cost to providers
- Drug quality
- Supply chain and capacity
Adherence

Ethiopia. Abreha et al, 2017

Thailand. Takeuchi et al. 2010
Generate evidence for better practice

- **Interventions to Improve Radical Cure:**
  - Directly observed treatment (DOT)
  - Semi supervised (e.g. every second day DOT)
  - Educational intervention
  - Reminders via sms or via village workers
  - Other...

- **Control group:** current standard of care (for most settings non-supervised PQ)
Reactivity

- Reactivity is a phenomenon that occurs when individuals alter their performance or behavior due to the awareness that they are being observed.
- Being in a study can change behavior.
- Issue for control group.
Questions

- How can we measure adherence?
- How can we reduce reactivity in control group?
- What are suitable outcome variables?
- What is a suitable study design?
Measure adherence: Self Reporting

- **Self reported** adherence after a full treatment course

- **How to ask**: Have you taken all tablets? How many tablets have you taken? How many have you left?

- **Visual analogues**: e.g. ask patient to pour beads from one glass into another to indicate the number of pills taken
Measure adherence: Self Reporting

- Risk for bias
  - **Recall bias**
    -> patient cant remember how many tablets taken
  - **Social desirability bias**
    -> patient answers the question as he/she thinks is expected
  - **Reactivity**
    -> patient behavior is changed because they are part of a study
Measure adherence: Pill count

- More objective than self-reporting
  - But tablets could be taken by someone else or kept for later
- How to do it?
  - Simple counting of remaining tablets
  - Electronic pill-cap -> pill bottle with electronic chip which registers time of bottle opening
    - Risk of pocket dosing
    - Overestimates adherence because of bottle openings unrelated to medication intake
  - Cost
Measure adherence: Pill count

• When to do it?
  
  o During clinic visit
    ▶ Patient has to know before to bring pill box or strip
    ▶ Risk of pill dumping before visit
    ▶ Altered behavior because patient is aware of pill count

  o Home visit or phone calls
    ▶ Would not need to be explained before
    ▶ Ethical challenges in a study setting if done as announced visit
Drug Concentrations in Blood

- Distinguishes failure from low drug concentration/low adherence vs failure from drug-resistant parasites

- **Primaquine** is rapidly metabolized to Carboxy-primaquine - <6 hours

- **Carboxy-primaquine** accumulates over a 14 day PQ course
Meth Hb

- Primaquine causes elevated Meth Hb levels
- Meth Hb saturation is expressed as the percentage of Hb
  - 1-2% Normal
  - <10% No symptoms
  - ≥ 10% Symptomatic
- Elevated in G6PD deficient patients
- No correlation between Meth-Hb (day 14) concentration and PQ intake based on pill count (Bangladesh study)
Study Design

- Patient encounter is similar to what will be experienced in clinical practice -> to try and come as close to the real life setting as possible
  - Eg If unsupervised Pq then no interaction during treatment

- Similar outcome measures than for efficacy
  - Symptomatic *P. vivax*
  - Asymptomatic *P. vivax*
  - Any recurrence
Study design

- **Follow up** after treatment could be more intense (unless looking at multiple events) -> but needs to reliably capture the outcome measure

- **Measure adherence** with several tools
  - e.g. pill count and blood levels

- **Qualitative studies** to contextualize findings
  - Understand *why* intervention works/doesn’t work
  - Understand how intervention could be modified to work better
Thank you