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Development and evaluation of a novel protocol to assess the efficacy of seasonal malaria chemoprevention using sulfadoxine, pyrimethamine and amodiaquine in an area of high drug resistance in Nampula, Mozambique

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Seasonal malaria chemoprevention with SPAQ is preventing clinical disease but is not preventing new sub-patent infections over 28 days despite therapeutic drug levels, suggesting prevention of clinical disease may be short-lived.

Introduction

Chemoprevention efficacy is a function of a drug's ability to clear existing sub-patent malaria infections and to prevent new infections over the desired period of protection (at least 28 days). This study presents a novel protocol to determine if sub-optimal protection occurs with adherence to a three-day regimen of sulfadoxine-pyrimethamine and amodiaquine (SPAQ), the antimalarials commonly used in seasonal malaria chemoprevention (SMC), and, if it occurs, whether it results from drug resistance or low drug exposure.[1]

Methods

- SPAQ was administered directly to children (3–59 months) on days 0, 1 and 2 during the first SMC cycle.
- Large-volume dry blood spot (DBS) samples and thick smear microscopy slides were collected on days 0, 7 and 28.
- Pharmacometric analysis of DBS samples was conducted on days 7 and 28, focusing on desethylamodiaquine (DAQ), sulfadoxine, and pyrimethamine.
- *Parasitaemia* detection, quantification and genotyping were conducted using microscopy and quantitative polymerase chain reaction (qPCR) to identify antimalarial drug resistant genes (fdhfr, Pfdhps, Pfcrt, Pfmdr1).
- Small-volume DBS were taken one month before the first SMC cycle and 28 days after the final cycle for genotyping.

Results

- Of 251 samples collected, 173 tested qPCR negative, while 78 were positive. Among the positive samples, 50 were new infections, three were recrudescent and 25 could not determined (Figure 1).
- The three recrudescent samples had blood DAQ concentrations of 5.24, 14.40 and 20.60 ng/mL (Figure 1).
- Pfdhps and pfdhfr mutations associated with SP drug resistance were highly prevalent, while pfcrt mutants were entirely absent. Pfmdr1 mutations were observed, including Y184F. DAQ concentration was normally distributed around 21.46 ng/mL with a standard deviation of 31.83 ng/mL (Figure 3).
- A high level of SP drug resistance was observed in all genotypes.
- A moderate level of AQ resistance was observed in the majority of samples.
- There did not appear to be a significant difference in drug resistance between the new and recrudescent infections.
- One recrudescent infection reached a very high level of *parasitaemia* (Figure 1).

Conclusion

Preliminary results suggest that while SMC is impacting malaria incidence, SPAQ is not clearing existing sub-patent infections despite the presence of therapeutic drug levels. This indicates that the effectiveness of this SMC drug regimen in northern Mozambique may be short-lived because of the highly drug resistant haplotypes detected. This protocol serves as a novel evidence-based method to measure chemoprevention efficacy of SMC medicines with good agreement between *parasitaemia* quantification, qPCR and microscopy, suggesting utility and reliability of this methodology. Further analysis of SP drug levels and drug resistance genotypes is ongoing.

Figure 1: The DAQ level on a logarithmic (log) normal scale 10 (y axis) plotted against the sample number (x axis). The line above represents *parasitaemia* along a log^10 scale, with red dots indicating rescrudescence and pink triangles indicating new infections. Blue circles represent undetermined cases. The figure on the left represents PCR results exclusively, while the figure on the right displays microscopy results only. Positive infections are marked on a log normal scale of 10 for *parasitaemia* , as indicated above each graph

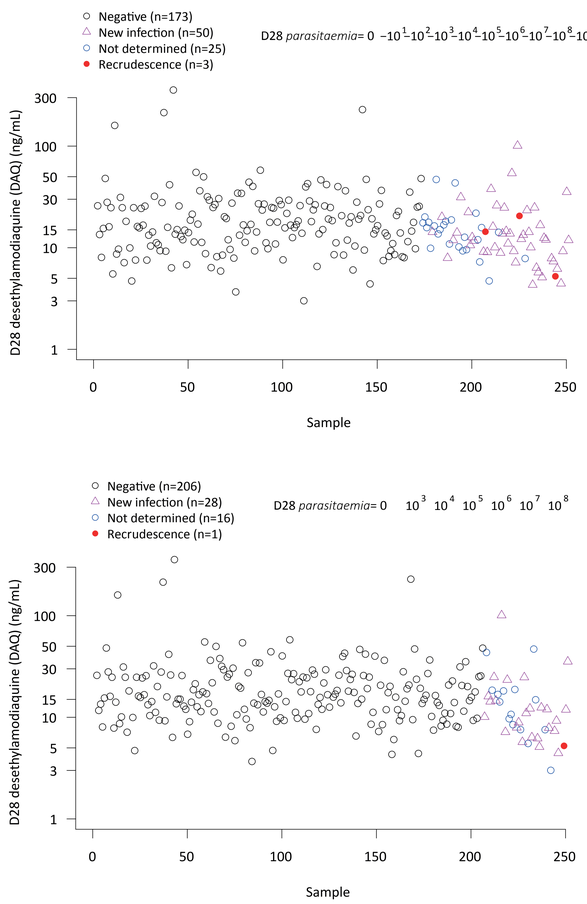


Figure 2: X axis (qPCR) and y axis (microscopy) based parasite per mL conversions
***A small number of mislabeled samples indicate slide positive but qPCR negative samples**

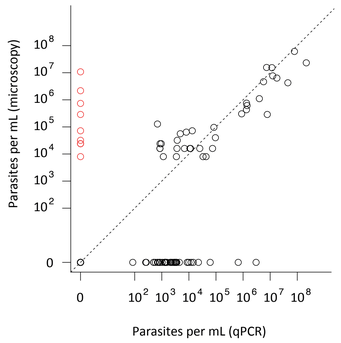
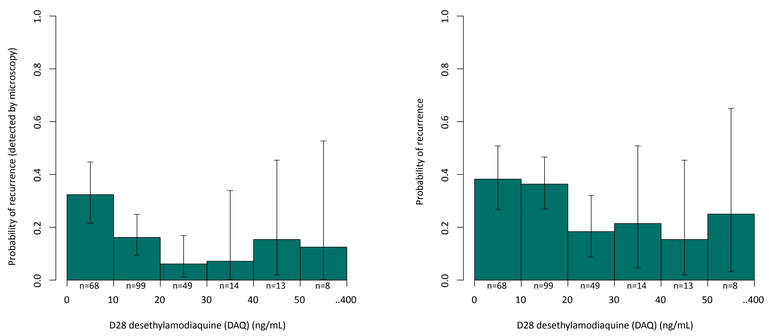


Figure 3: The probability of recurrence against DAQ ng/mL for qPCR (left) and microscopy (right)



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Reference

1. Baker K et al. Feasibility, acceptability, and protective efficacy of seasonal malaria chemoprevention implementation in Nampula province, Mozambique: Protocol for a hybrid effectiveness-implementation study. JMIR Research Protocol, 2022.