Project 2:

Recent successes in malaria control and elimination led to an increasing interest in transmission-reducing strategies. One of the tools available is single-low-dose (0.25 mg/kg of body weight) primaquine (PQ) added to artemisinin combination therapy (ACT). PQ is a drug that has been on the market for more than 70 years. In recent years, the addition of PQ to ACTs has received considerable interest because of its ability to rapidly clear P. falciparum gametocytes and reduce the infectious period compared to ACT alone. Unfortunately, PQ administration might also lead to anemia (decreased hemoglobulin levels) in treated individuals.

Gonçalves et al (2016) reported a randomized clinical trial in asymptomatic parasitaemic children from Burkina Faso. The trial had three arms: (i) ACT combined with a placebo; (ii) ACT combined with PQ at 0.25 mg/kg; and (iii) ACT combined with PQ at 0.40 mg/kg. The main objective of the trial was to understand the efficacy and the safety of each PQ-related therapies comparing to the placebo at day 7 after treatment administration. Efficacy of a treatment was defined as the absence of gametocytes at day 7. Safety was defined in terms of the following hemoglobulin levels at day 7: $\geq$11.0 g/dL for children with age up to 5 years old; $\geq$11.5 g/dL for children from 6 to 12 years old; $\geq$ 12.0 for children from 12 to 14 years old.

Describe the data of this clinical trial and analyze the efficacy and safety endpoints adjusting for potential confounding effects of age and gender. Use intention-to-treat approach in this analysis by identifying individuals in the database who were lost in the follow-up. These individuals should be considered non-responders to the treatments.

It is known that genetic variants on CYP2A6 gene have an impact on how fast many drugs including ACT and PQ are metabolized by the body (Pett et al, 2019). Therefore, genetic variants can naturally modulate the efficacy and the safety of the PQ treatments. In this scenario, repeat previous analysis using a Mendelian randomization related to CYP2A6 phenotype. Compare and interpret the results of the two analyses.

What are your recommendations for the efficacy and safety of PQ-related therapies given your results?

Reference:

Gonçalves, B.P., Tiono, A.B., Ouédraogo, A. et al. Single low dose primaquine to reduce gametocyte carriage and Plasmodium falciparum transmission after artemether-lumefantrine in children with asymptomatic infection: a randomised, double-blind, placebo-controlled trial. BMC Med 14, 40 (2016). https://doi.org/10.1186/s12916-016-0581-y

Pett H, Bradley J, Okebe J, et al. CYP2D6 Polymorphisms and the Safety and Gametocytocidal Activity of Single-Dose Primaquine for Plasmodium falciparum. Antimicrob Agents Chemother. 2019;63(10):e00538-19. Published 2019 Sep 23. doi:10.1128/AAC.00538-19

Variables:

- id – sample id
- treatment – treatment arm (0 – placebo, 0.25 – PQ at 0.25 mg/kg, 0.4 - PQ at 0.4 mg/kg)
- sex – (M – male, F – female)
- age – age in years
- CYPD6_phenotype - CYPD6 phenotype (0 – slow/intermediate CYPD6 metabolizer status, 1- extensive/ultrarapid metabolizer CYPD6 status)
- gametocytes_day_7 – presence of gametocytes at day 7 after treatment administration (0 – absent, 1 – present)
- hb_day_7 – Hemoglobulin levels at day 7 after treatment administration