Use of population pharmacokinetic-pharmacodynamic modelling to inform antimalarial dose optimisation in infants

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October 13, 2023

Abstract

Infants bear a significant malaria burden but are usually excluded from participating in early dose optimisation studies that inform dosing regimens of antimalarial therapy. Unlike older children, infants' exclusion from early-phase trials has resulted in limited evidence to guide accurate dosing of antimalarial treatment for uncomplicated malaria or malaria preventive treatment in this vulnerable population. Subsequently, doses used in infants are often extrapolated from older children or adults, with the potential for under or overdosing. Population pharmacokinetic-pharmacodynamic (PK-PD) modelling, a quantitative methodology that applies mathematical and statistical techniques, can aid the design of clinical studies in infants that collect sparse pharmacokinetic data as well as support the analysis of such data to derive optimised antimalarial dosing in this complex and at-risk yet understudied subpopulation. In this review, we reflect on what PK-PD modelling can do in programmatic settings of most malaria-endemic areas and how it can be used to inform antimalarial dose optimisation for preventive and curative treatment of uncomplicated malaria in infants. We outline key developmental physiological changes that affect drug exposure in early life, the challenges of conducting dose optimisation studies in infants, and examples of how PK-PD modelling has previously informed antimalarial dose optimisation in this subgroup. Additionally, we have discussed the limitations and gaps of PK-PD modelling when used for dose optimisation in infants and best practices for using population PK-PD methods in this subgroup.

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