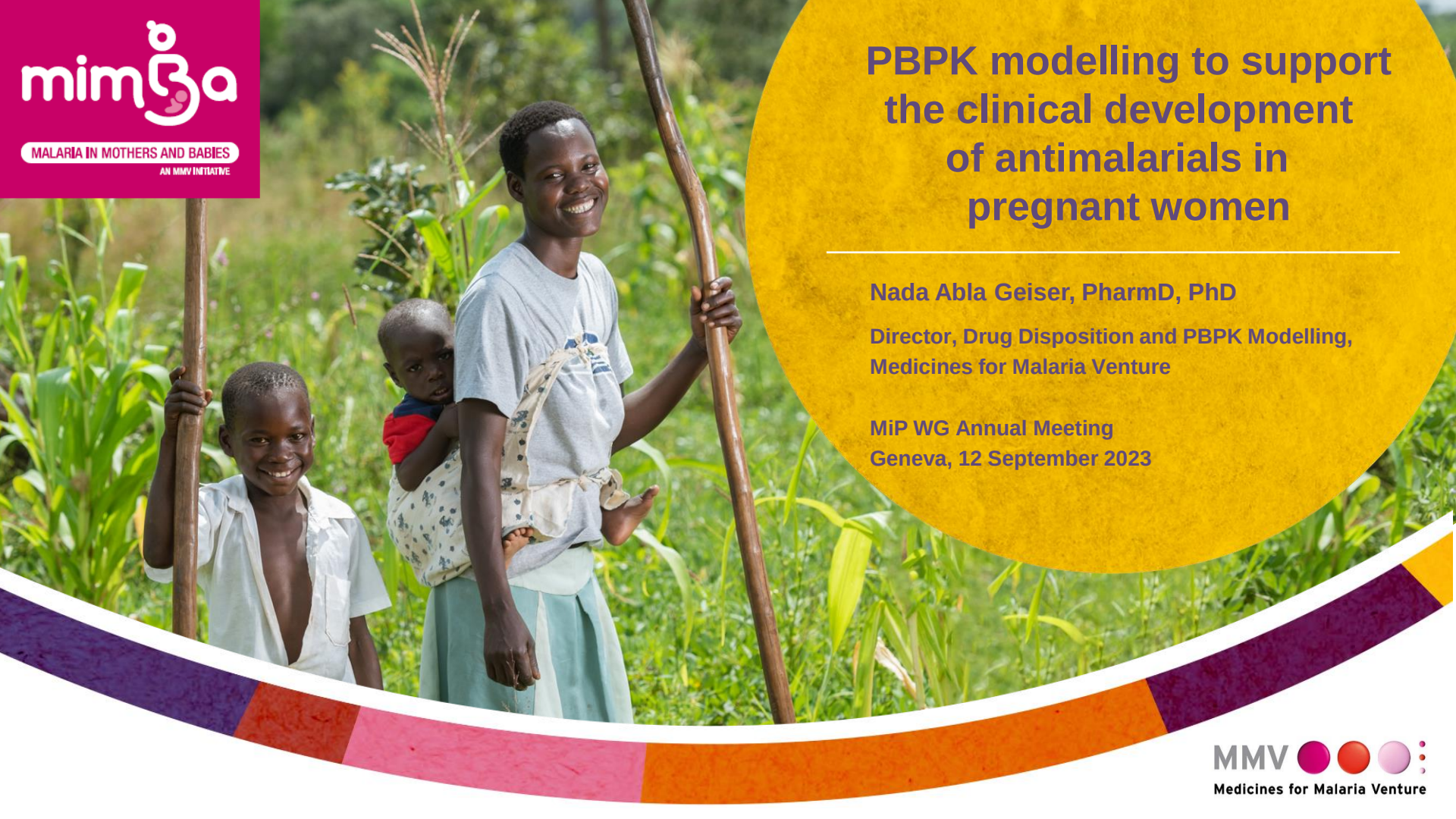

PBPK modelling to support the clinical development of antimalarials in pregnant women

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MiP WG Annual Meeting
Geneva, 12 September 2023

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MALARIA IN MOTHERS AND BABIES
AN MMV INITIATIVE

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Medicines for Malaria Venture

Significant gaps remain to serve the needs of women of reproductive age in malaria-endemic countries

MiMBa = Malaria in Mothers and Babies

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Physiologically based pharmacokinetic (PBPK) modelling is part of the MiMBa development strategy

El Gaaloul *et al. Malaria Journal* (2022) 21:121
https://doi.org/10.1186/s12936-022-04137-2

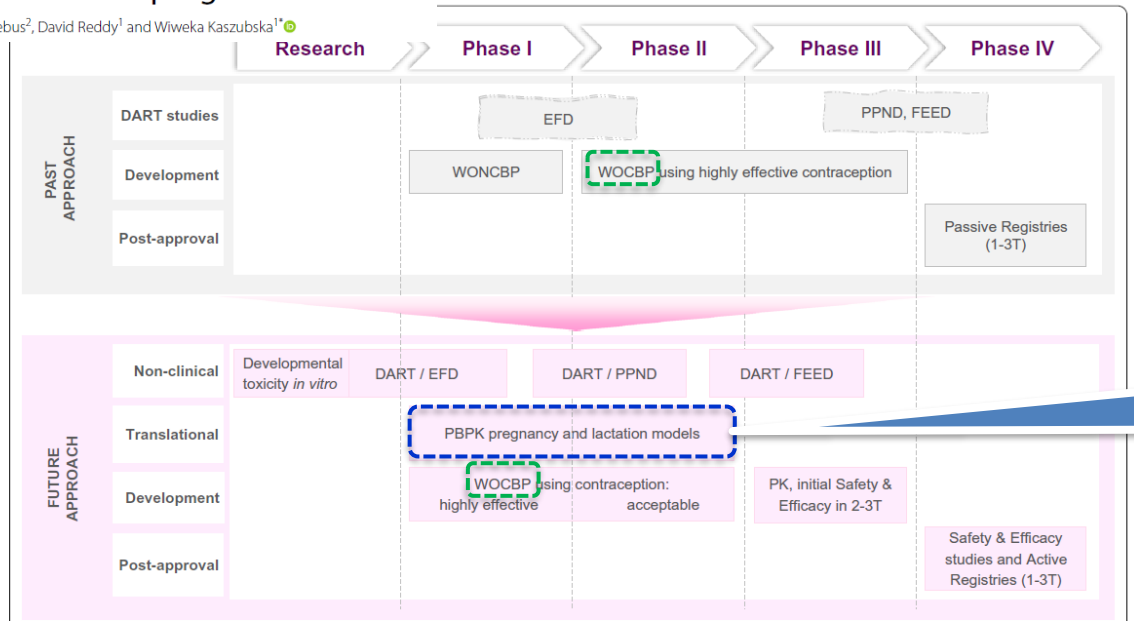
Malaria Journal

COMMENTARY Open Access

Re-orienting anti-malarial drug development to better serve pregnant women

Myriam El Gaaloul[1], Belen Tornesi[1], Flynn Lebus[2], David Reddy[1] and Wiweka Kaszubska[1*]

WONCBP: women of non-child-bearing potential
WOCBP: women of child-bearing potential



PBPK plays a key role in MiMBa strategy

Proposed changes to the antimalarial research and development to better integrate the needs of pregnant individuals in the future.

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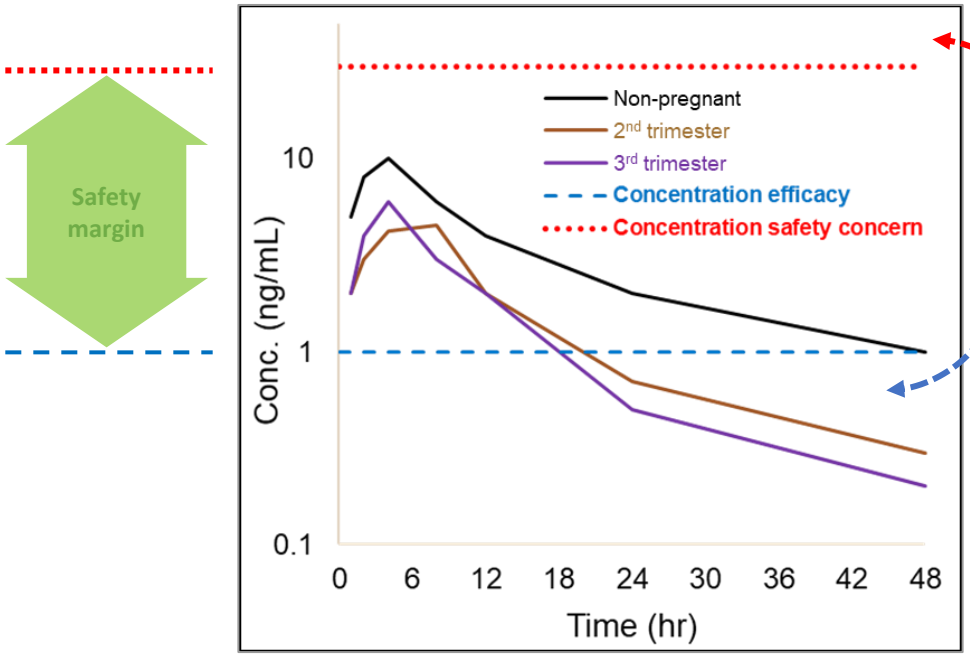
Pharmacokinetics can be affected by pregnancy

Pharmacokinetics (PK) = what the body does to the drug → drug concentrations in blood over time



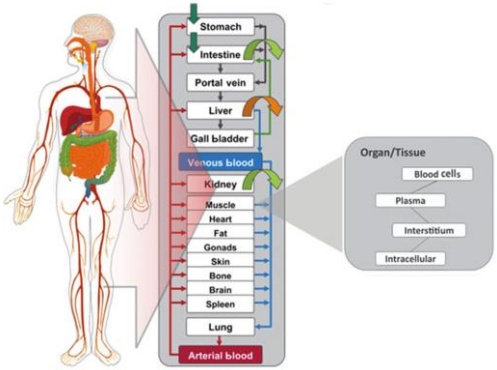
- This could result in:
  - Greater drug concentrations in blood → risk of toxicity
  - Lower drug concentrations in blood → risk of treatment failure

→ Characterizing PK changes is critical for dose selection and adjustment

→ These changes can be predicted using PBPK modelling

Physiologically based pharmacokinetic (PBPK) modelling

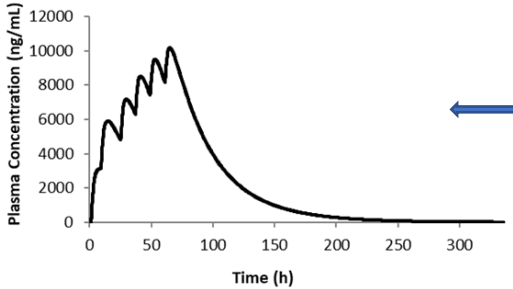
Physiology



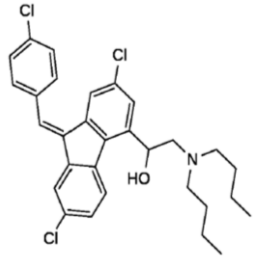
Thiel et al., J Pharm Sci, 2015

Population

Pharmacokinetics



Drug properties



PBPK combines information on human physiology + drug properties to understand and predict the PK of a drug.

- ✓ Prediction of drug-drug interactions (DDIs)
- ✓ Prediction of PK in special populations (eg: pregnant women)

→ *potential dose adjustments*
+ may be used in lieu of certain clinical studies

- ✓ Simcyp (www.certara.com) = PBPK software used at MMV

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MiMBa PBPK strategy for pregnancy and lactation

Objectives

- Predict PK of antimalarials during pregnancy to assess if a dose adjustment is needed
- Evaluate whether there is a passage to the foetus or into breastmilk.

Work Plan

1. **Evaluation of available models** with antimalarials for which clinical exposures in pregnant women and breastmilk are available:

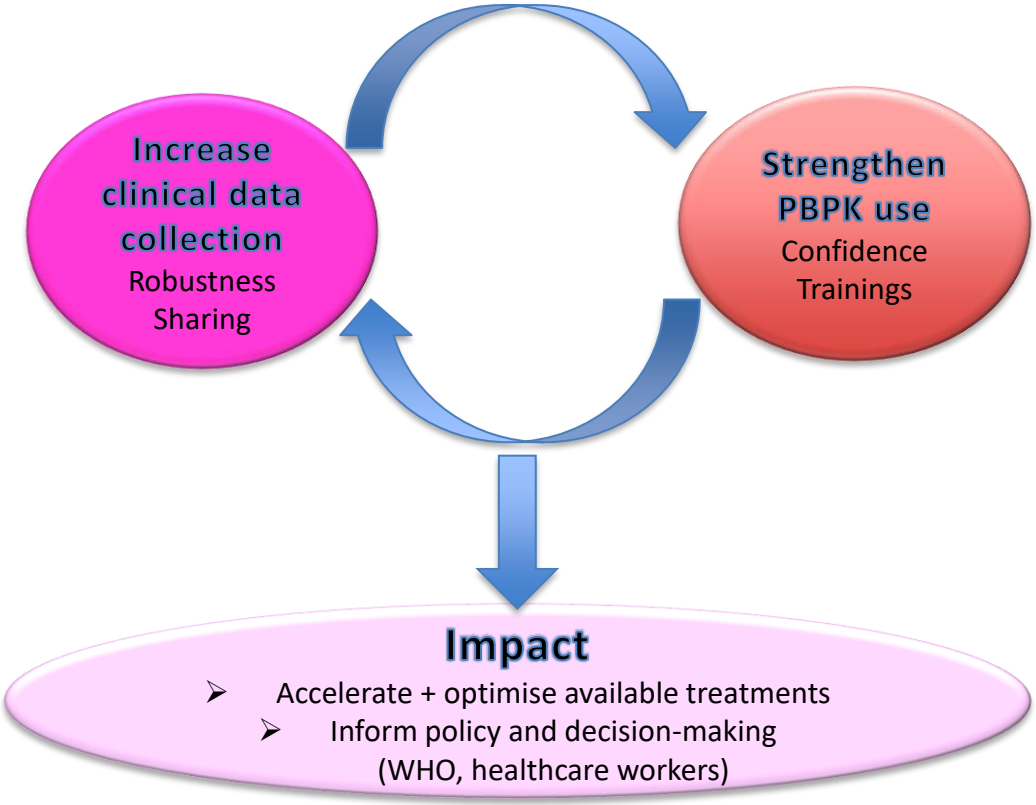
   Pregnancy: artemether, lumefantrine, piperaquine, atovaquone, proguanil, artesunate/DHA

   Lactation: chloroquine, pyrimethamine, piperaquine, primaquine, mefloquine

   → *completed, models generally predict properly clinical observations*

2. **Predict PK + placental passage + milk passage** of other antimalarials → *ongoing*
3. **Optimise** trial design in pregnancy, **evaluate** need for lactation study, and **generate data** to **adequately inform** on the use of antimalarials in pregnant and lactating women

Our ambition moving forward



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