36th ENTIS Conference 11th – 14th Sept 2025
ARISTOTLE UNIVERSITY'S RESEARCH DISSEMINATION CENTER (KEDEA)
THESSALONIKI, GREECE
E-Poster 1

Pragmatic and Contextualized Methods Selection for Safety Assessment of Infant Systemic Exposure Through Human Milk: The Milk4baby Decision Tree

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Introduction

- Over 90% of women take at least one medicine while lactating[1].
- The number of studies evaluating the safety of medicines during lactation is limited[2].
- Three methodological approaches are commonly used to evaluate infant exposure to medicines during lactation[3]:

Case reports

Definition:
- Adverse effects reporting (Y/N) in the breastfed child.
- Provide initial pharmacokinetic (PK) information on the excretion of a medication into human milk.

Strengths:
- Easy to report within the scientific community.
- Low cost and unique data availability.

Caveat:
- Difficult to assess causality between an effect and the medication.
- Difficult to interpret multiple cases for the same medication.

Population pharmacokinetic (PopPK)

Definition:
- Top-down modelling that enables describing inter-individual variability in human PK based on scarce clinical data.

Strengths:
- Few samples per patient required.
- Ability to predict medication exposure through simulations.

Caveat:
- Large number of patients required.
- Predictive performance of the model depends on the availability and quality of the data.

Physiologically based pharmacokinetic (PBPK)

Definition:
- Bottom-up modelling approach using physiological and drug-specific data to predict PK in specific populations.

Strengths:
- Does not strictly require clinical data.
- Supports simulation-based exposure predictions.
- Allows extrapolation to understudied populations.

Caveat:
- Detailed knowledge of ADME required.
- Predictive performance of the model depends on the quality and availabilty of the data.

1. Saha, M. R. et al. (2015).. *Int. Breastfeed. J.* doi:10.1186/s13006-015-0053-6 2. Byrne, J. J. et al. (2019). *N. Engl. J. Med.* doi:10.1056/NEJMp1817420 3. Cardoso, E. et al. (2023). *Expert Opin. Drug Metab. Toxicol.* doi:10.1080/17425255.2023.2221847

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Objectives of the milk4baby decision tree

- Determine the **most adequate methodological approach** to assess **safety in infants following systemic exposure to a medication during lactation.**
- Provide **a roadmap** to guide the decision of regulators, manufacturers, researchers, and healthcare professionals in **the design and/or interpretation** of future **lactation studies**.

Development of the Milk4baby decision tree

Evaluation 1:
Medication expected prevalence in the childbearing population

Methods
- Scientific articles.
- Medication prescription databases (ANSM,...), pregnancy and breastfeeding databases (EFFEMERIS, PrOBE registry,...).

Classification
- Low prevalence: usage <0.05%.
Ex: Lanreotide, Tamsulosin
- Intermediate prevalence: usage between 0.05 and 0.1%.
Ex: Methotrexate, Fluvoxamine
- High prevalence: usage >0.1%.
Ex: Citalopram, Acetaminophen

Evaluation 2:
Medication safety profile

Methods
Litterature review:
1. Safety in infants
2. Safety in adults
3. Safety in animals

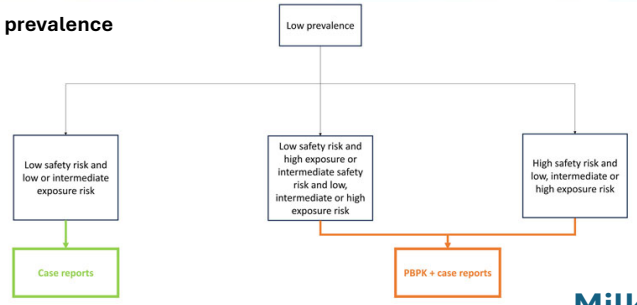
Classification
- Safe:
  - No adverse effects or only type A effects.
  - No dose adjustement required.
- Moderately safe:
  - Unconfortable adverse effects that interfere with activities.
  - Dose adjustement may be required.
- Unsafe:
  - Type B adverse effects.
  - Discontinuation of treatment.

Evaluation 3:
Medication exposure level

Methods
- In the mother:
  - Systemic absorption
  - Transfer into human milk
  - Risk of medication accumulation
  - Frequency of medication utilization
- In the infant:
  - Oral absorption

Classification of oral absorption
- Low: 0-30%.
- Intermediate: 30-70%.
- High: 70-100%.

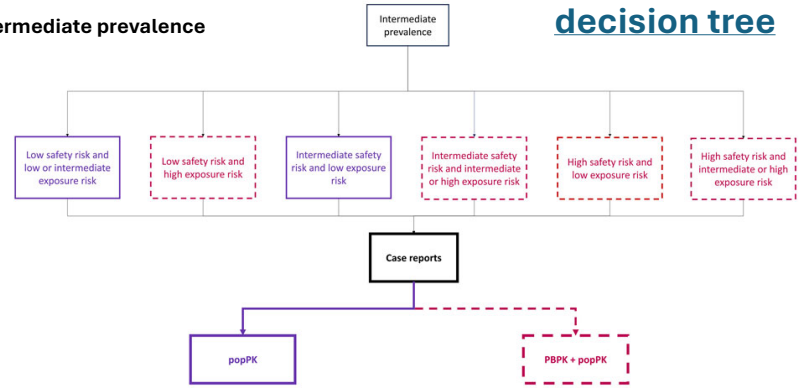
A Low prevalence



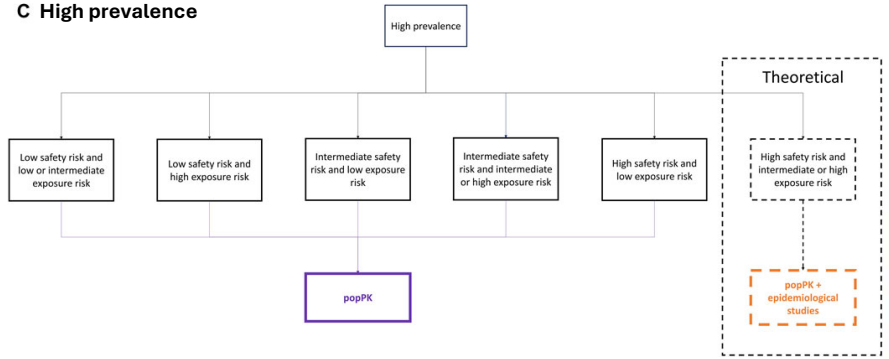
Scan Me!

Milk4baby decision tree

B Intermediate prevalence



C High prevalence



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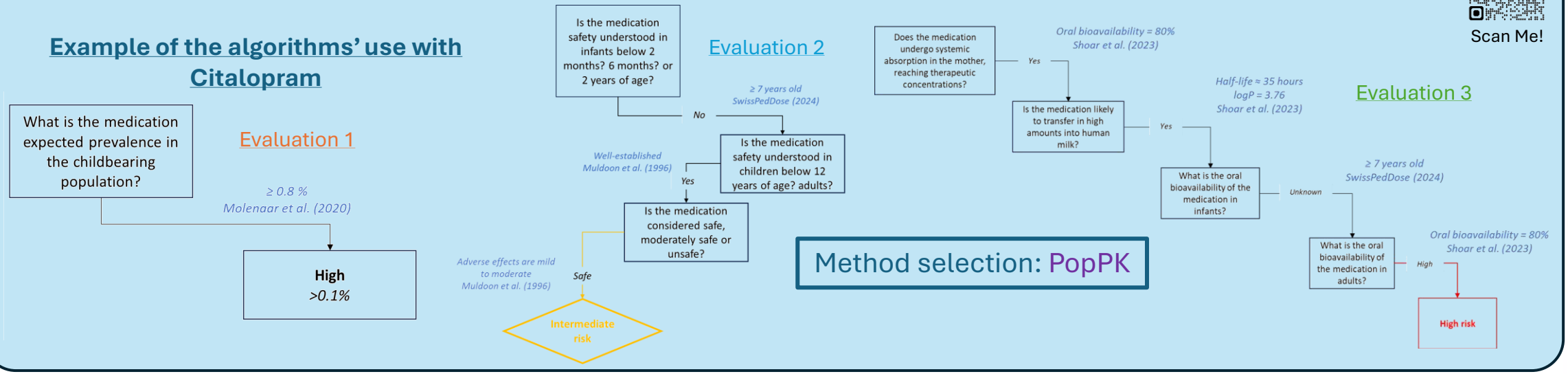
Verification of the milk4baby decision tree

Scan Me!

Example of the algorithms' use with Citalopram

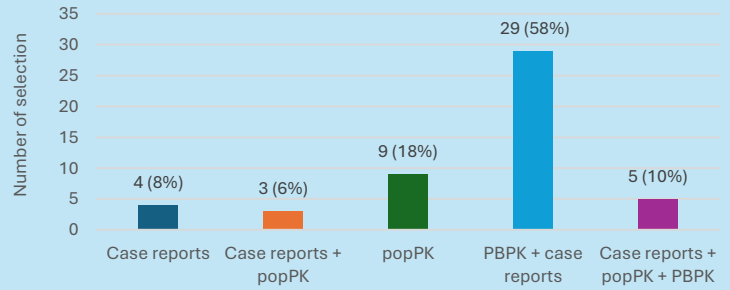


Method selection: PopPK

Extended verification of the Milk4baby decision tree

Medication	Evaluation 1	Evaluation 2	Evaluation 3	Method selection
Cyclopentolate (drops)	Low	Low risk	Intermediate risk	Case reports
Desonide (cream)	Intermediate	Low risk	Low risk	Case reports + PopPK
Betamethasone (cream)	High	Intermediate risk	Low risk	PopPK
Doxazosin	Low	Intermediate risk	Intermediate risk	PBPK + Case reports
Bisoprolol	Intermediate	Intermediate risk	High risk	Case reports + PBPK + popPK
Lidocain	High	Intermediate/High risk	Low risk	PopPK
Ocrelizumab	Low	Intermediate risk	Low risk	PBPK + Case reports
Protriptyline	Low	High risk	High risk	PBPK + Case reports
Phentermine	Low	Intermediate risk	High risk	PBPK + Case reports
Piperacillin and Tazobactam	Low	Low risk	Low risk	Case reports

Milk4baby method selection for 50 medications



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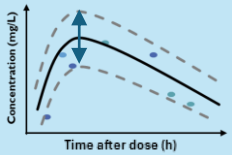
Design of clinical lactation studies

Number of women-infant dyads

Number of samples
- Rich
- Sparse
- Opportunistic

Type of samples
- Human milk
- Maternal blood and milk
- Maternal and infant blood



Medication pharmacokinetic variability
- Area under the curve (AUC)
- Clearance (CL)
- Volume of distribution (Vd)
- Bioavailability

Variables to collect
- Mother
- Infant
- Medication
- Lactation
- Mode of life
- Sample collection

Discussion

It sounds good in theory, but in practice? Currently lack of …

- …data on the prevalence of medication utilization during pregnancy and lactation.
- …data on medication safety and PK in infants.
- … verified models for PK prediction.

Difficulties in evaluating each step of the decision tree. Need more data on pregnant and lactating women and infants.

Conclusion

More data on the use and safety of medicines in lactation are needed.

Rational selection of methodological approaches to assess the safety of medicines in lactation.

Use Milk4baby to improve the efficiency and accuracy of assessing the safety of a medicine in a child exposed during lactation.

Improve recommendations to lactating women and healthcare professionals.

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