# PERSPECTIVE

# Model-Informed Assessment of Anti-Infectives for Young Children in Low- and Middle-Income Countries

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**Infectious diseases continue to threaten the lives of young children in low- and middle-income countries (LMICs). Pediatric assessment of anti-infectives for these children should be initiated early. This assessment can center around an iterative dose-selection process that is informed by an integrated prediction platform based on physiologically-based pharmacokinetic (PBPK) and pharmacodynamic (PD) models.**

## DEADLY INFECTIOUS DISEASE IN YOUNG CHILDREN IN LMICS – AN UNMET MEDICAL NEED

Infectious diseases continue to take a toll on the lives of young children in LMICs, especially in sub-Saharan Africa and Southern Asia. In 2016, pneumonia, diarrhea, and malaria remained the top three causes of death of children aged 1–59 months, each contributing 13%, 8%, and 5% of deaths around the world, respectively.[1] The striking prevalence of infection-related deaths in these children is due to various risk factors, including undernourishment, compromised immunity, poor sanitation, disease comorbidity, inadequate access to health care, and growing drug resistance that compromises already limited treatment options. Therefore, development of inexpensive, safe, and effective anti-infective medications for this vulnerable population remains a vital means to reduce morbidity and mortality.

Pediatric assessment is required by law in the United States to support the safe and effective use of drug products in children. Unlike developing drug products for adults, conduct of clinical trials in children is complicated by unique feasibility challenges and ethical considerations. By default, if an indication is relevant to both adults and children, a developer would first study an investigational drug extensively in adults before moving to children and then conduct pediatric studies in descending age cohorts sequentially, such as adolescents (12–16 years old), children (2–12 years old), infants (1–23 months old), and neonates (newborns to 1 month). Such conventional paradigms may not be practical and ethical if the target population is young children (e.g., under 5 years old) in LMICs, who are more vulnerable to death after infection. Risk factors mentioned above are difficult or impossible to translate from studies conducted in adults and/or older children.

In this perspective, we first demystify the conventional pediatric drug development paradigm by reviewing current regulatory requirements to answer the question "*Can pediatric assessment be initiated early in drug development?*" We then describe why dose selection is the basis of progressing pediatric assessment from first-in-pediatric (FIP) study to product labeling, value proposition of PBPK and PD models that fit the iterative process of dose selection in pediatric assessment, and how one can apply such model-informed approach to expedite development of safe and effective anti-infectives to treat young children in LMICs. Because the regulatory system in LMICs is generally weak, we assume that drug developers pursue a regulatory pathway for its pediatric development with a stringent regulatory authority (such as the US Food and Drug Administration (FDA), European Medicines Agency, or Japan's Pharmaceutical and Medical Device Agency, herein referred to as regulators).

## EARLY INITIATION OF PEDIATRIC ASSESSMENT

The conventional paradigm of extensively studying an investigational drug in adults prior to studying it in children in a descending age fashion is not required by regulators. Instead, regulators call for early initiation of pediatric assessment. For example, for diseases "predominantly or exclusively affecting pediatric patients," the entire development program can be conducted in "pediatric population except for initial safety and tolerability data, which will usually be obtained in adults." For products "to treat serious or life-threatening diseases, occurring in both adults and pediatric patients, for which there are currently no or limited therapeutic options," the pediatric study can be initiated "following assessment of initial safety data and reasonable evidence of potential benefit."[2] Both situations apply to developing drugs to combat deadly infections in young children in LMICs.

The call for early initiation of pediatric assessment is based on the following challenges recognized by regulators. First and foremost, because safety findings in adults may not be fully extrapolatable to children, larger safety database in adults beyond phase I studies may not add value, especially when developmental toxicity is evaluated.[3] As such, a safety trial is required in target pediatric population(s) under all development scenarios.[4] Second, extrapolation of drug efficacy from a reference population (e.g., adults or older children) to young children may not be straightforward. The assumption that the exposure–response or dose–response relationship is the same among different age groups is easily challenged
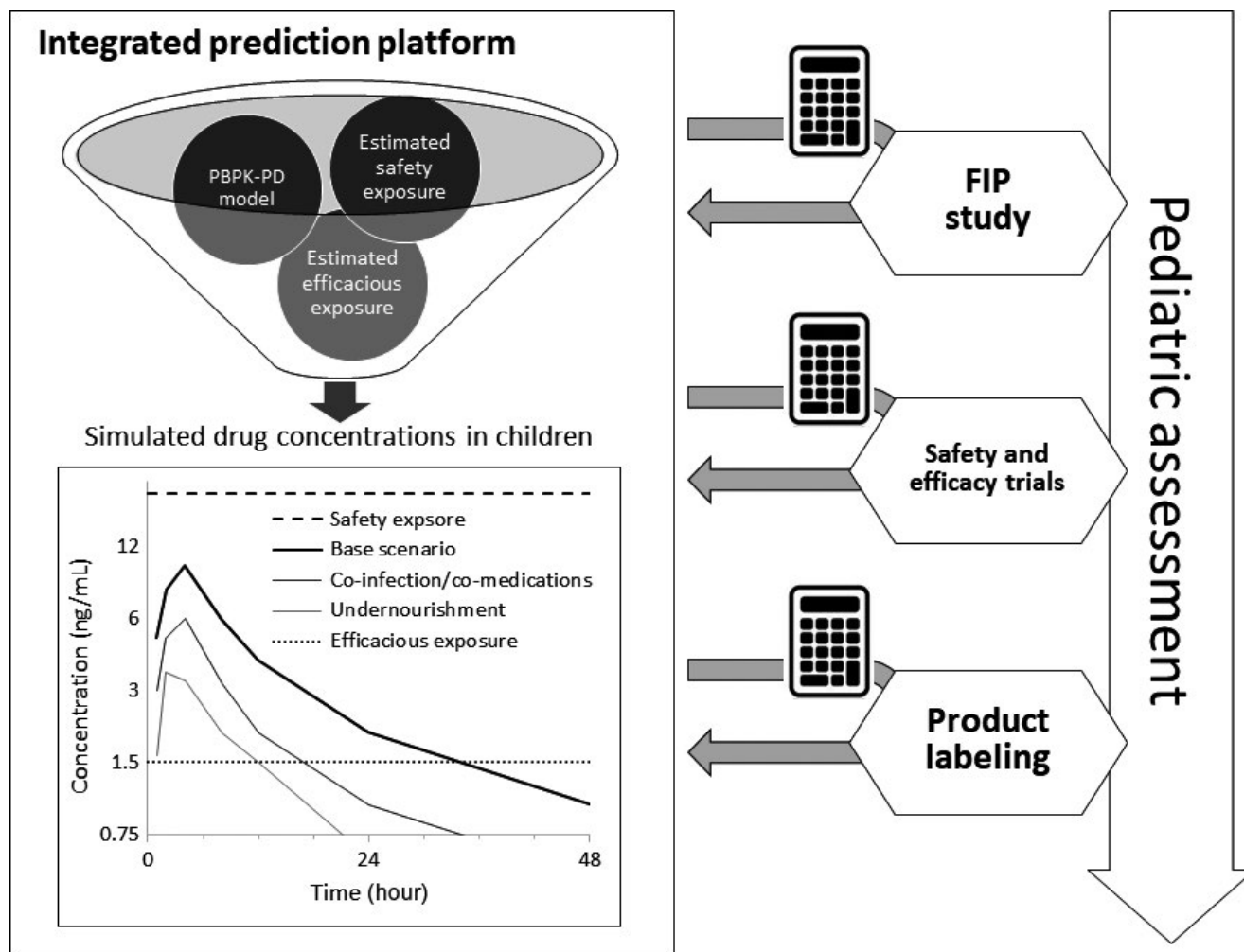
**Figure 1** Iterative dose selection process of pediatric assessment using an integrated prediction platform. A model-informed, integrated prediction platform (platform) incorporates three exposure determinants to support dose selection at three major stages (prior to first-in-pediatric (FIP) study, prior to subsequent safety/efficacy pediatric trial(s), and prior to product labeling; e.g., when communicating with regulators during filing). The platform is iteratively updated by findings from the studies and new knowledge that can enhance the physiological component of the model. Patient factors unique to the target population (e.g., physiological change under disease of interest, coinfection, concomitant medications, nutrition status, and performance of pediatric formulations) can be considered through simulations using physiologically-based pharmacokinetic (PBPK) and pharmacodynamic (PD) models.

when young children in LMICs are the target population (factors described in the section "Deadly infectious disease in young children in LMICs – an unmet medical need"). Last but not least, the stepwise approach of studying children with descending age may not be feasible and ethical in situations when infection does not manifest disease in older children.

**DOSE SELECTION AND FIP STUDY**

Initiation and subsequent clinical studies in young children involve an iterative dose selection process with the goal of minimizing the risk while offering treatment benefit to children enrolled in these trials. At the heart of this dose selection iteration are pharmacokinetic (PK) principles, which leverage three exposure-based determinants: drug exposure related to safety, drug exposure related to efficacy, and a PK model to predict drug PK in a target population (**Figure 1**).

To answer "*Can pediatric assessment be initiated early in drug development?*" one has to answer "How to initiate an FIP study?" The FIP study is a PK and safety study in pediatric patients with the disease for which an indication is sought. This way, patients may benefit from the investigational drug. Because efficacy is usually unknown, adequate rescue therapy or intervention is planned. **Table 1** includes elements for each exposure-based determinant to support initiation of an FIP study under the conventional pediatric assessment paradigm. According to the section "Early initiation of pediatric assessment," some elements are neither relevant nor useful when anti-infectives are developed for young children in LMICs. To initiate pediatric assessment early, safety exposure has to be estimated from results from a phase I study in adults and juvenile toxicity studies in animals, efficacy exposure has to be estimated from preclinical findings, and a model relevant to the target population has to be sufficiently mechanistic to connect these exposure estimates to support dose selection.

**Table 1 Determinants of FIP study**

| Exposure-based determinants | Conventional paradigm | Challenges for treating life-threatening infections in young children in LMICs | Expedited paradigm |
|---|---|---|---|
| Safety | Phase I study (single and multiple ascending doses in adults) <br> Safety in later phase study in adults and older children[a] <br> Juvenile animal toxicity study | Safety in diseased children unlikely to be predicted from adults <br> Infeasible to study older children if disease is not present | Phase I study (single and multiple ascending doses in adults) <br> Juvenile animal toxicity study |
| Efficacy | Human challenge studies in healthy adult volunteers[a] <br> Phase II studies in adults and/or older children[a] <br> Predicted efficacious exposure using findings from preclinical studies | Exposure–response relationship may not be assumed the same across age groups <br> Infeasible to study older children if disease is not present | Predicted efficacious exposure using findings from preclinical studies |
| PK prediction | Population pharmacokinetic models[a] <br><br> • PK from reference populations <br> • Parameters scaled to children using allometry methods <br> PBPK-PD models <br><br> • Toxicokinetics from juvenile animal studies <br> • Efficacy from preclinical studies <br> • PK from reference populations <br> • ADME properties of the drug <br> • Consider both drug and physiology information, as well as prior knowledge in developmental physiology and effect of specific patient factors | PK in older children does not necessarily add value to predicting PK in younger children <br> Infeasible to study older children if disease is not present | PBPK-PD models <br><br> • Toxicokinetics from juvenile animal studies <br> • Efficacy from preclinical studies <br> • PK from reference populations <br> • ADME properties of the drug <br> • Consider both drug and physiology information, as well as prior knowledge in developmental physiology and effect of specific patient factors |

ADME, absorption, distribution, metabolism, and excretion; FIP, first-in-pediatric; LMICs, low- and middle-income countries; PBPK, physiologically-based pharmacokinetic; PD, pharmacodynamic; PK, pharmacokinetic.
[a]Elements that may not be available when initiating an FIP study early.

## PBPK-PD AS INTEGRATED PREDICTION FRAMEWORK FOR PEDIATRIC ASSESSMENT

Among exposure-based mechanistic models, a PBPK-PD model is suitable to support early initiation of pediatric assessment. A PBPK-PD model describes drug behavior within a physiological context and can be iteratively updated using prior and new knowledge of drug, pathogen, and host (animal and human). The inherent ability of a PBPK model to predict target drug concentration–time profiles allows mechanistic description of PK/PD relationships for an investigational drug and effective translation of preclinical findings. Combining a PBPK disposition model with a mechanistic absorption model can address biopharmaceutical questions, which can be critical when pediatric formulation is developed. PBPK models are also recognized by the FDA as a key model-informed drug development decision tool.[5]

**Figure 1** illustrates the iterative process of pediatric assessment that can be informed by PBPK-PD models. In the beginning, one compiles preclinical drug data in an adult PBPK model structure. Drug-dependent parameters can be refined using adult phase I PK data. The updated drug parameters can be integrated into a pediatric (physiology) model that incorporates age-related changes. Estimation of exposure thresholds for safety and efficacy can be informed mechanistically by PK/PD relationships from juvenile toxicity, safety/PK characterized in adult phase I study, and preclinical efficacy studies.[6] These estimates and simulated PK in a target pediatric group are initial exposure determinants to select dose/dose regimen for FIP study. These determinants are updated after an FIP study to design subsequent pediatric trials and continue to be refined when new data become available. At any stage, the model coupled with the mechanistic absorption model can be used to evaluate performance of different pediatric formulations.

The iterative process informed by PBPK-PD offers a logical decision tool to product developers who plan to expedite their pediatric assessment of anti-infectives for young children in LMICs. First, many intrinsic patient factors unique to children in LMICs (see section "Deadly infectious disease in young children in LMICs – an unmet medical need") can be included in a pediatric physiological model. The field of PBPK has seen significant improvement of pediatric models in delineating growth and maturation of major drug disposition pathways in children. Second, because treatment and prevention of many infectious diseases are transitioning to the use of drug combinations, and under certain circumstances children coinfected with

different pathogens require concomitant medications, interactions among partner drugs and comedications need to be evaluated. To this end, confidence in using PBPK to predict clinical drug–drug interactions is considered the highest.[7] PBPK simulations of drug–drug interactions are routinely used to support dosing recommendations. Third, formulation development for young children in LMICs has to balance among affordability and convenience of use while ensuring quality and safety. *In silico* simulations of the *in vivo* performance of candidate formulations can effectively support decisions on formulation selection. Biopharmaceutical PBPK models are widely applied in the development of new and generic drug products. Finally, uptake of PBPK by major regulators has increased in the past decade. In 2017, the FDA committed to "facilitate the development and application of exposure-based, biological, and statistical models derived from preclinical and clinical data sources."[5] In 2018, the FDA published its final guidance on PBPK.[8] For pediatric assessment, a model considering "all available and relevant sources of existing knowledge" is expected by major regulators.[9]

PBPK-PD models should be constantly updated toward enhanced predictability. Availability of a pediatric physiological model representing young children in LMICs and other reusable systems models (e.g., mechanisms of action and disease progression models in both animals and humans) is important not only for investigational drugs targeting pathogens residing in tissues that are not easily assessed but also for situations when PD interactions need to be evaluated and reasonably predicted. The need to develop physiological models that characterize the effect of undernourishment[10] and disease (e.g., malaria; personal communication with Dr Zoe Barter and colleagues) on drug PKs should be assessed. The design of an FIP study of an investigational drug may take advantage of learning efficacy and safety of drugs in the same class within the PBPK-PD framework. The use of PBPK-PD to predict or to evaluate the performance of pediatric formulations is generally scarce. Enhancement of predictability of PBPK-PD for young children in LMICs will benefit from collaborations and dialogues among drug developers, academic researchers, and regulators.

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