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REVIEW

Predicting the correct dose in children: Role of computational Pediatric Physiological-based pharmacokinetics modeling tools

Xu Zhou | Jiening Dun | Xiao Chen | Bai Xiang | Yunjie Dang | Deying Cao

College of Pharmacy, Hebei Medical University, Shijiazhuang, China

Correspondence
Yunjie Dang and Deying Cao, College of Pharmacy, Hebei Medical University, Shijiazhuang, Hebei 050000, China.
Email: dangyunjie@hebmu.edu.cn and caody3@163.com

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Abstract

The pharmacokinetics (PKs) and safety of medications in particular groups can be predicted using the physiologically-based pharmacokinetic (PBPK) model. Using the PBPK model may enable safe pediatric clinical trials and speed up the process of new drug research and development, especially for children, a population in which it is relatively difficult to conduct clinical trials. This review summarizes the role of pediatric PBPK (P-PBPK) modeling software in dose prediction over the past 6 years and briefly introduces the process of general P-PBPK modeling. We summarized the theories and applications of this software and discussed the application trends and future perspectives in the area. The modeling software's extensive use will undoubtedly make it easier to predict dose prediction for young patients.

INTRODUCTION

Far fewer drugs have been licensed for use in children than in adults. Enrolling adequate numbers of children for clinical studies is difficult because the pediatric population is only a minority of the general population. Additionally, pediatric research can easily raise severe ethical issues. Children are not small adults. The differences between children of different age groups and adults are not merely due to body weight but also physiological and biochemical differences resulting in different rates of drug metabolism or renal clearance. These factors make it difficult to determine safe and effective doses in children.[1] Drug disposition processes change in a nonlinear relationship with growth and development.[2] Although allometric scaling may be sufficient in some cases for dosage prediction, more mechanistic models are frequently necessary to account for the complex interaction of physiological, biochemical, and drug-related developmental features in children.[3] Modeling and simulation have become a cornerstone of pediatric drug research by maximizing the use of existing data.[4] Physiologically-based pharmacokinetic PBPK modeling and simulation have become prominent in the model-informed drug development paradigm during the last decade.[5] PBPK modeling is a type of pharmacokinetic (PK) prediction method that can characterize the concentration-versus-time profile in the body, which is the foundation for determining whether a drug is therapeutic or harmful.[6] From early compound selection for first-in-human trials to dose recommendations in product labeling, PBPK modeling can impact drug development at numerous stages.[7] In recent years, PBPK modeling has often been used to advise dosing in children.[8] Between 2008

Xu Zhou and Jiening Dun have contributed equally to this work and share the first authorship.

and 2018, 15% of PBPK modeling drug submissions to the US Food and Drug Administration (FDA) contained pediatric simulations, according to a recent study.[9] Pediatric drug development was reported to be the second most common application of PBPK modeling in the FDA regulatory submissions, indicating the growing importance of PBPK modeling in pediatric drug development. PBPK is mainly used in clinical trials to determine the initial dose for pediatric patients.[10] PBPK modeling can be utilized for various purposes in pediatric drug development, including initial pediatric dose selection,[11] simulation-based trial design,[12] correlation with target organ toxicities, investigation of possible drug-drug interactions (DDIs) in pediatric populations,[13] and the effect of impaired organ function on PKs in pediatric populations.[14]

Because they are based on actual organs with their inherent volumes and blood flow connected by the vasculature,[15] as well as defined processes of absorption, distribution, metabolism, and excretion (ADME) as a function of anatomy, physiology, and biochemistry, PBPK models allow for rational scaling between species and developmental stages. Without a doubt, graphical user interface (GUI)-based tools have expanded the use and application of PBPK for users with little or no programming experience.[16] Pediatric PBPK (P-PBPK) modeling and simulation software includes GastroPlus, PK-Sim, Simcyp, R, and other physiological PK model software. Each software program has its own set of characteristics. These programs have been used to calculate PK parameters, solve complex equations, design models, conduct statistical analysis, simulate drug processes in vivo, anticipate medicine efficacy, and develop drug regimens, among other purposes. The extensive use of PK software facilitates preclinical and clinical research, drug development, and sensible drug use in child patients.

The primary aim of this article is to summarize examples of P-PBPK modeling for dose prediction using different software. We will also discuss each software's application trends and fields in pediatric dose prediction. Using PBPK models to support pediatric drug research is quite an attractive option, and making optimal use of various technologies will help accelerate this trend.

METHODS

Literature source and search

A systematic search was undertaken according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[17] A broad search of PubMed (National Center for Biotechnology Information, National Institutes of Health) was conducted up to and including September 6, 2022, using the following search terms: (Physiologically based pharmacokinetic modeling [Title/Abstract]) OR (PBPK [Title/Abstract]) AND (Pediatrics [Title/Abstract]) OR (Pediatric [Title/Abstract]) OR (Newborn [Title/Abstract]) OR (Infant [Title/Abstract]) OR (Children [Title/Abstract]) OR (Adolescents [Title/Abstract]) AND (drug [Title/Abstract]) OR (dose [Title/Abstract]). The final data set (P-PBPK_Final_Dataset.xlsx) in an Excel format is available in the Table S1.

P-PBPK modeling mechanism and workflow

Physiologically based pharmacokinetic modeling has recently gained regulatory approval as a valuable tool in the drug development decision-making process.[18,19] The ability of PBPK models to extrapolate knowledge between systems is advantageous in pediatric drug development, as adult PK data can be used to estimate PK changes in children. Modifying the adult PBPK model is a common technique for creating a P-PBPK model. However, when the modeler uses this technique, an inaccurate forecast by the adult PBPK model will be mirrored in the P-PBPK model, a source of concern for researchers working on pediatric models.[20] Following the definition of an adequate adult model, developing P-PBPK models require some assumptions that must be stated.[20] First, clearance routes in adults and children are assumed to be comparable. Second, the PBPK model's structure is similar to that of adults. This assumption may be ruled out in preterm infants with significant arterial shunting due to a patient's ductus arteriosus. Third, the model must maintain a stable health condition or illness diversity between adults and youngsters. A schematic representing the typical P-PBPK modeling workflow is depicted in Figure 1.[21] The initial step involves the development of an adult PBPK model utilizing drug-dependent parameters (e.g., physicochemical properties, ADME data) and system-dependent parameters (e.g., anatomic and physiological data, such as cardiac output and the flow of biofluid). After verifying the adult PBPK model, the pediatric model is developed using age-dependent changes in physiology.

P-PBPK dose prediction platform

PK-Sim

The Open Systems Pharmacology (OSP) community is a nonprofit organization dedicated to systems pharmacology and PBPK modeling. Under the GPLv2 License, the OSP Suite makes the previous commercial software tools

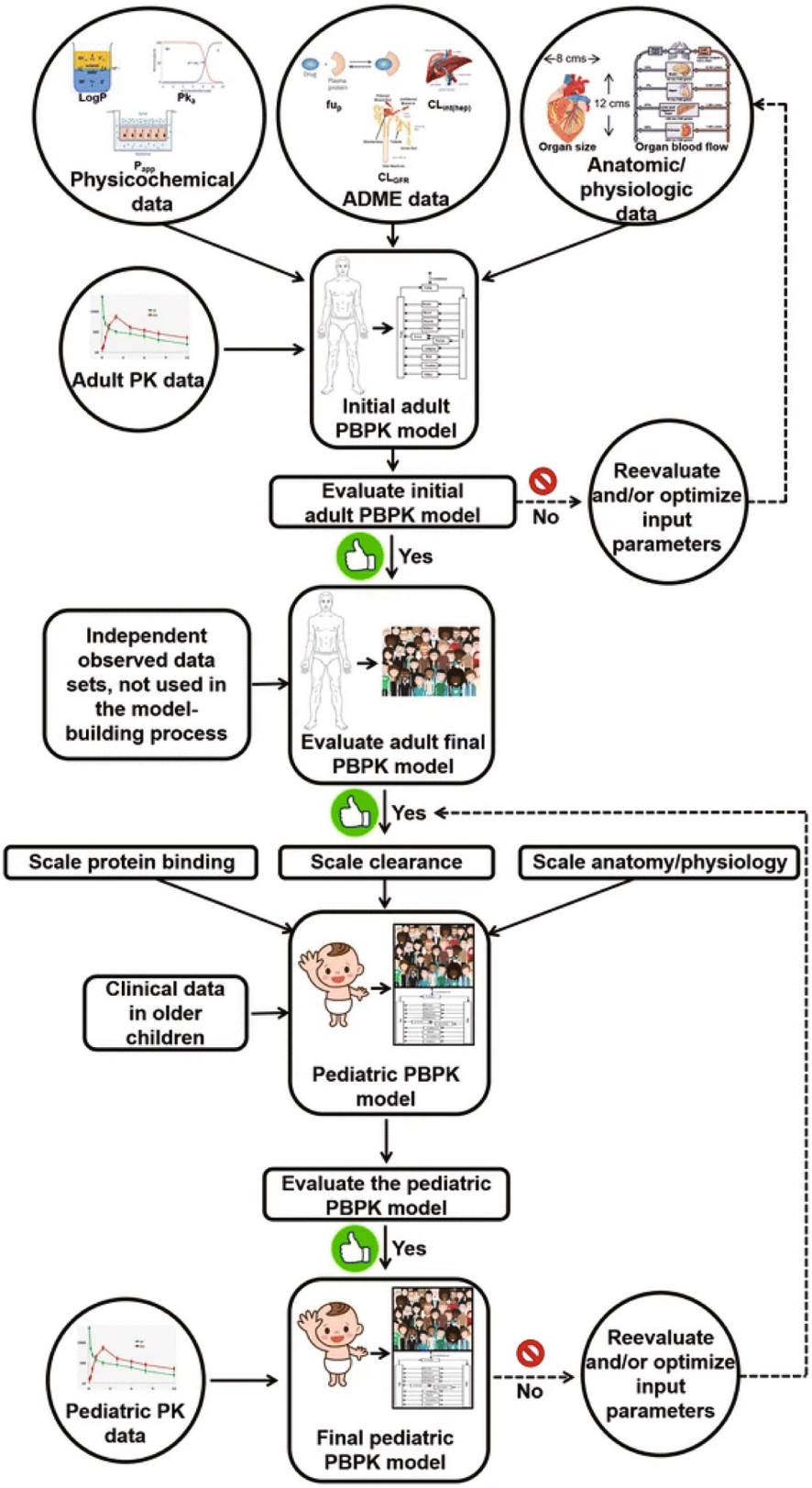

FIGURE 1 Schematic representing the pediatric physiologically-based pharmacokinetic (PBPK) development workflow. The figure was developed using information provided in reference [21]. ADME, absorption, distribution, metabolism, and excretion; PK, pharmacokinetic.

PK-Sim and MoBi freely available, with all source code and materials open to the public.[22] PK-Sim is a complete software tool for modeling PBPK in the whole body.[23] Individuals, Populations, Compounds, Formulations, Administration Protocols, Events, and Observes are the building pieces in PK-Sim.[24] The population parameters database included with PK-Sim contains information on the dependence of anatomic and physiological parameters, such as organ weights, blood flow rates, or tissue composition, on age, gender, body weight, and body

mass index, which was gathered through a thorough literature search. Age-specific physiological parameters and population-based parameters are supported. When modeling for pediatrics, the parameters for a specific age, weight, and height are updated as they are formed from data in the underlying database. The main adjustments are the organ volume, data related to drug distribution, and the scaling factor needed to scale the organ volume. It also has a group of "premature babies" in its database.

Simcyp

Simcyp comprises a complete PBPK model and substantial libraries on demography, developmental physiology, and drug elimination route ontogeny. Many ordinal differential equations are embedded in the software. Simcyp simulators not only function throughout the drug development cycle but also provide users with valuable advisory services. Simcyp has also developed specialized modules to enable targeted functions: Pediatric Simulator for pediatrics; Cardiac Safety Simulator (CSS) for cardiac patients; Long-Acting Injectable (LAI) module for LAI drug delivery, and Lactation module for lactating women. Simcyp Pediatric is a Simcyp Simulator module that allows one to simulate PK behavior in newborns, babies, and children.[25] That is valuable information for dosing decisions, DDI analysis, other safety issues, medication design and formulation for children, and pediatric clinical study design to reduce the number of required subjects. The software has a built-in Nordic Caucasus (NEC) child population model for easy pediatric modeling. It can determine and optimize the dose selection of children from neonates to 2 years, 2–6 years, 6–12 years, and adolescents in stages. It can simulate the PK changes of any pediatric age by adjusting physiological parameters.

GastroPlus

The GastroPlus was initially designed using the mechanical absorption model described in the Advanced Compartmental and Transit (ACAT) literature[26] to simulate the absorption of oral formulations from the gastrointestinal tract. It is now possible to model whole-body ADME to simulate absorption, biopharmaceuticals, PKs, and pharmacodynamics (PDs) in humans and animals, via intravenous, oral, ophthalmic, inhalation, dermal, subcutaneous, and intramuscular routes. As shown, GastroPlus currently has 10 modules available.[27] The PBPKPlus Module adds to GastroPlus by allowing the user to create a PBPK model with several tissues.[28] The module simplifies developing physiological model parameters for human tissues and organs so that users can conduct in vitro and in vivo transformations and interspecific extrapolation. Use GastroPlus' GastroPlus PEAR module to generate weight-matched organ weight, volume, and blood perfusion rate modules (population estimates of age-related physiology) to obtain demographic data for pediatric modeling. GastroPlus version 9.6 adds Chinese population data, including adults and children.[29]

RESULTS

Quantity of included studies

A total of 166 articles (Table S1) from January 01, 2017, to September 6, 2022, were retrieved from the electronic databases, and 38 articles were included for analysis. Full details of the method workflow are shown in Figure 2. Figure 3 shows P-PBPK dose prediction models published involving the leading commercial and open-source software. Of these 38 articles, 19 used PK-Sim, 14 used Simcyp, and five used GastroPlus.

Application of P-PBPK dose prediction

The P-PBPK dose prediction articles included in the study, the name of the drug, the platform, and the study's funding are described in Table 1. Verified PBPK models of drugs are presented in support of pediatric dose prediction (Figure 4): 13 articles reported results from P-PBPK models, which are presented in support of dose selection,[30–42] five articles were on the optimization of dosage in the design of future pediatric clinical studies,[3,29,43–45] and six articles reported findings from studies on determining dose regimens.[46–51] Fourteen publications were on some special pediatric populations and uncommon diseases with an assessment of renal impairment,[52–56] children with obesity,[57–60] and pediatric patients with severe coronavirus disease 2019 (COVID-19) disease.[61–65] Consistent with this trend, several big research funding/grants for computational pharmaceutics worldwide were launched (Table 1).

Dose selection

Conducting pediatric clinical trials to guide dose selection remains a considerable challenge given the vulnerability of this population.[1] In 2022, Nguyen et al.[41] presented the P-PBPK model development using Simcyp (version 16), and simulations were conducted to predict the pediatric dose regimens for gepotidacin in plague. P-PBPK models can be good predictors of gepotidacin dosing in a pediatric

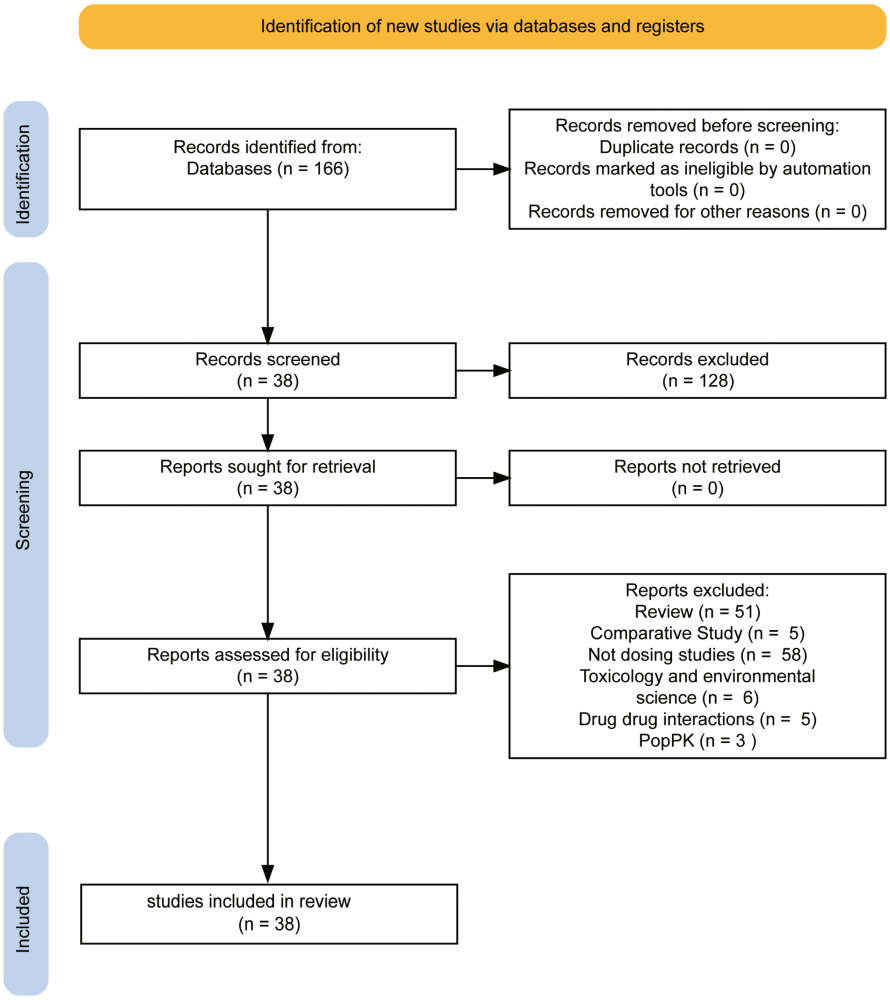

FIGURE 2 Flow chart of the study. PopPK, population pharmacokinetic

population. In 2021, Li et al.[30] developed a combining BJ-3DP and PBPK modeling approach to predict the drug-time profile of 3D-printed levetiracetam instant-dissolving tablets (LEV-IDTs) in children. That was the first time the PBPK model was used to estimate the dose of LEV in children instead of their body weight. The study offers a guideline for the individualized treatment of Chinese pediatric patients with epilepsy. All in vivo PK simulations in that study were performed in the PBPK model commercial software GastroPlus (version 9.8). In 2021, an infant's meropenem PBPK model was developed in PK-Sim (version 8) by Ganguly et al.[36] Their P-PBPK model supports the meropenem dosing regimens recommended in the product label for infants <3 months of age.

Dose optimization

The rapid changes in drug disposition due to physiological and metabolic development over childhood have been reported and characterized as an essential factor for pediatric dose optimization.[66] In children, Zheng et al.[3] have adopted a guidance-based workflow for P-PBPK model development by PK-Sim (version 7.4.0). According to the P-PBPK model, different intravenous doses should be given to children of different ages compared to a standard of 0.1 mg/kg in adults. In contrast, a progressively increasing dose with age growth following oral administration is recommended for children. The adult and pediatric PBPK model of voriconazole, which incorporated the time-dependent inhibition of CYP3A4, gene polymorphisms of CYP2C19, and developmental changes in physiology and metabolic enzymes, were able to describe the PKs in both populations.[44] The modeling work was also conducted in PK-Sim (version 8.0). Subsequent simulations revealed that age, CYP2C19 genotype, and infectious fungal genera influence target PK/PD index attainment and should be considered in dose optimization. In 2021, the first P-PBPK model for amlodipine dose optimization was developed in GastroPlus (version 9.8).[29] A personalized dosing strategy was developed, making this study a future guideline for individualized hypertension treatments in Chinese children. In 2019, a P-PBPK model was proposed using Simcyp (version 14.1) for the optimal chemoprophylactic dose of mefloquine in infant populations.[45] This approach offers a novel route to dose optimization in a vulnerable

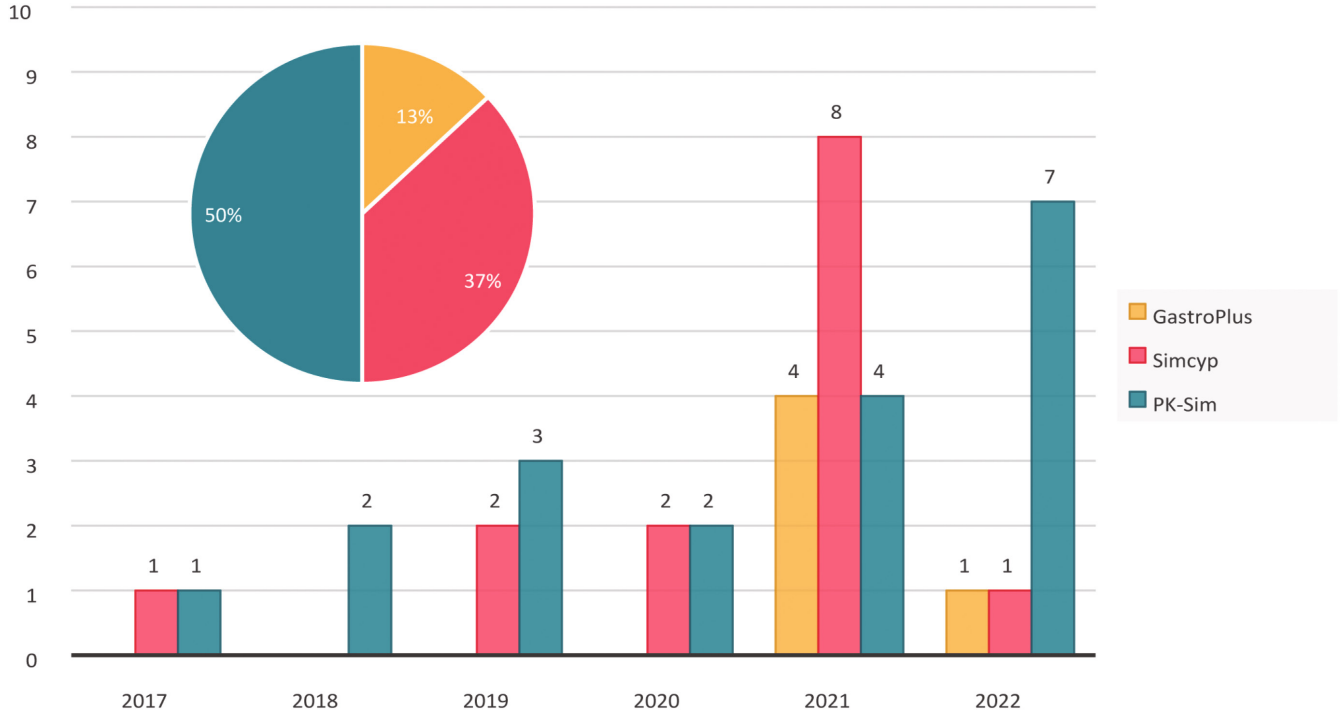

FIGURE 3 Histograms of contribution to P-PBPK software publications over 6 years. The pie chart represents their proportion. P-PBPK, pediatric physiologically-based pharmacokinetic

population, where clinical trials would be difficult to conduct.

Dose regimens

Overuse of antibiotics worldwide has led to the emergence of multidrug-resistant (MDR) bacteria. Many antibiotics in monotherapy use are no longer efficacious against MDR bacteria.[67] The drug resistance problem led to a renewed interest in colistin and polymyxin-B, which were discovered in 1949—but have not been frequently used since the 1980s, primarily because of nephrotoxicity.[68] One recent study has used the P-PBPK model to support pediatric dosing regimens of meropenem/colistin/sulbactam in a co-administration setting against infections in the blood, lung, skin, and heart tissues due to *Acinetobacter baumannii*. The P-PBPK models of meropenem, colistin, and sulbactam were developed using PK-Sim (version 10.0).[48] Given the challenges in conducting pediatric studies, it is beneficial to use verified PBPK models to predict changes in drug exposure in various scenarios to guide dosing information when clinical trials are not possible, especially in pediatric subjects <2 years old. Heeseung Jo et al. developed a verified P-PBPK model with UGT1A9 ontogeny for prospective monotherapy exposure predictions, and informed clinical trials in pediatric age groups between 1 month and 18 years. They create a mechanical, quantitative PBPK model of the dapagliflozin tablet using Simcyp (version 18).[51]

Renal impairment

Recently, there has been an increasing interest in using P-PBPK modeling to define the appropriate dosage regimen for pediatric patients with differing renal functions. Lingling Ye et al. established a PBPK model of daptomycin to simulate its disposition in healthy populations and adults with renal impairment using GrastroPlus (version 9.7), along with a daptomycin exposure simulated in pediatric patients with renal impairment. Their model may be a valuable tool for predicting the PKs of daptomycin and supporting dose adjustments or other relevant decisions in clinical settings.[53] Another study investigated the PK of apixaban alone and under the influence of interacting drugs. The P-PBPK model developed in Simcyp (version 14) provides a reasonable approach to guide dosage adjustment for the first use of apixaban in pediatrics.[54] In addition, in 2021, in the Bonner et al. work, the hydrocortisone P-PBPK model developed in Simcyp (version 16.1) investigated the clinical dosing regimens. The model is a valuable tool to predict adult and pediatric PK of both immediate- and modified-release hydrocortisone formulations.[55] Additionally, Jie Zhou et al.[56] used GastroPlus (version 9.7) simulation and found that their P-PBPK model was

TABLE 1 P-PBPK modeling software (application areas, drugs, and major funding)

Study types/ref	Drug	Platform	Major fundings
Dose selection			
30	Levetiracetam	GastroPlus	National Natural Science Foundation of China (No. 82073793) et al.
31	Rivaroxaban	PK-Sim	Bayer AG. and Janssen Scientific Affairs, LLC.
32	Fluconazole	PK-Sim	Pediatric Critical Care and Trauma Scientist (5K12HD047349) et al.
33	Moxifloxacin	PK-Sim	Bayer AG
34	Asunercept	PK-Sim	Apogenix AG
35	Lisinopril	PK-Sim	–
36	Meropenem	PK-Sim	National Institute of Child Health and Human Development contract (HHSN275201000003I)
37	Aminophylline	Simcyp	–
38	Trazodone	Simcyp	Angelini S.p.A.
39	Selumetinib	Simcyp	AstraZeneca
40	Radiprodil	Simcyp	–
41	Gepotidacin	Simcyp	–
42	Tadalafil	Simcyp	Eli Lilly and Company
Dose optimization			
43	Rifampin	PK-Sim	NICHD (1R01HD102949-01A1) et al.
29	Amlodipine	GastroPlus	National Natural Science Foundation of China (No. 82073793) et al.
3	Oxycodone	PK-Sim	–
44	Voriconazole	PK-Sim	–
45	Mefloquine	Simcyp	–
Dose regimens			
46	Vorinostat	PK-Sim	–
47	Rivaroxaban	PK-Sim	Bayer AG and Janssen Research & Development LLC
48	Meropenem, Colistin, Sulbactam	PK-Sim	Shandong Provincial Natural Science Foundation (ZR2019BC025)
49	Cefoxitin, Cefoxitin et al.	PK-Sim	Bill & Melinda Gates Foundation
50	Imatinib	Simcyp	–
51	Dapagliflozin	Simcyp	AstraZeneca
Renal impairment			
52	Teicoplanin	GastroPlus	Fujian Medical University Sailing Fund (No. 2020QH1058)
53	Daptomycin	GastroPlus	Fujian Medical University Education Reform Key Project Fund (No. J200010)
56	Ceftazidime	GastroPlus	–
54	Apixaban	Simcyp	National Natural Science Foundation of China (81603184)
55	Hydrocortisone	Simcyp	Diurnal Ltd., UK
Children with obesity			
57	Clindamycin, trimethoprim, sulfamethoxazole	PK-Sim	NICHD (R01HD096435) et al.
58	Fentanyl, methadone	PK-Sim	NICHD (5R01HD096435)
59	Metformin	PK-Sim	NICHD (R01HD096435) et al
60	Enoxaparin	PK-Sim	NICHD (5R01HD096435) et al

(Continues)

TABLE 1 (Continued)

Study types/ref	Drug	Platform	Major fundings
Pediatric COVID-19			
61	Hydroxychloroquine	PK-Sim	NICHD (HHSN275201000003I) et al.
62	Nafamostat	PK-Sim	NRF
63	Chloroquine	Simcyp	Bill & Melinda Gates Foundation
64	Hydroxychloroquine	Simcyp	MOST foundation for SARS-nCoV-02 research (grant no. 2020YFC0844500), Bill & Melinda Gates Foundation (INV-015694) et al.
65	Remdesivir	Simcyp	Gilead Sciences, Inc.

Abbreviations: COVID-19, coronavirus disease 2019; MOST, Ministry of Science and Technology of the People's Republic of China; NICHD, National Institute of Child Health and Human Development; NRF, National Research Foundation of Korea; P-PBPK, pediatric physiologically-based pharmacokinetic; SARS-nCoV-2, severe acute respiratory syndrome-novel coronavirus 2.

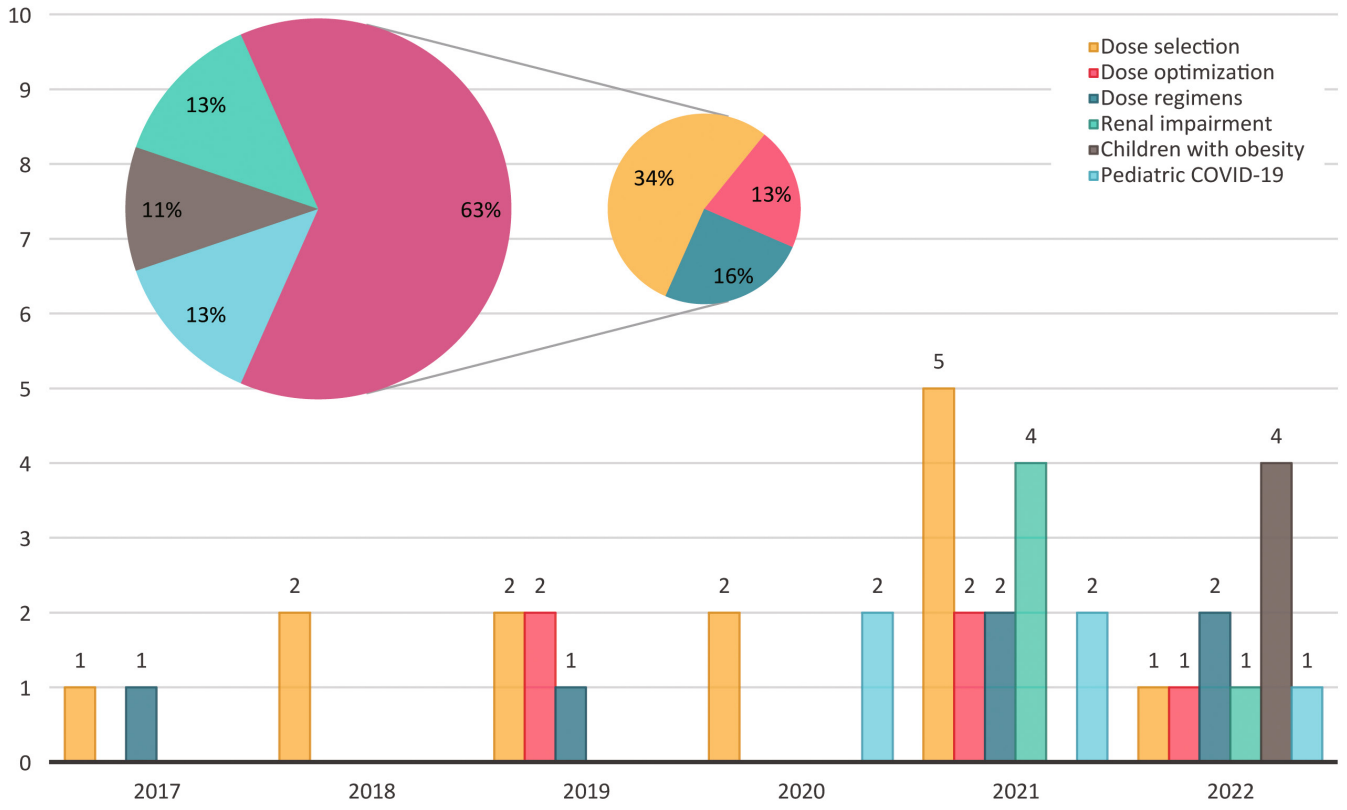

FIGURE 4 Distribution of different areas of the application over 6 years. COVID-19, coronavirus disease 2019

adequate to support ceftazidime dosing recommendations in pediatric patients with different degrees of renal impairment.

Children with obesity

Childhood obesity is one of the most severe global public health challenges of the 21st century, affecting every country in the world.[69] P-PBPK modeling can bridge the gap in understanding obesity-related physiological changes in children. In 2022, The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) funds a series of studies that address dosing guidance for children with obesity,[57–60] which Jacqueline G. Gerhart's group conducted. Authors have developed multiple PBPK models using PK-Sim (version 9.0) for children with obesity with different drugs or diseases. In one study, PBPK models were developed and scaled to children with obesity to evaluate the interplay of obesity, age, and genetic variation in the exposure to fentanyl and methadone and to avoid serious adverse events associated with overexposure.[58] Another study provides a deeper understanding of the influence of age and obesity on metformin PK

and offers guidance on dosing.[59] Additionally, Jacqueline G. Gerhart's group found that children with obesity have higher concentrations than children without obesity underlying recommended dosing. This result suggests that obesity status should be considered in enoxaparin dose selection for children.[60]

Pediatric COVID-19

COVID-19 was declared a global pandemic by the World Health Organization (WHO) on March 11, 2020.[70] The incidence of severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) infection in children is unknown; however, the proportion of COVID-19 diagnoses in children appears to be much lower than in adults. Yong-Soon Cho et al.[62] used PK-Sim (version 8.0) for modeling and found that the exposure of nafamostat slightly increased from neonate to infant, steadily decreased from infant to child, and then raised from child to adult after the administration of 0.2 mg/kg/h for 14 days. Another study investigated the dosing design of hydroxychloroquine (HCQ) in treating patients with COVID-19 in China.[64] Miao Zhang et al. developed a P-PBPK model of HCQ using Simcyp (version 9.5) and integrated antiviral effects into vitro. Additionally, Justin D. Lutz's group reported a Pediatric Population Model in Simcyp (version 18) for remdesivir dosing regimens.[65] The simulation showed that this model supported remdesivir dosing in planned pediatric clinical studies and dosing in emergency use authorization.

DISCUSSION

This review identified 38 articles that investigated P-PBPK modeling tools for pediatric dose prediction with their use. The use of P-PBPK in pediatric dose prediction has been increasing over the past 5 years. Quantitative reviews of the increasing role of P-PBPK modeling over the years have been reported previously.[21,71] However, those studies were not focused on a specific area of application and were limited to the overall trends,[71] or to the already approved drugs.[21] To the best of our knowledge, this is the first study to demonstrate an innovative perspective that explores the application of P-PBPK in pediatric dose prediction and is revelatory for the application that was reported in the literature.

Since the introduction of PBPK by Teorell et al. in 1937,[72] modeling and simulation have significantly increased pediatric drug development on user-friendly platforms with high computational power.[16] We summarize the development and application status of three commonly used PK software tools (Table 2). PK-Sim is an open

TABLE 2 The status of widely used P-PBPK software tools in development and applicability

Software	Open source	Complete user's manual	User-friendly interfaces	Any module can be defined flexibly	Each parameter can be defined flexibly	Have pediatric model and data	Can create pediatric models
Simcyp	No	Yes	Yes	No	No	Yes	Yes
PK-Sim	Yes	Yes	Yes	No	No	Yes	Yes
GastroPlus	No	Yes	Yes	No	No	Yes	Yes

Abbreviation: P-PBPK, pediatric physiologically-based pharmacokinetic.

source in contrast to Simcyp and GastroPlus; relatively, the last two are benefits of premium software in terms of follow-up training and support. These three GUI-based tools have been used in 100% of the PBPK publications in our data until 2022. This can be attributed to the development of user-friendly platforms with high computational power that can deal with this complexity and allow users to focus and pay more attention to the applications of the models.

From 2017 to 2022, PK-Sim, Simcyp, and GastroPlus contributed by 50%, 37%, and 13%, respectively. The number of publications in the early years was limited, with very little growing up to 2020, followed by a rapid increase (Figure 3). It is interesting to note that although there was a steep rise in all groups, an increasing number of contributions came from Simcyp and PK-Sim. In addition, the cost factor does not necessarily make software less popular as multiple factors are involved. For example, the relative contribution of Simcyp had increased much (Figure 3) in 2021, although it needs to pay, and the cost is high.

Application of P-PBPK in dose selection, dose optimization, and dose regimens covered 63% of all publications in the recent 6 years (Figure 4). Among these, the dose selection was the most addressed area overall. Significantly, the P-PBPK predicted that exposures directly affect the dose estimation because it is mainly seen as an essential affair with the dosing information. There was a slight relative contribution of special population studies, such as renal impairment, obese children, and COVID-19 pediatric patients in the previous years, but it increased rapidly from 2021. Designing optimized dosing regimens for renal injury and pediatric patients with COVID-19 is a growing area of interest in the P-PBPK modeling. These applications may indicate represented special populations in fast-growing clinical trials.[73] Conclusions from these P-PBPK modeling studies are profound because they give clues about how to explore the dosing of other critical drugs in children.

PBPK modeling is an essential tool for predicting PK or PD profiles in special populations, especially children and infants, where designing and conducting clinical studies is difficult. Specifically, of all applications included in the analysis, most studies focused on pediatric dose selection, and, as successfully proved, other applications guided specific clinical disorders. For some areas of applications, GastroPlus was mainly used for renal impairment studies (60% of its total usage), and PK-Sim studies were primarily in dose selection, dose regimen, and children with obesity (covering 74% of its total use; Figure 5). However, this does not mean that one of the software tools must be used for particular areas (e.g., the amount of Simcyp and PK-Sim were almost equal in the dose selection; Figure 5). For

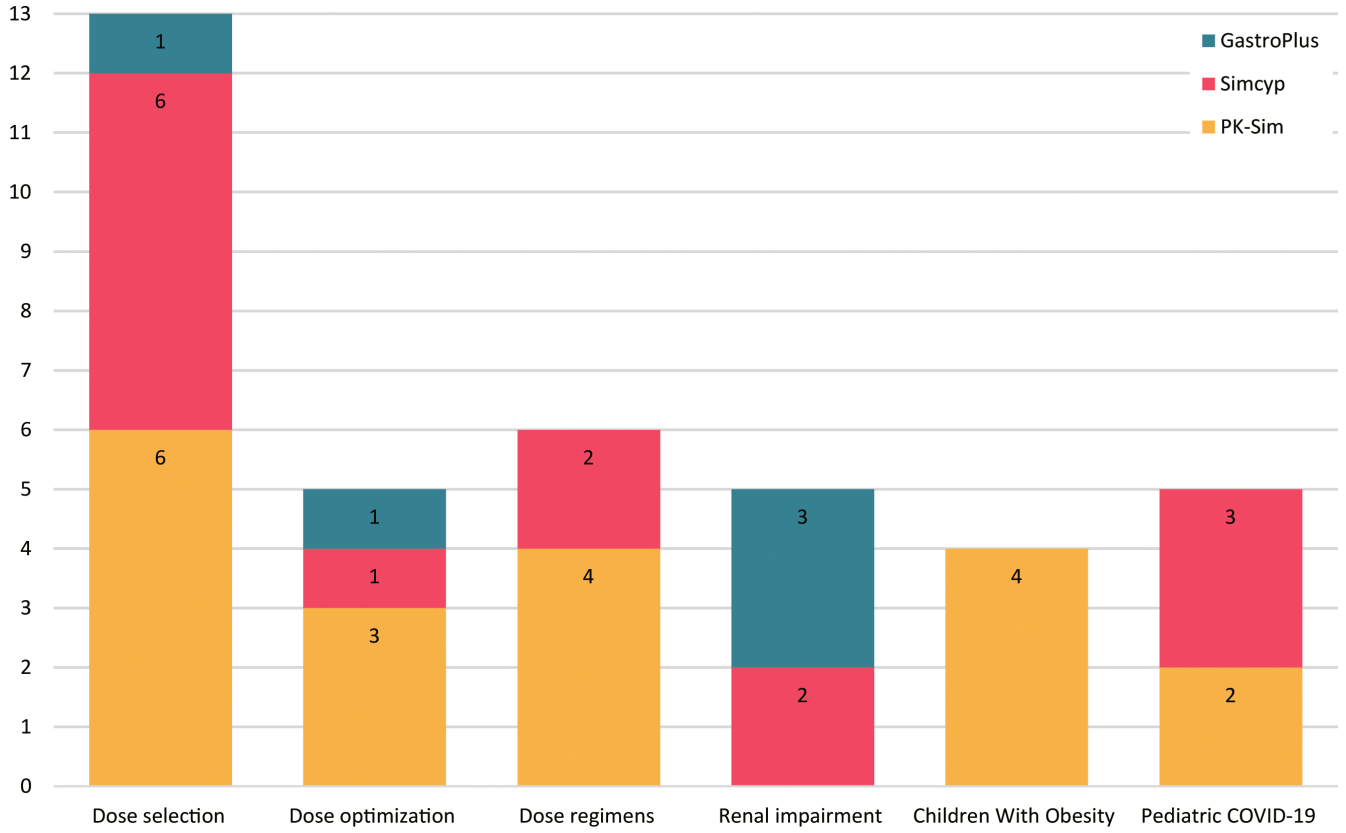

FIGURE 5 Histograms of contribution to P-PBPK software publications stratified by the application area. COVID-19, coronavirus disease 2019; P-PBPK, pediatric physiologically-based pharmacokinetic

the area of obesity, people preferred to use PK-Sim; however, this does not necessarily mean that the software was only used for the obesity area of applications, but because obesity research is completed by the same team.[57–60] These findings can be used to improve the design of the current P-PBPK model and highlight the need for childhood obesity dosing research. The COVID-19 infection in children has attracted attention from experts in pharmaceutics since 2020 (Figure 4). The pediatric dosing strategy for drugs that potently inhibits SARS-CoV-2 RNA polymerases in vitro was supported by P-PBPK modeling. Future efforts should focus on linking pharmacogenomics Clinical decision support to patient and economic outcomes to create value-based models. These applications demonstrate the reliability of the P-PBPK models and justify the use of dose prediction derived from these models as reference values. Our findings explained that user-friendly software tools with existing pediatric databases, such as Simcyp, GastroPlus, and PK-Sim, played a significant role in expanding P-PBPK applications.

Limitations and scope of the current analysis

Our study does have some limitations. First, the search strategy and articles reviewed focused on a singular, albeit significant, database, and reports may have been missed if they were not indexed at the time of the search. Second, this work does not compare the strategies and policies regarding the availability of free academic licenses. Ideally, more extensive research could do so. Last, we focused our analysis on the platform and thus application rather than the intrinsic factors affecting the kinetics, the latter requiring further research with PKs' analysis.

CONCLUSION

In the last few years, the PBPK modeling has seen a lot of considerable progress in the field of pediatric medication drug research. PBPK models for children have been developed and used in a range of studies and clinical treatments. In conclusion, the present review revealed that P-PBPK modeling is a helpful approach to predicting the dose of pediatric patients. This is the first report focusing on application analysis of overall P-PBPK publications in dose prediction from the past 6 years stratified by the platform used and area of applications. It highlights how the modeling method of user-friendly platforms could deal with the dosage of special pediatric populations, such as renal impairment or obesity, and also increase the interest in drug dosing design for pediatric patients with COVID-19. Our review shows the significant application aspects that influence pediatric dose prediction and justify the known P-PBPK models for child patients. As seen in the review results, extensive modeling software will make predicting dose doses for young patients easier. In this way, the role of modeling and simulation in dose prediction will undoubtedly increase, and particular effort should be invested in developing these models for children to exploit the immense potential of this evolution.

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CONFLICT OF INTEREST

The authors declared no competing interests for this work.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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