Received: 23 April 2020 | Revised: 26 October 2020 | Accepted: 5 December 2020

DOI: 10.1111/bcp.14705

REVIEW ARTICLE - THEMED ISSUE

No population left behind: Improving paediatric drug safety using informatics and systems biology

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Funding information
National Institute of General Medical Sciences, Grant/Award Number: R35 GM131905

Adverse drugs effects (ADEs) in children are common and may result in disability and death. The current paediatric drug safety landscape, including clinical trials, is limited as it rarely includes children and relies on extrapolation from adults. Children are not small adults but go through an evolutionarily conserved and physiologically dynamic process of growth and maturation. Novel quantitative approaches, integrating observations from clinical trials and drug safety databases with dynamic mechanisms, can be used to systematically identify ADEs unique to childhood. In this perspective, we discuss three critical research directions using systems biology methodologies and novel informatics to improve paediatric drug safety, namely child versus adult drug safety profiles, age-dependent drug toxicities and genetic susceptibility of ADEs across childhood. We argue that a data-driven framework that leverages observational data, biomedical knowledge and systems biology modelling will reveal previously unknown mechanisms of pediatric adverse drug events and lead to improved paediatric drug safety.

KEYWORDS
adverse drug reactions, informatics, padiatric drug safety, pharmacodynamics, pharmacovigilance, systems biology

1 | CHILDREN AND ADVERSE DRUG EFFECTS

Millions of children are prescribed medication every year[1,2] and adverse effects are common.[3] A meta-analysis showed the prevalence of adverse drug effects (ADEs) in paediatric patients is as high as 16.8% and that 0.4–10.3% of hospitalizations are due to ADEs.[4] Drugs associated to adverse effects are from various drug classes, with anti-epileptic, anti-neoplastic and antibiotic drugs being the most frequent culprits.[5,6] Notably, the observed effects can be severe and 87% were found to be preventable.[7] Adverse drug effects negatively impact the quality of life of children[8] and chronic treatments can lead to late-onset or long-term ADEs.[9] Few therapeutic studies have investigated long-term effects of drug exposures, making it difficult to anticipate the consequences of drug therapy during childhood.[10] Traditional methods for establishing drug safety, including preclinical studies, clinical trials, and post-marketing surveillance, are failing the paediatric population.

In preclinical studies, in silico screening for developmental toxicity does not consider growth and maturation of children from infancy through adolescence.[11,12] Additionally, juvenile animals in safety pharmacology studies have limited similarity in function and morphology to humans[13] leading to poor detection of toxicities during child development.[14] Clinical trials rarely include paediatric patients even if the drug is widely prescribed in this population (Figure 1). Moreover, paediatric clinical trials suffer from low completion rates, issues establishing generalizable study designs, lack of accepted and validated paediatric endpoints, scarce participants and inflated placebo effects, and inability to detect long-term ADEs.[15–18] Post-marketing and epidemiological studies of ADEs in children are exploratory and descriptive in nature,[19,20] and have limited clinical translation due to insufficient statistical control of bias and confounding.[21] The current

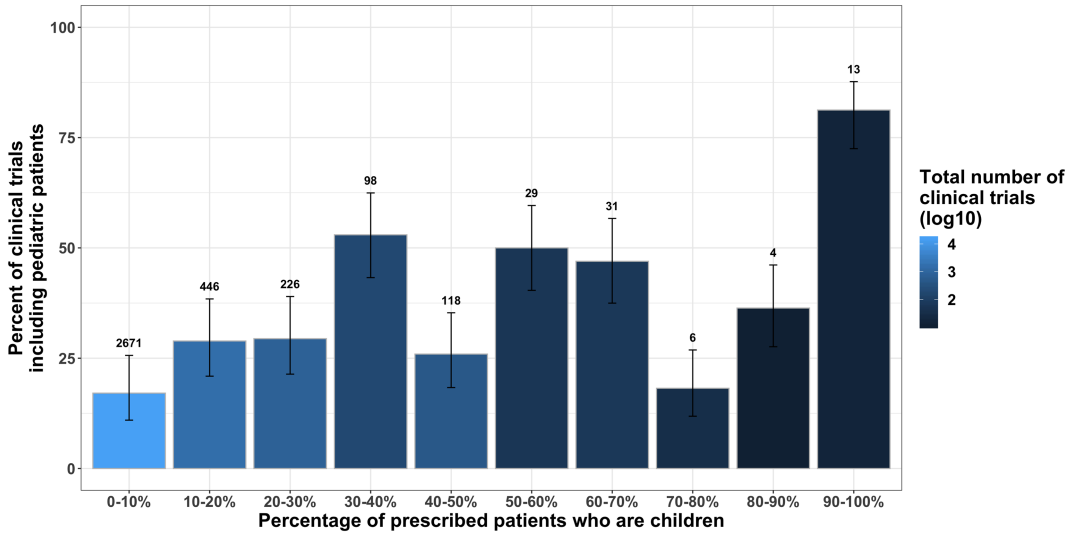

FIGURE 1 Relationship between the rate of drug prescription in an Academic Medical Center and evaluation in clinical trials for children. Note: all drugs prescribed clinically have been evaluated within clinical trials. The percentages on the x-axis indicate the proportion of paediatric patients (<18 years old) out of all patients prescribed a drug at Columbia University Irving Medical Center. The y-axis indicates the proportion of paediatric clinical trials (eligibility <18 years old) out of all clinical trials registered at clinicaltrials.gov. The error bars represent 95% confidence intervals. The number above the bars indicate the number of clinical trials including paediatric patients for the prescribed drugs in that category

drug safety pipeline treats children as small adults which has led to a lack of understanding how to safely treat this vulnerable population.[22] Improving drug safety in the paediatric population must follow from understanding paediatric biology and how drug actions and effects are altered during growth and development.

2 | PAEDIATRIC BIOLOGY AND PAEDIATRIC DRUG SAFETY

Unlike adults, children undergo dynamic biological and physical processes from accelerated growth and maturation.[23] Children undergo an evolutionarily conserved process of genomic imprinting, hormonal regulation and adaptive phenotype trajectories across the stages of development.[24] The obvious physical changes as children grow older are reflections of rapid and dynamic organ development, tissue differentiation and functional development across childhood. For example, the immune system dynamically develops where immune cells and immunoglobulins vary in number and concentration across many years, ultimately converging to adult levels.[25–27] The human brain is constantly changing, from increasing and decreasing white and gray matter through adolescence,[28,29] growth and elimination of synapses and neurons,[30] and adaptive expression of receptors and neurotransmitters from early life through adolescence.[31–33] One of the most fascinating and possibly influential processes in human biology stems from our endocrine system, and in childhood different hormones coordinated by the developing brain regulate tissue differentiation, cell proliferation and receptor expression during the different stages of development.[24,34,35] Advances in large-scale genomic technologies, as well as international collaborations such as the Pediatric Cell Atlas,[36] allow researchers to probe and illuminate the molecular landscapes that are a reflection of this developmental period.[37,38] A multi-omics perspective of the first week of life showed distinct molecular networks and pathways, such as increasing interleukin signalling and complement cascade, characterizing a stable developmental trajectory since birth.[39] Stevens et al. highlighted the developing molecular landscape across childhood, showing clusters of genetic programmes towards each phase of growth, including dynamics of signalling pathways across growth phases such as NOTCH, TFGB and VEGF signalling.[40] Moreover, concerted gene regulatory programmes are conserved across species, which is exemplified by distinct developmental trajectories in parallel with stages of child development from the mouse liver transcriptome.[41] Distinct and evolutionarily conserved biological mechanisms during the period of growth and development distinguish children from adults.

Paediatric drug safety must follow from an understanding of how pharmacology is altered during growth and development. Prenatally, perinatally and postnatally, the response and effect of drug treatment coincides with the dynamic molecular patterns underlying physiological and structural development in children.[42–47] For example, linear and nonlinear dynamics of cytochrome P450 and other metabolic enzymes influence drug disposition such as antipyrine,[48] fentanyl,[49] phenytoin,[50] and many other drugs.[51] Across child developmental stages, growth and maturation processes such as growth rates of immune and neural cell types may alter drug pharmacodynamics as well, resulting in hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen,[52,53] antiepileptic drugs such as phenobarbital,[54] and drugs like warfarin and cyclosporin.[55,56] The hypothalamus–pituitary–adrenal (HPA) axis, which secretes growth hormone and sex steroids, accelerates during puberty[57] and may affect drug response[58,59] and be affected by drug therapy.[60] This is an example where drug toxicity may depend on growth and maturation processes during developmental stages as well as from previous developmental stages, such as during early

life,[61–63] resulting in known but less characterized long-term drug effects.[64–67] Another less characterized but observed phenomenon is how dynamic growth processes interact with pharmacogenes during childhood.[68] Adverse drug effects manifest from disrupting gene variation, leading to hearing loss,[69] and altered gene expression profiles, leading to teratogenicity,[70] but genetic susceptibility to ADEs across childhood is largely unexplored. These and other effects during childhood, such as drug interactions,[71] emphasize the basis for and importance of uncovering pharmacodynamic determinants of ADEs in the paediatric population.

3 | SYSTEMS BIOLOGY AND INFORMATICS APPROACHES TO IMPROVE PAEDIATRIC DRUG SAFETY

Paediatric drug safety consistently considers children as small adults without incorporating the unique biology of children.[72–74] We highlight three key research directions that build upon foundational paediatric research and discuss novel approaches for improving paediatric drug safety (Figure 2).

3.1 | Child versus adult drug safety profiles

A known but still unsolved problem is detection of ADEs in children and their comparison to adults.[75] Population stratification is a popular approach to identify ADEs within the paediatric population and was used to discover the arrhythmogenic effects of short-acting beta-agonists from electronic health records.[76] In other applications, paediatric populations are compared directly to adult populations, as was used to identify renal toxicity associated with enalapril in EudraVigilance.[77] Recent work has started to refine these comparisons by comparing across developmental stages.[78,79] The use of these detection methods, which are efficient and essential for identifying drug–adverse event associations (see reviews on disproportionality measures and data mining[80,81]), are still burdened by potential confounding due to disease status, growth considerations at drug prescription and other extraneous factors. Methodologies must be nuanced enough to distinguish differences in adverse effects from differences in prescribing and reporting patterns. Moreover, fair and accurate comparisons of children to adults will potentially uncover effects of paediatric-specific mechanisms. Real-world data, like those found in electronic health record databases, gather clinical data on large populations of patients as a byproduct of the practice of medicine. As a result of their size, these resources can be used to identify less frequent but still clinically important adverse drug effects in children.[82,83] Additionally, analysis of real-world data can prioritize plausible ADEs from thousands of data-mined hypotheses, helping to identify the needles in the adverse event haystack.[84,85] As automated and computational methods become more commonplace, however, high-quality reference sets are required. Methodologies can be compared and evaluated against a common reference set, such as the one created by the GRiP consortium.[86] Our lab developed a machine-

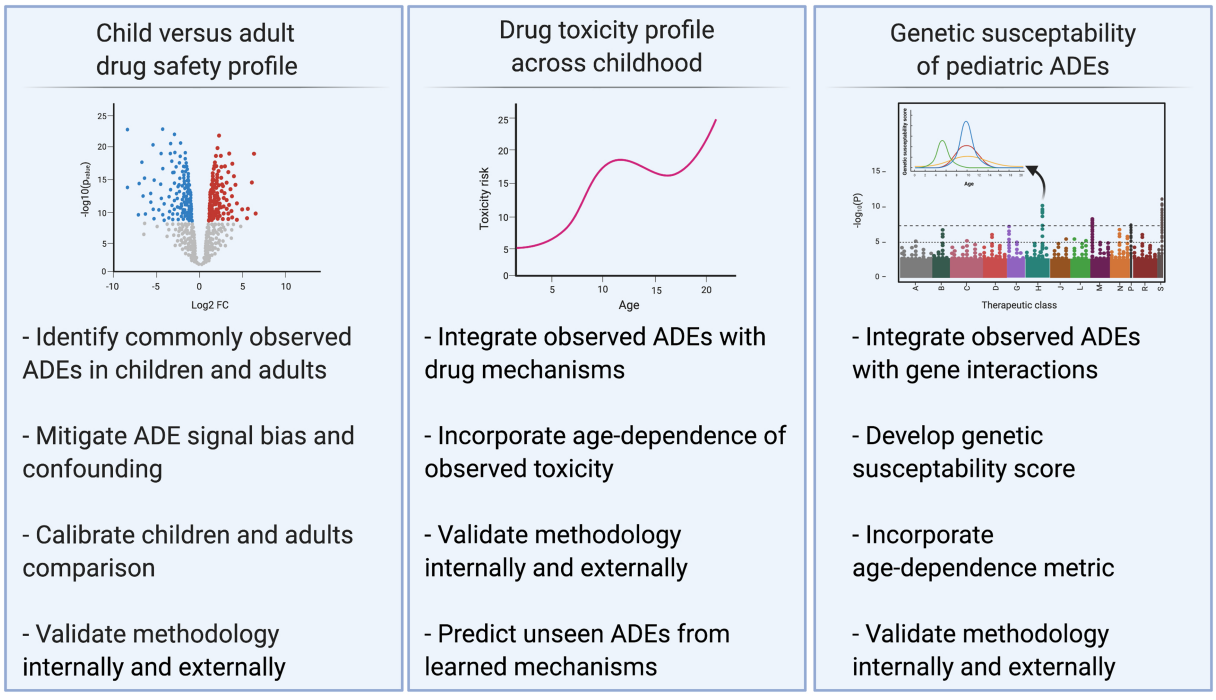

FIGURE 2 Three unsolved and critical research directions to enhance paediatric drug safety. Novel informatics and systems biology approaches are needed to tackle both signal identification and mechanistic evaluation of adverse drug effects in children. Observational databases are critical for systematic analyses but inherent bias and confounding requires correction for producing sound detection results. Mechanistic databases, such as Drugbank or Chembl, evaluate adverse drug effects using biomedical and chemical knowledge to predict drug toxicities. Developed methodologies require adequate internal and external validation to ensure method robustness and generalizable results

readable version of these data that is publicly available to the research community.[87] Detection of adverse drug effects during childhood through comparison to adults requires novel statistical approaches for sound population comparison and corroboration within real-world data and a paediatric-specific reference set.

3.2 | Drug toxicity profile across childhood

Paediatric drug safety can be evaluated in the pre-marketing phases by focusing on adverse drug reactions that may result from growth and maturation processes during childhood.[75] Systems biology methods offer a way to extrapolate from the biology of developmental processes to the clinical effects they may modulate in paediatric drug treatment. These methods can integrate observational with mechanistic data, such as drug pharmacology in Drugbank[88] and drug properties in Chembl,[89] to study how mechanisms of development may lead to drug toxicity.[90] For example, researchers have linked observed ADEs to mechanisms, such as drug targets associated with heart failure,[91] target inhibition associated with renal disorders,[92] and drug structures associated with QT prolongation.[93] However, the biological mechanisms characterizing ADEs during childhood require novel approaches that go beyond the guilt-by-association hypothesis[94] and incorporate temporal and dynamic changes of biological networks. Time-series-based machine learning approaches can learn drug properties for predicting adverse reactions across childhood, similar to Matlock et al., who developed a time-embedding algorithm to predict CYP enzyme activity across childhood.[95] Quantifying the age-dependence of toxicities across childhood would improve translation of effects during growth and maturation into developmental stage-specific clinical trials and clinical contexts. Approaches for validation are critical when developing these methodologies, including both internal validation for ensuring the method is accurate and external validation for assessing generalizability to other drugs, adverse effects and clinical settings. Once validated, drug toxicity hypotheses would be powerful for further investigation of metabolic, gene and clinical markers for incorporation into pharmacometrics and juvenile animal studies.[96,97] Systems biology and machine learning approaches can integrate observations and mechanisms to predict potential drug toxicity across childhood.

3.3 | Genetic susceptibility of paediatric adverse drug events

The genetic basis of adverse reactions from drug exposure remains largely unknown.[21,98] Genome wide association studies (GWAS) are established approaches that associate genetic polymorphisms with adverse drug reactions, such as anthracycline-induced cardiotoxicity in children.[99,100] GWAS are limited, however, to understanding genetic contributors with single, often common phenotypes[101] and lack the biological context that might be necessary to understand drug-induced phenotypes. There is an opportunity to use systems biology to provide the biological context needed to understand GWAS results of drug-induced phenotypes.[102] For example, building long QT syndrome genetic networks showed enrichment of known gene variants from GWAS likely to affect the QT interval[102] and the modular assembly of drug safety subnetworks (MADSS) algorithm significantly improved detection of adverse drug reactions by incorporating protein–protein interactions into adverse event neighbourhoods.[103] In children, the growth and developmental processes during childhood interact with genetic factors[104,105] and complicate direct associations with adverse drug reactions. Notwithstanding, our research group developed a methodology founded on hypothesized population-specific mechanisms addressing statistical bias and confounding that uncovered thousands of ADEs, many with a potential basis in genetics, showing increased safety risks in women.[106] Novel methodologies in paediatric drug safety are tasked to unravel both genetic mechanisms and their dependencies across child development to uncover paediatric-specific genetically-induced adverse drug effects.

4 | CONCLUSION

Integrating knowledge of paediatric-specific biology into systems biology approaches can incorporate mechanistic insights and improve paediatric drug safety. These approaches become more powerful when used together within an overarching drug safety framework. In fact, recent studies are showing how frameworks bridging pharmacoepidemiology and pharmacodynamics link biological explanations with detected ADEs. This approach has been used to understand serotonin syndrome reporting[107] and G protein-coupled receptor-mediated acetaminophen-induced movement disorders.[108] However, more is needed for teasing apart correlation from causation, validating results within external and reference datasets, and tailoring analyses towards understanding biological mechanisms in the paediatric population. In previous work, we have demonstrated a data-driven methodology that incorporates large-scale detection, clinical evaluation and experimental validation of ADEs that has uncovered unforeseen drug–drug interactions such as paroxetine with pravastatin increasing blood glucose levels[109] and lansoprazole with ceftriaxone prolonging the QT interval.[110] While this framework has been applied for discovering novel drug–drug interactions in adults, it demonstrates novel informatics coupled with orthogonal evaluation and validation strategies can identify unknown drug pharmacology and adverse effects. A similar approach that is adapted to account for human growth and development may be a systematic and efficient strategy to identify, evaluate and validate ADEs in the paediatric population.

ACKNOWLEDGEMENTS

The authors wish to acknowledge funding support from the National Institutes of General Medical Sciences (R35 GM1319050). N.P.G. and N.P.T. are both funded by R35 GM131905.

COMPETING INTERESTS

The authors have no conflict of interests to declare.

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How to cite this article: Giangreco NP, Elias JE, Tatonetti NP. No population left behind: Improving paediatric drug safety using informatics and systems biology. *Br J Clin Pharmacol*. 2022;88(4):1464-1470. https://doi.org/10.1111/bcp.14705