Population pharmacokinetic modelling for personalised medicine in paediatric immunodeficiencies and haematopoietic stem cell transplant patients : a focus on immunoglobulin, ciclosporin, and favipiravir

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I, Iek Leng Cheng, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the work.

Abstract

Children experience rapid developmental changes in how they absorb, distribute, metabolise, and eliminate medicines. These maturational effects are particularly critical in immunocompromised patients, where precise dosing can be pivotal in maximising therapeutic benefit while minimising the risk of serious harm. Children with primary immunodeficiencies may require haematopoietic stem cell transplantation (HSCT) for a definitive cure, a high-risk procedure that requires carefully coordinated use of supportive medicines such as immunosupressants and antimicrobials. This thesis addresses the evidence gap in this population by using pharmacokinetic (PK) modelling to study three key therapies in immunocompromised children, ciclosporin, immunoglobulin, and favipiravir, using real-world data from patients aged 0–18 years.

In HSCT, effective immunosuppression is essential to protect the donor graft while avoiding toxicity. Ciclosporin, a key agent in this setting, has a narrow therapeutic range, overexposure can lead to serious adverse effects, while underexposure may compromise graft survival. A pharmacokinetic model was developed to guide weight-banded dosing and account for factors such as blood counts, kidney function, developmental stage, and interactions with azole antifungals. The model provides practical, age-specific dosing recommendations that address these interaction risks, supporting safer and more effective immunosuppression in this vulnerable group.

Immunoglobulin is essential for children with antibody deficiencies, whether due to

an underlying immune disorder or acquired after medical treatments. As a limited, blood-derived resource, it must be used safely and cost-effectively. This research introduced an innovative approach, measuring IgM levels, to estimate a child's ability to produce their own antibodies thereby being able to build a model to describe the data. This can guide personalised dosing, ensuring those most in need receive adequate treatment while preserving supplies.

Favipiravir, an experimental antiviral, was studied in immunocompromised children for the first time. Its pharmacokinetic was characterised, revealing age-related differences. The findings inform local dosing guidance and provide a framework for the pharmacokinetic evaluation of novel therapeutics in rare or urgent clinical contexts. Across these medicines, the thesis demonstrates how paediatric PK modelling can translate into practical dosing strategies, bridge evidence gaps for vulnerable populations, and lay the groundwork for national prescribing recommendations and future clinical decision-support tools.

Impact Statement

This research addresses a critical gap in paediatric pharmacokinetics, focusing on medicines used in immunocompromised children, including those undergoing HSCT or living with primary and secondary antibody deficiencies. By developing population pharmacokinetic models for ciclosporin, immunoglobulin, and favipiravir using real-world clinical data, this work advances our ability to deliver safer, more effective, and resource-conscious treatment for some of the most vulnerable patients in paediatric medicine.

Academic impact

This thesis contributes novel PK data for three medicines that have historically been under-researched in children, particularly in those under two years of age, where developmental changes profoundly affect drug handling. The ciclosporin model is the first in paediatric HSCT to provide a clinician-friendly, weight-banded dosing algorithm that incorporates age, renal function, haematological parameters, and drug–drug interactions with azole antifungals. The immunoglobulin model introduces an innovative approach using IgM levels to estimate endogenous IgG production, enabling more individualised dosing. The favipiravir study represents one of the first PK characterisations of this antiviral in immunocompromised children. Collectively, these outputs provide a foundation for future studies, model refinement, and the integration of PK modelling into precision medicine strategies.

Clinical impact

The findings have immediate applicability in NHS settings and align closely with the NHS Fit for the Future: 10 Year Health Plan for England, the NHS Long Term Plan, and NHS Medicines Optimisation priorities. The ciclosporin model supports precision dosing in HSCT, reducing the risk of graft loss or toxicity. The immunoglobulin model offers a sustainable approach for using a scarce, blood-derived product, ensuring supply for those in greatest need. The favipiravir work demonstrates how urgent-access medicines for rare infections can be evaluated for safe paediatric prescribing. All models were developed using real-world data from hospital electronic prescribing and therapeutic drug monitoring systems, enabling direct integration into NHS clinical workflows. Future decision-support tools could incorporate artificial intelligence and machine learning to refine predictions over time, fully supporting the NHS ambition for digitally enabled, data-driven, personalised healthcare.

Policy and healthcare system impact

This research directly supports NHS priorities for precision medicine, digital transformation, and reducing unwarranted variation in care. It demonstrates a scalable way to harness routinely collected clinical data to optimise prescribing in rare and paediatric populations — groups that are often excluded from clinical trials and therefore lack robust evidence to guide practice. The approach could be further strengthened by integrating pharmacogenomic information, as genetic variation in drug metabolism and transport is increasingly recognised as an important determinant of pharmacokinetics and treatment outcomes. Incorporating these genomic factors into pharmacokinetic models offers the potential to tailor therapy at an individual level, aligning with the NHS Genomic Medicine Service and supporting the long-term ambition of embedding both genomics and pharmacokinetics into routine prescribing. Looking ahead, combining real-world data, genomic information, and pharmacokinetic modelling within AI-enabled clinical decision-support systems could transform prescribing practice, delivering truly personalised and adaptive treatment for every patient.

Future pathways to impact

The next step is external validation of these models through collaboration with other paediatric centres, followed by piloting the proposed dosing recommendations locally and, where appropriate, at national level to support consistent prescribing practice. In parallel, there is potential to embed the models into electronic prescribing systems as interactive bedside decision-support tools. Using a Bayesian forecasting approach, such tools could update individual patient predictions as soon as new therapeutic drug monitoring results become available, enabling precise, timely dose adjustments. However, because such digital tools would be classified as medical devices, they would require formal legal certification and regulatory endorsement before widespread clinical deployment. Early piloting of the dosing recommendations themselves therefore represents the most immediate route to impact, while development of certified digital tools offers a longer-term pathway. Collaboration with national networks (e.g. UK Neonatal and Paediatric Pharmacy Group, British Society of Immunology Clinical Immunology Professional Network) and international partners will help ensure broad adoption and integration into clinical workflows.

Ultimately, this work demonstrates how paediatric PK modelling, harnessing the power of real-world clinical data alongside digital health and genomics, can bridge evidence gaps for vulnerable populations, guide responsible resource use, and improve outcomes in high-risk clinical settings. Unlike tightly controlled clinical trials, which often exclude these groups, real-world data captures the full complexity of paediatric care, making the resulting models directly applicable to everyday clinical practice.

Acknowledgements

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I owe profound thanks to Professor Joe Standing, Dr Austen Worth and Professor Claire Booth — for handing me the map, showing me how to read it, and encouraging me to explore the uncharted.

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This journey was made possible by the National Institute for Health and Care Research (NIHR), whose support gave this project the scaffolding it needed to take shape.

And to Jaime Law — thank you for being the still point that made the leap possible. Your quiet courage reminded me who I was, and who I could become.

Contents

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List of Abbreviations

$t_{1/2}$	Half-life
AAAAI	American Academy of Allergy, Asthma & Immunology
ADD	Additive error model
ADR	Adverse drug reaction
aGHVD	Acute graft-versus-host disease
AIC	Akaike Information Criterion
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AO	Aldehyde oxidase
AS	Allometric scaling
AST	Aspartate transaminase
AUC	Area under the concentration-time curve
AUTO	Autologous
BD	Twice a day
BDE	Bodyweight-dependent exponent
BMTDAY	Number of days post-haematopoietic stem cell transplantation
BSA	Body surface area
BSV	Between-subject variability
C_{max}	Maximum plasma concentration
CAR	Chimeric antigen receptor
CBAS	Baseline immunoglobulin G level
CES2	Carboxylesterase-2
cGVHD	Chronic graft-versus-host disease
CI	Confidence level
CL	Clearance

CL/F	Apparent clearance
Co-med	Co-administration medicine
CR	Creatinine
CrCL	Creatinine clearance
CSA	Ciclosporin
CVVH	Continuous veno-venous haemofiltration
CWRES	Conditional weighted residuals
CYP	Cytochrome
EAP	European Academy of Paediatrics
EBMT	European Society for Blood and Marrow Transplantation
EC_{50}	Concentration required to achieve 50% inhibition
EC_{90}	Concentration required to achieve 90% inhibition
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
ESDPPP	European Society for Developmental Perinatal and Paediatric Pharmacology
ETA	Random effect term representing inter-individual variability
EudraCT	European clinical trials database
F	Bioavailability
FAVI-RTP	Favipiravir ribofuranosyl-5'-triphosphate
FDA	Food and Drug Administration
FOCEI	First-order conditional estimation method with interaction
FPIA	Fluorescence polarisation immunoassay
GFR	Glomerular filtration rate
GGT	Gamma-glutamylyransferase
GMC	General Medical Council

GOSH	Great Ormond Street Hospital
GST	Glutathione S-transferase
GTP	Guanosine-5'-triphosphate
GVHD	Graft-versus-host disease
HAPLO	Haploidentical
Hb	Haemoglobulin
HCT	Haematocrit
Hill	Hill coefficient
HIV	Human immunodeficiency virus
HLA	Human Leukocyte Antigens
HLH	Haemophagocytic lymphohistiocytosis
HPIV-3	Human parainfluenza type 3
HPLC	High-performance liquid chromatography
HSCT	Haematopoietic stem cell transplantation
Ht	Height
IC_{50}	Half maximal inhibitory concentration
IFD	Invasive function disease
Ig	Immunoglobulin
IgRT	Immunoglobulin replacement therapy
IIV	Inter-individual variability
IL	Interleukin
IMPDH	Inosine-5'-monophosphate dehydrogenase
IQ	Inhibitory quotient
IV	Intravenous
IVIG	Intravenous immunoglobulin
Ka	Absorption constant
LLOQ	Lower limt of quantification
LOESS	Locally Estimated Scatterplot Smoothing
LRTI	Lower respiratory track infection

MF	Maturation function
MFD	Matched family donor
MHRA	Medicines and Healthcare products Regulatory Agency
MLE	Maximum likelihood estimation
MMSD	Mismatched sibling donor
MMUD	Mismatched unrelated donor
MPS1	Mucopolysaccharidosis type 1
MSD	Matched sibling donor
MUD	Matched unrelated donor
NCA	Non-compartmental analysis
NLS	Non-linear least squares
NPPG	Neonatal and Paediatric Pharmacy Group
OFV	Objective function value
P-gp	P-glycoprotein
pcVPC	Prediction-corrected visual predictive check
PDCO	Paediatric Committee
PID	Primary immunodeficiency
PIP	Paediatric Investigation Plan
PK	Pharmacokinetics
PM_{50}	Postmenstrual age at which clearance reaches 50% of adult values
PMA	Postmenstrual age
PNA	Postnatal age
POD	Post-operation/transplant day
popPK	Population pharmacokinetic
PPIE	Patient and public involvement and engagement
PRIME	Priority Medicines
PROP	Proportional error model

PTA	Probabilities of target attainment
Q	Intercompartment clearance
QDS	Acute respiratory distress syndrome
RBC	Red blood cell
RdRp	RNA-dependent RNA polymerase
RIA	Radioimmunoassay
RSE	Relative standard error
RSV	Respiratory syncytial virus
SAD	Secondary antibody deficiency
SC	Subcutaneous
SCIG	Subcutaneous immunoglobulin
SCR	Serum creatinine
SmPC	Summary of Product Characteristics
T_{max}	Time to reach maximum concentration
TBIL	Total bilirubin
TDM	Therapeutic drug monitoring
TDS	Three times a day
TSCR	Typical serum creatinine concentration
UDP	Uridine diphosphate
UDP1A1	Uridine diphosphate-glucuronosyltransferase 1A1
UGT	Uridine 5'-diphospho-glucuronosyltransferase
UKPIN	United Kingdom Primary Immunodeficiency Network
UPLC-MS/MS	Tandem mass spectrometry
Vc/V1	Central volume of distribution
Vd	Volume of distribution
VOD	Veno-occlusive disease
Vp/V2	Peripheral volume of distribution

VPC	Visual predictive check
WT	Weight
YPAG	Young person' advisory group

Chapter 1

Introduction

1.1 Unlicensed medicine in the paediatric population

Unlicensed and off-label prescribing remains a common and often necessary aspect of paediatric medical practice. The European Medicines Agency (EMA) has reported that up to 60% of hospital prescriptions for children are either unlicensed or used off-label [1], and a more recent systematic review observed similarly high rates in primary care, with up to 51.7% of prescriptions falling into these categories [2]. An unlicensed medicine refers to a product that lacks authorisation from the relevant national regulatory body [3], whereas off-label use pertains to administering a medicine outside the specifications of its marketing authorisation, including unapproved indications, age groups, dosages, durations, or routes of administration [4, 5]. A principal reason for this widespread practice is the historical exclusion of children from clinical trials. As a result, many drugs lack paediatric-specific data on safety, efficacy, pharmacokinetics, and dosing. This leaves clinicians with limited guidance and forces them to rely on extrapolated adult data or professional judgement, while families and patients are often unable to make fully informed decisions due to a lack of accessible, evidence-based information [6]. Without the support of rigorous scientific evaluation, children are exposed to avoidable risks of treatment failure, toxicity, and adverse drug reactions.

Grieve *et al.* (2005) [7] examined the international regulatory landscape for paediatric medicines and found significant discrepancies. Of the 79 drugs granted paediatric exclusivity in the United States, 58 (73%) were licensed for paediatric use there; however, only 31 (52%) to 33 (55%) of the 60 medicines also licensed for adults in the UK, Australia, and New Zealand were approved for use in children under 12 years of age. Similarly, Ragupathy *et al.* (2010) [8] highlighted a concerning trend in the UK: although it had the highest number of licensed and appropriately formulated paediatric medicines in 1998, the numbers declined over the following decade. Sutherland and Waldek (2015) [9] called for an urgent reassessment of how unlicensed medicines are used in clinical practice, arguing that the current systems do not sufficiently protect children or support prescribers. This echoes wider concerns about the normalisation of off-label use in paediatrics — a necessity borne out of lack of alternatives, rather than a marker of clinical innovation.

1.1.1 Regulatory Framework in the UK

In the UK, pharmaceutical companies must apply to the Medicines and Healthcare products Regulatory Agency (MHRA) for a Marketing Authorisation before marketing a medicinal product for human use [3]. This process involves rigorous assessment of quality, efficacy, and safety in specified patient populations, and the final licence is reflected in the Summary of Product Characteristics (SmPC). Similar systems are in place in the United States (via the Food and Drug Administration (FDA)) and the European Union (via the EMA). However, licensing only governs marketing, not prescribing. Clinicians in the UK are legally permitted to prescribe off-label or unlicensed medicines when it is in the patient's best interest. Such prescribing is governed not by the MHRA, but by professional standards set by bodies such as the General Medical Council (GMC), which emphasises the importance of clinical judgement, familiarity with the drug, and ensuring informed consent [10]. In addition to UK-specific regulatory guidance, broader European recommendations have helped shape professional standards. The European Academy of Paediatrics (EAP) and the European Society for Developmental Perinatal and Paediatric Pharmacology (ESDPPP) jointly issued a policy statement providing detailed guid-

ance on the ethical and clinical considerations for off-label prescribing in neonates, infants, children, and adolescents [11]. This statement reinforces that off-label use may be justified when no licensed alternatives exist, but emphasises the need for a structured, transparent decision-making process, including documentation of rationale, dose selection, and patient/family communication. These principles complement UK guidance and support paediatricians in balancing innovation with patient safety.

1.1.2 Risk of Unlicensed/Off-Labelled Medicines in Children

Despite its prevalence, off-label and unlicensed prescribing in children carries significant risk. An estimated two-thirds of medicines available in the EU are not authorised for paediatric use [12], and only a minority of new therapeutics (around 14%) receive paediatric indications at the time of approval [13]. In hospital settings, age-inappropriate prescribing is the leading cause of off-label use, followed by unapproved indications and dosing adjustments (Figure 1.1) [14]. As a result, clinicians often rely on limited evidence or extrapolate adult data when treating children — approaches that may compromise both safety and efficacy. These limitations are particularly acute in infants and neonates, who often require multiple medications to support vital functions. Studies report that between 55% and 96% of babies admitted to neonatal intensive care units receive at least one off-label or unlicensed medicine during their stay [15, 16]. At the same time, children under two years receive more prescriptions per capita than any other paediatric age group, between 2.2 and 4.7 per year, despite their highly variable pharmacokinetics due to rapid growth and organ maturation [17].

This mismatch between prescribing practice and biological variability increases the risk of harm. For example, the risk of adverse drug reactions (ADRs) rises by around 25% for each additional authorised medicine and by 23% for each additional off-label or unlicensed medicine prescribed [18]. In the United States, preventable medication errors in children are estimated to exceed 7.5 million annually [19]. In Europe, Aagaard *et al.* (2011) [20] found that one-fifth of ADRs reported in Danish

children over a ten-year period were associated with off-label use, with the most serious events occurring in hormonal, dermatological, and allergenic therapies. EMA pharmacovigilance data from 2001 to 2004 identified 820 serious suspected ADRs in children linked to off-label or unlicensed use, including 130 fatalities [21].

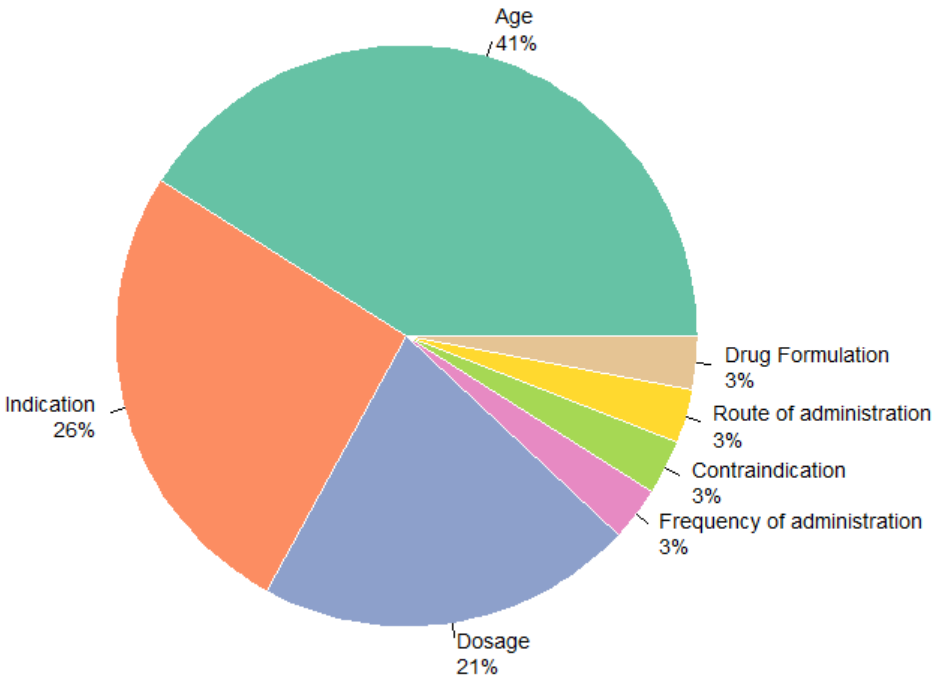


Figure 1.1: Most common off-label prescription categories reported. Recreated from Shuib *et al.* (2021) [14].

The availability of supporting evidence also matters. A Canadian study showed that off-label prescribing without evidence carried a 50% greater risk of ADRs, whereas evidence-supported off-label use did not differ significantly from on-label prescribing. These findings highlight that risk is not inherent to off-label use itself, but to the absence of robust paediatric evidence [22]. Underlying this vulnerability are the limitations of conventional dosing strategies. Linear scaling by weight or body surface area often fails to account for maturational differences in organ function, particularly in neonates and infants [23, 24]. As Rocchi and Tomasi (2011) [25] note, drug doses may vary by up to 100-fold across childhood, making empiric extrapolation from adult data unreliable. Taken together, these findings underscore the cumulative risks associated with paediatric polypharmacy and the urgent need

for robust, age-appropriate pharmacological data and precision dosing strategies tailored to developmental stage. Importantly, variability in drug response is not explained by age alone, meaning that even within the same age group, children may face very different risks of under- or overexposure.

The lack of appropriately licensed paediatric medicines also drives widespread manipulation of adult formulations to suit paediatric needs. These practices include splitting or crushing tablets, dispersing contents in liquids, or diluting injectable products to achieve smaller doses [26]. Paulsson *et al.* (2025) [27] found that 15–37% of oral paediatric drug administrations involve some form of manipulation, often resulting in dose inaccuracy, altered solubility, and unpredictable pharmacokinetics, particularly for poorly soluble compounds or those administered via enteral tubes. Richey *et al.* (2013) [26] also highlighted the need for additional dilution steps when available concentrations do not allow accurate measurement of small doses. Such manipulation practices not only introduce pharmacokinetic variability but also increase the risk of incompatibility, instability, and administration errors, especially when compounded products lack formal validation.

An illustrative example of the mismatch between licensed formulations and clinical need is phenobarbital. The UK-licensed oral liquid contains 38% ethanol, an excipient that poses significant toxicity risks in young children. A typical dose for a 15 kg toddler may result in ethanol exposure equivalent to 200 mL of beer per day [28]. Due to this risk, clinicians often resort to unlicensed, ethanol-free alternatives in routine practice. This example highlights how even medicines with licensed paediatric indications may not be pharmaceutically suitable, reinforcing the need for regulatory and industry action to ensure safe and age-appropriate formulations are readily available.

1.1.3 Barriers to Paediatric Drug Development

Despite the clear need for age-appropriate medicines, a persistent gap exists between the therapeutic requirements of children and the availability of appropriately developed and licensed medicines for this population [29]. A key driver of this

gap is the historically low prioritisation of paediatric populations in pharmaceutical development. A review assessing paediatric clinical trial activity in high-burden diseases found that while children bore 59.9% of the global disease burden in the conditions studied, only 12% of clinical trials were conducted in children [29]. Furthermore, just 41.4% of these paediatric trials were sponsored by industry [29]. This imbalance in research attention has led to children being labelled as "therapeutic or pharmaceutical orphans" [30, 31].

Drug development for children is hindered by a series of interrelated challenges. First, many childhood conditions, especially those affecting neonates or involving rare genetic disorders, have low prevalence and small patient populations. This leads to difficulties in powering clinical trials adequately and makes conventional large-scale trial designs less feasible [32, 33]. Children also represent a heterogeneous group, with profound age-dependent differences in physiology, disease manifestation, and drug handling. This diversity requires age-specific study arms and consideration of tailored formulations and dosing regimens. Thus, a single drug for children may require multiple developmental pathways to support use across different paediatric age bands, making paediatric trials complex [34, 35].

Second, ethical considerations present a unique barrier. Children are a legally and ethically vulnerable population, and the inclusion of minors in clinical research requires additional safeguards [36]. While this has historically led to the exclusion of children from clinical trials in the name of protection, it has increasingly been recognised that this practice paradoxically exposes children to greater harm by denying them evidence-based treatments [37]. Ensuring truly informed consent obtained from parents or legal guardians and assent from older children adds complexity to trial protocols and can lengthen enrolment timelines significantly. Recruitment into paediatric trials is also inherently more difficult. According to Eurostat data, children represented just 15.2% of the EU population in 2019, equating to approximately 67.8 million individuals [38]. This limited patient pool must be further subdivided by age group, disease severity, and treatment strata. Multi-centre, and

often multinational, studies are typically required to achieve sufficient statistical power. This introduces additional logistical and regulatory hurdles, and increases trial costs.

Another key obstacle is the lack of commercial incentives. The pharmaceutical industry's reluctance to invest in paediatric drug development is largely economic. Children represent a relatively small market for new medicines, and the development of orphan drugs in particular carries a high financial risk. Jayasundara *et al.* (2019) [39] estimated the average cost of developing an orphan drug to be approximately $166 million per product, with limited potential to recover these costs from small patient populations. While regulatory incentives (detailed below) offer benefits including market exclusivity, fee reductions, and scientific advice, their impact has been variable and often insufficient to overcome the underlying economics of new drug development. Paediatric drug development often does not align with the strategic priorities of pharmaceutical companies, which are typically driven by adult disease pipelines and anticipated returns on investment. As a result, most paediatric development remains closely linked to adult product pipelines, while diseases that primarily or exclusively affect children struggle to attract attention or resources. In response, drug development in this space has increasingly relied on niche biotechnology firms with a specific focus on rare or paediatric conditions, as well as publicly funded initiatives or collaborative public–private partnerships such as the EU's Innovative Medicines Initiative [40].

There is also a notable lack of natural history data for many paediatric diseases. This knowledge gap impairs the ability to design effective studies and may hinder stratification by disease severity or progression [37]. In diseases with a rapid onset or complex trajectories, such as some immunological or neurodevelopmental conditions, this limitation makes trial design especially challenging and may require adaptive or innovative trial methodologies. Taken together, these ethical, logistical, clinical, and financial challenges contribute to prolonged development timelines, higher attrition rates, and continued therapeutic inequity for children. Overcoming

these barriers requires not only regulatory reform but also sustained academic, governmental, and industry collaboration to ensure that children benefit from the same standards of evidence-based care as adults.

1.1.4 Improving accessibility of medicines for children

In response to the widespread reliance on unlicensed and off-label medicines in paediatrics, regulatory agencies have introduced targeted legislation and incentives aimed at improving the development and availability of licensed medicines for children. One of the most significant regulatory advances in this area was the introduction of the Paediatric Regulation in the EU in 2006 [41]. The Regulation was specifically designed to promote the generation of robust, high-quality data on the use of medicines in children aged 0 to 17 years, and to ensure that medicines used in paediatric populations are subject to the same rigorous evaluation as those used in adults. Under this framework, pharmaceutical companies are required to submit a Paediatric Investigation Plans (PIPs) to the EMA's Paediatric Committee (PDCO) as part of the process for obtaining marketing authorisation for a new product, unless a waiver is granted [41]. These PIPs outline how the sponsor intends to study the medicine in the paediatric population, including timelines, study designs, and age group stratification. In return, companies may be granted incentives such as an extension of the supplementary protection certificate by six months, or, in the case of orphan medicines, an additional two years of market exclusivity [41, 42]. The EMA's PRIority MEdicines (PRIME) scheme [43] complements these measures by offering early, enhanced scientific support and the possibility of accelerated assessment for medicines addressing unmet medical needs, which may be particularly relevant for high-risk or rare paediatric conditions. These incentives were designed to balance the additional costs and complexities associated with paediatric research and encourage industry investment in this previously neglected area.

A ten-year evaluation of the EU Paediatric Regulation demonstrated tangible progress. According to Tomasi *et al.* (2017) [35], there was a marked increase in the number of new medicines authorised for children, particularly in therapeutic

areas such as rheumatology, endocrinology, and infectious diseases. Figure 1.2 illustrates the upward trend in new paediatric medicines approved in the EU in the decade following implementation of the Regulation. Data from the European clinical trials database (EudraCT) indicated a 50% relative increase in paediatric clinical trials involving children between 2007 and 2016, rising from 8.25% to 12.4%. Notably, neonatal studies, almost absent prior to this regulation, became increasingly represented, addressing a critical gap in age-specific evidence. In total, 260 new medicines were authorised for children during this period, either through new paediatric indications or entirely new products.

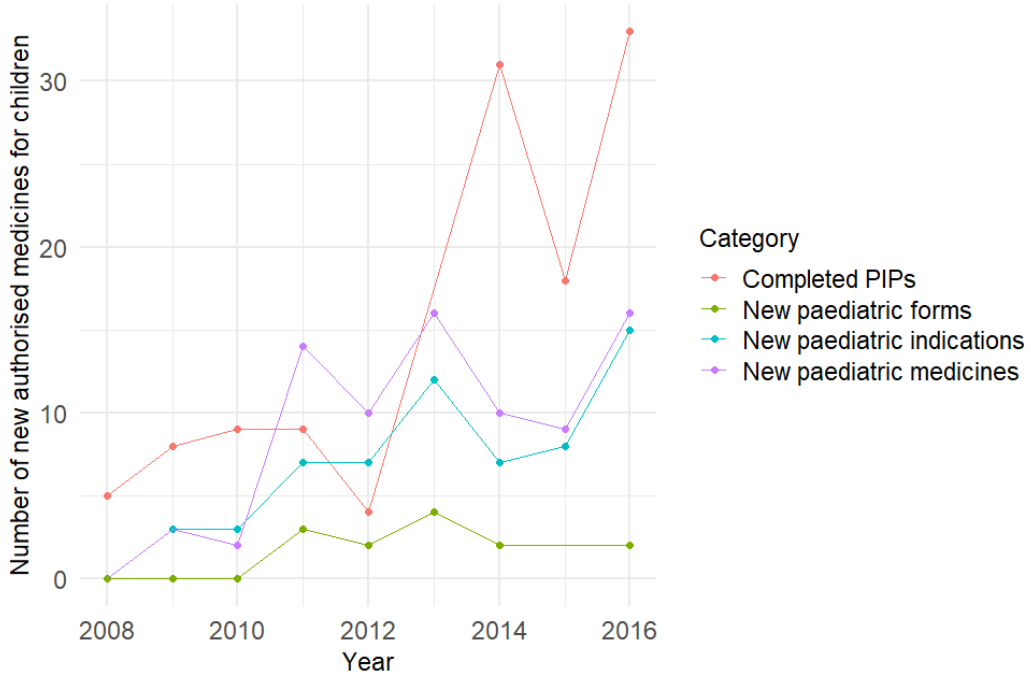


Figure 1.2: New authorised medicines for children in the EU ten years after the implementation of Paediatric Regulation. Re-created from Tomasi *et al* 2017 [35]

Building on the progress and limitations identified in earlier evaluations of the Paediatric Regulation, in 2020, the European Commission published the first comprehensive joint evaluation of both the Orphan and Paediatric Regulations [44]. This evaluation confirmed that both frameworks have stimulated research and increased the availability of medicines for rare diseases and children. However, their impact has been uneven, with limited progress in areas of greatest unmet clinical need, par-

ticularly paediatric-only conditions, and persistent disparities in access across EU Member States. The findings emphasise the need to adapt current legislation and incentive schemes so they not only increase the number of paediatric authorisations but also target those populations and conditions most likely to benefit.

Despite these advances, the Paediatric Regulation still falls short in meeting the needs of children with rare or exclusively paediatric conditions. The overall rise in completed PIPs has not been matched by equivalent progress in developing medicines for diseases that only affect children, or for conditions where paediatric patients show distinct biological differences from adults. As shown in Figure 1.3, most orphan product designations between 2000 and 2020 were for conditions affecting both adults and children, with only 5% focused solely on paediatric conditions [45]. This reflects commercial realities - drug development pipelines are still oriented toward adult diseases, with paediatric indications pursued primarily when aligned with adult markets. Moreover, follow-up data show that only 33.8% of mandatory paediatric postmarketing studies have been completed after a median of 6.8 years, and most drug labels still lack information critical for safe and effective paediatric use [46].

This imbalance is particularly concerning given the epidemiology of rare diseases. Approximately 71% of rare diseases are genetic in origin, and nearly 70% present exclusively in childhood [47]. The low prevalence of individual rare diseases means that each represents a small market segment, which in turn limits the commercial attractiveness of developing targeted therapies. Paediatric-only conditions, such as certain congenital syndromes, metabolic disorders, and paediatric cancers, often lack adult counterparts, making co-development strategies less feasible.

Although the Regulation has incentivised the inclusion of paediatric data in new marketing applications, it has had less success in fostering innovation for conditions unique to children. Industry strategies remain heavily aligned to the adult drug market, and paediatric-specific indications are often underexplored. Furthermore, exemptions and waivers, while sometimes scientifically justified, can also

lead to missed opportunities to generate essential paediatric data. The absence of a PIP requirement for off-patent medicines, which form much of routine paediatric prescribing, represents a major gap. Addressing accessibility therefore requires broader initiatives, including studies to appropriately license older, widely used medicines.

To overcome these challenges, proposals include strengthening incentives for child-only conditions, expanding public–private partnerships, and increasing funding for investigator-led research. Such collaborations can de-risk early-stage development, pool resources, and align academic, regulatory, and industry efforts to meet unmet needs in paediatric medicine [40]. International regulatory coordination could also reduce duplication and promote harmonisation of paediatric development strategies. Without such systemic changes, inequities in access to safe, effective, and licensed medicines for children, especially for rare and underserved conditions, are likely to persist.

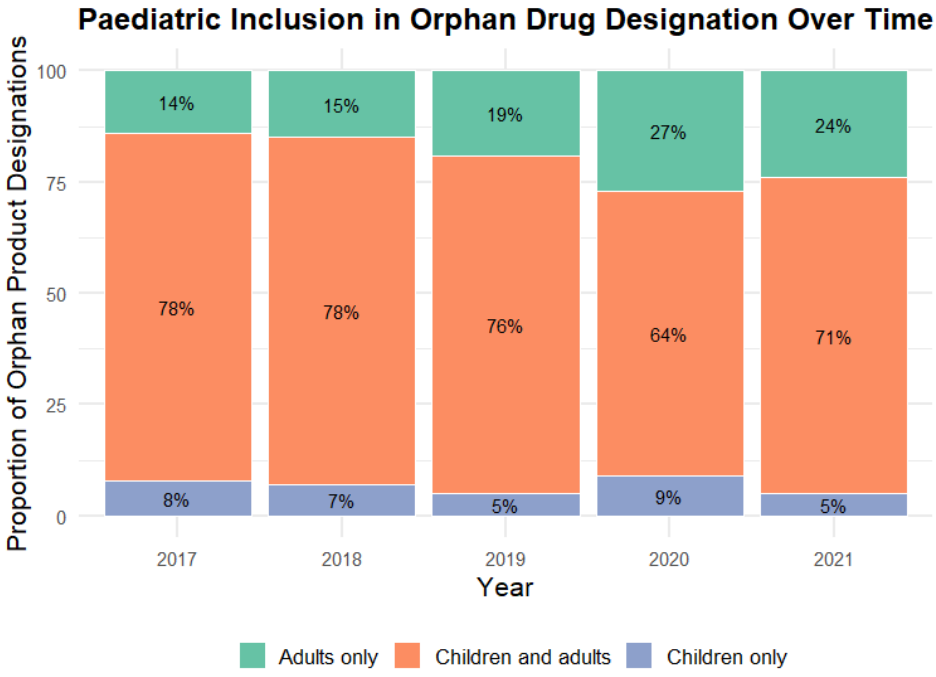


Figure 1.3: Orphan product designation in adults and children. Recreated from European Medicines Agency 2020 [45]

1.2 Pharmacokinetics

In order to determine a safe and effective dose, it is crucial to understand the disposition of the drug being investigated, especially in children whose bodies change dynamically with growth. Pharmacokinetics describes how the body affects a drug after administration. It describes the time course of the concentration of a drug in the body after a dosage regimen has been taken. The four stages that determine the time course of drug concentration are absorption, distribution, metabolism, and excretion. These stages vary across different age groups: neonates, infants, children, adolescents, and adults. The differences are not merely due to variations in body weight; rather, there are physiological and biochemical differences at different stages of life. Figure 1.4 depicts the physiological differences between children and adults that affect pharmacokinetic properties. Variations in body composition, organ function maturation, or decline in the function of organs responsible for eliminating drugs contribute to differences in rates of metabolism and drug clearance [23]. Due to these differences, dosing of drugs in children requires careful consideration. The parameters used to describe the pharmacokinetics of drugs are volume

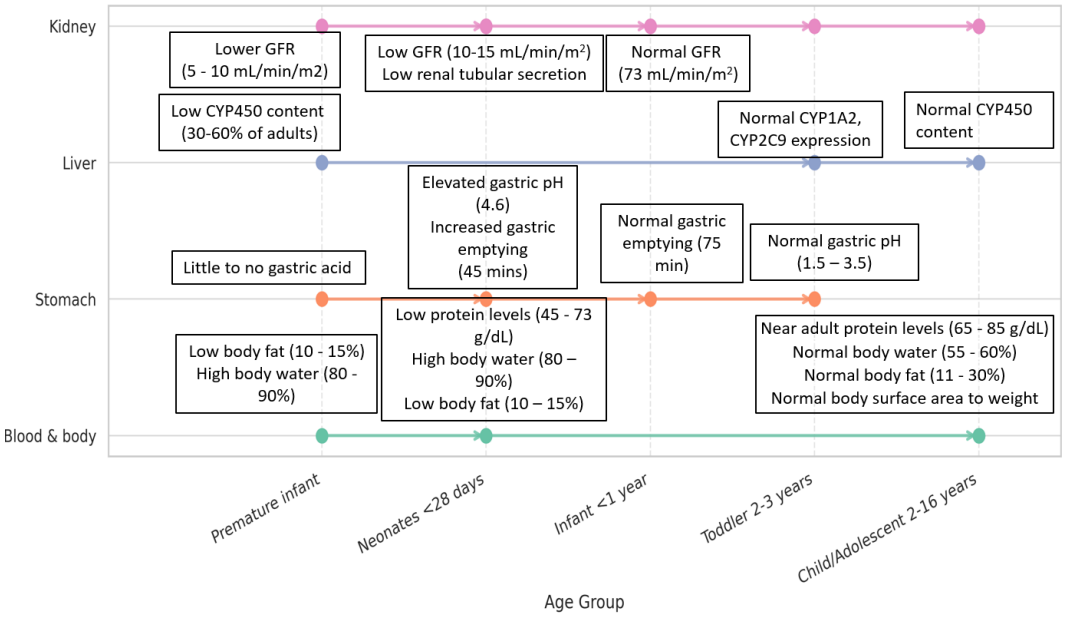


Figure 1.4: Developmental changes across the paediatric age range. GFR: Glomerular filtration rate Recreated from Yellepeddi *et al.* 2019 [48]

of distribution (Vd) and clearance (CL). Vd is defined as a proportionality constant

that relates the amount of drug administered (dose) with the measured plasma concentration. CL, on the other hand, reflects the efficiency of drug elimination and represents the volume of blood or plasma from which the drug is irreversibly removed per unit of time [49]. Half-life is determined by both Vd and CL: a decrease in clearance or an increase in Vd will each result in a longer half-life. When both occur simultaneously, the prolongation of half-life is even more pronounced. These interrelated parameters govern the persistence of a drug in systemic circulation and are essential in determining appropriate dosing intervals. However, before a drug can be distributed or eliminated, it must first enter the body, making absorption the first critical step in the pharmacokinetic process.

1.2.1 Absorption

There are different ways to administer a drug, namely via the gastrointestinal tract, skin, lungs, nasal and corneal. The most common route of administration is oral absorption, and for its non-invasiveness, convenience, and patient acceptability. It can be influenced by physiological parameters such as gastric pH, intestinal transit time, drug-metabolising enzymes in the gut and drug transporters [50]. Gastric pH plays an important role in drug absorption, as it affects the stability, dissolution and ionisation of a drug. Babies have a neutral pH at birth, however the time of change of gastric pH after birth remains unclear [51]. 24 to 48 hours after birth, the gastric pH reduces to 3 with a further rise to neutral 3 to 10 days, followed by a gradual reduce to acidic values (pH 2-3) by the age of 2-3 years to reach adult values [49, 52, 53]. The difference in pH at different ages may affect drug absorption for drugs of particular physiochemical properties of the drug. For example, itraconazole is a weakly basic drug (pKa = 3.7) and its absorption is affected by the gastric pH because of increased ionisation. Patient with lower gastric pH levels were found to have higher drug levels in the serum [54]. Reduced bile secretion in the 2-3 weeks after birth is known to result in lower gut bile concentrations than in adult intestines. High bile salt concentration is known to increase drug solubility for absorption. The poor secretion in neonates may affect drug solubility, particularly those who are poorly soluble such as hydrocortisone [55].

Gastric emptying and intestinal motility determine the rate and extent to which a drug is absorbed. The gastric emptying time is delayed in neonates and infants which may result in drug absorption and reduced absorption rate of drugs that are dependent on the rate and extent of gastric emptying [56]. Intestinal transit time determines the length of time in which a drug can be absorbed from the intestine. Shorter transit times in young children may affect drugs that have delayed drug release formulations, such as theophylline sustained-release formulations [53].

The intestines contain a range of influx and efflux drug transporters and drug-metabolising enzymes. The efflux transporter P-glycoprotein (P-gp) is responsible for transporting substances, such as a drug, from the intracellular to the extracellular compartments within the membranes of the gastrointestinal tract, thus modulating drug absorption. Intestinal drug-metabolising enzymes are responsible for pre-hepatic metabolism, and thereby reduced absorption and bioavailability, of a variety of drugs, including ciclosporin [57]. The major enzyme family involved in the gut wall metabolism of drugs is the cytochrome (CYP) P450 family. CYP3A enzymes, especially CYP3A4 and CYP3A5, are abundant in the adult small intestine. In children, evidence has historically been limited. Emerging paediatric tissue proteomics indicate that intestinal CYP3A4 is the most abundant CYP in the duodenum, with age-related trends observed [58]. Other enzymes that can be found in the gut include glutathione-stransferase (GST), carboxylesterase-2 (CES2) and uridine 5'-diphosphoglucuronosyltransferases (UGTs) [59]. While other routes such as intranasal, transdermal, and inhalational are clinically relevant, their absorption mechanisms differ substantially and are outside the scope of this work.

1.2.2 Distribution

After a drug has been absorbed into the circulation, it will be distributed in different tissues or organs, affecting the efficacy and duration of action. How a drug is being distributed depends on its physical (e.g. whether the drug is water soluble or lipophilic, degree of ionisation) and physiological (e.g. protein binding, tissue uptake) properties. The distribution of drugs is dependent upon body composition,

which varies greatly at different development stages. Neonates and infants differ markedly in body composition compared with older children and adults. They have proportionally more total body water, less muscle mass, and less fat at birth, with fat peaking at 20–25% by the end of infancy. Consequently, hydrophilic drugs tend to have a larger Vd in neonates due to their higher total body water, whereas lipophilic drugs exhibit a smaller volume of distribution at birth, increasing during infancy as fat content rises before stabilising towards adult levels [49]. Total body water is proportionally higher in neonates (70% of body weight) and decreases to around 61% by 1 year of age [52]. This increased water content results in a larger volume of distribution for hydrophilic drugs, meaning that higher doses per kilogram are required in neonates and infants compared with adults. For example, the aminoglycoside gentamicin requires a higher mg/kg dose in early life.

Protein binding also influences drug distribution. Ciclosporin is highly bound to plasma proteins and lipoproteins, with only around 20% present as free (unbound) drug at birth. With increasing concentrations of albumin and lipoproteins during development, the unbound fraction decreases to below 5% in adults [60]. In general, acidic drugs mainly bind to albumin while basic drugs bind to globulins, α1-acid glycoprotein and lipoproteins [53]. Neonates and infants have lower plasma protein concentrations; however, these reach adult values in infancy. Hence the impact of plasma protein concentrations on drug levels is likely to be most significant in newborns and young infants. The drugs most influenced by this effect are those with a narrow therapeutic drug index which are highly protein bound [61]. Reduced protein binding increases the free concentration in plasma, thereby making a more free fraction of the drug available to diffuse more easily to other compartments and increase the Vd. This will also result in an increase in the CL of the drug. Therefore, the target concentrations for neonates and young children may be lower for those with a defined therapeutic serum concentration relation, such as theophylline, to take into account less protein binding capacity/greater free drug concentration.

1.2.3 Metabolism

The metabolism of drugs, particularly hydrophobic molecules, is essential for their elimination from the body and typically involves a two-phase biotransformation process carried out predominantly in the liver. These are classified as Phase I and Phase II reactions. Phase I metabolism involves chemical modification of the drug through reactions such as oxidation, reduction, and hydrolysis. These processes introduce or expose functional groups on the drug molecule, converting it into a more reactive metabolite that can subsequently undergo further processing. The principal enzymes responsible for these oxidative reactions are members of the CYP superfamily, although non-CYP enzymes such as aldehyde oxidase and xanthine oxidase also contribute significantly to drug metabolism. For example, favipiravir, a broad-spectrum antiviral, undergoes metabolism predominantly via aldehyde oxidase, as will be discussed in detail in Chapter 5. Phase II metabolism follows and involves conjugation reactions, where polar groups such as glucuronic acid, sulfate, or glutathione are added to the Phase I metabolite to increase its water solubility and facilitate excretion, primarily via the kidneys or bile.

The activity of both Phase I and Phase II enzymes is developmentally regulated. At birth, the enzymatic systems involved in drug metabolism are immature, and their activities undergo significant maturation over the first months and years of life. This ontogeny of metabolic enzymes has profound implications for drug disposition in neonates and infants, contributing to the differences in pharmacokinetics observed between children and adults. Delayed or reduced activity of these enzymes in very young children can result in drug accumulation or insufficient conversion to active or inactive metabolites, impacting both drug efficacy and toxicity profiles.

The cytochrome P450 enzyme system, especially the CYP3A subfamily, plays a central role in Phase I metabolism. In adults, CYP3A4 is the dominant enzyme, responsible for metabolising a wide variety of clinically important drugs and associated with a high potential for drug–drug interactions. However, in neonates and young infants, the expression of CYP3A4 is low. Instead, a related fetal enzyme,

CYP3A7, which shares 88% sequence identity with CYP3A4 [62], predominates during the early postnatal period. Despite their structural similarity, CYP3A7 and CYP3A4 differ in their metabolic activity and sensitivity to inhibitors [63], leading to different pharmacokinetic behaviours in neonates compared to older children and adults.

The temporal switch from CYP3A7 to CYP3A4 during the first year of life represents a critical developmental transition that influences drug metabolism. This shift, along with the maturation of other isoenzymes, complicates the prediction of drug–drug interactions in young children. As a result, neonates and infants may exhibit unexpected responses or toxicities to medications that are otherwise safe in older populations, highlighting the necessity for age-specific pharmacokinetic data and dosing strategies.

Phase II metabolism, particularly glucuronidation, also exhibits developmental immaturity at birth. This is clinically evident in conditions such as neonatal jaundice, which results from the reduced capacity of the neonatal liver to conjugate bilirubin [53]. The enzyme Uridine diphosphate (UDP)-glucuronosyltransferase 1A1 (UGT1A1), which mediates bilirubin conjugation, is expressed at only about 1% of adult levels in the fetal liver[49]. Similarly, other UGT isoforms, such as UGT2B7, which is responsible for the glucuronidation of drugs like chloramphenicol, are immature in neonates. Inadequate metabolism of chloramphenicol has been linked to 'grey baby syndrome', a condition characterised by cardiovascular collapse, cyanosis, and often death, historically associated with impaired hepatic clearance in neonates due to insufficient UGT activity [64].

Understanding the maturation patterns of drug-metabolising enzymes is crucial for paediatric pharmacotherapy. Knowledge of how and when specific enzymes become functionally active can be used to predict drug disposition in different paediatric age groups. This information underpins the design of age-appropriate dosing regimens that aim to optimise therapeutic outcomes while minimising the risk of adverse effects. Integrating developmental pharmacokinetics into model-based drug

development is therefore essential to ensure the safe and effective use of medicines in children across all developmental stages.

1.2.4 Excretion

The excretion of drugs by the kidneys depends on glomerular filtration, tubular secretion, and tubular reabsorption. Renal clearance is the net result of these three processes, each with an independent rate and maturational pattern. Glomerular filtration rate (GFR) is often used as a marker of renal function and strongly influences the elimination of water-soluble drugs and metabolites. At birth, GFR is approximately 10–20 mL/min/m^2, doubles within the first week of life, and typically reaches adult values by 3–5 months of age [49]. In contrast, population pharmacokinetic modelling suggests a more gradual trajectory, with about 90% of adult GFR achieved closer to one year of age [65].

The estimation of GFR in neonates and children presents additional challenges. GFR can be measured directly using inulin clearance or exogenous markers, but these methods are rarely practical in clinical settings. Instead, creatinine clearance is most commonly used. Serum creatinine concentration, however, is influenced by both production and elimination, and immediately after birth reflects maternal creatinine rather than the neonate's own renal function [66, 67]. Creatinine-based equations are therefore unreliable in the first days of life. In paediatrics, the modified Schwartz formula is widely used, where GFR is estimated from serum creatinine normalised to body length [68]. While simple and practical, the modified Schwartz equation assumes stable creatinine generation and has not been validated in preterm neonates, who have immature tubular function and low muscle mass. These limitations mean that creatinine-based estimates can both under- and over-estimate the true GFR in the youngest patients. As renal excretion is a major elimination pathway for many medicines, these developmental changes and measurement challenges highlight the importance of age-appropriate dose adjustment and careful therapeutic monitoring in children.

In summary, the change in body composition and the maturation of organ functions

at different growth stages profoundly affect drug handling. Children require age-dependent dose adjustments to avoid toxicity and improve dosing precision.

1.3 Pharmacokinetic modelling

Pharmacokinetic modelling is a quantitative approach used to describe the absorption, distribution, metabolism, and elimination of a drug within the body. It allows the concentration–time profile of a drug to be characterised using mathematical equations. Population pharmacokinetic modelling enables the behaviour of a drug to be described across a population using sparse sampling data, making it especially valuable in vulnerable populations such as children, where frequent blood sampling is often not feasible. This approach supports efforts to address the persistent lack of age-appropriate prescribing information in paediatrics and facilitates evidence-based dosing recommendations. Population pharmacokinetic models evaluate concentration–time data from all individuals in a cohort simultaneously. These models describe the pharmacokinetic properties of the drug and the time course of drug exposure at a population level, while also accounting for variability in exposure between individuals (inter-individual variability) and within individuals (residual or intra-individual variability). By quantifying both explained and unexplained variability, these models offer insight into how patient-specific characteristics such as age, weight, renal function, or co-medication may influence drug kinetics. Importantly, the magnitude of unexplained variability is crucial, as high levels of residual error reduce the precision of parameter estimates, ultimately impacting the reliability of dosage predictions and potentially affecting the safety and efficacy of therapy. Pharmacokinetic modelling can be broadly classified into two major approaches: individual (non-population) pharmacokinetic analysis and population pharmacokinetic analysis. The choice of method depends on the clinical or research objectives, the structure of the available data, and the need to quantify variability across individuals [69]. An overview of these methods is presented in Figure 1.5.

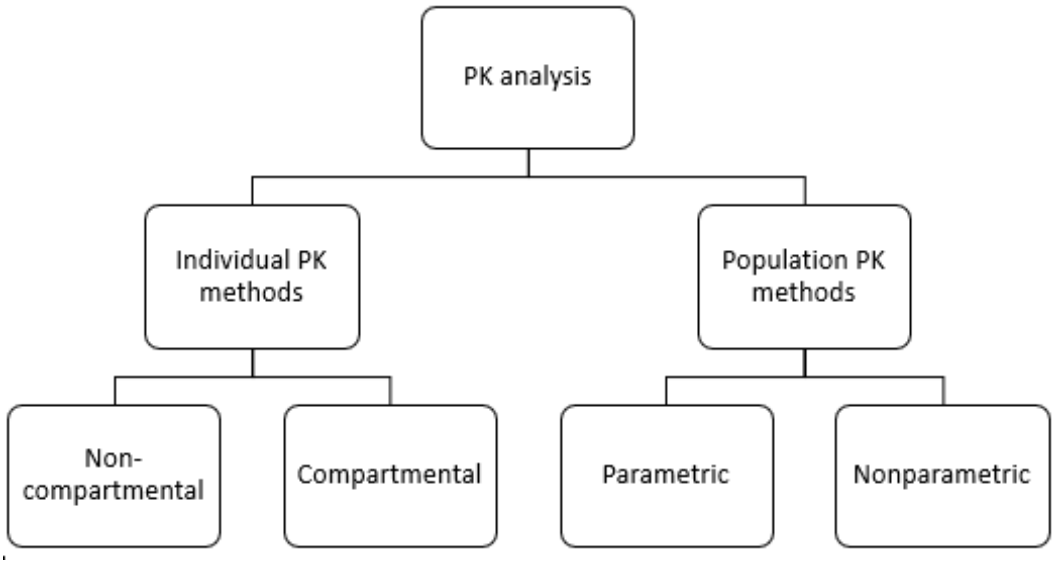


Figure 1.5: Overview of pharmacokinetic analysis methods

1.3.1 Non-compartmental and individual compartmental analysis

The most basic method is non-compartmental analysis (NCA), which does not require the assumption of a specific compartmental model. Instead, it uses simple mathematical methods, such as the trapezoidal rule, to estimate the area under the concentration–time curve (AUC), a key measure of drug exposure following a dose. From NCA, one can also derive other pharmacokinetic parameters such as clearance, elimination half-life ($t_{1/2}$), maximum plasma concentration (C_{max}), and time to reach maximum concentration (T_{max}), as illustrated in Figure 1.6. While NCA is easy to implement and interpret, it requires dense sampling and cannot be used to explore the effects of covariates or to simulate alternative dosing scenarios. In contrast, individual compartmental analysis uses mathematical models (typically one- or two-compartment models) to describe the concentration–time data of each subject individually. This standard two-stage approach first fits a model to each individual's data separately, estimating parameters such as clearance and volume of distribution. These individual estimates are then summarised across the population to obtain the mean and standard deviation of pharmacokinetic parameters.

Assuming negligible measurement error, the pharmacokinetic model for estimating

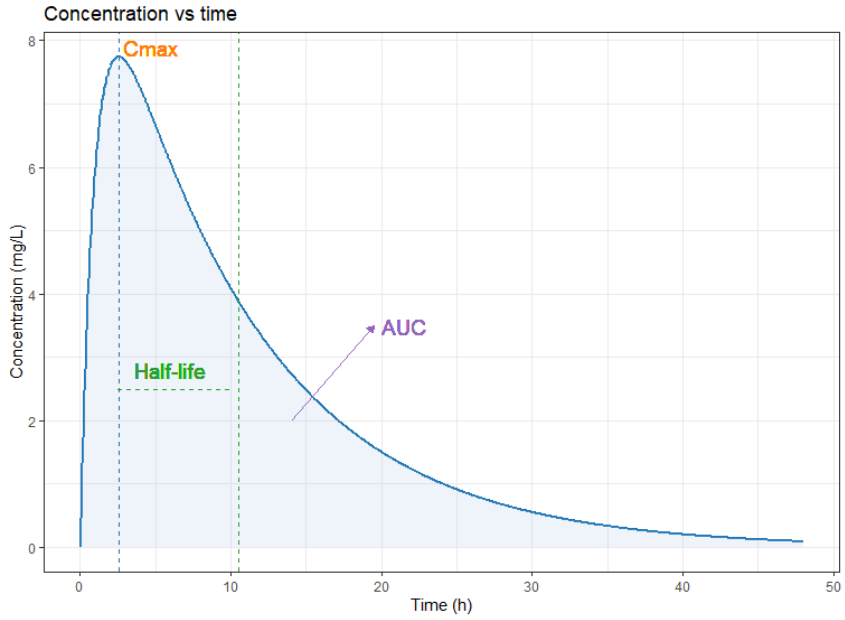


Figure 1.6: Concentration-time curve showing the pharmacokinetic parameters. Cmax: maximal concentration AUC: Area under the curve

the parameters of the jth individual can be expressed as [70]:

$$y_j = f(\phi_j, x_j) + \varepsilon_j \tag{1.1}$$

where y_j is the observed concentration (dependent variable), f is the model function that predicts concentration using individual parameters ϕ_j, and x_j is a vector of known design variables such as dose, time, or body size. ε_j represents the residual error or measurement noise. If the statistical properties of ε_j are known or assumed, maximum likelihood estimation (MLE) can be applied to identify the parameter values that make the observed data most probable.

For instance, if ε_j is assumed to follow a normal distribution with zero mean and constant variance, the MLE simplifies to ordinary least-squares estimation, and the optimal parameter estimates can be obtained by minimising an objective function $O_j(\theta_j)$. Alternative error models may also be used, such as log-normal, exponential, or combined additive and proportional error models, depending on the characteristics of the data.

Individual pharmacokinetic modelling is particularly suitable for first-order (linear) pharmacokinetic models, and because it does not require strong assumptions about between-subject distributions, it is useful for exploratory data analysis. For example, when a drug is administered in multiple doses, this approach can help detect nonlinearity in drug kinetics (e.g. saturation of metabolism). However, the method has key limitations: it does not account for covariate effects across the population, and it requires intensive sampling per individual to yield reliable estimates. These constraints limit its utility in clinical settings with sparse data and hinder its ability to generalise findings across patient subgroups.

1.3.2 Population pharmacokinetic models

Population pharmacokinetic methods allow the concentration–time profiles from multiple subjects to be analysed collectively as a population. The modelling process involves the evaluation of various compartmental models, elimination pathways, and sources of variability. The final model provides estimates of the mean population pharmacokinetic parameters, characterises variability between subjects (between-subject variability, BSV), and captures variability within individuals (intra-individual or residual variability). Some of the observed variability can be explained and quantified using covariates, while unexplained differences are incorporated into the residual error model. Covariate modelling plays a central role in this process, as it can inform dose selection, support individualised treatment strategies, and guide the design of future trials in specific subgroups, while balancing clinical relevance with model stability [71].

Parametric maximum likelihood methods enable the use of prior information to inform the model and estimate the set of parameters that maximise the joint likelihood of the observed data [72]. In contrast, non-parametric maximum likelihood methods do not make distributional assumptions about the parameters, making it possible to detect subpopulations. However, a limitation of the non-parametric approach is the difficulty in estimating confidence intervals around the parameter estimates [73].

Population pharmacokinetic modelling requires a more elaborate statistical frame-

work to accommodate sparse data, which typically consists of limited observations collected from a cohort of individuals [74]. The observed response (e.g. plasma concentration) in an individual within the population nonlinear mixed-effects modelling framework can be described by:

$$y_{ij} = f(\phi_j, x_{ij}) + \varepsilon_{ij} \tag{1.2}$$

Here, y_{ij} denotes the observed value (e.g. blood plasma level) at time point x_{ij} for the ith observation in the jth subject, where $i = 1,...,n_j$ and $j = 1,...,N$, with N representing the total number of subjects. The function f describes the structural model used to predict the observation (e.g. a mono- or multi-exponential function), and ε_{ij} denotes the residual variability (i.e. measurement error).

The individual pharmacokinetic parameters ϕ_j are described by:

$$\phi_j = g(\theta, z_j) + \eta_j \tag{1.3}$$

In this expression, the function g represents a predetermined or hypothesised relationship that defines the expected value of the individual pharmacokinetic parameter vector ϕ_j as a function of the population parameters θ and a set of covariates specific to the jth individual, denoted z_j. These covariates are clinically and biologically relevant characteristics that are hypothesised to influence drug pharmacokinetics. Common examples include age, weight, body surface area, sex, renal and hepatic function (often measured through creatinine or bilirubin levels), concomitant medications (such as enzyme inducers or inhibitors), disease status, or even genetic polymorphisms affecting drug metabolism.

In most models, covariates are assumed to be time-invariant — that is, they are considered constant throughout the observation period for a given individual. This assumption simplifies the model and is often reasonable for static factors like sex or genotype. However, for dynamic variables such as weight in growing children, creatinine levels in patients with acute kidney injury, or days post-transplant, it may

be more appropriate to model covariates as time-varying. This is achieved by allowing the pharmacokinetic parameters ϕ_j to also depend on the observation index i, making them ϕ_{ij}, thereby capturing intra-individual changes over time.

The term η_j represents the random effect, a vector of inter-individual random deviations that account for the difference between the individual's actual parameter values and those predicted solely by the covariates. These random effects are typically assumed to follow a normal distribution with mean zero and variance-covariance matrix Ω. The inclusion of η_j enables the model to capture residual between-subject variability that cannot be explained by observed covariates, reflecting factors that are unknown, unmeasured, or inherently stochastic. The combination of fixed effects (population estimates and covariates) and random effects allows population pharmacokinetic models to accommodate both systematic and unexplained sources of variability, improving both the accuracy and generalisability of the model.

1.3.3 Model development

The base model is normally a one- or two-compartment model Figure 1.7. One-compartment (Figure 1.7a) assumes that the drug is distributed throughout the body immediately after administration and the drug equilibrates instantaneously between tissues. In contrast, a two-compartment model (Figure 1.7b) , divides the body

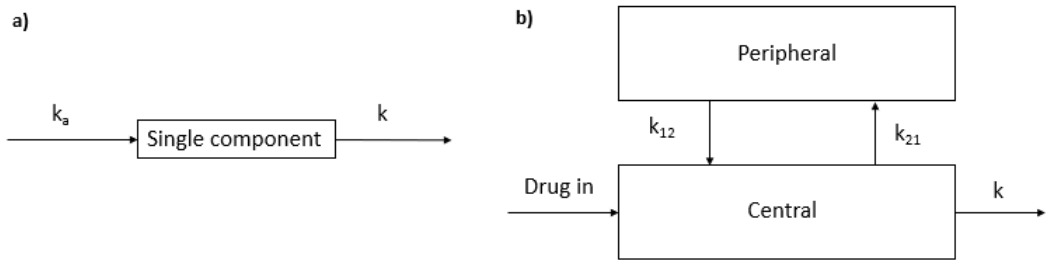


Figure 1.7: Compartment models. Figure 1.7a depicts a one-compartment model. k= elimination rate constant (h^{-1}), k_a = absorption rate constant (h^{-1}). Figure 1.7b illustrates a two-compartment model. k_{12}, k_{21} and k are first-order rate constants; k_{12} is rate of transfer from central to peripheral compartment and k_{21} is the rate of transfer from peripheral to central compartment; k= rate of elimination from central compartment. Recreated from Dhillon and Gill 2006 [75].

into a central compartment, representing highly perfused organs such as the heart,

lungs, kidneys, liver, and brain, and a peripheral compartment, representing less well perfused tissues such as fat and muscle. After administration into the central compartment, drug distribution between the two compartments occurs over time and equilibrium is not instantaneous. The choice between compartment models is often guided by prior pharmacokinetic knowledge of the compound, early visual exploration of the data, and biological plausibility.

Once the base model is established, sources of inter-individual variability (IIV) are explored through the inclusion of covariates. Common covariates include demographic factors (e.g. weight, age, sex), markers of organ function, co-medications, and, increasingly, genomic predictors of drug disposition. Covariates can be incorporated using multiplicative or additive relationships, often formalised through exponential models for clearance and volume parameters. Sanghavi *et al.* (2023) [71] emphasise that covariate identification should follow a systematic, biologically informed approach rather than relying solely on data-driven stepwise testing. This reduces the risk of spurious associations and ensures that included covariates reflect plausible mechanistic relationships.

Scaling of pharmacokinetic parameters to account for differences in body size is fundamental when modelling across populations with wide weight ranges. Holford (2013) [76] proposed that allometric scaling using fixed exponents, 0.75 for clearance and inter-compartmental clearance and 1.0 for volumes of distribution, should serve as a pharmacokinetic "standard" applicable to neonates and adults alike. This approach not only improves parameter comparability across studies but also enables extrapolation between age groups. In fixed allometric weight scaling, or theory-based allometry, the scaling equation for an individual parameter is:

$$\text{Parameter}i = \text{Parameter}_{\text{pop}} \times \left(\frac{c_i}{\overline{c}}\right)^{\theta} \tag{1.4}$$

where $\text{Parameter}_{\text{pop}}$ is the typical population value, c_i represents the individual covariate value (ie weight), and $\overline{c}$ is set to 70 kg to facilitate the comparison of volume estimates across different studies. The exponent θ is fixed at 0.75 for clearance and

inter-compartmental clearance for metabolic rate, reflecting the well-established metabolic scaling relationship between body size and basal metabolic rate observed across mammalian species [77]. This exponent implies that clearance increases more slowly than body weight, whereas the allometric exponent for volume of distribution is fixed at 1, indicating linear proportionality between volume and weight [78].

While the use of fixed exponents is widespread, it is not without controversy. Drug-specific analyses, such as propofol pharmacokinetics across neonates, infants, children, and adults, have shown that the optimal clearance exponent can range from as low as 0.20 to 2.01 when neonates are included, far outside the fixed 0.75 value [79]. The fixed 0.75 exponent may over-predict clearance in neonates and under-predict it in infants [23, 79–81]. Meta-analyses of multiple drugs suggest that clinically useful exponent estimates often fall between 0.63 and 0.78, but may vary substantially by drug and age group [82]. As a solution, bodyweight-dependent exponent (BDE) models, where the exponent transitions from higher values in neonates to around 0.75 in older children and adults, have been shown to better capture maturation-driven clearance changes [83]. However, González-Sales *et al.* (2022) [84] highlighted that reliably estimating allometric exponents from empirical data requires large, diverse datasets, at least 1,000 subjects spanning a wide range of body sizes in general populations, and a minimum of 100 subjects in combined paediatric–adult datasets. Such numbers are rarely available in paediatric pharmacokinetic studies, which often include fewer than 50 participants. In these situations, fixed theory-based exponents (0.75 for clearance, 1 for volume) provide a physiologically justified and statistically stable default. When larger datasets are available, exponent estimation can be explored, ideally in conjunction with body composition metrics (e.g. fat-free mass) and maturation functions.

Accounting for developmental changes is especially important in paediatric populations, where organ function, enzyme expression, and transporter activity evolve rapidly in early life. Maturation functions, often sigmoidal models of postmenstrual

or postnatal age, can be incorporated alongside allometric scaling to capture age-related changes in clearance not explained by size alone [78, 85]. This combined size–maturation approach is now widely recommended in paediatric modelling, allowing for physiologically plausible extrapolation to neonates and infants.

Finally, once the base model structure, scaling, and key covariates are in place, residual unexplained variability is described using an appropriate error model, which may be additive, proportional, or combined, depending on the characteristics of the data. This residual model captures measurement error and other sources of variability not explained by the structural or covariate model, and its form is selected based on both statistical criteria and diagnostic plots.

1.3.4 Model evaluation

After a model has been built, it can be evaluated to assess goodness of fit, reliability, and stability. Goodness-of-fit checks included diagnostic plots such as observed vs population predictions (PRED), observed vs individual predictions (IPRED), and conditional weighted residuals (CWRES) vs time or predictions. Observed vs PRED plots assess the adequacy of model prediction against the central tendency of the observed data, while observed vs IPRED plots highlight unexplained residual variability at the individual level. CWRES plots are useful for diagnosing structural model misspecification and residual error patterns. A horizontal line across the x-axis range indicates that the constant variance assumption is not violated. Visual predictive checks (prediction-corrected VPCs) compare the observed median and quantiles to those from simulated datasets, with prediction correction adjusting for variability due to different dosing or covariate values. This approach provides a graphical evaluation of the model's ability to capture both the central tendency and variability of the observed data. The change in magnitude of the objective function value (OFV) is a numerical way of evaluating nested (covariate) models. For non-nested comparisons, such as different compartmental structures or error models, the Akaike Information Criterion (AIC) can be applied, with lower values indicating a more parsimonious and better-fitting model. % relative standard error (%RSE) and

bootstrap confidence intervals (CI) measure estimation precision. %RSE for mean and random effects parameters should not exceed 25% and 50%. Bootstrapping can be used for model selection, determination of stability, parameter reliability check and validation.

1.4 Stratified medicine using population pharmacokinetic approach

Population pharmacokinetic (popPK) modelling provides an essential framework for stratified medicine, particularly in paediatrics, where conventional pharmacokinetic studies are limited by ethical and practical constraints. The sparse sampling strategy inherent in popPK models significantly reduces the required blood volume, making it a more feasible and safer option for neonates and young children. These models offer a powerful tool for personalising treatment to improve the safety and efficacy of medicines in paediatric populations.

Personalised medicine refers to a clinical approach that tailors medical treatment to individual patients or defined subgroups, using information on genetic, environmental, and lifestyle factors to optimise therapeutic strategies [86]. This approach aims to move beyond the traditional ”trial-and-error” method of drug prescribing by predicting therapeutic outcomes and minimising adverse effects. Such targeted strategies can also help reduce healthcare costs by avoiding ineffective or unnecessary treatments.

Using popPK models, dosing strategies for ciclosporin with or without azole antifungals, immunoglobulin replacement therapy and favipiravir can be refined to better reflect patient-specific pharmacokinetic variability. In particular, model-based estimates can be used to define safe trough thresholds, optimise target exposures, and individualise treatment regimens.

1.4.1 Ciclosporin and azole antifungals

Haematopoietic stem cell transplantation (HSCT) is a curative procedure for various paediatric haematological malignancies and immunological disorders. However, it is associated with prolonged immunosuppression, particularly when immunoablative conditioning regimens and immunosuppressants such as ciclosporin are used to prevent and/or treat graft-versus-host disease (GVHD). Acute GVHD affects 30–50% of HSCT recipients [87, 88], while invasive fungal disease (IFD) occurs in up to 15% of patients and carries a high mortality rate [89].

Historically, IFD was the leading cause of infection-related mortality post-HSCT, with reported mortality rates exceeding 90% [90]. The introduction of azole antifungals, including itraconazole, posaconazole, and voriconazole, has substantially improved outcomes; however, significant challenges remain. Voriconazole and itraconazole are recommended as first-line prophylactic agents in HSCT patients [91]. Voriconazole is also the first-line treatment for primary invasive aspergillosis [92, 93], although concerns persist regarding its potential for acute toxicity [94]. Recent randomised controlled trials have demonstrated that posaconazole is non-inferior to voriconazole for treating invasive aspergillosis, supporting its use as a recommended alternative [95]. Despite their widespread use, there is a lack of paediatric-specific controlled studies supporting their efficacy and safety. Itraconazole is not licensed for use in children, while posaconazole and voriconazole are licensed only for children aged two years and older. Dosing in paediatric populations is typically extrapolated from adult pharmacokinetic data, with therapeutic drug monitoring (TDM) used to guide adjustments. However, due to high inter-individual variability, erratic absorption, and non-linear pharmacokinetics, children often require frequent dose modifications or even treatment switches. Voriconazole exhibits age-dependent, non-linear pharmacokinetics and has been associated with sub-therapeutic levels in up to 66% of paediatric patients [96]. Similarly, posaconazole absorption is highly variable and may be compromised by gastrointestinal disturbances or concurrent use of proton pump inhibitors. A popPK model for posaconazole developed by Boonsathorn *et al.* (2019) [97] revealed saturable

bioavailability with the oral suspension and low target attainment in children even at maximum feasible doses. This work also highlighted the need to quantitatively assess posaconazole's inhibitory impact on ciclosporin clearance, consistent with findings from independent studies [98, 99]. Due to the absence of robust paediatric dosing guidelines and the uncertainty around managing sub-therapeutic exposures contribute to prolonged periods of inadequate antifungal coverage.

Ciclosporin, a calcineurin inhibitor, is a cornerstone of GVHD prophylaxis following HSCT but is characterised by a narrow therapeutic index and highly variable pharmacokinetics. These factors are particularly pronounced in children due to developmental variation in drug metabolism. Ciclosporin is primarily metabolised by the CYP enzyme CYP3A4, and its clearance is significantly impacted by co-administration of azole antifungals, which inhibit CYP450 enzymes. This interaction is clinically important: insufficient ciclosporin levels may increase the risk of GVHD, while excessive exposure may lead to nephrotoxicity and other adverse effects. Azoles, by inhibiting CYP3A4, elevate ciclosporin concentrations and necessitate careful dose adjustment.

Ciclosporin, like many drugs, undergoes hepatic biotransformation through the CYP3A4 pathway [100]. The broader CYP450 system plays a critical role in drug-drug interactions and the activation of prodrugs [101, 102]. The non-linear developmental expression of various metabolic enzymes alters drug clearance, bioavailability, and interaction profiles in children, differentiating them significantly from adults.

Despite the well-recognised interaction between ciclosporin and azoles in adults, paediatric-specific pharmacokinetic data to inform dosing remain scarce. By integrating knowledge of drug-drug interactions, enzyme ontogeny, and developmental pharmacokinetics into a unified modelling framework, this project aims to support safer and more effective co-administration of ciclosporin and azoles in paediatric HSCT recipients. In doing so, it seeks to move beyond the current empirical dosing approach, offering a model-informed pathway to individualised dosing and im-

proved clinical outcomes.

1.4.2 Immunoglobulin

In the UK, the majority of patients with antibody deficiency receive immunoglobulin replacement therapy via the subcutaneous route [103]. Historically, intravenous immunoglobulin was the predominant route of administration, but over the past two decades, there has been a gradual shift towards subcutaneous delivery. Subcutaneous immunoglobulin (SCIG) not only allows for home-based treatment and improved patient autonomy [104], but also produces more stable IgG concentrations with reduced peak–trough fluctuations, which has altered both the pharmacokinetic profile and clinical management of immunoglobulin replacement therapy [105]. Immunoglobulins are essential components of the adaptive immune system, and deficiencies in specific isotypes are characteristic of several primary immunodeficiency syndromes. These deficiencies increase susceptibility to infection, with the pattern of vulnerability depending on the type and degree of immunoglobulin loss. Immunoglobulin G (IgG) replacement remains the cornerstone of treatment for patients with clinically significant antibody deficiency and can be administered either intravenously or subcutaneously.

The efficacy of immunoglobulin replacement therapy has traditionally been assessed by monitoring serum trough IgG concentrations. However, the optimal minimum IgG level required to prevent infections remains unclear. Since therapeutic immunoglobulin is a plasma-derived product, its use is not without risk. Potential complications include infusion-related adverse reactions and a theoretical risk of infectious transmission. In light of increasing demand, rising costs, and periodic supply disruptions, efforts to rationalise immunoglobulin use are ongoing. Defining safe and effective IgG targets could enable more precise dosing, reducing treatment costs while maintaining or improving clinical outcomes.

A meta-analysis of intravenous pre-infusion (trough) IgG levels demonstrated a relationship between IgG concentration and pneumonia risk, but failed to establish a definitive protective threshold [106]. There is a notable lack of paediatric-specific

popPK studies in this area, and no studies to date have investigated the link between subcutaneous dosing regimens and clinical outcomes [107]. Substantial intra- and inter-individual variability in IgG pharmacokinetics among patients with primary immunodeficiency highlights the opportunity to apply model-based approaches to personalise dosing in this vulnerable population [107].

1.4.3 Favipiravir

Favipiravir is a purine nucleic acid analogue and broad-spectrum antiviral agent approved for the treatment of influenza in adults. It functions as a prodrug, entering host cells where it is intracellularly converted into its active ribofuranosyl 5'-triphosphate form [108]. The active metabolite inhibits viral replication by targeting RNA-dependent RNA polymerase (RdRp), an enzyme essential for viral genome transcription and replication but absent in human cells. Favipiravir is primarily metabolised via hydroxylation by the hepatic enzyme aldehyde oxidase (AO), with the majority of the inactive metabolite excreted in urine.

Beyond influenza, favipiravir has been explored as a treatment for a range of RNA virus infections, including Ebola, Lassa fever, norovirus, rabies, severe fever with thrombocytopenia syndrome, and COVID-19 [109, 110]. It has been administered both as monotherapy and in combination with other antivirals such as oseltamivir and nitazoxanide [111–114].

Favipiravir displays complex, nonlinear pharmacokinetics influenced by time, dose, and body weight [108]. Notably, it undergoes metabolism by AO, which it also inhibits, leading to time-dependent self-inhibition of its own clearance [115]. The ontogeny of AO shows that enzyme activity increases postnatally and reaches a plateau by approximately one year of age [116]. However, significant inter-individual variability in AO activity is observed thereafter, with correlations reported with age, body weight, body surface area, and ethnicity [116, 117]. Given the immaturity of AO in infants under 12 months of age and the wide variability in enzyme activity beyond infancy, caution is warranted when extrapolating adult pharmacokinetic data to paediatric populations. These factors highlight the need for age- and devel-

opmentally informed dosing strategies for favipiravir in children.

In summary, despite regulatory advances and scientific progress have improved paediatric drug availability, there remains a substantial lack of evidence to guide safe and effective dosing for medicines commonly used in children, particularly those undergoing haematopoietic stem cell transplantation or living with antibody deficiencies. Existing recommendations for ciclosporin, immunoglobulin, and favipiravir largely rely on extrapolation from adult data and do not adequately account for the physiological and developmental factors that influence pharmacokinetic variability in childhood. These include differences in organ function, maturation of metabolic pathways, disease state, and concurrent therapies, all of which can significantly alter drug exposure and response. These uncertainties hinder precision dosing and contribute to inconsistent treatment outcomes. This thesis seeks to address these evidence gaps through population pharmacokinetic modelling of ciclosporin, immunoglobulin, and favipiravir in paediatric patients, using real-world clinical data to characterise sources of variability, optimise dosing strategies, and advance the application of personalised pharmacotherapy in this vulnerable population.

1.5 Ethics approval

As a retrospective study using anonymised data, the ethics committee has confirmed that ethics approval and parent and patient consent will be exempt (21/LO/0646).

Chapter 2

Scaling of ciclosporin and azole antifungals pharmacokinetics from early life to old age

The pharmacokinetics of medicines in children are non-linear and shaped by a dynamic interplay of developmental processes. Key contributors to this variability include changes in body size and composition, the maturation of enzymatic pathways, and evolving organ function over time [118]. Among these, size, maturation, and organ function are recognised as the principal determinants of pharmacokinetic differences. Beyond the age of two years, children are considered broadly comparable to adults with respect to maturity, differing largely in terms of size [76]. In contrast, neonates and infants represent a distinct population, as the maturation of drug-eliminating systems occurs rapidly and non-linearly in the first two years of postnatal life [80, 119].

One of the most clinically significant enzyme families involved in drug metabolism is the CYP superfamily, particularly CYP3A4. As the most abundant isoform in adult liver and intestinal tissue [118], CYP3A4 is responsible for the metabolism of approximately two-thirds of all clinically used medicines [120], including ciclosporin, itraconazole, and midazolam. During fetal development, CYP3A7 pre-

dominates until 6–12 weeks postnatally [63], after which CYP3A4 gradually increases. By 6–12 months of age, CYP3A4 reaches approximately 50% of adult expression [121], eventually becoming the dominant isoform in later childhood and adulthood [122]. Despite structural similarity, CYP3A4 and CYP3A7 demonstrate marked differences in their catalytic capabilities [123], and azole antifungals inhibit these enzymes to varying extents, CYP3A4 consistently more so than CYP3A7 [63]. These developmental differences in enzyme expression and function substantially influence drug metabolism in paediatric populations [124]. Voriconazole is primarily metabolised by CYP2C19, an isoenzyme that begins to express from approximately 8 weeks of gestation. Expression of CYP2C19 increases linearly in early infancy, reaching half of adult levels around 1 year of age [125], with substantial inter-individual variability reported across early childhood, up to a 21-fold difference between 5 months and 10 years [126]. Posaconazole is metabolised through UGT enzymes, whose expression begins around 20 weeks of gestation and continues to rise into early childhood and beyond two years of age [127].

At the opposite end of the age spectrum, ageing is also associated with physiological decline, including reductions in renal and hepatic function, which can impact both drug metabolism and excretion. Age-related reductions in CYP enzyme expression and activity have been observed, with liver P450 content remaining relatively constant from 20–40 years, declining thereafter, and falling more sharply beyond 70 years of age [128]. These age-dependent changes further support the incorporation of ontogeny into pharmacokinetic modelling as a means to individualise therapy across the life course [124].

Given that drug clearance is affected not only by size but also by maturational and functional changes with age, it is often modelled as a composite function of these physiological determinants [129]:

$$CL_{typ} = CL_{std} \times \left(\frac{BW}{70}\right)^{0.75} \times MF \times OF \tag{2.1}$$

Here, CL_{std} represents typical adult clearance scaled to 70 kg, MF is a maturation

function, and OF reflects age-related changes in organ function.

The allometric component describes the effect of body size, while the maturation function captures age-related developmental changes in clearance capacity [130]. These changes are most commonly attributed to the ontogeny of drug-metabolising enzymes, but they also encompass the maturation of renal excretion and other physiological processes relevant to drug elimination. Because many drug-metabolising enzymes begin to develop before birth, postmenstrual age (PMA), the sum of gestational and postnatal age, can provide a more accurate reflection of developmental maturity than postnatal age alone, particularly in preterm neonates [131]. Mathematically, the maturation function is typically expressed using a sigmoidal Hill function, which describes the gradual progression of clearance capacity from neonatal levels to adult values:

$$MF = \frac{PMA^{Hill}}{PMA^{Hill} + (PM_{50})^{Hill}} \tag{2.2}$$

where PM_{50} is the PMA at which half of adult clearance is reached, and the Hill coefficient describes the steepness of this developmental curve [129, 131].

To capture both the ontogenic increase and the subsequent decline in clearance across the lifespan, a maturation-decline function can be used [132]:

$$CL_{typ} = CL_{std} \times \left(\frac{BW}{70}\right)^{0.75} \times \left(\frac{PMA^{Hill_1}}{PMA^{Hill_1} + PMA_{50}^{Hill_1}}\right) \times \left(1 - \frac{AGE^{Hill_2}}{AGE^{Hill_2} + AGE_{50}^{Hill_2}}\right) \times \exp(\varepsilon) \tag{2.3}$$

In this equation, AGE represents age in years, AGE_{50} is the age at which 50% of decline in clearance has occurred, and the Hill coefficients modulate the shape of both the maturation and decline functions.

2.0.1 Drugs used in haematopoietic stem cell transplant

HSCT is a high-risk intervention associated with complications such as GVHD and opportunistic infections, particularly fungal infections [91, 133]. To mitigate these risks, immunosuppressive agents like ciclosporin and antifungal prophylaxis with

azole drugs are routinely administered. At Great Ormond Street Hospital (GOSH), ciclosporin is used for GVHD prophylaxis in a predominantly paediatric population, with a median age of 3.3 years (range 0.1–20 years; see Chapter 3). One centre reported their 23-year experience in transplanting children under 2 years of age, noting an acute GVHD incidence of 31.5%, with 8.7% experiencing severe (grade III–IV) disease [134]. As outlined earlier, pharmacokinetics in early life is shaped by both size and the maturation of drug-metabolising enzymes, and it is vital that models developed for this population account for these physiological changes.

As outlined earlier, pharmacokinetics in early life are shaped by both size and the maturation of drug-metabolising enzymes. Models developed for this population must therefore account for these physiological changes. To estimate enzyme maturation parameters for these drugs, clearance data from the neonatal period onwards are essential. Accordingly, a structured literature review was undertaken to identify published pharmacokinetic models of ciclosporin, itraconazole, posaconazole, and voriconazole. These drugs were selected because they are commonly co-administered in children undergoing HSCT, a group with distinct pharmacokinetic profiles due to their young age and differing physiological characteristics compared to solid organ transplant patients. Clearance values were extracted and standardised to a 70 kg adult equivalent using allometric scaling to enable cross-study comparisons independent of size. A non-linear least squares (NLS) method was used to investigate whether a maturation function could be fitted to describe developmental changes in clearance. This approach provided a practical means of estimating population-level clearance and exploring the extent to which each drug's clearance is modulated by enzyme development, while making minimal assumptions about inter-individual variability. This chapter harnesses published pharmacokinetic data for ciclosporin, itraconazole, posaconazole, and voriconazole to characterise clearance across the lifespan, incorporating both enzyme maturation and age-related physiological decline.

Ciclosporin was first introduced to the market as Sandimmun® in 1983, which was

associated with variable bioavailability and poor gastrointestinal tolerance [135]. In 1995, a microemulsion formulation, Neoral®, was launched, providing more consistent absorption and improved bioavailability, and subsequently became the preferred formulation [136]. Neoral® administration results in a 59% increase in C_{max} and approximately 29% higher bioavailability compared to Sandimmun® [137]. However, the trough concentrations of both formulations were found to be comparable [137].

Itraconazole, posaconazole, and voriconazole are triazole antifungals widely used for the prophylaxis and treatment of invasive fungal infections in immunocompromised patients (Figure 2.1). Although they share a common antifungal mechanism, primarily inhibition of the fungal cytochrome P450 enzyme lanosterol 14α-demethylase, their pharmacokinetic profiles, metabolic pathways, and age-related behaviour differ substantially [138–140]. Itraconazole is extensively metabolised by the cytochrome P450 enzyme CYP3A4. In paediatric populations, achieving therapeutic plasma concentrations is challenging, with studies reporting subtherapeutic levels in up to 76.8% of children [141–144]. Pharmacokinetic variability is considerable, and younger children and infants often require higher doses than adults, likely due to increased clearance or reduced oral bioavailability [141–145]. Itraconazole is also highly protein-bound, with only 0.2% present in the free (pharmacologically active) form. Its pharmacokinetics are non-linear, leading to plasma accumulation with repeated dosing.

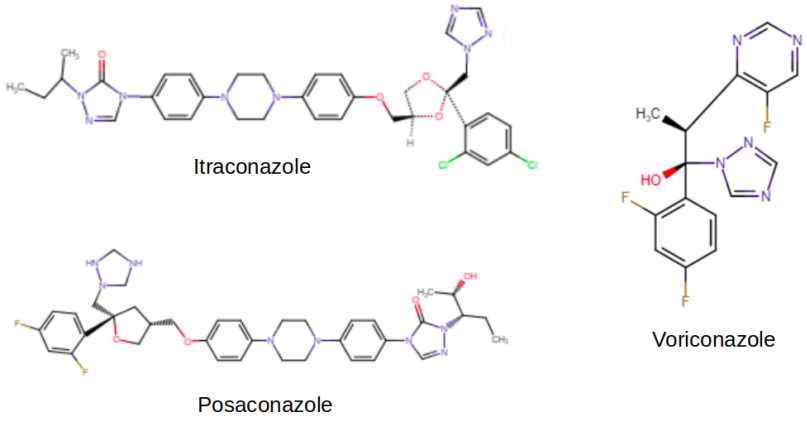


Figure 2.1: Chemical structure of itraconazole, posaconazole and voriconazole

Posaconazole is available in the UK as an oral suspension, modified-release tablet, and intravenous formulation, with marked pharmacokinetic variability across and within formulations [146]. Absorption is formulation-dependent and influenced by clinical factors such as gastrointestinal function and concurrent medications. In 2019, Boonsathorn *et al.* (2019) [97] developed a population pharmacokinetic model that identified saturable bioavailability in the oral suspension formulation in adults, which contributed to reduced and variable systemic exposure. Their work demonstrated that therapeutic target attainment could be as low as 30% with suspension formulations, even at the highest feasible doses. Bioavailability is further reduced in the presence of diarrhoea and concurrent proton pump inhibitor therapy.

Voriconazole, in contrast, exhibits highly variable and non-linear pharmacokinetics due to saturable metabolism, primarily by CYP2C19 with contributions from CYP2C9 and CYP3A4 [140]. Genetic polymorphisms in CYP2C19 significantly influence clearance, leading to marked inter-individual differences in exposure [140, 147, 148]. Paediatric patients often display higher clearance compared to adults, necessitating relatively higher weight-normalised doses [149–151]. The complexity of its metabolism, combined with variability in absorption and drug–drug interactions, makes voriconazole a challenging but important agent to study in the paediatric population.

2.1 Aim

To describe age-related changes in the clearance of ciclosporin and commonly co-administered azole antifungals from early life to adulthood, and to identify developmental patterns that can inform paediatric dosing strategies.

2.2 Objectives

- To systematically review and extract pharmacokinetic parameters for ciclosporin, itraconazole, posaconazole, and voriconazole across the age continuum.

- To apply allometric scaling and maturation models to normalise clearance estimates to a 70 kg reference.

- To evaluate developmental trends in clearance and bioavailability and identify age-appropriate model functions for use in subsequent paediatric analyses

2.3 Method

A structured literature review was conducted using the US National Library of Medicine PubMed search engine (including the MEDLINE database) and the EMBASE electronic database via the Wolters Kluwer OVID search interface. The following search terms were used:

- *ciclosporin OR cyclosporine OR cyclosporin A* AND *pharmacokinetic OR pharmacometric* (searched on 30th June 2024)

- *azoles OR triazoles OR itraconazole OR voriconazole OR posaconazole* AND *pharmacokinetic OR pharmacometric* (searched on 13th February 2023)

Studies were excluded if they were non-human, not in English, or if the full text was unavailable despite best efforts. Only studies that reported original pharmacokinetic data or derived pharmacokinetic parameters from previously unpublished data were included. Ciclosporin concentrations may be measured in whole blood, serum, or plasma; however, only those measured in whole blood were considered as it is the gold standard for therapeutic drug monitoring due to extensive erythrocyte binding [152]. As there is no reliable or validated method for converting between plasma and whole blood levels, only studies reporting whole blood ciclosporin concentrations were retained.

Data extraction was performed independently by three reviewers. Extracted information included: number of participants, patient population, method of pharmacokinetic parameter estimation, summary statistics for age and weight, and reported clearance values. Studies without reported or derivable body weight information

were excluded, as this precluded allometric scaling. Publications involving multiple populations, formulations, or cohorts were treated as distinct data points.

Pharmacokinetic clearance values were standardised to a 70 kg adult equivalent using allometric scaling (Equation 2.3) to facilitate cross-study comparisons independent of body size. NLS regression was then applied to examine clearance trends across age. Given that only summary pharmacokinetic data were available from the literature, NLS provided a practical and interpretable method to estimate typical clearance values across different age groups and disease states. This approach enabled the incorporation of covariates such as age (via maturation models), body size (through allometric scaling), and route of administration, while making minimal assumptions about inter-individual or inter-study variability. Although NLS does not capture random effects or within-population variability, it is well suited to synthesising heterogeneous summary-level data and exploring developmental trends in drug clearance across the lifespan. Importantly, the use of nonlinear mixed-effects modelling (e.g. NONMEM) was not feasible here, as individual-level repeated measures were unavailable, underscoring the appropriateness of NLS for this type of analysis.

Bioavailability (F) describes the proportion of an administered dose that reaches the systemic circulation in an unchanged form. For oral and other extravascular routes, it is typically expressed relative to intravenous administration (which is considered 100% bioavailable). In this analysis, two approaches were used to account for oral bioavailability. First (method 1), where intravenous clearance data were available, bioavailability was estimated by comparing oral clearance to intravenous clearance values. Absolute bioavailability can be calculated using dose-normalised AUC values: is defined as the fraction of an orally administered dose that reaches the systemic circulation. When both oral and intravenous data are available, absolute bioavailability can be calculated from dose-normalised AUC values:

$$F = \frac{AUC_{PO} \times Dose_{IV}}{AUC_{IV} \times Dose_{PO}} \tag{2.4}$$

where AUC_{PO} and AUC_{IV} are the areas under the AUC for oral and intravenous

administrations respectively and represent drug exposure over time. As clearance is inversely proportional to AUC, bioavailability may alternatively be expressed as: $F = \frac{CL_{IV}}{CL_{PO}}$ where CL_{IV} and CL_{PO} represent intravenous and oral clearances, respectively. This relationship assumes linear pharmacokinetics and consistent bioavailability across all oral formulations. Second (method 2), in cases where sufficient oral concentration–time data were available, F was incorporated into the NLS regression model to estimate the fraction absorbed ($\mathrm{F}_{\mathrm{enteral}}$) directly:

$$CL_{typ} = CL_{std} \times \left(\frac{BW}{70}\right)^{0.75} \times F \times \left(\frac{PMA^{Hill_1}}{PMA^{Hill_1} + PMA_{50}^{Hill_1}}\right) \times \left(1 - \frac{AGE^{Hill_2}}{AGE^{Hill_2} + AGE_{50}^{Hill_2}}\right) \times \exp(\varepsilon) \tag{2.5}$$

Here, F is defined as:

$$F = \left(\frac{1}{F_{enteral}} \times form_{ent} + 1 \times form_{IV}\right) \tag{2.6}$$

where form_{ent} and form_{IV} are binary indicators (0 or 1) identifying the formulation type. This allows for differentiation between enteral and intravenous preparations, assuming a single $\mathrm{F}_{\mathrm{enteral}}$ value for all enteral forms. If different enteral formulations (e.g., liquids vs capsules) had distinct bioavailabilities, the model was extended as follows: F can be expressed as:

$$F = \left(\frac{1}{F_{liquid}} \times form_{liq} + \frac{1}{F_{capsule}} \times form_{cap} + 1 \times form_{IV}\right) \tag{2.7}$$

where $\mathrm{F}_{\mathrm{liquid}}$ and $\mathrm{F}_{\mathrm{capsule}}$ represent the bioavailability of liquid and capsule/tablet formulations, respectively. $form_{liq}$, $form_{cap}$, and $form_{IV}$ are indicator variables for formulation type.

Because many of the included studies involved oral formulations, and absorption can substantially influence systemic exposure, it was essential to account for bioavailability. This ensured that clearance estimates derived from oral and intravenous data could be meaningfully compared. Formulation-specific assumptions applied: ciclosporin capsule and liquid preparations were considered bioequivalent in earlier pharmacokinetic studies and thus analysed together [137]. The bioavail-

ability of itraconazole differs between liquid and capsule forms and these were analysed separately in sensitivity analyses [153]. Posaconazole suspension and modified-release tablets were analysed separately due to their well-documented differences in absorption [139, 154], while voriconazole tablets and oral solution were treated as equivalent given their demonstrated bioequivalence [140].

2.4 Results

A total of 1,687 publications on ciclosporin were identified through MEDLINE (via OVID), and 1,678 through EMBASE. For the azole antifungals, 2,186 publications were identified through MEDLINE, and 2,640 through EMBASE. After de-duplication, titles and abstracts were screened for relevance, followed by full-text screening. Of these, 241 publications reporting ciclosporin pharmacokinetics were included in the final analysis. For azole antifungals, 155 full publications were retained, comprising 271 distinct data points (i.e. separate populations or cohorts within the same study were counted individually): 48 on itraconazole, 35 on posaconazole, and 72 on voriconazole (Appendix A). Figure 2.2 presents the literature search process.

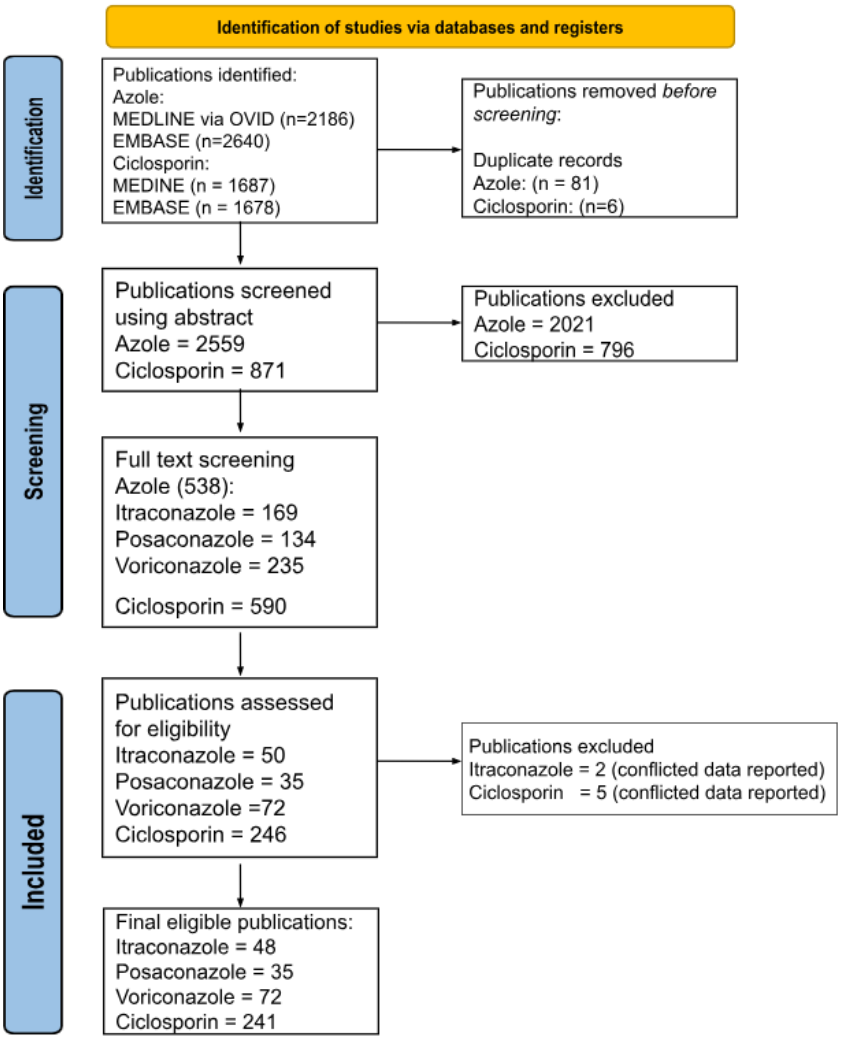


Figure 2.2: Flow diagram of studies identified in the review of azole antifungals pharmacokinetics

2.4.1 Ciclosporin

Table 2.1 summarises the characteristics of the ciclosporin publications included in the analysis, which were published between 1982 and 2024. A total of 241 papers were included, contributing 279 data points. The majority of studies were based on enteral preparations. As many publications did not specify the brand or formulation used, all oral data were analysed collectively. Capsule and liquid formulations were considered bioequivalent [137] and treated as such.

Table 2.1: Data characteristics extracted from 242 ciclosporin publications

	Intravenous	Oral
No of data points	39	240
Healthy volunteers	6 (15%, 6/39)	43 (18%, 43/240)
Median age (years) (range)	31 (1 - 60)	38 (2 - 73)
Median weight (kg) (range)	65 (13 - 89)	67 (11 - 97)
Median dose per body weight (mg/kg)	2.51 (0.7 - 13)	3.82 (0.14 - 19.77)

The data were heterogeneous, encompassing a broad range of comorbidities, age groups, and analytical methods for whole blood ciclosporin concentration (Figure 2.3). The age range for intravenous preparations spanned 1 to 60 years, while for oral preparations it ranged from 2 to 73 years. Renal transplant/impairment patients accounted for 45.5% of data points, followed by healthy subjects (18.3%), liver transplant patients (10.4%) and HSCT recipients (8.2%). The majority of whole blood ciclosporin measurements were performed using high-performance liquid chromatography (HPLC, 36.6%), followed by radioimmunoassay (RIA, 24.7%) and fluorescence polarisation immunoassay (FPIA, 23.7%).

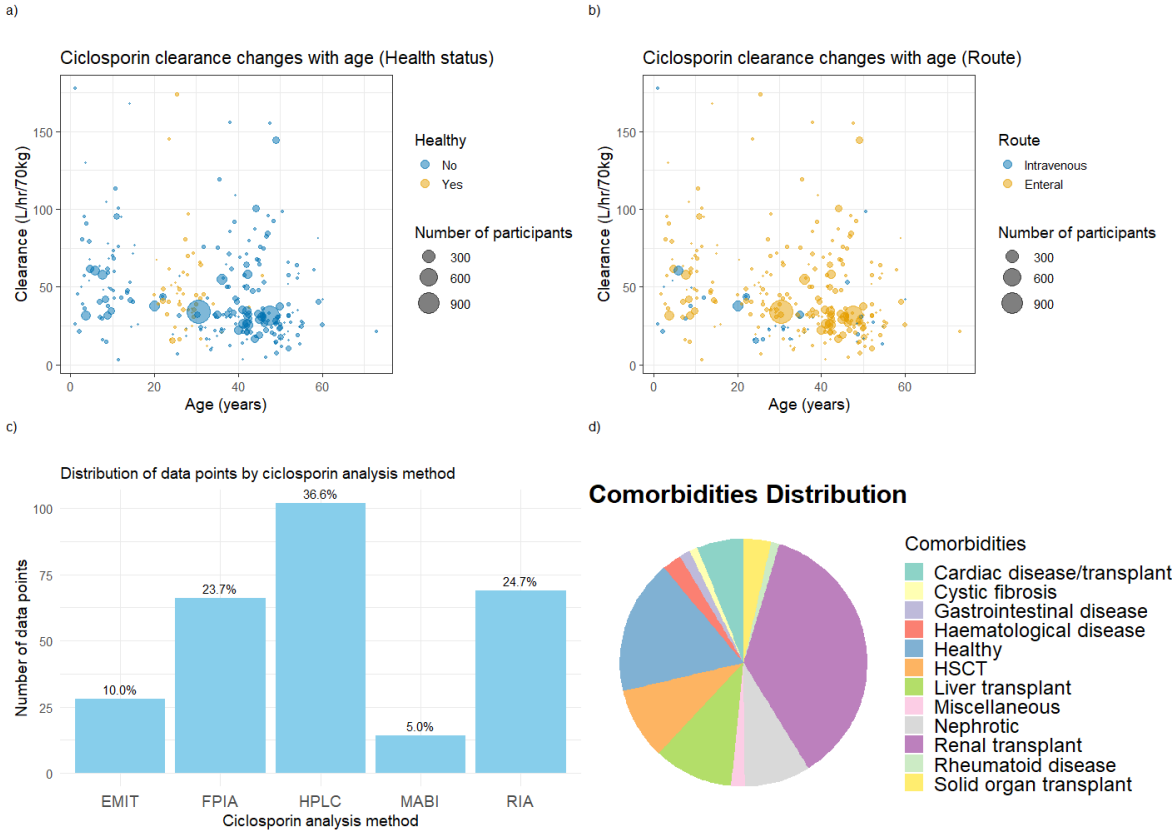


Figure 2.3: Characteristics of ciclosporin pharmacokinetic data points. Panels a), b), and c) illustrated the relationship between ciclosporin clearance and age, categorised by health status, route of administration, and analysis method, respectively. Panel d) displayed the distribution of comorbidities. The size of each data point represented the number of participants in the study. EMIT: Enzyme Multiplied Immunoassay Technique, FPIA: Fluorescence Polarization Immunoassay, HPLC: High-Performance Liquid Chromatography, MABI: Monoclonal Antibody-Based Immunoassay. RIA: Radioimmunoassay, HSCT: Haematopoietic Stem Cell Transplant.

Due to a paucity of data for patients at the extremes of age (i.e., under two years and over 70 years), it was not possible to estimate maturation and age-related organ decline using Equation 2.3. As ciclosporin and midazolam are both metabolised by CYP3A4 [121, 155], the PM_{50} and Hill coefficient (Hill_1) from midazolam models were applied *a priori* to approximate age-related changes in ciclosporin clearance. Anderson and Larsson (2011) [155] used physiologically based pharmacokinetic models to characterise midazolam clearance maturation, reporting a PM_{50} of 73.6 weeks PMA and a Hill_1 coefficient of 3. These parameters were incorporated into the model to estimate the effect of age-related decline in organ function on clearance:

$$CL_{typ} = CL_{std} \times \frac{PMA^3}{(PMA^3 + 73.6^3)} \times \left(1 - \frac{AGE^{Hill_2}}{AGE^{Hill_2} + AGE_{50}^{Hill_2}}\right) \times \exp(\varepsilon) \quad (2.8)$$

However, the model failed to converge to a global minimum. Stratifying the data by route of administration did not improve convergence. To reduce heterogeneity and potential confounding, the dataset was further stratified by five major comorbidities: renal transplant, nephrotic syndrome, liver transplant, HSCT, and healthy subjects. Yet, even this grouped analysis failed to reliably estimate the impact of age-related decline on clearance. Consequently, the maturation function was applied only to estimate age-dependent maturation of clearance:

$$CL_{typ} = CL_{std} \times \frac{PMA^3}{(PMA^3 + 73.6^3)} \quad (2.9)$$

The model was extended to incorporate the bioavailability of enteral formulations, allowing both intravenous and enteral data to be analysed together:

$$CL_{typ} = CL_{std} \times F \times \frac{PMA^3}{(PMA^3 + 73.6^3)} \quad (2.10)$$

where F is defined as in Equation 2.6, distinguishing between intravenous and oral preparations.

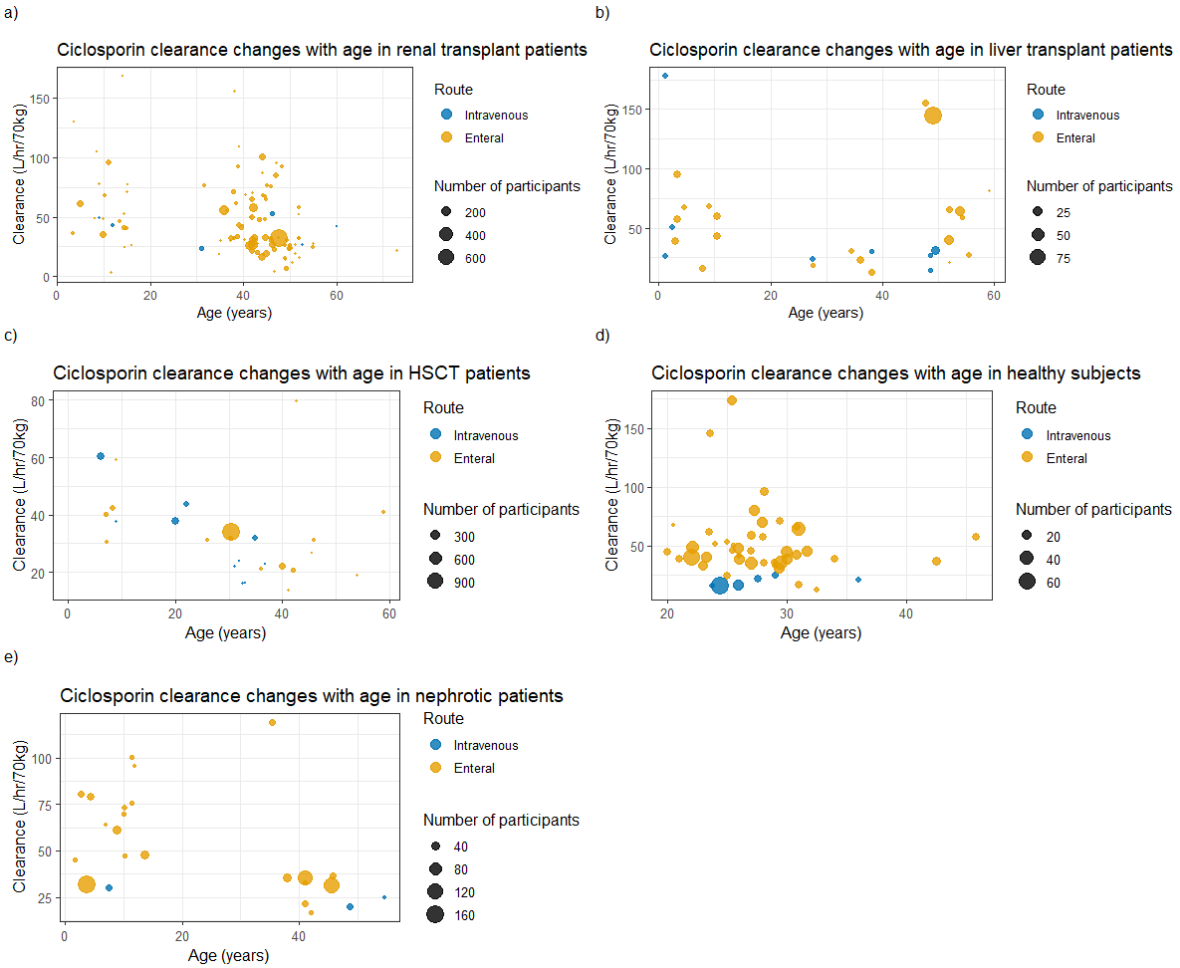


Figure 2.4: Illustration of the relationship between ciclosporin clearance and age, categorised by route for a) renal transplant patients, b) liver transplant patients, c) HSCT patients, d) healthy subjects, and e) nephrotic patients.

Table 2.2 presents the estimated clearance and bioavailability across comorbidity groups. HSCT and liver transplant patients exhibited similarly reduced clearance and lower estimated bioavailability, while renal transplant patients had higher bioavailability and correspondingly higher clearance estimates. These estimates were consistent with reported literature values [137]. The final estimates were used to simulate ciclosporin clearance across age groups (Figure 2.5), using the midazolam-based maturation function as a fixed input.

Table 2.2: Estimated ciclosporin clearance for various populations allometrically scaled to 70kg. CL_{IV} = predicted intravenous ciclosporin clearance, CL/F = predicted apparent itraconazole clearance, CI = confidence interval. IV = intravenous route, PO = oral route. Bioavailability was estimated using Method 1: absolute bioavailability. Method 2: non-linear estimation

Population	Median age in years (range)	Method 1			Method 2	
		Predicted CL_{IV} (L/h/70kg) [95% CI]	Predicted CL/F (L/h/70kg) [95% CI]	Bio-availability (%)	Predicted CL_{IV} (L/h/70kg) [95% CI]	Bio-availability (%) [95% CI]
Total	Total: 36.6 (1.2 - 73) IV: 1.2 - 60 PO: 1.8-73	34.4 [24.2, 44.5]	47.9 [44.0, 51.8]	72	31.3 [21.4, 412]	65 [44, 86]
Renal transplant	Total: 42.2 (3.4 - 73) IV: 38.6 (9-60) PO: 42.2 (3.4 - 73)	39.9 [27.6, 52.3]	47.6 [41.3, 53.9]	84	39.9 [15.6, 64.3]	84 [32, 130]
Renal impairment	Total: 11.75 (1.8 - 54.5) IV: 48.6 (7.5 - 54.5) PO: 11.5 (1.8 - 45.7)	24.9 [11.8, 38.0]	57.9 [45.0, 70.8]	43	24.9 [0, 55.1]	43 [0, 96]
Liver transplant	Total: 36.7 (1.2 - 59) IV: 36.6 (1.2 - 49.5) PO: 36.7 (2.9 - 59)	30.1 [18.8, 41.49]	46.4 [35.2, 58.9]	64	30.1 [0, 63.2]	49 [0, 105]
HSCT	Total: 32.75 (8.1 - 59) IV: 32 (8.8 - 36.7) PO: 40 (7.1 - 59)	28.1 [20.4, 35.9]	32.7 [22.8, 42.6]	86	28.1 [18.3, 38.0]	86 [53, 131]
Healthy	Total: 27 (20 - 45.8) IV: 26.8 (23.8 - 36) PO: 27 (20 - 45.8)	19.5 [15.6, 23.4]	53.4 [44.3, 62.4]	37	19.5 [6.2, 42.6]	37 [0, 79]

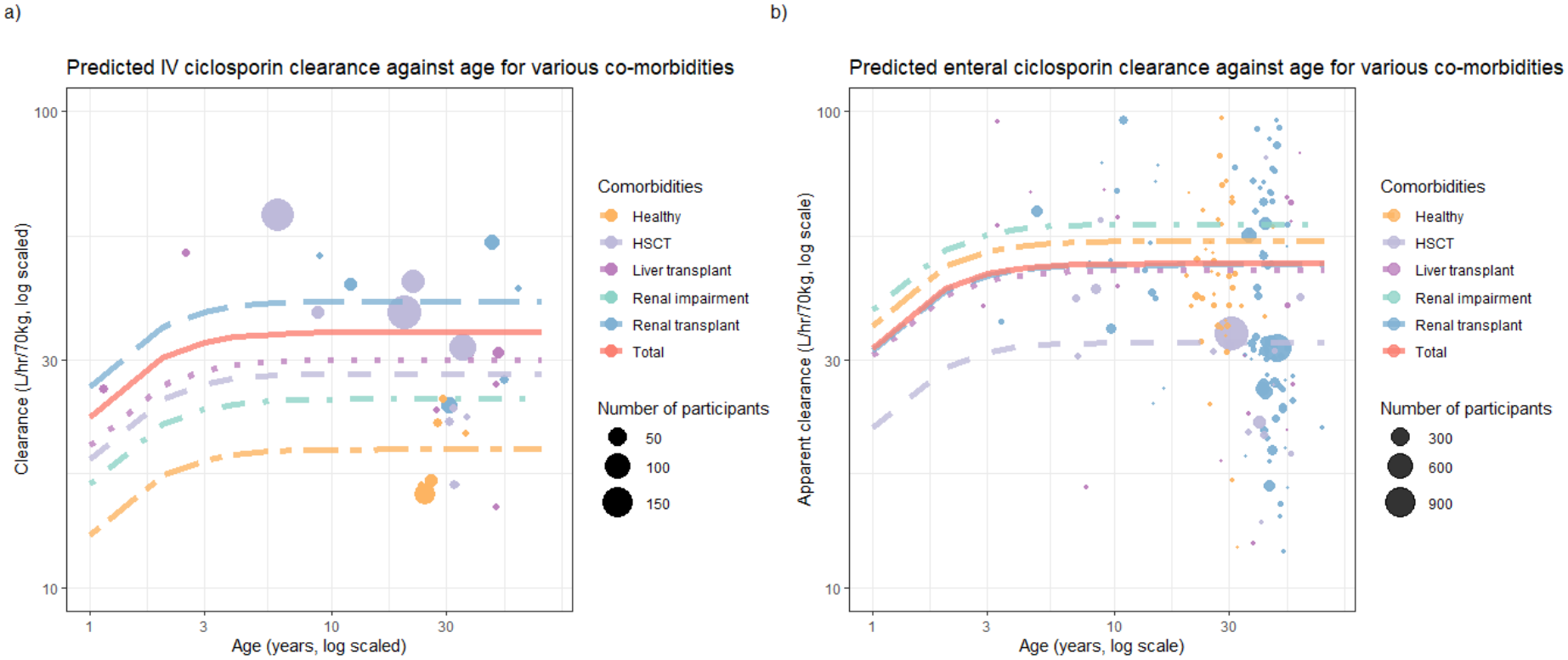


Figure 2.5: Simulated ciclosporin clearance against age for various co-morbidities.

2.4.2 Itraconazole

To investigate whether an effect of organ maturation or deterioration could be identified for itraconazole, pharmacokinetic parameters were extracted from the literature and analysed in relation to age. Table 2.3 summarises the characteristics of the 48 included studies. Data were drawn from studies evaluating intravenous, liquid, and capsule formulations. Most publications reported data from healthy young adults, with median age of 28 years (range 1 to 65 years). The capsule formulation was used predominantly in healthy adult cohorts, with 76% of subjects falling into this category and no paediatric data available in that subgroup. In contrast, the intravenous and liquid formulations were employed in more clinically diverse populations, including paediatric and critically ill patients.

To visualise age-related trends in clearance, a scatter plot of body weight–normalised clearance (scaled to 70 kg) versus age was generated (Figure 2.6). This plot provides an overview of the data and forms the basis for exploring whether a developmental trend in clearance, potentially reflecting CYP3A4 maturation, can be observed across the age spectrum.

The grouping of data based on formulations allowed for a more detailed inspection of clearance values across age groups. Figure 2.7 presents the clearance (scaled to 70 kg) and age range across the included studies, stratified by formulation. While a limited number of studies described children under two years of age for the liquid and intravenous preparations, all studies involving capsule formulations were restricted to young adult populations. The estimation of the itraconazole clearance for each preparation was performed using Equation 2.3. The lack of data in children under two years of age did not support the estimation of a maturation function for itraconazole. Similar to midazolam, itraconazole is predominantly metabolised by the CYP3A4 enzyme [155]. Therefore, the reported maturation half-time of 73.6 PMA weeks and the Hill_1 coefficient of 3 was incorporated *a priori* into Equation 3.2 again and thereby enabled the estimation of the itraconazole clearance using Equation 2.8.

Table 2.3: Data characteristics extracted from 48 itraconazole publications

	Intravenous	Capsule	Liquid
No of data points	13	38	20
Healthy volunteers	9 (69%, 9/13)	29 (76%, 29/38)	8 (40%, 8/20)
Median age (years) (range)	23 (1 - 65)	29 (21 - 38)	30 (1 - 65)
Median weight (kg) (range)	65 (9 - 83)	65 (45 - 81)	70 (9 - 83)
Median dose per weight (mg/kg)	2.5 (1.4 - 4.24)	2.6 (1.27 - 4.44)	2.55 (1.25 - 5.4)

Each formulation (intravenous, oral liquid, and capsule) was analysed separately. However, the lack of data in older adults precluded the reliable estimation of organ-function–related clearance decline, and attempts to fit a model with an age-related decline component failed to converge to a global minimum. Consequently, Equation 2.9, which excludes the decline term, was used for clearance estimation for all three formulations.

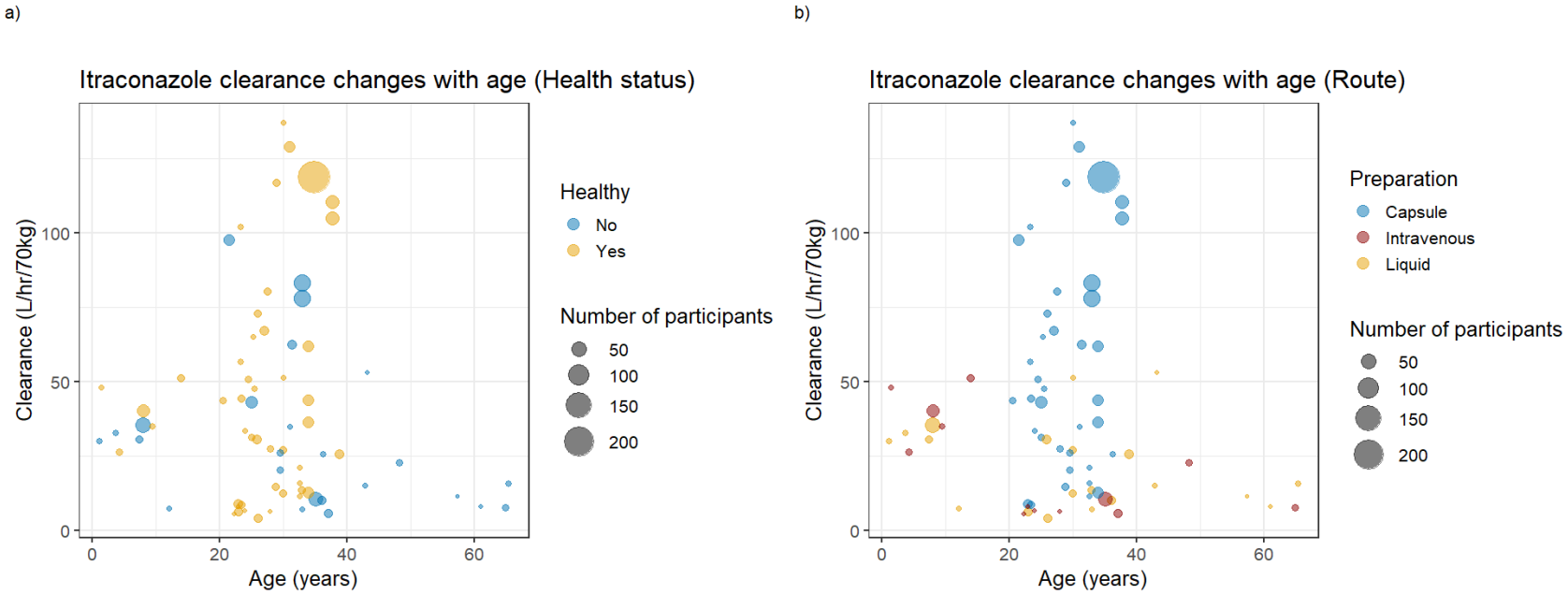


Figure 2.6: Scatter plot of clearance, standardised to 70kg, of all itraconazole publications analysed against age according to a) health status and b) formulations. The size of each data point represents the number of participants in the study.

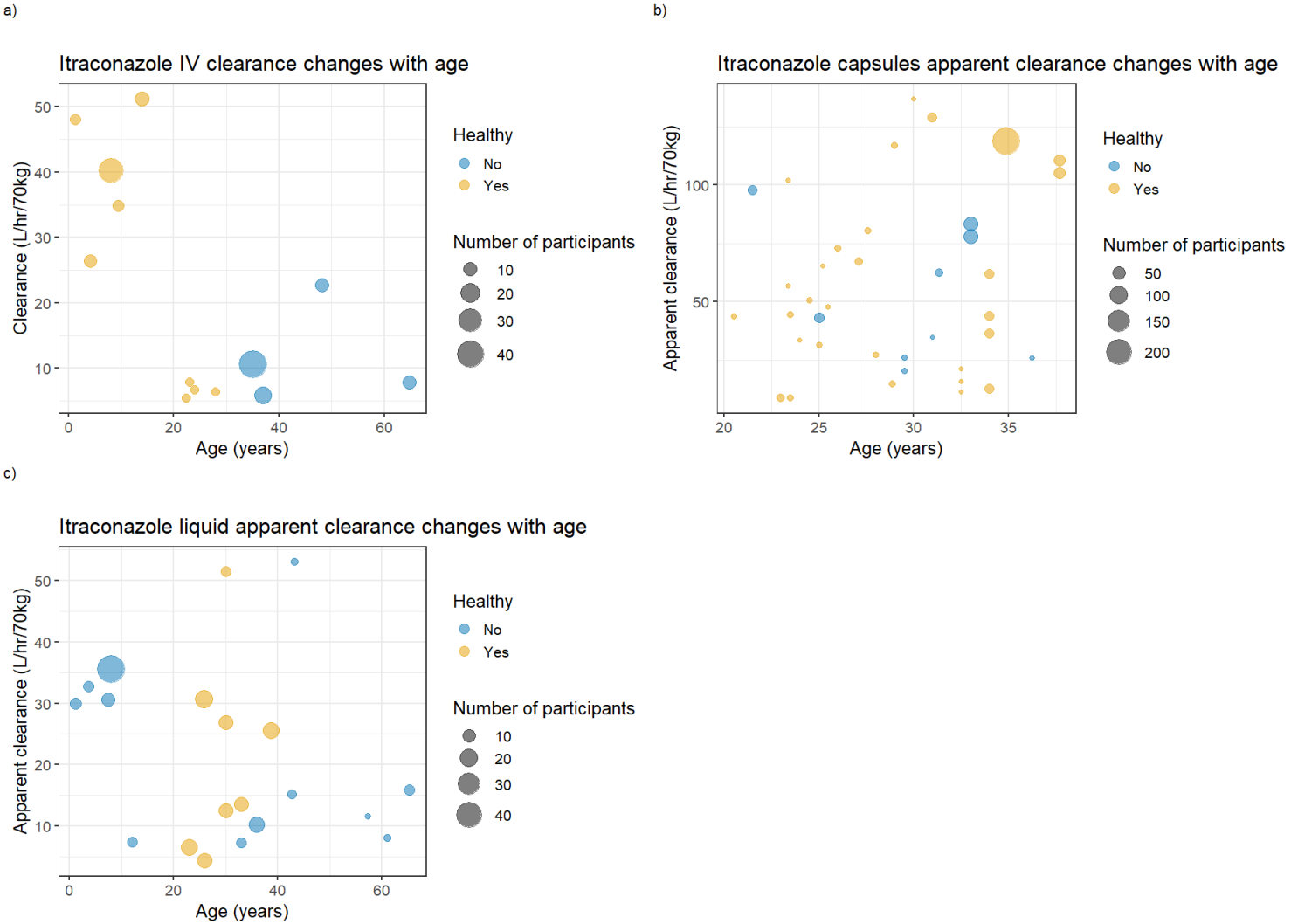


Figure 2.7: Scatter plot of clearance, standardised to 70kg, of itraconazole publications by formulations

Table 2.4: Estimated itraconazole clearance for various populations allometrically scaled to 70kg. CL_{IV} = predicted intravenous itraconazole clearance, CL/F = predicted apparent itraconazole clearance, CI = confidence interval

Preparation	Median age in years (range)	Method 1			Method 2	
		Predicted CL_{IV} (L/h/70kg) [95% CI]	Predicted CL/F (L/h/70kg) [95% CI]	Bio-availability (%)	Predicted CL_{IV} (L/h/70kg) [95% CI]	Bioavailability (%) [95% CI]
Capsule	29 (20.5 - 37.7)	-	29.3 [20.5 - 37.7]	37	-	37 [8, 66]
Liquid	30 (1 - 65)	-	21.6 [14.5, 8.6]	97	-	97 [2, 100]
Intravenous injection	23 (1 - 65)	20.9 [9.9, 32]	-	-	20.9 [4.7, 37.2]	-

Parameter estimates from the final models are presented in Table 2.4, and the predicted clearance versus age is shown in Figure 2.8. The collated literature data spanned a broad age range, from one year to 75 years, but insufficient data were available in neonates, infants, and elderly adults to robustly support estimation of both enzyme maturation and age-related decline.

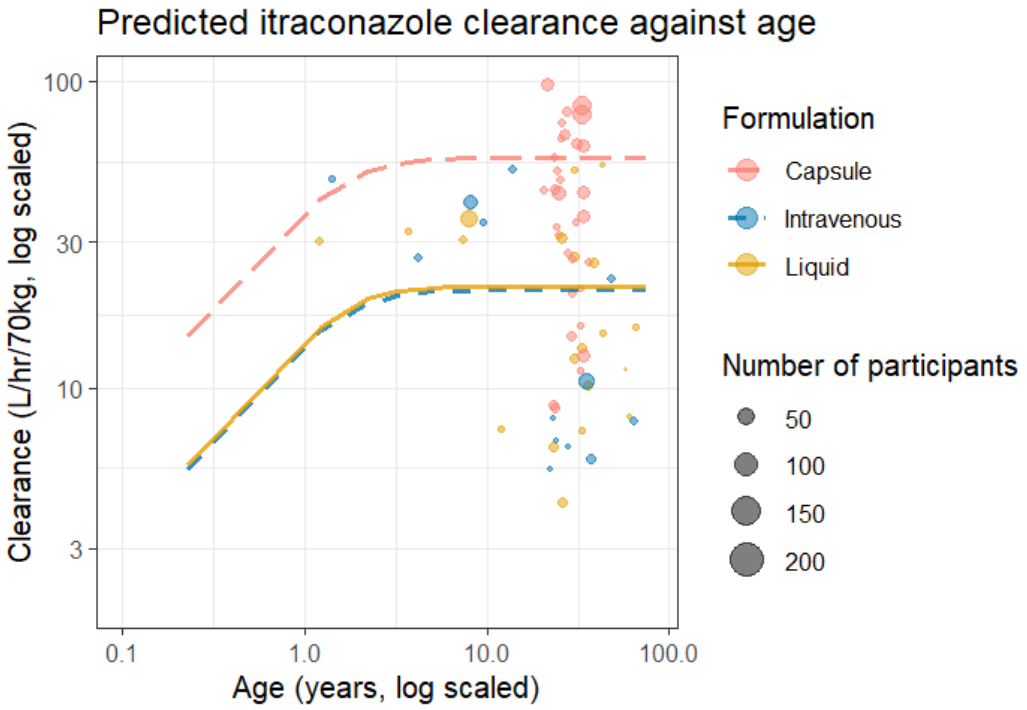


Figure 2.8: Simulated itraconazole clearance by age. Each colour represents a different preparation of the datapoint

2.4.3 Posaconazole

The characteristics of the 35 included publications are summarised in Table 2.5. The age distribution and clearance values scaled to 70 kg are displayed in Figure 2.9, revealing limited data in paediatric ($<$18 years) and elderly ($>$ 60 years) populations. The median age across all studies was 44 years, with a range of 6 to 71 years. As the oral suspension was the first formulation to be licensed, it accounts for the largest share of available data, followed by the modified-release tablets and intravenous injection.

Table 2.5: Data characteristics extracted from 35 posaconazole publications.

	Intravenous	Liquid	Tablet
No of data points	11	22	19
Healthy volunteers	3 (27%, 3/11)	7 (32%, 7/22)	11 (58%, 11/19)
Median age (years) (range)	46 (25-52)	46 (7 - 71)	36 (6 - 57)
Median weight (kg) (range)	71 (60 - 120)	78 (20 - 123)	75 (18 - 86)
Median dose per weight (mg/kg)	3.21 (1.66 - 5.6)	4.85 (2.47 - 11.02)	3.89 (2.59 - 4.28)

When stratified by formulation (Figure 2.10), the liquid formulation exhibited the greatest variability in reported clearance, likely reflecting heterogeneity in patient populations, many of whom had underlying comorbidities. Intravenous posaconazole demonstrates saturable clearance at higher doses, exhibiting linear pharmacokinetics at lower exposures and non-linearity as doses increase [156]. A wide range of doses per kg was observed across all formulations, with the greatest variability seen in tablet studies (Figure 2.9c).

Initial analysis of each formulation was conducted using Equation 2.3. Due to the lack of data in neonates and infants, a data-driven estimation of a maturation function was not feasible. Unlike itraconazole, posaconazole is not significantly metabolised via the CYP450 system, but rather through Phase II glucuronidation pathways, predominantly via UGT enzymes [157]. Given this metabolic pathway, a previously published morphine maturation function (metabolised by UGT2B7) was

used to inform the model. The model published by Anand *et al.* (2008) [158], which used two cohorts of ventilated and post-operative neonates, was adopted. Their reported PMA_{50} of 54.2 weeks and $Hill_1$ coefficient of 3.92 were incorporated *a priori* into Equation 2.8. Due to the absence of sufficient data in older adults, age-related organ function decline could not be estimated reliably. Therefore, Equation 2.10, which includes fixed maturation but no decline term, was employed to estimate bioavailability and clearance for the liquid and tablet formulations. Parameter estimates are shown in Table 2.6. The predicted clearance versus age is shown in Figure 2.11.

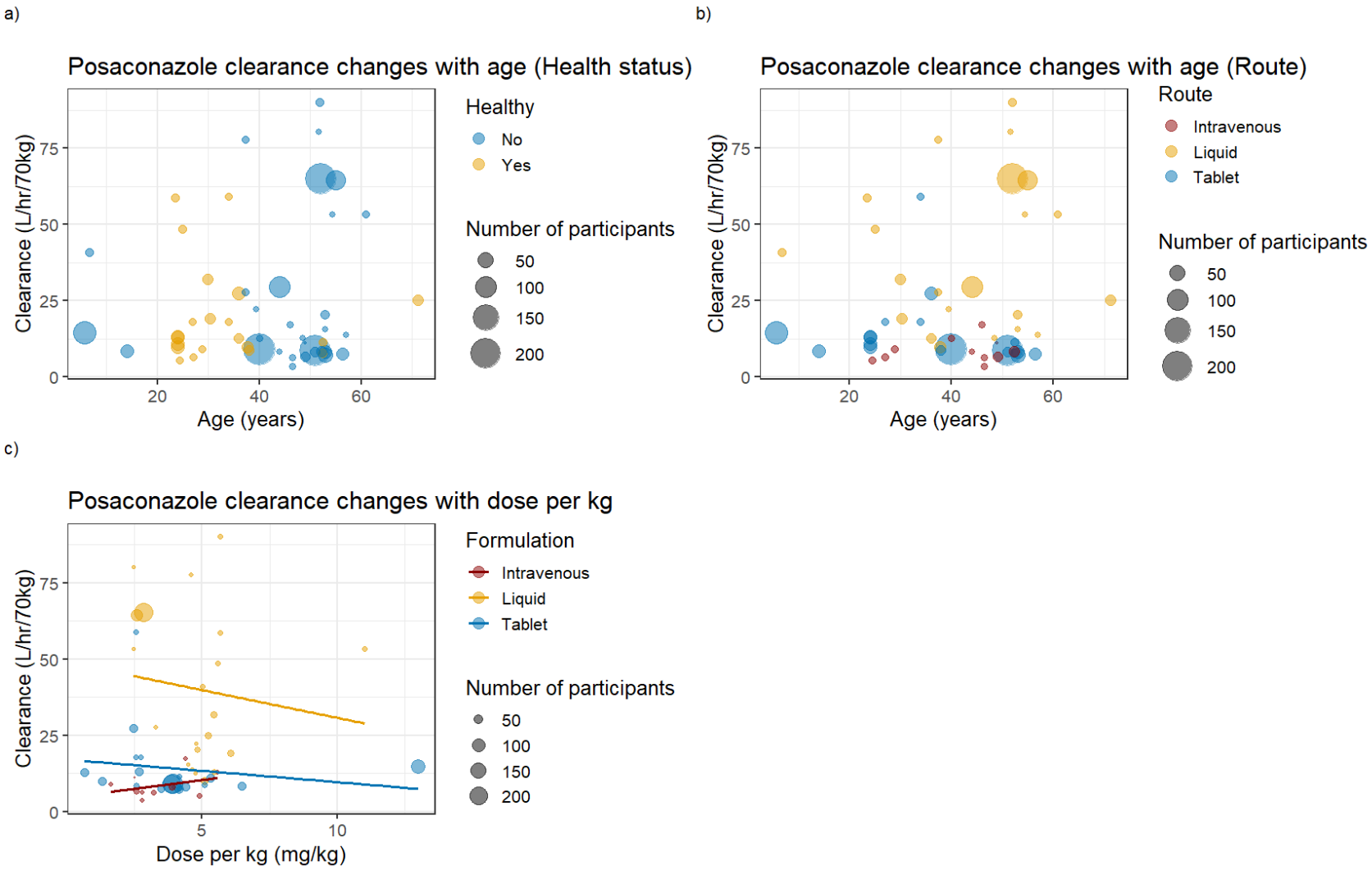


Figure 2.9: Scatter plot of posaconazole clearance (standardised to 70 kg) versus age across all publications analysed: a) by health status, b) by route of administration, and c) by dose per kg. Point size represents the number of study participants.

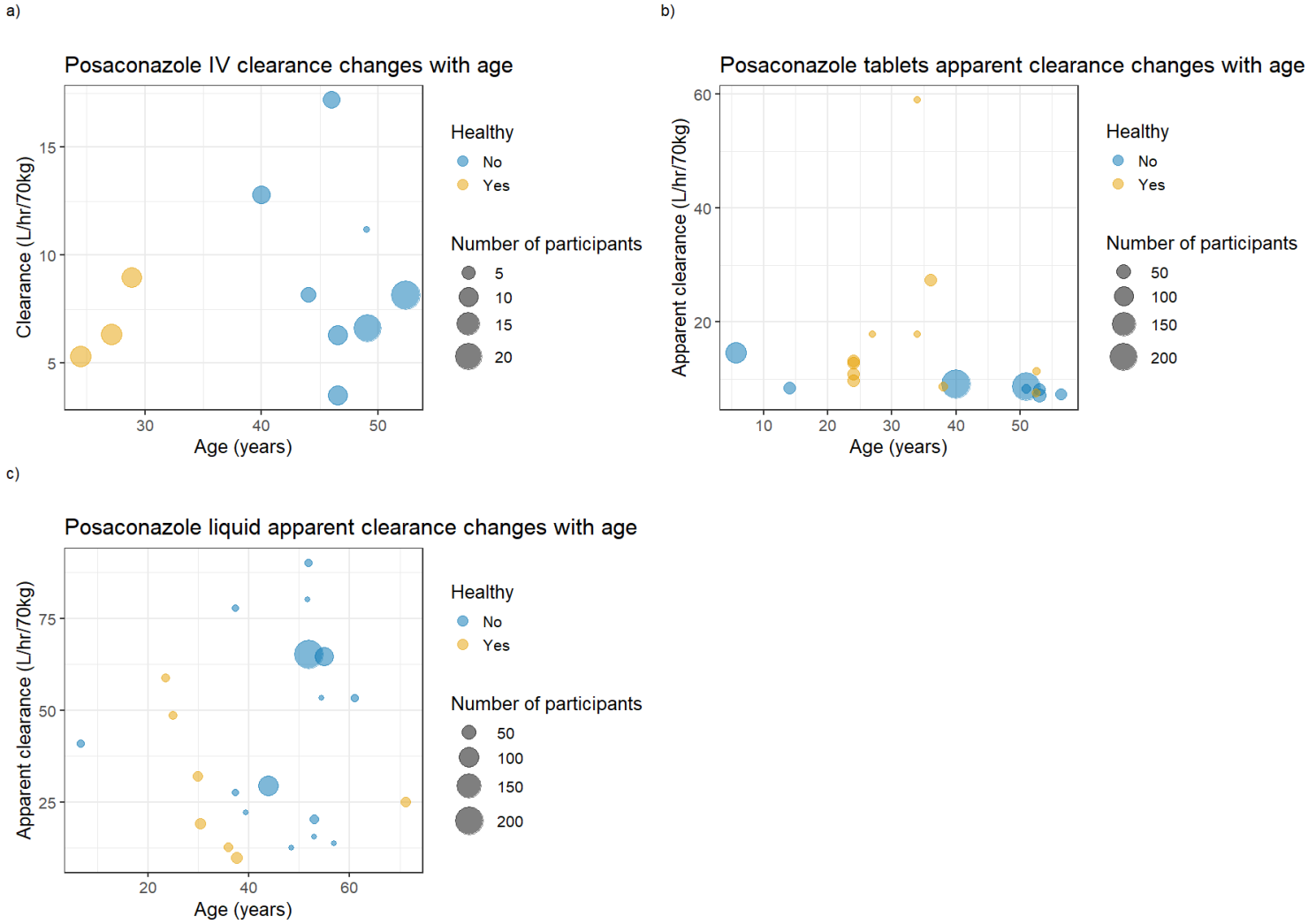


Figure 2.10: Scatter plot of posaconazole clearance (standardised to 70 kg) versus age, grouped by formulation. Point size represents the number of study participants.

Table 2.6: Estimated posaconazole clearance for various populations allometrically scaled to 70 kg. CL_{IV} = predicted intravenous posaconazole clearance, CL/F = predicted apparent posaconazole clearance, CI = confidence interval

Preparation	Median age in years (range)	Method 1			Method 2	
		Predicted CL_{IV} (L/h/70kg) [95% CI]	Predicted CL/F (L/h/70kg) [95% CI]	Bio-availability (%)	Predicted CL_{IV} (L/h/70kg) [95% CI]	Bioavailability (%) [95% CI]
Modified release tablets	36 (6 - 57)	-	14.1 [8.4, 19.8]	61	-	61 [19, 100]
Liquid	46 (7 - 71)	-	39.6 [28.6, 50.6]	22	-	22 [0, 58]
Intravenous injection	46 (6 - 71)	8.6 [6, 11.2]	-		8.6 [5.0, 38.2]	-

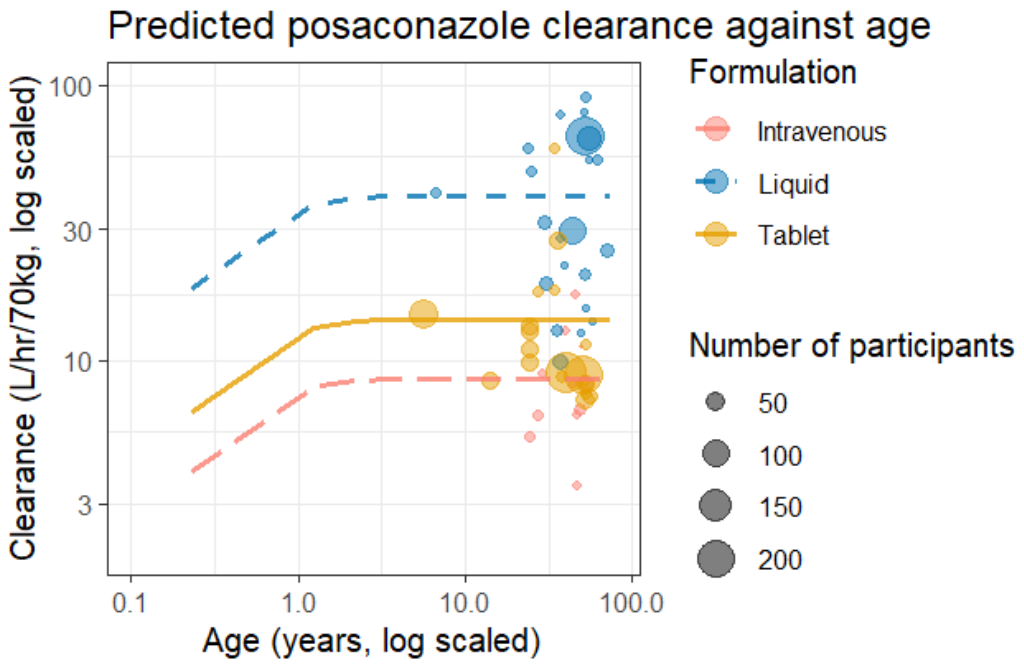


Figure 2.11: Predicted posaconazole clearance versus age, with colours indicating formulation type.

2.4.4 Voriconazole

Voriconazole was the most frequently reported azole antifungal in the literature, with 72 publications included, spanning an age range of 2 to 72 years (median age = 29 years). The characteristics of the included studies are summarised in Table 2.7, and the distribution of clearance values (allometrically scaled to 70 kg) against age is shown in Figure 2.12. Data for patients under 20 and over 40 years were largely drawn from real-world clinical cohorts with existing comorbidities, whereas studies of healthy adults primarily represented the 20–40 year age group. Clearance was previously reported to be dose-dependent [148]. However, as shown in Figure 2.12d, the current dataset did not exhibit a trend of decreasing clearance with increasing dose, contrary to expectations for saturable metabolism.

Table 2.7: Data characteristics extracted from 72 voriconazole publications.

	Intravenous	Oral
No of data points	65	74
Healthy volunteers	14 (22%, 14/65)	34 (46%, 34/74)
Median age (years) (range)	32 (3 - 72)	28 (2 - 67)
Median weight (kg) (range)	65 (1 - 134)	72 (9 - 133)
Median dose per body weight (mg/kg)	4 (1.24 - 10)	3.25 (1.5 -10.6)

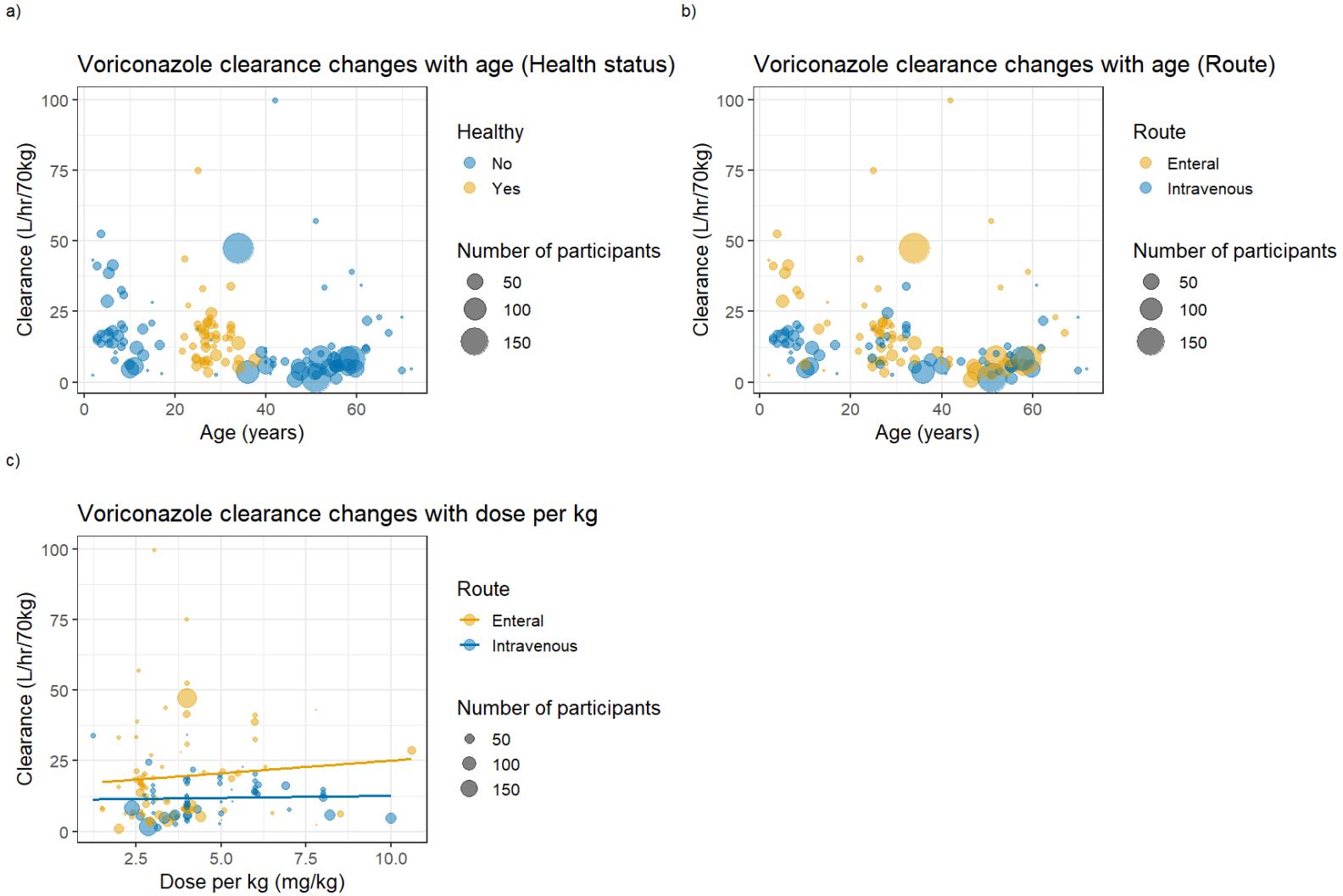


Figure 2.12: Scatter plot of voriconazole clearance (standardised to 70 kg) versus age across all publications analysed: a) by health status, b) by formulation, and c) by dose per kg. Point size represents the number of study participants.

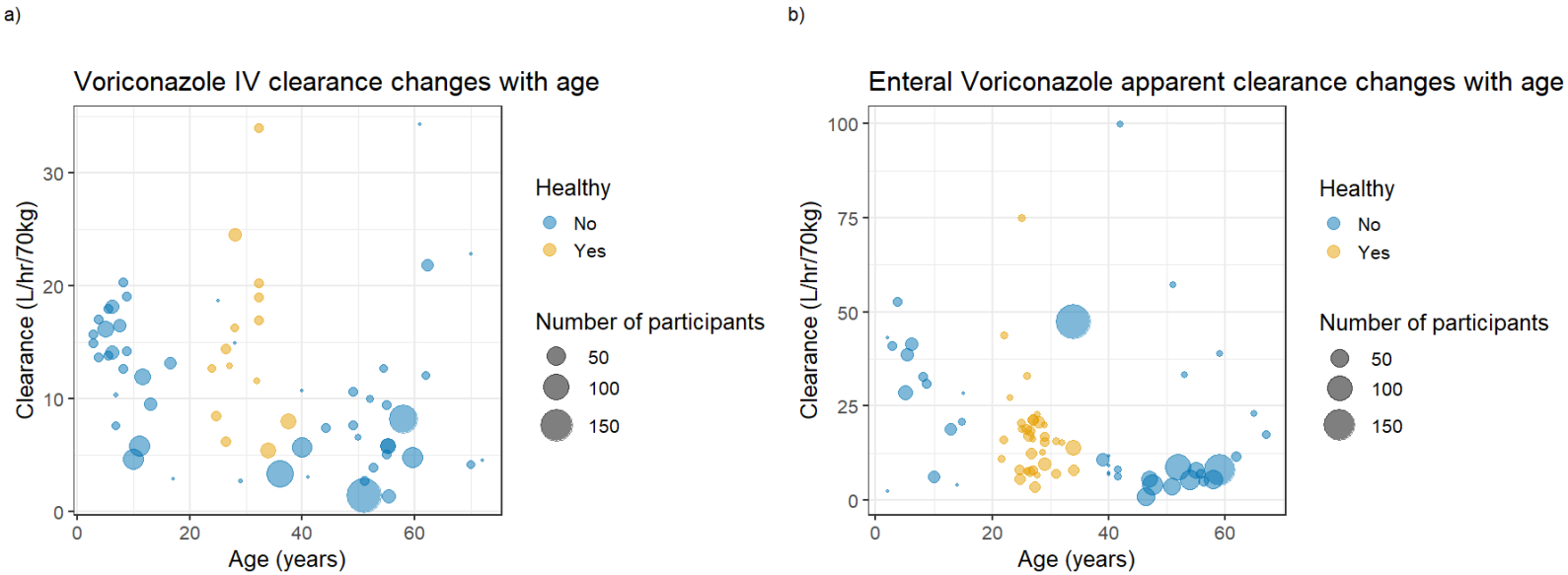


Figure 2.13: Scatter plot of clearance, standardised to 70kg, of voriconazole publications by formulations

Neonates are known to express only 20–25% of adult CYP2C19 levels, increasing to 40–50% by one year of age [159]. However, the dataset included no pharmacokinetic data in children under two years, precluding direct estimation of a maturation function. With CYP2C19 as the main metabolic enzyme, a CYP2C19 ontogeny model based on *in vitro* omeprazole metabolism data was used to inform the developmental component of clearance. Upreti *et al.* (2016) [160] described this maturation as a sigmoidal function of age in years:

$$Fraction_{adult} = \left(\frac{Adult_{Max} - F_{Birth}}{Age_{50}^{n} + Age^{n}}\right) \times Age^{n} + F_{Birth} \tag{2.11}$$

where Adult_{Max} is the maximal response from adult samples, F_{Birth} is the fraction of adult response at birth, Age_{50} is the age at which half-maximal adult response is obtained, Age is the age of the subject at the time of sample collection in years, and n is an exponential factor. The omeprazole in vitro data was found to be Adult_{Max} = 1.1, F_{Birth} = 0.11, Age_{50} = 0.21 and n = 1.5 which allows the maturation of voriconazole to be estimated using this factor.

Incorporating the bioavailability into the equation, the adult clearance (CL_{adult}) and bioavailability of voriconazole can be estimated as a fraction of adult clearance using equation 2.12

$$VoriMF = \left(\left(\frac{1}{f_{enteral}} \times F_{enteral}\right) + 1 \times F_{IV}\right) \times Fraction_{adult} \times CL_{adult} \tag{2.12}$$

where $\text{f}_{enteral}$ denotes the bioavailability of enteral formulation, $\text{F}_{enteral}$ and F_{IV} are binary indicators for formulation route, and Fraction_{adult} is the age-based maturation factor derived from the omeprazole model. Estimated parameters are shown in Table 2.8, and predicted clearance across the age range is visualised in Figure 2.14.

Table 2.8: Estimated voriconazole clearance for various population allometrically scaled to 70kg. CL_{IV} = predicted intravenous posaconazole clearance, CL/F = predicted apparent posaconazole clearance, CI = confidence interval

Preparation	Median age in years (range)	Method 1			Method 2	
		Predicted CL_{IV} (L/h/70kg) [95% CI]	Predicted CL/F (L/h/70kg) [95% CI]	Bio-availability (%)	Predicted CL_{IV} (L/h/70kg) [95% CI]	Bioavailability (%) [95% CI]
Modified release tablets	28 (2- 67)	-	17.6 [15.8, 19.3]	59	-	59 [46, 74]
Intravenous injection	32 (3 - 72)	10.3 [9.6, 11.0]	-	-	10.1 [8.1, 12.1]	-

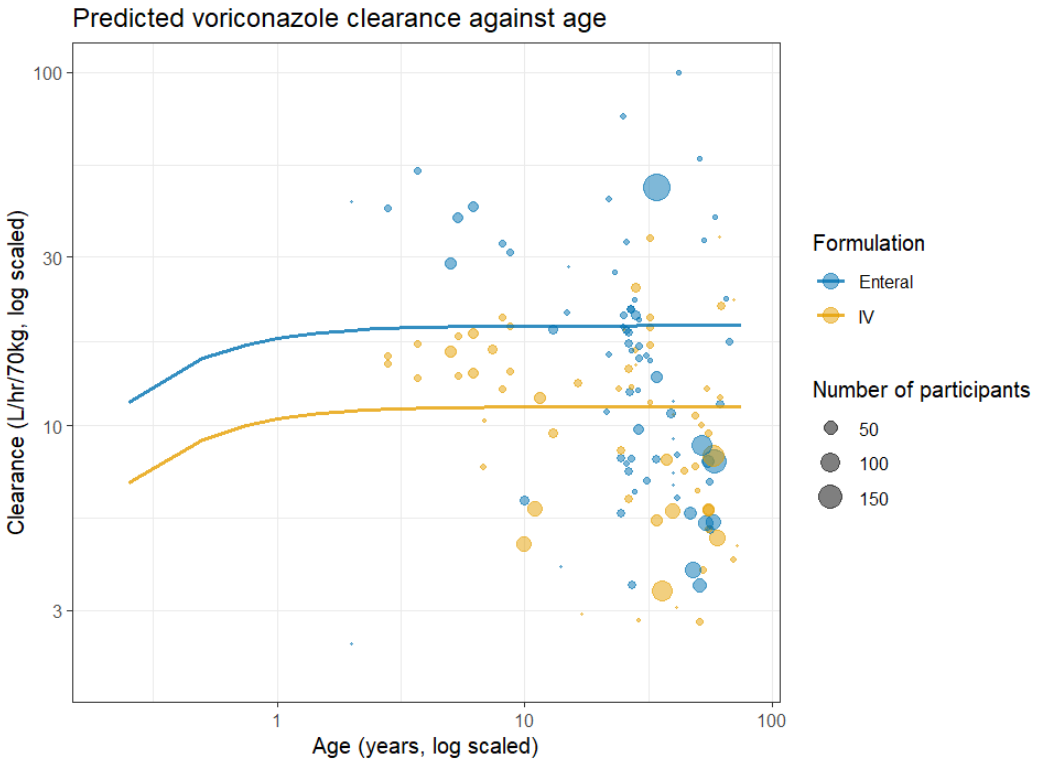


Figure 2.14: Scatter plot of clearance, standardised to 70kg, of voriconazole publications by formulations

2.5 Discussion

This chapter aimed to synthesise and analyse published pharmacokinetic data for ciclosporin and three azole antifungals, itraconazole, posaconazole, and voriconazole, to estimate age-related changes in clearance and bioavailability. Despite the size of this dataset and the broad age ranges represented, important gaps remained: studies in children under two years of age were too few to permit empirical estimation of enzyme maturation, and data in adults over 65 years were insufficient to characterise age-related decline in clearance. Most pharmacokinetic data in the 20 – 40 year range originated from healthy volunteer studies, whereas data for younger and older patients largely came from real-world clinical cohorts with comorbidities.

Despite these limitations, the estimated population clearances for ciclosporin, itraconazole, posaconazole, and voriconazole were broadly consistent with published values. Although two approaches were used to estimate bioavailability, the resulting estimates were very similar across drugs and subgroups. This convergence is reassuring, as it suggests internal consistency between the direct AUC-based method and the model-based approach. Nonetheless, both methods ultimately depend on the same underlying oral and intravenous clearance data and are therefore not fully independent. The primary distinction is that Method 1 relies on directly reported AUC values, while Method 2 allows estimation of bioavailability alongside other pharmacokinetic parameters in a single framework. In practice, the lack of robust intravenous data for most drugs introduced significant uncertainty into the estimation of absolute clearance and bioavailability. This challenge was compounded by heterogeneity in study designs, populations, doses, and sampling strategies, which limited the ability to disentangle clearance from bioavailability in non-intravenous studies.

Covariates known to influence pharmacokinetics, such as comorbidities, food intake, sex, concurrent medications, and pharmacogenetics, were frequently unreported in the publications reviewed, and therefore could not be incorporated into the modelling process. This is particularly relevant for ciclosporin, where protein

binding strongly influences disposition; for posaconazole, where oral absorption is highly variable and dependent on gastrointestinal conditions; and for voriconazole, where CYP2C19 genotype exerts a major effect on clearance.

To address the absence of paediatric data, maturation models based on ontogeny of relevant metabolic pathways (e.g., CYP3A4 for itraconazole, UGT for posaconazole, and CYP2C19 for voriconazole) were incorporated *a priori* from the literature. While this approach provided a reasonable approximation, it introduced assumptions that may not fully reflect the pharmacokinetics of the specific compounds studied. These findings therefore highlight a broader limitation in the field: the reliance on extrapolation from other drugs due to a lack of direct evidence in children. Dedicated pharmacokinetic studies in paediatric populations, particularly in neonates and infants, remain essential to support rational dose selection, minimise variability in drug exposure, and improve treatment outcomes. Greater inclusion of intravenous reference arms and consistent reporting of relevant covariates would also enhance the interpretability of pharmacokinetic data in both children and adults.

2.5.1 Ciclosporin

Ontogeny of CYP3A4 is clinically important, and ciclosporin clearance has been shown to be higher in children than in adults, consistent with age-dependent changes in drug metabolism [161]. Nevertheless, there is a marked lack of pharmacokinetic data in children under two years of age, preventing the development of a robust, data-driven maturation function. At the other end of the age spectrum, studies in patients over 70 years are also scarce, limiting evaluation of potential age-related decline in clearance.

Ciclosporin is 41–58% bound to erythrocytes [137], and changes in haematocrit with age or disease may also affect clearance. However, insufficient data were available to quantify this effect. Midazolam serves as a useful reference drug due to its similar metabolic pathway and high plasma protein binding [80]. Its well-characterised clearance and maturation profile across age groups (including

neonates and infants) [80, 121] make it a suitable CYP3A probe [162]. Midazolam clearance is significantly reduced in neonates and preterm infants [163, 164] until approximately two years of age [165]. Although midazolam served as a reasonable proxy for estimating the maturation function, there are important pharmacokinetic differences that must be acknowledged. Midazolam is typically administered intravenously and therefore bypasses first-pass metabolism, whereas in our systematic review ciclosporin was predominantly given orally, meaning absorption and gut metabolism play a significant role in its pharmacokinetics. Given that intestinal CYP3A4 plays a substantial role in first-pass metabolism [57], and the high proportion of enteral ciclosporin data in this review, the use of an intravenous midazolam-based maturation function may not fully reflect its ontogeny. The midazolam model primarily characterises hepatic CYP3A4 development from IV data, whereas ciclosporin undergoes extensive intestinal metabolism in addition to hepatic clearance. This limitation highlights the need for a ciclosporin-specific ontogeny function that accounts for both hepatic and intestinal CYP3A development.

To further explore the observed variability in ciclosporin clearance, subgroup analysis was performed based on the five major disease categories: nephrotic syndrome, healthy subjects, HSCT, liver transplant, and renal transplant. This approach aimed to account for disease-related differences in physiology and drug handling.

In this review, the estimated oral clearance was 47.9 L/h/70 kg, intravenous clearance was 34.4 L/h/70 kg, and the pooled population clearance was 31.3 L/h/70 kg. These values were consistent with published data in healthy adult volunteers [166], but the subgroup analysis revealed notable differences across disease cohorts. When considering bioavailability, the pooled estimate across all populations was 72% (Method 1), notably higher than the manufacturer-reported range of 20–50% [137]. Similarly elevated values were observed in liver transplant (64%), renal transplant (84%), and HSCT (86%) populations. Even in healthy volunteers, the estimated bioavailability was 37%, which falls within the expected range but is at the upper end. These findings may reflect limitations in the source data, model assumptions,

or variability in absorption influenced by formulation differences or clinical setting. Notably, Method 2 (non-linear estimation) produced wide confidence intervals and in some cases implausible values (e.g. 0–105% in liver transplant), highlighting uncertainty in these estimates.

In renal impairment patients, ciclosporin clearance was estimated to be approximately one-third lower than the overall population. This finding aligns with the SPC-reported reduction in clearance in patients with impaired renal function and may be attributed to altered protein binding, reduced renal function, or changes in haematocrit. However, the specific mechanism remains unclear. Renal transplant patients, on the other hand, showed higher clearance and higher estimated bioavailability. This may reflect more stable gastrointestinal absorption under clinical monitoring, restoration of renal perfusion post-transplant, or differences in co-administered medications. The improved clearance could also reflect the influence of body composition or haematocrit normalisation following transplant.

In HSCT and liver transplant patients, ciclosporin clearance and bioavailability were estimated to be lower than in the total population. This pattern is plausible given the hepatic metabolism of ciclosporin and the likely presence of impaired liver function, altered gut motility, or reduced intestinal perfusion in these populations. The similarity in pharmacokinetic profiles between the HSCT and liver transplant groups suggests overlapping pathophysiological mechanisms, including inflammation, malabsorption, and enzyme inhibition. In addition, unique features of the HSCT population may further reduce absorption and metabolism, such as mucositis (either active or healing), gastrointestinal GVHD, and chronic viral enteropathy associated with prolonged immunosuppression—factors not typically present in liver transplant patients.

Surprisingly, healthy subjects demonstrated the lowest estimated clearance, despite having no known disease-related factors that would be expected to impair drug metabolism or excretion. This may reflect the limited number of healthy data points in the dataset (only 20%), which could reduce the stability of the pa-

rameter estimates for this subgroup. Additionally, most healthy volunteer studies involved single-dose administration, which may underestimate clearance compared to steady-state conditions. Single-dose studies do not account for potential time-dependent changes in metabolism or distribution, and may be influenced by early-phase disposition or variability in absorption, particularly when using non-compartmental analysis. In contrast, clearance in disease populations may be elevated due to physiological or compensatory changes, such as reduced protein binding, altered hepatic blood flow, or enzyme induction. These differences highlight the complexity of comparing pharmacokinetic parameters across diverse clinical populations.

Several findings from individual studies were consistent with the subgroup results generated in this review, providing reassurance that the pooled NLS regression estimates reflect published observations. For instance, Eljebari *et al.* (2012) reported a clearance of 28.1 L/h/70 kg in HSCT patients (mean age 28.8 years, range 7.5–50), which is closely aligned with the estimates obtained here [167]. Similarly, Irtan *et al.* (2007) described a higher apparent clearance of 38.7 L/h/70 kg in paediatric renal transplant recipients (median age 9.5 years), reflecting the increased metabolic activity typical of children [168]. In adult renal transplant cohorts, Rousseau *et al.* (2004) [169] and Yoshida *et al.* (2001) [170] observed clearance values of 26.9 and 32.4 L/h/70 kg, respectively, which fall within the range derived in this analysis. Together, these consistencies illustrate how patient demographics, disease status, and formulation influence ciclosporin pharmacokinetics, and demonstrate that the pooled regression approach used here captures clinically plausible values across populations.

Ciclosporin's extensive protein binding and changes in haematocrit due to anaemia, renal disease, or inflammation may also affect clearance, though insufficient data were available to explore this further. Furthermore, five different analytical methods were used across the studies, many of which are not interchangeable [171–173], introducing potential variability in reported concentrations. Although several

covariates were identified as potential contributors to ciclosporin variability, clearance estimates across diverse studies and populations were broadly consistent. This raises the possibility that some covariates exert limited influence at the population level. However, they are still likely to be clinically important in specific subgroups, particularly in children undergoing HSCT where absorption and metabolism may be highly variable. The large number of pharmacokinetic studies and ongoing efforts to refine dosing strategies highlight persistent uncertainty about optimal dosing, especially in solid organ transplant and HSCT populations, where more individualised approaches are likely to be required.

Overall, this review demonstrates that ciclosporin pharmacokinetics are influenced by age, formulation and comorbidity. However, the published literature does not adequately support the estimation of a maturation function in neonates or infants, nor the quantification of clearance decline in older adults. This gap is particularly significant in high-risk populations such as children undergoing HSCT, where accurate dose prediction is critical to balancing efficacy and toxicity.

To improve pharmacokinetic understanding in these populations, prospective studies are needed that include rich sampling in neonates, infants, and elderly adults, and apply harmonised analytical methods. Longitudinal studies that track enzyme activity, body composition, haematocrit, and ciclosporin exposure across development would allow for more accurate modelling of ontogeny and organ function decline. Until such data are available, the use of proxy maturation function, while imperfect, remains a pragmatic approach.

2.5.2 Itraconazole

While ciclosporin illustrated the challenges of high protein binding and disease-related variability, itraconazole presents a contrasting case where saturable metabolism and formulation differences are the dominant factors. Itraconazole undergoes saturable hepatic metabolism [174], with bioavailability increasing with dose. Repeated dosing or higher doses may lead to reduced apparent clearance. In this study, the median mg/kg dose was comparable across formulations, limiting

dose-dependent bias and permitting the assumption of similar bioavailability within formulation groups.

The estimated clearance for intravenous itraconazole was 20.9 L/h/70 kg, consistent with previously reported values [175]. The estimated bioavailability for the oral liquid was 97%, higher than expected, whereas capsule bioavailability estimates aligned with published values. The reported absolute bioavailability of the oral liquid under fed conditions is approximately 55%, increasing by around 30% when administered while fasting [175]. In contrast, capsule bioavailability is reported to be 30–33% lower than the oral liquid [153]. The elevated estimate for liquid bioavailability in this review may reflect limitations in the available intravenous data or variability in study design. Additionally, most intravenous and capsule data were derived from healthy adult volunteers receiving single or limited doses, thereby limiting the ability to detect saturation effects in hepatic metabolism.

In conclusion, the current body of published pharmacokinetic data for itraconazole does not support independent estimation of enzyme maturation or age-related organ function decline. The lack of data in neonates and infants is particularly limiting, and the reliance on sparse intravenous data further complicates the estimation of absolute bioavailability. These findings underscore the need for dedicated pharmacokinetic studies in younger paediatric populations and in clinical contexts where itraconazole dosing remains empirically guided.

2.5.3 Posaconazole

The estimated clearance for intravenous posaconazole was 8.6 L/h/70 kg, comparable to the reported mean value of 7.3 L/h following administration of 300 mg IV [175]. Bioavailability estimates derived from Method 1 suggest that liquid formulations exhibit a lower bioavailability (22%) compared to modified-release tablets (61%). Method 2 confirmed similar trends but with wide confidence intervals, reflecting uncertainty due to sparse intravenous and tablet data. The reported absolute bioavailability of delayed-release tablets under fasting conditions is approximately 54%. This is consistent with a recent study by Kane *et al.* (2023) [176] evaluat-

ing bioavailability in paediatric patients reported values of 66% for tablets and a variable range of 3.8 - 32.2% for liquids depending on dose and feeding status.

Overall, posaconazole pharmacokinetics remain highly formulation-dependent, with the greatest inter-individual variability observed in the oral suspension. While the use of a morphine-derived UGT maturation function provided a proxy for scaling paediatric clearance, the absence of data in neonates and elderly adults limits the interpretation of age effects. The estimated bioavailability values were broadly consistent with published reports but were subject to uncertainty due to underlying heterogeneity and sparse intravenous reference data. These findings highlight the continued need for paediatric-specific pharmacokinetic studies for posaconazole, especially in populations with altered gastrointestinal physiology or polypharmacy.

2.5.4 Voriconazole

Voriconazole differs further from the other azoles in that CYP2C19 metabolism and pharmacogenetic variability are the dominant determinants of clearance and exposure. The estimated clearance for intravenous voriconazole (10.3 L/h/70 kg) aligns closely with reported literature values. The estimated bioavailability of enteral formulations was 59%, lower than the manufacturer's stated value of 96% [140]. However, published studies have demonstrated reduced bioavailability in real-world settings: Walsh *et al.* (2010) [177] reported 65% in immunocompromised children, and Veringa *et al.* (2017) [178] found 83% in hospitalised adults. As 65% of the data in this analysis were from patients with medical comorbidities, the observed reduction in bioavailability is likely driven by altered absorption in this population. These findings emphasise that voriconazole pharmacokinetics are particularly sensitive to genetic and clinical covariates such as CYP2C19 polymorphisms, comorbidities, and gastrointestinal function. The absence of data in children under two years of age is a significant gap, especially given the developmental trajectory of CYP2C19 expression.

Taken together, the findings across ciclosporin and the azole antifungals highlight both the value and the limitations of the existing pharmacokinetic literature. While

each drug showed distinctive pharmacokinetic features: protein binding and comorbidity effects for ciclosporin, saturable metabolism and formulation differences for itraconazole, strong formulation dependence for posaconazole, and pharmacogenetic sensitivity for voriconazole, the same challenges recurred across compounds. In particular, the absence of robust data in neonates and infants, the paucity of evidence in older adults, and the limited use of intravenous reference arms consistently restricted the ability to separate clearance from bioavailability.

These observations underscore the need for prospective pharmacokinetic studies across the full age spectrum, with harmonised analytical approaches and systematic reporting of covariates such as food intake, concomitant medications, and pharmacogenetic status. Such efforts would allow for more accurate modelling of ontogeny, disease effects, and age-related decline, ultimately supporting rational dosing in high-risk patient populations.

2.6 Conclusion

While the clearance estimates derived in this analysis were generally aligned with the literature, the inability to empirically estimate age-related changes in clearance from the available data reflects a persistent evidence gap. Future research should prioritise characterising developmental pharmacokinetics in vulnerable populations and improve the quality and granularity of published pharmacokinetic data.

Chapter 3

Ciclosporin

HSCT, sometimes being referred to as bone marrow transplant, is offered as a treatment for malignant and non-malignant diseases including leukaemia, lymphoma, primary immune deficiencies, bone marrow failure, haemoglobinopathies and congenital metabolic diseases [179]. HSCT involves administering healthy haematopoietic stem cells to patients with dysfunctional or depleted bone marrow to replace dysfunctional bone marrow with functional cells, restore immune system function, or destroy malignant tumour cells. The transplanted haematopoietic stem cells can originate from the patient (autologous HSCT) or an appropriately Human Leukocyte Antigen (HLA) matched donor (allogeneic HSCT). For inherited disorders, such as immunodeficiencies, high levels of HLA matching are optimal for restoring functional immunity, whilst minimising complications such as Graft Versus Host Disease (GVHD). However, in malignancies, a small degree of HLA mismatch can be advantageous in targeting cancerous cells (”Graft Versus Leukaemia” effect) [91]. The selection of donor cell type, cell dose, conditioning regimens, and immunosuppressants is carefully tailored to optimise the elimination of dysfunctional or malignant cells while promoting the engraftment and proliferation of healthy donor cells [91].

The engraftment of the haematopoietic stem cells and the ability to reconstitute the immune repertoire signify the success in providing a long-term cure to the underly-

ing disease. However, while rapid immune reconstitution is pivotal for improving overall survival [180], it may lead to undesirable post-transplant complications, including immune dysregulation and GVHD [181].

Despite significant advances in many areas of HSCT, GVHD remains a challenge. GVHD is a severe, immune-mediated life-threatening complication where T-cells from the donor (graft) recognise the recipient's (host's) tissues as foreign antigens and initiate an immune response against them. There are two types of GVHD, acute (aGVHD) and chronic (cGVHD). aGVHD typically manifests in the first 3 months post-HSCT as a characteristic rash, secretory diarrhoea, cholestatic liver dysfunction or a combination of these. Overall, 30–50% of patients undergoing allogeneic-HSCT will develop aGVHD, and around 10% will have severe aGVHD (grades III–IV) [87, 182]. cGVHD occurs in 28 - 42% of patients following allogeneic-HSCT [183, 184] and typically presenting $\geq$ 6 months after HSCT. Whilst children have a lower incidence rate (6 - 40%) [185], cGVHD is the most significant non-relapse cause of morbidity and mortality following allogeneic-HSCT for malignant disease [186]. aGVHD and cGVHD have different pathophysiology causes, with the former driven by an inflammatory response caused by T cells, cGVHD is caused by immune dysregulation, including impaired immune tolerance [133, 187]. Prevention and treatment of GVHD involve the use of immunosuppressants including ciclosporin, methotrexate, mycophenolate and steroid [187, 188]. Striking a balance between the level of immunosuppression to prevent or treat GVHD while maintaining sufficient immunocompetence to counter microbial infections is paramount yet challenging. HSCT patients are given anti-infective prophylaxis, including azole antifungals. With the advances in the application of personalised medicine (such as tailored conditioning regimens, precise HLA-typing) and improved supportive therapy and antimicrobial prophylaxis regime, transplantation-associated morbidity and mortality rates have significantly improved in recent years [182, 189, 190].

3.1 Ciclosporin pharmacokinetics

Ciclosporin, a calcineurin inhibitor, is a cornerstone immunosuppressant used in HSCT for the prevention of GVHD. Its immunosuppressive effect is mediated through inhibition of interleukin-2 (IL-2) production, a cytokine critical for T-cell proliferation. Ciclosporin is highly lipophilic and exhibits saturable binding to erythrocytes, with 41–59% of the total blood concentration associated with red blood cells. This distribution is influenced by haematocrit, temperature, and plasma protein concentrations [137, 191, 192]. In plasma, ciclosporin predominantly binds to lipoproteins, with a lower affinity for albumin.

Given its narrow therapeutic range and high inter-individual pharmacokinetic variability, TDM is routinely implemented in clinical practice to optimise dosing. Subtherapeutic exposure may lead to GVHD, while overexposure increases the risk of nephrotoxicity and other adverse effects. Ciclosporin is extensively metabolised by CYP3A4 enzymes in the gut and liver. In paediatric patients, developmental changes in body composition, including variations in adipose tissue, lipoprotein concentrations, albumin levels, and haematocrit, affect ciclosporin distribution [119, 161, 193]. In HSCT, additional factors further complicate pharmacokinetics. Conditioning regimens often include chemotherapy that causes gastrointestinal mucosal damage, leading to nausea, vomiting, diarrhoea, and mucositis [133]. These effects, along with gastrointestinal GVHD, can impair drug absorption and reduce the bioavailability of oral formulations. Moreover, hepatic complications such as veno-occlusive disease (VOD) may reduce hepatic clearance and alter volume of distribution due to fluid shifts and compromised liver function [91]. These clinical and physiological complexities distinguish HSCT patients from solid organ transplant recipients and underscore the need for tailored dosing strategies, especially in children where ontogenic changes further compound variability.

CYP3A expression and activity show considerable interindividual variation, contributing significantly to the variability in ciclosporin clearance. For instance, interindividual differences in CYP3A-mediated clearance of substrates can range from

4- to 13-fold, whereas intraindividual variability is notably lower, typically 5–20% as reported for midazolam, a prototypical CYP3A substrate [121]. This highlights that the wide variability in ciclosporin clearance among paediatric patients is largely due to differences between individuals, such as age, genetic variation in CYP3A4, or body composition, rather than random fluctuations within the same patient over time.

At GOSH, ciclosporin is initiated as a two-hour intravenous infusion starting three days before stem cell infusion (Day –3) to achieve steady-state concentrations in time for engraftment. Trough levels are monitored twice weekly, immediately before the next dose. The recommended target trough concentration was 150 - 200 mcg/L for T cell depleted regimes whereas a lower therapeutic range of 100 - 150 mcg/L for patients who are having T cell depleting conditioning regimes including alemtuzumab or anti-thymocyte globulin.

3.2 Literature review

Unlike the quantitative review in Chapter 2, which focused on reported clearance values to explore developmental trends across the lifespan, this section reviews published population pharmacokinetic models of ciclosporin. The aim is to identify modelling strategies, structural assumptions, and covariates that have previously been found to influence ciclosporin pharmacokinetics. A comprehensive review of published population pharmacokinetic models for ciclosporin was conducted to inform the development of this model. These studies, summarised in Table 3.2, include 26 population pharmacokinetic models spanning a wide range of transplant populations, age groups, model structures, and covariate evaluations.

Several studies focused specifically on paediatric patients undergoing HSCT, including those by Willemze *et al.* (2008) [194], Schrauder *et al.* (2009) [195], Ni *et al.* (2013) [196], Sarem *et al.* (2015) [197], Li *et al.* (2019) [198], and Gao *et al.* (2022) [199]. These studies enrolled children ranging from infancy through adolescence and early adulthood, making them particularly representative of the present

cohort (ages 0.6 to 20 years).

Across these paediatric HSCT models, estimated clearance values normalised to 70 kg typically ranged from 21 to 58 L/h, reported either as apparent clearance in oral studies or as absolute clearance in intravenous studies. Variability in clearance was attributed to age, body weight, haematocrit, and renal function. Volume of distribution estimates also varied substantially between models, likely reflecting both physiological differences across developmental stages and methodological variability in structural model selection. Collectively, these findings underscore the pharmacokinetic complexity in paediatric HSCT and the need for stratified modelling strategies in this population.

Ciclosporin is also widely used in solid organ transplantation, with most pharmacokinetic models in this setting based on adult populations. A notable exception is the study by Fanta *et al*. (2007) [200], which included paediatric patients evaluated prior to renal transplantation. This study stands out due to its rigorously designed sampling strategy, enabling rich characterisation of ciclosporin absorption and distribution. The use of a three-compartment model allowed a detailed analysis of drug disposition kinetics, with haematocrit and plasma cholesterol emerging as significant covariates for clearance. Similarly, Eljebari *et al*. (2012) [167] conducted a pharmacokinetic analysis in a mixed-age HSCT cohort that included both paediatric and adult patients. This study also implemented a well-considered sampling design to capture ciclosporin concentrations over the dosing interval, enabling high-quality model development. Despite the strength of the dataset, the authors did not identify any significant covariates influencing pharmacokinetic parameters. This negative finding is informative, suggesting that in this particular cohort ciclosporin exposure may be less influenced by the covariates typically retained in other models. Alternatively, it may reflect challenges in statistical power or population heterogeneity. Nonetheless, Eljebari *et al.* 2012's [167] study reinforces the importance of systematic sampling and offers a valuable comparative dataset.

Structural model complexity varied across the literature. One- and two-

compartment models were most common, with simpler models generally applied in paediatric settings where sparse sampling limited the utility of more complex structures (e.g., Ni *et al.* (2013) [196]). In contrast, richer datasets supported the use of three-compartment or transit absorption models, as in Fanta *et al.* (2007) [200] and Kim *et al.* (2015) [201].

Covariate selection and evaluation were central to model development. Body weight was universally tested and often incorporated directly or through allometric scaling due to its well-established impact on both CL and Vd. Haematocrit, reflecting ciclosporin's erythrocyte binding, was a key covariate in several models (e.g. Fanta *et al.* (2007) [200], Zhou *et al.* (2012) [202]), influencing both clearance and distribution. This is especially relevant in HSCT, where haematocrit varies widely due to conditioning regimens and disease state.

Although ciclosporin is primarily hepatically eliminated, renal function markers, most commonly serum creatinine or creatinine clearance, were frequently explored as surrogate indicators of overall clinical status or multisystem dysfunction. Significant associations with clearance were reported in several studies (e.g. Ni *et al.* (2013) [196], Chen *et al.* (2020) [203]). Coadministration of azole antifungals, strong inhibitors of CYP3A4, was another important covariate across multiple transplant studies, with well-documented effects on ciclosporin exposure. Post-transplantation time was included variably, with some studies (e.g., Kim *et al.* (2015) [201], Sarem *et al.* (2015) [197]) identifying temporal trends in clearance, though the covariate was not consistently retained.

Liver function markers such as total bilirubin and albumin were also assessed for their impact on clearance, though results were inconsistent across models. These parameters provide only indirect information: albumin reflects synthetic capacity but can also be reduced by capillary leak, proteinuria, or systemic inflammation, while bilirubin reflects mixed hepatocellular and cholestatic processes but may also be elevated due to haemolysis. Pharmacogenetic variables (e.g. CYP3A4/CYP3A5 polymorphisms) were incorporated in a subset of studies (Xue *et al.* (2019) [204],

Kim *et al*. (2015), Li *et al*. (2019), indicating potential for genotype-guided dosing, particularly in populations with rich pharmacogenetic diversity.

Reported oral bioavailability (F) ranged widely, from 23% to 82%, reflecting interindividual and interstudy differences influenced by age, disease state, formulation, and concomitant medications.

Despite variability in model structure and population characteristics, consistent covariates emerged: body size, haematocrit, creatinine, albumin, azole coadministration, and post-transplant time were frequently evaluated and often retained. Their biological plausibility and repeated significance across independent datasets justify their inclusion in prospective models, particularly in the paediatric HSCT setting.

Whilst most studies measured ciclosporin concentrations in whole blood, some reported serum levels, adding complexity to interpretation. Given ciclosporin's high erythrocyte affinity and haematocrit-dependent distribution, particularly in patients with anaemia or fluctuating haematocrits, standardisation or adjustment for haematocrit is important in pharmacokinetic modelling to improve precision in estimating clearance and exposure.

Table 3.2: Ciclosporin Model Papers (Part 1 of 5)

	Yee *et al*. 1988 [205]	Gupta *et al*. 1990 [206]	Yoshida *et al*. 2001 [170]	Rousseau *et al*. 2004 [207]	Hesselink *et al*. 2004 [208]	Lukas *et al*. 2005 [209]	Rosenbaum *et al*. 2005 [210]
Population	HSCT	Healthy	Renal transplant	Renal transplant	Kidney and heart transplant	Renal transplant	Cardiopulmonary transplant
Median age (range) (years)	22 (1–52)	29 (26–32)	37.4 (18–68)	46.2 (22–71.5)	44.9 (±12.6)	44.2 (24–61)	42 (19–66)
No of patients	85	8	69	70	151	11	48
Compartments	2	2	2	2	2	1	1
Median weight (kg)	–	64	56.1	67.8	75.2	63.1	58.7
CL at 70kg (L/h/70kg)	Pop. mean = 43.7 $\leq$10 years old = 55.0	24.6	32.4	26.9	29.1	18.4	23.6
Vd at 70kg (L/70kg)	665	84.7	633.6	201.2	224.6	148.7	175.3
F (%)	–	23	–	–	–	77	82
Ka (L/h)	–	–	3.59	–	1.27	4 (fixed)	0.25 (fixed)
Q (L/h)	–	–	24.5	23.9	31.7	–	–
Covariate tested	Age, TBIL, Cr, glutamic oxalacetic transaminase, HCT, blood urea nitrogen, triglyceride	Diet	None	Age, Wt, BSA, Cr, POD	Genetic characteristics, sex, ethnicity, Wt, dose, POD	None	Age, gender, and type of transplant, itraconazole, cystic fibrosis, Wt
Significant covariate	Age, HCT	Diet	None	None	CYP3A4*1B	None	Itraconazole, cystic fibrosis, Wt

Abbreviations: ALB: albumin, ALP: Alkaline phosphatase, ALT: Alanine aminotransferase, AST: aspartate transaminase, BSA: body surface area, Co-med: co-administration medicine, Cr: creatinine, CrCL: creatinine clearance, GFR: glomerular filtration rate, GGT:gamma-glutamyl yransferase, Hb: haemoglobulin, HCT: haematocrit, Ht = height, POD: post-operation/transplant day, RBC: red blood cells, TBIL: total bilirubin, Wt = weight.

Ciclosporin Model Papers (Part 2 of 5)

	Wu *et al*. 2005 [211]	Fanta *et al*. 2007 [200]	Irtan *et al*. 2007 [168]	Willemze *et al*. 2008 [194]	Schrauder *et al*. 2009 [195]	Wilhelm *et al*. 2011 [212]	Eljebari *et al*. 2012 [167]
Population	Renal transplant	Pre-renal transplant	Renal transplant	HSCT	HSCT	HSCT	HSCT
Median age (range) (yrs)	42.3 (16–66)	6.3 (0.36–17.5)	9.5 (1.5–20.7)	7 (1.8–16.1)	9.2 (0.9–20)	26 (7.5–50)	54 (37–66)
No of patients	120	162	20	17	27	30	20
Compartments	1	3	2	2	2	2	2
Median weight (kg)	57.9	13	35.2	29	32.2	54	84
CL at 70kg (L/h/70kg)	32.9	21.6	38.7	21.9	27.4	30.9	19.1
Vd at 70kg (L/70kg)	160.8	157.8	397.7	184.4	209.1	657.1	422.4
F (%)	–	36	–	38.6	–	–	71
Ka (L/h)	1.28	0.68	–	0.831	–	0.214	0.28
Q (L/h)	–	1.5, 3	10.9	12.9	6.28	5	24.2
Covariate tested	Age, ALP, ALT, BMI, co-med, GGT, HCT, Ht, POD, sex, TBIL, Wt	Cholesterol, Cr, HCT, Wt	POD, WT	Age, GFR, Ht, Wt	Age, co-med, Wt	Age, ALP, ALT, AST, BSA, Cr, POD, sex, TBIL, Wt	BSA, inducers, inhibitors, Wt
Significant covariate	Age, concurrent metabolic inhibitors, HCT, POD, TBIL, Wt	Allometric scaling, Cr, HCT, plasma cholesterol	None	None	Itraconazole, tobramycin	None	None

Ciclosporin Model Papers (Part 3 of 5)

	Zhou *et al*. 2012 [202]	Ni *et al*. 2013 [196]	Sarem *et al*. 2014 [213]	Woillard *et al*. 2014 [214]	Xue *et al*. 2014 [215]
Population	HSCT	HSCT	HSCT	HSCT	HSCT
Median age (range) (yrs)	30.32 (16–51)	8.8 (0.9–17.6)	10.4 (1–18.3)	59 (24–67)	35 ± 9
No of patients	73	102	39	45	117
Compartments	1	1	2	2	1
Median weight (kg)	59.44	70	35.5	71	63
CL at 70kg (L/h/70kg)	31.9	31.5	25.7	40.8	31.6
Vd at 70kg (L/70kg)	1512	178	133.3	711.8	605
F (%)	71.1	–	–	–	61.9
Ka (L/h)	1.28 FIXED	0.68 FIXED	0.8	0.8	1.25 FIXED
Q (L/h)	–	–	13.49	33.7	–
Covariate tested	Age, gender, Wt, dose, POD, HCT, RBC, ALT, AST, TBIL, ALB, total protein, Cr, BUN, co-med	Wt, Cr, stanozolol, prednisolone, neutrophil count	Wt, age, sex, dosage form, urea nitrogen, ALB, ALP, TBIL, ALT, AST, GGT, total protein, Hb, HCT, RBC, POD, corticosteroid, calcium channel blocker, azole antifungal	Wt, Hb, HCT, total protein, TBIL, ALP, ALT, AST, ALB, Cr	Age, ALB, BSA, ht, wt, ABCB1, ALT, AST, cholesterol, Cr, co-meds, CYP3A4, CYP3A5, GGT, glucose, Hb, HCT, platelets, POD, red/white blood cell count, TBIL, total protein, urea nitrogen, uric acid, treatment length, triglycerides, route, sex
Significant covariate	ALB, HCT, itraconazole	Cr, stanozolol, Wt	Age, ALP	None	Antifungals, HCT, treatment length, triglycerides, Wt

Ciclosporin Model Papers (Part 4 of 5)

	Kim *et al*. 2015 [201]	Li *et al*. 2019 [198]	Xu *et al*. 2019 [204]	Chen *et al*. 2020 [203]
Population	HSCT	Chinese HSCT	HSCT	Chinese HSCT
Median age (range) (yrs)	36 (18–62)	8.38 (1.1–16.8)	30.5 (2–72)	1.22 (0.29–6.49)
No of patients	34	86	563	18
Compartments	1	1	1	1
Median weight (kg)	61	31.93	56.1	7.6
CL at 70kg (L/h/70kg)	21.2	52.5	35.9	29.2
Vd at 70kg (L/70kg)	430	3100	1090.6	6550
F (%)	–	–	81.2	–
Ka (L/h)	–	–	1.25 FIXED	0.68 FIXED
Q (L/h)	–	–	–	–
Covariate tested	Age, ALB, ALP, ALT, AST, cholesterol, Cr, CYP drugs, genetics, Hb, GFR, HCT, Ht, platelets, steroid dose, RBC, sex, TBIL, Wt	Age, ALT, ALB, BMI, ALP, co-meds, Cr, disease type, eGFR, Hb, HCT, Ht, POD, polymorphism, sex, TBIL, Wt	Azole, CrCL, HCT, rifampicin, sex, total protein, uric acid	Age, Sex, ALB, ALT, AST, bile acid, Cr, co-meds, HCT, Hb, MCH, MCHC, POD, urea, total protein, TBIL, sex, Wt
Significant covariate	Wt	azoles, CYP3A4*1G, eGFR, POD, Wt	Azole, CRCL, HCT, rifampicin, sex, total protein, uric acid	POD, Wt

Ciclosporin Model Papers (Part 5 of 5)

	Umpiérrez *et al*. 2021 [216]	Gao *et al*. 2022 [199]	Ling *et al*. 2022 [217]	Feng *et al*. 2023 [218]	Cai *et al*. 2024 [219]
Population	Renal transplant + HSCT	Chinese haematology	HSCT	HSCT	Thalassemia
Median age (range) (yrs)	34.4 (±15.85)	7.8 (1.5–18.8)	42 (13 - 60)	6 (1 - 17)	7 (2–16)
No of patients	37	157	59	176	74
Compartments	2	1	1	1	1
Median weight (kg)	64.3	28	65	16.5	20
CL at 70kg (L/h/70kg)	32.3	57.7	20.9	60.5	40.4
Vd at 70kg (L/70kg)	454.9	1467.5	1443.1	8627.1	211.1
F (%)	–	–	67.2	-	83
Ka (L/h)	0.523	1.26	1.25 FIXED	-	1.25
Q (L/h)	17	3.1 FIX	–	–	-
Covariate tested	Age, co-meds, CrCL, treatment reason, sex, Wt	Age, ALB, Cr, co-meds, gender, Hb, HCT, TBIL, Wt	Age, ALB, ALP, ALT, AST, co-med, Cr, CRP, cystatin C, GFR, Hb, HCT, platelets, POD, RBC, sex, TBIL, total bilirubin, uric acid, white blood cell, wt	Age, ALB , ALP, ALT, ASP, bile acid, Cr, Hb, HCT, POD, RBC, sex, TBIL, total protein, WBC, Wt	Age, ALB, AST, ALT, ALP, BMI, BSA, Cr, co-meds, cystatin C, GGT, graft source, Hb, HCT, HLA compatibility, Ht, platelets, POD, RBC, TBIL, total protein, urea, uric acid, thalassemia type, acute GVHD, gender, WBC, Wt
Significant covariate	CrCL	Allometric scaling, TBIL	C-reaction protein, dose, HCT, itraconazole, total bile acid, voriconazole	HCT, Wt	Azole antifungals, POD, RBC, Wt

3.3 Aim

To develop and evaluate a population pharmacokinetic model for ciclosporin in children undergoing HSCT, identifying clinical and physiological factors that contribute to variability in drug exposure.

3.4 Objectives

- To describe ciclosporin pharmacokinetics using real-world therapeutic drug monitoring data.
- To identify key covariates influencing ciclosporin clearance and volume of distribution.
- To perform model-based simulations to assess dosing adequacy across age and weight groups and propose optimised dosing strategies for clinical practice.

3.5 Method

3.5.1 Patient population

A retrospective study was conducted using de-identified data extracted from electronic health records. All children who received ciclosporin related to HSCT between April 2019 and June 2023 and had more than one ciclosporin level taken were included. Each patient received ciclosporin intravenously or orally twice a day. For patients who were not on ciclosporin prior to transplant, ciclosporin was initiated at 2.5mg/kg twice a day intravenously 3 days prior to HSCT (Day -3). To capture steady-state levels, only ciclosporin whole blood plasma levels reported from the date of transplant (Day 0) onward were included. HSCT patients routinely had trough levels (12 hours post-dose) taken at least twice a week. Anonymised data was collated from the electronic health records including demographic details (age, sex, height and weight), laboratory data (ciclosporin whole blood plasma level and the time in which the corresponding samples were being taken, creatinine, haematocrit and albumin), medical history (HSCT indication, date of HSCT) and treatment

details (days after HSCT, dose and dosing times of ciclosporin, type, dose and dosing time of concomitant azole antifungals). Whole blood ciclosporin plasma levels were measured using tandem mass spectrometry (UPLC-MS/MS) with a lower limit of quantification of 25 mcg/L.

3.5.2 Population pharmacokinetic analysis

3.5.2.1 Structural model

To determine the model that best described the data, one- and two-compartment models were compared. The model parameters such as CL and Vd were log-transformed. Residual variability was modelled using an additive error structure on the log-transformed concentration, while inter-individual variability (IIV) in CL and Vd was assessed under the assumption of a log-normal distribution. The Akaike Information Criteria (AIC) and objective function value (OFV) were applied to identify the most suitable base model, while the OFV was utilised for nested model comparisons.

Allometric size based on weight scaling of clearance and volume terms were added *a prior*:

$$Parameter_i = Parameter_{pop} \times \left(\frac{c_i}{\overline{c}}\right)^{\theta} \tag{3.1}$$

Parameter$_{pop}$ represents the population estimate of the parameter, while $Parameter_i$ denotes the individual parameter estimate. The covariate value for each individual, *ci*, is compared to the population's typical covariate value, $\overline{c}$. In the fixed allometric weight scaling, c_i refers to individual body weight, with $\overline{c}$ set to 70 kg. The parameter θ applies a scaling power of 0.75 for clearance and inter-compartmental clearance, whereas the volume of distribution is scaled with a power of 1. For age, the typical covariate value, $\overline{c}$, corresponds to the population's median age.

A sigmoidal maturation function was incorporated *a priori* to describe the ontogeny of ciclosporin clearance in paediatric patients, particularly in those under two years of age. This function relates postmenstrual age (PMA) to a fractional maturation

factor using a Hill equation of the form:

$$MF = \frac{PMA^{Hill}}{PMA^{Hill} + (PM_{50})^{Hill}} \tag{3.2}$$

where PM_{50} is the postmenstrual age at which 50% of mature clearance is achieved, and the Hill coefficient governs the steepness of the maturation curve [129, 131]. This approach allowed for the inclusion of a biologically informed age effect without introducing additional covariate testing steps or increasing model complexity.

3.5.2.2 Covariates

Covariates were selected to be tested based on their known effects on ciclosporin pharmacokinetics as informed by the literature review, including serum creatinine, haematocrit, albumin, number of days post-HSCT and concomitant use of azole antifungals. To account for IIV in clearance, serum creatinine concentrations were standardised using the method described by Ceriotti *et al.* (2008) [220]. This approach adjusts each individual's creatinine level relative to a typical serum creatinine concentration (TSCR) based on their age, allowing renal function to be interpreted consistently across a paediatric population. TSCR accounts for the physiological variation in serum creatinine that occurs with age, particularly in children, where creatinine production reflects age-related changes in muscle mass and kidney maturation. By expressing renal function as a ratio of observed to expected creatinine, this method avoids the age-related bias that would occur if raw creatinine were used directly. TSCR (in mmol/L) was calculated using the following equation:

$$TSCR(mmol/L) = -2.37330 - 12.91367 \times ln(PMA_{years} + 23.93581 \times (PMA_{years})^{0.5} \tag{3.3}$$

where PMA_{years} represents postmenstrual age in years. This generated a typical reference value for each individual, against which observed creatinine could be compared. The resulting serum creatinine function ($SCR_{function}$)was calculated as:

$$SCR_{function} = \frac{(SCR_i)^{\theta_{SCR}}}{TSCR} \tag{3.4}$$

This ratio captures the deviation of an individual's renal function from what would be expected at their age: values > 1 suggest reduced renal function, and values < 1 suggest relatively enhanced renal clearance. $SCR_{function}$ was incorporated as a covariate on clearance, modelled using a power function (Equation 3.4), to assess whether age-standardised creatinine could explain IIV in clearance. This approach facilitates a biologically meaningful interpretation of renal function relative to age, improves parameter stability, and supports the detection of clinically relevant relationships between renal function and drug disposition.

In addition to the TSCR-based method described above, renal function was also estimated using the Modified Bedside Schwartz equation, which is commonly employed in clinical practice to calculate estimated glomerular filtration rate (eGFR) in paediatric patients [221]. For children over 1 month of age, the equation is defined as:

$$\text{eGFR (mL/min/1.73 m}^2) = 35 \times \frac{\text{height (cm)}}{\text{serum creatinine (mmol/L)}} \tag{3.5}$$

This approach provides an estimate of creatinine clearance (CrCL), adjusted for body surface area, and is suitable for use in growing children, whose serum creatinine levels are influenced by age, muscle mass, and developmental stage. Although the Cockcroft–Gault formula is typically recommended for estimating renal function in adults, it is not validated for use in children and tends to overestimate renal function in younger patients. One individual in the cohort was 20 years old, for whom the Cockcroft–Gault method would have been more appropriate. However, for consistency across the dataset and because this patient was treated within a paediatric setting, the Modified Bedside Schwartz equation was applied to all individuals.

Creatinine clearance estimated by the Schwartz method was evaluated as a covariate on clearance using two approaches. First, it was tested as a continuous covariate, expressed as a ratio to the population median value of 126 mL/min/1.73 m² and incorporated using a power function to assess its influence on inter-individual variability in clearance.

Second, CrCL was examined as a categorical covariate by stratifying patients into renal function groups:

- CrCL $<$ 30 mL/min/1.73 m²
- 30–59 mL/min/1.73 m²
- 60–89 mL/min/1.73 m²
- $\geq$ 90 mL/min/1.73 m² (reference category)

Renal function groups were coded as binary indicators rather than as an ordinal variable to reflect clinical practice, where dosing recommendations are typically expressed in discrete categories (mild, moderate, severe impairment), and to avoid imposing a linear relationship between renal function and clearance that may not hold biologically. These two methods allowed exploration of both linear and nonlinear relationships between renal function and ciclosporin clearance across the study population.

The concomitant use of azole was coded as a binary variable (0 for no concomitant use of azole, 1 for concomitant use of any type of azole). Azole utilised included itraconazole, posaconazole and voriconazole. Its effect on clearance was introduced into the model parameterised by θ_{Azole}. The model equation for CL was given by:

$$CL_i = CL_{pop} \times (1 + \theta_{Azole}) \times \exp(\eta_1) \tag{3.6}$$

The effects of haematocrit and albumin on CL and Vd were evaluated using a standard power model:

$$CL_i = CL_{pop} \times \left(\frac{c_i}{\overline{c}}\right)^{\theta_{\text{Covariate}}} \times \exp(\eta_1) \tag{3.7}$$

where c_i is the individual covariate value (haematocrit or albumin), and $\overline{c}$ represents the median value of the covariate (0.26 L/L for haematocrit and 34 g/L for albumin),

used for normalisation.

Both covariates were considered on CL and Vd due to ciclosporin's well-established binding characteristics. Ciclosporin binds extensively to erythrocytes and plasma proteins, including albumin and lipoproteins [119, 161, 193]. Variations in haematocrit can influence the proportion of ciclosporin partitioned into red blood cells, affecting the apparent volume of distribution and potentially altering clearance through changes in the free (unbound) drug fraction. Similarly, reduced albumin levels may increase the unbound fraction of ciclosporin, which can be more readily cleared or distributed into tissues.

To account for the time-dependent changes in drug exposure following HSCT, the number of days post-transplant (BMTDAY) was tested as a covariate on clearance using an asymptotic function:

$$\mathrm{C}L_i = CL_{\mathrm{pop}} \times [\theta_6 + (1-\theta_6)\,(1-\exp(-\theta_7 \times \mathrm{BMTDAY}))] \times \exp(\eta_1) \qquad (3.8)$$

This functional form reflects an initially steep effect that gradually plateaus over time. It was selected based on exploratory plots of BMT days versus dose-normalised ciclosporin concentrations (Figure 3.3), which demonstrated a curved relationship indicative of a time-varying effect on clearance. This trend aligns with the clinical course of haematopoietic stem cell transplant patients. Ciclosporin is typically initiated on day –3 relative to transplant, with this study including only samples from day 0 onwards to ensure steady-state concentrations were captured. After transplantation (day 0), patients often experience a period of clinical deterioration due to conditioning chemotherapy-related toxicity (e.g. nausea, vomiting, mucositis), followed by possible complications such as aGVHD and VOD. These evolving physiological conditions may influence drug absorption, metabolism, or clearance, but the effect is expected to stabilise over time. The asymptotic function captures this trajectory by allowing for a rapid initial change in clearance that approaches a steady value in the later post-transplant period.

Population pharmacokinetic modelling and simulation were performed using the first-order conditional estimation method with interaction (FOCEI) in NONMEM version 7.5.1. Model development was guided by graphical diagnostics generated using Xpose (version 4.7.2). One- and two-compartment structural models were compared to identify the model that best described the data. Residual unexplained variability was evaluated using additive and proportional error structures, and IIV on CL and Vd was assumed to follow a log-normal distribution.

Model selection was informed by the AIC and the OFV. Covariate selection followed a stepwise approach: forward inclusion was first performed using intravenous data only, and the best-performing IV model was then extended to the combined intravenous and oral dataset. This ensured that absorption-related parameters did not confound identification of clearance covariates. Backward elimination was subsequently applied to the combined model to confirm the significance of retained covariates. Covariate inclusion and elimination were evaluated using the likelihood ratio test, with significance determined by a drop in the OFV exceeding 3.84 per degree of freedom ($p < 0.05$), based on the Chi-squared distribution.

In addition to statistical criteria, model selection was supported by several diagnostic tools: goodness-of-fit plots (observations vs. population predictions, observations vs. individual predictions, conditional weighted residuals (CWRES) vs. time, and CWRES vs. population predictions), prediction-corrected visual predictive checks (pcVPCs), non-parametric bootstrap resampling (1000 replicates), and assessment of parameter plausibility.

3.6 Result

A total of 216 HSCT patients, ranging in age from 6 weeks to 20 years (median age: 3.3 years) and with a median weight of 15 kg (range: 2–97 kg), provided 3972 ciclosporin blood levels taken at various time points (Table 3.7). 38% (1505) of the ciclosporin blood levels were measured without the concurrent use of azole antifungals, while 44% (1742) of the levels taken whilst on itraconazole, 10% (396) on posaconazole and 8% (329) on voriconazole. The majority of patients required HSCT for haematological conditions (52%), followed by immunodeficiencies (35%). Most patients underwent transplants with an unrelated donor, either fully matched or mismatched, as well as transplants from matched sibling donors. All observations were above the limit of quantification.

Figure 3.2 shows observed ciclosporin concentrations versus time after dose for both intravenous and oral routes. Dose-normalised ciclosporin plasma concentrations were plotted against key clinical covariates to explore their potential impact on pharmacokinetics (Figure 3.3). These scatterplots revealed a temporal decline in ciclosporin levels during the first 10 days post-HSCT. Serum creatinine and haematocrit appeared to have the strongest visual associations with ciclosporin concentrations, suggesting a role in modulating clearance and distribution, respectively. Albumin and total bilirubin showed a weaker relationship, consistent with its lesser contribution to ciclosporin binding relative to haematocrit.

Table 3.7: Patient demographics. Csa: ciclosporin

Characteristics	Median Value (range)
No of patients	216
Age (years)	3.3 (0.1 - 20)
Sex (M)	139 (40%, 139/216)
Dose/kg (mg/kg)	1.7
Weight (kg)	15 (2 - 97)
Creatinine (mmol/L)	26 (13-231)
Haematocrit	0.26 (0.11 - 0.46)
Total bilirubin (mmol/L)	9 (2 - 178)
Albumin (g/L)	34 (20 - 48)
No of days post HSCT	25 (0 - 180)
No of csa levels with no azole	1505
No of csa levels given with itraconazole	1742
No of csa levels given with posaconazole	396
No of csa levels given with voriconazole	329

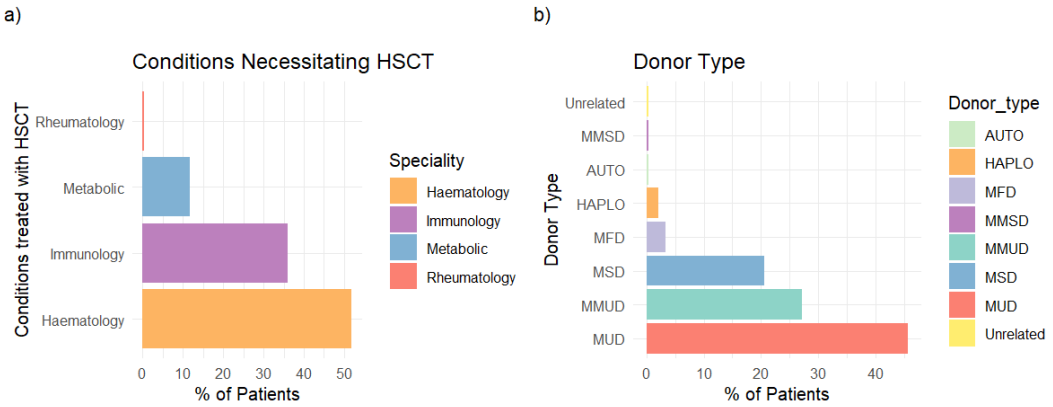


Figure 3.1: HSCT indications and donor type. AUTO = autologous; HAPLO: haploidentical related donor; MSD: matched sibling donor; MFD: matched family donor; MUD: matched unrelated donor; MMUD: mismatched unrelated donor; MMSD: mismatched sibling donor.

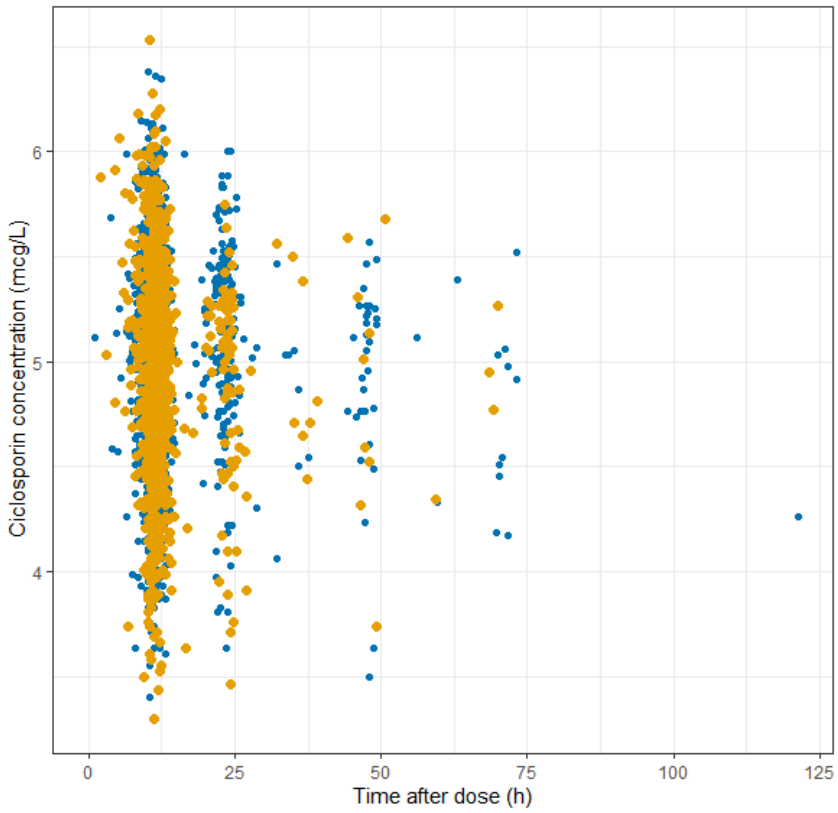


Figure 3.2: Observed serum IgG concentrations versus time after dose for all patients stratified by route of administration. Blue = intravenous, orange = oral

To complement these trends, a correlation matrix (Figure 3.4) was used to quantify associations between covariates including post-HSCT day, concurrent azole antifungal use, haematocrit, albumin, creatinine, sex, and weight. Among these, weight was positively correlated with creatinine, haematocrit, and albumin. The strongest observed correlation was between weight and creatinine (r = 0.55), indicating a moderate relationship. This level of correlation is important to consider in model development, as multicollinearity may influence parameter estimates and model robustness [222].

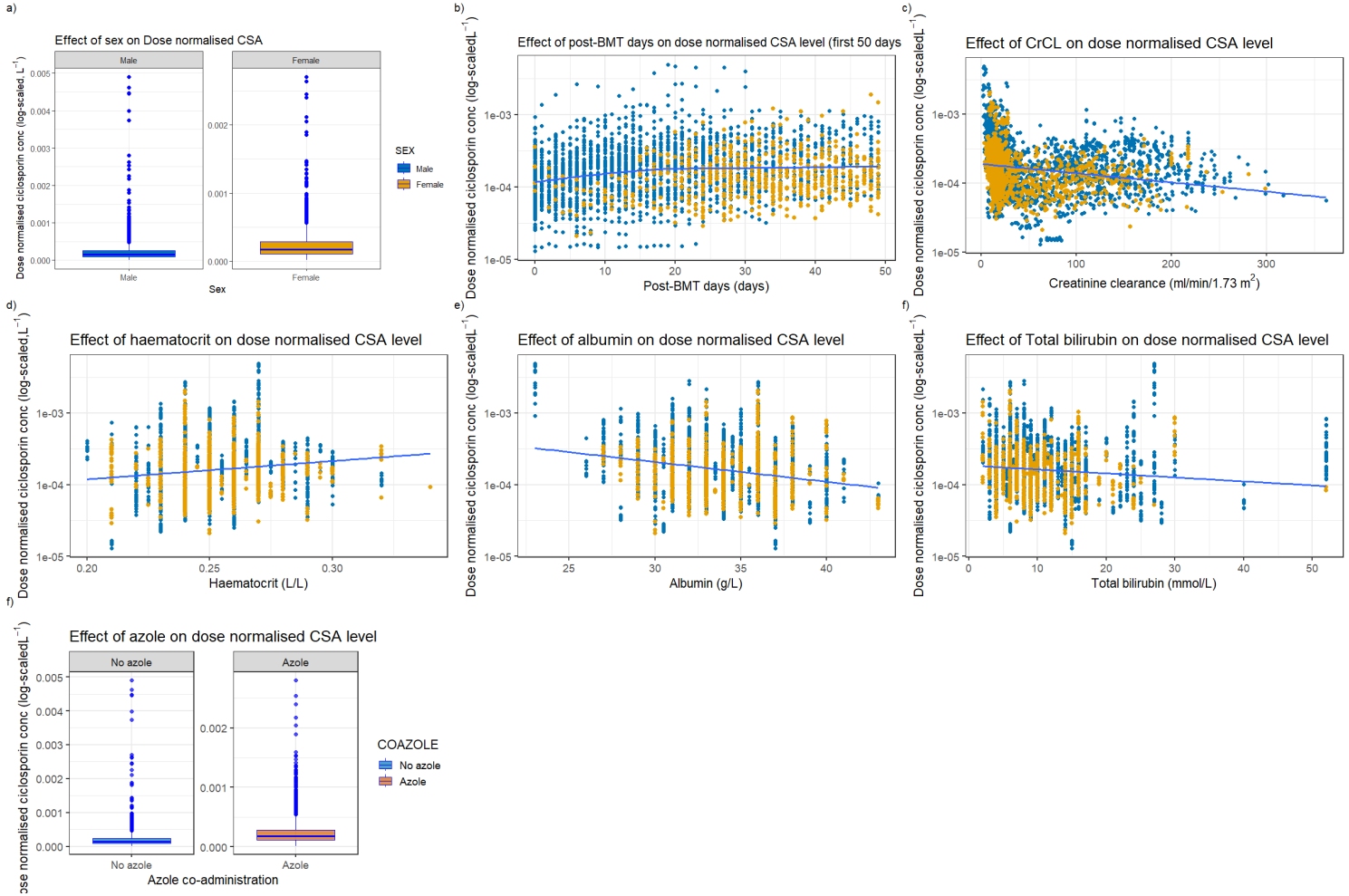


Figure 3.3: Effect of different covariates on ciclosporin plasma levels. CSA: ciclosporin, CrCL: creatinine clearance; Blue = intravenous, orange = oral

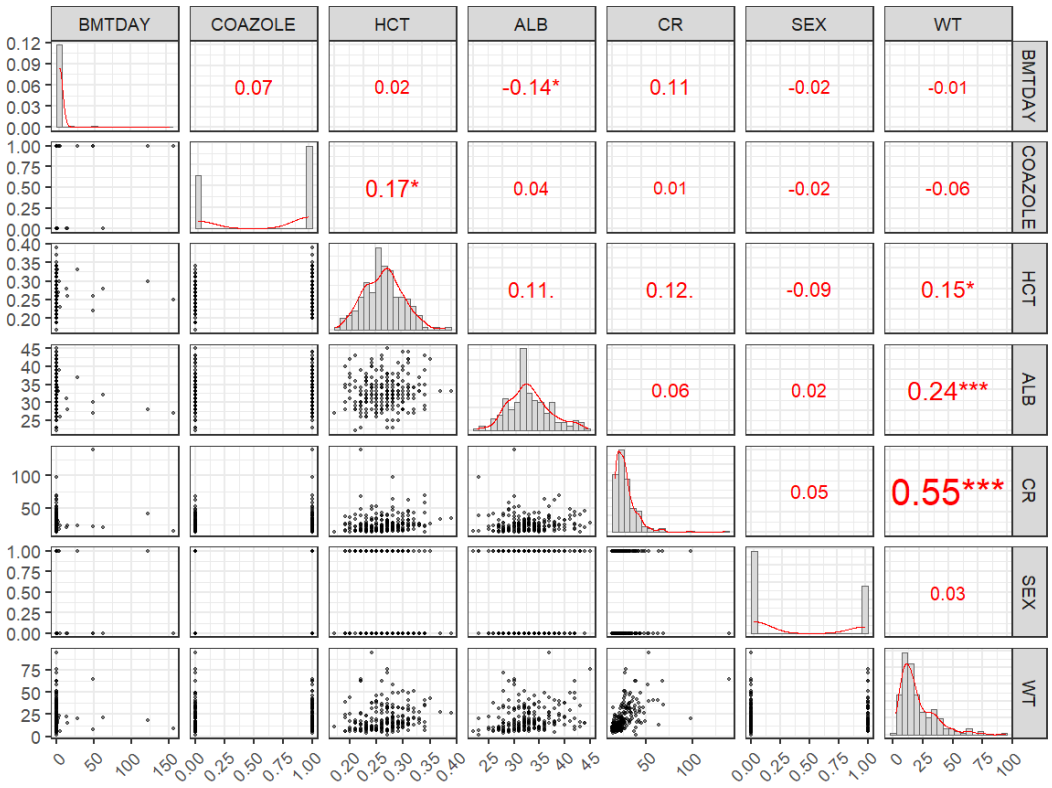


Figure 3.4: Correlation matrix of candidate covariates for ciclosporin clearance. Rows and columns correspond to individual covariates: BMT Day = number of days post-HSCT; COAZOLE = concurrent use of azole antifungals; HCT = haematocrit; ALB = albumin; CR = creatinine; TBIL = total bilirubin; WT = weight. The displayed number represents the correlation coefficient, with size proportional to correlation strength.

3.6.1 Pharmacokinetic modelling

3.6.1.1 Base model development

The base model was developed using a one-compartment disposition structure with first-order absorption. Both additive and proportional residual error models were tested; the log-transformed additive model provided the most stable fit and residual distribution. Comparison of one- and two-compartment structures showed no improvement in fit with the two-compartment model, likely reflecting the predominance of trough sampling (12 hours post-dose). Allometric scaling of clearance and volume to a 70 kg reference weight was included a priori.

Parameter estimates for the base model are summarised in Table 3.8, with a

prediction-corrected VPC and goodness-of-fit plots presented in Figure 3.6 and 3.5. The model demonstrated adequate predictive performance and no major bias, supporting its use as the foundation for covariate exploration.

Table 3.8: Pharmacokinetic parameter estimates for the base model. All parameters are allometrically scaled to 70kg.

Base model parameter estimates	Estimates (%RSE) [Shrinkage %]
CL (L/h/70kg)	49.9 (0.9)
V1 (L/70kg)	4242.83 (0.7)
IIV CL (%)	49.1 (5.4) [3]
IIV V1 (%)	72.3 (6.6) [12]

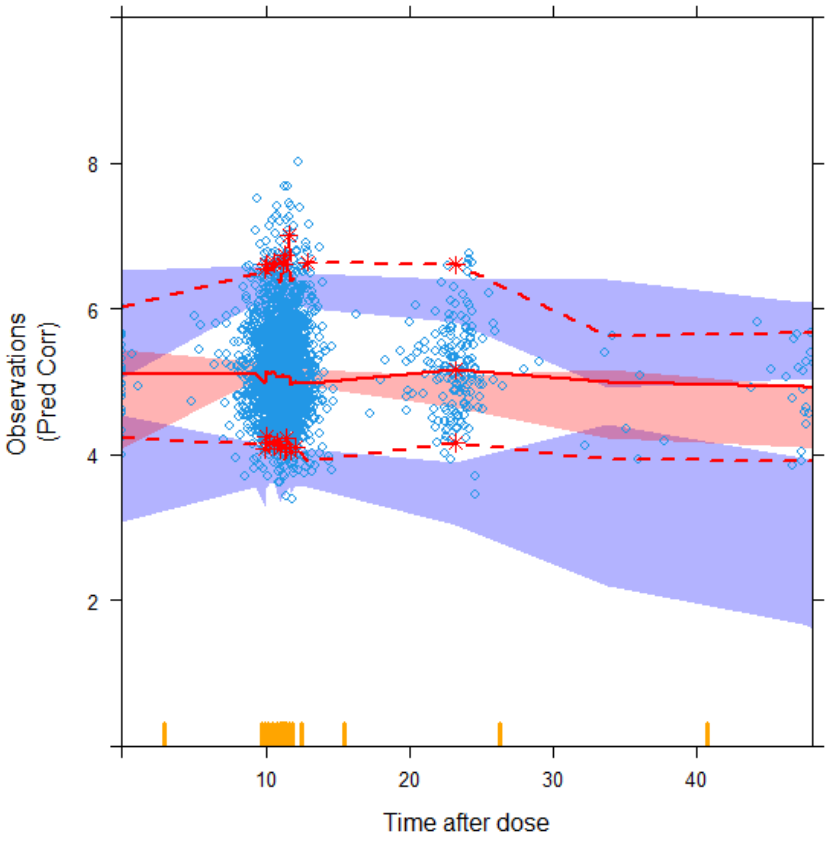


Figure 3.5: Prediction-corrected visual predictive check of the base model showing the 5th, 50th, and 95th percentiles of the observed data (lines with closed circles) compared with the 90% confidence intervals of the corresponding simulated percentiles from the final model (shaded areas).

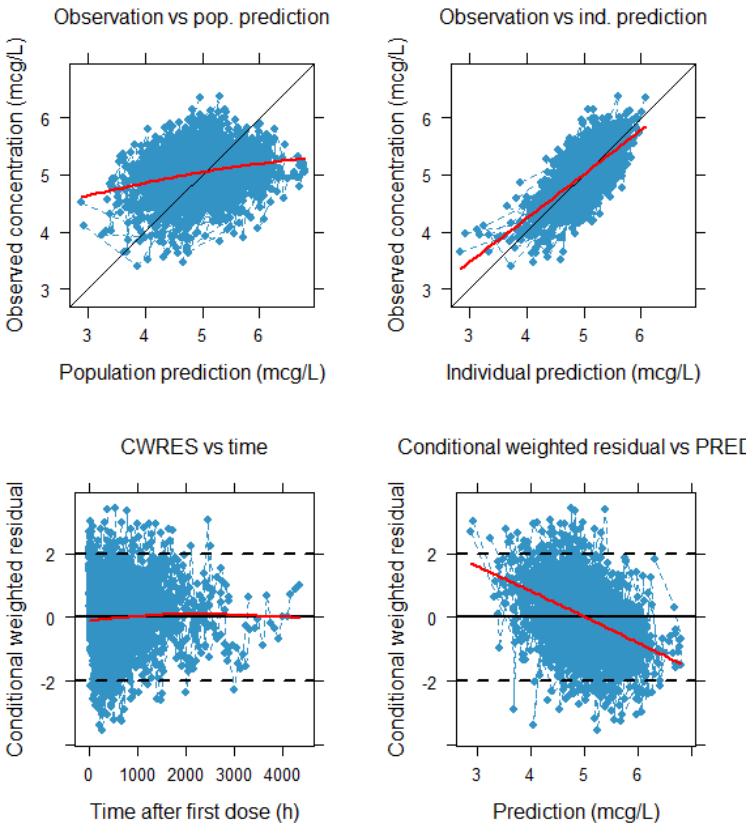


Figure 3.6: Goodness of fit plots of the ciclosporin base model. Top panels: observed versus population (left) and individual (right) predictions with line of identity (solid black) and locally weighted regression (LOESS, red) overlaid. Bottom panels: conditional weighted residuals (CWRES) versus time (left) and predictions (right), with reference lines at 0 and ±2 (dashed black) and LOESS smoothing (red). The LOESS curve illustrates systematic trends or bias in the data relative to the model fit.

3.6.1.2 Covariate model development

Systematic covariate evaluation identified concurrent azole antifungal therapy and creatinine as significant predictors of clearance, and haematocrit as a significant predictor of volume of distribution. Incorporating these covariates produced a reduction in the OFV (ΔOFV $= 35.5$) and AIC (ΔAIC $= 33$), with improved diagnostic plots and reduced between-subject variability.

The final structural model was a one-compartment model with first-order absorption, allometric scaling, and a sigmoidal maturation function on clearance. Significant covariate effects were included for concurrent azole administration and age-

adjusted creatinine on clearance, and haematocrit on volume of distribution (Table 3.10).

3.6.1.3 Final Model

The final model estimated a typical clearance of 57.4 L/h/70 kg and a large volume of distribution, with good precision (%RSE = 1% for both). Ka was estimated with greater uncertainty (%RSE 16%), but still acceptable and consistent with the predominantly trough sampling design. Oral bioavailability was estimated at 39%, reflecting moderate systemic availability after oral dosing. All key covariates (azole use, haematocrit, and standardised creatinine on CL) had stable and statistically significant effects. Between-subject variability was moderate to high (CL 47%, V1 62%, F 54%), but shrinkage remained within acceptable limits, supporting reliable estimation. Bootstrap analysis confirmed stability, with medians and 95% CIs closely matching the final estimates. The final parameterisation is shown in Equation 3.9 and 3.10.

$$CL_i = CL_{\text{pop}} \times \left(\frac{WT_i}{70}\right)^{0.75} \times \left(\frac{\text{SCR}_i}{\text{TSCR}_i}\right)^{-0.21} \times (1 - 0.29 \times \text{Azole}_i) \times MF_i \times e^{\eta_{CL,i}} \tag{3.9}$$

$$V_i = V_{\text{pop}} \times \left(\frac{WT_i}{70}\right)^{1} \times \left(\frac{HCT_i}{\overline{HCT}}\right)^{-0.4} \times e^{\eta_{V,i}} \tag{3.10}$$

Table 3.9: Pharmacokinetic parameter estimates for the final model, including bootstrap analysis. All parameters are allometrically scaled to 70 kg. Q = inter-compartmental clearance; Ka = absorption rate constant.

Final model parameter estimates	Estimates (%RSE)[Shrinkage%]	Bootstrap median	Bootstrap 95% confidence interval
CL (L/h/70 kg)	57.4 (1%)	56.1	53.0 - 60.9
V1 (L/70 kg)	4105.2 (1%)	4105.2	3703.4 - 4712.6
Ka (h^{-1})	1.47 (16%)	1.77	0.71 - 4.85
Bioavailability (%)	39.3 (3%)	39.6	36.9 - 41.8
Azole effect on CL	-0.29 (4%)	-0.28	-0.31 - -0.23
Haematocrit on Vd	-0.40 (13%)	-0.40	-0.55 - -0.33
Creatinine on CL	-0.21 (8%)	-0.21	-0.34 - -0.1
IIV CL (%)	46.5 (5.5)[3]	46.8	41.2 - 49.9
IIV V1 (%)	62.2 (6)[14]	61.2	43.0 - 53.2
IIV Bioavailability (%)	53.6 (6)[19]	54	42.5 - 73.1

Table 3.10: All model runs tested in ciclosporin PK model development.

Model No	Compartment	Covariate tested	Ref model	OFV	ΔOFV	AIC	Eta	CL	V	Comment
IV dataset										
1	One	-	-	-2734.8	-	2249	CL, Vd	49.9	4230.2	
2	Two	-	1	-	-		CL, Vd			Unable to converge
3	One	(AZOLE-CL)	1	-3010.2	-275.384	2059.8	CL, V	60	4023.9	Ref
4	One	(HCT-CL)	1	-	-	-	CL, V			Unable to converge
5	One	(HCT-V)	1	-2790.4	-55.5	2279.6	CL, V	49.9	4230.2	
6	One	(CR-CL)	1	-2788.3	-53.4	2281.7	CL, V	48.9	4023.9	
7	One	(ALB-V)	1	-2735.0	-0.19	2335.0	CL,V	39.9	4188.1	
8	One	(BMT-CL)	1	-2827.9	-93.0	2244.1	CL, V	40.4	3677.5	
9	One	(TBIL-CL)	1	-2739.2	271.0	2330.8	CL, V	49.9	4146.4	
10	One	(TBIL-V)	1	-2723.8	275.4	2335.2	CL, V	49.9	3498.2	
11	One	(AZOLE-CL) & (BMT-CL)	3	-3102.8	-92.6	1971.2	CL, V	54.6	4628.55	Minimisation failed
12	One	(AZOLE-CL) & (HCT-V)	3	-3074.2	-63.9	1997.8	CL, V	60.9	4023.9	Ref
13	One	(AZOLE-CL) & (HCT-CL)	3	-3051.8	-41.6	2020.2	CL, V	59.1	4023.9	
14	One	(AZOLE-CL) & (CR-CL)	3	-3050.1	-39.8	2021.9	CL, V	59.1	3866.1	
15	One	(HCT-V) & (CR-CL)	3	-2838.7	171.5	2233.3	CL, V	48.9	4064.3	
16	One	(HCT-CL) & (CR-CL)	3	-	-	-	CL,v	-	-	Unable to converge
17	One	(HCT-V) & (BMT-CL)	3	-2839.4	170.9	2234.6	CL, V	51.4	5541.4	
18	One	(HCT-CL) & (BMT-CL)	3	-	-	-	CL, V	-	-	Unable to converge
19	One	(CR-CL) & (BMT-CL)	3	-	-	-	CL, V	-	-	Unable to converge
20	One	(HCT-CL) & (HCT-V)	3	-2840.0	170.2	2232.0	CL, V	48.9	4230.2	
21	One	(AZOLE-CL) & (BMT-CL) & (HCT-V)	12	-3093.2	-19.0	1982.8	CL,V	62.2	4769.5	Minimisation failed
22	One	(AZOLE-CL) & (BMT-CL) & (HCT-CL)	12	-3124.5	-50.3	1951.5	CL, V	51.9	3533.3	Minimisation failed

Continued on next page

Model No	Compartment	Covariate tested	Ref model	OFV	ΔOFV	AIC	Eta	CL	V	Comment
23	One	(AZOLE-CL) & (BMT-CL) & (CR-CL)	12	-	-	-	CL, V	-	-	Unable to converge
24	One	(AZOLE-CL) & (HCT-V) & (CR-CL)	12	-3109.2	-35.0	1964.8	CL,V	59.1	3904.9	Ref
25	One	(AZOLE-CL) & (HCT-CL) & (CR-CL)	12	-3096.2	-22.0	1977.8	CL, V	58.0	3866.1	
26	One	(AZOLE-CL) + (HCT-CL) & (HCT-V)	12	-3120.4	-46.2	1953.6	CL, V	59.7	4023.9	
27	One	(HCT-CL) & (HCL-V) & (CR-CL)	12	-	-	-	CL, V	-	-	Unable to converge
28	One	(HCT-CL) & (HCL-V) & (BMT-CL)	12	-	-	-	CL,V	-	-	Unable to converge
29	One	(AZOLE-CL) & (BMT-CL) & (HCT-CL) & (HCL-V)	22	-3184.7	-60.2	1893.4	CL, V	52.5	3604.7	Minimisation failed
30	One	(AZOLE-CL) & (HCT-CL) & (HCT-V) & (CR-CL)	24	-3160.0	-50.8	1916.0	CL, V	58.0	3866.1	Minimisation failed
31	One	(AZOLE-CL) & (BMT-CL) & (CR-CL) & (HCT-V)	24	-	-	-	CL, V	-	-	Unable to converge
32	One	(HCT-CL) & (HCL-V) & (CR-CL) & (BMT-CL)	24	-2939.3	169.7	2138.7	CL, V	49.4	5166.8	
33	One	(AZOLE-CL) & (HCT-CL) & (HCL-V) & (CR-CL) & (BMT-CL)	24	-	-	-	CL,V	-	-	Unable to converge
Final IV model = Run 24 (AZOLE-CL) & (HCT-V) & (CR-CL) OFV = -3109.2										
IV and oral combined dataset										
34	One	(AZOLE-CL)& (HCT-V) & (CR-CL)	-	-3625.6	-	3602.8	CL, V, F	59.1	3904.9	
Backward elimination										
35	One	Eliminate (CR-CL)	34	-3564.7	60.94	3661.7	CL, V, F	59.1	4315.6	
36	One	Eliminate (HCT-V)	34	-3567.5	58.2	3659.0	CL, V, F	57.4	4023.9	
37	One	Eliminate (AZOLE-CL)	34	-3358.8	266.9	3867.7	CL, V, F	53.0	4188.1	
38	One	Eliminate (HCT-V) & (CR-CL)	34	-3581.6	44.0	3642.9	CL, V, F	47.9	4188.1	
39	One	Eliminate (AZOLE-CL) & (CR-CL)	34	-3288.1	337.6	3936.4	CL, V, F	48.9	4491;8	
40	One	Eliminate (AZOLE-CL) & (HCT-V)	34	-3309.1	316.5	3915.4	CL, V, F	47.9	4146.4	

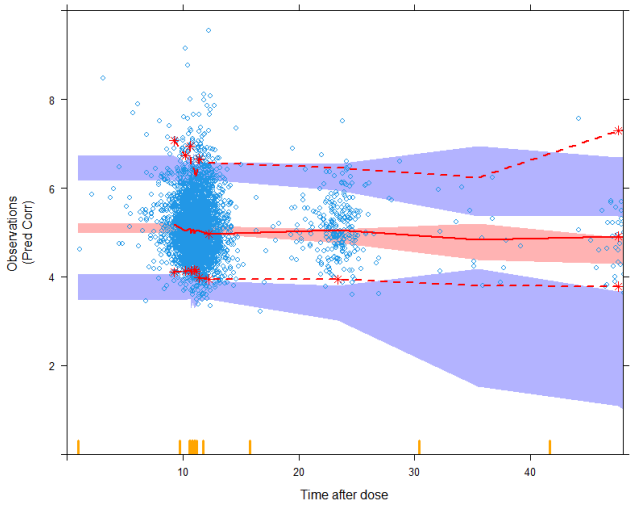


Figure 3.7: Prediction-corrected visual predictive check of the final model showing the 5th, 50th, and 95th percentiles of the observed data (lines with closed circles) compared with the 90% confidence intervals of the corresponding simulated percentiles from the final model (shaded areas).

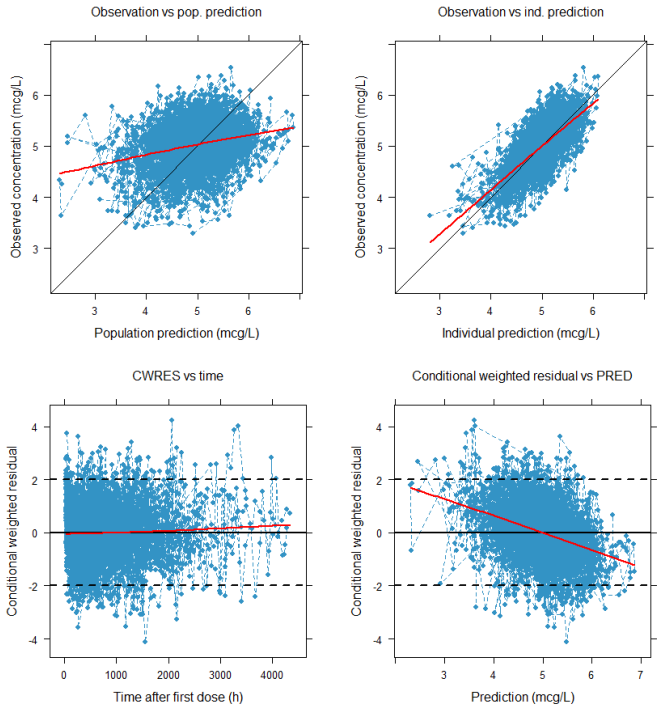


Figure 3.8: Goodness of fit plots of the ciclosporin final model. Top panels: observed versus population (left) and individual (right) predictions with line of identity (solid black) and locally weighted regression (LOESS, red) overlaid. Bottom panels: conditional weighted residuals (CWRES) versus time (left) and predictions (right), with reference lines at 0 and ±2 (dashed black) and LOESS smoothing (red). The LOESS curve illustrates systematic trends or bias in the data relative to the model fit.

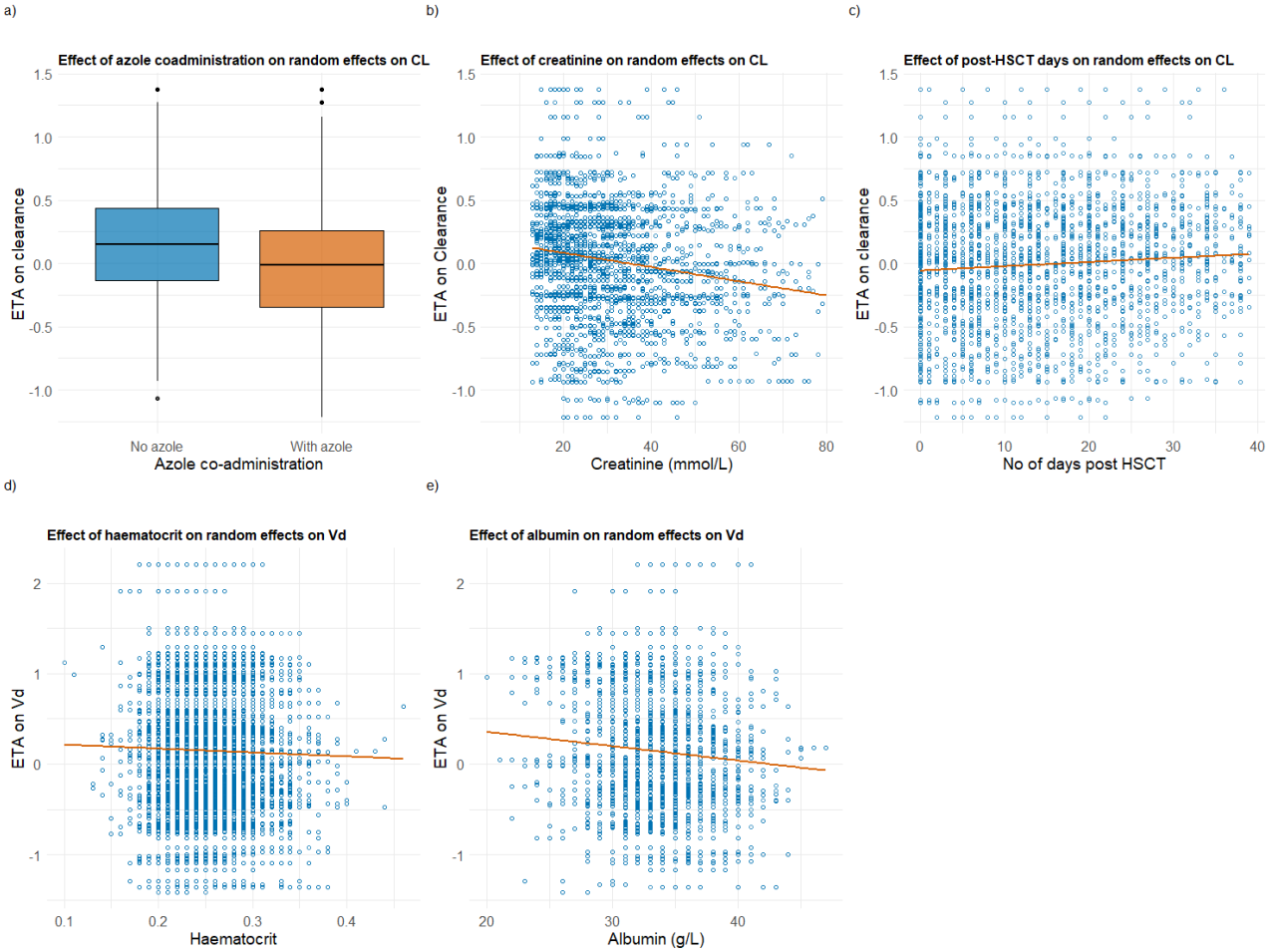


Figure 3.9: Effects of various covariates on random effects on CL and Vd of base ciclosporin model.

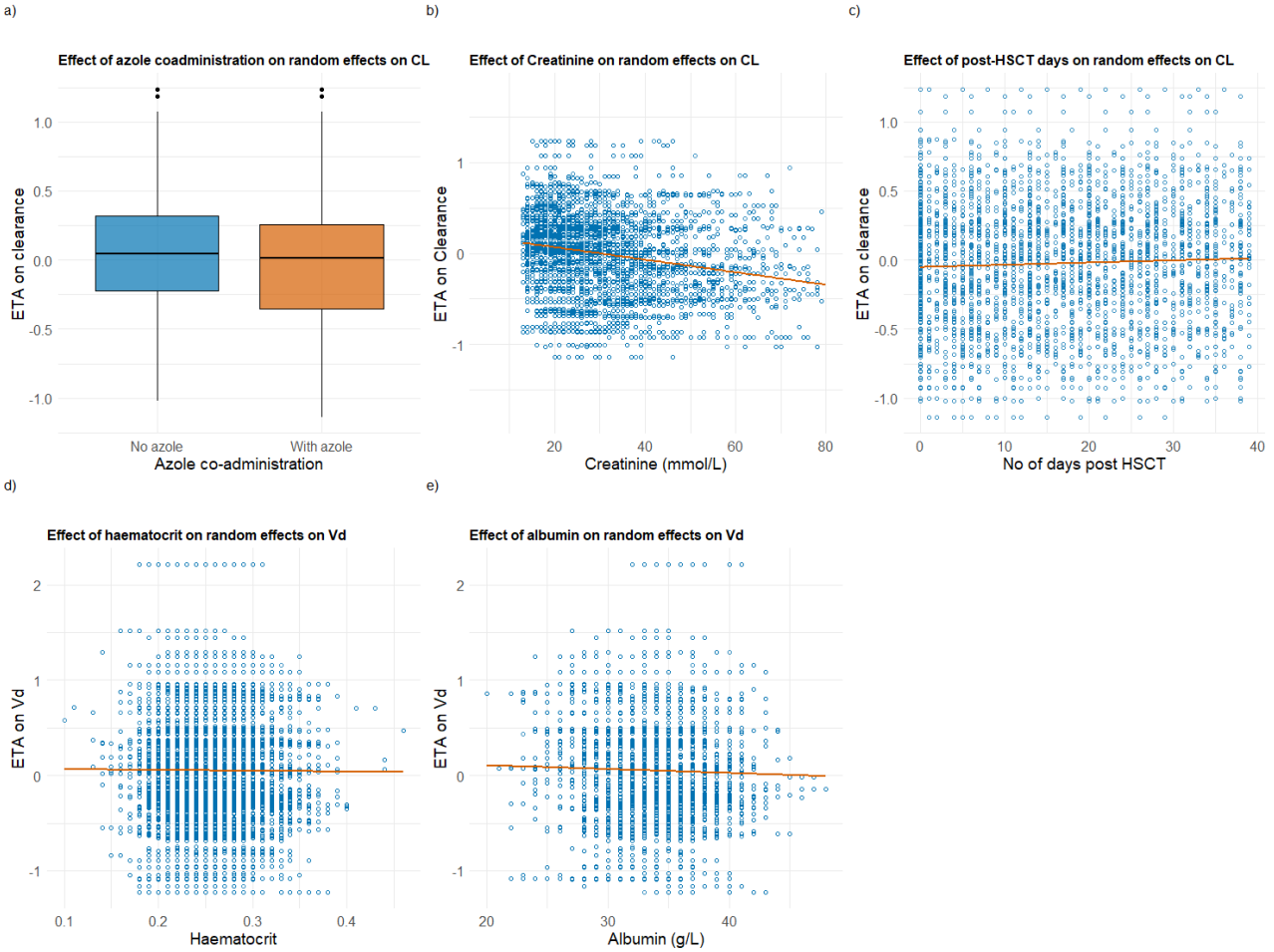


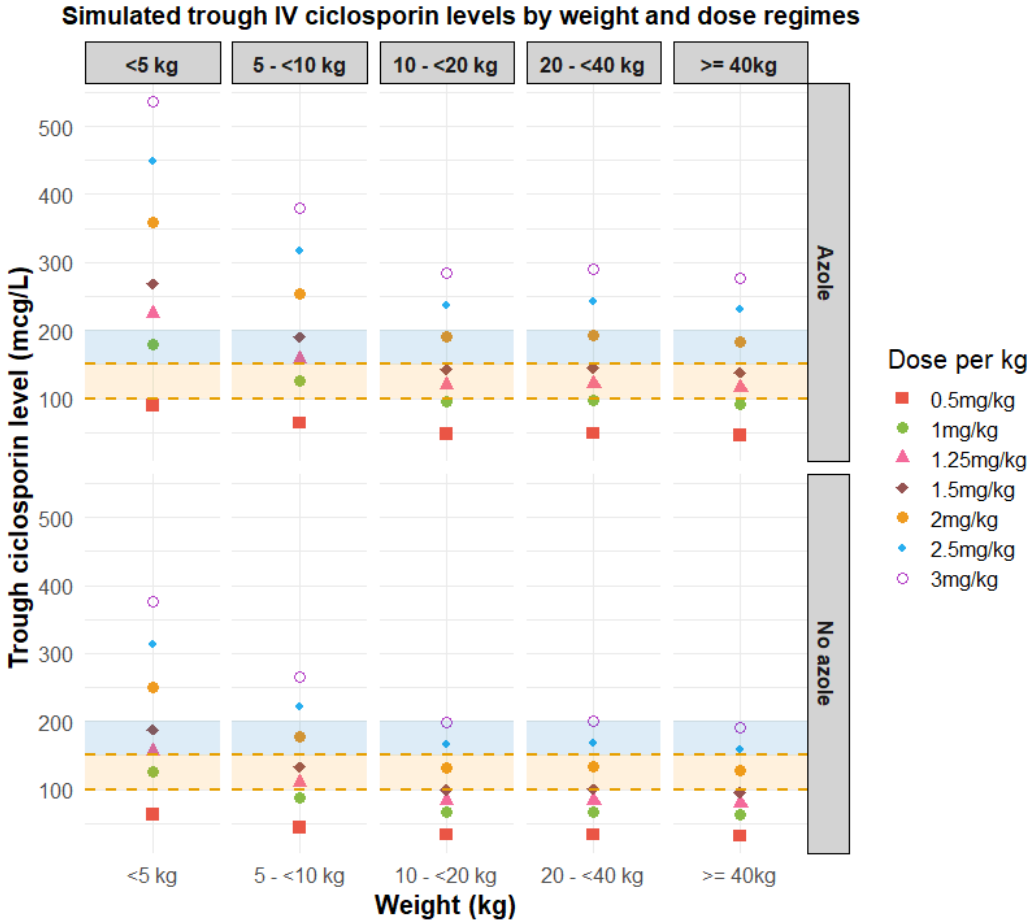
Figure 3.10: Effects of various covariates on random effects on CL and Vd of the ciclosporin final model.

3.6.2 Simulation

To evaluate the expected ciclosporin exposure under different dosing regimens, simulations were performed using the final population pharmacokinetic model. A total of 1,000 virtual patients were generated based on the median values of relevant covariates in the modelled population. Simulations were conducted to predict ciclosporin trough concentrations (12-hour post-dose) following various intravenous weight-based dosing strategies: 0.5 mg/kg, 1 mg/kg, 1.25 mg/kg, 1.5 mg/kg, 2 mg/kg, 2.5 mg/kg, and 3 mg/kg. These doses were selected to reflect clinically practical increments that are easy for prescribers to implement, and were intended as initial twice-daily intravenous doses.

Simulations were stratified by weight categories commonly encountered in paediatric clinical practice: < 5 kg, $5 - < 10$ kg, $10 - < 20$ kg, $20 - < 40$ kg, and ≥ 40 kg. These groups roughly correspond to typical age bands from neonates and infants through to older children and adolescents. The aim was to determine which weight-based dose regimens would most reliably achieve target trough ciclosporin concentrations within two commonly applied therapeutic ranges: 100 – 150 mcg/L and 150 – 200 mcg/L.

The median (50th percentile) trough concentrations for each weight group and dose level are displayed in Figure 3.11a. Shaded areas in the plot indicate the target concentration ranges, allowing visual identification of dose levels associated with achieving therapeutic exposures. Based on these simulations, dose recommendations were summarised in tabulated form (Figure 3.11b), highlighting the dose required to achieve a median trough concentration within the specified therapeutic range, with and without concomitant azole antifungal coadministration.



(a) Simulated median trough ciclosporin levels across weight categories. Yellow shading = 100–150 mcg/L; blue shading = 150–200 mcg/L.

Target 100 - 150 mcg/L

Weight	<5kg	5 - <10kg	10 - <20kg	20 - <40kg	>=40kg
IV dose with Azole (mg/kg)	0.75	1	1.5	1.5	1.5
IV dose with no azole (mg/kg)	1	1.5	2	2	2

Target 150 - 200 mcg/L

Weight	<5kg	5 - <10kg	10 - <20kg	20 - <40kg	>=40kg
IV dose with Azole (mg/kg)	1	1.25	2	2	2
IV dose with no azole (mg/kg)	1.5	2	2.5	2.5	2.5

(b) Dose recommendation based on simulation for intravenous ciclosporin with or without concomitant azole antifungals.

Figure 3.11: Simulated initial intravenous dosing recommendations, administered twice daily, stratified by weight category and azole co-administration. Doses were selected to achieve therapeutic ciclosporin trough concentration targets of 100–150 mcg/L and 150–200 mcg/L.

3.7 Discussion

This study established a clinically relevant population pharmacokinetic model of ciclosporin in paediatric HSCT recipients, integrating key developmental and clinical covariates to explain inter-individual variability within a highly heterogeneous cohort. The model is built on real-world therapeutic drug monitoring data from what is, to our knowledge, the largest single-centre cohort of paediatric HSCT patients studied to date. Spanning a broad paediatric age range, from infants to adolescents, this dataset enhances the model's generalisability and translational utility for informing personalised dosing in routine clinical practice. A one-compartment model with first-order absorption was identified as the most appropriate to describe the observed data. Although a two-compartment model was initially explored, the dataset consisted almost exclusively of trough concentrations, limiting identifiability and precluding robust estimation of distribution parameters.

The final model demonstrated good overall performance. Goodness-of-fit plots showed no major bias, and individual predictions tracked observed concentrations well. CWRES were evenly distributed across time and predicted values. Prediction-corrected visual Predictive Checks confirmed that observed concentrations were well-captured within the 5th–95th percentile prediction intervals. Shrinkage in IIV for both CL and Vd remained below 16%, supporting the reliability of eta–covariate relationships. The inclusion of maturation, azole effect, and haematocrit resulted in a biologically plausible and stable model structure suitable for simulation and dose optimisation.

The estimated typical clearance of ciclosporin was higher than values typically reported in adult populations, but consistent with previous paediatric HSCT studies [198, 199]. This elevated clearance likely reflects increased CYP3A-mediated metabolism in children. Developmental pharmacokinetic data indicate that hepatic and intestinal CYP3A4 activity exceeds adult levels during early childhood [121], with rapid postnatal increases that may peak during infancy. This may contribute to higher oral clearance and reduced bioavailability of ciclosporin in younger patients.

To account for these age-related differences in enzyme maturation, postmenstrual age was incorporated using a sigmoidal maturation function as a priori on clearance. Although most patients in the cohort were beyond infancy, this approach enhances the model's physiological plausibility across the full paediatric age range and ensures applicability to younger children. The maturation function helped reduce unexplained inter-individual variability and avoided overestimation of clearance in the youngest subjects. While attempts were made to estimate the PM_{50} and Hill coefficient, the dataset did not support precise estimation, despite including 49 patients under 1 year and 17 under 6 months. Therefore, values were fixed based on published data for midazolam, a well-characterised CYP3A4 substrate. This decision was previously evaluated in Chapter 2 and shown to produce plausible results, supporting its continued use here to improve numerical stability and avoid overfitting.

Despite higher estimated CL and Vd, the simulated doses required to reach target ciclosporin concentrations closely aligned with doses used in clinical practice. The EBMT handbook recommends initiating ciclosporin at 3 mg/kg/day IV until engraftment, followed by oral therapy [188]; however, this guidance does not specify age- or weight-based adjustments, nor does it account for azole coadministration. The current model provides greater precision for individualised dosing across age and weight groups.

Compared with other paediatric HSCT popPK models, including those by Li *et al.*, 2019, Gao *et al.*, 2022, and others [195, 196, 203, 213], the parameter estimates in this study are broadly consistent, particularly given the focus on trough data. Fanta *et al.*, 2007 [200] and Eljebari *et al.* (2012) [167] provided valuable comparative datasets, although their inclusion of richer sampling allowed for more complex compartmental models. The current model reflects real-world clinical data characterised by sparse sampling, which limits structural model complexity but enhances clinical relevance.

3.7.1 Covariate Effects

Three covariates, azole co-administration, haematocrit, and serum creatinine, were identified as both statistically and clinically significant, and were retained in the final pharmacokinetic model. Their inclusion improved model stability, reduced inter-individual variability, and yielded more physiologically plausible parameter estimates. Additional variables, such as albumin, total bilirubin, and post-HSCT day, were evaluated but ultimately excluded based on their lack of statistical significance or consistency across studies.

Concomitant use of azole antifungals was associated with a significant reduction in ciclosporin clearance, consistent with the known inhibition of CYP3A4. This was implemented as a binary covariate on the log-scale for clearance. In the base model, the distribution of individual clearance estimates (eta CL) differed markedly between patients receiving and not receiving azoles (Figure 3.9); this difference was effectively resolved upon covariate inclusion (Figure 3.10). Azole co-administration (including itraconazole, posaconazole, and voriconazole) reduced clearance by approximately 29%, consistent with literature estimates ranging from 15% to 50% [195, 202, 210]. This supports the robust pharmacokinetic interaction and underscores the necessity of incorporating azole use into dosing algorithms.

Haematocrit was retained as a covariate on Vd using a power model normalised to the median value. Given ciclosporin's extensive binding to erythrocytes, changes in haematocrit can substantially influence whole-blood concentrations. In the base model, eta on Vd showed a clear inverse trend with haematocrit; this was flattened in the final model, indicating improved explanatory power. The effect estimate (–0.40, RSE 13%) was consistent across bootstrap replicates and tightly bounded (95% CI: –0.55 to –0.33). The inclusion of haematocrit is especially relevant during the early post-HSCT period, when values fluctuate significantly due to anaemia and transfusions [223]. This finding aligns with several published models [200, 202, 204, 205, 211, 215] that report an inverse association between haematocrit and ciclosporin clearance or distribution.

Serum creatinine was investigated as a marker of overall clinical status rather than direct renal elimination, as ciclosporin is primarily hepatically cleared. Several parameterisations were explored; age-adjusted creatinine (Ceriotti *et al*. 2008 [220]) yielded the most stable model. Nevertheless, residual ηCL trends remained, suggesting creatinine only partially accounts for observed variability. It may serve as a surrogate for multisystem dysfunction, including fluid overload, hepatic congestion, or systemic inflammation, that impacts drug disposition. Similar associations have been observed in previous studies [200, 204].

Despite biological plausibility, neither albumin nor bilirubin improved model fit. Albumin plays a role in protein binding and reflects liver synthetic function, while bilirubin is commonly used to assess hepatic function. However, these parameters were not retained in the final model due to weak associations with clearance or Vd. Prior studies show inconsistent findings: only Zhou *et al*. (2012) [202] reported a significant negative correlation between albumin and clearance, and Gao *et al*. (2022) [199] found an inverse relationship between total bilirubin and clearance. These findings suggest that while biologically plausible, albumin and bilirubin may not be reliable predictors of ciclosporin pharmacokinetics in paediatric HSCT populations, potentially due to multifactorial influences on liver function and the complex interplay of other clinical variables.

Post-transplant day was evaluated as a time-varying covariate on clearance. Despite a biologically plausible rationale, early post-transplant inflammation, mucositis, and variable absorption, this covariate was not statistically significant in the final model. Dose-normalised concentrations showed an early upward trend that plateaued around day 14, aligning with expected physiological recovery and engraftment [224]. This trend may also reflect cytokine-induced downregulation of CYP3A4 (e.g., interleukin-6, tumour necrosis factor-α), as reported in HSCT contexts [225, 226]. However, the wide inter-individual variability in post-HSCT complications likely masked any consistent temporal pattern. Other covariates (e.g., creatinine, haematocrit) may have indirectly captured some of these effects.

3.7.2 Simulation

Model-based simulations demonstrated that the ciclosporin dose required to achieve target trough concentrations increased with body weight but did so in a non-linear pattern. For example, infants on T cell depleted regimes (target 150 - 200 mcg/L) weighing less than 5 kg not on an azole antifungal required lower doses, approximately 1 mg/kg every 12 hours while children in the 5–10 kg group required around 1.25 mg/kg. For children weighing more than 10 kg, doses of 2 mg/kg twice daily were needed to achieve therapeutic exposure, with dosing requirements plateauing beyond this weight threshold.

This trend reflects the ontogeny of CYP3A4, the primary enzyme responsible for ciclosporin metabolism. CYP3A4 expression begins after birth, with substantial inter-individual variability in the early months. The observed increase in simulated dose from $<$ 5 kg to 10 kg aligns with this developmental window, after which enzyme activity, and by extension, ciclosporin clearance, plateaus. Given that 10 kg roughly corresponds to the average weight of a 1-year-old child, these findings are consistent with known physiological maturation and suggest that weight and age together are key drivers of ciclosporin disposition during early childhood.

Notably, the European Society for Blood and Marrow Transplantation (EBMT) recommends a standard starting dose of 3 mg/kg/day, typically administered as 1.5 mg/kg every 12 hours, irrespective of age, weight, target therapeutic range or co-medication status [188]. However, according to these simulations, this uniform approach may lead to overexposure in smaller infants and underexposure in heavier children, particularly when azoles are not co-administered. These findings underscore the limitations of fixed-dose strategies and highlight the clinical value of model-informed, weight-adjusted dosing, particularly in the early post-transplant period when therapeutic drug monitoring is still being established. Incorporating developmental pharmacology into initial dose selection may reduce time to therapeutic exposure and minimise the risk of suboptimal immunosuppression or toxicity.

3.8 Limitations and future directions

While the final model demonstrated good predictive performance, several limitations should be acknowledged. First, the dataset was derived from sparse, real-world therapeutic drug monitoring data, primarily consisting of trough concentrations. Although ciclosporin levels are measured frequently in clinical practice, samples are almost exclusively troughs obtained for routine dose adjustment. Opportunistic sampling outside of troughs is rare, and additional non-essential blood draws are not ethically or practically feasible in this high-risk paediatric population. Consequently, the dataset was unsuited for accurately characterising absorption parameters or supporting multi-compartment structural models. A richer sampling design—including multiple post-dose time points—would improve estimation of absorption and distribution processes and allow evaluation of more complex model structures.

Second, the analysis did not include some clinically important but unmeasured factors that may influence ciclosporin pharmacokinetics, such as diarrhoea and severity of comorbidities (e.g. presence of GVHD). These unmeasured covariates could contribute to residual inter-individual variability not explained by the included model predictors.

Third, the study was conducted at a single centre, which may introduce site-specific biases due to local assay methodology, supportive care practices, or dosing strategies. External validation in multi-centre cohorts is needed to confirm the model's generalisability.

Future work should focus on prospective validation of the model in independent datasets, integration with clinical decision support tools, and exploration of Bayesian forecasting approaches to enable adaptive dosing. Incorporating real-time covariate updates, such as fluctuations in haematocrit, renal function, or co-medication use, may further improve precision dosing during the early post-transplant phase. This is particularly relevant in the first 2–3 weeks after HSCT, when pharmacokinetic variability is greatest, mucositis and gut dysfunction can

compromise absorption, and ciclosporin exposure has been shown to strongly influence the risk of acute GVHD [227]. A prospective evaluation of model-informed, real-time dosing during this high-risk window would be especially valuable to determine whether tighter exposure control can translate into improved time in therapeutic range and reduced rates of toxicity or GVHD.

3.9 Clinical implications

Tailoring initial doses to patient-specific covariates, such as weight, age, and comedication status, could improve target attainment, particularly during the early post-transplant phase when pharmacokinetic variability is greatest. Achieving appropriate ciclosporin exposure during this early period is critical not only for effective GVHD prophylaxis but also for long-term clinical outcomes. Evidence from T-cell depleted, reduced-intensity conditioning allografts in acute myeloid leukaemia has shown that excessive ciclosporin exposure within the first 21 days post-transplant is associated with an increased risk of relapse and reduced overall survival [228]. These findings underscore the importance of avoiding overexposure through model-informed, individualised dosing strategies, particularly in high-risk transplant subgroups.

The model's structure and covariate relationships are suitable for integration into Bayesian therapeutic drug monitoring platforms or clinical decision support systems. As outlined in the 10 Year Health Plan for England policy paper [229], there is a national commitment to digitise prescribing and leverage digital health data and technologies to improve patient care. In this context, there may be future potential to embed model-informed dose suggestions directly into electronic prescribing workflows locally and nationally. With further validation, the model could support proactive dose individualisation before therapeutic drug monitoring data are available, and enable real-time dose refinement based on sparse sampling and evolving clinical parameters.

3.10 Conclusion

This study presents a validated population pharmacokinetic model of ciclosporin in paediatric HSCT patients, developed using the largest real-world dataset of its kind. The model incorporates key physiological and clinical covariates, including allometric weight scaling, postmenstrual age, haematocrit, serum creatinine, and azole coadministration, to explain inter-individual variability in ciclosporin clearance and distribution. Its alignment with established developmental pharmacology and observed clinical dosing patterns supports its relevance and applicability in routine practice.

Simulations using the model demonstrated that weight-adjusted, covariate-informed dosing is necessary to achieve therapeutic ciclosporin concentrations across age groups. The findings advocate for model-informed precision dosing in the paediatric cohort, moving beyond empiric dosing strategies. This work contributes a practical, mechanistic foundation for optimising ciclosporin exposure in children undergoing stem cell transplantation.

Chapter 4

Immunoglobulin

4.1 Introduction

Immunoglobulin replacement therapy (IgRT) is an established treatment modality for managing both primary immunodeficiency (PID) and secondary antibody deficiency (SAD). While PID arises from intrinsic genetic defects affecting the immune system, SAD results from extrinsic factors such as malnutrition, human immunodeficiency virus (HIV) infection, and haematological malignancies or their associated treatments [230–233]. Recent years have seen the introduction of novel therapies targeting B cells, such as rituximab and chimeric antigen receptor T-cell (CAR-T) therapy, which has transformed the management of autoimmune and haematological conditions in children [234, 235]. Increased use of B-cell depleting novel therapies, as well as improved diagnostic capability of primary immunodeficiency disorders, has contributed to a 6-8% annual increase in the demand for Ig globally between 2010 to 2018 [236]. Given the geographic disparity in plasma supply and the considerable financial burden associated with IgG products, optimising and rationalising its use is of increasing clinical importance.

4.1.1 Ontogeny of immunoglobulin in infancy and childhood

The development of the humoral immune system during early life is a dynamic process that underpins the variability in immunoglobulin production observed in

infants and young children. B cells, the lymphocytes responsible for antibody generation, are present in relatively high numbers at birth, with an initial postnatal increase followed by a gradual decline towards adult levels over the first decade of life [237]. However, the majority of neonatal B cells are naïve or immature, and the peripheral B-cell compartment evolves slowly, with immature B cells comprising approximately 20% of circulating B cells in children aged 5–10 years — still above the typical adult level of 10% [238]. During foetal life, antigenic exposure is minimal, resulting in low numbers of memory B cells at birth. The frequencies of memory B cells that continue to produce the original antibody type (non-switched, producing more general IgM antibodies) and those that change to other antibody types such as IgG or IgA (switched, providing more specialised and longer-lasting protection) increase gradually over time, reaching adult proportions by adolescence (10–15 years of age) [238]. Following class-switch recombination and affinity maturation, antigen-specific B cells differentiate along two key pathways: plasma cells and memory B cells. Long-lived plasma cells migrate to tissues such as the bone marrow, where they continuously secrete large amounts of antigen-specific antibody and are responsible for the majority of detectable IgG and IgA in plasma. By contrast, memory B cells enter a quiescent state, recirculating through blood and secondary lymphoid organs, ready to mount a rapid and robust humoral response upon re-exposure to antigen. It is important to note that plasma cells are not detected in standard peripheral blood immunophenotyping, which means B-cell counts alone do not necessarily correlate with serum immunoglobulin levels.

Immunoglobulins, the effectors of the humoral immune response, exist in several isotypes including IgM, IgA, and IgG. These molecules neutralise pathogens, facilitate opsonisation (coating microbes with antibody to enhance their uptake by phagocytes), and contribute to mucosal defence. Following antigen exposure, IgM is the first antibody to be secreted, with IgG and IgA arising after class-switch recombination. Antibody class switching begins in clonally expanded antigen-specific B cells from around six days after primary activation, enabling the production of other antibody classes such as IgG and IgA [239]. In neonates, limited pathogen expo-

sure and immune immaturity result in very low levels of class-switched B cells in peripheral blood. After birth, exposure to environmental antigens drives maturation of the antibody response, increasing both the proportion of class-switched B cells and the diversity of the IgG repertoire. Nonetheless, at one year of age, IgG levels reach only 70% of adult concentrations, while IgA remains at approximately 30% [240]. Despite this developmental immaturity, neonates are partially protected by passively acquired maternal IgG, which is actively transported across the placenta during the third trimester. This transport results in higher IgG titres in term neonates than in their mothers at birth, providing passive immunity for up to six months while the neonatal immune system is immature [241]. However, preterm infants receive less maternal IgG and are more susceptible to infections during early infancy as these passively transferred antibodies wane more quickly.

4.1.2 Immunoglobulin use in PID children

Children with PID and SAD can have serious, prolonged, and sometimes life-threatening infections [242, 243]. While PID can occur in both adults and children, it is more frequently diagnosed in childhood. Therapeutic immunoglobulin preparations used in IgRT are primarily composed of pooled human IgG, which is the main active component providing passive immunity, although trace amounts of Ig isotypes may also be present [244].

Children with PIDs characterised by severely impaired or absent humoral immunity are typically managed with a combination of prophylactic antimicrobials and IgRT. Despite its routine use, there is a paucity of published evidence on the management of IgRT in PID children. The British Society for Immunology and the United Kingdom Primary Immunodeficiency Network (UKPIN) published a consensus on the management of PID patients, with a cumulative starting dose of 0.4 to 0.5 g/kg every month and an optimal IgG target $\geq$ 8 - 10 g/L [245]. The American Academy of Allergy Asthma and Immunology (AAAI) recommended a starting dose of 0.4 - 0.6 g/kg every 3-4 weeks with maintenance of IgG levels above 5 - 8 g/L in hypogammaglobulinemia PID patients to reduce infectious consequences [246]. NHS

England has adopted a starting dose of 0.4 - 0.6 g/kg every month with no definitive trough maintenance target [247]. All agencies suggested adjusting doses according to clinical response.

4.1.3 Cause of SAD

Patients with SAD experience decreased serum IgG levels or an impaired antibody production (hypogammaglobulinemia) secondary to external factors [230]. Low serum IgG levels expose SAD patients to an increased risk of infections and impair their quality of life [248]. Those with persistent low serum IgG levels and recurrent infections may need IgRT to reduce the risk of infectious events and preserve long-term health and development. [247, 249, 250].

Rituximab is a chimeric murine/human monoclonal antibody targeting the CD20 antigen expressed on peripheral B cells, whereas CAR-T therapies are engineered to target CD19+ cell, leading to profound B-cell depletion. B cell suppression typically lasts for six months but can persist for years with profound effects [251, 252]. Children are particularly susceptible to prolonged and severe hypogammaglobulinaemia following CAR-T therapy when compared to adults [252, 253].

4.1.4 Immunoglobulin use in SAD children

The use of IgRT is well-established in the treatment of PIDs and is supported by decades of clinical experience, consensus guidelines, and pharmacoeconomic assessments due to its substantial cost implications [103, 248]. However, in contrast to PID, the role of IgRT in SAD remains less clearly defined and is supported by comparatively limited evidence [254].

Due to the paucity of robust clinical trials and the lack of large-scale, randomised studies in SAD, current dosing practices for IgRT in this population are often extrapolated from experience in PID patients [249]. This empirical approach presents challenges, particularly when attempting to individualise therapy or assess its long-term efficacy in a highly heterogeneous patient population. Despite this, several professional organisations have attempted to address this evidence gap. Consen-

sus guidance documents and expert recommendations from the American Academy of Allergy, Asthma & Immunology (AAAAI), UKPIN, NHS England, and various European working groups have outlined indications and practical considerations for initiating and monitoring IgRT in SAD patients [245, 247, 249, 255]. Nevertheless, therapeutic targets and monitoring strategies remain inconsistent and vague. The recommended starting dose of IgRT for SAD is similar to that for PID, typically 0.4–0.6 g/kg administered every four weeks, with subsequent adjustments guided by clinical response, particularly the frequency and severity of infections [254, 255]. The optimal trough level for SAD patients is not clearly defined, and no universally accepted threshold exists [245, 247, 249, 255]. Expert consensus statements suggest maintaining IgG trough levels above 6 g/L as a minimum target in SAD, although this is largely based on observational data and clinical experience rather than interventional trials [245, 249]. In patients with more severe or recurrent infections, particularly those with high disease burden or comorbidities, a higher target trough level of up to 10 g/L may be necessary to prevent breakthrough infections and hospitalisations [245, 249].

In the paediatric population, the guidance becomes even more limited. Due to the physiological variation in serum immunoglobulin levels with age, establishing a universal target is particularly difficult. NHS England suggests that, at a minimum, IgRT should aim to maintain IgG trough levels above the lower limit of the age-specific reference range [247]. However, this recommendation is not supported by strong clinical trial evidence and may not be sufficient for all children with SAD. Furthermore, individual responses to IgRT can be highly variable, and the correlation between serum IgG concentrations and clinical efficacy remains poorly understood, especially in children.

The lack of age-specific dosing algorithms and monitoring strategies in paediatric SAD underscores the urgent need for prospective studies to evaluate the pharmacokinetics, pharmacodynamics, and clinical outcomes associated with IgRT in this group. In the absence of high-quality evidence, treatment decisions must continue to

be guided by clinical judgement, individualised risk–benefit assessment, and evolving expert consensus.

4.1.5 Immunoglobulin pharmacokinetics

To provide context for the subsequent model structure, Figure 4.1 collates systemic intravenous IgG clearance estimates from studies, scaled to a 70 kg reference using an allometric exponent of 0.75. CL typically lies between 0.12 – 0.20 L/day across childhood into adulthood, with neonates lower and some disease-specific outliers (Appendix D). Between-study variability is substantial, reflecting differences in product, assay, baseline correction and study design.

A summary of published pharmacokinetic models of immunoglobulin is provided in Table 4.1. Most studies have focused on patients with PID. Covariates evaluated include disease type and severity, age, total body weight, concurrent use of immunosuppressants, gender, and comorbidities. Incorporating weight as a covariate consistently improved model performance across these studies. Baseline (endogenous) IgG was usually fixed at 4 or 5 g/L, with only three studies measuring or estimating baseline concentrations [256–258].

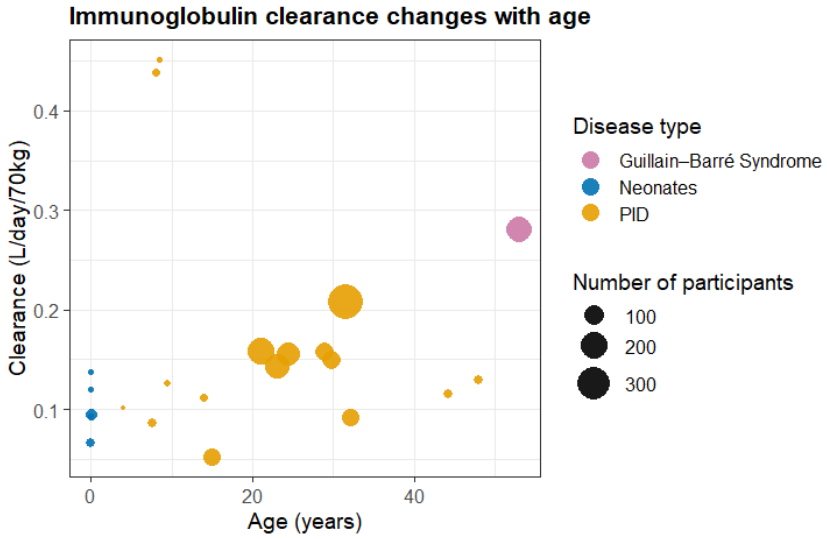


Figure 4.1: Systemic clearance of intravenous immunoglobulin across published studies, scaled to a 70 kg reference. The size of each data point represents the number of participants in the study. Colours denote disease groups. Only IV data are shown; non-IV apparent clearances (CL/F) are excluded.

Table 4.1: Published population pharmacokinetic model summary. PID = Primary immunodeficiency, PNA = postnatal age, SAD = Secondary antibody deficiency, IV= intravenous, SC= subcutaneous, Vc: central volume of distribution, Vp: peripheral volume of distribution CI = confidence interval, NR = not reported

Author Year [Ref]	Patient cohort	Median age, year (range)	Median weight, kg (range)	Sample size	Dose	Model compartment	Covariates tested	Significant covariates	Endogenous Ig level (g L-1)	CL (L/day/70kg)	V (L)
Landersdorfer et al., 2013 [259]	PID	24 (3–81)	64 (13–135)	151	IV: 451–460 mg/kg 3–4 weekly SC: 118.7–234 mg/kg weekly	2	Wt	Wt on CL and Vc	4 (FIX)	0.155 (0.143–0.165)	Vc = 4.45 (3.97–5.26) Vp = 4.72 (3.83–5.85)
Tortorici et al., 2019 [260]	PID + SID	PID: 29.8 (3–81) SID: 69.5 (21-84)	72 (18–135)	187	IV: 473 ± 133 mg/kg monthly (PID) IV: 216 ± 106 mg/kg monthly (SID)	2	Age, sex, disease type, wt	Wt on CL and Vc, Disease type on Vc	4 (FIX)	0.149 (0.137–0.157)	PID: Vc = 2.99 (2.42–3.55) SAD: Vc = 8.50 (3.53–14.90) Both: Vp = 1.75 (1.45–2.04)
Dumas et al., 2019 [261]	PID	32.1 (3–81)	63.7 (13.2–161.8)	81	IV: 300–1000 mg/kg 3–4 weekly SC: weekly equivalent doses	1	Age, geographic region, race, sex, wt	Wt on CL	Not reported	0.0922 (NR)	Vc = 4.01 (NR)
Zhang et al., 2020 [262]	PID	23 (3–81)	54–72.5 (13–135)	173	IV: 451–460 mg/kg 3–4 weekly SC: 118.7–234 mg/kg weekly to biweekly	2	Wt	Wt on CL and Vc	4 (FIX)	0.144 (0.135-0.154)	Vc = 4.05 (3.23–4.86) Vp = 4.71 (3.12–6.29)
Luo et al., 2020 [263]	PID	21 (3–81)	58.7 (13–135)	202	IV: 268.5–472.9 mg/kg 3–4 weekly SC: 108.0–209.0 weekly to biweekly	2	Age, ethnicity, sex, wt	Wt on CL and Vc	4 (FIX)	0.159 (0.148-0.17)	Vc = 4.79 (3.98–5.72) Vp = 4.19 (2.66–4.73)
Tegenge et al., 2020 [264]	Very low birth weight neonates	Chronological age of neonates: 3 days (1–6)	1.14 (0.78–1.5)	20	Single IV low dose: 500 mg/kg Single IV high dose: 750 mg/kg	2	Wt	None	5 (FIX)	0.0666 (NR)	Vc = 0.558 (NR) Vp = 3.532 (NR)
Lee et al., 2021 [257]	Ab deficiency on long term IVIG	9.5 (3–64)	26.65 (9.3-51)	10	IV: 360–600 mg/kg 3–4 weekly	1	Age, ethnicity, bronchiectasis, genotype, sex, wt	Wt	0.7	0.1261 (0.097 - 0.1456)	Vc = 5.10 4.38–5.62)
Fokkink et al., 2022 [265]	Guillain–Barré Syndrome	53 (5–89)	72 (18-122)	177	IV: 0.4 g/kg/day for 5 days	2	Age, disease severity, diarrhoea methylpredisolone, mechanical ventilation, sex, variable number of tandem repeats	GBS disability score, methyl-prednisolone	10.3 - 15.9	0.28 (0.24 - 0.34)	Vc = 2.87 Vp= 2.65
Li et al., 2022 [266]	PID with ab deficiency	31.5 (2.0–83.0)	66 (11.9 - 162)	394	0.04 to 1.2 g/kg weekly to 4 weekly	2	Age, BMT, IG product type, LBM, sex, wt	Wt	6.15	0.208 (0.097-0.1456)	Vc = 3.58 (3.39–3.77) Vp = 1.66 (1.07–2.26)
Navarro-Mora et al., 2022 [267]	PID	29 (2 - 72)	65.7 (16.7–153.0)	95	IV: 495mg/kg every 3-4 weeks SC: 184.8mg weekly	2	Age, SC formulation, sex, wt	Wt	4 (FIX)	0.157 (0.148-0.167)	Vc = 3.19 (3.05–3.34) Vp = 2.06 (1.57–2.55)
Lee et al., 2024 [258]	PID	15 (0.08 - 70)	43	79	IV 360-600 mg/kg every 3-4 week	2	Age, disease type, baseline IgG, comorbidity, ethnicity, genotype, sex, weight	Disease type, weight	9.08	0.0519 (0.0346–0.0692)	Vc = 1.95 (1.04–2.88) Vp = 0.85 (0.114–1.77)

A common challenge in IgG pharmacokinetics is the quantification of exogenous IgG following infusion, as measured serum IgG levels reflect the sum of both endogenous and administered IgG. To isolate the exogenous IgG component, most studies have assumed a fixed endogenous IgG level of 4 g/L. However, this approach may not be appropriate for PID or SAD patients. In clinical practice, immunoglobulin replacement is typically initiated in SAD patients only when serum IgG levels fall below 4 g/L, meaning endogenous levels in this group are often substantially lower than the assumed fixed value. For patients with PID, particularly those with agammaglobulinaemia or profound B cell dysfunction, the ability to generate any functional endogenous IgG may be entirely absent. In both cases, applying a universal endogenous IgG value of 4 g/L risks overestimating endogenous contribution and underestimating exogenous pharmacokinetics. Additionally, age has a known influence on immunoglobulin production, with younger children, especially infants, having lower baseline levels due to an immature immune system. In light of this, identifying a clinically accessible and reliable surrogate of B cell function is essential to appropriately characterise endogenous IgG levels in pharmacokinetic models, particularly in paediatric patients with PID or SAD.

Fokkink *et al.* (2022) [265] and Li *et al.* (2022) [256] addressed this limitation by estimating endogenous IgG as a model parameter. The presence of B cells, which produce IgG, offers a potential biomarker of endogenous IgG production. CD19 is a well-characterised surface antigen expressed from the pre-B cell stage through to plasma cell differentiation, making CD19+ cell count a reliable marker for humoral competence [268]. Fokkink *et al.* (2022) tested the influence of CD19+ cell count on baseline IgG levels and found it significantly improved model performance.

IgM plays a central role in the early humoral immune response and can serve as an informative marker of B-cell function. Upon initial antigen exposure, naïve B cells secrete IgM as the first line of antibody defence, which is subsequently replaced by IgG following class-switch recombination [269]. This process is often immature in neonates and young infants, who typically exhibit lower levels of both IgM and IgG

due to limited antigen exposure, underdeveloped germinal centres, and immature B-cell responses [270, 271]. In older children, particularly those with SAD or those who have received B cell depleting therapies such as rituximab or CAR T-cell therapy, IgM levels may remain suppressed, reflecting impaired B-cell reconstitution or persistent functional deficits.

In this context, IgM serves not only as a surrogate for active B-cell function but also as a developmental marker of humoral competence in children. Unlike CD19+ cell counts, the use of IgM as a covariate has not been widely explored in pharmacokinetic models of immunoglobulin. However, IgM is routinely measured in clinical immunology practice as part of standard immunoglobulin panels, making it a practical and accessible parameter. Incorporating IgM into PK models may enable more accurate estimation of endogenous IgG production capacity, particularly in paediatric patients with dynamic or therapy-altered immune systems. When combined with IgM levels, which reflect active immunoglobulin synthesis, CD19+ cell count can offer complementary insights into B-cell maturation and function. In pharmacokinetic modelling, both IgM and CD19+ cell count may act as surrogates for endogenous IgG synthesis potential, particularly in patient populations where direct quantification of endogenous IgG is confounded by ongoing therapeutic replacement.

This study aims to develop a population pharmacokinetic model of intravenous immunoglobulin to inform dosing strategies for paediatric patients with PID and SAD, with particular focus on covariates relevant to endogenous IgG production and B cell function.

4.2 Aim

To characterise the pharmacokinetics of intravenous immunoglobulin in children with PID and SAD and explore factors influencing inter-individual variability.

4.3 Objectives

- To develop a population pharmacokinetic model using clinical data from paediatric patients receiving intravenous immunoglobulin.
- To assess the probability of maintaining serum IgG concentrations within target ranges under existing dosing regimens
- To conduct model-based simulations to explore alternative dosing strategies predicted to enhance target attainment.

4.4 Materials and methods

4.4.1 Patient Data

A retrospective analysis of de-identified data captured by electronic health records in a tertiary paediatric hospital was performed. Children who received intravenous Ig for PID and SAD between April 2019 and April 2024 were included. Current dosing policy mirrors that of NHSE immunoglobulin commissioning policy [247], where PID patients receive 0.4 - 0.6 g/kg every 4 weeks and SAD patients receive 0.5 g/kg every 4 weeks.

De-identified data were collected, including demographics (age, weight, sex), treatment details (dose and timing of Ig), medical history (cause of SAD), and immunology blood results (baseline IgG levels, absolute CD19+ cell count, IgM and IgG plasma levels). Plasma IgG levels were measured using an immunoturbidimetric assay, with a lower limit of quantification (LLOQ) of 0.07 g/L.

4.4.2 Model development

The base structural model was first evaluated as one- and two-compartment models. Residual variability was assessed according to an additive and/or proportional error model. IIV was evaluated for clearance, volume of distribution and baseline IgG, assuming a log-normal distribution. For the base model selection, the AIC was used to compare non-nested models, while the OFV was utilised for nested model comparisons. Tested covariates were selected based on known potential effects on

Ig pharmacokinetics, including patient demographics (sex, weight, age) and laboratory data (absolute CD19+ cell count, IgM) and type of antibody deficiency.

In this study, measured IgG was assumed to be the sum of endogenous IgG, the baseline IgG (CBAS) level prior to treatment, and exogenous therapeutic Ig [265]. Therefore, individual prediction of total IgG in the model incorporated both the baseline of Ig and the prediction from the model representing the contribution of the therapeutic drug.

The IgG levels prior to treatment initiation for children with SAD were assumed to be baseline Ig levels (median 3.11 g/L). As all PID patients were established long-term patients on IgRT, their baseline IgG levels were assumed to be 4 g/L [259, 260, 262, 263, 267, 272].

Due to the presence of younger children (under two years old) in the population, PMA was evaluated using the sigmoid hyperbolic or Hill's model (Equation 3.2). Allometric weight-based scaling of clearance and volume terms was included *a priori*. Covariate effects were modelled using a general power function:

$$Parameter_i = Parameter_{pop} \times \left(\frac{c_i}{\overline{c}}\right)^{\theta} \times \exp(\eta_1) \tag{4.1}$$

where $Parameter_i$ is individual parameter estimate (e.g. CL, Vd, or CBAS), Parameter_{pop} is the typical population value. c_i is the individual value of the covariate and $\overline{c}$ is the population median of that covariate. θ quantifies the covariate effect, and η_1 accounts for inter-individual variability.

For allometric weight scaling, c_i was the individual body weight with $\overline{c}$ fixed to 70 kg; θ was fixed to 0.75 for clearance and inter-compartmental clearance and 1.0 for volumes of distribution [130]. Additional covariates were evaluated using the same equation, including age, absolute CD19+ B cell count, IgM concentration, and sex. CBAS, the typical baseline IgG concentration for the population, was modelled as a parameter that could vary according to CD19+ cell count and IgM, reflecting the contribution of B cell number and function to endogenous IgG production.

The effects of sex and antibody deficiency (PID vs SAD) on CL and Vd were explored. Sex and disease type were denoted by c_i, with males and PID coded as 0, and females and SAD coded as 1. Each covariate effect was introduced into the model using an exponential function parameterised by a fixed effect, θ_{cov}. The model equation for clearance was:

$$CL_i = CL_{\text{pop}} \times (\theta_{\text{cov}})^{c_i} \times \exp(\eta_i) \tag{4.2}$$

and similarly for Vd, with corresponding population parameters.

Stepwise forward inclusion and backward elimination were guided by the likelihood ratio test. A covariate was considered significant if it reduced the OFV by more than 3.84 points per degree of freedom ($p < 0.05$) during inclusion, and retained if its removal increased the OFV by more than 6.63 points per degree of freedom ($p < 0.01$) during elimination.

Population pharmacokinetic modelling was conducted using a FOCEI in NONMEM (7.5.1). Graphical diagnostics developed with Xpose (4.7.2) guided model development. In conjunction with the AIC, the goodness of fit plots (observation versus population prediction, observation versus individual prediction, CWRES versus time, CWRES vs PRED) and prediction-corrected VPC, nonparametric bootstrap (1,000 samples) and realistic parameter estimates were used as criteria for model selection.

4.4.3 Simulation

Simulations were performed using the final population pharmacokinetic model in NONMEM (7.5.1) with parameter uncertainty incorporated via sampling from the variance–covariance matrix (n = 1,000 replicates). A total of 1,000 virtual paediatric patients were generated using the median values of relevant covariates (weight, IgM level and type of immunodeficiency) observed in the modelled cohort, with between-subject and residual variability retained from the model. Simulated regimens included maintenance doses of 0.4, 0.5, and 0.6 g/kg every 21 or 28 days,

with and without a single loading dose of 1 g/kg on day 0. These regimens were selected to reflect clinically practical dosing used in PID and SAD patients. For each regimen, median and 95% prediction intervals for plasma IgG concentrations over the dosing interval were generated. The probability of target attainment (PTA) was then calculated as the proportion of simulated patients whose IgG concentrations remained above the recommended therapeutic thresholds (PID $\geq$ 8 g/L; SAD $\geq$ 6 g/L) across the dosing interval.

4.5 Result

Sixty-four children, aged between 3 weeks to 16.8 years, with a median weight of 18.6 (3.15 - 95.3 kg), received intravenous Ig for PID and SAD during the study period. 444 blood samples were taken at various time points (Table 4.2). The cohort consisted of 44 PID and 20 SAD patients, of which 15 of SAD patients had antibody deficiencies due to rituximab, and five due to CAR T-cell therapy. The overall median baseline IgG level before the initiation of IgRT was 4 g/L (0.64 - 6.1 g/L) and the absolute CD19+ cell count was 0.07 x 10^{-9} cell/L (0 - 6.07 x 10^{-9} cell/L). The median dose given was 0.56 g/kg (0.24 to 1.38 g/kg) every 28 days. All observations were above the limit of quantification.

Table 4.2: Patient demographics. PID: primary immunodeficiency; SAD: secondary antibody deficiency.

Patient demographics	**Total**	**PID**	**SAD**
No. of patients	64	44	20
Median age (yrs)	4.08 (0.06–16.8)	4.02 (0.06–16.8)	8.37 (0.6–16.2)
Median weight (kg)	18.6 (3.15–95.3)	13.65 (3.15–56.6)	22.1 (5.6–95.3)
Sex (M)	41	29	12
Median dose (g/kg)	0.56 (0.24–1.38)	0.64 (0.24–1.38)	0.52 (0.27–1.09)
Median baseline IgG (g/L)	4 (0.64–6.1)	4 (fixed)	4 (0.64–6.1)
Median IgM (g/L)	0.21 (0.03–5.61)	0.23 (0.03–4.97)	0.22 (0.05–5.61)
Median CD19+ cell count ($\times 10^9$/L)	0.07 (0–6.07)	0.12 (0–6.07)	0.07 (0–0.85)

Figure 4.2 shows the observed serum IgG concentrations versus time after infusion for all patients. Each point represents an individual measured concentration prior to model fitting. The dataset included both PID and SAD cohorts receiving maintenance IVIG therapy.

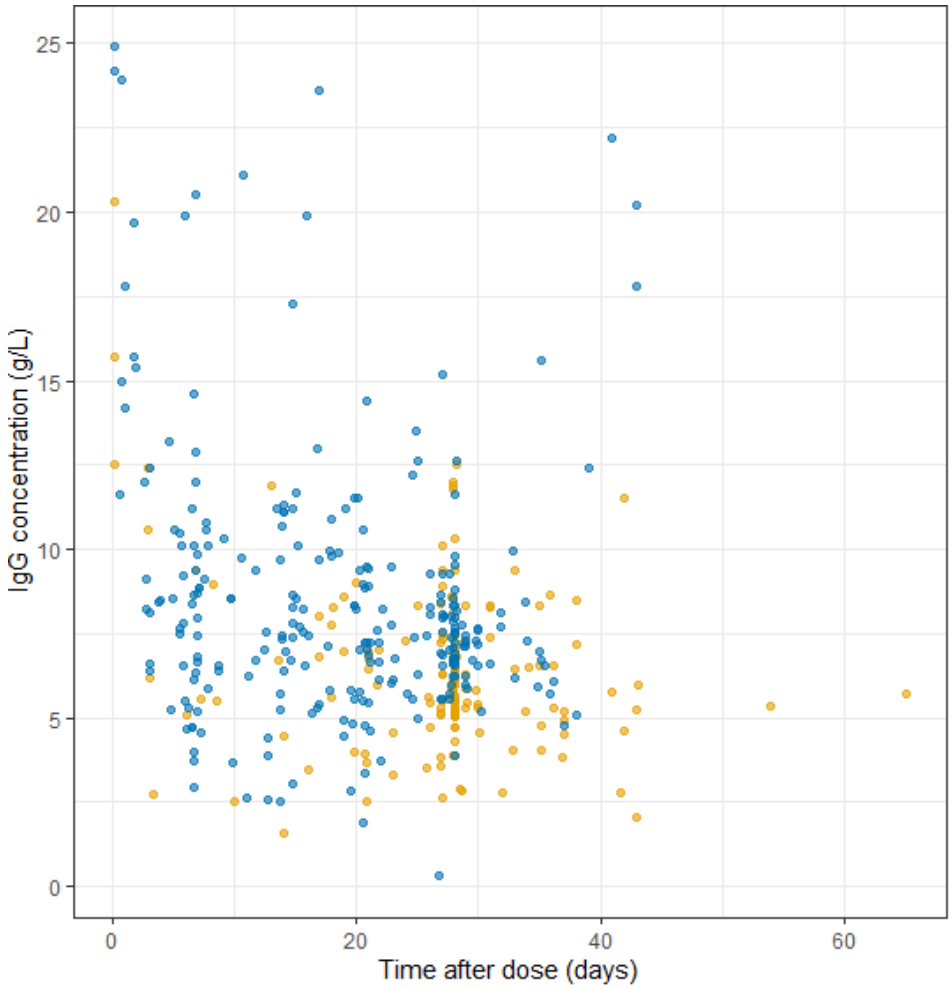


Figure 4.2: Observed serum IgG concentrations versus time after infusion for all patients. Each point represents an individual observation prior to model fitting. Blue = primary immunodeficiency, orange = secondary antibody deficiency

4.5.1 Pharmacokinetic modelling

4.5.1.1 Base model development

The pharmacokinetic data were adequately described by a two-compartment model, which showed a significant reduction in the OFV by 115.0 and the AIC by 162.6 compared to the one-compartment model. Typical parameter estimates for the base model are summarised in Table 4.3. Goodness-of-fit plots (Figure 4.3) and prediction-corrected VPC plot (Figure 4.4) also indicated a better fit to the observed data. IIV was parameterised using a variance-covariance matrix to quantify population variability for CL, Vd and CBAS. A combined error model (additive and proportional) was employed to describe residual variability. Allometric exponents for clearance (θ_{CL}) and volume (θ_V) were first estimated in the base model. The estimated θ_{CL} was 0.783 (SE 0.119; 95% CI 0.55–1.02) and θ_V was 0.743 (SE 0.128; 95% CI 0.492–0.994). Both confidence intervals included the theory-based values of 0.75 (clearance) and 1.0 (volume) [130]. However, estimating θ_V was associated with a marked loss of precision in distribution volumes and intercompartmental clearance (e.g. V1 RSE increased from 10.7% to 30.5%), indicating parameter collinearity. When only θ_{CL} was estimated, the value (0.788; SE 0.109; 95% CI 0.574–1.002) remained close to the theoretical 0.75 without improving model fit (ΔOFV = 0.17, not significant). Based on these results, the exponents of the model were fixed.

Table 4.3: Base model parameter estimates for immunoglobulin pharmacokinetics. All parameters are allometrically scaled to 70 kg. CBAS = baseline IgG

Base model parameter estimates	**Estimate (%RSE)**
CL (L/day/70kg)	0.193 (13.5)
V1 (L/70kg)	3.65 (10.7)
Q (L/day/70kg)	1.09 (13.6)
V2 (L/70kg)	6.84 (33)
CBAS (g/L)	4.14 (10.4)
IIV CL (%)	62.4 (19.7) [29]
IIV V2 (%)	121.1 (24.4)[34]
IIV CBAS (%)	60.1 (14.1)[15]

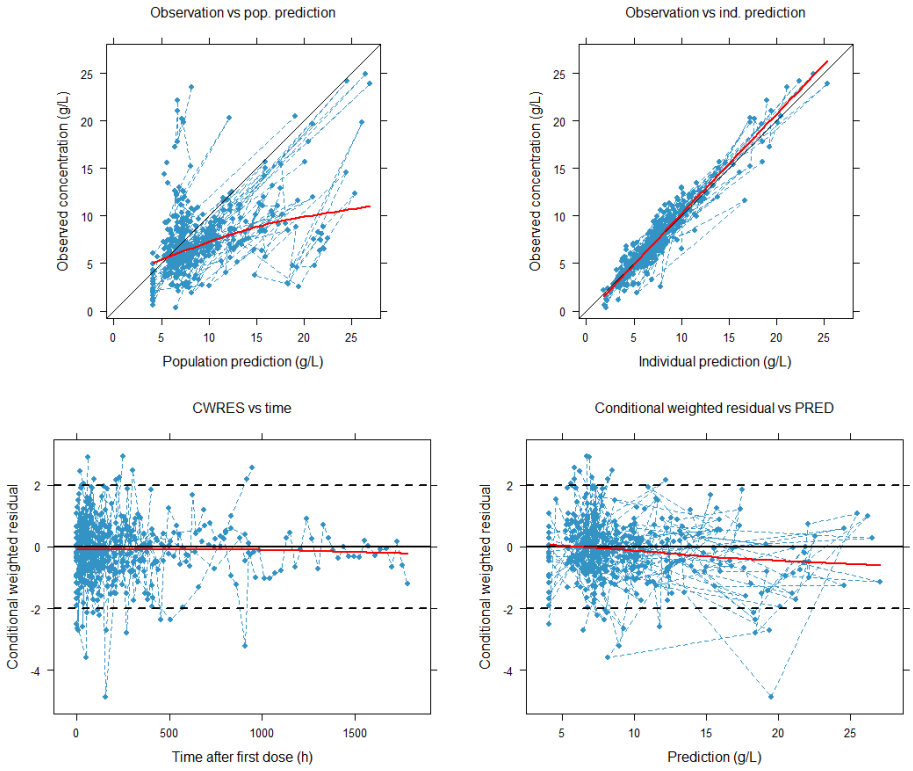


Figure 4.3: Goodness-of-fit graph for the base IG model. Top panels: observed versus population (left) and individual (right) predictions with line of identity (solid black) and locally weighted regression (LOESS, red) overlaid. Bottom panels: conditional weighted residuals (CWRES) versus time (left) and predictions (right), with reference lines at 0 and ±2 (dashed black) and LOESS smoothing (red). The LOESS curve illustrates systematic trends or bias in the data relative to the model fit.

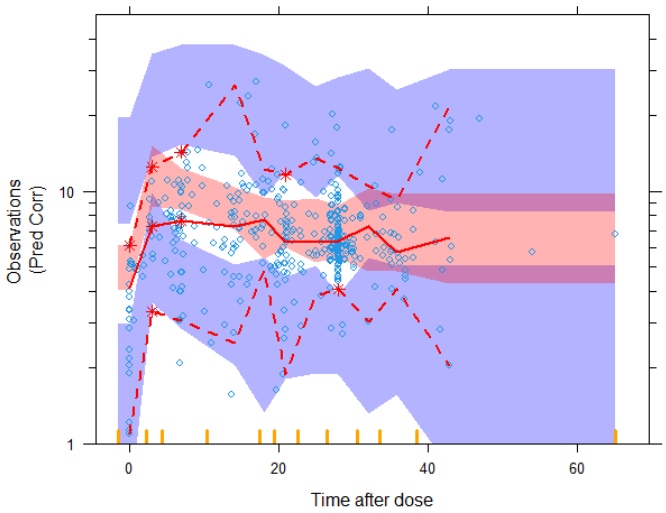


Figure 4.4: Prediction-corrected visual predictive check of the base model showing the 5th, 50th, and 95th percentiles of the observed data (lines with closed circles) compared with the 90% confidence intervals of the corresponding simulated percentiles from the final model (shaded areas).

4.5.1.2 Covariate model development

Incorporating antibody deficiency type on both CL and CBAS, as well as IgM cell count on CBAS, significantly improved the model's fit, with a reduction in the OFV by 52.5 and improved visual diagnostic plots. The difference in apparent clearance between SAD and PID patients resulted in a significant variation in clearance rates, with the clearance for SAD patients being half that of PID patients. In contrast, no significant decrease in OFV was found when introducing age, PMA, sex, and absolute CD19+ cell count, hence, not significantly contribute to further improvement of the model.

4.5.1.3 Final Model

The final model estimated values were 0.308 L/day/70kg for CL and 10.96 L/70kg for Vd (Table 4.4). All typical parameter estimates had RSE below 20%, and shrinkage for the random effects was no larger than 40%. The model demonstrated good robustness, as confirmed by bootstrap analysis, with bootstrap estimates closely matching the final parameter estimates. Goodness-of-fit plots for the final model (Figure 4.5) showed close agreement between observed and predicted concentrations, with points distributed around the line of identity and no systematic trends in residuals. The prediction-corrected VPC (Figure 4.6) demonstrated that the observed medians and variability were well contained within the corresponding simulation-based prediction intervals across time; no major bias was evident across deficiency types or sampling windows. Together with acceptable imprecision and shrinkage, these diagnostics support the adequacy of the final model for inference and simulation. The final model, described by Equations 4.3 and 4.4, where $\kappa_{CL}^{\text{TYPE}_i}$ represents the effect of antibody deficiency type.

$$CL_i = CL_{\text{pop}} \times \left(\frac{WT_i}{70}\right)^{0.75} \times \kappa_{CL}^{\text{TYPE}_i} \times \exp(\eta_{CL,i}) \tag{4.3}$$

$$V1_i = V1_{\text{pop}} \times \left(\frac{WT_i}{70}\right)^{1.0}, \quad V2_i = V2_{\text{pop}} \times \left(\frac{WT_i}{70}\right)^{1.0} \times \exp(\eta_{V2,i}) \tag{4.4}$$

Table 4.4: Pharmacokinetic parameter estimates for the final model including the bootstrap analysis. All parameters are allometrically scaled to 70 kg

Final model parameter estimates	**Estimates (RSE%)[Shrinkage%]**	**Bootstrap median**	**Bootstrap 95% confidence interval**
CL (L/day/70kg)	0.308 (15)	0.401	0.23 - 0.67
V1 (L/70kg)	3.59 (15)	3.8	2.37 - 4.59
Q (L/day/70kg)	1.08 (16)	1.09	0.91 - 5.44
V2 (L/70kg)	7.37 (20)	6.97	3.6 - 11.2
CBAS (g/L)	5.67 (10)	6.02	5.0 - 7.22
Type of immunodeficiency on CBAS	0.541 (18)	0.502	0.37 - 0.64
Type of immunodeficiency on CL	0.542 (21)	0.44	0.22 - 0.65
IgM on CBAS	0.11 (10)	0.1	0.03 - 0.16
IIV CL (%)	42.7(27)[36]	47.83	28.5 - 75.9
IIV V2 (%)	138.6 (30)[35]	137.1	80.5 - 187.8
IIV CBAS (%)	49.3 (16)[13]	44.7	32.1 - 57.9
Additive error (g/L)	0.812 (11)[11]	0.595	0.09728 - 0.9964
Proportional error (%)	11.7 (10%)[11]	2.27	0.786 - 7.68

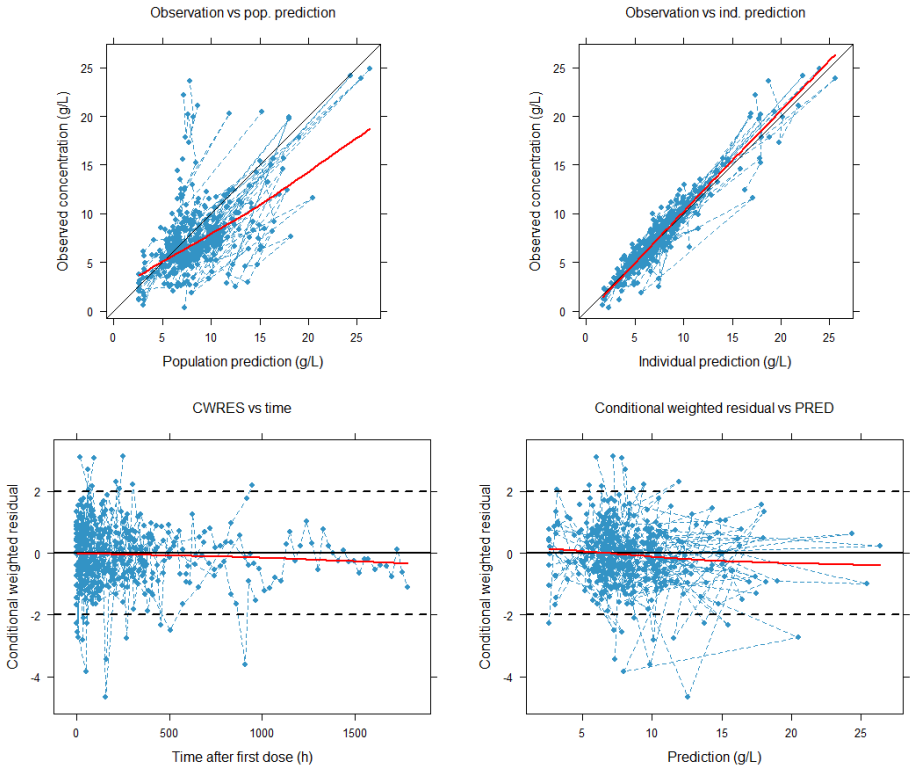


Figure 4.5: Goodness-of-fit graph for the final IG model. Top panels: observed versus population (left) and individual (right) predictions with line of identity (solid black) and locally weighted regression (LOESS, red) overlaid. Bottom panels: conditional weighted residuals (CWRES) versus time (left) and predictions (right), with reference lines at 0 and ±2 (dashed black) and LOESS smoothing (red). The LOESS curve illustrates systematic trends or bias in the data relative to the model fit.

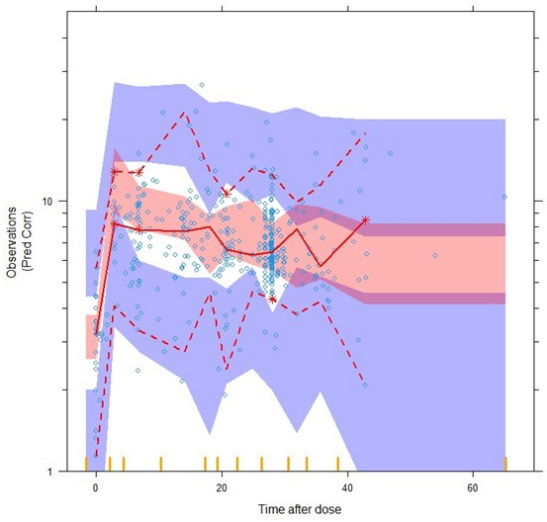


Figure 4.6: Prediction-corrected visual predictive check of the final model showing the 5th, 50th, and 95th percentiles of the observed data (lines with closed circles) compared with the 90% confidence intervals of the corresponding simulated percentiles from the final model (shaded areas).

Table 4.5: All model runs tested in immunoglobulin model development. Ab CD19+: absolute CD19+ cell count; AIC: Akaike Information Criterion; ADD: additive error model; AS: allometric scaling; CBAS: baseline Ig level; IIV: interindividual variability; MF: maturation function; OFV: objective function value; PROP: proportional error model, Type: Type of immunodeficiency, V1: Central volume of distribution, V2: Peripheral volume of distribution.

Model no.	Compartment	Covariate	Error model	IIV	Ref model	OFV	ΔOFV	AIC	Comments
1	One	AS	Combined	CL, V, CBAS	–	1083.978	–	1914.0	
2	Two	AS	Combined	CL, V1, Q, V2, CBAS	1	911.416	-114.992	1751.43	IIV V1 RSE% = 898
IIV									
3	Two	AS	Combined	CL, V1, V2, CBAS	2	917.515	6.099		
4	Two	AS	Combined	CL, V1, Q, CBAS	2	1041.25	129.844		
5	Two	AS	Combined	CL, Q, V2, CBAS	2	911.474	0.058		
6	Two	AS	Combined	CL, V2, CBAS, Q	2	919.87	8.454	1755.89	RSE(%) of parameters acceptable
7	Two	AS	Combined	CL, V1, CBAS	2	1041.369	129.953		
8	Two	AS	Combined	CL, Q, CBAS	2	1040.022	129.506		
9	Two	AS	Combined	CL, CBAS	2	971.265	59.849		
Variance–covariance matrix									
10	Two	AS	Combined	CL, V2, CBAS, Q; OMEGA block	6	913.526	-6.344	1755.54	
Allometric scale coefficient									
11	Two	AS	Combined	CL, V, CBAS; AS CL & V coeff.	1	903.474	-10.052	1749.49	RSE(%) on V not acceptable
12	Two	AS	Combined	CL, V, CBAS; AS CL coeff.	1	913.474	0.172	1757.72	
Residual error model									
13	Two	AS	ADD	CL, V2, CBAS, Q; OMEGA block	10	933.164	19.638		
14	Two	AS	PROP	CL, V2, CBAS, Q; OMEGA block	10	959.837	46.311		
Covariates									
15	Two	AS; SEX on CL	Combined	CL, V2, CBAS, Q; OMEGA block	10	913.378	-0.148		
16	Two	AS; SEX on V2	Combined	CL, V2, CBAS, Q; OMEGA block	10	913.289	-0.237		
17	Two	AS; AGE on CL	Combined	CL, V2, CBAS, Q; OMEGA block	10	913.546	0.020		
18	Two	AS; AGE on V2	Combined	CL, V2, CBAS, Q; OMEGA block	10	913.560	0.034		
19	Two	AS; AGE on CBAS	Combined	CL, V2, CBAS, Q; OMEGA block	10	910.303	-3.233		
20	Two	AS; MF on CL	Combined	CL, V2, CBAS, Q; OMEGA block	10	913.519	-0.007		
21	Two	AS; MF on CBAS	Combined	CL, V2, CBAS, Q; OMEGA block	10	931.256	17.737		
22	Two	AS; Ab CD19 on CL	Combined	CL, V2, CBAS, Q; OMEGA block	10	914.052	0.526		

Continued on next page

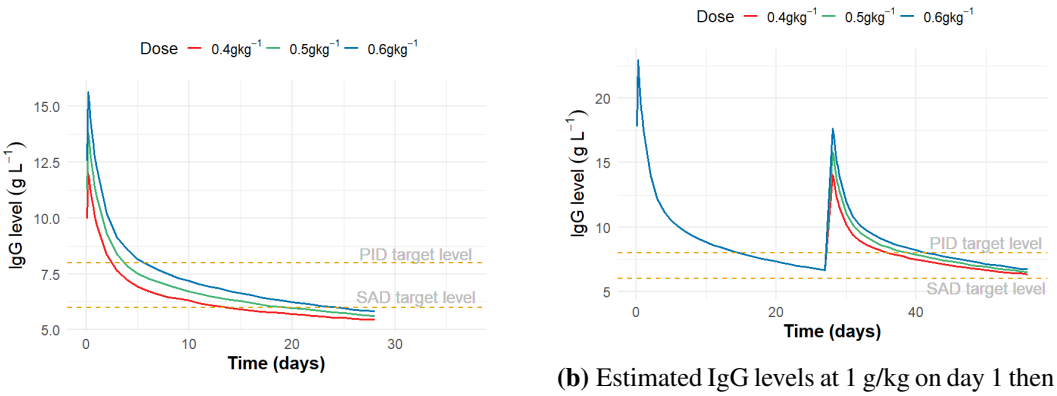
Table 4.5 (continued)

Model no.	Compartment	Covariate	Error model	IIV	Ref model	OFV	ΔOFV	AIC	Comments
23	Two	AS; Ab CD19 on V2	Combined	CL, V2, CBAS, Q; OMEGA block	10	911.328	-2.198		
24	Two	AS; Ab CD19 on CBAS	Combined	CL, V2, CBAS, Q; OMEGA block	10	907.354	-6.172	1995.71	
25	Two	AS; IgM on CBAS	Combined	CL, V2, CBAS, Q; OMEGA block	10	878.029	-37.497	2011.38	
26	Two	AS; IgM on CL	Combined	CL, V2, CBAS, Q; OMEGA block	10	913.564	0.038		
27	Two	AS; IgM on V2	Combined	CL, V2, CBAS, Q; OMEGA block	10	913.761	0.235		
28	Two	AS; Type on CL	Combined	CL, V2, CBAS, Q; OMEGA block	10	913.520	-0.006		
29	Two	AS; Type on V2	Combined	CL, V2, CBAS, Q; OMEGA block	10	913.486	-0.040		
30	Two	AS; Type on CBAS	Combined	CL, V2, CBAS, Q; OMEGA block	10	905.629	-7.900		
31	Two	AS; CD19+ & IgM on CBAS	Combined	CL, V2, CBAS, Q; OMEGA block	23	907.431	29.402		
32	Two	AS; CD19+ & Type on CBAS	Combined	CL, V2, CBAS, Q; OMEGA block	23	901.499	23.470		
33	Two	AS; Type on CL; CD19+ on CL	Combined	CL, V2, CBAS, Q; OMEGA block	23	906.715	28.686		
34	Two	AS; IgM on CBAS; Type on CBAS	Combined	CL, V2, CBAS, Q; OMEGA block	23	868.268	-9.761		
35	Two	AS; Type on CL & CBAS	Combined	CL, V2, CBAS, Q; OMEGA block	23	902.906	24.877		
36	Two	AS; Type on V & CBAS	Combined	CL, V2, CBAS, Q; OMEGA block	23	905.049	27.020		
37	Two	AS; Type on CL; IgM on CBAS	Combined	CL, V2, CBAS, Q; OMEGA block	23	875.315	-2.714		
38	Two	AS; Type on CL & CBAS; IgM on CBAS	Combined	CL, V2, CBAS, Q; OMEGA block	23	861.022	-17.007	1709.04	
Backward elimination									
39	Two	– Type on CL	Combined	CL, V2, CBAS, Q; OMEGA block	36	868.256	7.234		
40	Two	– Type on CBAS	Combined	CL, V2, CBAS, Q; OMEGA block	36	875.138	14.120		
41	Two	– Type on CBAS; – IgM on CBAS	Combined	CL, V2, CBAS, Q; OMEGA block	36	913.520	52.500		
42	Two	– Type on CBAS; – Type on CL	Combined	CL, V2, CBAS, Q; OMEGA block	36	905.629	44.610		
43	Two	– Type on CBAS & CL	Combined	CL, V2, CBAS, Q; OMEGA block	36	878.313	17.291		

4.6 Simulation Results

The median concentrations (50^{th} percentile) at each simulation time point are shown in Figure 4.7. Following infusions of 0.4 g/kg, 0.5 g/kg, and 0.6 g/kg, the predicted exposure, measured as AUC, was 200.2, 211.5, and 222.4 $g \cdot day/L$ respectively over a 28-day interval. The probability of attaining the therapeutic target for patients with SAD, defined as maintaining IgG $\geq$ 6 g/L, ranged from 63.8% to 72.1% (Table 4.6). In contrast, the probability of maintaining levels above the PID target of 8 g/L was lower, ranging from 43.8% to 51.9%. Simulated plasma levels dropped below 8 g/L at approximately 5, 6, and 7 days post-infusion for the 0.4, 0.5, and 0.6 g/kg doses, respectively.

To evaluate optimal dosing strategies, simulations compared a one-off 1 g/kg loading dose on day 0 against standard maintenance regimens without loading. For example, following 0.5 g/kg infusions with and without a 1 g/kg loading dose, the time-normalised AUCs were 17.9 and 7.6 g/L/day, respectively. These corresponded to PTA above 8 g/L for 62.7% and 48.7% of the dosing interval (Figure 4.8). Reducing the dosing interval from 0.4 g/kg every 28 days to 0.3 g/kg every 21 days did not improve predicted exposure, yielding time-normalised AUCs of 7.2 and 6.9 g/L/day, respectively. However, when combined with a 1 g/kg loading dose at day 0, the PTA increased with a shorter dosing interval, indicating a potential benefit to front-loading in this context.



(a) Estimated IgG levels at various doses.

(b) Estimated IgG levels at 1 g/kg on day 1 then various doses at day 28

Figure 4.7: Estimated IgG levels at various dosing regimes. Dotted lines represent suggested therapeutic levels of 6 and 8 g/L.

Table 4.6: Probability of target attainment for various recommended dosing regimens of immunoglobulin, measured at target levels of 6 g/L and 8 g/L. The PTA percentages indicate the proportion of the population predicted to achieve the target drug concentration for each dosing regimen

Dose regime	Estimated % no of days $\geq$ 6 g/L	Estimated % no of days $\geq$ 8 g/L
0.4 g/kg every 28 days	63.8	43.8
0.5 g/kg every 28 days	68.2	48.7
0.6 g/kg every 28 days	72.1	51.9
1 g/kg stat + 0.4 g/kg on day 28	81.0	60.7
1 g/kg stat + 0.5 g/kg on day 28	82.5	62.7
1 g/kg stat + 0.6 g/kg on day 28	83.6	64.4

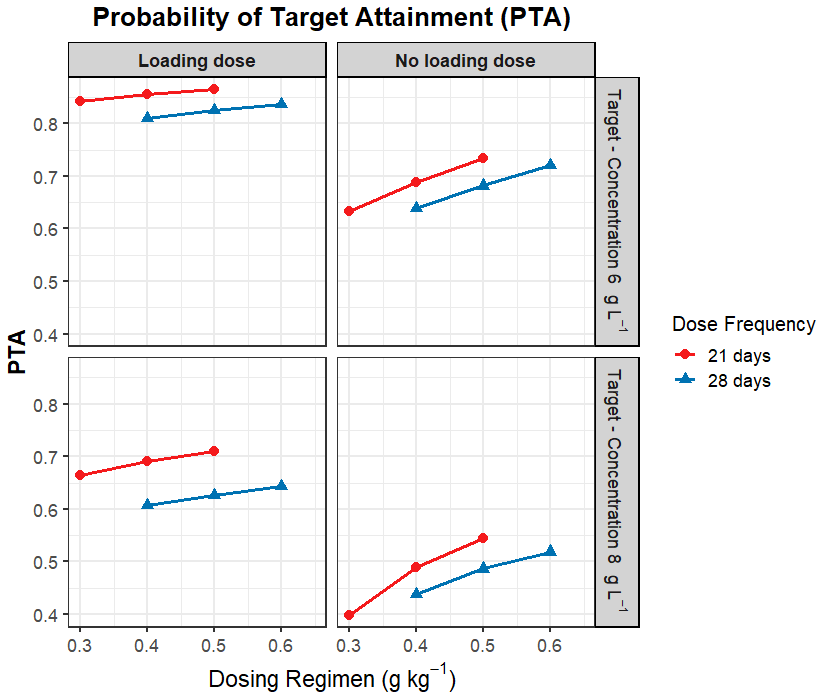


Figure 4.8: Estimated probability to achieve the recommended levels of 6 and 8 g/L with or without loading dose. Loading dose = 1 g/kg day 0 then various maintenance doses at day 21 or day 28. The y-axis shows the probability of maintaining concentrations above the target threshold, scaled from 0.1 to 1 (where 1 = 100% probability).

4.7 Discussion

This study elucidates the pharmacokinetic properties of intravenous Ig in paediatric patients with PID and SAD using real-world clinical data from a diverse cohort. The pharmacokinetics were adequately described by a two-compartment model, allometrically scaled to a 70 kg body weight, and included interindividual variability on CL, Vd and baseline IgG level. The maturation function was evaluated because age-related maturation of IgG handling is biologically plausible: neonatal B cells are largely naïve and class-switching is limited [238], and although switched B cells and memory subsets gradually increase, they only reach adult-like frequencies by adolescence and IgG levels reach only 70% of adult concentrations by one year of age [240]. As González-Sales *et al.* (2022) [84] note, reliable estimation of allometric exponents requires wide dispersion in the size metric (e.g. body weight) and sufficient data across developmental stages. While the dataset covered a substantial weight range (3.15–95.3 kg), the sample size was relatively small (n=64) and entirely paediatric, with limited coverage of older adolescents and no adults. Under these conditions, simultaneous estimation of size exponents and a maturation function proved unstable and did not improve model fit or reduce unexplained variability. For these reasons, fixed theory-based allometric exponents ($CL \propto WT^{0.75}$, $V \propto WT^{1.0}$) were applied. Some studies have questioned the use of theory-based allometry in combination with maturation models, as this approach can risk over-parameterisation or obscure the true maturation signal [273, 274]. In this case, fixing the exponents allowed size effects to be standardised, reducing collinearity with age and enabling a cleaner evaluation of maturation. The absence of improvement in fit suggests that any maturation effect was either small relative to inter-individual variability or not sufficiently informed by the available data. A contributing factor may be the presence of maternally transferred IgG, which can sustain IgG levels in infants for up to six months post-birth [275].

The PID clearance (0.308 L/day/70 kg) is moderately higher than several adult-leaning PID models (Table 4.1). which is plausible given residual maturation effects in children (even after theory-based allometry), as well as trough-enriched

sampling and inter-study assay/formulation differences. In contrast, the estimated Ig clearance in our paediatric SAD cohort was lower than in PID. At first glance this conflicts with Tortorici *et al.* (2019) [260], who reported similar CL in adult PID and SAD with a larger Vd in SAD. One explanation lies in cohort differences. In the UK, SAD patients usually initiate IgRT when baseline IgG is < 4 g/L [247], and in our cohort many had profound B-cell depletion after rituximab or CAR-T therapy. These children are typically heavily pre-treated, having failed multiple lines of leukaemia therapy, which may alter Ig metabolism and less compensatory capacity through impaired B-cell compartments, reduced plasma cell survival, or disrupted neonatal Fc receptor (FcRn)-mediated recycling. By contrast, adult SAD and PID groups are generally more balanced in their treatment histories, reducing this effect.

A second explanation is methodological. Previous models often fixed baseline IgG at 4 g/L or estimated higher values. If the true baseline is lower, fixing it too high forces the model to increase CL to match trough observations. Here, baseline IgG was estimated directly, with IgM included as a proxy for humoral capacity. The estimated baseline IgG level was 5.67 g/L for PID patients, which is consistent with values reported by Li *et al.* (2022) [256] in a large cohort of PID patients aged less than 2 to 83 years. In contrast, SAD children showed roughly 50% lower baselines, in line with their profound B-cell depletion. This lower baseline naturally yielded a lower apparent clearance, linking the two findings. Taken together, these results suggest that the apparently reduced clearance in SAD reflects both the biology of a heavily pre-treated paediatric population and the need to estimate baseline IgG rather than fix it. Incorporating IgM as a covariate further stabilised baseline estimation and improved the biological plausibility of clearance results.

This model incorporated estimated baseline IgG levels to account for endogenous antibody and evaluated the ability of absolute CD19+ B cell count and IgM plasma levels to inform these baseline IgG levels. IgM levels directly reflect B cell activity and antibody production, providing a snapshot of the functional capacity of the humoral immune system. In contrast, absolute CD19+ cell count measures the number

of B cells but does not directly assess their functional capacity to produce specific antibodies such as IgG. While absolute CD19+ cell count is a reliable marker for identifying B cells, it does not provide information on their activation status or antibody-producing capability. Therefore, IgM levels is a more direct and dynamic indicator of B cell function, as it reflects the immediate antibody response and the ongoing activity of the humoral immune system. Including IgM levels in the model better informs the endogenous IgG levels being produced, thereby enhancing the understanding of the effect of the therapeutic IgG being administered.

The recommended dose for SAD, ranging from 0.4 to 0.6 g/L every 4 weeks [247, 249, 254], maintains the therapeutic target ($\geq$ 6 g/L) for at least 63.8% of days during the dosing interval for the studied population (Figure 4.8). However, for PID patients with a higher recommended therapeutic target, only a smaller fraction (between 43.8 - 51.9%) of the simulated population reached their target at the recommended dose. Initiating therapy with a single loading dose of 1 g/kg followed by 0.4 g/kg on day 28 increases the proportion of days above the therapeutic level to 60.7%, and normalised AUC per day to 17.5 g/L/day. Reducing the dosing interval from 0.4 g/kg every 28 days to 0.3 g/kg every 21 days, when combined with a loading dose of 1 g/kg, further increases the likelihood of maintaining Ig levels above 8 g/L to 66.5%. This approach may accelerate the time to reach steady-state IgG levels and reduce the overall maintenance Ig requirement. This regimen would be particularly beneficial for patients with severe clinical conditions, such as end-organ disease or severe bronchiectasis, who may require rapid elevation of IgG plasma levels [245, 249, 254, 276]. Linking plasma IgG levels with therapeutic biomarkers, such as quality of life including infection rates, would be useful in guiding future model development and dose-efficacy assessment and thereby providing a more personalised approach to managing children with PID and SAD.

This model aimed to investigate the pharmacokinetic properties of IG in a paediatric cohort. Despite the relatively small sample size of 64 paediatric patients, we managed to capture a wide spectrum of age and body size range of the paediatric

population and be statistically powered with a sufficient number of optimally timed samples to yield the unbiased and precise pharmacokinetic parameters [277]. However, the majority of the samples collected were trough levels. While trough samples are useful for understanding steady-state conditions and minimum drug concentrations, they do not provide a comprehensive picture of the pharmacokinetic profile, particularly for assessing peak levels and overall exposure. The inability to accurately obtain the baseline IgG levels for PID patients and variability in baseline IgG levels observed for SAD in this study (0.64 to 6.1 g/L underscores the challenge of accurately describing endogenous IgG contributions as there is no reliable method to measure endogenous IgG levels when receiving IgRT directly. Future studies with larger sample sizes, a more comprehensive sampling strategy, and prospective designs are warranted to validate these findings and address the limitations identified in this analysis.

4.8 Conclusion

This study developed and evaluated a pharmacokinetic model of intravenous immunoglobulin in children with primary and secondary antibody deficiencies. Using real-world monitoring data, it is demonstrated that disease type and IgM levels influence IgG disposition, and that standard dosing strategies may be inadequate for a proportion of children with primary immunodeficiency. Model-based simulations support the use of loading doses or shortened dosing intervals to improve target attainment in high-risk patients. Although limited by a modest sample size and trough-enriched data, these findings provide new insights into the determinants of IgG pharmacokinetics in children and illustrate how population modelling can inform rational, individualised dosing. Future studies should validate these results in larger prospective cohorts and link pharmacokinetic predictions to clinical outcomes such as infection rates, organ protection, and quality of life, with the ultimate goal of optimising immunoglobulin therapy in paediatrics.

Chapter 5

Favipiravir

Favipiravir is a broad-spectrum antiviral agent that selectively inhibits viral RNA-dependent RNA polymerase (RdRp), a key enzyme required for the replication of RNA viruses [278, 279]. Originally developed in Japan for the treatment of influenza A and B, favipiravir emerged as a promising candidate for broader antiviral use due to its unique mechanism of action and ability to target a wide range of RNA viruses. As a purine analogue prodrug, it is metabolised intracellularly to its active form, favipiravir ribofuranosyl-5'-triphosphate (FAVI-RTP), which structurally mimics natural nucleosides and is incorporated into viral RNA by RdRp [280] (Figure 5.1). Incorporation of FAVI-RTP into the nascent viral RNA strand

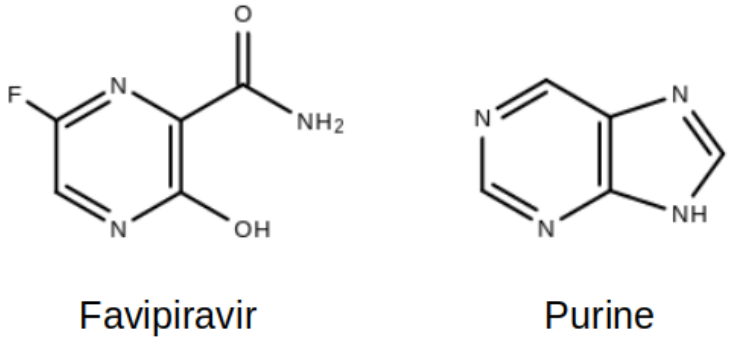


Figure 5.1: Chemical structure of favipiravir (left) and purine (right) [278]

leads to chain termination and disruption of elongation, ultimately halting replication [117, 279, 281]. Through this action, favipiravir interferes with the production of viable viral progeny. This mechanism contrasts with other antiviral agents

which often act on entry, fusion, or viral protein processing. Compared with other RdRp-targeting nucleoside analogues, favipiravir shares the need for intracellular activation to a 5'-triphosphate and the ability to disrupt viral RNA synthesis, but the dominant mechanism differs by agent. Remdesivir is phosphorylated intracellularly into an active metabolite which is incorporated by the polymerase and causes delayed chain termination after a few additional nucleotides are added [282]. Molnupiravir (the prodrug of N-hydroxycytidine) also targets RdRp but functions as a potent mutagen, driving an "error catastrophe" that collapses viral fitness [283]. Ribavirin is mechanistically broader: beyond acting as an RdRp substrate that can increase mutation rates, it inhibits inosine-5'-monophosphate dehydrogenase (IMPDH) to deplete intracellular guanosine-5'-triphosphate (GTP) and it can interfere with RNA capping. Because of these multiple actions, its antiviral effect varies by virus and context [284]. Together, these agents illustrate two main strategies against RNA viruses: mutagenesis (favipiravir, molnupiravir, partly ribavirin) versus polymerase stalling/termination (remdesivir), with shared themes of nucleoside mimicry and triphosphate activation but distinct biochemical consequences at the replication complex.

Favipiravir's broad-spectrum activity includes efficacy against influenza A and B viruses, including those resistant to standard neuraminidase inhibitors such as oseltamivir and zanamivir [278]. Moreover, preclinical studies and clinical observations have reported antiviral activity against an array of other RNA viruses including flaviviruses (e.g. Zika, dengue), alphaviruses (e.g. chikungunya), filoviruses (e.g. Ebola), bunyaviruses, arenaviruses, and noroviruses [280]. This has positioned favipiravir as a candidate for pandemic preparedness and treatment of emerging or neglected viral diseases. During the 2014–2016 West African Ebola outbreak and the recent COVID-19 pandemic, favipiravir was repurposed and trialled under emergency protocols [115, 285, 286]. Its potential to treat COVID-19 was also actively explored through multiple clinical studies and observational trials during the pandemic [287].

RNA viruses remain among the most significant global public health threats. The WHO includes several RNA viruses, such as influenza, dengue, Ebola, and HIV, among the top ten global health threats [288]. Alongside these is antimicrobial resistance, highlighting an urgent need for innovative therapeutic strategies. In this context, the repurposing of existing antivirals like favipiravir offers a pragmatic solution to bridge the gap between emerging viral threats and the very limited number of antiviral candidates currently in the development pipeline.

The therapeutic landscape for RNA viral infections, especially in vulnerable populations such as children and immunocompromised patients, remains limited. Existing antiviral options include neuraminidase inhibitors like oseltamivir and zanamivir for influenza, and ribavirin, a guanosine analogue often used off-label for respiratory syncytial virus (RSV) and other RNA viruses [289]. However, these agents have limitations in terms of efficacy, spectrum of activity, route of administration, and availability of paediatric formulations. For instance, oseltamivir is administered orally, zanamivir is available via inhalation or intravenous infusion, and ribavirin is used across various formulations but lacks robust evidence for many of its indications. While the toxicity of ribavirin is well established (haemolytic anaemia, teratogenicity) [284], the safety profiles of newer agents such as remdesivir and molnupiravir remain incompletely characterised.

The COVID-19 pandemic catalysed a renewed focus on antiviral therapeutics, accelerating the clinical evaluation of several agents including remdesivir (administered intravenously) and molnupiravir (an oral antiviral) [290]. Nevertheless, the rapid emergence of viral resistance remains a critical concern. RNA viruses possess high mutation rates, short replication cycles, and a propensity for recombination, all of which enable them to adapt quickly and render single-agent therapies less effective [291]. While antiviral resistance does not always equate to treatment failure, it can reduce clinical efficacy and necessitate revised dosing strategies tailored to the viral load, infection stage, and host immune status [292, 293]. Immunocompromised individuals are especially vulnerable to persistent infections due to impaired

viral clearance. In such populations, even partial resistance can lead to prolonged infection and allow resistant strains to dominate. The risk of resistance emergence underscores the importance of optimising dosing regimens and exploring combination therapies that enhance efficacy while mitigating resistance selection pressure [292–294]. Pharmacodynamic parameters such as the effective concentration required to reduce viral titres are commonly used in *in vitro* antiviral studies. While EC_{50} (the concentration reducing viral replication by 50%) is widely reported and useful for comparing relative potency across agents, it does not necessarily correlate with clinical efficacy [295]. For many RNA viruses, particularly in immunocompromised hosts, the EC_{90}, the concentration required to achieve 90% inhibition, is considered more clinically relevant, as near-complete suppression may be required to prevent resistance and ensure viral clearance [296–298]. However, *in vitro* antiviral assays are highly variable, as results depend strongly on the cell line, multiplicity of infection, assay readout, and duration of exposure. As a consequence, potency values (EC50 or EC90) for the same drug–virus pair can differ by orders of magnitude across studies [299, 300]. Ultimately, comparing these *in vitro* values to pharmacokinetic exposures achieved *in vivo* can inform the likelihood of therapeutic success, though these relationships remain complex and not fully defined.

Despite its promising antiviral profile, favipiravir is not without limitations. Preclinical studies have demonstrated teratogenicity and embryotoxicity in animal models, making it contraindicated during pregnancy [301]. In non-pregnant populations, however, it is generally well tolerated. Adverse effects are typically mild and include asymptomatic hyperuricaemia, gastrointestinal upset, transient neutropenia, and reversible elevations in hepatic transaminases [115, 278, 302]. These findings have prompted further research into its use in paediatric and immunocompromised populations, where dosing and safety profiles may differ from those in healthy adults.

5.1 Mode of Action

The mechanism of action of favipiravir is illustrated in Figure 5.2. Favipiravir is a prodrug that undergoes intracellular activation via host enzymes. Upon cellular uptake, it is ribosylated and subsequently phosphorylated to yield the pharmacologically active metabolite, FAVI-RTP [278, 279]. This metabolite structurally mimics purine nucleotides and is selectively recognised by viral RdRp, a critical enzyme in the replication and transcription of RNA viral genomes.

In contrast to neuraminidase inhibitors, which act extracellularly to inhibit viral entry or release, favipiravir targets intracellular replication by interfering directly with the viral polymerase complex [303]. RdRp is essential for synthesising viral RNA from an RNA template, and its inhibition disrupts the production of progeny virions, thereby halting viral propagation. Although the full mechanism is not entirely elucidated, two complementary antiviral actions have been proposed. First, favipiravir-RTP may be misincorporated into the nascent viral RNA strand during replication. This misincorporation can lead to premature chain termination, thereby impeding RNA elongation and resulting in non-functional genomes [280]. Second, FAVI-RTP is believed to induce lethal mutagenesis by increasing the error rate during viral RNA synthesis. The resulting accumulation of deleterious mutations may reduce the infectivity of progeny virions, leading to collapse of the viral population through an error catastrophe mechanism [304–306].

This mutagenic mechanism has been observed across multiple RNA viruses, including influenza, norovirus, and hepatitis C [304–306]. Because RNA viruses typically rely on high-fidelity replication to maintain infectivity, favipiravir's disruption of this fidelity offers a distinct advantage, particularly for viruses prone to rapid mutation. Moreover, the potential to suppress viral replication without promoting resistance emergence makes favipiravir a valuable candidate for managing chronic or persistent infections. Favipiravir-RTP demonstrates high selectivity for viral RdRp, with minimal interaction with host polymerases. *In vitro* studies report a half maximal inhibitory concentration (IC_{50}) of 0.022 mg/L against viral polymerase activity,

while no significant inhibition was observed against human DNA polymerases α, β, or γ even at concentrations up to 100 mg/L [281]. This favourable selectivity contributes to its generally good safety profile.

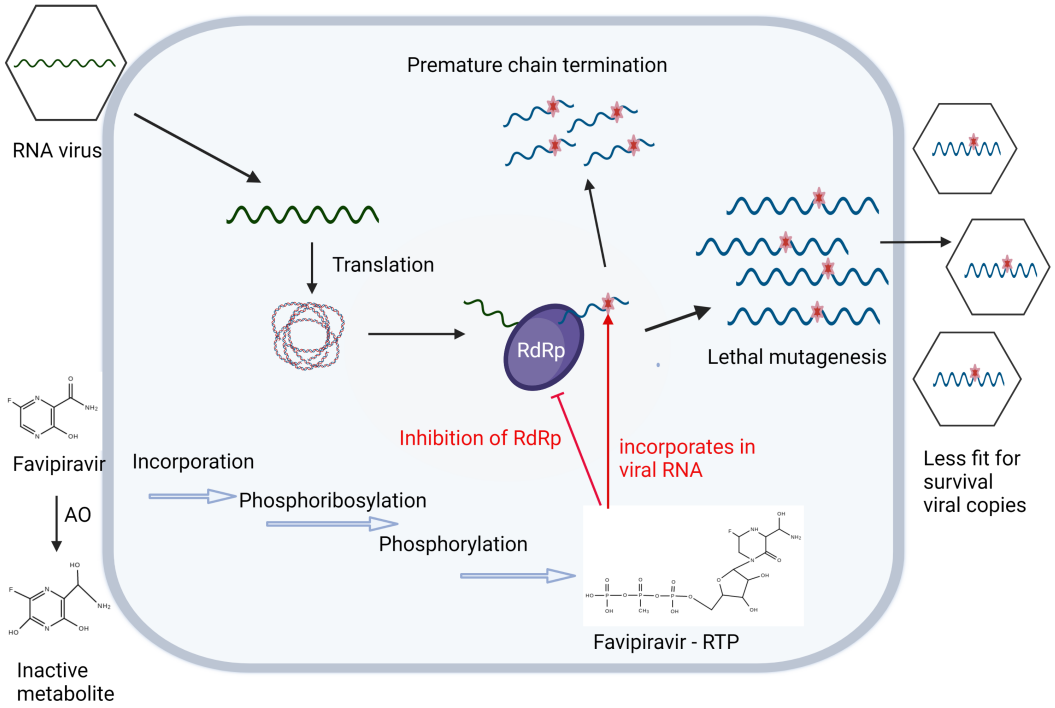


Figure 5.2: Mechanism of action of favipiravir. AO: aldehyde oxidase [280][307]

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5.2 Pharmacokinetics of favipiravir

Favipiravir exhibits complex, nonlinear pharmacokinetics that are both dose- and time-dependent [278]. It has high oral bioavailability (97.6%) and is primarily excreted renally in a hydroxylated form following hepatic metabolism [308]. In healthy volunteers, after a single day of dosing, favipiravir reached its maximum plasma concentration (T_{max}) within 1.5 hours (range: 0.75 – 4 hours), with an area under the curve (AUC_{0-t}) of 446.09 mcg·h/mL and a mean elimination half-life of 4.8 ± 1.1 hours [278]. By day 6, despite repeated dosing, (T_{max} remained around 1.5 hours (0.75–2 hours), but exposure increased (AUC: 553.98 mcg·h/mL), and the half-life extended to 5.6 ± 2.3 hours, reflecting time-dependent changes in drug clearance. Approximately 54% of favipiravir is bound to plasma proteins [309].

Favipiravir is metabolised predominantly by aldehyde oxidase (AO) in the liver, with a minor contribution from xanthine oxidase, forming an inactive metabolite excreted in urine [115]. *In vitro* studies show that favipiravir irreversibly inhibits AO in a concentration- and time-dependent manner, resulting in self-inhibition of its own metabolism upon repeated dosing [278]. This mechanism underlies the observed nonlinearity and may also contribute to enhanced tissue accumulation with chronic use. In mouse models, repeated dosing led to 25 – 50% lower plasma concentrations but a 2–5-fold increase in favipiravir levels within liver, stomach, brain, and muscle tissue, suggesting enhanced intracellular retention of the active ribosylated and phosphorylated form [310]. However, clinical studies in humans have also shown declining plasma concentrations with continued dosing [302, 311, 312], indicating that additional time-dependent processes may contribute beyond AO inhibition. Favipiravir also inhibits several cytochrome P450 enzymes. It shows dose-dependent inhibition of CYP2C8 and weak inhibition of CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4, although it does not inhibit xanthine oxidase [278].

Aldehyde oxidase is a significant source of inter-individual variability in favipiravir metabolism. Its expression and activity differ markedly across species and are influenced by both genetic polymorphisms and developmental factors [117, 313]. AO activity is low at birth and increases postnatally, with a strong correlation to age, body weight, and body surface area [116]. Recent ontogeny modelling by Subash *et al*. (2024) [124] quantified AO maturation: AO activity reaches 50% of adult levels by 0.82 years of age and AO content by 3.2 years. Neonates have AO levels approximately 20-fold lower than adults, suggesting that using adult clearance assumptions in neonates and infants would significantly underestimate drug exposure [124]. These developmental changes are critical to consider when extrapolating adult pharmacokinetics to paediatric populations, particularly in neonates and infants.

5.3 Literature review

Favipiravir has been repurposed as a treatment option for several life-threatening RNA viruses lacking approved therapies. The West African Ebola virus outbreak (2014–2016) highlighted the urgent need for effective antiviral interventions, as supportive care remained the mainstay of treatment and very few therapeutic trials had been conducted prior to the epidemic. Favipiravir was investigated in two non-randomised, single-arm clinical trials using varying doses and treatment durations (up to 11 days). In the JIKI trial, Sissoko *et al*. (2016) [314] reported a non-significant reduction in mortality among patients with low baseline viral loads, despite high dosing regimens (e.g. 6000 mg on Day 0, followed by 2400 mg daily for nine days). The drug was generally well tolerated without severe adverse effects [314]. Bai *et al*. (2016) [315, 316] reported a statistically significant reduction in mortality; however, both studies were limited by the absence of control groups and trial design biases.

In vitro studies have demonstrated favipiravir's activity against human parainfluenza type 3 (HPIV-3) and norovirus [285, 317]. Its clinical application was explored in a 48-year-old man with common variable immunodeficiency and chronic norovirus infection [318]. The patient exhibited chronic enteropathy symptoms including diarrhoea, malabsorption, and villous atrophy. After failure of multiple therapies, including ribavirin and nitazoxanide, he was initiated on favipiravir (2000 mg TDS on day 1, then 1200 mg BD). While only modest reductions in norovirus viral load were observed, the patient's gastrointestinal symptoms improved, and body weight increased. Interruptions due to elevated liver enzymes correlated with symptom recurrence, and reintroduction of favipiravir yielded clinical improvement. Despite treatment challenges, the case highlighted favipiravir's potential in chronic viral infections in immunocompromised hosts.

The global SARS-CoV-2 pandemic catalysed numerous clinical trials examining favipiravir's utility. Table 5.1 summarises selected studies. Findings were mixed, with some open-label trials reporting shorter times to symptom resolution, clini-

cal recovery, or hospital discharge [319–322]. However, higher-quality placebo-controlled and blinded studies have generally failed to demonstrate significant reductions in viral load, viral clearance, or mortality [112, 323–325]. Collectively, these data indicate that while favipiravir may provide symptomatic benefit in some settings, robust evidence to support its widespread use in COVID-19 remains lacking.

Table 5.1: Studies using favipiravir for COVID-19 infections. BD: twice a day, TDS: three times a day, QDS: four times a day

Study	Type of study	No of subjects	Treatment	Dose	Efficacy results
Chen *et al.* 2020 [326]	Prospective, randomised, controlled open-labelled, multicentre trial	240 adults, 116 favipiravir	Favipiravir vs umifenovir	Day 1: 1600mg BD Day 2-15: 600mg BD	Favipiravir did not significantly improve the clinical recovery rate at day 7 when compared to umifenovir
Udwadia *et al.* 2020 [320]	Randomised, comparative, open-labelled, phase 3 clinical trial	150 adults, 75 favipiravir	Favipiravir with standard supportive care vs supportive care alone	Day 1: 1800mg BD Day 2-15: 800mg BD	Failed to reach primary endpoint to reduce time to cessation of oral shredding of SARS-CoV2 virus. Significant improvement to clinical cure time in mild to moderate COVID-19 patients
Doi *et al.* 2020 [321]	Prospective, randomised, open-labelled, multicentre trial	89 adults, 44 favipiravir	Early treatment group (day 1) vs late treatment group (day 6)	Day 1: 1800mg BD Day 2-10: 800mg BD	Favipiravir did not significantly improve viral clearance by day 6 but was associated with numerical reduction in time to defervescence. Neither disease progression nor death occurred in both arms
Lou *et al.* 2020 [327]	Exploratory trials	30 adults, 10 favipiravir	Favipiravir vs baloxavir marboxil vs control (lopinavir/ritonavir, darunavir/cobicistat or arbidol)	Day 1: 1600mg or 2200mg BD Day 2 -15: 600mg TDS	Neither baloxavir marboxil nor favipiravir prove to be beneficial when given together with control in time taken to achieve viral negativity and clinical symptoms
Ivashchenko *et al.* 2021 [322]	Randomised trial	60 adults, 20 favipiravir lower dose, 20 favipiravir higher dose	Favipiravir lower dose vs favipiravir higher dose vs supportive care	Lower dose: Day 1: 1600mg BD Day 2-14: 600mg BD Higher dose: Day 1: 1800mg BD Day 2-14: 800mg BD	Both favipiravir-treated groups who achieved negative PCR on day 5 was twice as high as the control group
Khamis *et al.* 2021 [328]	Randomised, controlled, open labelled	89 adults 44 favipiravir	Favipiravir + inhaled interferon beta-1b vs hydroxychloroquine	Day 1: 1600mg BD Day 2-11: 600mg BD	No significant difference between 2 groups in overall length of stay, requirement of critical care, discharges or overall mortality
Bosaeed *et al.* 2022 [323]	Randomised, double-blinded, multicentre, place-controlled trial	231 adults, 112 favipiravir	Favipiravir vs placebo	Day 1: 1800mg BD Day 2-8: 800mg BD	No significant difference in primary endpoints for mild COVID-19 patients (viral clearance, time to clinical improvement and hospital admission
Terada *et al.* 2022 [319]	Open-labelled, phase 3 study	121 adults 56 favipiravir, 61 combined therapy	Favipiravir vs favipiravir + camostat + ciclesonide	Day 1: 1800mg BD Day 2-10: 800mg BD	No significant difference in primary outcome (length of stay) Time to discharge was statistically significantly lower
Lowe *et al.* 2022 [324]	Randomised, double blind, 2x2 factorial placebo-controlled trial	240 adults 61: favipiravir+lopinavir -ritonavir 59 adults: favipiravir +placebo	Favipiravir + lopinvir-ritonavir vs favipiravir + placebo or opinavir-ritonavir+placebo vs placebo	Day 1: 800mg BD then Days 2-7:400mg QDS	No significant viral load reduction in all arms. no significant interaction between favipiravir and lopinavir + ritonavir
Smith et al. 2022 [112]	Randomised, double-blind, placebo-controlled	240 adults	Favipiravir vs arbidol	1800 mg BD Day 1, then 800 mg BD for Days 2–10	Despite the expected exposure, no difference in symptom resolution, hospitalisation, or progression to severe disease. Favipiravir had more adverse effects
Iwata *et al.* 2024 [325]	Randomised, double blind, placebo-controlled trial	84 adults 41 favipiravir 43 placebo	Favipiravir vs placebo	Day 1: 1800mg BD then Days 2-10:800mg BD	Achieved and maintained therapeutic plasma concentrations. No clear relationship between area under the curve, maximum or minimum concentration and the time to SARS-CoV-2-negative conversion. Discontinued due to slow enrollment.

Combination antiviral therapy has been explored to enhance efficacy and prevent resistance. Favipiravir was trialled with oseltamivir in critically ill influenza patients [111], yielding higher rates of undetectable viral RNA and clinical improvement, though not significant in mortality outcomes. In COVID-19, similar combination strategies (e.g. with camostat, ciclesonide, or interferon beta-1b) largely failed to

meet primary endpoints [319, 327, 328]. Additionally, the FLARE trial, a rigorous randomised, double-blind, factorial, placebo-controlled study, evaluated favipiravir alone, lopinavir-ritonavir alone, the combination, and placebo. This trial found no significant reduction in viral load at Day 5 in any arm, and combination treatment unexpectedly led to lower favipiravir plasma concentrations, likely due to gastrointestinal effects impairing absorption [324].

In addition to clinical efficacy studies, Hayden *et al*. (2024) [312] investigated favipiravir pharmacokinetics in two large adult cohorts with uncomplicated influenza. They observed wide inter-individual variability in plasma concentrations following standard oral dosing, with levels declining markedly over five days. This pattern was consistent with time-dependent, non-linear pharmacokinetics of favipiravir. An exposure–response relationship was identified: higher drug exposure correlated with greater reductions in viral load. However, many participants failed to achieve or maintain plasma levels above therapeutic thresholds. Body weight was inversely associated with drug exposure and antiviral efficacy, highlighting the limitations of fixed dosing regimens. These findings underscore the importance of considering body weight and metabolic capacity in dose optimisation, key considerations that may be even more pronounced in paediatric populations due to developmental enzyme ontogeny.

5.4 Reported favipiravir use in children

Clinical experience with favipiravir in children remains limited, yet spans a diverse range of clinical scenarios, including viral haemorrhagic fevers, respiratory infections, and immunocompromised hosts. These reports offer early insights into tolerability, feasibility, and potential efficacy, though often in the absence of pharmacokinetic or mechanistic modelling.

Bouazza *et al*. (2015) [329] proposed a weight-based dosing regimen using allometric scaling from adult data to guide favipiravir administration in children with Ebola virus disease. This was later implemented in the JIKI trial, which included a

small paediatric subgroup [302]. Of the 66 patients included in the pharmacokinetic sub-study, only six were children. Plasma concentrations measured on days 2 and 4 showed a significant drop (nearly 50%), and exposures were lower than predicted, even under very high dosing regimens. Favipiravir also failed to significantly improve survival among patients with high baseline viral loads, raising doubts about whether intensive dosing can achieve sufficient in vivo antiviral activity.

Table 5.2: Dosing regimen proposed by Bouazza *et al*. 2015 [329]

Age group	Day 1 (8 hours apart)			Days 2-10
10-15 kg	500mg	500mg	200mg	200mg three times a day
16-21 kg	800mg	800mg	400mg	400mg twice a day
22-35 kg	1200mg	1200mg	600mg	600mg twice a day
36-45 kg	1600mg	1600mg	800mg	800mg twice a day
46-55 kg	2000mg	2000mg	1000mg	1000mg twice a day
>55kg (adults)	2400mg	2400mg	1200mg	1200mg twice a day

Palich *et al*. (2016) [330] described favipiravir use in a six-year-old with severe Ebola virus disease who survived despite high initial viral load and prolonged viraemia. Prolonged treatment (day 1: 1200/1200/600 mg; then 600 mg BD) led to delayed viral clearance but eventual recovery. Clinical deterioration from the disease made attribution of side effects difficult. These early Ebola case studies highlight both the feasibility and pharmacokinetic uncertainty of favipiravir use in children, with evidence pointing toward rapid clearance and the need for more robust exposure–response modelling.

Lumby *et al*. (2020) [331] reported using favipiravir (60 mg/kg/day loading; 23 mg/kg/day maintenance) alongside zanamivir and nitazoxanide in a 23-month-old post-HSCT patient with chronic influenza B. A rapid reduction in viral load occurred after favipiravir initiation, followed by recurrence and subsequent retreatment, which led to full clearance. Zanamavir partial resistance was detected prior to favipiravir being introduced. The authors attributed the rapid decline of the viral load to favipiravir which introduced lethal mutation to the virus. The synergistic effects of favipiravir and zanamavir also played a role in increasing the ability of zanamavir to target the virus.

Ozsurekci *et al*. (2021) [332] evaluated favipiravir safety in 11 children with renal impairment and COVID-19, using JIKI-based dosing. No major adverse effects occurred, and the authors concluded that dose adjustment may not be necessary in renal impairment.

Alkan *et al*. (2021) [333] reported successful favipiravir use in a 6.5-year-old boy with NEMO deficiency and COVID-19 pulmonary involvement. Favipiravir was part of a multi-drug regimen including azithromycin, hydroxychloroquine, immunoglobulin, and oxygen. The patient recovered without complications.

Tabatabaei *et al*. (2022) [334] conducted a retrospective cohort study in 95 hospitalised children (1–18 years) with COVID-19, 25 of whom received favipiravir. Dosing was 60 mg/kg/day (max 3200 mg/day) on day 1, followed by 23 mg/kg/day (max 1200 mg/day) for 7–14 days. There was no significant difference in mechanical ventilation or mortality between favipiravir and control groups. However, favipiravir recipients had significantly longer hospital stays and higher ICU admission rates. Adverse effect, such as decreased appetite, hypotension, chest pain, were more frequent in the favipiravir group. The study raised concerns about the drug's tolerability in children and found no evidence of clinical efficacy. Limitations include retrospective design, small sample size, and absence of PK data, preventing dose–exposure–response analysis. This underscores the urgent need for prospective PK studies to inform paediatric dosing strategies.

5.5 Pharmacokinetic studies

Literature review yielded 6 studies investigating the pharmacokinetics of favipiravir. They were all performed in adults of similar median ages and similar dosing regimes. The majority of papers reported 1-compartment models with first order elimination to be the best fit for their data. Treatment duration and dose consistently emerged as significant covariates. To enable comparison across studies, CL and Vd were allometrically scaled where the median weight was provided in Table 5.3. Reported CL values span a large range, from 2.96 L/hr/70kg to 46.45 L/hr/70kg

with a corresponding large range of reported Vd, ranging from 37.1 L/70kg to 87.45 L/hr/70kg.

Favie *et al*. (2018) [335] observed unexpectedly high CL and Vd in a patient receiving continuous veno-venous haemofiltration (CVVH), despite extracorporeal renal support. This resulted in subtherapeutic favipiravir levels and suggested that dose reduction in CVVH patients may not be necessary. Wang et al. (2020) [111] explicitly modelled the time-dependent nonlinearity of favipiravir, demonstrating that clearance increased with duration of therapy, which may explain declining drug concentrations over time. Similarly, Gulhan et al. (2022) [336] reported a positive correlation between clearance and treatment duration. Dose was negatively correlated with clearance, further supporting a non-linear, dose-dependent pharmacokinetic profile [337]. Drug–drug interactions are another important source of variability in favipiravir pharmacokinetics. The FLARE trial, a rigorous randomised, double-blind, placebo-controlled study, demonstrated that co-administration of lopinavir/ritonavir substantially reduced favipiravir plasma levels, most likely due to gastrointestinal intolerance impairing absorption, despite no obvious metabolic mechanism for drug interaction[324]. In addition, Pertinez et al. (2021) [300] performed a modelling and simulation study based on published PK data, which showed that standard dosing regimens were unlikely to achieve the EC_{90} for SARS-CoV-2 even in the absence of drug–drug interactions.

Table 5.3: Summary of favipiravir pharmacokinetic models in literature. BD = twice a day; TDS = three times a day; NCA = non-compartmental analysis

Study	Cohort	No. of subjects	Median age (years)	Dose	Time from 1st dose (days)	Median weight	Model	CL/F (L/h)	CL/F (L/h/70kg)	Vd/F (L)	Vd/F (L/70kg)	Significant covariates
Madelain *et al*. 2016 [115]	Healthy subjects	2	-	400mg and 600mg BD	Steady state	-	Non-compartmental	2.07 and 1.28	-	13.4 and 10.7	-	-
Favie *et al*. 2018 [335]	CVVH critically ill influenza	1	62	Day 1: 1800mg BD, then 400mg BD for 4 days	3	67	Non-compartmental	44.95	46.45	83.7	87.45	-
Wang *et al*. 2020 [338]	Influenza	35	63.5 (53.5–70.9)	Day 1: 1600mg BD then 600mg BD for 9 days	10	-	1 compartment	-	2.96	-	37.1	Length of treatment
Irie *et al*. 2021 [337]	COVID-19	39	68 (27–89)	Day 1: 1600mg BD then 600mg BD for 9 days or Day 1: 1800mg BD then 800mg or 600mg BD for 9 days	-	64	1 compartment	5.11	5.47	41.6	45.50	BSA, dose, disease severity
Gulhan *et al.* 2022 [336]	COVID-19	21	58 (48.5–76)	Day 1: 3200mg then 1200mg/day for 4 days	2	-	1 compartment	13.84	-	63.77	-	-
					4	-	1 compartment	13.11	-	44.63	-	
Siripong-boonsitti *et al*. 2022 [339]	Healthy adults	24	32	200 mg single dose	0	62.3	NCA	8.55	9.31	20.7	23.25	-

5.5.1 Clinical use of favipiravir in children at Great Ormond Street Hospital (GOSH)

Favipiravir has been used at GOSH as a compassionate-use antiviral in immunocompromised children with life-threatening RNA viral infections that lack licensed treatment options. It serves as a bridging therapy during periods of profound immunosuppression, such as in severe combined immunodeficiency, post-chemotherapy, or post-haematopoietic stem cell transplantation. Pulmonary disease is a common complication in children with T-cell immunodeficiency. T cells play a crucial role in orchestrating phagocytic function, mediating humoral responses, and clearing infected cells, all of which are essential for fighting viral infections [340]. T-cell deficiency may be congenital or acquired due to immunosuppressive therapies or HSCT conditioning regimens. Impaired immune responses lead to prolonged viral shedding, delayed recovery, and increased morbidity. Hall et al. (1986) [341] and Lehners et al. (2016) [342] demonstrated that viral shedding was significantly more prolonged in children receiving steroids, chemotherapy, or those with immunodeficiency.

Respiratory syncytial virus (RSV) is one of the most frequently identified causes of lower respiratory tract infection (LRTI) in this group, with a reported mortality rate of 30–60% in immunocompromised children [341, 343]. Reinfection is common as RSV does not induce long-lasting immunity [344]. Until recently, no vaccine or preventive immunisation was widely available. Palivizumab, a monoclonal antibody targeting the RSV fusion protein, has been licensed and used for prophylactic protection in high-risk infants under strict NHS commissioning criteria [345]. However, in 2022, nirsevimab (Beyfortus®), a long-acting monoclonal antibody against RSV, was licensed by the Medicines and Healthcare products Regulatory Agency (MHRA) for the prevention of RSV LRTIs in infants [345]. Nirsevimab inhibits membrane fusion required for viral entry into human airway cells and provides extended protection through its prolonged half-life (approximately five months), allowing for single-dose administration to cover an entire RSV season [345–348]. It

is now the recommended first-line immunisation. However, as of the most recent RSV season in 2024, despite being both licensed and commissioned in the UK, nirsevimab has not been made available due to supply and implementation challenges. Consequently, palivizumab remained the antibody of choice for eligible infants during that period. Ribavirin is the only licensed antiviral for RSV treatment in young children, but due to formulation and supply challenges, it is not readily available in the UK [345].

Favipiravir has also been used for viral gastroenteritis caused by norovirus, sapovirus, and astrovirus, which can be life-threatening in immunocompromised children [349, 350]. In immunocompetent patients, these infections are typically self-limiting. However, in immunocompromised patients, they can cause chronic diarrhoea, failure to thrive, electrolyte imbalance, and prolonged hospitalisation. Norovirus is the most common cause of acute gastroenteritis in children requiring medical care and is associated with high rates of prolonged shedding in immunocompromised children [351, 352]. Currently, there are no licensed antivirals to treat these viral infections. Non-polio enterovirus infections, particularly in patients with B- or T-cell immunodeficiencies, have a high risk of neurological complications including encephalitis, sensorineural deafness, and cognitive impairment. Halliday *et al.* (2003) [353] reported a two-year survival rate of only 57% in patients with non-polio enteroviral CNS infection. There is currently no licensed treatment available. Astrovirus encephalitis has been reported only in rare case reports [354–358]. These describe severe neurological features, including progressive encephalopathy, sensorineural hearing loss, and cognitive decline. No standard antiviral treatment exists.

Favipiravir has been used at GOSH alongside other antivirals, including nitazoxanide, to provide a broader spectrum of activity against RNA viruses. Its use is not limited to immunocompromised patients; favipiravir has also been administered to immunocompetent children with severe RNA viral infections where no other treatment options were available. The hospital imported favipiravir from Japan and

adopted the dosing regimen from Bouazza *et al.* (2015) [329] due to the lack of paediatric-specific data at the time (Table 5.4).

Table 5.4: Favipiravir dosing guide at Great Ormond Street Hospital

Weight Band	Day 1 (Loading Dose)	Maintenance dose Can increase to TDS in severe cases
2.5–5 kg	200 mg 12 hourly	100 mg 12 hourly
5–8 kg	400 mg 12 hourly	200 mg 12 hourly
8–15 kg	800 mg 12 hourly	200 mg 12 hourly
15–25 kg	1000 mg 12 hourly	400 mg 12 hourly
25–40 kg	1600 mg 12 hourly	600 mg 12 hourly
>40 kg	1800 mg 12 hourly	800 mg 12 hourly

Favipiravir appeared to be well tolerated in this small retrospective cohort at GOSH, involving 15 patients, with adverse events mostly mild and reversible [114]. These included rash (n=9), gastrointestinal symptoms (n=6), and transient ALT elevations (n=5), all of which resolved without treatment discontinuation. Cytopenias were frequent but attributed to underlying disease. One case of reversible scleral discolouration was observed. No treatment-limiting toxicities occurred. The authors concluded that favipiravir, particularly in combination with nitazoxanide, facilitated virological control and provided a crucial bridge to curative interventions, such as gene therapy, thymic transplant or HSCT. However, the outcomes were less clear in post-HSCT patients, possibly due to delayed initiation, early discontinuation, or its use in more severely ill children. These findings underscore the need for pharmacokinetically guided therapy to optimise efficacy and ensure timely intervention in these vulnerable patients. However, with such a small sample size, these findings should be interpreted cautiously, as they cannot exclude the possibility of clinically significant adverse effects [32, 359].

5.5.2 Inhibitory quotient

Given favipiravir's mechanism of action, lethal mutagenesis through incorporation into viral RNA polymerase, there is theoretical concern that subtherapeutic drug levels may facilitate the development of resistance mutations [360–362]. The inhibitory quotient (IQ) provides a framework to evaluate whether a given exposure

is sufficient to overcome viral resistance [363]. Defined as the ratio between drug concentration and viral susceptibility, IQ serves as a pharmacodynamic index linking pharmacokinetic variability to antiviral effect:

$$\textit{Inhibitory Quotient} = \frac{\text{Drug Concentration}}{\text{Viral Susceptibility}} \tag{5.1}$$

Viral susceptibility, typically quantified as EC_{50} or EC_{90} values, is determined through *in vitro* phenotypic assays that measure the concentration required to inhibit viral replication by 50% or 90%, respectively. These metrics serve as surrogate markers of resistance, as they reflect the relative sensitivity of a virus to a given antiviral. Historical data from HIV therapy support the utility of IQ in evaluating regimen efficacy. Duval *et al.* (2002) [364] observed that patients with an IQ $<$ 1 for amprenavir achieved virological suppression in only 25% of cases, while patients with IQ $>$ 1 had significantly improved responses, suggesting that increasing drug exposure may partially overcome reduced susceptibility. Similarly, Casado *et al.* (2004) [365] reported improved responses in patients treated with nelfinavir or saquinavir when IQ $>$ 1 was achieved. This concept is particularly relevant for agents where resistance is acquired gradually via multistep mutations, such as protease inhibitors or favipiravir, rather than abrupt resistance conferred by single point mutations, as seen with non-nucleoside reverse transcriptase inhibitors.

Goldhill *et al.* (2018, 2021) [360, 361] demonstrated that favipiravir resistance in influenza virus arises through at least two distinct mutations: PB1 K229R confers reduced susceptibility, while PA P653L is required to restore viral fitness. This two-step resistance pattern reinforces the concept that resistance to favipiravir is gradual and associated with a fitness trade-off, making the likelihood of clinical resistance emergence relatively low under adequate exposure conditions.

While therapeutic drug monitoring provides data on plasma drug concentrations achieved *in vitro*, susceptibility testing identifies the viral exposure threshold necessary to suppress replication. Together, they form the basis of the inhibitory quotient, linking pharmacokinetics with virological response. When considered together,

they provide a composite view of antiviral efficacy. Importantly, antiviral resistance exists on a spectrum, measured as a fold reduction in susceptibility rather than as an absolute binary state. Thus, IQ offers a rational metric to integrate real-world exposure data with susceptibility thresholds derived from laboratory models.

5.6 Aim

To characterise the pharmacokinetics of favipiravir in immunocompromised paediatric patients and evaluate the adequacy of existing dosing in achieving therapeutic target concentrations.

5.7 Objectives

- To develop a population pharmacokinetic model characterising inter-individual and developmental variability in favipiravir disposition in children.
- To evaluate the probability of achieving therapeutic targets using the IQ approach based on the current dosing regimen.
- To perform model-based simulations to explore alternative dosing strategies predicted to improve target attainment across paediatric weight groups.

5.8 Method

5.8.1 Patient population

All children who received favipiravir at Great Ormond Street and had therapeutic drug levels taken between January 2020 to August 2023 were included in the study. Each patient received favipiravir enterally at 300mg to 1200mg daily in two to three divided doses (median 600mg daily, given as 200mg three times a day). Anonymised data was collated from the electronic health records including demographic details (age, sex and weight), laboratory data (favipiravir blood plasma level and the time in which the corresponding samples were being taken, creatinine), medical history (primary diagnosis, concurrent therapies, treatment outcomes) and treatment details (indication, dose information, length of time that the patient had

been on treatment and adverse drug reactions reported).

5.8.2 Sample collection

Blood levels were taken at least 3 days after initiation of treatment. Blood samples collected from patients were collected in 1mL EDTA. Frozen plasma samples were shipped to AP-HM, Laboratoire de Pharmacocinétique-Toxicologie, Hôpital La Timone, Aix-Marseille Université, Marseille, France for favipiravir concentration analysis. Quantification of favipiravir in plasma was performed by a sensitive and selective ultra-performance liquid chromatography coupled with tandem mass spectrometry (UPLC-MS/MS) method (UPLC-TQD, Waters, USA) with a lower limit of quantification of 0.5 mg/L (0.25 mg/L for M1). Validation of the assay was performed in accordance with the 2012 EMA guidelines and the ISO15189 guidelines [366].

5.8.3 Population pharmacokinetic analysis

5.8.3.1 Structural model

Population pharmacokinetic modelling and simulation were conducted using a FOCEI in NONMEM (7.5.1). Graphical diagnostics developed with Xpose (4.7.2) guided model development. One- and two-compartment models were compared to find the best model that most adequately described the data. Residual variability was assessed according to an additive and/or proportional error model. IIV was evaluated for clearance and Vd assuming a log-normal distribution. AIC and OFV were used in the base model selection. The typical population values of favipiravir CL, Vd and time taken to reach the maximum concentration (Tmax) were estimated. Allometric scaling of clearance and volume terms to a 70 kg standard body weight was applied a priori (Equation 4.1).

5.8.3.2 Covariates

To identify significant covariates, step-wise forward inclusion and backward elimination were used to select covariates following the Chi-squared distribution; a drop in the log-likelihood ratio of >3.84 per degree of freedom, corresponding to each covariate being tested, was needed to be significant at a level of $p<0.05$.

In conjunction with the information criterion, the goodness of fit plots (observation versus population prediction, observation versus individual prediction, CWRES versus time, CWRES vs PRED and prediction-corrected visual predictive checks, nonparametric bootstrap (1,000 samples) and realistic parameter estimates were also used as criteria for model selection.

Covariates were selected based on their known effects on favipiravir pharmacokinetics, including:

- Patient demographics: Sex, weight, age, post-menstrual age.
- Laboratory data: Serum creatinine levels.
- Length of treatment: time expressed in days from the initiation of treatment.

Sex was coded as a binary variable (0 for males, 1 for females). Its effect on clearance and Vd was introduced into the model, both parameterised by θ_{sex}. The model equation for CL and Vd are given by:

$$CL_i = CL_{pop} \times (1 + \theta_{sex}) \times \exp(\eta_1) \tag{5.2}$$

and similarly for Vd, with corresponding population parameters.

The impact of age and length of treatment on CL was also evaluated. These covariates were incorporated into the model using a power function normalised to the population median, as shown in the following equation:

$$CL_i = CL_{\text{pop}} \times \left(\frac{c_i}{\overline{c}}\right)^{\theta_{\text{Covariate}}} \times \exp(\eta_i) \tag{5.3}$$

where CL_i is the individual clearance, CL_{pop} is the typical population clearance, c_i is the individual's covariate value (e.g. age or length of treatment), and $\overline{c}$ is the population median of that covariate (3.3 years for age and 49 days for length of treatment). $\theta_{\text{Covariate}}$ represents the covariate effect exponent, and η_i accounts for inter-individual variability. The same approach was applied to volume of distribu-

tion (Vd) with corresponding population parameters.

The impact of patient development on clearance was evaluated using both age as a covariate (as described above) and through an enzyme maturation function. Since favipiravir is predominantly metabolised by aldehyde oxidase, age-related differences in enzyme activity may contribute to inter-individual variability in clearance, particularly in younger children. Two approaches were explored to capture the developmental effect: a general Hill function based on PMA, and a specific ontogeny model derived from the maturation profile of aldehyde oxidase. Firstly, the Hill function was applied to represent general age-related maturation of clearance, as previously used in paediatric pharmacokinetic models [131]. This model assumes that clearance increases in a non-linear fashion with age, described as:

$$MF = \frac{PMA^{Hill}}{PMA^{Hill} + (PM_{50})^{Hill}} \tag{5.4}$$

where PM50 represents the postmenstrual age at which clearance reaches 50% of adult levels, and the Hill coefficient defines the steepness of the maturation curve. Its effect on clearance was incorporated as:

$$CLi = CL_{pop} \times MF \times \exp(\eta_1) \tag{5.5}$$

On the other hand, Subash *et al*. (2024) [367] characterised the ontogeny of aldehyde oxidase using human liver samples, reporting both enzyme content and enzymatic activity across age. They used a sigmoidal Emax (Hill-type) model to describe enzyme maturation:

$$CL_i = CL_{pop} + \frac{(\text{Plateau} - CL_{pop}) \times AGE^K}{\text{AGE50}^K + AGE^K} \tag{5.6}$$

where Age_{50} is the age at which 50% of adult enzymatic activity is achieved, and K is the Hill coefficient. For aldehyde oxidase activity, the reported AGE_{50} was 0.82 years, with $K = 1.28$ and plateau = 206.

As favipiravir clearance was already allometrically scaled for body weight a priori, the plateau component (reflecting adult clearance capacity) was not needed. Allometric scaling accounts for size-related variability, enabling the ontogeny function to isolate only the maturational component. The model was therefore simplified to a normalised Hill function:

$$MF = \frac{AGE^K}{AGE^K + AGE_{50}^K} \tag{5.7}$$

$$CL_i = CL_{pop} \times MF \times \exp(\eta_1) \tag{5.8}$$

Both PMA-based and aldehyde oxidase activity-based maturation models were tested as covariates on clearance. This dual approach allowed assessment of whether general developmental stage (PMA) or enzyme-specific maturation better explained the observed inter-individual variability in favipiravir clearance within this paediatric cohort.

In order for the effect of serum creatinine to be evaluated, the typical serum concentration (TSCR) for age was calculated using Equation 5.9 where PNA is post-natal age expressed in years:

$$TSCR(\mu mol) = -2.37330 - 12.91367 \times ln(PNA_{years}) + 23.93581 \times (PNA_{years})^{0.5} \tag{5.9}$$

and standardised using equation 5.10 [220]:

$$SCR_{function} = \frac{SCR_i^{\theta}}{TSCR} \tag{5.10}$$

Its effect on CL was expressed as:

$$CL_i = CL_{pop} \times SCR_{function} \times \exp(\eta_1) \tag{5.11}$$

5.8.3.3 Simulations

Simulations were conducted using the final population pharmacokinetic model to evaluate expected favipiravir exposures under different dosing regimens. For each weight band, 1,000 virtual paediatric patients were generated by sampling from log-normal distributions informed by the observed median and standard deviation of weight and age in the modelled cohort. For under-represented groups, such as neonates under 3 months and adolescents over 12 years, weight–age data were derived from the 2006/2007 WHO growth reference standards [368].

All regimens assumed twice-daily administration (12-hour interval) at steady state, consistent with typical clinical use. Simulated exposures were summarised as steady-state peak (C_{max}) and trough (C_{trough}) concentrations, reported as medians (50th percentiles). Weight bands were stratified according to current clinical dosing recommendations for favipiravir (e.g. 2.5–5 kg, 5–8 kg, 8–15 kg), broadly corresponding to key developmental stages.

To assess the adequacy of dosing, antiviral effect was evaluated using the Hill equation, which describes the relationship between drug concentration and observed effect [369, 370]:

$$E = \frac{E_{\max}}{1 + \left(\frac{EC_{50}}{C}\right)^{\text{Hill}}} \tag{5.12}$$

where C is the drug concentration, E the observed effect above baseline, and Hill the Hill coefficient.

This equation can be rearranged to estimate the concentration that generates a specific percentage of maximal effect (e.g. EC_{90}):

$$EC_F = EC_{50} \times \left(\frac{F}{100 - F}\right)^{1/\text{Hill}} \tag{5.13}$$

where F is the desired percent effect (e.g. 90 for EC_{90}).

Assuming a standard Hill coefficient of 1, a common simplification when detailed

data are not available, the EC_{90} can be estimated as

$$EC_{90} = 9 \times EC_{50}. \tag{5.14}$$

The 90% effective concentration (EC90) was selected as the primary pharmacodynamic threshold, as partial suppression of viral replication is often inadequate in vivo, particularly in high-burden or rapidly replicating infections [297]. These values serve as reference points for assessing whether simulated drug concentrations are likely to achieve meaningful antiviral activity. By comparing model-predicted exposures against these thresholds, it is possible to evaluate the adequacy of existing dosing regimens in suppressing the target viruses. Reported EC50 and EC90 values for relevant viruses are summarised in Table 5.5.

Table 5.5: EC_{50} and EC_{90} of favipiravir for various viruses

Virus	EC_{50} (mcg/mL)	EC_{90} (mcg/mL)
Astrovirus [371]	38.6	347.4
Enterovirus 71 [279]	23	207
H1N1 [279]	0.13 - 3.53	1.17 - 31.77
Influenza B [372]	0.039 - 0.089	0.351 - 0.801
Newcastle virus [373]	5.33	48
Norovirus [279]	19 - 39	171 - 351
Rotavirus	Not reported	Not reported
Parainfluenza 3 [373]	4.3	36
RSV [372]	41	369
Sapovirus	Not reported	Not reported

To integrate pharmacokinetics with viral susceptibility, the inhibitory quotient (IQ) was also calculated as:

$$IQ = \frac{\text{Drug Concentration}}{\text{Viral Susceptibility}} \tag{5.15}$$

where viral susceptibility is represented by the EC90 and EC90 value obtained from in vitro studies. IQ values were calculated using simulated median trough concentrations, as these represent the lowest plasma exposures encountered by replicating viruses.

5.9 Results

A total of 20 paediatric patients contributed 95 plasma concentration samples for favipiravir. The median age of the cohort was 3.3 years (range: 0.1 – 16 years), and the median body weight was 10 kg (range: 4 – 38.9 kg). At the time of pharmacokinetic sampling, patients had received favipiravir for a median of 49 days (range: 4 – 248 days). Detailed demographic, clinical, and laboratory characteristics are presented in Table 5.6, with an overview of viral indications stratified by medical background shown in Table 5.7. Most patients were immunocompromised due to underlying primary or secondary immunodeficiency. Favipiravir was administered in combination with nitazoxanide in all cases, $\pm$ ribavirin and/or fluoxetine. Figure 5.3 shows the observed serum favipiravir concentrations versus time after infusion for all patients. Each point represents an individual measured concentration prior to model fitting. As several patients received more than one treatment episode, Figure 5.4 illustrates the concentration–time profiles for each patient, showing the variability between and within episodes.

Table 5.6: Patient demographics

Characteristics	Value
No of patients	20
Median age (years)	3.3 (0.1 - 16)
Sex (M)	10
Median dose (mg)	200 (100 - 400)
Weight (kg)	10 (4 - 38.9)
Creatinine (mmol/L)	32 (7 - 58)
No of treatment days (days)	49 (4 - 248)

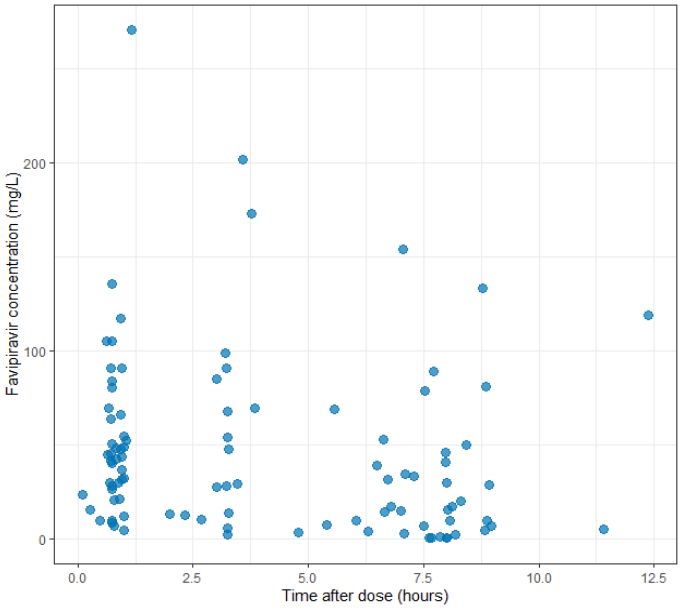

Figure 5.3: Observed favipiravir concentrations versus time after dose for all participants. Each point represents an individual observation prior to model fitting.

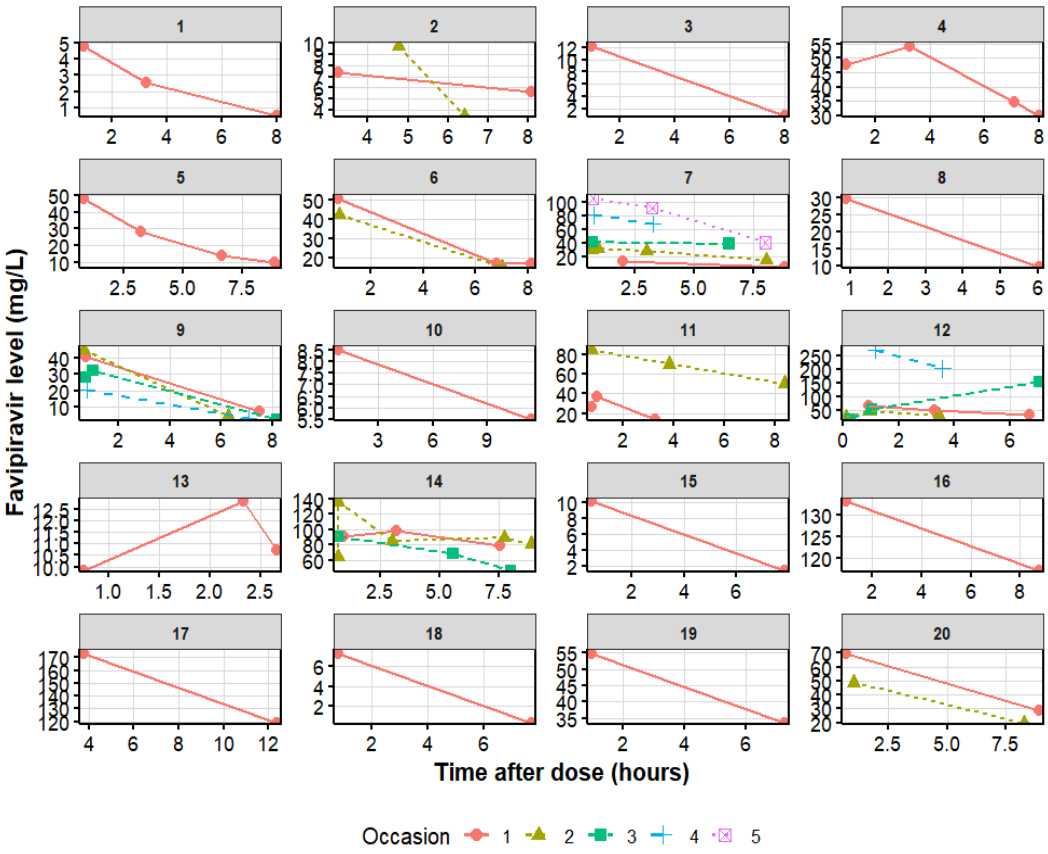

Figure 5.4: Data plot of favipiravir plasma levels for each patient.

Table 5.7: Indications for favipiravir use in the studied cohort. ARDS: Acute respiratory distress syndrome; CAR T: chimeric antigen receptor T-cells therapy; HLH: haemophagocytic lymphohistiocytosis; HSCT: haematopoietic stem cell transplantation; MPS1: Mucopolysaccharidosis type I; RSV: respiratory syncytial virus

Viral infection Medical background	Astrovirus	Enterovirus	H1N1	Influenza B	Newcastle virus	Norovirus	Norovirus, Rotavirus	Parainfluenza 3	Respiratory syncytial virus	Sapovirus
ARDS	0	0	0	1	0	0	0	0	2	0
CAR T cells	0	0	0	0	0	0	0	0	1	0
HLH	0	0	0	0	1	0	0	0	0	0
HSCT	0	0	0	0	0	0	0	0	3	0
Immunodeficiency	1	1	1	0	0	2	1	2	1	0
MPS1	0	0	0	0	0	0	0	1	0	0
Nephrotic syndrome	1	0	0	0	0	0	0	0	0	0
Post cardiac transplant	0	0	0	0	0	0	0	0	0	1

5.9.1 Pharmacokinetic data and model development

5.9.1.1 Base model

Initial model development compared one- and two-compartment structures (Table 5.10). To enable cross-study comparisons with adult data, CL and Vd were allometrically scaled to a 70 kg standard *a priori*, with exponents of 0.75 and 1, respectively. A one-compartment model with first-order absorption and proportional residual error provided the most robust and parsimonious fit to the data. The two-compartment model did not improve model performance based on OFV, AIC, and goodness-of-fit diagnostics, and presented challenges in parameter estimation. Goodness-of-fit plots for the base model (Figure 5.5) and the corresponding prediction-corrected VPC (Figure 5.6) demonstrated an adequate description of the observed data, without major bias or systematic deviation across the concentration range. Typical parameter estimates for the base model are summarised in Table 5.8.

Table 5.8: Favipiravir pharmacokinetic parameter estimates for the base model. All parameters are allometrically scaled to 70 kg.

Base model parameter estimates	Estimates (%RSE)
CL (L/h/70kg)	4.59 (35.3)
V1 (L/70kg)	42.8 (25.2)
KA	1.5 FIX
IIV CL (%)	101.5
IIV V (%)	40.5

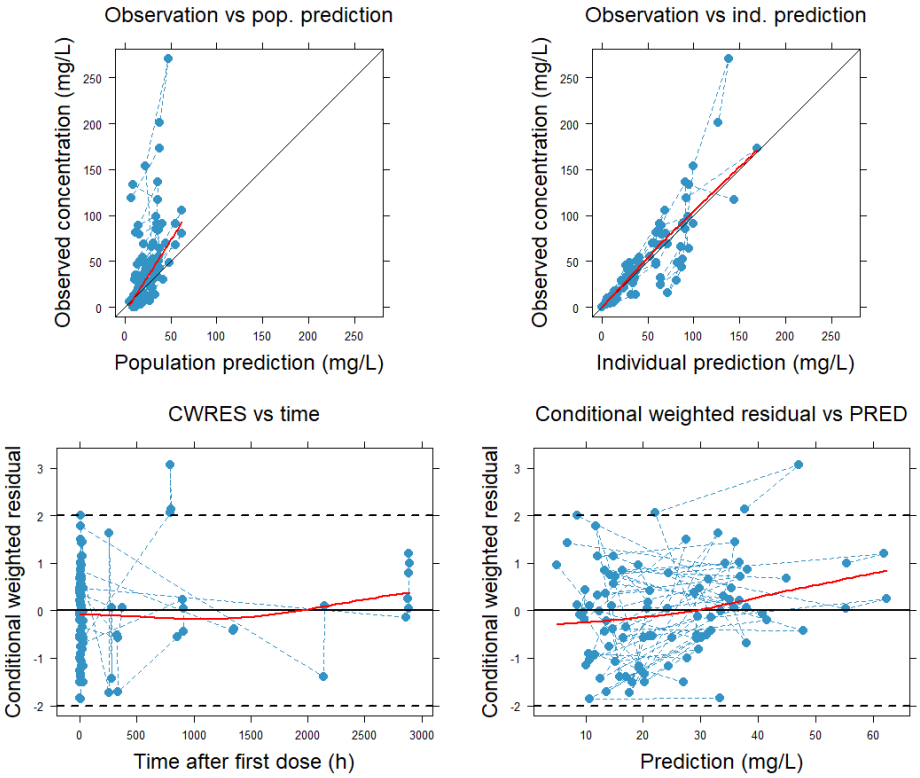

Figure 5.5: Goodness-of-fit diagnostics for the favipiravir base model. Observed concentrations are plotted against both population and individual predictions, with a line of identity included.

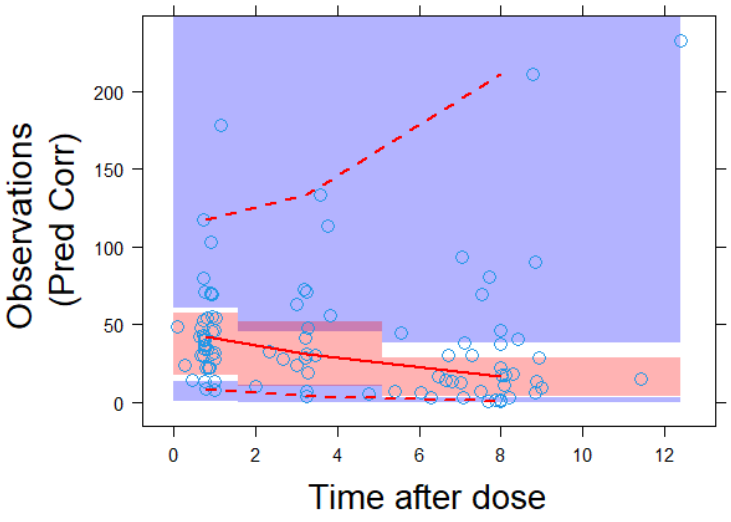

Figure 5.6: Prediction-corrected visual predictive check (pcVPC) for the favipiravir base model. The observed median and variability (5th and 95th percentiles) are well captured within the simulation-based prediction intervals, demonstrating adequate model performance across the concentration–time profile.

5.9.1.2 Covariate model development

Covariate analysis was conducted using a stepwise approach. Figure 5.7 shows the relationship between dose-normalised concentrations and candidate covariates, including sex, weight, serum creatinine, and treatment duration. None of these covariates significantly improved the model fit.

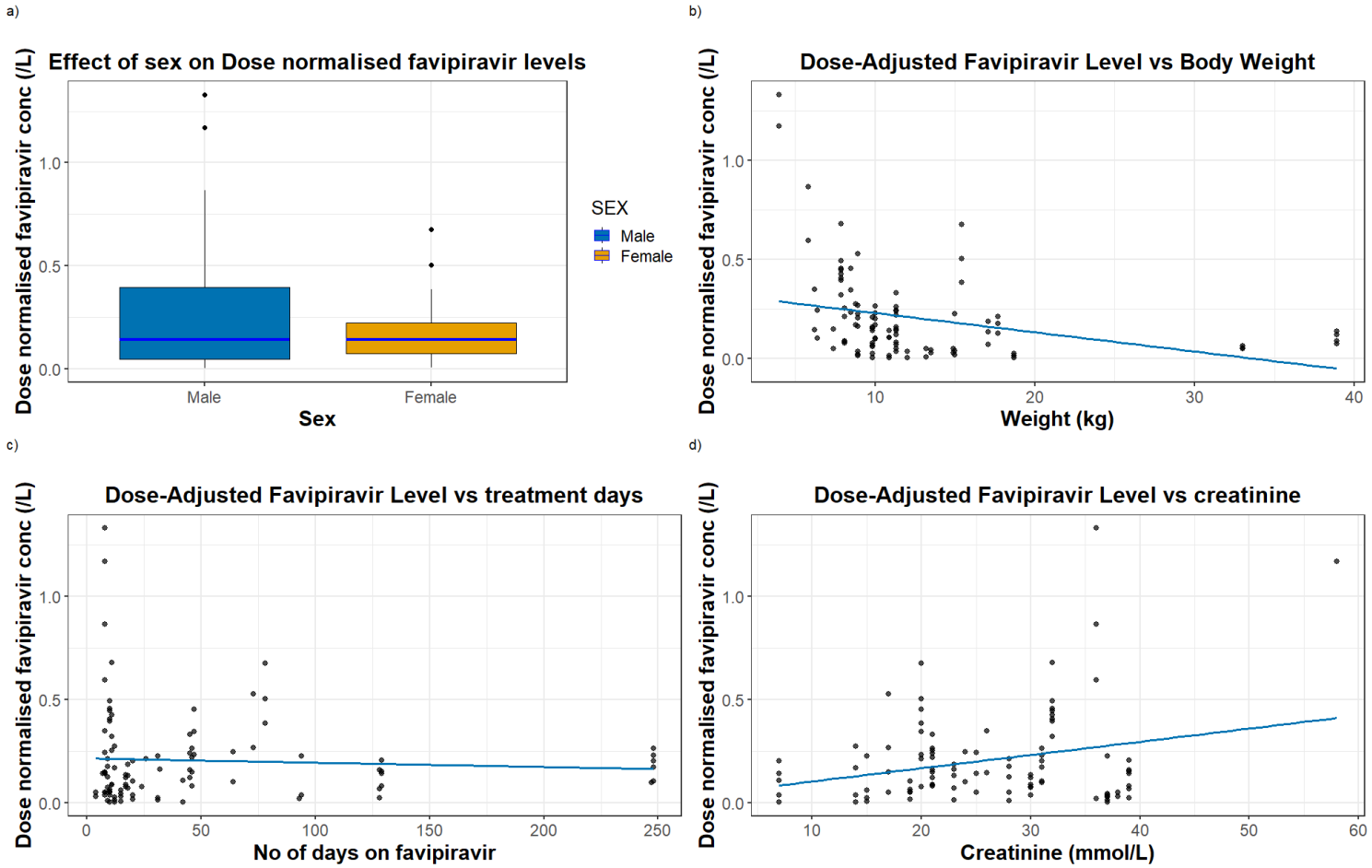

Figure 5.7: Relationship between sex, body weight, treatment duration, and creatinine, and dose-adjusted favipiravir concentrations.

5.9.1.3 Final model

The final favipiravir population pharmacokinetic model was a one-compartment oral absorption model with first-order elimination. A postnatal ontogeny function for aldehyde oxidase, adapted from Subash *et al*. (2024) [367], was incorporated to capture age-dependent enzyme maturation and improved both model fit and biological plausibility. The ka was fixed to literature values (Wang *et al*. (2020) [338]. Inter-individual variability was estimated on CL and Vd using a block omega structure, and a proportional residual error model was applied. Final model evaluation included individual versus prediction fits (Figure 5.10), visual predictive check (Figure 5.8), and diagnostic plots (Figure 5.9). Estimated pharmacokinetic parameters are provided in Table 5.9, with full model specifications detailed in Appendix G. The final model structure was defined by Equations 5.16 and 5.17, which describe clearance and volume of distribution, respectively.

$$CL_i = CL_{\text{pop}} \times \left(\frac{WT_i}{70}\right)^{0.75} \times MF_i \times \exp(\eta_{CL,i}) \tag{5.16}$$

$$V_i = V_{\text{pop}} \times \left(\frac{WT_i}{70}\right)^{1.0} \times \exp(\eta_{V,i}) \tag{5.17}$$

Table 5.9: Favipiravir pharmacokinetic parameter estimates for the final model, including the bootstrap analysis. All parameters are allometrically scaled to 70 kg.

Final model parameter estimates	Estimates (RSE%)	Bootstrap median	Bootstrap 95% confidence interval
CL (L/h/70 kg)	7.6 (28.7)	7.7	5.86 - 11.56
V (L/70 kg)	42.7 (21.2)	43.1	36.38 - 66.79
KA	1.5 FIX	-	-
IIV CL(%)	89.1 (27.3) [2]	88.3	68.6 - 109.1
IIV V(%)	39.1 (52.3) [12]	33.2	21.7 - 63.2
Proportional error (%)	37.8 (6.1) [10]	35.1	24-5 - 47.9

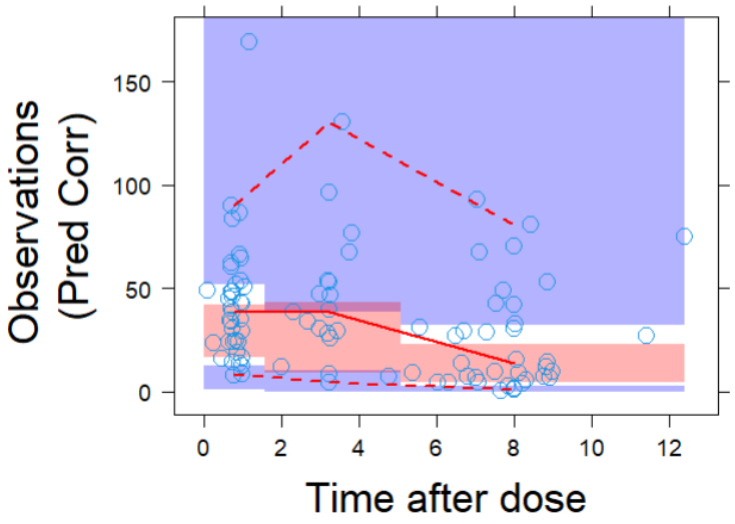

Figure 5.8: Prediction-corrected visual predictive check of the final model showing the 5th, 50th, and 95th percentiles of the observed data (lines with closed circles) compared with the 90% confidence intervals of the corresponding simulated percentiles from the final model (shaded areas).

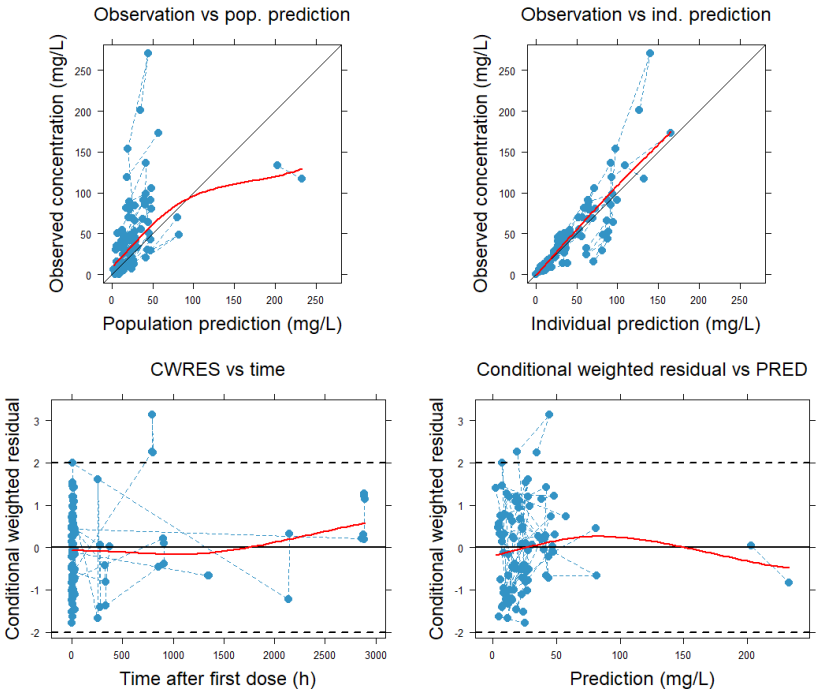

Figure 5.9: Goodness of fit plots of the final model. Top panels: observed versus population (left) and individual (right) predictions with line of identity (solid black) and locally weighted regression (LOESS, red) overlaid. Bottom panels: CWRES versus time (left) and PRED (right), with reference lines at 0 and ±2 (dashed black) and LOESS smoothing (red). The LOESS curve illustrates systematic trends or bias in the data relative to the model fit.

Table 5.10: Summary of all model runs conducted during favipiravir PK model development. AO: maturation of aldehyde oxidase; CR: age-corrected serum creatinine; PMA: maturation function based on postmenstrual age.

Model No	Compartment	Covariate tested	Error model	Reference model	OFV	Δ OFV	AIC	Omega structure	Eta	CL	V	Ka	Comment
1	One	-	Combined	-	615.0	-	805.6	Block	CL, Vd	4.61	6.98	0.292	Parameter estimate near its boundary
2	Two	-	Combined	1	-	-	-	Block	CL, Vd	-	-	-	Unable to converge
3	One	-	Combined	1	619.1	4.1	807.7	Block	CL, V	4.6	42.6	1.5 FIX	Ref
4	Two	-	Combined	3	610.8	-8.3	809.4	Block	CL, V	5.05	35.3 + 309	1.5 FIX	Parameter estimate near its boundary
5	One	-	Additive	3	739.9	120.8	926.5	Block	CL, V	3.08	35.9	1.5 FIX	
6	One	-	Proportional	3	619.4	0.346	806.0	Block	CL, V	4.59	42.8	1.5 FIX	Ref Better RSE
7	One	Age - CL	Proportional	6	615.3	-4.2	803.8	Block	CL,V	5.55	42.4	1.5 FIX	
8	One	PMA - CL	Proportional	6	610.2	-9.2	800.8	Block	CL, V	6.41	41.8	1.5 FIX	High RSE on Hill coefficient
9	One	PMA - CL	Proportional	6	612.6	-6.9	801.2	Block	CL, V	7.2	41.9	1.5 FIX	Hill coefficient FIX
10	One	CR - CL	Proportional	6	616.4	-3.0	805.0	Block	CL, V	4.67	44.4	1.5 FIX	
11	One	SEX - CL	Proportional	6	619.4	-0.4	807.7	Block	CL, V	5.1	42.5	1.5 FIX	
12	One	SEX - V	Proportional	6	618.9	-0.6	807.5	Block	CL, V	4.58	39.1	1.5 FIX	
13	One	Days on treatment	Proportional	6	617.0	-2.4	805.6	Block	CL, V	5.1	42.5	1.5 FIX	
14	One	AO - CL	Proportional	6	611.7	-7.8	798.3	BLOCK	CL, V	7.56	42.7	1.5 FIX	Age_{50} & K FIX Final model
15	One	AO - CL	Proportional	6	611.4	-8.03	800.12	Block	CL, V	6.83	42.3	1.5 FIX	K FIX High RSE on Age_50
16	One	BACKWARD minus AO-CL	Proportional	14	619.3	7.8	806.0	BLOCK	CL, V	4.59	42.8	1.5 FIX	Age_{50} & K FIX

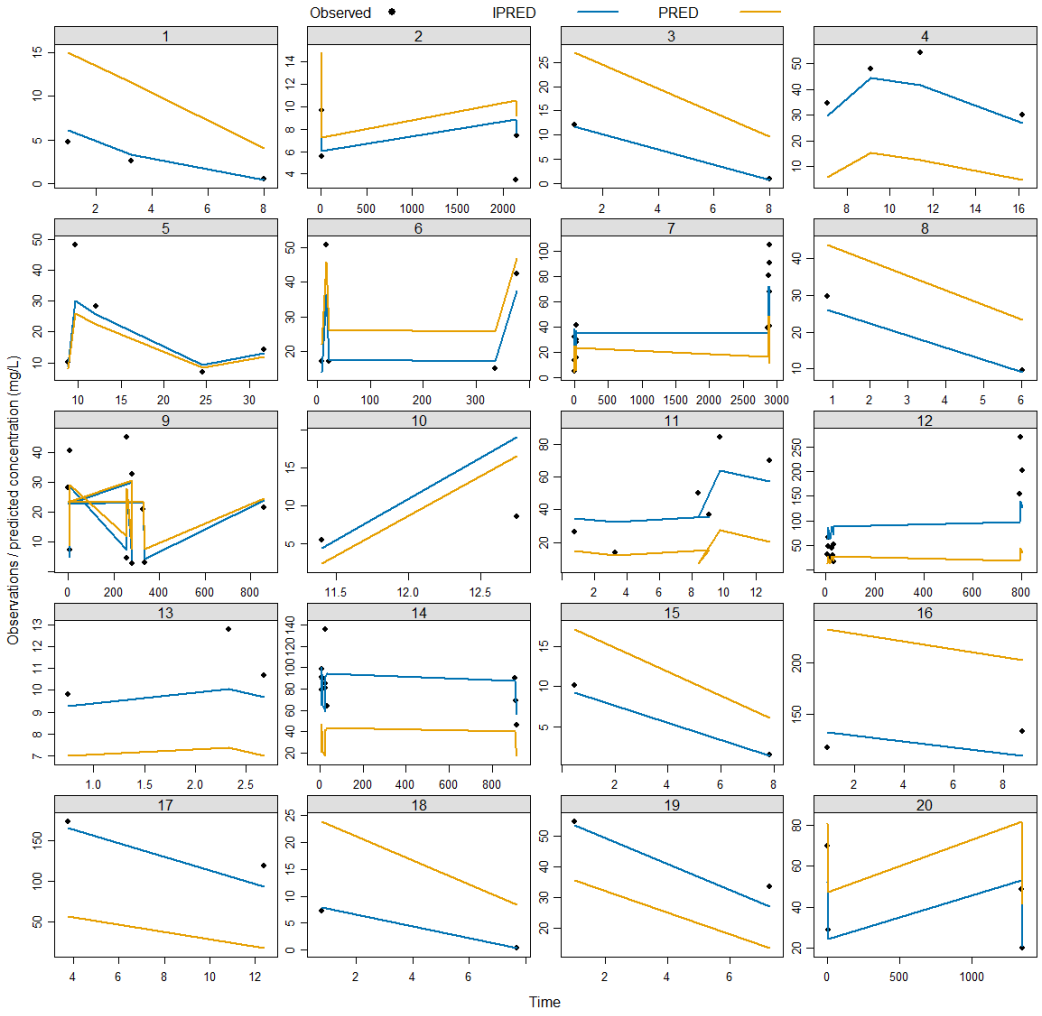

Figure 5.10: Predicted vs observed favipiravir concentrations (mg/L) of each episode. DV: observed drug concentration, IPRED (blue): individual predicted concentration, PRED (orange): population predicted concentration

5.9.2 Simulation

Simulations were conducted at steady state, assuming twice-daily dosing to reflect clinical practice. Outputs were summarised as median steady-state peak (C_{max}) and trough (C_{trough}) concentrations across recommended weight bands. EC_{90} values for respiratory syncytial virus, norovirus, astrovirus, and enterovirus 71 were overlaid on concentration–time plots to facilitate comparison (Figure 5.11).

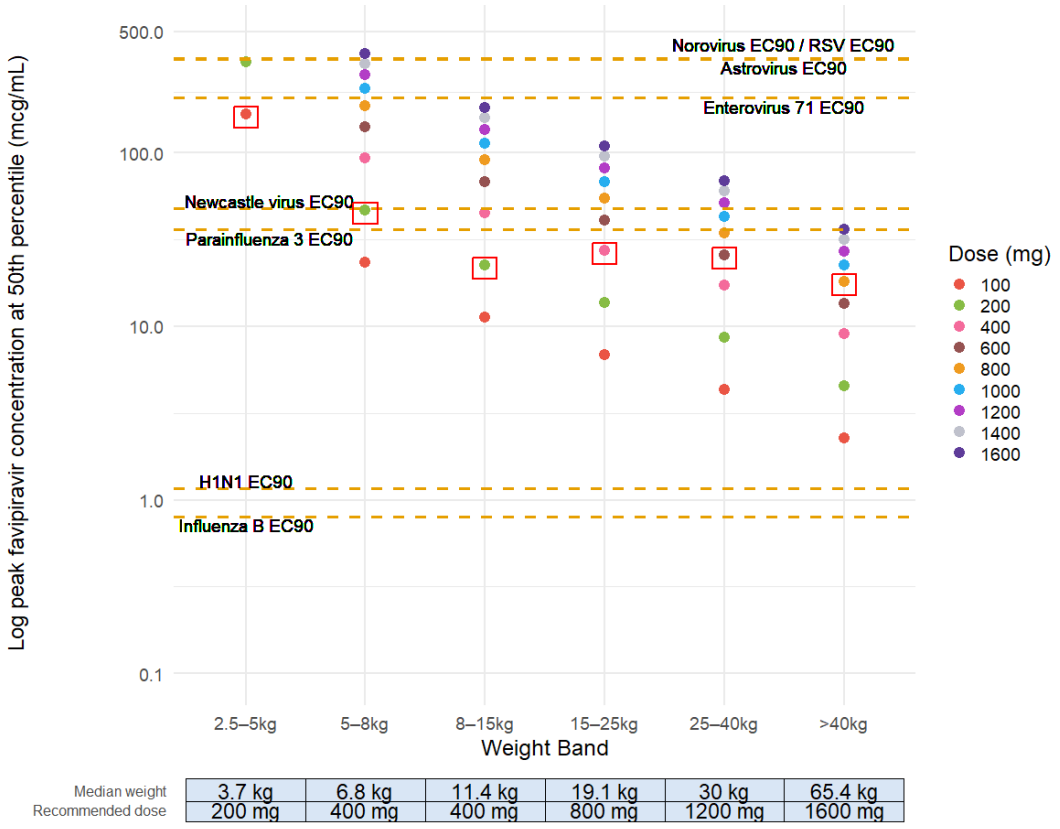

Figure 5.11: Simulated steady-state peak favipiravir concentrations (50th percentile) across weight bands and doses (administered every 12 hours). Dashed horizontal lines indicate EC_{90} thresholds for selected target viruses. Red boxes highlight currently recommended dosing regimens. Median weight refers to the median of the simulated population within each respective weight band.

Simulated median C_{max} concentrations under current weight-based dosing regimens fell below the EC_{90} for most target viruses across all weight bands, with notable underexposure in children above 8 kg. Infants in the 2.5–5 kg weight band achieved median exposures approaching the EC_{90} for RSV, norovirus, and astrovirus, suggesting current regimens may be sufficient in this group. However, in children weighing more than 8 kg, exposures remained below inhibitory thresholds even with escalated doses up to 1600 mg/day. This was particularly evident for RSV, enterovirus 71, astrovirus, and norovirus, common and potentially fatal infections in immunocompromised paediatric populations. These findings underscore the challenge of optimising favipiravir therapy in paediatric populations and suggest that favipiravir may be insufficient as monotherapy, particularly in older children, where

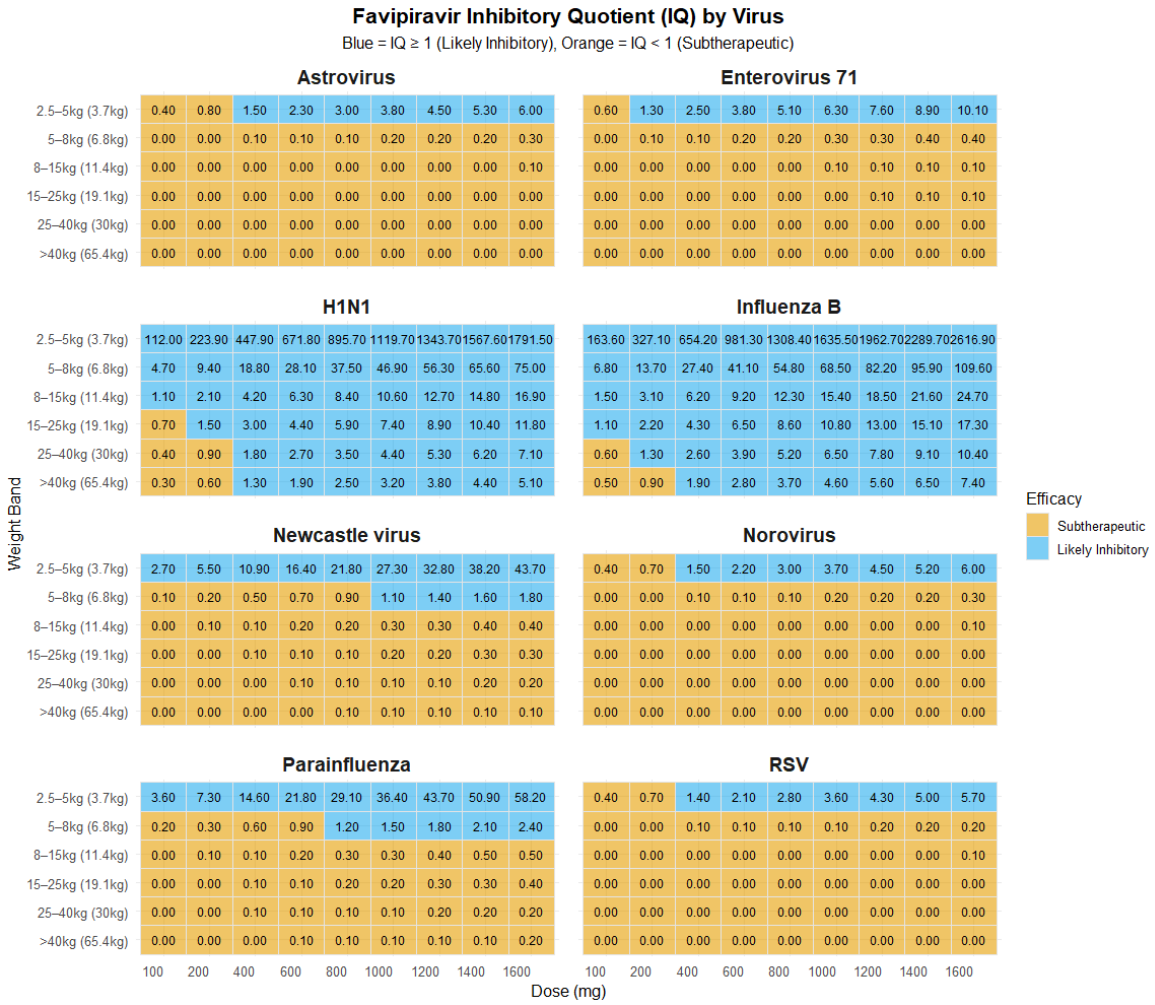

Figure 5.12: Inhibitory quotient plot of favipiravir against various viruses at different dose regimens for each weight group. Blue = IQ $>$ 1 (predicted trough concentrations exceed the viral EC_{90}, suggesting likely antiviral activity); orange = IQ $<$ 1 (trough concentrations fall below EC_{90}, indicating insufficient exposure).

simulated exposures consistently fall below inhibitory thresholds.

The inhibitory quotient was evaluated to integrate simulated drug exposures with viral susceptibility thresholds. IQ values, calculated from median trough concentrations, are presented in Figure 5.12, with EC_{90} values summarised in Table 5.5. IQ values exceeded 1 across all weight bands only for H1N1 and influenza B. For RSV, norovirus, astrovirus, and enterovirus 71, IQ $>$ 1 was achieved only in the lowest weight band (2.5–5 kg) and fell below 1 in heavier children, even at the highest simulated doses.

5.9.3 Discussion

This study represents the first population pharmacokinetic analysis of favipiravir in a cohort of young children receiving prolonged treatment courses. The estimated pharmacokinetic parameters, scaled to a 70 kg standard using allometric principles, were broadly consistent with previously published adult data. The estimated CL of 7.56 L/h falls within the reported range of 2.96 to 9.31 L/h [338, 339]. Vd was estimated at 42.71 L, and the calculated half-life was 3.92 hours. A one-compartment model with first-order absorption and elimination best described the observed concentration-time data, consistent with several published models (Table 5.3). Although Wang *et al*. (2020) [338] initially explored two-compartment models in adults, their reliance on sparse peak and trough sampling limited model resolution. Our dataset, similarly comprised of sparse data, demonstrated greater stability with a one-compartment structure. Ka was fixed at 1.5 h^{-1} based on prior estimates to avoid identifiability issues [338]. A richer sampling across the absorption phase would improve characterisation of absorption kinetics and allow estimation of Ka without the need to fix it. However, the sampling time points were chosen with both pharmacokinetic and clinical considerations in mind. While early and frequent samples around the time of dosing would enhance model resolution, such rich sampling protocols are often not feasible in children. Repeated blood draws within a short time frame place a burden on clinical staff and can be distressing for patients, particularly those who are critically unwell. The sampling schedule was therefore designed to capture key pharmacokinetic phases while minimising invasiveness and impact on patient care.

Interestingly, contrary to previous findings suggesting time-dependent reductions in clearance with prolonged therapy [338, 374], no such trend was observed in our paediatric cohort. This may reflect an eventual steady-state equilibrium during chronic administration, which extended up to 248 days in some patients, far exceeding the 5–14 day regimens reported in adults. Developmental effects on clearance were explored using two approaches: a general maturation function based on postmenstrual age and a more mechanistic enzyme maturation model derived from the ontogeny

of aldehyde oxidase, the primary enzyme responsible for favipiravir metabolism. Incorporating aldehyde oxidase ontogeny provided greater model stability and biological plausibility, especially given that the enzyme activity matures rapidly in infancy. This highlights the need for age-appropriate scaling beyond body size alone when modelling drugs with age-dependent enzymatic clearance.

Despite favipiravir's primary renal excretion as the inactive metabolite M1 [115], standardised creatinine did not emerge as a significant covariate on clearance. This suggests that renal function, at least as captured by serum creatinine, may not adequately reflect favipiravir elimination capacity or its variability in this population. This is consistent with its non-renal route of clearance and the limited utility of creatinine as a generalised health marker in this setting.

Dosing simulations indicated that the current favipiravir regimen used at GOSH is insufficient to achieve the EC_{90} targets for key RNA viruses such as respiratory syncytial virus (RSV), norovirus, astrovirus, and enterovirus 71 (Figure 5.11). Only infants weighing less than 5 kg consistently achieved plasma concentrations exceeding these thresholds. While simulated dose escalations (e.g. 1600 mg twice a day) improved exposures modestly, they remained below the EC_{90} for most weight bands, particularly in older children. This presents a clinical dilemma: increasing the dose may enhance antiviral effect but raises concerns regarding cumulative toxicity, especially in immunocompromised patients requiring prolonged treatment.

Trough median simulated concentrations were used for IQ calculations, as these represent the lowest plasma levels encountered by replicating viruses. In chronic or persistent infections, where viral replication is continuous, trough levels are likely the most critical point of exposure. If concentrations fall below the EC_{90} at trough, even when peak levels are adequate, there may be an increased risk of virological escape and resistance selection. The IQ simulations demonstrated that trough values only exceeded EC_{90} in H1N1 and influenza B, even at the highest simulated doses (Figure 5.12). For most other viruses, including RSV, norovirus, astrovirus, and enterovirus 71, IQ values were above 1 only in the lowest weight band (2.5–5

kg) and fell below 1 in heavier children, despite dose escalation. These findings indicate that current dosing regimens used as a monotherapy are unlikely to achieve sufficient antiviral pressure in older children, particularly in the context of chronic infections or poor immune control, where subtherapeutic trough levels may increase the risk of resistance.

EC_{90} was used to guide both dosing simulations and IQ calculations in this study, but it is important to acknowledge the limitations of this parameter. EC_{90} values are derived from *in vitro* assays, which are not standardised across laboratories and may show limited correlation with *in vitro* efficacy [375]. Viral susceptibility is often virus- and host-cell-line-specific, and the translation of these values into clinical settings remains uncertain. More fundamentally, favipiravir's antiviral activity is mediated by its intracellular metabolite, FAVI-RTP, not the parent compound measured in plasma. As such, mapping plasma concentrations to antiviral effect introduces additional uncertainty. Unfortunately, direct measurement of intracellular FAVI-RTP remains technically challenging in routine clinical practice.

Despite these caveats, the rationale for IQ-based interpretation remains valid. Duval *et al.* (2002) [364] showed that patients with IQ < 1 for amprenavir had poor virological outcomes, whereas those with IQ > 1 experienced significantly better suppression. Casado *et al.* (2003) [376] similarly demonstrated improved response rates for protease inhibitors when IQ > 1 was achieved. These findings underscore the importance of drug exposure relative to susceptibility, particularly for antivirals with gradual resistance mechanisms. Goldhill *et al.* (2018, 2021) [360, 361] confirmed that favipiravir resistance in influenza A virus required at least two mutations, with fitness trade-offs limiting the likelihood of resistance emerging *in vitro* under adequate exposure.

Clinical improvements have been observed in adults despite subtherapeutic plasma concentration [319–321]. The patients also demonstrated clinical responses even when plasma concentrations were below the EC_{90} for their infecting viruses. Kreins et al. (2024) [113] investigated whether favipiravir induced mutagenesis in the viral

RNA polymerase gene and explored correlations with drug concentrations and clinical outcomes, including data from some patients within this cohort. The findings showed favipiravir-specific sequence changes in the RdRp region even at subtherapeutic plasma levels. These changes were associated with clinical improvement, supporting the hypothesis that favipiravir exerts its effect not solely by reducing viral load, but by compromising viral fitness through mutagenesis. Notably, all patients in that study also received nitazoxanide, an immunomodulator known to inhibit human norovirus and enhance the innate antiviral response, which may have provided synergistic benefit.

The concern remains that prolonged exposure to mutagenic antivirals may promote resistance. In our study, while viral mutations were observed during therapy, none corresponded to known favipiravir resistance markers, supporting its continued utility as a viable antiviral. Moreover, studies suggest that the intracellular half-life of FAVI-RTP may extend up to nine days post-treatment [300], indicating that drug effects may persist even after plasma levels decline. This further complicates the interpretation of plasma concentrations as a surrogate for antiviral efficacy.

Overall, favipiravir monotherapy appears insufficient for reliable viral eradication in older children and adolescents. In patients with impaired immune responses, subtherapeutic exposures may permit the development of resistance. Combination therapy with agents such as nitazoxanide may help to lower the effective EC_{90} through synergistic mechanisms and warrants further evaluation. Favipiravir's role may be best understood as supportive, stabilising viral replication until immune reconstitution or definitive therapy (e.g. stem cell transplant or gene therapy) becomes feasible.

This study has several limitations. The pharmacokinetic dataset was derived from a relatively small and heterogeneous cohort, spanning a broad age and weight range with variable degrees of immunocompetence. While this reflects real-world clinical use and enhances generalisability, it introduces variability that may obscure covariate effects. The aldehyde oxidase ontogeny model was extrapolated from *in vitro*

data, and while biologically plausible, direct *in vitro* confirmation remains lacking. In addition, the model captured only total parent drug levels, not the intracellular active metabolite. Given that favipiravir's pharmacological effect is mediated by FAVI-RTP, future studies should prioritise quantifying intracellular concentrations. Ongoing work by our collaborators to quantify intracellular favipiravir metabolite levels may support future integration of such data into a biologically relevant and predictive model.

The patient's immunocompetency, such as lymphocyte count and reconstitution kinetics, likely impacts viral clearance and should be integrated into future pharmacokinetic–pharmacodynamic models. Madelain *et al.* (2020) [377] proposed a mechanistic framework linking intracellular FAVI-RTP concentrations to viral inhibition using an E_{max} model. Quantifying this active metabolite in paediatric immune cells could enable more precise characterisation of age-related enzyme maturation, particularly of aldehyde oxidase and nucleotide kinases. Combined with viral load and immune markers, such data could inform biologically relevant exposure targets and optimise favipiravir dosing in immunocompromised children.

In conclusion, favipiravir, particularly when used alongside other antivirals, remains an important option for managing severe RNA viral infections in children, especially as a bridging therapy in those awaiting immune reconstitution. Our model supports weight-based dosing but highlights the inadequacy of current regimens in achieving therapeutic IQ values in most paediatric patients. The findings underscore the need for combination therapy, improved biomarkers of drug effect, and refined dosing strategies that consider both pharmacokinetics and host immunity. Despite its limitations, favipiravir contributed meaningfully to virological control and clinical stability in this vulnerable population.

Chapter 6

Patient and Public Involvement, Clinical Impact, and Research Reflection

6.1 Patient and public involvement and engagement

Patient and public involvement and engagement (PPIE) is a cornerstone of high-quality health research. It ensures that research is shaped by the needs, experiences, and priorities of the people it ultimately aims to serve. From the outset, this project has been driven by the perspectives of families and young patients. Their input has been instrumental in shaping the project's direction and grounding it in real-life challenges.

At the inception of the project, an advisory panel was formed, comprising three families with lived experience of the conditions studied. One advisor, a parent whose son underwent HSCT, shared her concerns around drug interactions. She recognised that ciclosporin was essential for the success of the transplant, but noticed frequent dose changes after her son was prescribed an azole antifungal. While she waited for the antifungal to reach therapeutic levels, she was informed that her son's liver and kidney function had deteriorated. Although she expressed gratitude for the care

received, she wished there was a way to reduce the number of dose adjustments required.

Another advisor spoke about her experience with intravenous immunoglobulin. Her son's IgG levels were low, necessitating frequent hospital visits for top-up infusions. On one occasion, this led to the family missing an important school event for the patient's sibling. The parent, the patient, and the sibling were all saddened by having to choose between attending the event and going to the hospital for the infusion. It was a difficult decision, and one that highlighted how the need for frequent hospital visits can disrupt everyday family life. For this parent, optimising immunoglobulin dosing was not only about clinical efficacy, but about restoring a sense of normality and routine for the whole family, who were still adjusting to a new diagnosis.

Their experiences were deeply impactful, and their perspectives were integrated throughout the project. As the work progressed, I held a number of PPIE events to further engage with patients, families, and the public. A consistent theme emerged from these discussions: the need to raise awareness of the complexities and challenges surrounding paediatric medicine dosing. Many of the young people involved were surprised to learn about the complexities of paediatric medicine dosing and the frequent need for dose adjustments. They expressed a strong desire for these challenges to be highlighted at a national level, believing that greater awareness could lead to meaningful change. Their feedback underscored the importance of not only addressing these issues through research, but also ensuring that the public, policymakers, and healthcare professionals are better informed about the realities faced by children and families.

To amplify these voices, I collaborated with a fellow NIHR researcher and a production company to create a short film highlighting the role of paediatric pharmacists, the challenges of paediatric medicine, and how pharmacokinetic research can help. We held a dedicated PPIE session with young people to shape the format and content of the film. Their ideas guided the tone, narrative, and key messages, ensuring the film would be both engaging and authentic. The final version was reviewed and

refined with input from the Young Persons' Advisory Group (YPAG) at GOSH.

The completed film, 'The Right Dose', was premiered at GOSH in a well-attended event featuring the Mayors of Holborn and Islington, young contributors and their families, GOSH executives, and members of the public. The event included a panel discussion where young people and dignitaries explored how children and young people can have a voice in shaping healthcare policies and research. Early career researchers, including pharmacists from across London and a physiotherapist, also showcased their work.

The film has since received a couple of recognitions, including the "Best Innovation" award at the Neonatal and Paediatric Pharmacy Group (NPPG) Conference and an honourable mention in the "Advocacy and Community Building" category of the UCL Open Science and Scholarship Awards. These recognitions reflect the powerful impact of involving patients and the public in every stage of the research process. It has found a permanent home on the GOSH Charity YouTube channel, where it can continue to raise awareness, spark conversation, and inspire more patient-centred research and policy long into the future.

Through this PPIE work, I have learned that research becomes stronger, more clinically relevant, and more translatable to real-world practice when it listens to the lived experiences of those it seeks to help. It helps ensure that the questions we ask, and the solutions we seek, truly matter to those affected. Embedding patient and public insight has made my work more focused, more patient-centred, and ultimately more impactful. Their voices have not only guided the direction of this project, but have also inspired me personally, driving me forward. It is my hope that this film, and the conversations it has helped spark, continue to raise national awareness of the importance of involving children, young people, and their families in shaping the future of paediatric medicine. By sharing their stories and insights, we can help ensure that future research and healthcare policy are driven by those with lived experience.

6.2 Clinical impact and research reflection

The clinical relevance and potential translation of each pharmacokinetic model developed in this thesis have been actively explored and disseminated through professional and clinical networks. I presented the ciclosporin model during the Paediatric Bone Marrow Transplant (BMT) Audit Meeting, an annual meeting jointly hosted by the two largest paediatric HSCT centres in the UK (GOSH and Newcastle). This platform was ideal, as both centres share similar patient cohorts but differ in dosing practices. The presentation demonstrated not only the model's findings but also the broader potential of pharmacokinetic modelling to inform dose optimisation. The audience showed strong interest in the simulated dose recommendations, particularly given that the early post-transplant period is critical for engraftment and associated complications. I emphasised that further external validation is required before clinical implementation, ideally using an independent dataset to strengthen the model's robustness. The Newcastle team expressed enthusiasm in collaborating to validate the model with their own patient data and were particularly excited by the prospect of translating the model into a practical dosing interface (calculator), which could reduce variability in prescribing, standardise clinical practice, and support timely decision-making. They encouraged me to pursue this work further as a postdoctoral project.

Similarly, I presented the immunoglobulin model results to the North London Subregional Immunoglobulin Advisory Panel, a multidisciplinary forum of consultants, pharmacists, and nurses overseeing regional immunoglobulin use. The panel recognised the novelty and clinical value of this work, particularly in the context of limited pharmacokinetic evidence available for immunoglobulin therapy in children. They strongly encouraged publication, recognising its potential to influence national immunoglobulin dose commissioning. Given that immunoglobulin prescribing in England is governed by evidence-based commissioning frameworks, this work could directly inform policy and rationalise resource allocation. The chapter has since been submitted for publication and is currently under review.

The favipiravir model was presented to the GOSH Antiviral Committee, where it informed discussions on the optimal use of antivirals in immunocompromised children. While the evidence base was not yet sufficient to support standalone use of favipiravir, the findings provided robust pharmacokinetic support for combination therapy, which has since been incorporated into local formulary guidance. The model has also been applied to simulate drug exposure in a collaborative publication (Kreins et al., 2024 [113]), and I have contributed to a subsequent clinical paper on real-world paediatric experience (Arlabosse et al., 2024 [114]). Following these contributions and conference presentations, including at the Neonatal and Paediatric Pharmacy Group (NPPG), I have become a national point of contact for advice on favipiravir use in children, with other centres seeking clinical and pharmacokinetic guidance. As co-chair of the London NPPG Regional Group (LNPPG), I organise quarterly meetings for members and use this platform to promote research engagement, create opportunities for members to showcase their work, and provide an outlet for disseminating pharmacy-led research.

This research was conducted under NIHR funding, with the overarching aim of fostering clinical academics within the NHS. Throughout my PhD journey, I have stepped beyond my comfort zone, developing confidence and leadership in advocating for safer and more effective medicines for children. This process has also deepened my commitment to patient and public involvement in research, amplifying the voices of young people and their families in decisions about their care. Within the GOSH pharmacy department and the LNPPG, I have been recognised as a research leader and have actively mentored peers, creating opportunities and encouraging a culture of clinical inquiry and evidence-based practice.

Chapter 7

Future work

This research has sought to address the significant gaps in pharmacokinetic knowledge among paediatric populations, particularly in the context of immunocompromised children. The work presented here demonstrates that children, especially those under two years of age, require dedicated pharmacokinetic investigations. Extrapolation from adult data is insufficient due to the dynamic developmental changes affecting drug absorption, distribution, metabolism, and excretion in early life. Across all three therapeutic areas explored (ciclosporin, immunoglobulin, and favipiravir), this research provides a foundation for more precise, personalised, and developmentally appropriate dosing strategies.

7.1 Ciclosporin: Advancing personalised therapy in paediatric HSCT

Ciclosporin remains a cornerstone of immunosuppression in paediatric HSCT patients. The model developed in this project is, to our knowledge, the only population pharmacokinetic model in HSCT patients that provides a clinician-friendly, weight-banded dosing strategy. While published paediatric HSCT models often focus on covariate identification, none have proposed pragmatic, implementable dosing guidance. This model incorporates several biologically plausible covariates: azole co-administration, haematocrit, serum creatinine, postmenstrual age (for CYP3A on-

togeny), and patient weight via allometric scaling, and was built using real-world trough level data. In attempting to further refine the model, several biochemical markers were evaluated as candidate covariates for organ function: haematocrit, serum creatinine, albumin, and total bilirubin. Of these, only haematocrit and age-adjusted serum creatinine were retained as significant covariates. Creatinine served as a surrogate marker for overall physiological status, whereas albumin and total bilirubin, despite representing hepatic synthetic function and cholestasis respectively, did not improve model fit. This suggests that liver function is not fully captured by these standard biochemical tests alone. Notably, other published models have also attempted to incorporate such biomarkers, although success has varied and their utility in paediatric HSCT remains an open question.

7.1.1 Incorporating disease-state covariates: GVHD and diarrhoea

Two clinically relevant but understudied covariates, GVHD and diarrhoea, have emerged as important candidates for future research. GVHD affects up to 50% of patients post-HSCT [87, 88], and gastrointestinal involvement may directly impact ciclosporin absorption, particularly in orally administered regimens. Diarrhoea, whether from GVHD, infection, or chemotherapy toxicity, could influence both ciclosporin and azole antifungal exposure, yet neither covariate is consistently captured in structured electronic health record fields. Due to their heterogeneous documentation (e.g. diarrhoea may be described variably as “loose stools,” “opened bowels,” or “increased stool output”), standardised recording practices are urgently needed. For future pharmacokinetic studies in HSCT patients, a uniform, binary documentation system (e.g. “GVHD present: yes/no,” “diarrhoea present: yes/no”) would greatly facilitate data extraction and enhance model precision.

7.1.2 Quantifying the effect of azole antifungals

In the current model, the interaction between azole antifungals and ciclosporin is handled as a binary covariate. However, this fails to capture interindividual variability between azoles, and their dynamic pharmacokinetics over time. With abundant

therapeutic drug monitoring data available, there is an opportunity for future work to move beyond binary classification by integrating published pharmacokinetic models of azoles directly into the ciclosporin model. For example, Boonsathorn *et al.* 2019 [97] developed a posaconazole model in paediatric patients from the same institution, providing an excellent opportunity for integration. By incorporating time-varying azole exposure as a continuous covariate (or using model-predicted concentrations from joint or linked models), it would be possible to more accurately quantify the inhibitory effects of each agent on ciclosporin clearance. This approach could also support simulations to explore switching between azoles or adjusting doses based on therapeutic drug monitoring.

7.1.3 Towards clinical implementation

External validation is critical for the wider adoption of any population pharmacokinetic model. Collaboration with other paediatric HSCT centres, particularly Newcastle which serves a similar paediatric cohort, would be an ideal partner to provide robust external validation in a comparable population. Once validated, the model can be incorporated into clinical workflows using a Bayesian forecasting approach. A simple web-based application (e.g. R/Shiny) could allow clinicians to input patient-specific variables and measured drug concentrations to generate tailored dosing recommendations in real time. A prospective evaluation of model-informed, real-time dosing would be especially valuable to determine whether tighter ciclosporin exposure, especially during the acute phase of HSCT, would reduce rates of toxicity or GVHD. Integration with electronic prescribing systems and point-of-care therapeutic drug monitoring would close the loop, enabling rapid, personalised dose adjustments at the bedside, truly realising the promise of personalised medicine.

7.2 Immunoglobulin: Optimising dosing strategies and linking to clinical outcomes

The immunoglobulin model developed in this project introduced a novel approach by incorporating IgM levels to estimate baseline endogenous IgG production. This is a critical step toward individualising therapy, as patients vary significantly in their endogenous IgG production capacity. Simulations suggested that current recommended doses may not consistently sustain therapeutic IgG levels, while a single loading dose strategy could allow better maintenance and potentially lower maintenance requirements.

7.2.1 Impact of dose rounding and weight metrics

In the UK, immunoglobulin use is strictly rationed due to cost and limited supply. National and local policies support dose rationalisation strategies such as rounding down doses to the nearest vial size and using ideal rather than total body weight. However, these practices are not tailored to paediatrics and have not been formally evaluated in a pharmacokinetic context. Dose rounding may have minimal clinical impact in patients with immunodeficiency, whose doses are titrated to trough IgG levels. However, in immunomodulatory settings, this practice may reduce efficacy. Notably, Hodkinson et al. (2015) [378] found divergent outcomes in obese versus lean adults receiving immunoglobulin, underscoring the complexity of weight-based dosing. In children, these issues are further complicated by growth and development, and several weight estimation methods are in use (Table 7.1). Investigating the pharmacokinetics of immunoglobulin in children with extreme body weights, particularly in the context of immunomodulation indications, remains an important area of research.

7.2.2 Subcutaneous dosing and real-world data challenges

The majority of immunodeficient children now receive subcutaneous immunoglobulin at home, creating challenges for accurate dosing history documentation and extraction. This lack of precise dosing time data makes pharmacokinetic interpretation of measured IgG levels difficult. The MyGOSH app, already widely used by

Table 7.1: Different measures of weight used when dosing medicines in childhood obesity [379]

Weight measure	How/What to measure/calculate
Total Body Weight (TBW)	Weight in kg (no adjustment necessary)
Body Mass Index (BMI)	TBW (kg) / (Height in m^2)
Ideal Body Weight (IBW)	Moore's Method - Using STAMP tool or UK WHO growth chart, cross-reference height centile to weight for that centile
Adjusted Body Weight (AdjBW)	IBW + Adjustment Factor (0.3) × (TBW – IBW)

GOSH patients and families, could be leveraged in future studies to prompt users to log the time of their last dose prior to scheduled blood tests, significantly improving data quality not only for model development, but also in clinical settings which aid the interpretation of clinical data for all patients on medicines that require therapeutic drug monitoring.

7.2.3 Linking pharmacokinetics to clinical outcomes and quality of life

Pharmacokinetics alone do not capture the full clinical impact of immunoglobulin therapy. The British Society of Immunology and UKPIN recommend monitoring infection rates, antibiotic usage, and hospitalisations as outcome measures [245]. These can be incorporated into time-to-event models (e.g. time to next infection). Additionally, tools like pulmonary function tests and imaging can help track chronic complications such as bronchiectasis.

Another under-explored domain is quality of life. Peshko *et al.* (2019) [380] found that patients with primary immunodeficiencies report lower health-related quality of life than those with other chronic conditions. There is a need to develop validated, disease-specific quality of life instruments for children and assess how pharmacokinetics, route and frequency of administration, and IgG levels influence these outcomes.

7.3 Favipiravir: Pioneering pharmacokinetics in novel therapeutics

The favipiravir study represents a successful example of rapid translation from bedside to model. In response to clinical need and the absence of paediatric data, a therapeutic drug monitoring framework was established in collaboration with an external laboratory to support the compassionate use of this novel antiviral and characterise favipiravir pharmacokinetics in immunocompromised children. Pharmacokinetic analysis informed local dosing guidelines and provided insights into clinical outcomes and virological response, including viral mutagenesis, despite EC_{90} targets not being consistently met.

Future directions include integrating immunological biomarkers such as lymphocyte subsets to refine model predictions, a concept introduced in Chapter 5. As precision diagnostics continue to evolve, the need for re-purposed and off-label therapies in rare diseases will grow. This work highlights the potential for clinical-academic partnerships and the value of clinician-led pharmacokinetic research in bridging gaps between novel therapies and evidence-based dosing.

7.4 Concluding remarks

This thesis has provided novel insights into the pharmacokinetics of three distinct but clinically significant therapies in paediatric populations. Across all models, several themes emerge: the need for child-specific data, the value of embedding pharmacokinetics within clinical workflows, and the promise of real-world data in supporting model development and refinement.

The immediate next step is to validate these models across multiple paediatric centres and embed them into NHS digital prescribing systems, where they could link directly with resources such as the BNF for Children. In doing so, model-informed precision dosing could provide real-time, evidence-based recommendations that reduce unwarranted variation in prescribing and improve equity of care for children with rare and complex conditions.

Yet the long-term vision extends beyond national implementation. By creating interoperable platforms and forging collaborations with international partners, these tools could form the backbone of a global learning health system for paediatric therapeutics, one in which every data point contributes to continuously improving dosing models. Integrating pharmacokinetics with genomics, immunology, and patient outcomes would ultimately allow for adaptive, personalised dosing strategies that benefit children worldwide.

Realising this vision will require collaboration between researchers, clinicians, regulators, and policymakers, as well as investment through national and international funding schemes. But the goal is clear: a future in which no child is treated as a "small adult," but as an individual whose therapy is informed by data, tailored to their biology, and delivered with precision and compassion.

Appendix A

Publications included in the scaling of ciclosporin and azole antifungals pharmacokinetics from early life to old age.

Pubmed ID	Author	Drug	Population / Study Context	No of subjects	Healthy sub-jects	Median age (years)	Median weight (kg)
6627824	Follath *et al.* 1983 [381]	Ciclosporin	Renal failure	4	No	54.5	Not reported
6487505	Robson *et al.* 1984 [382]	Ciclosporin	Primary biliary cirrhosis	10	No	55.5	67
3898491	Henny *et al.* 1985 [383]	Ciclosporin	Renal transplant	14	No	35	62
3896612	Ptachcinski *et al.* 1985 [384]	Ciclosporin	Renal transplant	41	No	31	Not reported
3895624	Ptachcinski *et al.* 1985 [385]	Ciclosporin	Influence of diet	18	No	39	Not reported
3803418	Grevel *et al.* 1986 [386]	Ciclosporin	Pharmacokinetic study	14	Yes	42.5	73
3540030	Burckart *et al.* 1986 [387]	Ciclosporin	Liver transplant	16	No	2.9	14.4
3964534	Johnston *et al.* 1986 [388]	Ciclosporin	Pharmacokinetic study	12	Yes	34	67
3274407	Yee *et al.* 1986 [389]	Ciclosporin	Haematopoietic stem cell transplant	85	No	22	Not reported
3680581	Ptachcinski *et al.* 1987 [390]	Ciclosporin	Pharmacokinetic study	5	Yes	23.8	Not reported
3318898	Gupta *et al.* 1987 [391]	Ciclosporin	Renal transplant	5	No	60	55.6
3606938	Freeman *et al.* 1987 [392]	Ciclosporin	Drug-drug interaction	10	Yes	23.6	68.1
3544377	Wadhwa *et al.* 1987 [393]	Ciclosporin	Drug-drug interaction	14	No	38	Not reported
3541320	Lorber *et al.* 1987 [394]	Ciclosporin	Renal transplant	212	No	36	Not reported
3047931	Yee *et al.* 1988 [205]	Ciclosporin	Haematopoietic stem cell transplant	85	No	22	Not reported
3287355	Cipolle *et al.* 1988 [395]	Ciclosporin	Pancreas transplantation	5	No	37	76
3065480	Mallet *et al.* 1988 [396]	Ciclosporin	Haematopoietic stem cell transplant	188	No	20	43
3275522	Frey *et al.* 1988 [397]	Ciclosporin	Renal transplant	58	No	50	Not reported
2651227	Naoumov *et al.* 1989 [398]	Ciclosporin	Liver transplant	13	No	38	Not reported
2723114	Grevel *et al.* 1989 [399]	Ciclosporin	Renal impairment	33	No	38	65.7
2655218	Flechner *et al.* 1989 [400]	Ciclosporin	Renal transplant	35	No	46.2	65.1
2642778	Awni *et al.* 1989 [401]	Ciclosporin	Renal transplant	21	No	45.1	78.7
2655217	Speck *et al.* 1989 [402]	Ciclosporin	Renal transplant	10	No	52.5	Not reported
2391396	Gupta *et al.* 1990 [206]	Ciclosporin	Influence of diet	8	Yes	29	64

Pubmed ID	Author	Drug	Population / Study Context	No of subjects	Healthy sub-jects	Median age (years)	Median weight (kg)
2315970	Brunner *et al.* 1990 [403]	Ciclosporin	Haematopoietic stem cell transplant	9	No	32	71
2350530	Lindholm *et al.* 1990 [404]	Ciclosporin	Influence of diet	11	Yes	28	79.5
2338116	Misteli *et al.* 1990 [405]	Ciclosporin	Diabetic children and adolescents	19	No	10.6	Not reported
2340843	Brockmoller *et al.* 1990 [406]	Ciclosporin	Renal transplant	22	No	49	67
2274997	Tan *et al.* 1990 [407]	Ciclosporin	Heart and lung transplant	11	No	25.6	48.6
2253667	Couet *et al.* 1990 [408]	Ciclosporin	Renal transplant	10	No	36.4	62.9
2025515	Hoppu *et al.* 1991 [409]	Ciclosporin	Renal transplant	10	No	1.76	10.5
1884727	Tredger *et al.* 1991 [407]	Ciclosporin	Liver transplant	9	No	34.5	Not reported
1777368	Schwinghammer *et al.* 1991 [410]	Ciclosporin	Haematopoietic stem cell transplant	5	No	33	Not reported
2045532	Sandborn *et al.* 1991 [411]	Ciclosporin	Pharmacokinetic study	5	Yes	32.5	70
1958443	Hoppu *et al.* 1991 [412]	Ciclosporin	Liver transplant	20	No	3.4	Not reported
1721274	Jain *et al.* 1991 [413]	Ciclosporin	Liver impairment/transplant	7	No	27.5	74.5
1424418	Hebert *et al.* 1992 [414]	Ciclosporin	Pharmacokinetic study	6	Yes	36	78.5
1640354	Luke *et al.* 1992 [415]	Ciclosporin	Haematopoietic stem cell transplant	10	No	31	70
1425874	deLorgeril *et al.* 1992 [416]	Ciclosporin	Heart transplant	10	No	50.6	46.2
1330397	Lindholm *et al.* 1992 [417]	Ciclosporin	Renal impairment	187	No	42.1	74.1
1473336	Messori *et al.* 1992 [418]	Ciclosporin	Haematopoietic stem cell transplant	10	No	32.5	63
1455195	Brynskov *et al.* 1992 [419]	Ciclosporin	Crohn's disease	12	No	36.5	63
8491066	Tan *et al.* 1993 [420]	Ciclosporin	Heart and lung transplant	20	No	24.3	45.3
8227465	Mueller *et al.* 1993 [421]	Ciclosporin	Drug-drug interaction	24	Yes	27.9	74.3
8354028	Lindholm and Kahan *et al.* 1993 [422]	Ciclosporin	Renal transplant	160	No	41.2	Not reported
8366176	Kovarik *et al.* 1993 [423]	Ciclosporin	Pharmacokinetic study	24	Yes	27.3	74.4
8236361	Gardier *et al.* 1993 [104]	Ciclosporin	Cardiac disease/transplant	11	No	54.6	73.9
8451783	Klompmaker *et al.* 1993 [424]	Ciclosporin	Liver transplant	6	No	38	Not reported
8466958	Bourget *et al.* 1993 [425]	Ciclosporin	Liver transplant	5	No	27.6	66.4
8302687	Kovarik *et al.* 1993 [426]	Ciclosporin	Bioequivalence study	24	Yes	26	74
8130357	Meyer *et al.* 1993 [427]	Ciclosporin	Renal transplant	14	No	41.5	Not reported
8500786	Morel *et al.* 1993 [428]	Ciclosporin	Renal transplant	10	No	47.1	61.2
7988626	Jacqz-Aigrain *et al.* 1994 [429]	Ciclosporin	Renal transplant	42	No	12	29.5
8132853	Aweeka *et al.* 1994 [430]	Ciclosporin	Renal impairment	8	No	41	68
8159594	Whipple *et al.* 1994 [431]	Ciclosporin	Liver transplant	7	No	9.1	24.1
8009562	Cooney *et al.* 1994 [432]	Ciclosporin	Renal impairment	8	No	42	Not reported
8070508	Tsang *et al.* 1994 [433]	Ciclosporin	Heart and lung transplant	3	No	41	60
7849332	Sketris *et al.* 1994 [434]	Ciclosporin	Renal transplant	57	No	42	68
7708271	Passfall *et al.* 1994 [435]	Ciclosporin	Drug-drug interaction	1	No	52	63
8085277	Kovarik *et al.* 1994 [436]	Ciclosporin	Renal transplant	11	No	47.4	68.2
11271221	Mueller *et al.* 1994 [437]	Ciclosporin	Renal transplant	18	No	46	70.6
8178343	Mueller *et al.* 1994 [438]	Ciclosporin	Renal transplant	18	No	48.3	71.2
7940876	Cooney *et al.* 1994 [439]	Ciclosporin	Renal and liver transplant	7	No	9	Not reported
8545871	Dunn *et al.* 1994 [440]	Ciclosporin	Liver transplant	9	No	2.5	14.3
7712671	Tan *et al.* 1995 [441]	Ciclosporin	Renal transplant	16	No	50.4	Not reported
7624927	Galla *et al.* 1995 [442]	Ciclosporin	Psoriasis	63	No	50.2	77
7768070	Ducharme *et al.* 1995 [443]	Ciclosporin	Influence of diet	10	Yes	27.6	76
7576013	Kovarik *et al.* 1995 [444]	Ciclosporin	Renal transplant	14	No	46.5	72.3
7560248	Fluckiger *et al.* 1995 [445]	Ciclosporin	Crohn's disease	19	No	35	68
7589056	Tan *et al.* 1995 [446]	Ciclosporin	Heart and lung transplant	5	No	26	53.4
7667170	Cooney *et al.* 1995 [447]	Ciclosporin	Renal transplant	3	No	8	21.3
7742156	van den Borne *et al.* 1995 [448]	Ciclosporin	Rheumatoid arthritis	12	No	58	71
7570970	Wahlberg *et al.* 1995 [449]	Ciclosporin	Renal transplant	59	No	47	71
8844439	Mochon *et al.* 1996 [450]	Ciclosporin	Renal transplant	18	No	3.5	13.1
8653992	Chang *et al.* 1996 [451]	Ciclosporin	Drug-drug interaction	10	Yes	31	64.5
8824473	Kovarik *et al.* 1996 [452]	Ciclosporin	Renal transplant	28	No	44.7	74.2
8885119	Kaplan *et al.* 1996 [453]	Ciclosporin	Pancreas/kidney transplant	14	No	33.4	65.6
8693526	Min *et al.* 1996 [454]	Ciclosporin	Renal transplant	10	No	44	85.3
8881898	Chawla *et al.* 1996 [455]	Ciclosporin	Atopic dermatitis	11	No	38	Not reported
8875790	Krmar *et al.* 1996 [456]	Ciclosporin	Renal transplant	6	No	15.2	52

Pubmed ID	Author	Drug	Population / Study Context	No of subjects	Healthy subjects	Median age (years)	Median weight (kg)
8990355	Keown *et al.* 1996 [457]	Ciclosporin	Renal transplant	737	No	47.6	Not reported
9243350	Gruber *et al.* 1997 [458]	Ciclosporin	Renal transplant	6	No	40	74
9278195	Fu *et al.* 1997 [459]	Ciclosporin	Lupus nephritis	10	No	11.5	Not reported
9210501	Dunn *et al.* 1997 [460]	Ciclosporin	Liver transplant	27	No	3.3	Not reported
9203180	Kabasakul *et al.* 1997 [461]	Ciclosporin	Renal transplant	9	No	8.94	Not reported
9089419	Lares-Asseff *et al.* 1997 [462]	Ciclosporin	Renal transplant	11	No	14.5	44
9431838	Simon *et al.* 1997 [463]	Ciclosporin	Renal transplant	12	No	42	Not reported
9723362	Gusmano *et al.* 1998 [464]	Ciclosporin	Renal impairment	17	No	10.3	28.8
9723233	Wacke *et al.* 1998 [465]	Ciclosporin	Nephrotic syndrome	20	No	48.6	71.6
9597565	Doose *et al.* 1998 [466]	Ciclosporin	Healthy	14	Yes	28.1	74.7
9734620	Keown and Niese *et al.* 1998 [467]	Ciclosporin	Renal transplant	86	No	44.1	71
9753208	Schroeder *et al.* 1998 [166]	Ciclosporin	Bioequivalence study	36	Yes	29.5	74.8
10492062	Caraco *et al.* 1999 [468]	Ciclosporin	Kidney and heart transplant	8	No	39.25	74.9
10604829	Pollak *et al.* 1999 [469]	Ciclosporin	Renal transplant	44	No	38.75	Not reported
10071349	van Mourik *et al.* 1999 [470]	Ciclosporin	Liver impairment/transplant	8	No	4.5	Not reported
10456488	Asberg *et al.* 1999 [471]	Ciclosporin	Renal transplant	9	No	52	83
10561143	Curtis *et al.* 1999 [472]	Ciclosporin	Renal transplant	20	No	44.3	Not reported
10435879	Sud *et al.* 1999 [473]	Ciclosporin	Renal transplant	6	No	39.2	59.8
10610595	Takahara *et al.* 1999 [474]	Ciclosporin	Renal transplant	19	No	31.7	55.6
10603112	Meier-Kriesche *et al.* 1999 [475]	Ciclosporin	Renal transplant	19	No	13.5	Not reported
10083157	Fisher *et al.* 1999 [476]	Ciclosporin	Liver transplant	26	No	52	Not reported
10228992	Filler *et al.* 1999 [477]	Ciclosporin	Renal transplant	78	No	11	43
10071350	Cooney *et al.* 1999 [478]	Ciclosporin	Liver transplant	14	No	7.7	Not reported
10450062	Canafax *et al.* 1999 [479]	Ciclosporin	Pharmacokinetic study	20	Yes	30.8	66.2
10487284	Medeiros *et al.* 1999 [480]	Ciclosporin	Nephrotic syndrome	10	No	10	Not reported
10620203	Binet *et al.* 2000 [481]	Ciclosporin	Pharmacokinetic study	10	Yes	25	77.9
10919600	Higgins *et al.* 2000 [482]	Ciclosporin	Renal transplant	19	No	38	Not reported
11019845	Schultz *et al.* 2000 [483]	Ciclosporin	Haematopoietic stem cell transplant	14	No	42.6	Not reported
11149104	Tam *et al.* 2000 [484]	Ciclosporin	Renal transplant	14	No	11.5	38.6
11049011	Parke and Charles *et al.* 2000 [485]	Ciclosporin	Cardiac transplant	46	No	52	78
10665942	David-Neto *et al.* 2000 [486]	Ciclosporin	Renal transplant	46	No	14.3	Not reported
11103750	Min *et al.* 2000 [487]	Ciclosporin	Pharmacokinetic study	22	Yes	25.95	74.4
11095000	Meier-Kriesche *et al.* 2000 [488]	Ciclosporin	Renal transplant	14	No	9.7	42
11079273	Brunner *et al.* 2000 [489]	Ciclosporin	Renal transplant	6	No	14	43.8
10741627	Villeneuve *et al.* 2000 [490]	Ciclosporin	Liver transplant	26	No	53.9	76.2
10984808	Lill *et al.* 2000 [491]	Ciclosporin	Solid organ transplant	100	No	49	77
11475470	Latteri *et al.* 2001 [492]	Ciclosporin	Inflammatory bowel disease	46	No	37.7	Not reported
12099384	Asberg *et al.* 2001 [493]	Ciclosporin	Renal transplant	23	No	52	Not reported
11261685	Niaudet *et al.* 2001 [494]	Ciclosporin	Nephrotic syndrome	7	No	12	42
11549208	Malingre *et al.* 2001 [495]	Ciclosporin	Solid organ cancer	9	No	53	73
11269572	Lee *et al.* 2001 [496]	Ciclosporin	Influence of diet	23	Yes	23.3	74.5
11371999	Stein *et al.* 2001 [497]	Ciclosporin	Pharmacokinetic study	9	Yes	28.9	93.5
11903387	Brown *et al.* 2001 [498]	Ciclosporin	Renal transplant	28	No	50	Not reported
11161541	Santos *et al.* 2001 [499]	Ciclosporin	Haematopoietic stem cell transplant	5	No	36.7	61.1
11719733	Tsunoda *et al.* 2001 [500]	Ciclosporin	Influence of diet	12	Yes	29.4	62.7
11295581	Akhlaghi *et al.* 2001 [501]	Ciclosporin	Heart transplant	11	No	54	78
11750351	Yoshida *et al.* 2001 [170]	Ciclosporin	Renal transplant	69	No	37.4	56.1
11591896	Filler *et al.* 2001 [502]	Ciclosporin	Renal transplant	23	No	14.8	48.8
11579295	Canadian Neoral Renal Transplantation Study Group 2001 [503]	Ciclosporin	Renal transplant	38	No	46	Not reported
11825098	Leger *et al.* 2002 [504]	Ciclosporin	Renal transplant	20	No	45	66
11825097	Schadeli *et al.* 2002 [505]	Ciclosporin	Renal transplant	50	No	46.6	Not reported
12394847	Roza *et al.* 2002 [506]	Ciclosporin	Renal transplant	50	No	49.8	77.6
11808830	Kovarik *et al.* 2002 [507]	Ciclosporin	Drug-drug interaction	24	Yes	31.7	79.1
12231373	Balram *et al.* 2002 [508]	Ciclosporin	Heart transplant	15	No	47.9	63.5
12099517	International Neoral Renal Transplantation Study Group 2002 [509]	Ciclosporin	Renal transplant	31	No	49	Not reported

Pubmed ID	Author	Drug	Population / Study Context	No of subjects	Healthy sub-jects	Median age (years)	Median weight (kg)
12099989	Kovarik *et al*. 2002 [510]	Ciclosporin	Influence of diet	34	Yes	27	75.6
11868803	Le Guellec *et al*. 2002 [511]	Ciclosporin	Renal transplant	20	No	46	66
12520626	Hebert *et al*. 2003 [512]	Ciclosporin	Liver impairment/transplant	6	No	48.5	66.2
14517200	Zimmerman *et al*. 2003 [513]	Ciclosporin	Drug-drug interaction	21	Yes	30	74.6
12973109	Knoop *et al*. 2003 [514]	Ciclosporin	Lung transplant	10	No	32.6	53.6
12551705	Najib *et al*. 2003 [515]	Ciclosporin	Bioequivalence study	20	Yes	25.4	70.7
12890006	Trompeter *et al*. 2003 [516]	Ciclosporin	Renal transplant	18	No	10.3	Not reported
12548141	Rousseau *et al*. 2003 [169]	Ciclosporin	Heart transplant	19	No	41.4	58
12766558	Min and Ellingrod 2003 [517]	Ciclosporin	Pharmacogenetic study	14	Yes	25.5	68.3
12817518	Yates *et al*. 2003 [518]	Ciclosporin	Renal transplant	10	No	46	82.4
12826146	Karamperis *et al*. 2003 [519]	Ciclosporin	Renal impairment	19	No	41	74
12780669	Emovon *et al*. 2003 [520]	Ciclosporin	Renal transplant	32	No	43	Not reported
12766880	Jacobson *et al*. 2003 [521]	Ciclosporin	Haematopoietic stem cell transplant	129	No	40	77
15138297	Kovarik *et al*. 2004 [522]	Ciclosporin	Psorasis	14	No	39.4	89.6
14749545	Rousseau *et al*. 2004 [207]	Ciclosporin	Renal transplant	80	No	46.2	67.8
15592326	Hesselink *et al*. 2004 [208]	Ciclosporin	Kidney and heart transplant	151	No	44.9	75.2
14749551	David-Neto *et al*. 2004 [523]	Ciclosporin	Renal transplant	18	No	44.7	71.4
15385835	Min *et al*. 2004 [524]	Ciclosporin	Pharmacogenetic study	16	Yes	27	74.6
14742751	Taylor *et al*. 2004 [525]	Ciclosporin	Liver impairment/transplant	6	No	54.3	Not reported
15116055	Anglicheau *et al*. 2004 [526]	Ciclosporin	Renal transplant	106	No	44.7	67.4
15561259	Wang *et al*. 2004 [527]	Ciclosporin	Heart transplant	13	No	47.2	Not reported
15108262	Luck *et al*. 2004 [528]	Ciclosporin	Liver impairment/transplant	20	No	49.5	72
15167630	Tokui *et al*. 2004 [529]	Ciclosporin	Renal transplant	125	No	41.9	59.8
15581264	Choi *et al*. 2004 [530]	Ciclosporin	Pharmacokinetic study	8	Yes	25.4	61
15237382	Vogel *et al*. 2004 [531]	Ciclosporin	Liver transplant	2	No	55.5	79.5
16027407	Hebert *et al*. 2005 [532]	Ciclosporin	Drug-drug interaction	27	Yes	30	71.7
16336287	Lukas *et al*. 2005 [209]	Ciclosporin	Renal transplant	11	No	44.2	63.1
15795639	Rosenbaum *et al*. 2005 [210]	Ciclosporin	Heart and lung transplant	48	No	42	58.7
15919450	Iwahori *et al*. 2005 [533]	Ciclosporin	Renal transplant	9	No	40.1	52.7
16133554	Wu *et al*. 2005 [534]	Ciclosporin	Renal transplant	52	No	39.6	56.9
15932953	Wu *et al*. 2005 [211]	Ciclosporin	Renal transplant	99	No	42.3	57.9
16175132	Fradette *et al*. 2005 [535]	Ciclosporin	Renal transplant	37	No	49.2	87.5
15606436	Bourgoin *et al*. 2005 [536]	Ciclosporin	Renal transplant	84	No	42	66
15919452	Takeuchi *et al*. 2005 [537]	Ciclosporin	Renal transplant	7	No	37.1	Not reported
16715103	Choi *et al*. 2006 [538]	Ciclosporin	Haematopoietic stem cell transplant	32	No	7.1	25.5
16928152	Saint-Marcoux *et al*. 2006 [539]	Ciclosporin	Heart, lung and kidney transplant	147	No	42	65
16509024	Dupuis *et al*. 2006 [540]	Ciclosporin	Haematopoietic stem cell transplant	24	No	8.8	Not reported
16884914	Casale *et al*. 2006 [541]	Ciclosporin	Liver impairment/transplant	11	No	52	69
16778713	Kees *et al*. 2006 [542]	Ciclosporin	Bioequivalence study	12	Yes	25	72
16995870	Schwarz *et al*. 2006 [543]	Ciclosporin	Influence of diet	12	Yes	28.1	70
16716132	Yin *et al*. 2006 [544]	Ciclosporin	Heart transplant	38	No	46	59
17542765	Sansone-Parsons *et al*. 2007 [545]	Ciclosporin	Heart transplant	4	No	54	91.8
18089380	Lehle *et al*. 2007 [546]	Ciclosporin	Pre-heart transplant	7	No	50	89
17304156	Irtan *et al*. 2007 [168]	Ciclosporin	Renal transplant	98	No	9.7	35.2
17662086	Fanta *et al*. 2007 [200]	Ciclosporin	Renal impairment	162	No	3.8	22.2
17624028	Hu *et al*. 2007 [547]	Ciclosporin	Pharmacogenetic study	26	Yes	20	60
17524940	Sorkhi *et al*. 2007 [548]	Ciclosporin	Renal transplant	10	No	40.5	Not reported
17053886	Medeiros *et al*. 2007 [549]	Ciclosporin	Renal impairment	7	No	7	Not reported
17452906	Irani *et al*. 2007 [550]	Ciclosporin	Lung transplant	20	No	48	73
18035203	Pineyro-Lopez *et al*. 2007 [551]	Ciclosporin	Bioequivalence study	34	Yes	22.08	78.2
18840028	Mendonza *et al*. 2008 [552]	Ciclosporin	Renal transplant	8	No	51	93
18790206	Al Wakeel *et al*. 2008 [553]	Ciclosporin	Renal transplant	42	No	37.9	70.4
18192894	Fanta *et al*. 2008 [554]	Ciclosporin	Renal transplant	104	No	4.8	18.3
19034006	Falck *et al*. 2008 [555]	Ciclosporin	Renal transplant	25	No	58	76
18175948	Takeuchi *et al*. 2008 [556]	Ciclosporin	Renal transplant	20	No	42.7	53.5
18641547	Sibbald *et al*. 2008 [557]	Ciclosporin	Haematopoietic stem cell transplant	24	No	8.8	Not reported
19448042	Xiaoli and Qiang *et al*. 2009 [558]	Ciclosporin	Nephrotic syndrome	106	No	41	67.6

Pubmed ID	Author	Drug	Population / Study Context	No of subjects	Healthy sub-jects	Median age (years)	Median weight (kg)
19656203	Felipe *et al.* 2009 [559]	Ciclosporin	Renal transplant	53	No	39.2	Not reported
19057979	Shirai *et al.* 2009 [560]	Ciclosporin	Nephrotic syndrome	19	No	35.4	Not reported
19725595	Falck *et al.* 2009 [561]	Ciclosporin	Renal transplant	29	No	55	78.5
19384170	Amundsen *et al.* 2009 [562]	Ciclosporin	Renal transplant	9	No	51	96.5
18547379	Sorkhi *et al.* 2009 [563]	Ciclosporin	Renal transplant	10	No	14.2	50.5
20354687	Press *et al.* 2010 [564]	Ciclosporin	Renal transplant	16	No	48.9	76
20224513	Duncan *et al.* 2010 [565]	Ciclosporin	Haematopoietic stem cell transplant	8	No	45.5	74
21105879	Inoue *et al.* 2011 [566]	Ciclosporin	Haematopoietic stem cell transplant	12	No	41	Not reported
22286813	Suchy *et al.* 2011 [567]	Ciclosporin	Rheumatoid disease	38	No	46.82	Not reported
21618566	Garg *et al.* 2011 [568]	Ciclosporin	Drug-drug interaction	10	Yes	45.8	68.5
21161198	Chen *et al.* 2011 [569]	Ciclosporin	Renal transplant	146	No	42.2	56.5
21923441	Ji *et al.* 2011 [570]	Ciclosporin	Renal transplant	74	No	42	59.1
22947591	Song *et al.* 2012 [571]	Ciclosporin	Renal transplant	69	No	42	60.6
21942970	Jin *et al.* 2012 [572]	Ciclosporin	Heart transplant	5	No	41	74
23070347	Henriques *et al.* 2012 [573]	Ciclosporin	Nephrotic syndrome	10	No	10.3	Not reported
22527344	Eljebari *et al.* 2012 [167]	Ciclosporin	Haematopoietic stem cell transplant	30	No	26	53
22446981	Zhou *et al.* 2012 [202]	Ciclosporin	Haematopoietic stem cell transplant	73	No	30.32	59.4
21988410	Wilhelm *et al.* 2012 [212]	Ciclosporin	Haematopoietic stem cell transplant	20	No	54	84
22116269	Ushijima *et al.* 2012 [574]	Ciclosporin	Nephrotic syndrome	36	No	9.1	Not reported
21317937	Kong *et al.* 2012 [575]	Ciclosporin	Haematopoietic stem cell transplant	27	No	46	Not reported
23908147	Tornatore *et al.* 2013 [576]	Ciclosporin	Renal transplant	54	No	52	78.5
23400901	Fruit *et al.* 2013 [577]	Ciclosporin	Heart transplant	118	No	50	63
23624757	Ni *et al.* 2013 [196]	Ciclosporin	Haematological diseases	102	No	8.83	31.3
23179472	Ehinger *et al.* 2013 [578]	Ciclosporin	Bioequivalence study	65	Yes	24.4	70.4
23354298	Zheng *et al.* 2013 [579]	Ciclosporin	Pharmacogenetic study	24	Yes	27	69
24151438	Kokuhu *et al.* 2013 [580]	Ciclosporin	Renal transplant	81	No	41	53
24698009	Woillard *et al.* 2014 [214]	Ciclosporin	Haematopoietic stem cell transplant	45	No	59	71
25247760	Xue *et al.* 2014 [215]	Ciclosporin	Haematopoietic stem cell transplant	117	No	35	63
25408261	Anlamlert *et al.* 2015 [581]	Ciclosporin	Influence of diet	18	Yes	23	62.6
25818517	Kim *et al.* 2015 [201]	Ciclosporin	Haematopoietic stem cell transplant	34	No	36	61
25976223	Tao *et al.* 2015 [582]	Ciclosporin	Pharmacogenetic study	56	Yes	22	58
26328482	Tsuji *et al.* 2015 [583]	Ciclosporin	Connective tissue diseases	36	No	60	46.9
25975616	Philippe *et al.* 2015 [584]	Ciclosporin	Haematological diseases	20	No	8.5	34
28620753	Okada *et al.* 2017 [585]	Ciclosporin	Renal transplant	98	No	45	59
30335563	Ree *et al.* 2018 [586]	Ciclosporin	Haematological diseases	34	No	2.2	12.9
31341257	Li *et al.* 2019 [198]	Ciclosporin	Haematopoietic stem cell transplant	86	No	8.38	31.9
31210099	Kelsen *et al.* 2019 [587]	Ciclosporin	Severe traumatic brain injury	10	No	34.5	79.3
31873806	Xue *et al.* 2019 [204]	Ciclosporin	Haematopoietic stem cell transplant	1126	No	30.475	60
31088392	Gackler *et al.* 2019 [588]	Ciclosporin	Renal transplant	31	No	49.3	78.3
30936972	Wang *et al.* 2019 [589]	Ciclosporin	Nephrotic syndrome	18	No	2.75	15
32557653	Albitar *et al.* 2020 [590]	Ciclosporin	Renal transplant	113	No	44	63
31319907	Liu *et al.* 2020 [591]	Ciclosporin	Nephrotic syndrome	127	No	45.52	68.6
31382792	Wang *et al.* 2020[592]	Ciclosporin	Haematological diseases	25	No	3.7	16.3
33928146	Umpierrez *et al.* 2021 [216]	Ciclosporin	Solid organ and HSCT	37	No	34.4	64.3
33560100	Liang *et al.* 2021 [593]	Ciclosporin	Haematological diseases	1	No	4.62	13
34779003	Ling *et al.* 2022 [217]	Ciclosporin	Haematopoietic stem cell transplant	59	No	42	65
35979231	Gao *et al.* 2022 [199]	Ciclosporin	Haematological diseases	157	No	7.8	27.5
37643815	Feng *et al.* 2023 [218]	Ciclosporin	Haematopoietic stem cell transplant	176	No	6	16.5
38329479	Cai *et al.* 2024 [219]	Ciclosporin	Haematopoietic stem cell transplant	59	No	7	20
2848442	Hardin *et al.* 1988 [594]	Itraconazole	Pharmacokinetic study	15	Yes	32.5	65.1
2544431	Van Peer *et al.* 1989 [595]	Itraconazole	Influence of diet	24	Yes	30	71
1357148	Smith *et al.* 1992 [596]	Itraconazole	Acquired immune deficiency syndrome	8	No	36.25	60.1
8388198	Barone *et al.* 1993 [597]	Itraconazole	Influence of diet	17	Yes	23	70.9
8039534	Zimmermann *et al.* 1994 [598]	Itraconazole	Influence of diet	72	Yes	34	70
7814285	Prentice *et al.* 1994 [599]	Itraconazole	Prophylaxis	2	No	50	75.8
8591940	Prentice *et al.* 1995 [600]	Itraconazole	Prophylaxis	52	No	42.8	64.9
8529326	Ducharme *et al.* 1995 [443]	Itraconazole	Drug-drug interaction	13	Yes	27.6	77.4

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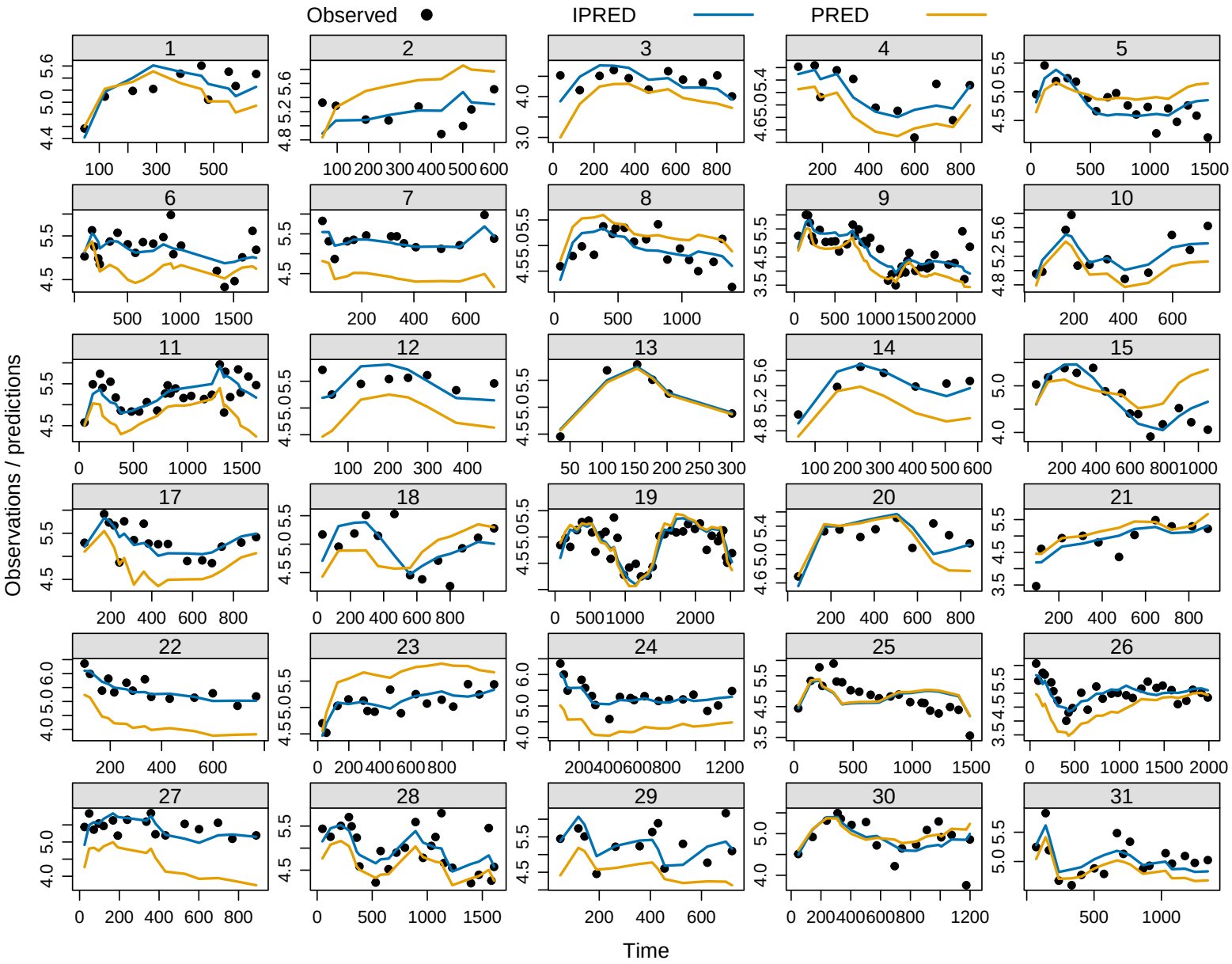
8726601	Van de Velde *et al.* 1996 [601]	Itraconazole	Influence of diet	24	Yes	30	70
9390107	Kaukonen *et al.* 1997 [602]	Itraconazole	Interaction	9	Yes	25	64
9371367	Reynes *et al.* 1997 [603]	Itraconazole	HIV patients with oral candidiasis	12	Yes	33	65
9208361	Lange *et al.* 1997 [54]	Itraconazole	Influence of diet	11	Yes	26	78.9
9218932	Jaruratanasirikul and Keepkaew 1997 [604]	Itraconazole	Influence of diet	16	Yes	23.4	58.6
9527794	de Repentigny *et al.* 1998 [143]	Itraconazole	Mucosal fungal infection	26	No	1.2	8.7
9545149	Barone *et al.* 1998 [605]	Itraconazole	Influence of diet	30	Yes	23	75.7
9797792	Varis *et al.* 1998 [606]	Itraconazole	Drug-drug interaction	10	Yes	24.5	62
9695720	Kantola *et al.* 1998 [607]	Itraconazole	Drug-drug interaction	10	Yes	28	65
9661037	Barone *et al.* 1998 [153]	Itraconazole	Bioequivalence study	5	Yes	24	75.8
9626921	Jaruratanasirikul and Sriwiriyajan 1998 [608]	Itraconazole	Drug-drug interaction	11	Yes	29	58.1
9626920	Jaruratanasirikul and Sriwiriyajan 1998 [609]	Itraconazole	Healthy and HIV patients	6	Yes	25.2	64
10426160	Varis *et al.* 1999 [610]	Itraconazole	Drug-drug interaction	9	Yes	20.5	62.5
9869578	Suarex-Kurtz *et al.* 1999 [611]	Itraconazole	Bioequivalence study	18	Yes	27.1	63.9
11762559	Zhao *et al.* 2001 [612]	Itraconazole	Human Immunodeficiency Virus	30	No	37	75
11932960	Damle *et al.* 2002 [613]	Itraconazole	Drug-drug interaction	25	Yes	31	78.4
12657919	Koks *et al.* 2003 [614]	Itraconazole	Human Immunodeficiency Virus	5	No	31	52
15098799	Gubbins *et al.* 2004 [615]	Itraconazole	Influence of diet	20	Yes	25.9	74.7
15900286	Jaakkola *et al.* 2005 [616]	Itraconazole	Drug-drug interaction	12	Yes	23.5	70
16928786	Uno *et al.* 2006 [617]	Itraconazole	Drug-drug interaction	33	Yes	22	56.9
16885720	Uno *et al.* 2006 [618]	Itraconazole	Pharmacokinetic study	8	Yes	25.5	62.3
17048974	Henning *et al.* 2006 [145]	Itraconazole	Cystic fibrosis and HSCT	49	No	8	29.3
17053894	Yun *et al.* 2006 [619]	Itraconazole	Influence of diet	168	Yes	31.35	64.4
16982783	Mouton *et al.* 2006 [620]	Itraconazole	Formulation studies	16	Yes	23	71.3
17517842	Abdel-Rahman *et al.* 2007 [621]	Itraconazole	Children at risk of fungal infection	66	No	8.1	31.1
17073891	Hennig *et al.* 2007 [622]	Itraconazole	Cystic fibrosis	30	No	25	46
17342480	Jaruratanasirikul and Sriwiriyajan 2007 [623]	Itraconazole	Drug-drug interaction	12	Yes	28.9	55.4
18520601	Timmers *et al.* 2008 [624]	Itraconazole	Haematological malignancies	10	No	48.2	83
18359202	Kanbayashi *et al.* 2008 [625]	Itraconazole	Haematological malignancies	7	No	65.3	52.2
18172627	Gubbins *et al.* 2008 [626]	Itraconazole	Influence of diet	20	Yes	24.5	Not reported
19646080	Lee *et al.* 2009 [627]	Itraconazole	Neutropenia	42	No	35.1	64.9
20799049	Hagihara *et al.* 2011 [628]	Itraconazole	Critically ill	10	No	64.8	58.7
22108774	Karonen *et al.* 2012 [629]	Itraconazole	Drug-drug interaction	12	Yes	23.5	73
26149987	Abuhelwa *et al.* 2015 [630]	Itraconazole	Influence of diet	244	Yes	34.9	78.3
26022135	Kim *et al.* 2015 [631]	Itraconazole	Haematopoietic stem cell transplant	6	No	12	29
30028640	Dragpkevoc-Simic *et al.* 2018 [632]	Itraconazole	Influence of diet	38	Yes	37.71	78.5
31696544	Hava *et al.* 2020 [633]	Itraconazole	Asthma & healthy subjects	17	Yes	38.8	82.1
33349869	Kaewpoowat *et al.* 2020 [634]	Itraconazole	Drug-drug interaction	20	No	29.5	55.5
32457106	Thompson *et al.* 2020 [635]	Itraconazole	Bioequivalence study	24	Yes	34	81.3
34370587	Stott *et al.* 2021 [636]	Itraconazole	Disseminated Infection	130	No	33	45
12936975	Courtney *et al.* 2003 [637]	Posaconazole	Pharmacokinetic study	36	Yes	24	75
14982768	Courtney *et al.* 2004 [638]	Posaconazole	Influence of diet	12	Yes	34	77.7
15647411	Courtney *et al.* 2005 [639]	Posaconazole	Chronic renal disease	6	No	39.5	83.6
15656699	Ezzet *et al.* 2005 [640]	Posaconazole	Pharmacokinetic study	18	Yes	36	81.9
16723557	Gubbins *et al.* 2006 [641]	Posaconazole	Haematopoietic stem cell transplant	30	No	54.4	81.1
16436724	Ullmann *et al.* 2006 [642]	Posaconazole	Neutropenia or refractory invasive fungal infection	98	No	45.3	71.7
17559737	Krishna *et al.* 2007 [643]	Posaconazole	Drug-drug interaction	36	Yes	36	80.2
17355736	Krishna *et al.* 2007 [644]	Posaconazole	Drug-drug interaction	12	Yes	27	73
17101682	Sansone-Parsons *et al.* 2007 [645]	Posaconazole	Pharmacokinetic study	48	Yes	30	73.7
19029316	Conte *et al.* 2009 [646]	Posaconazole	Pharmacokinetic study	25	Yes	30.4	66.1
19433558	Dodds Ashley *et al.* 2009 [647]	Posaconazole	Pharmacokinetic study	15	Yes	25	71.6

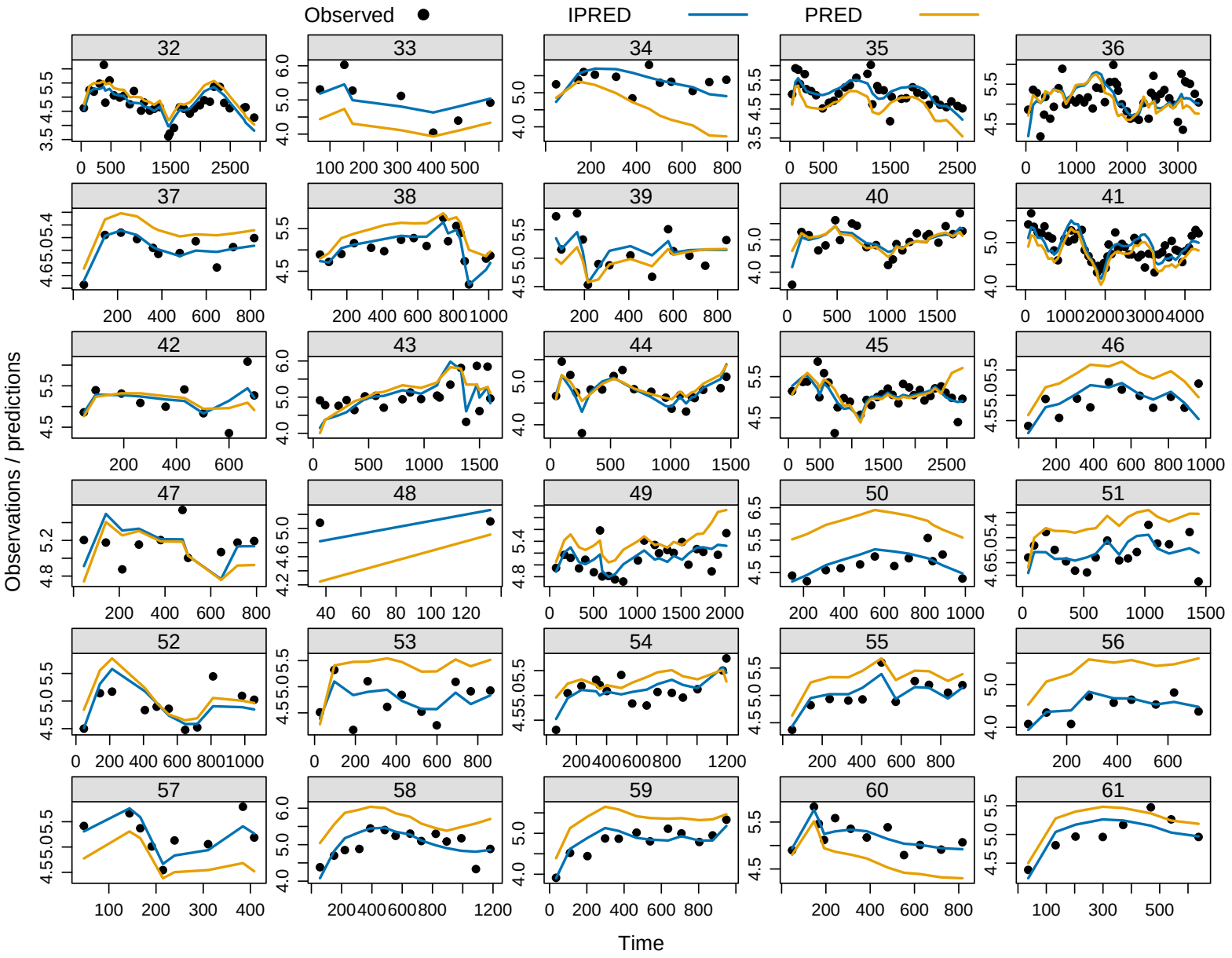
Pubmed ID	Author	Drug	Population / Study Context	No of subjects	Healthy subjects	Median age (years)	Median weight (kg)
20194702	Krishna *et al.* 2010 [648]	Posaconazole	Pharmacokinetic study	30	Yes	37.7	79.1
20667889	Bruggemann *et al.* 2010 [649]	Posaconazole	Drug-drug interaction	20	Yes	36	73
20001450	AbuTarif *et al.* 2010 [650]	Posaconazole	Haematological diseases	215	No	52	70
19886860	Moton *et al.* 2010 [651]	Posaconazole	Liver impairment	37	No	53	82.5
22833639	Krishna *et al.* 2012 [652]	Posaconazole	Pharmacokinetic study	22	No	46.5	71
22286158	Vehreschild *et al.* 2012 [653]	Posaconazole	Pharmacokinetic study	84	No	55	77.7
25049247	Duarte *et al.* 2014 [654]	Posaconazole	Neutropenia	33	No	51	76
24798274	Kraft *et al.* 2014 [655]	Posaconazole	Drug-drug interaction	20	Yes	38	78.2
24733463	Maertens *et al.* 2014 [656]	Posaconazole	Haematological diseases	66	No	49.1	77.2
25199779	Dolton *et al.* 2014 [657]	Posaconazole	Pharmacokinetic study	102	No	44	72.5
25824210	Kersemaekers *et al.* 2015 [658]	Posaconazole	Influence of diet	17	Yes	52.5	72
27367040	Gesquiere *et al.* 2016 [659]	Posaconazole	Gastric bypass	11	No	37.4	123
27021324	Zhang *et al.* 2016 [660]	Posaconazole	Cystic fibrosis	19	No	36	56.7
26612870	Cornely *et al.* 2016 [661]	Posaconazole	Haematological malignancy or HSCT	210	No	51	77.1
26544987	Vanstraelen *et al.* 2016 [146]	Posaconazole	Pharmacokinetic study	14	No	6.7	19.9
28848009	Petitcollin *et al.* 2017 [662]	Posaconazole	Haematological malignancies	49	No	53	72
30031203	Sime *et al.* 2018 [663]	Posaconazole	Critically ill patient on continuous veno-ovenous haemodiafiltration	1	No	49	120
29712663	van Iersel *et al.* 2018 [664]	Posaconazole	Pharmacokinetic study	231	No	40	76.3
29581122	Sime *et al.* 2018 [665]	Posaconazole	Critically ill	8	No	46	68
29679234	Boonsathorn *et al.* 2019 [97]	Posaconazole	Pharmacokinetic study	117	No	5.7	17.8
33305723	Ji *et al.* 2020 [666]	Posaconazole	Pharmacokinetic study	36	Yes	28.9	60.2
33517360	van Daele *et al.* 2021 [667]	Posaconazole	Critically ill patients during extracorporeal membrane oxygenation	6	No	44	76
34458906	Bentley *et al.* 2021 [668]	Posaconazole	Cystic fibrosis	37	No	14	45.6
34699939	Pena-Lorenzo *et al.* 2022 [669]	Posaconazole	Allogeneic stem cell transplant	36	No	53	68.3
12121931	Purkins *et al.* 2002 [670]	Voriconazole	IV to oral switch PK study	41	Yes	26.5	78.7
14616407	Purkins *et al.* 2003 [671]	Voriconazole	Pharmacokinetic study	18	Yes	24	72
14616408	Purkins *et al.* 2003 [672]	Voriconazole	Pharmacokinetic study	43	Yes	26	74
14616409	Purkins *et al.* 2003 [673]	Voriconazole	Effect of food	12	Yes	29	74
14616412	Purkins *et al.* 2003 [674]	Voriconazole	Drug-drug interaction	11	Yes	29	77
14616414	Purkins *et al.* 2003 [675]	Voriconazole	Drug-drug interaction	12	Yes	29	75
14616415	Wood *et al.* 2003 [676]	Voriconazole	Drug-drug interaction	18	Yes	26.3	75.1
14616416	Purkins *et al.* 2003 [677]	Voriconazole	Drug-drug interaction	9	Yes	22	74
15175271	Robatel *et al.* 2004 [678]	Voriconazole	Patient on continuous veno-venous haemodiafiltration	1	No	70	60
16003289	Rengelshausen *et al.* 2005 [679]	Voriconazole	Drug-drug interaction	34	Yes	27	79
16890574	Mikus *et al.* 2006 [680]	Voriconazole	Drug-drug interaction	20	Yes	28	73
17414408	Santos *et al.* 2007 [681]	Voriconazole	Premature infant with cutaneous aspergillosis	1	No	25	0.7
17646413	Liu *et al.* 2007 [682]	Voriconazole	Pharmacokinetic study	13	Yes	31	77.6
17855725	Fuhrmann *et al.* 2007 [683]	Voriconazole	Patient on continuous veno-venous haemodiafiltration	9	No	62	77
18223474	Quintard *et al.* 2008 [684]	Voriconazole	Patient on continuous veno-venous haemodiafiltration	1	No	72	87
18544001	Abel *et al.* 2008 [685]	Voriconazole	Renal impaired	37	No	51	78
18563460	Nomura *et al.* 2008 [686]	Voriconazole	Haematological malignancies	9	No	54.5	59.2
19218271	Spriet *et al.* 2009 [687]	Voriconazole	Critically ill patients during extracorporeal membrane oxygenation	2	No	29	72.5
19299322	Lei *et al.* 2009 [688]	Voriconazole	Pharmacogenetic study	7	Yes	22	59.4
19383934	Carbonara *et al.* 2009 [689]	Voriconazole	Acquired immune deficiency syndrome	5	No	40	75
19933691	Bruggemann *et al.* 2010 [649]	Voriconazole	Haematopoietic stem cell transplant	20	No	49	82.8
19933807	Johnson *et al.* 2010 [690]	Voriconazole	Liver transplant	15	No	56.3	84.1
19951112	Neely *et al.* 2010 [148]	Voriconazole	Pharmacokinetic study	40	No	16.5	54.2
20188523	Myrianthefs *et al.* 2010 [691]	Voriconazole	Critically ill	18	No	62.3	65
20368400	Hafner *et al.* 2010 [692]	Voriconazole	End-Stage Renal Failure on haemodialysis and haemodiafiltration	10	No	52.6	72.1

Pubmed ID	Author	Drug	Population / Study Context	No of subjects	Healthy subjects	Median age (years)	Median weight (kg)
20547816	Michael *et al.* 2010 [693]	Voriconazole	Immunocompromised	24	No	6.8	24.2
20660687	Walsh *et al.* 2010 [177]	Voriconazole	Immunocompromised	48	No	2.8	15.1
20679503	Han *et al.* 2010 [694]	Voriconazole	Lung transplant	45	No	50.9	68
20963460	Spriet *et al.* 2011 [695]	Voriconazole	Haematologic malignancies and cystic fibrosis	4	No	15	32
21294597	han *et al.* 2011 [696]	Voriconazole	Liver transplant	13	No	55.8	83.5
21383338	Lee *et al.* 2012 [697]	Voriconazole	Pharmacogenetic study	18	Yes	26.7	71.2
21422207	Pai and lodise *et al.* 2011 [698]	Voriconazole	Obese	22	No	41.6	133.4
21911570	Driscoll *et al.* 2011 [699]	Voriconazole	Immunocompromised	26	No	13	57.1
21968355	Driscoll *et al.* 2011 [700]	Voriconazole	Immunocompromised	75	No	5	18.9
22284963	Markantonis *et al.* 2012 [701]	Voriconazole	Cystic fibrosis	8	No	14.8	44.6
22610925	Pascual *et al.* 2012 [702]	Voriconazole	Invasive fungal infections	55	No	58	68
23296095	Spriet *et al.* 2013 [703]	Voriconazole	Critically ill patient on therapeutic plasma exchange	1	No	61	74
23400848	Moriyama *et al.* 2013 [704]	Voriconazole	Pharmacogenetic in obese patients	2	No	17	102.1
23629717	Amsden *et al.* 2013 [705]	Voriconazole	Pre- and post-autologous peripheral stem cell transplantation	10	No	67.1	77.6
24084636	Wang *et al.* 2014 [706]	Voriconazole	Invasive fungal infections	151	No	59	59.1
24913161	Liu and Mould *et al.* 2014 [707]	Voriconazole	Invasive fungal infections	305	No	54	68
25645660	Kiser *et al.* 2015 [708]	Voriconazole	Critically ill patients undergoing continuous renal replacement therapy	10	No	55	83
25801557	Muto *et al.* 2015 [709]	Voriconazole	Immunocompromised Japanese children	21	No	10	31.5
25886578	Akers *et al.* 2015 [710]	Voriconazole	Penetration wound in combat-related injuries	1	No	28	60.1
26406771	Wang *et al.* 2015 [711]	Voriconazole	Invasive fungal infections	15	No	62	65
25910879	Vanstraelen *et al.* 2015 [712]	Voriconazole	Pharmacokinetic study	10	No	55	65.9
26133710	Chen *et al.* 2015 [713]	Voriconazole	Critically ill patients with pulmonary disease	62	No	59.71	60.1
26239045	Imamura *et al.* 2016 [714]	Voriconazole	Pharmacogenetic study	18	Yes	27.7	63.9
27432796	Zhu *et al.* 2017 [715]	Voriconazole	Pharmacogenetic study	24	Yes	29	71.5
28370390	Hohmann *et al.* 2017 [716]	Voriconazole	Pharmacogenetic study	12	Yes	32.2	80.8
28604474	Li *et al.* 2017 [147]	Voriconazole	Pharmacogenetic study	56	No	40	55
29607533	Lin *et al.* 2018 [352]	Voriconazole	Pharmacogenetic study	106	No	36	56.1
30744151	Kim *et al.* 2019 [717]	Voriconazole	Pharmacogenetic study	193	No	34	66
30851209	Ruiz *et al.* 2019 [718]	Voriconazole	Critically ill	33	No	55.3	65.1
31041728	Chen *et al.* 2019 [719]	Voriconazole	Haematopoietic stem cell transplant	23	No	39	58.8
31079860	Liu *et al.* 2019 [720]	Voriconazole	Haematological malignancies	41	No	47	62.7
31136417	Perez-Pitarch *et al.* 2019 [721]	Voriconazole	Haematopoietic stem cell transplant	40	No	55	73
31562869	Ren *et al.* 2019 [722]	Voriconazole	Liver Cirrhosis	180	No	51.1	69.7
31768008	Knight-Perry *et al.* 2020 [723]	Voriconazole	Haematopoietic stem cell transplant	59	No	10	Not reported
32109625	Lin *et al.* 2020 [724]	Voriconazole	Liver impairment	12	No	51	55
32461666	Lee *et al.* 2020 [725]	Voriconazole	Pharmacogenetic study	12	Yes	32	71.4
32468741	Cho *et al.* 2020 [726]	Voriconazole	Pharmacokinetic study	23	Yes	28	70
32899425	Khan-Asa *et al.* 2020 [727]	Voriconazole	Haematological diseases	65	No	47.65	58.6
32947557	Chantharit *et al.* 2020 [728]	Voriconazole	Invasive fungal infections	106	No	52	55
32988816	Takahashi *et al.* 2020 [729]	Voriconazole	Obese haematopoietic stem cell transplant children	35	No	11.5	41.4
33010043	Tang *et al.* 2021 [730]	Voriconazole	Liver impairment	51	No	46.4	58
33064889	Wang *et al.* 2021 [731]	Voriconazole	Liver Cirrhosis	120	No	57.9	63
33952830	Tanaka *et al.* 2021 [732]	Voriconazole	Critically ill	5	No	65	53.9
34097481	Takahashi *et al.* 2021 [733]	Voriconazole	Haematopoietic stem cell transplant	58	No	11	34
34683408	Grensemann *et al.* 2021 [734]	Voriconazole	Acute-on-chronic liver failure and continuous renal replacement therapy	9	No	70	85
34655497	Lin *et al.* 2022 [735]	Voriconazole	Liver impairment	26	No	55.5	64

Appendix B

Observed vs Predicted Plots for Each Individual using ciclosporin Final model


Observed
IPRED
PRED
Observations / predictions
Time


Observed
IPRED
PRED
32
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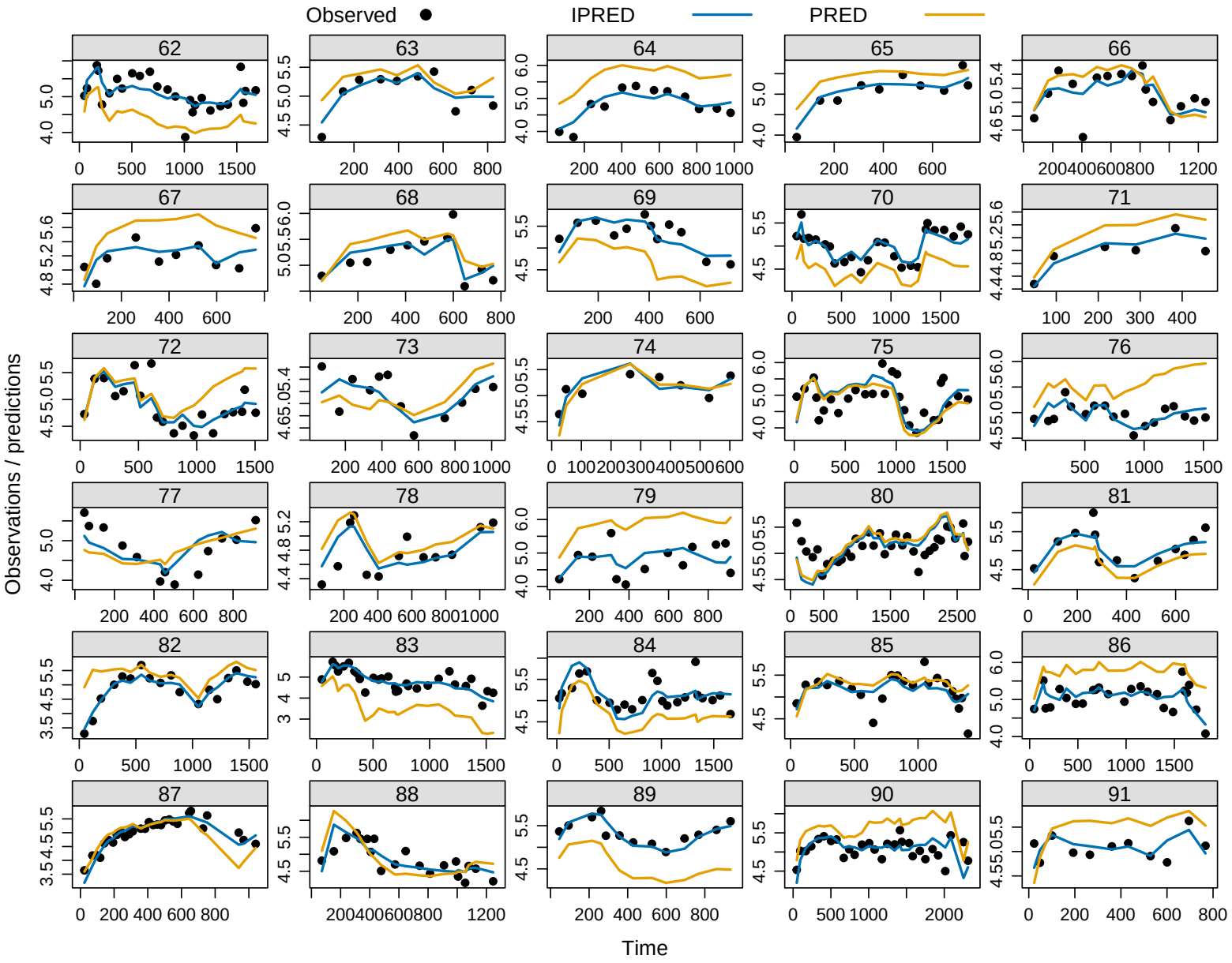
58
59
60
61
Observations / predictions
Time


Observed
IPRED
PRED
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63
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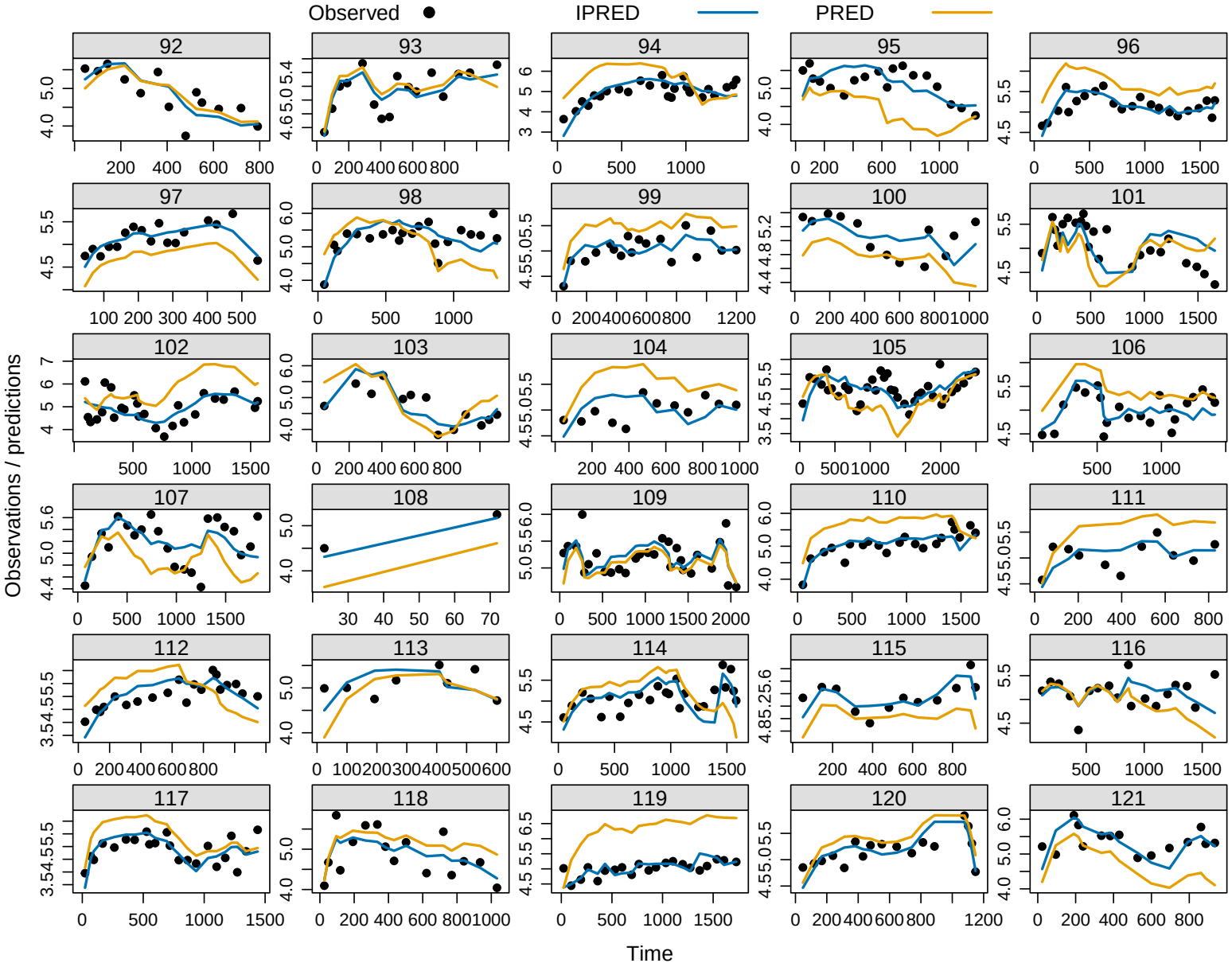
88
89
90
91
Observations / predictions
Time


Observed
IPRED
PRED
92
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94
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100
101
102
103
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106
107
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112
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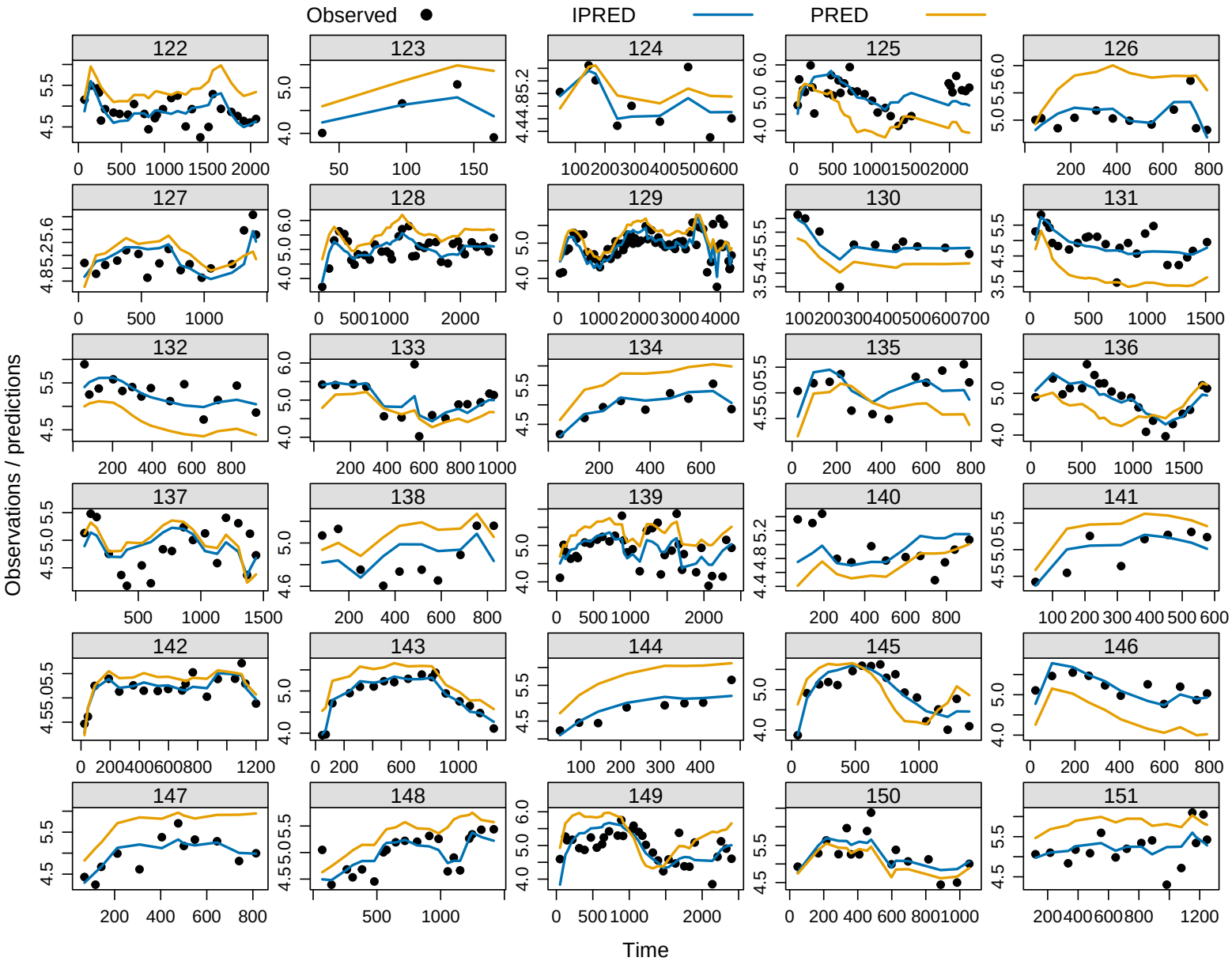
114
115
116
117
118
119
120
121
Observations / predictions
Time


Observed
IPRED
PRED
122
123
124
125
126
127
128
129
130
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132
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134
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136
137
138
139
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143
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145
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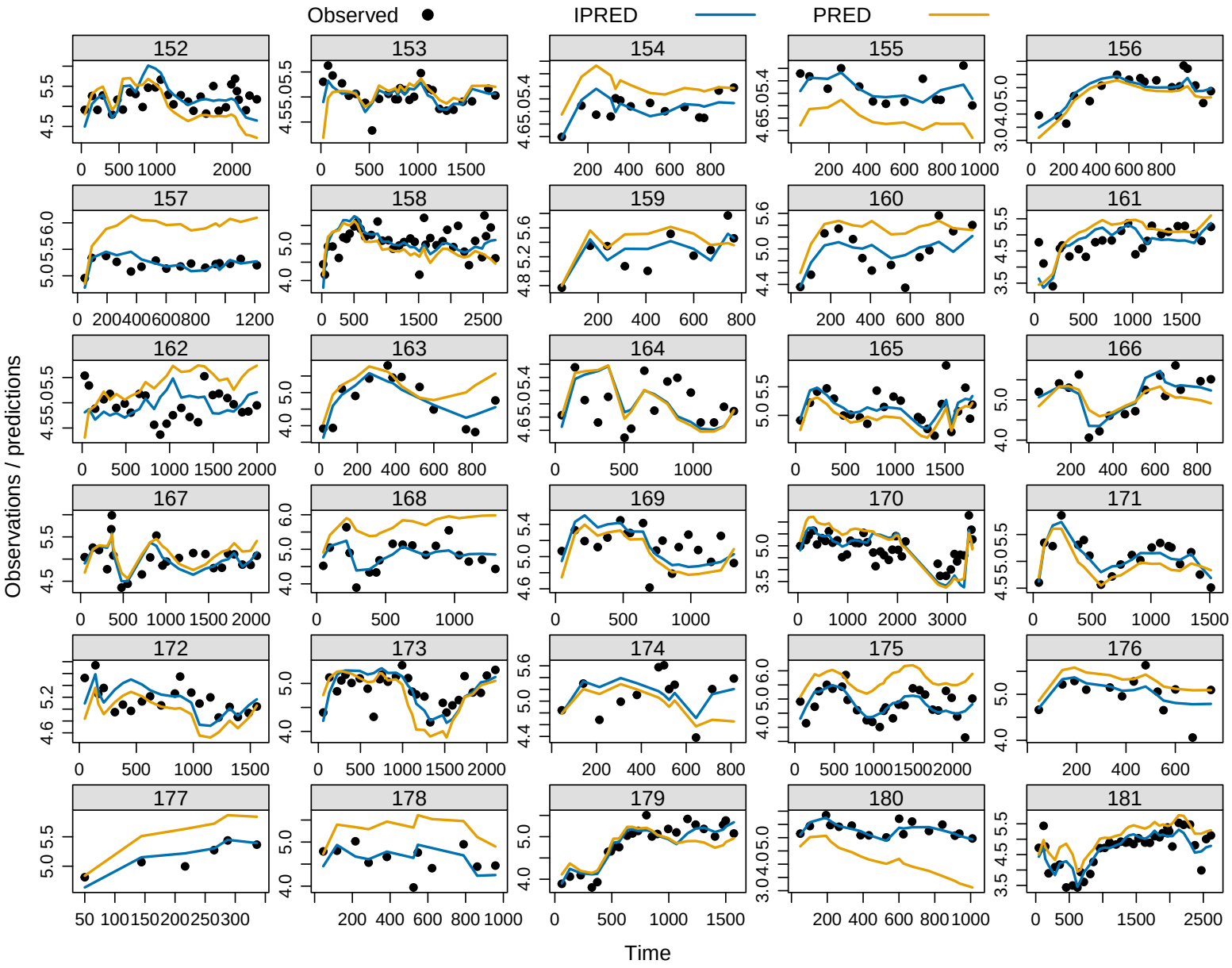
147
148
149
150
151
Observations / predictions
Time


Observed
IPRED
PRED
152
153
154
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156
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158
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160
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169
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175
176
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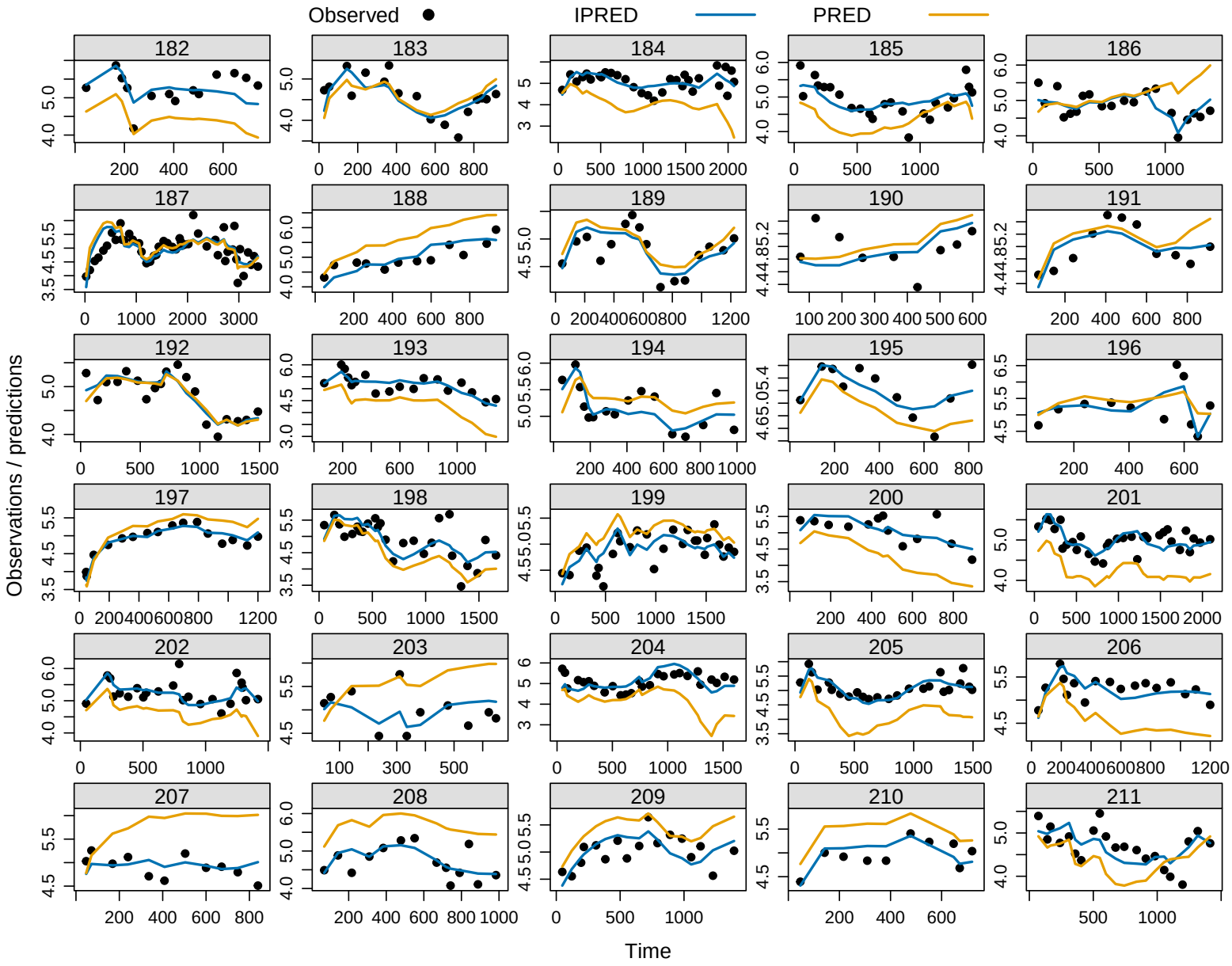
178
179
180
181
Observations / predictions
Time


Observed
IPRED
PRED
182
183
184
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186
187
188
189
190
191
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199
200
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202
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204
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206
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208
209
210
211
Observations / predictions
Time

Observed
IPRED
PRED
212
213
214
215
216
217
Observations / predictions
Time

Appendix C

Ciclosporin final model

```
$PROBLEM 1-COMPARTMENT LOG-TRANSFORMED FOCEI
;; Description: 1-COMPARTMENT LOG-TRANS AZOLE HCT-V CR
$INPUT C ID DV TIME AMT DOSE RATE ROUTE OCC MDV EVID WT HT AGE PMA SEX
 CR ALB TBIL HCT COAZOLE AZOLETYPE MWT BMTDAY MCR MAGE MALB MTBIL MHCT TAD CMT TSCR
$DATA 2025.04.29zBMTCombinedModeldataNONMEM.csv IGNORE=C
$SUBROUTINE ADVAN2 TRANS2
$ABBREVIATED DERIV2=NO

$PK
;--- Log-scale parameters ---
TVCL = THETA(1)          ; ln
TVV  = THETA(2)          ; ln
TVAZOLE = THETA(3)       ; 3. AZOLEEFFECT
TVVHCT  = THETA(4)       ; 4. HAEMATOCRIT
TVVSCR = THETA(5)  ; 5. RENAL
TVF1 = THETA(6)           ; 6. Bioavailability (oral)
TVKA = THETA(7)          ; 7 KA
TVPMA1  = THETA(8) ; 4. HILL COEFFICIENT
TVPMA2  = THETA(9) ; 5. TM50

;---------AZOLE EFFECT---
IF(COAZOLE==0) AZOLEEFFECT = 1 ; No azole
IF(COAZOLE==1) AZOLEEFFECT = ( 1 + TVAZOLE)

;---------HAEMATOCRIT---
TVHCT = (HCT/0.26)**TVVHCT

;---------CREATININE---
TVSCR = (CR/TSCR)**TVVSCR
```

```
;--- Bioavailability (F) ---
    BIO1 = DLOG(TVF1 / (1 - TVF1)) ; (-inf, inf)
    BIO2 = BIO1 + ETA(3) ; IIV now on normal scale
    F1 = 1 / EXP(-BIO2) ;  Transform F1 to be between 0 and 1

;----------MATURATION FUNCTION
TPMA = PMA**TVPMA1 / (PMA**TVPMA1 + TVPMA2**TVPMA1)

;--- Allometric scaling (identical to nlmixr2) ---
LWT = LOG(WT/70)
CL = EXP(TVCL + ETA(1) + 0.75*LWT) * AZOLEEFFECT * TVSCR * TPMA
V  = EXP(TVV  + ETA(2) + 1*LWT) * TVHCT
KA = EXP(TVKA)

S2 = V                   ; Concentration = A1/V

$ERROR
;--- Log-transform ---
  IPRED=LOG(0.0001)
  IF(F.GT.0)IPRED=LOG(F)
 W=1
  IF(F.GT.0) W = SIGMA(1,1)  ; add.err
  IRES = DV-IPRED
  IWRES = IRES/W
  Y = IPRED+W*EPS(1); Additive error on log-scale

$THETA
(4.05) ;1: tcl = ln(30) 3.3
(8.32) ;2: tv = ln (500)  8.27
(-0.285) ;3. AZOLE
(-0.404) ;4. [HCT]
(-0.206) ;5. [RENAL]
(0, 0.394,1) ;6. Bioabilability
(0.387) ;7 KA
(3) FIX ;8 Hill
(73) FIX ;9 PM50

$OMEGA BLOCK(2)
 0.216
 0.0872 0.387
$OMEGA
 0.287

$SIGMA
 0.468 ;
```

```
$ESTIMATION METHOD=1 INTERACTION
$COVARIANCE PRINT=E MATRIX=S
$TABLE ID TIME IPRED IWRES CWRES EVID MDV PRED NOPRINT ONEHEADER FILE=sdtab34 FORMAT=s1PE13.6
$TABLE ID TIME TVCL TVV CL ETA1 ETA2 NOPRINT NOAPPEND ONEHEADER FILE=patab34 FORMAT=s1PE13.6
$TABLE ID TIME AMT DOSE WT AGE PMA CR ALB TBIL HCT BMTDAY MCR MAGE MALB MTBIL
       TAD NOPRINT ONEHEADER FILE=cotab34 FORMAT=s1PE13.6
$TABLE ID SEX COAZOLE ROUTE NOPRINT NOAPPEND ONEHEADER FILE=catab34 FORMAT=s1PE13.6
```

Appendix D

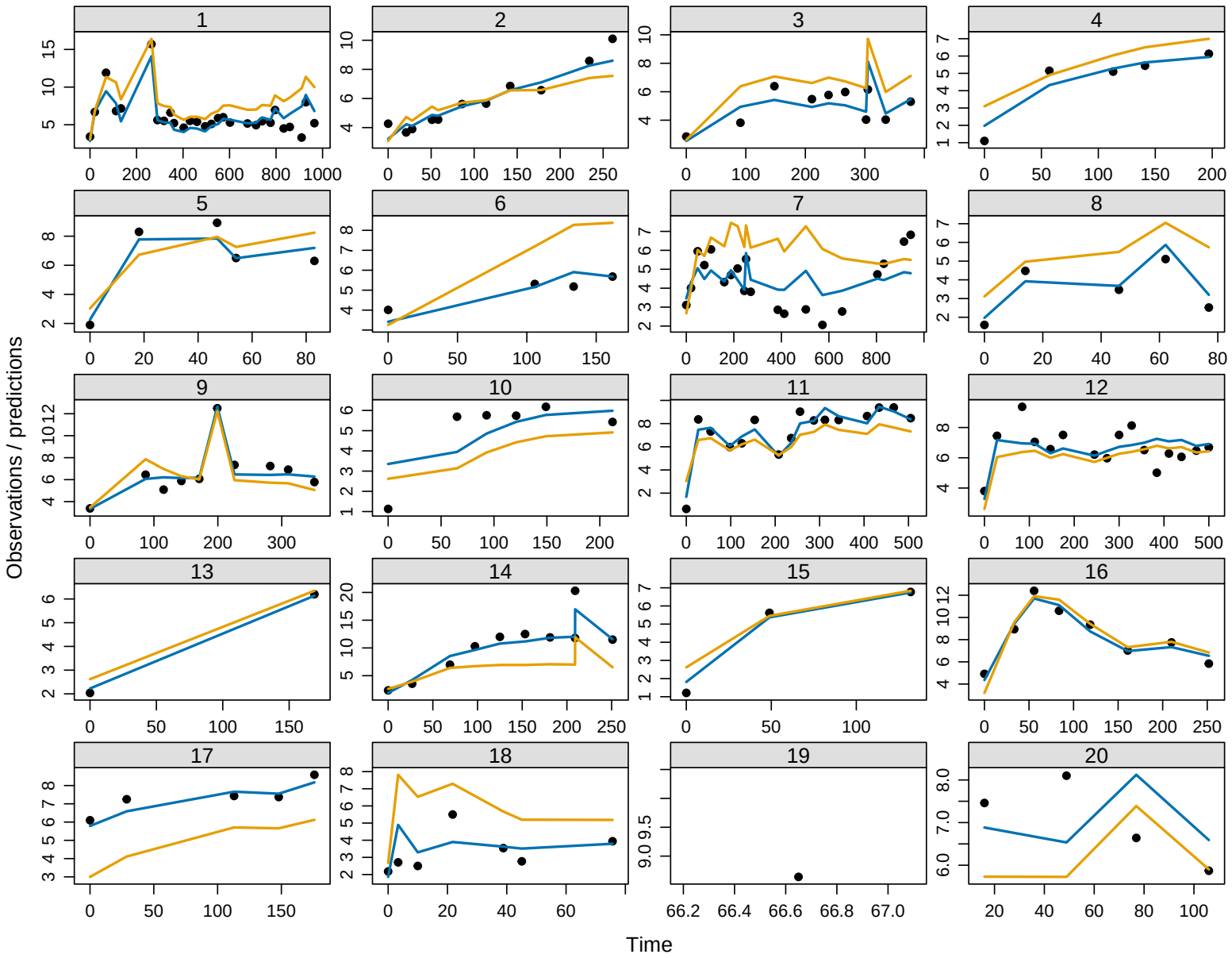
Systemic clearance of intravenous immunoglobulin across published studies, scaled to a 70 kg reference

Table D.1: Scatter plot source table for published intravenous immunoglobulin clearance scaled to 70 kg.

PubMed ID	Author	Patient cohort	Drug	No of subjects	Median age	Median weight	CL_70
2480576	Noya et al., 1989 [736]	Neonates	Immunoglobulin	7	0.007	1.12	0.12
2480576	Noya et al., 1989 [736]	Neonates	Immunoglobulin	8	0.008	1.06	0.138
2480576	Noya et al., 1989 [736]	Neonates	Immunoglobulin	6	0.007	1.16	0.093
2694604	Weisman et al., 1989 [737]	Neonates	Immunoglobulin	30	0.06	3.037	0.0945
16635071	Bjorkander et al., 2006 [738]	PID	Immunoglobulin	22	48	77.5	0.1296
22212346	Bleasel et al., 2012 [739]	PID	Immunoglobulin	19	44.21	66.1	0.115
35008008	Landersdorfer et al., 2013 [259]	PID	Immunoglobulin	151	24.5	62	0.155
28316003	Wasserman et al., 2017 [740]	PID	Immunoglobulin	16	8	75.5	0.439
28316003	Wasserman et al., 2017 [740]	PID	Immunoglobulin	6	8.5	38.82	0.451
30088423	Ochs et al., 2018 [741]	PID	Immunoglobulin	3	4	19.9	0.101
30088423	Ochs et al., 2018 [741]	PID	Immunoglobulin	18	7.6	26	0.0856
30088423	Ochs et al., 2018 [741]	PID	Immunoglobulin	15	13.9	55.5	0.112
30447530	Tortorici et al., 2019 [260]	PID	Immunoglobulin	90	29.8	62.6	0.149
30952104	Dumas et al., 2019 [261]	PID	Immunoglobulin	81	32.1	81	0.0922
31806567	Zhang et al., 2020 [262]	PID	Immunoglobulin	173	23	173	0.144
31910997	Luo et al., 2020 [263]	PID	Immunoglobulin	202	21	202	0.159
31931361	Tegenge & Mahmood, 2020 [264]	Neonates	Immunoglobulin	20	0.008	20	0.06656
33377197	Lee et al., 2021 [257]	PID	Immunoglobulin	10	9.5	10	0.1261
36461591	Li et al., 2022 [266]	PID	Immunoglobulin	340	31.5	47	0.208
35781631	Fokkink et al., 2022 [265]	Guillain–Barré Syndrome	Immunoglobulin	177	53	177	0.28
35008008	Navarro-Mora et al., 2022 [267]	PID	Immunoglobulin	95	29	95	0.157
39366801	Lee et al., 2024 [258]	PID	Immunoglobulin	79	15	79	0.0519

Appendix E

Observed vs Predicted Plots for Each Individual using Immunoglobulin Final model


1
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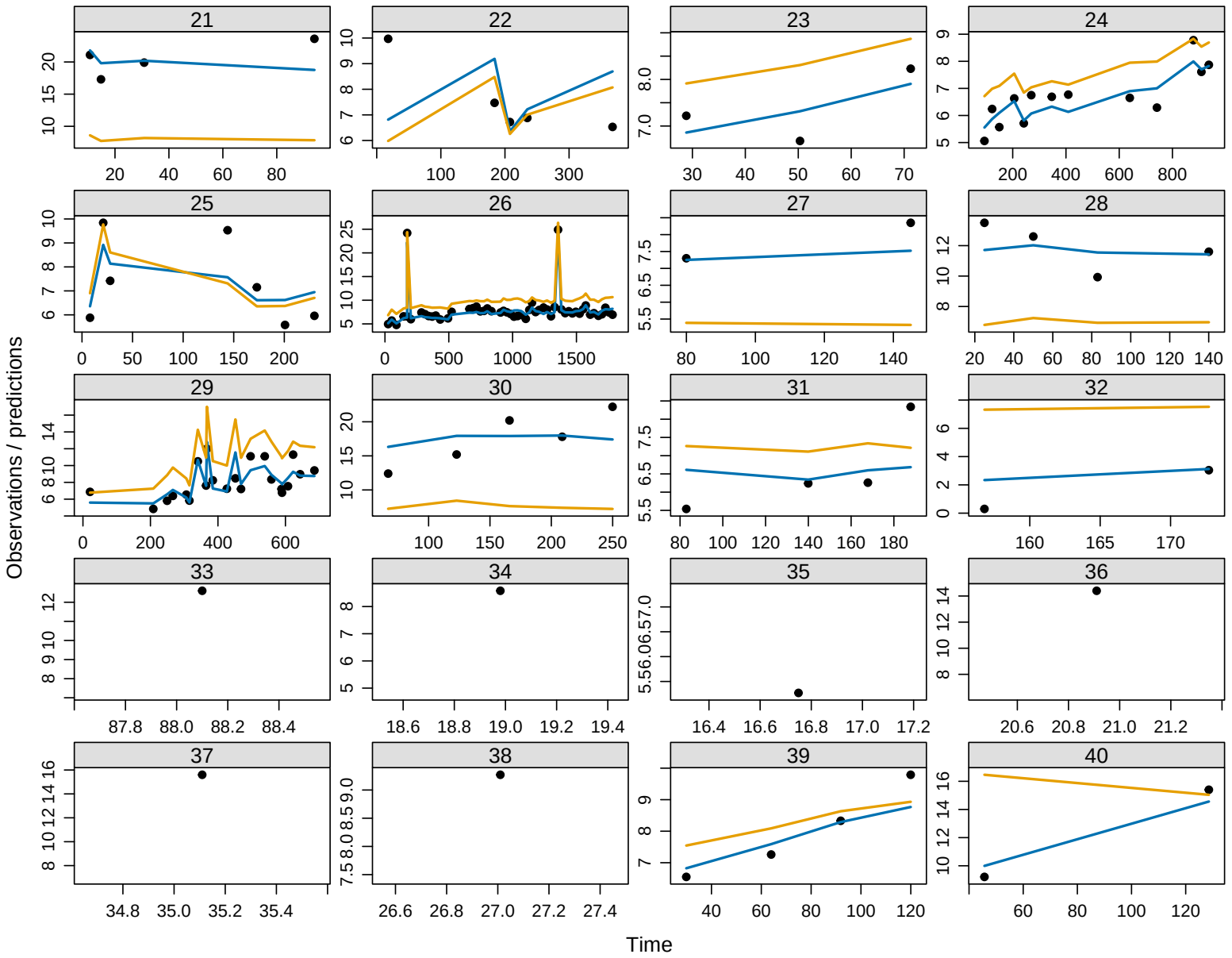
15
16
17
18
19
20
Observations / predictions
Time


21
22
23
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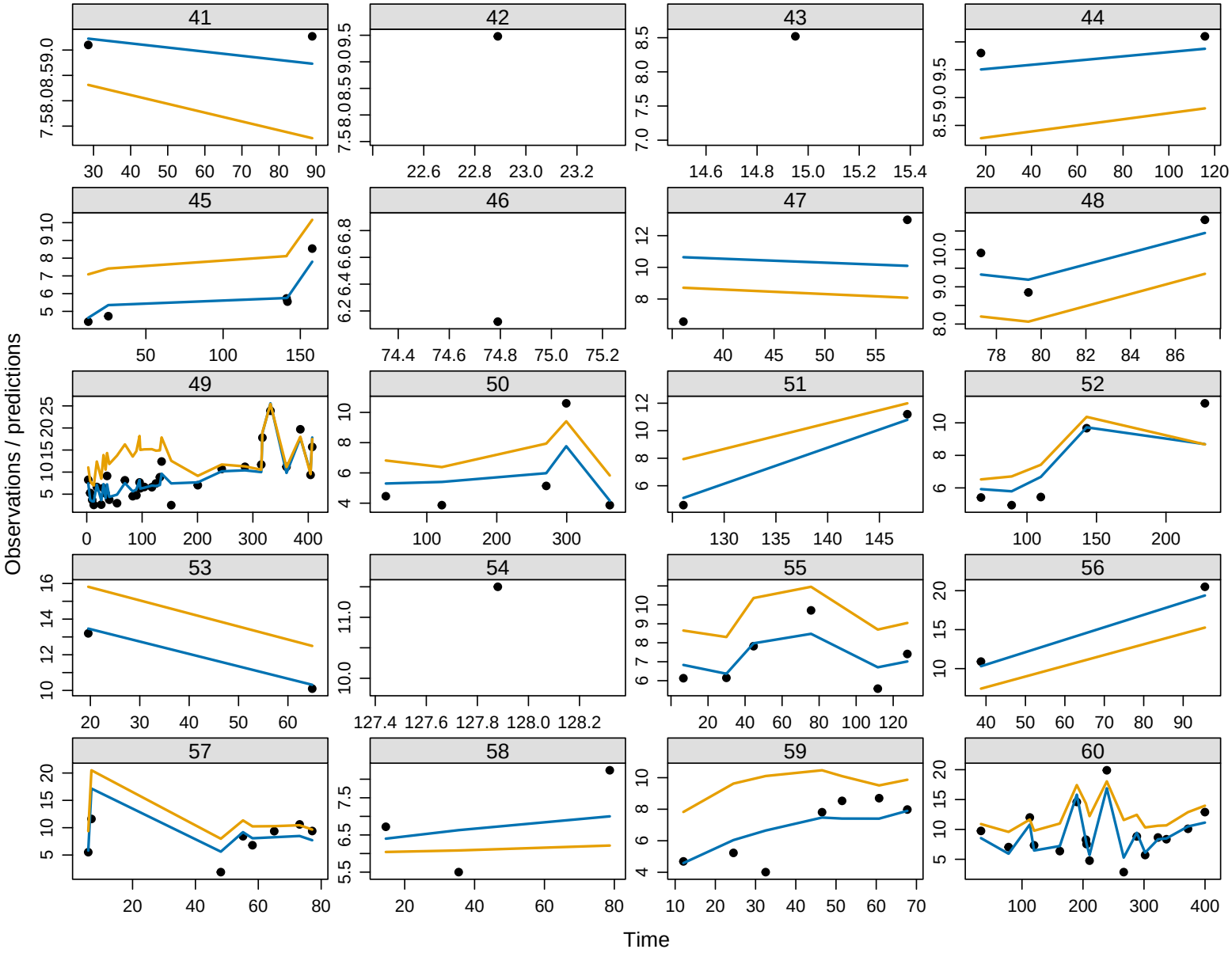
34
35
36
37
38
39
40
Observations / predictions
Time


41
42
43
44
45
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47
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49
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51
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53
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59
60
Observations / predictions
Time

61
62
63
64
Observations / predictions
Time

Appendix F

Immunoglobulin final model

```
$PROB RUN# 36
;; 1. Description: RUN# 36 TYPE on CL + Type on CBAS + IgM on CBAS
$INPUT C ID TIME DV AMT BaselineIg IGM AB_CD19 CD19 WT TAD SEX AGE PMA RATE TYPE CMT EVID
$DATA FinaldatasetHa.csv IGNORE=C
$SUBROUTINES  ADVAN3 TRANS4

$PK
 TVCL=THETA(1)*(WT/70)**0.75
 TVV1=THETA(2)*(WT/70)**1
 TVQ=THETA(3)*(WT/70)**0.75
 TVV2=THETA(4)*(WT/70)**1
 TVCBAS = THETA(5)

; IgM
 TVIGM = ((IGM) / 0.21)**THETA(8)  ; 0.21 = IgM

 CL=TVCL*EXP(ETA(1))*THETA(7)**TYPE
 V1=TVV1
 Q=TVQ
 V2=TVV2*EXP(ETA(2))
 CBAS = TVCBAS * EXP(ETA(3)) * (THETA(6)**TYPE) * TVIGM
S1=V1

$ERROR
FTOT = F + CBAS
IPRED = FTOT
Y = IPRED * (1 + EPS(2)) + EPS(1)
;------ Calculate IWRES
 IRES  = DV-IPRED
```

```
 ADD   = SQRT(SIGMA(1,1))
 PROP  = SQRT(SIGMA(2,2))*IPRED
 SD    = SQRT(ADD**2 + PROP**2)
 IWRES = IRES/SD

;for VPC
IF(Y <= 0) THEN
  Y = 0.01
ENDIF

TDV=DV
IF(TDV<=0.07) TDV = 0.07   ; lower quantification

$THETA
(0, 0.308) ;1. [CL]
(0.1, 3.59) ;2. [V1]
(0, 1.08) ;3. [Q]
(0, 7.37) ;4. [V2]
(0, 5.67) ;5. [CBAS] 5
(0, 0.541) ;6. [TYPE on CBAS]
(0, 0.542) ;7. [TYPE on CL]
(0, 0.11) ;8. [TVIGM on CBAS]

$OMEGA  BLOCK(3)
 0.182  ;     IIV CL
 -0.179 1.92  ;     IIV V2
 0.0869 0.141 0.243  ;   IIV CBAS

$SIGMA
 0.66 ;     [ADD]
 0.0138 ;      [PROP]

$ESTIMATION METHOD=1 MAXEVAL=9999 INTER PRINT=5 FORMAT=1PE13.6
$COV PRINT=E MATRIX=S
$TABLE ID TIME IPRED IWRES CWRES MDV NOPRINT ONEHEADER FILE=sdtab36 FORMAT=s1PE13.6
$TABLE ID TIME TVV1 TVV2 TVCL V1 Q V2 CL CBAS ETA1 ETA2 ETA3 NOPRINT
       NOAPPEND ONEHEADER FILE=patab36 FORMAT=s1PE13.6
$TABLE ID WT TAD AGE PMA NOPRINT ONEHEADER FILE=cotab36 FORMAT=s1PE13.6
$TABLE ID SEX TYPE NOPRINT NOAPPEND ONEHEADER FILE=catab36 FORMAT=s1PE13.6
```

Appendix G

Favipiravir model details

```
$PROB RUN# 14 ONECMPT PROP
;; 1. Description: RUN# 6 ONECMPT PROP IIV CL V ka FIX AO FIX
;; x1. Author: fanie
$INPUT C ID DV AMT TIME TAD EVID II SS ADDL WT TXDAY AGE CR SEX DOSE PMA TSCR
$DATA 2024.09.05favidatatotal.csv IGNORE=C
$SUBROUTINES ADVAN2 TRANS2

$PK
; === AO ontogeny: Subash \textit{et al}.. (2024), scaled between 0 and 1 ===

AO = (AGE**1.28) / (0.82**1.28 + AGE**1.28)



TVCL = THETA(1) * (WT/70)**0.75 * AO
TVV  = THETA(2) * (WT/70)**1

CL = TVCL * EXP(ETA(1))
V  = TVV * EXP(ETA(2))
KA = THETA(3)
S2 = V

$ERROR
IPRED = F
Y = IPRED * (1 + EPS(1))

;------ Calculate IWRES
IRES = DV - IPRED
PROP = SQRT(SIGMA(1,1)) * IPRED
SD = PROP
IWRES = IRES / SD
```

```
; For VPC
IF (Y <= 0) THEN
  Y = 0.01
ENDIF

TDV = DV
IF (TDV <= 0.5) TDV = 0.25   ; half of lower quantification

$THETA
(0, 7.56) ;[CL]
(0.1, 42.7) ;[V]
(1.5) FIX ;[KA] Wang \textit{et al}. 2020

$OMEGA BLOCK(2)
 0.794  ; [IIV CL]
 0.314 0.153  ; [IIV V]

$SIGMA
 0.143 ; [PROP]

$ESTIMATION METHOD=1 MAXEVAL=9999 NOABORT INTER PRINT=5 FORMAT=,1PE13.6
$COV PRINT=E MATRIX=S
$TABLE ID TIME IPRED IWRES CWRES MDV NOPRINT ONEHEADER FILE=sdtab14 FORMAT=s1PE13.6
$TABLE ID TIME TVV TVCL V CL KA ETA1 ETA2 NOPRINT NOAPPEND
       ONEHEADER FILE=patab14 FORMAT=s1PE13.6
$TABLE ID WT TAD WT TXDAY AGE CR NOPRINT ONEHEADER FILE=cotab21 FORMAT=s1PE13.6
$TABLE ID SEX NOPRINT NOAPPEND ONEHEADER FILE=catab14 FORMAT=s1PE13.6
```

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