ESDPPP

The European Society for Developmental, Perinatal And Paediatric Pharmacology

Liverpool Congress 2022

27-30 June

With thanks to

Welcome

Welcome to the 2022 meeting of the European Society for Developmental, Perinatal, and Paediatric Pharmacology!

Liverpool has a long tradition in basic and clinical pharmacology, particularly the University of Liverpool. Alder Hey Children's Hospital has the strongest paediatric clinical pharmacology team in the UK, with three accredited specialists. Liverpool is the only centre for training in paediatric clinical pharmacology in the UK.

Several universities and hospitals collaborate in the Liverpool Paediatric Medicines Research Unit (PMRU), https://bit.ly/3HfJJkR. The PMRU portfolio includes formulation studies (including 3D printing), drug safety, Phase 1 studies, hospital clinical Pharmacy, and community Pharmacy (including medicines use in schools). This work is based on joint working with local Schools of Pharmacy and Nursing.

Collaboration with all stakeholders is central to medicines research. Working with industry is fundamental. We are grateful to Proveca for their support of this Conference which reflects their strong commitment to paediatric medicines development. The UK approach to paediatric patient and public involvement was pioneered in Liverpool by Jenny Preston.

The ESDPPP is Europe's group for paediatric medicines research. This meeting is intended to promote exchange between colleagues in this area. The programme is intended to provide opportunities to learn about familiar and unfamiliar topics. There is a particular emphasis on young scientists presenting work. We invite all attendees to contribute actively to all the presentations and to expand on discussions during the breaks and the social programme.

The meeting is also intended to stimulate collaboration between the meetings of the Society. Many of the contributions by experts are followed by discussion time that will allow us to define action points for working groups.

Networking is central to the future of medicines development, particularly in paediatrics. As the landscape evolves for paediatric research in medicines, associated technologies, and data, ESDPPP can be a bridge between different communities.

We look forward to the next meeting of the Society in Prague in 2023 which will benefit from the leadership of Prof. Pavla Pokorna. We hope that some of the strands will be continued between the 2022 and 2023 meetings.

The Local Organizing Committee
Mark Turner, President ESDPPP 2019-2022
James Moss
Dan Hawcutt

ESDPPP Congress Liverpool 2022

Timetable

MONDAY 27 JUNE, PRE-CONGRESS COURSE

Inform appropriate dosing in pregnancy and paediatrics with physiologically-based pharmacokinetic (PBPK) models: hands-on workshop for non-modellers
09.30-17:00

Venue: G-Flex room in the CTH on the ground floor, Central Teaching Hub Faculty of Science & Engineering, University of Liverpool, Off Brownlow Hill, Liverpool L69 3BX, Building number 221

Time	Session	Speaker(s) / tutor(s)
09.30	Registration and coffee (if not yet done, install Amazon Workspace on your own laptop)	
10.00	Welcome and introduction	Jolien Freriksen, Radboud UMC
10.05	Plenary Basic principles of PBPK modelling	Karen R.Yeo, Certara Simcyp
10.20	Plenary Quantifying ontogeny: what you should know about contemporary paediatric PBPK modelling	Trevor Johnson, Certara Simcyp
10.35	Hands-on Session 1: Dose selection in young children	All tutors
11.05	Hands-on Session 1: Dose selection in young children (continued)	All tutors
12.15	Lunch	
12.55	Interactive plenary session Session 1: Report-back by each group	Trevor Johnson, Certara Simcyp
13.35	Plenary Virtual Pregnancy: What you should know about contemporary pregnancy PBPK modelling	Amita Pansari, Certara Simcyp
13.50	Hands-on Session 2: Dose selection in pregnant women during 3rd trimester	All tutors
14.55	Break: Coffee/tea	-
15.05	Interactive plenary session Session 2: Report-back (focus on take home messages)	Amita Pansari, Certara Simcyp
15.45	Regulatory and clinical considerations: update on collaborations to advance model-informed dosing in special populations	Susan Cole, MHRA
16.00	Closing and Reception	Jolien Freriksen, Radboud UMC / All

Social event at PINS Social Club from 19:00
www.pinssocialclub.co.uk | 45-61 Duke St, Liverpool L1 5AP
Food, drink, table tennis, bowling etc.

TUESDAY 28 JUNE

Location: Central Teaching Hub
Faculty of Science & Engineering, University of Liverpool, Off Brownlow Hill,
Liverpool L69 3BX, Building number 221

Coffee from 08:30

Time	Abstract number	Title	Speaker
		Keynote 1	
09:00		Welcome	Mark Turner
09:05		Keynote: Clinical Pharmacology and the Regulation of Medicines	Prof Sir Munir Pirmohamed
		Pregnancy and Lactation 1	
09:35		Placental pharmacology studies to characterize the effects and disposition of pharmaceuticals: lessons from human tissues and cells for improving drug safety in pregnancy	Rick Greupink
09:55		Update on PKSim in Pregnancy	Andre Dallmann
10:15		Science behind pregnancy and Lactation PBPK modelling in Simcyp: Concepts and applications	Amita Pansari
10:35		An Integrated in vitro Approach for Testing Developmental and Reproductive Toxicity (DART) Endpoints for Next-Generation Risk Assessment (NGRA)	Iris Muller
10:55		Lactation pharmacometrics	Catriona Waitt
11:15		Coffee	
		Pregnancy and Lactation 2	
11:45	1	The exposure to and efficacy of doravirine in pregnant women as assessed by physiologically-based pharmacokinetic modelling.	Hedwig van Hove
12:00	2	The Risk of Miscarriage Following Exposure to NSAIDs During Early Pregnancy: A Systematic Review and Meta-Analysis	Ilan Matok
12:15	3	Psychomotor development of children exposed to Ondansetron during pregnancy: a prospective cohort study	Tal De-Haan
12:30	4	A structured search on physiology-based pharmacokinetic modelling reports in preterm neonates: growing science.	Karel Allegaert
12:45		Lunch	

* Indicates remote presenters

13:10		**Poster Walk 1**	
		Keynote 2	
14:00		Antimicrobial PKPD	Prof William Hope
14:30	15	The influence of sepsis on the tissue penetration of piperacillin-tazobactam in children: a microdialysis study in the juvenile pig	Eline Hermans
		Sites and networks 1	
14:45		Supporting excellence for networked PK trials	Prof Saul Faust*
15:05		PPI in early phase studies	Jenny Preston
15:25		Discussion: can ESDPPP support a network of clinical pharmacology sites?	
15:40		Coffee	
		Sites and networks 2	
16:10	16	The flood of study feasibilities and the value of a centralised approach	Eva Degraeuwe
16:25	17	Development of Pedmed-NL	Fenna Mahler
16:40	18	Paediatric clinical trial needs and requirements within Belgium	Eva Degraeuwe
16:55	19	Clinical, methodological, and patient/parent Expert advice in paediatric drug development via conect4children	Fenna Mahler
17:10	20	Collaboration in Neonatal and Paediatric Clinical Pharmacology: creating a peer-based mentoring platform in a pan-European clinical trial network	Eva Degraeuwe
17:25		End of day	
17:30		Young ESDPPP (Location to be confirmed)	

Social event from 19:30 onwards
Location: Hard Day's Night
Central Buildings, North John Street, Liverpool L2 6RR
Food, drink, dancing

POSTER WALK 1, TUESDAY 28 JUNE

Time	Abstract number	Title	Speaker
13:10	5	Risks associated with antidepressants in patients with hypertension during pregnancy: a retrospective cohort study	Peter Ter Horst
13:15	6	Prediction of pharmacokinetics of long acting cabotegravir in pregnancy	Shakir Atoyebi
13:20	7	Maternal pharmacokinetics and pharmacodynamics of benzylpenicillin for prevention of early onset neonatal group B streptococcal infections	Kate Navaratnam
13:25	8	The Magnitude of Excretion of the "New" Anti-Epileptic Medications in Breastmilk	Elkana Kohn
13:30	9	The perceived barriers and facilitators for model-informed dosing in pregnancy: a qualitative stakeholder analysis	Charlotte Koldeweij
13:35	10	PBPK model-informed dosing guidelines in pediatric clinical care – initiation and drug prioritization	Jolien Freriksen
13:40	11	Landscaping signals on the effects of pharmacogenetics on pharmacokinetics and pharmacodynamics in infants: a systematic literature review	Nadir Yalcin
13:45	12	Efficacy and safety of hydrocortisone to treat hypotension in neonates: A systematic review and meta-analysis	Katelyn Sushko
13:50	13	Multicenter prospective validation of a model-based dosing regimen for vancomycin in preterm and term neonates	Kinga N. Fiebig
13:55	14	Collaboration in Neonatal and Paediatric Clinical Pharmacology: Involving Medical Students Within (Inter)National Clinical Trial Networks	Sabina Pavlíková

* Indicates remote presenters

WEDNESDAY 29 JUNE

Location: Central Teaching Hub
Faculty of Science & Engineering, University of Liverpool, Off Brownlow Hill, Liverpool L69 3BX, Building number 221

Coffee from 08:30

Time	Abstract number	Title	Speaker
		Real World Data / Evidence: sponsored by Proveca	
09:00		Real World Data: Clinical perspective	Jennifer Duncan
09:20		Real World Data: Industry perspective	Helen Shaw
09:40		Real World Data: Academic perspective	Ilan Matok
10:00		Real World Data: Discussion – who is interested in sharing RWD?	
10:15	21	Melatonin prescription in children in relation to body weight	Jenny Kindblom
10:30	22	Using real-world data to support rituximab dosing strategies for pediatric patients with frequent-relapsing or steroid-dependent nephrotic syndrome: a prospective pharmacokinetic-pharmacodynamic study	Yewei Chen*
10:45	23	Maternal antidepressant use in pregnancy and major birth defects	Florentia Kaguelidou*
11:00		Coffee	
		Therapeutic Drug Monitoring	
11:30		Utilisation of Clinical Pharmacology Studies to Support the Treatment of Neonates and Infants	Gareth Veal
11:50		Establishing a national TDM service in the United Kingdom	Shelby Barnett
12:10		Pitfalls and opportunities for centralized TDM services: A Belgian singe-centre experience	Pieter de Cock
12:30		TDM: Discussion – how can ESDPPP share practice in TDM?	
12:45	24	Feasibility of the pragmatic PBPK modelling approach – Towards model-informed dosing in paediatric clinical care	Joyce van der Heijden
13:00		Lunch	
13:25		**Poster Walk 2**	

Continued overleaf...

Wednesday 29 June continued...

Time	Abstract number	Title	Speaker
		Models, methods, and mechanisms	
14:15		Maternal and Pediatric Precision in Therapeutics Knowledgebase (MPRINT)	Lang Li Aditi Shendre
14:45	34	The impact of age on intestinal CYP3A activity, assessed with the Ussing methodology	Eva Streekstra
15:00	35	Microdosing/microtracer based pediatric drug development	Esther van Duijn
15:15	36	In vitro investigation of Vancomycin-Induced Kidney Injury: Development of a 2D cellular model	Lawrence Rhodes
15:30	37	The Inflammation in the Pathology of Patients with Mucopolysaccharidosis	Anna-Maria Wiesinger
15:45		Coffee	
		PK/PD	
16:15	38	Prednisolone pharmacokinetics after oral prednisone administration in paediatric patients with kidney transplant	Naïm Bouazza
16:30	39	Exposure following oral and intravenous amoxicillin in neonates: a population pharmacokinetic analysis	Stef Schouwenburg
16:45	40	Predicting Treatment Response to Vancomycin Using Bacterial DNA Load as a Pharmacodynamic Marker in Premature and Very Low Birth Weight Neonates: A Population PKPD Study.	Amadou Samb
17:00	41	Physiologically based pharmacokinetic model to simulate midazolam pharmacokinetics in a paediatric US population.	Trevor Johnson
17:15	42	Favipiravir pharmacokinetics in immunocompromised infants and children with chronic RNA viral infections	Iek Cheng
17:30	43	Plasma renin activity in young children with heart failure: Influence of age, disease and ACE inhibitor treatment	Melina Steichert
17:45		End of day	
18”00		Business Meeting	

Social event: Please arrive for 19:30
Location: One Fine Day, Cotton Exchange, Old Hall St, Liverpool L3 9BS
Conference Dinner: Three course meal, followed by band

* Indicates remote presenters

POSTER WALK 2, WEDNESDAY 29 JUNE

Time	Abstract number	Title	Speaker
13:25	25	Population pharmacokinetics of enteric-coated mycophenolate sodium in children after renal transplantation and initial dosage recommendation based on body surface area	Guangfei Wang*
13:30	26	A comparison of age-banded and weight-based oral paracetamol dosing in hospitalised children	Kirstie Wright
13:35	27	The relation between the serum trough concentration of paracetamol and pain reduction in preterm and term neonates: a retrospective observational study	Roland B. van den Berg
13:40	28	Poor availability of age-appropriate drug formulations in DR Congo: a barrier to switch from intravenous to oral antibiotics in children admitted to Kisantu Hospital	Bieke Tack
13:45	29	Antibiotic consumption in asthmatic and non-asthmatic children: a national cohort study	Florentia Kaguelidou*
13:50	30	Development of a comprehensive search query for an in-depth study of scientific literature on paediatric drug use	Marika de Hoop-Sommen
13:55	31	Prescribing pattern of anti-asthma medication and antibiotics among asthmatic children and adolescents in Manitoba	Arun Paul*
14:00	32	Inspiration to mRNA-Based COVID-19 Vaccination: Acute Myocarditis associated with Hepatitis B Vaccine	Jinmiao Lu
14:05	33	First preliminary pharmacokinetic and pharmacodynamic data on alpelisib use in TIE-2 mutated venous malformations	Niina Kleiber

THURSDAY 30 JUNE

Location: Central Teaching Hub
Faculty of Science & Engineering, University of Liverpool, Off Brownlow Hill,
Liverpool L69 3BX, Building number 221

Coffee from 08:30

Time	Abstract number	Title	Speaker
		National formularies	
09:00		National formularies: introduction	Tjitske Van der Zanden
09:10		National formularies: Discussion – how can ESDPPP support work on national formularies?	
		Psychopharmacology	
09:30	44	Medical Cannabis for the Treatment of Comorbid Symptoms in Children with Autistic Spectrum Disorder: An Interim Analysis of Biochemical Safety	Matitiahu Berkovitch
09:45	45	Antipsychotics use and weight gain in children compared to adults: analysis of spontaneous adverse drug reaction reports	Florentia Kaguelidou*
10:00	46	Stimulant drug use in children before six years of age and antipsychotic add-on therapy: a population based longitudinal study	Hans Jürgen Gober
		Clinical pharmacology 1	
10:15	47	Point Prevalence Study of Paediatric Polypharmacy	James Moss
10:30	48	Introduction of the project of the Czech drug database in neonatology and pediatrics in 2022	Sabina Pavlíková
10:45	49	Risk factors of augmented renal clearance in critically ill children using iohexol clearance for renal function assessment	Evelyn Dhont
11:00		Coffee	
11:15		**Poster Walk 3**	
		Clinical Pharmacology 2	
12:10	60	Mapping Variation between National and Local Clinical Practice Guidelines for Acute Paediatric Asthma from the United Kingdom and the Netherlands	Charlotte Koldeweij
12:25	61	Deprescribing long acting beta2 agonists in children and adolescents with stable asthma: a systematic review	Wiktoria Drozdz

* Indicates remote presenters

12:40	62	Innovative High-Fidelity Simulation for vaccination training of pharmacist including emergency cases - a randomised controlled study	Shahzad Sayyed
12:55	63	Inhaled antiasthmatic drugs and the risk of dental caries in children: a pharmacovigilance analysis	Alexandra Henry*
13:10	64	KiDSafe - Improving medication safety for children and adolescents: implementation and evaluation of a new form of care	Irmgard Toni
13:25		Concluding Comments	Mark Turner
13:30		Lunch	

POSTER WALK 3, THURSDAY 30 JUNE

Time	Abstract number	Title	Speaker
11:15	50	Off-label, but on-evidence? A review of the evidence of pediatric pharmacotherapy.	Tjitske van der Zanden
11:20	51	Paediatric Medication Error Prevention (PMEP) A tripartite alliance working together	Pramodh Vallabhaneni*
11:25	52	What domains related to medicines were measured in studies of burden of care for paediatric patients? A systematic review	Tharshiya Thatparan
11:30	53	Utilization of and Barriers to Individual Treatment Trials in Mucopolysaccharidosis - Interim Results of an Expert Survey	Anna-Maria Wiesinger
11:35	54	The impact of paediatric dose range checking software	Elena Rybka
11:40	55	mHealth Diabetes Apps for the delivery of Pharmaceutical Care and inter-professional point of care communication in adolescent Type 1 Diabetes Mellitus patients	Armin Dabidian
11:45	56	Rapid drop in midazolam concentration may be linked to paediatric delirium in critically ill children – an observational pilot study	Mathieu Bolhuis
11:25	57	Off-label use of drugs in paediatric (specialised) outpatient clinics – what has changed between 2009 and 2019?	Irmgard Toni
11:55	58	Attitudes of children and young people and their parents towards polypharmacy – pilot study	James Moss
12:00	59	What is known about the pharmacology of intramuscular therapeutics in Duchenne Muscular Dystrophy? A Systematic Review.	Eve Roberts

PREGNANCY AND LACTATION 1 – ABSTRACTS FROM GUEST SPEAKERS

Placental pharmacology studies to characterize the effects and disposition of pharmaceuticals: lessons from human tissues and cells for improving drug safety in pregnancy

Rick Greupink[1]
1: Department of Pharmacology and Toxicology, Radboud university medical center, Nijmegen, The Netherlands

The placenta plays a key role in maintaining a healthy pregnancy. In order to improve drug safety during pregnancy, it is therefore relevant to understand to which extent and at which rate drugs are transferred across the placenta and how pharmaceuticals may affect placental function. Translational and predictive pharmacology studies based on human tissues and cells are becoming increasingly important in characterizing the effects and disposition of pharmaceuticals. With regard to the placenta, such approaches may for example be readily combined with physiology-based pharmacokinetic (PBPK) modeling to predict fetal exposure of drugs, as well as placental tissue exposure in the clinic. In addition, placental tissue and cells can be used to study potential effects of drugs, as well. The current presentation, will highlight several studies that investigated the placental disposition and effects of both small and large molecule pharmaceuticals, as well as how such data can help to better understand the clinical pharmacology of therapeutics.

Science behind pregnancy and Lactation PBPK modelling in Simcyp: Concepts and applications

Amita Pansari[1]
1: Certara UK Ltd, Simcyp Division, Sheffield, UK

Most drug labels do not provide dosing guidance for pregnant and lactating women, yet in the U.S. alone, more than 6 million women are pregnant each year, and it is estimated that more than 90 percent take at least one medication while pregnant or lactating. Various physiological and biochemical changes in many maternal organs during pregnancy can affect drug pharmacokinetics. For drugs that can cross the placental barrier, changes in maternal exposure may affect fetal exposure, depending on the degree of drug distribution into the fetal circulation. Recently, there has also been an increased interest in understanding the pharmacokinetics (PKs) in lactating women and the rate, and extent of drug distribution into the milk to guide neonatal/infant risk assessments, where such information is not available.

Simcyp PBPK model includes time-varying physiological changes in the maternal, fetal, and placental parameters over the course of pregnancy. PBPK approach with case studies examples will be shared to facilitate the prediction of maternal and fetal drugs exposure and to support its use in the maternal/fetal exposure assessments. Prediction of milk drug exposure in breastfeeding mothers and estimation of infant dose and infant risk assessment will also be discussed.

Lactation Pharmacometrics

Catriona Waitt[1]
1: Clinical Pharmacology and Global Health, University of Liverpool, UK

Worldwide, many women need to take medication during breastfeeding. These women deserve access to evidence-based clinical decision making in partnership with their healthcare providers. However, systematic exclusion from clinical trials and lack of pharmacokinetic data can render this impossible. Lactation pharmacology has been identified as a clinical priority by agencies including the EMA and the US FDA, but such studies are rarely done in a timely manner. Moreover, when lactation studies are undertaken, there are often limitations in design and analysis.

This overview of lactation pharmacology will summarise the current landscape and major gaps in clinically relevant data. Best practice in study design will be described with an emphasis on how both physiologically based pharmacokinetics and population pharmacokinetics can enhance both study design and interpretation of data.

ABSTRACT NUMBER 1

The exposure to and efficacy of doravirine in pregnant women as assessed by physiologically-based pharmacokinetic modelling

Hedwig van Hove[1], Vera Bukkems[2], Damian Roelofsen[2], Jolien Freriksen[1], Joris van Drongelen[3], Elin Svensson[2], Angela Colbers[2], Rick Greupink[1]
1: Pharmacology and Toxicology, Radboud university medical center; 2: Pharmacy, Radboud university medical center; 3: Obstetrics and Gynaecology, Radboud university medical center

INTRODUCTION
Doravirine is currently not recommended for pregnant women living with HIV due to the lack of efficacy and safety data. Physiological changes during pregnancy can significantly decrease drug exposure, and, thereby, lower the efficacy. Awaiting clinical data, this study aimed to predict maternal and fetal doravirine exposure by integrating human placenta perfusion experiments with pregnancy physiologically-based pharmacokinetic (PBPK) modelling.

METHODS
An existing and validated three-compartment PBPK model of doravirine for a healthy, non-pregnant population was modified to a 18-compartment PBPK model using Simcyp Simulator V20. The permeability-limited placenta model was included in the extended PBPK model to study placental transfer to the fetus. To parameterize the placenta model, ex vivo human cotyledon perfusion experiments were performed, and a mechanistic model was developed to derive placental transfer constants. The final pregnancy PBPK model was used to predict the maternal and fetal geometric mean (GM) concentration at 24h after dosing (C24h) at 26, 32 and 40 weeks of pregnancy. The GM C24h was compared to the target derived from in vivo exposure-response analysis of 0.23 mg/L.

RESULTS
Perfusion experiments showed that doravirine extensively crosses the placenta. In comparison to non-pregnant women, the final pregnancy PBPK model estimated a maternal decrease in GM C24h of 55% for 40 weeks pregnancy. All predicted maternal GM C24h were <0.23 mg/L.

CONCLUSIONS
Substantially reduced maternal doravirine exposure was predicted during pregnancy, possibly resulting in impaired efficacy. Therapeutic drug and viral load monitoring are advised for pregnant women treated with doravirine, and the use should preferentially be restricted to clinical trials.

ABSTRACT NUMBER 2

The Risk of Miscarriage Following Exposure to NSAIDs During Early Pregnancy: A Systematic Review and Meta-Analysis

Ilan Matok[1], Alexandra Litvin[1], Maya Berlin[2], Victoria Rotshild[1], Asnat Walfish[3], Benjamin Bar-Oz[4]
1: School of Pharmacy, Faculty of Medicine, The Hebrew University of Jerusalem; 2: *Clinical Pharmacology and Toxicology Unit, Shamir Medical Center (Assaf Harofeh), Affiliated to Sackler Faculty of Medicine, Tel-Aviv University, Tel Aviv, Israel. 3: Department of Obstetrics and Gynecology, Hadassah Medical Center, The Hebrew University of Jerusalem, Jerusalem, Israel.; 4: Department of Neonatology, Hadassah-Hebrew University Medical Centers and Assuta Ashdod Medical Center, Israel.*

INTRODUCTION
Non-steroidal anti-inflammatory drugs (NSAIDs), are widely used by women of childbearing age and by pregnant women. Data regarding NSAIDs exposure safety during early pregnancy is controversial.
Objective: To evaluate whether exposure to NSAIDs during early pregnancy (up to 20th week of gestation) increases the risk of spontaneous abortions.

METHODS
We followed the PRISMA guidelines. We used database, including MEDLINE, EMBASE, Cochrane Library, and Scopus. The databases were searched up to June 2019.
We included randomized controlled trials and observational studies in which pregnant women were exposed to NSAIDs. Two independent reviewers screened abstracts, titles and full texts against inclusion and exclusion criteria.
Data Extraction and Synthesis: Study characteristics, HR, and OR estimates were extracted from each study. Estimates were pooled and analysis was conducted through CMA software using random-effects model.

RESULTS
Thirteen studies involving 11,182 pregnant women exposed to NSAIDs were analyzed. Risk of spontaneous abortion was not increased following NSAIDs exposure
(OR, 1.29; 95% CI, 0.77-2.15 for studies reporting OR, HR, 1.05; 95% CI, 0.90-1.23 for studies reporting HR) with considerable heterogeneity across the studies (I2 = 85% and I2 = 54%, respectively). Further sensitivity and subgroup analyses including high quality studies, typical NSAIDs, and one study removed analysis corroborated these results.

CONCLUSIONS
This systematic review and meta-analysis did not observe a significantly increased risk of spontaneous abortion following NSAIDs exposure during early pregnancy.

ABSTRACT NUMBER 3

Psychomotor development of children exposed to Ondansetron during pregnancy: a prospective cohort study

Tal De- Haan[1], Maya Berlin[2]Maayan Beckenstein[3], Irina Tolchinsky[3], Rana Cohen[2], Gideon Koren[2], David Stepensky[3], Mati Berkovitch[4]
1: Pharmacology & Toxicology Unit, Shamir Medical Center; 2: Clinical Pharmacology and Toxicology Unit, Shamir Medical Centre; 3: The School of Pharmacy, Ben-Gurion University of the Negev; 4: Clinical Pharmacology and Toxicology Unit, Shamir Medical Center (Assaf Harofeh), Affiliated to Sackler Faculty of Medicine, Tel-Aviv University, Tel Aviv, Israel.

INTRODUCTION
Nausea and Vomiting in Pregnancy (NVP) is a very common phenomenon, affecting up to 85% of pregnant women. Severe NVP and Hyperemesis Gravidarum (HG) are both hazardous for the mother and the fetus. Ondansetron's safety in pregnancy is controversial. The data regarding the psychomotor development of children following ondansetron use during pregnancy is scarce. We aimed to evaluate the psychomotor development of children exposed to Ondansetron in pregnancy.

METHODS
A prospective cohort study. Mothers with NVP who contacted TIS Zerifin seeking information regarding NVP treatment were followed-up. The psychomotor development was assessed by Pediatric Quality of Life (PedsQL) and Denver scale.

RESULTS
260 women were recruited, 137 women exposed to Ondansetron and 123 women exposed to non-teratogenic medications for NVP. No difference between the groups in malformations was observed. Children exposed to Ondansetron and those in the control group both had very high PedsQL scores with no statistical significance. The only statistically-significant finding was in emotional function category. The median score of emotional function in the study group was 95, while non-exposed had the median score of 90 (P=0.04). No statistical significance between the groups was found in Denver development scale. Regression models adjusted to maternal age and education, PUQE score and other psychotropic medications failed to show increased risk for negative PedsQL score – psychosocial health: aOR 0.89, 95%CI (0.47,1.67), p=0.7, physical health: aOR 1.08, 95%CI (0.46, 2.54), p=0.9. There was a trend in Cognitive functioning below 90: aOR 1.99, 95%CI (0.95, 4.22), p=0.07.

CONCLUSIONS
Exposure to Ondansetron during pregnancy was not associated with negative psychomotor offspring's development

ABSTRACT NUMBER 4

A structured search on physiology-based pharmacokinetic modelling reports in preterm neonates: growing science

Yassen Mohammed[1], Olusola Olafuyi[2], Pieter Annaert[3], Karel Allegaert[4]
1: Division of Clinical Pharmacology, Department of Medicine, Indiana University School of Medicine, Indianapolis, Indiana, USA; 2: School of Life Sciences, , University of Nottingham, Nottingham, United Kingdom; 3: Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, Belgium; 4: Department of Development and Regeneration, KU Leuven, Belgium.

INTRODUCTION
We aimed to assess the extent, variety in applications and limitations of physiology-based pharmacokinetic (PBPK) models in preterm neonates.

METHODS
A structured search was performed on February 16, 2022 (Medline, Embase, Cochrane central).

RESULTS
Based on 172 initial results, 38 papers were assessed, and 24 records (original papers, letters or abstracts) were retained. Besides the development reports on preterms (PKSim, Simcyp), one ad hoc probalistic PBPK model was retrieved (applied to piperacillin+tazobactam). Applications and optimization efforts applied within PKSim [small molecules (zidovudine), GFR+tubular secretion (meropenem)], therapeutic proteins and monoclonals, drug-drug interactions (sildenafil+fluconazole, buprenorphine+clarithromycin, itraconazole, rifampicin), specific compartments (CSF, tissue, both fluconazole), or performance comparisons (to allometrics)] or within Simcyp [PK/pharmacodynamics for antibiotics, middle out approach (propofol), lactation-related theophylline exposure, the ontogeny of biliary excretion, impact of reduced cardiac output (paracetamol), or performance comparisons (to allometrics)]. Finally, we retrieved one ad hoc model to predict first pass and systemic drug metabolism (midazolam, CYP3A first pass ontogeny).

CONCLUSIONS
We generated a robust snapshot of currently published experience on development and use of PBPK models in preterm neonates, reflecting a diversity in applications. Almost all papers consistently mention limitations related to data access on (patho)physiology in preterms, while their search strategy to retrieve these data is only very marginally described.

ABSTRACT NUMBER 5

Risks associated with antidepressants in patients with hypertension during pregnancy: a retrospective cohort study

Peter Ter Horst[1], Marlieke Oude Weernink[1], Elvera Damer[2],Mireille Edens[3], Marieke Hemels[4]
1: Clinical Pharmacy, Isala;2: Psychiatry, Isala 3: Epidemiology, Isala; 4: Neonatology

INTRODUCTION

Given the proportion of pregnant women with gestational hypertension or pre-eclampsia using an antidepressant we aimed to gain insight into the effects concerning for both mother and neonate especially on birth weight, APGAR score, and pregnancy duration.

STUDY DESIGN

Retrospective cohort study of women with hypertension disorders, whether or not using antidepressants.
Main outcome measures: Birth weight, APGAR score, admittance to Obstetrical High Care unit (OHC) and or Neonatal Intensive Care Unit and pregnancy duration

RESULTS

The use of antidepressants was associated with lower APGAR scores at 10 minutes, p= 0.008, OR = 2.298; 95% CI 1.255-4.273, compared to neonates from mothers without antidepressants. Women using antidepressants were more often admitted to the OHC (crude OR= 1.95; p=0.049; 95% CI 0.99-3.77). Multivariable logistic regression analysis revealed that thyroid disease and preterm ending of pregnancy contributed to the model, where use of antidepressants remained significant (OR=6.28; 95% CI 2.32-18.31).

CONCLUSIONS

Women with hypertension disorders during pregnancy and using antidepressants might have an increased risk for complications leading to OHC admission.

ABSTRACT NUMBER 6

Prediction of pharmacokinetics of long acting cabotegravir in pregnancy

Shakir Atoyebi[1], Fazila Bunglawala[1], Nicolas Cottura[1], Maiara Camotti-Montanha[1], Marco Siccardi[1], Catriona Waitt[1]
1: Department of Pharmacology & Therapeutics, University of Liverpool

INTRODUCTION

The objective of this study was to use physiologically-based pharmacokinetic (PBPK) models to predict the PK of long-acting (LA) cabotegravir (CAB) in pregnancy.

METHODS

An adult PBPK model was developed in SimBiology (MATLAB R2019a) and qualified against clinical PK data in adults for single doses of 400 mg and 800 mg intramuscular (IM) CAB, and 400 mg oral raltegravir (RAL). A virtual pregnant population was developed by incorporating pregnancy-induced biological changes known to influence drug PK into the qualified adult model. Activity of key enzyme UGT1A1 during pregnancy was validated with clinical PK data of probe substrate (RAL) in pregnant women. The qualified pregnancy model was used to predict the PK of 400 mg single dose of LA CAB during pregnancy.

RESULTS

Absolute average fold errors (AAFE) of the PK parameters for oral RAL and LA CAB in adults were within the 2-fold acceptance criteria. AAFE values of oral RAL in pregnancy were also within the 2-fold acceptance criteria. Predicted geometric mean of PK of 400 mg LA CAB in non-pregnant adults, second and third trimesters of pregnancy were: Cweek4 0.74, 0.77 & 0.76 µg/mL; Cmax 0.89, 0.91 & 0.91 µg/mL; and 534, 550 & 549 µg.hr/mL.

CONCLUSIONS

These data suggest dosage adjustments are not necessary for LA CAB to maintain therapeutic concentrations and clinical efficacy during pregnancy. This approach could be utilised to predict the risk related to altered PK during pregnancy for LA therapy and support the design of future clinical trials in pregnant women.

ABSTRACT NUMBER 7

Maternal pharmacokinetics and pharmacodynamics of benzylpenicillin for prevention of early onset neonatal group B streptococcal infections

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INTRODUCTION

Group B Streptococcal infections (GBS) are the most common cause of severe early onset neonatal sepsis. The RCOG advise intrapartum prophylaxis with intermittent boluses of Benzylpenicillin throughout labour, using regimens from early trials. However, benzylpenicillin has time dependent pharmacokinetics/pharmacodynamics (PK-PD) whereby more frequent administration or continuous infusions maximises antibacterial efficacy. In populations comparable to pregnant women (e.g. critical illness with increased volume of distribution and augmented renal clearance), continuous infusions are associated with improved outcomes. Whether CI results in improved clinical outcomes for GBS is not known.

SCIENTIFIC OBJECTIVES

To determine the PK-PD of intrapartum intermittent benzylpenicillin boluses in women at risk of having an infant affected by early onset group B streptococcal disease. Use population PK-PD modelling and simulation to develop new benzylpenicillin regimens that are likely to be more effective.

METHODS

We will recruit 30 women during a prospective cohort study at Liverpool Women's Hospital. Pregnant women, requiring intrapartum benzylpenicillin according to RCOG criteria, will be identified. Women with pyrexia or penicillin allergy will be excluded. Maternal plasma, cord plasma and placental tissue will be obtained. Optimal design theory will ensure the information associated with each sample is maximal. Benzylpenicillin concentrations will be measured using liquid chromatography mass spectrometry. We will construct a population pharmacokinetic model and perform Monte Carlo simulation to propose new regimens to achieve pharmacodynamic targets that optimise antibacterial effects and trial these through a hollow fibre mode.

ABSTRACT NUMBER 8

The Magnitude of Excretion of the "New" Anti-Epileptic Medications in Breastmilk

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INTRODUCTION

Information on the "old" anti-epileptic medications in breastfeeding is ubiquitous. Less information is available on the safety of the "new" anti-epileptic medication (AED) in lactation. We assessed the magnitude of lamotrigine (LAM), levetiracetam (LEV) and lacosamide (LAC) breastmilk excretion and its correlation with maternal dose and serum concentrations.

METHODS

Breastfeeding women with epilepsy treated with at least one of the new AED were recruited. Demographic and medical data were collected. Maternal trough serum and breastmilk samples were collected, as well as breastmilk samples at 1,3,6,9,12 hours after AED administration. Trough breastmilk/serum ratios (M/S ratio) and breastmilk AUC values were calculated.

RESULTS

Thirty eight breastfeeding women were enrolled. Twenty samples were measured for LEV, 17 for LAM and 2 for LAC. Two women were on polytherapy (LEV/LAC, LEV/LAM). The trough breastmilk/serum ratio was 0.98±0.2, 0.66±0.2 and 0.83±0.5 for LEV, LAM and LAC, respectively. Relative infant dose was 13.8±3.1% and 6.9±1.6% and 6.7±6.1% for LEV, LAM and LAC, respectively. Substantial correlation between maternal serum and breastmilk trough concentrations, and breastmilk AUC values was found. Three women treated with LEV reported somnolence in their fully-breastfed infants, which resolved after switching to partial breastfeeding.

CONCLUSIONS

High correlation between maternal trough serum concentration and the breastmilk AUC values was found in LEV and LAM, implying that monitoring maternal serum concentrations can be useful for predicting the exposure of infants to LEV, LAM via the breastmilk. LAC results support this conclusion. However, a larger group of women treated with lacosamide is needed.

ABSTRACT NUMBER 9

The perceived barriers and facilitators for model-informed dosing in pregnancy: a qualitative stakeholder analysis

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INTRODUCTION
The lack of evidence for drug dosing in pregnancy represents a large unmet need for pregnant women and their unborn child. This study examines Dutch stakeholders' perceptions of model-informed dosing in pregnancy as part of an effort to build a model-informed pregnancy formulary (MIPF).

METHODS
Online focus groups and individual interviews were conducted with health care practitioners (HCPs) from various specialties (gynecology, pharmacy, general medicine, midwifery and other medical specialties) and with currently or recently pregnant women. The perceived barriers and facilitators for implementing a MIPF were identified using a hybrid thematic analysis.

RESULTS
30 HCPs and 10 pregnant women participated in nine focus groups and three interviews. The awareness of pharmacokinetic changes in pregnancy varied across focus group participants. While a majority of HCPs and pregnant women found a MIPF to be a relevant innovation, several participants across both groups indicated that the lack of information on fetal safety constituted another important gap to address. The information needs of HCPs in order to be willing to apply model-informed dosing recommendations varied. A majority of participants indicated that they preferred model predictions to be clinically verified for the concerned drug. HCPs expressed different preferences with regards to the most appropriate website for publishing model-informed dosing advice. Several pregnant women indicated that they wanted to be informed on the evidence behind model-informed dosing recommendations.

CONCLUSIONS
Stakeholders' views on the barriers and facilitators for relying on model-informed dosing in pregnancy will be further investigated through an online survey and will inform the design of a MIPF.

ABSTRACT NUMBER 10

PBPK model-informed dosing guidelines in pediatric clinical care – initiation and drug prioritization

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INTRODUCTION
With approximately 50% of the drugs being prescribed off-label, the pediatric population is in need for an innovative approach to establish harmonized, best evidence-based dosing guidelines. Physiologically-based pharmacokinetic (PBPK) modelling is a valuable approach to predict drug pharmacokinetics (PK) and to support dosing. As a first step to implement PBPK-informed dosing in pediatric clinical care, we aimed to identify drugs suitable to verify the PBPK approach and prioritize drugs in need of model-informed dosing.

METHODS
To select a drug, it required to be listed on: 1. the Model List of Essential Medicines for Children (EMLc) of the WHO and on 2. the Dutch Pediatric Formulary (DPF). Also, a Simcyp® PBPK compound model had to be available. The level of evidence of the dosing recommendations in the DPF, the availability of pediatric pharmacokinetic data, and the opinion of clinicians on the relevance of the drug were reviewed for further prioritization.

RESULTS
Of all drugs on the EMLc, 199 are listed in the DPF. For 76 of them, a Simcyp® compound model is available, either directly in the software, its repository, or from scientific literature. Eleven drugs have sufficient PK data to verify the PBPK modeling approach. For 48 drugs, we identify a moderate to high priority for a model-informed dose.

CONCLUSIONS
This work now provides input for the next steps which include verification of PBPK model performance in pediatrics and subsequent PBPK modelling to establish dosing guidelines. A joint effort and an internationally accessible platform are needed to share information on pediatric PBPK modelling to eventually implement model-informed doses in clinical practice.
This abstract is based on research funded by the Bill & Melinda Gates Foundation.

ABSTRACT NUMBER 11

Landscaping signals on the effects of pharmacogenetics on pharmacokinetics and pharmacodynamics in infants: a systematic literature review

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INTRODUCTION
We aimed to identify signals on the impact of pharmacogenetics (PG) on pharmacokinetics (PK) and –dynamics (PD) in newborns and infants (<1 year).

METHODS
A structured search was performed (Medline, Embase, WoS]. Applying PRISMA guidelines, studies were selected based on predefined inclusion criteria (infants, PG data, any trial). In addition, the Pediatrix top 100 drug (Stark, J Pediatr 2022) was screened in PubMed [drug + pharmacogen* + (newborn OR infant)].

RESULTS
789 records were screened, 55 retained. On phase I polymorphisms, significant signals for CYP2A6 (dexmedetomide PK), CYP2D6 (tramadol, dextromethorphan, ritonavir, dihydrocodeine PK/PD), CYP2B6 (nevirapine PK), CYP3A5 (tracrolimus PK), CYP2C8/2C9 (phenytoin PK, coumarin PD, indomethacin ductus PD), CYP2C18 (coumarin PD) and CYP2C19 (pantoprazole, omeprazole) were selected. On phase II, signals on GSTM1 (busulfan PK, neuroblastoma PD), NAT1 (neuroblastoma PD), NAT2 (isoniazid PK, neuroblastoma PD, trimethoprim PD), UGT1A9 (acetaminophen PK) or UGT2B7 (morphine PK) were retained. On transporters, OCT1 (morphine, tramadol PK), MRP3 (morphine), ABCG2 (topotecan), ABCB1 (omeprazole PK, tacrolimus PK and PD (nephrotoxicity, infectious complications), leukemia outcome, opioid-induced urinary retention), MRD1 (tacrolimus PK, leukemia outcome) were found. On (post)receptor mechanisms, signals on KCNJ6, OPRM1, PNOC and COMT (opioids PD), vitamin D binding protein (PK and PD), VKORC1 (coumarin), NR1I2 (nevirapine), and TNF and MAPK8 (immune response HBV vaccine, PD) were retrieved.

CONCLUSIONS
This landscaping effort displays a diverse, but fragmented picture of significant signals of PG PK/PD in newborns and infants. How to translate these data to clinical practice remains underexplored.

ABSTRACT NUMBER 12

Efficacy and safety of hydrocortisone to treat hypotension in neonates: A systematic review and meta-analysis

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INTRODUCTION
Recent evidence supports glucocorticoids in the treatment of neonatal hypotension. Inconsistency regarding prescribed dosing regimens to balance efficacy and safety in neonates is of concern.

METHODS
We conducted a systematic review and planned a meta-analysis (MA) to evaluate the effect of (1) hydrocortisone (HC) vs. placebo or vasoactive agents and (2) low-dose vs. high-dose HC on end-organ perfusion and mortality. We searched MEDLINE, EMBASE, CENTRAL and Web of Science from inception to January 2022 for randomized controlled trials (RCTs), non-randomized trials and cohort studies on the use of HC in neonatal hypotension.

RESULTS
We included 8 articles (5 RCTs, 3 cohorts) describing HC in the treatment of hypotension in 1,859 neonates. For end-organ perfusion, in 2 and 4 studies, improvement in blood pressure and reduction in inotropes was statistically significant in HC-treated neonates. In 1 study, mortality or severe bronchopulmonary dysplasia at 36 weeks and mortality at 1 year was statistically significantly higher in HC-exposed neonates. In one other study, mortality was statistically significantly higher in neonates exposed to high- versus low-dose HC. Two cohorts reported a statistically significantly higher occurrence of necrotizing enterocolitis in HC-exposed neonates.

CONCLUSIONS
HC may improve markers of end-organ perfusion in critically ill neonates. Yet, reports of increased mortality among HC-exposed neonates urge caution in decision-making. Next, we will (1) assess risk of bias and evidence certainty and (2) complete an MA on the effect of HC vs. placebo or vasoactive agents on the primary outcomes. Only one study compared high- versus low-dose HC. Thus, we are unable to conduct a meta-analysis for this comparison.

ABSTRACT NUMBER 13

Multicenter prospective validation of a model-based dosing regimen for vancomycin in preterm and term neonates

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INTRODUCTION
Vancomycin is commonly used to treat neonatal late-onset sepsis. Currently used regimens often result in inadequate exposure. A novel vancomycin dosing regimen based on a population pharmacokinetic (popPK) model was implemented in 3 neonatal intensive care units (NICU), as standard of care. The guideline advises a loading dose (16-23 mg/kg), followed by a dose and dosing interval (5-15 mg/kg 3-4 times daily), both depending on postnatal age (PNA), birthweight (BW), and ibuprofen co-administration, to achieve an area under the concentration-time curve (AUC24hours) ≥400 mg×h/L. The objective was to evaluate the popPK model using real-world clinical and therapeutic drug monitoring (TDM) data from (pre)term neonates.

METHODS
374 TDM samples were available from 175 neonates with PNA <29 days. To evaluate the model performance, observations were compared to model-based predictions using NONMEM 7.5 and fixed parameters. Goodness-of-fit (GOF) was assessed using classical diagnostic plots, and GOF plots stratified by quartiles of the included covariates.

RESULTS
Concentrations were adequately predicted by the model, also when stratified by patient demographics even though a slight overprediction was observed in the neonates ≤700g BW and underprediction in case of BW ≥2500g. The newly introduced dosing regimen resulted in target attainment in the first 24h of therapy in 82% of neonates with BW >700g and 30% of neonates with BW ≤700g.

CONCLUSIONS
This multicenter prospective validation based on real-world data supports that this model-based vancomycin regimen with a loading dose, results in adequate early target exposure in most neonates. Based on simulations, a further dosing optimalisation will be developed for the subgroup with BW ≤700g.

ABSTRACT NUMBER 14

Collaboration in Neonatal and Paediatric Clinical Pharmacology: Involving Medical Students Within (Inter)National Clinical Trial Networks

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INTRODUCTION
Between 50 and 96% of drugs prescribed to neonatal and paediatric populations are used off-label, creating a clear need for clinical pharmacology studies and subsequent labelling. Key to the successful future of paediatric drug development is creating a collaborative community of professionals focusing on neonatal/paediatric clinical pharmacology. Offering the opportunity for students to participate in a pan-European project such as conect4children (c4c) may enhance their enthusiasm for the field of neonatal/paediatric clinical pharmacology. The primary objective of the concept is to evaluate the motivations and barriers medical students encounter when volunteering in neonatal/paediatric clinical pharmacology and to evaluate the role their tutors play.

METHODS
A systematic approach to volunteering in this area includes the definition of learning objectives and activities. Conceptual subjects are students and tutors of undergraduate medicine, in the 4th - 6th year, with interest in the field. The c4c Young Investigators Community (YIC) will be used as a platform to interact with established investigators in order to reach the primary objective.

RESULTS
Student activities include taking online training courses such as Good Clinical Practice (GCP), translating documents into local languages, actively participating in national/international meetings, and communicating with other healthcare professionals and/or the general public. Investing into involving a younger generation also aids the sustainability of international and clinical trial networks.

CONCLUSIONS
The concept of medical students volunteering in neonatal and paediatric clinical pharmacology is feasible, motivating for tutors and supports clinical trial network sustainability.

ABSTRACT NUMBER 15

The influence of sepsis on the tissue penetration of piperacillin-tazobactam in children: a microdialysis study in the juvenile pig

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INTRODUCTION
Antibiotics are the cornerstone in the treatment of sepsis. Microdialysis (MD) data from adults suggest an impaired antibiotic tissue penetration in the case of sepsis. Tissue pharmacokinetics (PK) remain largely understudied in children. Juvenile pig models have proven to provide an accurate prediction of PK behavior in pediatric patients. This study aimed to investigate the influence of sepsis on antibiotic tissue penetration in a piglet model.

METHODS
In 17 piglets, piperacillin (PIP) - tazobactam (TAZ) was administered (75 mg/kg IV over 30 minutes, 6h dosing interval) over 4 days. Blood and MD samples (muscle) were collected in first-dose (FD) and steady-state (SS) conditions. In 11 piglets a continuous LPS infusion (36h) was administered to induce a septic state. In the 6 control animals (no LPS) time effects during the study period were evaluated. Non-compartmental PK analysis was used to determine the tissue penetration (AUC-ratio tissue/plasma). The AUC ratios were pairwise compared between the healthy and septic states in each piglet, data are reported as mean ± SD.

RESULTS
For PIP, the AUC ratio in FD conditions was significantly lower in the septic state (0.84 ± 0.22) compared to the healthy baseline measurement (1.06 ± 0.46) (P = 0.042). In SS conditions, comparable results were found with an AUC ratio of 1.09 ± 0.27 during baseline and 0.80 ± 0.22 in the septic state (p=0.009). The results for TAZ were similar to PIP. There were no time effects found in the control group.

CONCLUSION
In this juvenile piglet model, sepsis impaired the PIP-TAZ tissue penetration. The results of this study warrant further research into the tissue PK of septic children to optimize the antibiotic dosing in this population.

ABSTRACT NUMBER 16

The flood of study feasibilities and the value of a centralised approach

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INTRODUCTION
Due to an increase in multicentric paediatric clinical trials after 2007 following the EU Paediatric Regulation, there has been a substantial increase in the number of feasibility questionnaires (FQ). Paediatric clinical trial conduct has made unique advances through the conect4children (c4c) pan-European network, funded by the Innovative Medicines Initiative (IMI2). We examined the role of a national, centralized coordination center in Belgium to pre-fill feasibility questionnaires and quality control responses from sites.

METHODS
This report describes the 4-year learnings of prefilling and performing quality control for FQ by the Belgian Network representative. Additional information has been included from a broad survey sent to sites in the Belgian Network, of which 13 of the 15 sites have responded.

RESULTS
PIs are confronted by between 10 to 50 FQ requests per year, each taking at average 60 minutes. The number of redundant questions asked by sponsors is on average 43% of the FQ. Of the 112 completed feasibilities, approximately 82% required quality control adjustments by our national coordinating center. Inconsistencies were primarily found in PIs' report of experience, number of paediatric studies conducted, recruitment estimates and site qualifications. With a centralized and repetitive collection of FQ, a prefill of 65% of the requested information and potential corrections can be performed. A time reduction of 10 to 46% is estimated when a FQ is facilitated through the national representative.

CONCLUSIONS
The increase in paediatric clinical trials has substantially burdened sites within Belgium. Quality control and adjustments by a national central organization could be beneficial to increase feasibility quality and efficiency.

ABSTRACT NUMBER 17

Development of Pedmed-NL

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INTRODUCTION
High quality paediatric clinical trials are of utmost importance in the quest to improve medicines for children. Since high quality infrastructure is missing in the Netherlands, we aimed to develop a paediatric clinical trial network: Pedmed-NL The Pedmed-NL consortium facilitates paediatric clinical trials with the ultimate goal to realise better medicines for children.

METHODS
First, the academic hospitals were invited to join the Pedmed-NL consortium, followed by other hospitals and patient organizations. Additionally, Pedmed-NL became the Dutch national hub within the pan-European collaborative network conect4children. Support for both investigator as industry initiated clinical trials regarding feasibilities, budgets, IMP, contracting, application to the ethical committee and competent authority, as well as trial coordination has been set up. Pedmed-NL is continuously growing via regular meetings with consortium members, the set up of working groups and the implementation of needs from the field.

RESULTS
Since 2019, we formed a consortium of 18 partners, including all university medical centres, hospitals and patient organization. Pedmed-NL has supported over 100 requests for trial feasibilities, 4 grant applications, 2 applications to the ethical committee and national authority. As c4c national hub, Pedmed-NL supports the proof-of-viability trials of to test the c4c infrastructure.

CONCLUSIONS
Since 2018, Pedmed-NL has developed as a Dutch network for paediatric clinical trials, offering support to both industry and academia and acting as match maker between sponsors and sites.. Pedmed-NL empowers collaborative efforts, promotes harmonization between centres and acts as a direct contact point for researchers and industry.

ABSTRACT NUMBER 18

Paediatric clinical trial needs and requirements within Belgium

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INTRODUCTION
Due to the Paediatric Regulation in 2007, the number of paediatric clinical trials within Europe has substantially increased. Consequently, potential sites for paediatric clinical trials were overrun by trial opportunities, infrastructure pressure and their limited experience. To support sites and facilitate research, the pan-European network conect4children (c4c) was established and funded by the Innovative Medicines Initiative (IMI2). In order to attain sustainable research networks, site requirements innovation needs require further investigation.

METHODS
A questionnaire was conducted within the c4c Belgian Clinical trial network. An inquiry was made into the role of a national hub and other topics for support. Due to multiple responses per site, answers were grouped per site.

RESULTS
Of the 15 connected sites, we received 32 responses coming from 13 unique sites. Within the Belgian network, around 4 (30%) of sites do not have a paediatric clinical trial unit to support trials. All sites agreed or strongly agreed that a national hub is useful for the site to conduct clinical trials. The majority namely 11 (84%) of sites identified human resources as a core improvement need for sites, specifically finding dedicated clinical research nurses and finding time for principal investigators (PI) to perform study tasks aside from clinical work. A strong need for financing of infrastructure from 10 (76%) of sites is acknowledged for consultation areas, imaging, and a biobank structure.

CONCLUSIONS
In order to foster sustainable development of new medicines in paediatric diseases, site need's must to be taken into account and prioritized. The primary need is in human resources and financing of infrastructure.

ABSTRACT NUMBER 19

Clinical, methodological and patient/parent Expert advice in paediatric drug development via conect4children

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INTRODUCTION
Children have the right to new and improved medicines.conect4children (c4c) aims to promote innovative trial design to optimise paediatric development plans while ensuring the voice of young patients and their families is heard. To address this a multidisciplinary advice service was set up

METHODS
A network of Experts, divided into Expert Groups, was set-up via an open call for Experts. In parallel a Patient and Public Involvement (PPI) database was formed to include the expert opinion of paediatric patients and their parents. Advice is given according to the following process: (1) Sponsors contact c4c (2) a scoping interview is held (3) formation of ad-hoc Strategic Feasibility Advice Group (5) an advice meeting is held (6) an advice report is provided. To continuously improve this process, feedback from Experts and requestors on the service was collected

RESULTS
24 clinical and innovative methodology Expert Groups, consisting of >300 Experts, diverse in gender, seniority and geographical location were established. The PPI database includes registrations in 4 subgroups. To date (Dec 2021) 30 advice requests were received from academia and industry and 23 have been completed. Clinical, methodology and PPI Experts participated in several of these requests. Sponsors appreciated the diversity of the Expert Groups as well as the quality of the advice which in many cases significantly contributed to shaping the paediatric development strategy. Experts and PPI participants were satisfied with the advice process

CONCLUSIONS
c4c has shown a successful proof of concept for a European, multidisciplinary, advice service for paediatric drug development, tailored to industry and academia. This service presents a new framework for innovative and feasible paediatric trials

ABSTRACT NUMBER 20

Collaboration in Neonatal and Paediatric Clinical Pharmacology: creating a peer-based mentoring platform in a pan-European clinical trial network

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INTRODUCTION
In recent years, substantial improvements in clinical trial facilitation have been made through a pan-European network conect4children (c4c), funded by the Innovative Medicines Initiative 2. Within c4c, collaboration and experience-based teaching were attainable due to live meetings and structured social interactions. Since the COVID-19 pandemic, meeting platforms were limited and strictly virtual, creating an artificial communication environment and a gap for young talent to interact and learn.

METHODS
In light of c4c's main objective to build strong collaborations and connections between different national clinical trial networks, the younger generation was in need of support. In May 2021, the young investigators community (YIC) platform was launched to facilitate an informal teaching and connecting vehicle. However, interaction with the experienced and leading generation was lacking, in order to mentor the 'starters' for a durable network.

RESULTS
Within the first year, the YIC created an open platform in which the 32 members could interact on a regular basis. Topics included involving medical students, how to build and prepare sustainable business plans and working and interacting with industry partners. Inspired by Erasmus+ funded Pathway project and McBride at al (2017) Mentorship profiling, a 4-page intake questionnaire for both mentor and mentee has been designed, that focuses on specific skills and a plan-of-action for the mentorship session, maximizing efficiency of the interaction.

CONCLUSION
Within YIC, a questionnaire was designed to approach mentor and mentee selection, to be used to minimize the gap between young talent and the established community. The method could be beneficial to other national and international networks.

REAL WORLD DATA / EVIDENCE – ABSTRACTS FROM GUEST SPEAKERS

Real World Data: Industry Perspective

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50% to 90% of medicines used in children are not developed, formulated or licensed for them. The European Medicines Agency sought to improve the situation and introduced the need for all New Chemical Entities (NCE) to be developed for children (where applicable) as part of the granting of an adult licence. But many older medicines are used in children and are not subject to the NCE requirements. In 2007 EMA introduced the PUMA (Paediatric Use Marketing Authorisation) initiative which incentivises companies to develop and licence older medicines. The market size and cost and complexity of development continues to disincentivise bigger pharmaceutical companies from pursuing PUMAs. Proveca was created with the sole focus being the development and licensing of medicines for children mostly via the PUMA route. A PUMA licence requires all the elements of any license and development programmes and can become extensive in terms of both time and cost. This can often mean there is no acceptable investment case and the product development does not progress. Proveca have been using real world data to circumvent the need for prospective efficacy or safety trials in certain circumstances to excellent effect. Awareness of, and access to, real world data sets can make a material difference to the likelihood of more products being developed for children.

ABSTRACT NUMBER 21

Melatonin prescription in children in relation to body weight

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INTRODUCTION
The prescription of melatonin to children and adolescents has increased dramatically in Sweden during the last ten years. Melatonin is recommended for sleeping disorders in children and adolescents as a second line of treatment after non-pharmacological alternatives in national guidelines. In the present study we aimed to evaluate the prescription of melatonin in relation to body weight.

METHODS
The population-based BMI Epidemiology Study cohort has height and weight available from school health care records for school children in the city of Gothenburg, Sweden´s second largest city. Information on melatonin prescription was retrieved through linkage with the National Prescribed Drug Register for individuals in the cohort. We included the first prescription of melatonin for boys who also had a weight measurement not earlier than three months before, or later than six months after the dispensing date, and present descriptive data on the included cohort and tablet dosage in relation to body weight.

RESULTS
We included 562 individuals with mean age 11.1 years (standard deviation [SD] 3.4), mean weight 44.1 kg (SD 19.6) and mean dosage of 2.5 mg (SD 0.93). The individuals in the cohort were prescribed 0.07 mg per kg (SD 0.05), range 0.01-0.48 mg per kg. The included prescriptions represent a first (n=393) or iterated prescription (n=169). Individuals with a first prescription received lower dosage than individuals with iterated prescription ($p<0.004$).

CONCLUSIONS
Melatonin is commonly used in children and adolescents. In the present study we demonstrate that the dosage in relation to body weight displays large variability. More knowledge that can support optimal use of melatonin is needed.

ABSTRACT NUMBER 22

Using real-world data to support rituximab dosing strategies for pediatric patients with frequent-relapsing or steroid-dependent nephrotic syndrome: a prospective pharmacokinetic-pharmacodynamic study

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INTRODUCTION
Rituximab use is now widely recommended for the treatment of frequent-relapsing/steroid-dependent nephrotic syndrome (FRNS/SDNS) in pediatric patients. However, the dosing schedules of rituximab for FRNS/SDNS has not been determined. The objective of this study was to establish a population pharmacokinetic-pharmacodynamic (PK-PD) model of the effect of rituximab on eliminating B lymphocytes when used to treat FRNS/SDNS in pediatric patients, and to investigate dosing regimens that provide adequate suppression of B lymphocytes.

METHODS
A prospective, open-label, single-center study was conducted in Nephrology Department at Children's Hospital of Fudan University, and a two-compartment PK model of rituximab in pediatric FRNS/SDNS has been developed previously by our group. CD19+ lymphocyte count profiles were obtained from these patients. PK-PD analyses were performed describing the life cycle of CD19+ lymphocytes, with rituximab assumed to increase the death rate. Monte Carlo simulation was conducted to evaluate different improved dosing approaches.

RESULTS
In total, 102 measurements of CD19+ lymphocyte counts were available for PK-PD analysis. A turnover model with rituximab stimulatory Emax model best characterized the relationship between rituximab concentration and CD19+ lymphocytes elimination. Emax and EC50 were estimated as 99.6*106/L and 5.87 μg/ml, respectively. Simulations indicated that a single infusion of 750 mg/m2 and 2 infusions of 375 mg/m2 yielded similar 10-week suppression of CD19+ lymphocytes.

CONCLUSIONS
A body surface area-based starting dosing regimen in combination with individualized Bayesian estimation is proposed for the first time to inform rituximab precision dosing in pediatric children with FRNS/SDNS.

ABSTRACT NUMBER 23

Maternal antidepressant use in pregnancy and major birth defects

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INTRODUCTION
Antidepressants (AD) are increasingly used during pregnancy. Several studies have raised concerns about the impact of this exposure on the developing fetus. Our aim was to assess the association between in utero AD exposure and the risk of MBD.

METHODS
In a cohort study using the French national healthcare insurance system database (SNDS), we assessed the association between first-trimester exposure to antidepressants (ATC N06A) and MBD, defined according to EUROCAT classification system. Multiple pregnancies and those exposed to known teratogens or to multiple antidepressants were excluded. Prior maternal AD use was assessed based on data during the year before pregnancy start. We compared the risk of MBD in the offspring of women with first trimester AD exposure (exposed) with the risk in the offspring of women without first trimester exposure but with prior AD use in a propensity score-matched analysis.

RESULTS
Among 2,434,830 pregnancies in our cohort, 79,302 (3.3 %) were not exposed to AD during the first trimester but had prior AD use and 45,349 (1.9%) were exposed to one AD during the first trimester, mainly escitalopram (n=11,911) or paroxetine (n=6,231). A total of 1,161 (2.6%) and 1,909 (2.4%) MBD, mainly limb and cardiac defects, were identified in the offspring of exposed women and unexposed women with prior AD use, respectively. Propensity score-matched ORs [95% CI] for overall MBD vs. women with prior AD use 1.03 [0.94-1.13], respectively. No statistically significant association was found for AD use and cardiac defects.

CONCLUSIONS
Our study shows no difference in overall MBD among the offspring of women exposed to AD during pregnancy, compared to women with prior AD use.

THERAPEUTIC DRUG MONITORING – ABSTRACTS FROM GUEST SPEAKERS

Establishing a National TDM Service in the United Kingdom

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In recent years, a therapeutic drug monitoring (TDM) programme of work has been rolled out by the Newcastle Cancer Centre Pharmacology Group. This is a national clinical study (ISRCTN 10139334) involving the treatment of particularly challenging paediatric oncology patients, including neonates, obese patients and those with renal impairment, across. For these patient groups standard chemotherapy dosing regimens are not appropriate, as they are likely to handle drugs differently from the standard paediatric population, due to differences in drug metabolism and elimination. Inappropriate dosing can lead to over-exposure, which can result in excessive toxicity, or under-exposure which can result in sub-therapeutic treatment and response. The TDM process involves analysis of patient blood samples in real-time, to determine if appropriate drug levels are being achieved. Clinicians can then use this information to adjust doses based on a pharmacological rationale, reducing the high variability in exposures frequently observed in these patient populations. 200 paediatric patients (66% infants) have been recruited onto the study from 16 primary treatment centres across the UK. For many of these patients, multiple chemotherapeutic agents have been measured in plasma samples over multiple cycles of chemotherapy. Data generated to date have been used to inform new national treatment guidelines for a range of tumour types. This study demonstrates the feasibility and potential benefits of TDM for the infant cancer patient. Furthermore, this study provides a framework to facilitate the development of additional TDM services for other drug classes of interest in paediatric patients.

Pitfalls and opportunities for centralized TDM services: A Belgian singe-centre experience

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Therapeutic drug monitoring (TDM) requires a multidisciplinary approach with different stakeholders (nurse, bio-analyst, pharmacist, pharmacologist, pharmacometrician, physician). In recent years, a pharmacist-guided TDM dosing advice service, mainly for anti-infective therapy, has been installed at the Ghent University Hospital, a tertiary hospital in Flanders, Belgium. From this experience, advantages, pitfalls and opportunities for centralized TDM services are being summarized. Together with the previous talk, this talk will serve as a basis for discussion with the audience.

ABSTRACT NUMBER 24

Feasibility of the pragmatic PBPK modelling approach – Towards model-informed dosing in paediatric clinical care

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INTRODUCTION
More than half of all drugs are still prescribed off-label to children. To support off-label dosing, pharmacokinetic (PK) data are needed. Physiologically-based pharmacokinetic (PBPK) models are increasingly used to study PK and guide dosing decisions. We hypothesize that combining existing compound models with a paediatric population model can be used to pragmatically predict paediatric exposure.

METHODS
Seven drugs, with various pharmacokinetic characteristics, were selected (i.e. meropenem, ceftazidime, azithromycin, propofol, midazolam, lorazepam, and caffeine). Simcyp v20 was used to predict exposure in adults, paediatrics and preterm neonates by combining an existing compound file with various virtual populations. Predictive performance was evaluated by calculating the ratio of predicted-to-observed PK parameter values (0.5 to 2-fold acceptance range) and by a visual predictive check.

RESULTS
Overall, model predictions in adults were able to capture clinical observed PK data and confidence in PBPK model performance for predicting PK in this population was therefore considered high. However, predictive performance decreased when predicting PK in the paediatric population, even more so in preterm neonates.

CONCLUSIONS
Pragmatic PBPK modelling in paediatrics is feasible, though the approach is not straight forward as limitations, such as inadequate parameterization with respect to paediatric-specific ADME properties, have been observed. A thorough understanding of the models assumptions and limitations is required, before dose recommendations can be generated for use in clinical practice.
This abstract is based on research funded by the Bill & Melinda Gates Foundation.

ABSTRACT NUMBER 25

Population pharmacokinetics of enteric-coated mycophenolate sodium in children after renal transplantation and initial dosage recommendation based on body surface area

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INTRODUCTION
This study aimed to develop a population pharmacokinetic (PPK) model of mycophenolic acid (MPA) in children who were treated with enteric-coated mycophenolate sodium (EC-MPS) after renal transplantation, and to optimize sampling time points and to recommend initial dosage.

METHODS
Pediatric patients who had undergone renal transplantation and received EC-MPS as immunosuppressing therapy were included. Data on demographic characteristics, biochemical tests, blood routine examinations, MPA plasma concentrations, dosing amount and frequency of EC-MPS and co-administered medications were retrospective collected from the electronic medical records in Children's Hospital of Fudan University from June 2018 to August 2019. Non-linear mixed effect modeling methods were used to develop a PPK model with the data above. Additional data from September 2019 to July 2020 were used to validate the model. Simulations under different dosage regimen were conducted to evaluate the percentage of target attainment (PTA, AUC0-12h 30 – 60 mg·h/L).

RESULTS
Total of 96 pediatric patients aged at 13.3 (range 4.3 – 18.0) years were included in the modeling group. Data from 32 patients aged at 13.0 (range 3.6 – 18.3) years were used to validate the model. A one-compartment model with a double extravascular absorption was developed. Body surface area (BSA) was added as a covariate. Simulations showed that for different dosing regimens the highest PTA is around 50%.

CONCLUSIONS
BSA could affect the AUC of MPA with the administration of EC-MPS. Considering the inflexibility of the dosage form, future development of tablets with smaller amount per unit is warranted to suit the need of younger children.

ABSTRACT NUMBER 26

A comparison of age-banded and weight-based oral paracetamol dosing in hospitalised children

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The British National Formulary for Children contains two dosing strategies for oral paracetamol: age-banded and weight-based. Weight-based is used in our hospital. This study compares dosing strategies in inpatients.

Retrospective analysis over 4 years was undertaken in a single tertiary paediatric hospital. Data was collected from electronic patient records. Patients 3 months to 18 years were included. One measurement per admission was allowed. This was compared the Health Survey England (HSE) and National Child Measurement Programme (NCMP).

Of 161150 admissions it was possible to match weight to 115466 (58287 patients) and height to 18806 (4892 patients). Of 95598 paracetamol prescriptions, doses <10mg/kg occurred in 5427(5.7%) prescriptions and doses >20mg/kg in 691(0.72%) prescriptions. Of the doses <10mg/kg, 1003 were in patients >66.7kg. Applying age-banded doses to all admissions would result in doses <10mg/kg in 20748 (18%) of admissions (13111 patients) and doses >20 mg/kg would occur in 4420 (3.8%) of admissions (2054 patients), most commonly in teenagers. Weight-based dosing (maximum 1g/dose) would lead to doses <10mg/kg in 931 admissions (395 patients).

The potential for inadequate or excessive paracetamol dosing is greater with age-banded doses compared with weight-based doses in hospitalised children. Compared to NCMP and HSE data, obesity is more common in hospitalised children across all ages. Compared to NCMP data, underweight is more common in reception aged hospitalised children but not in year 6. Therefore, atypical body weights are more common in hospitalised children than the general population. A higher proportion of low body weight is seen in young children and teenagers. As a result, age-banded dosing should not be used in hospitalised children.

ABSTRACT NUMBER 27

The relation between the serum trough concentration of paracetamol and pain reduction in preterm and term neonates: a retrospective observational study

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Measuring concentrations of paracetamol could be a strategy to optimize the treatment of pain. It is not known if the serum trough concentration of paracetamol at steady state conditions could predict a decrease in pain scores in preterm and term neonates. Low trough concentration can result in inadequate pain relief. The aim of this study was to determine the association between the serum trough concentration of paracetamol and pain reduction in preterm and term neonates.

In this retrospective observational study a hospital database was used to select neonates who were treated with at least 48 hours of paracetamol intravenously or rectally. Linear regression was performed to determine if serum trough concentration of paracetamol at steady state conditions was a predictor for pain reduction. Pain reduction was defined as the difference between COMFORTneo scores before administration and after the fifth administration of paracetamol.

21 neonates were included for determining the association between serum trough concentration paracetamol and pain reduction. The median (IQR) of serum trough concentration of paracetamol after the fifth dose was 4.5 mg/L (2.7–8.5 mg/L). At steady state conditions the serum trough concentration of paracetamol was not a significant predictor of pain reduction in preterm and term neonates ($p = 0.79$ for preterm neonates and $p = 0.49$ for term neonates).

No association was found between the serum trough concentration of paracetamol at steady state conditions and pain reduction in preterm and term neonates. The absence of a significant association could be due to inadequate trough concentrations paracetamol. Further research is needed to investigate the association between serum trough concentrations paracetamol of ≥ 10 mg/L and pain reduction.

ABSTRACT NUMBER 28

Poor availability of age-appropriate drug formulations in DR Congo: a barrier to switch from intravenous to oral antibiotics in children admitted to Kisantu Hospital

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In children with severe bacterial infection in low-resource settings, switch from intravenous to oral antibiotics is important to reduce nosocomial infections and costs. We report barriers to reliable oral antibiotic administration in children under five admitted to Kisantu hospital (DR Congo) with bloodstream infection. Qualitative observations were compiled during field studies (DeNTS/TreNTS study: NCT04473768/04850677). Antibiotics were procured by the hospital pharmacy and part of routine care.Oral switch mostly relied on Watch antibiotics (ciprofloxacin/azithromycin) due to predomination of multiresistant Salmonella bloodstream infections. Available oral formulations were conventional tablets and powders/granules for reconstitution. Water for reconstitution was rarely sterile and volumes were not exactly measured. Instructions on reconstitution and/or a volume mark on the bottle were missing for some in-country produced antibiotics. Accurate oral dosing was impeded by complex dose calculations and absence of dosing devices. Vomiting after administration suggested poor palatability. Bottle antisepsis was endangered by use of the cap for administration. Treatment compliance suffered from non-affordability.Insufficient availability of age-appropriate antibiotic formulations is a biohazard and driver of inappropriate antibiotic use, fuelling antimicrobial resistance. WHO should integrate antibiotics in pediatric drug optimization and medicine prequalification. National regulatory authorities should adopt stringent specifications for formulations and dosing devices when granting marketing authorizations. To enable safe and effective oral switch in low-resource settings, solid flexible dosing formulations based on age/weight bands of Watch antibiotics are needed.

ABSTRACT NUMBER 29

Antibiotic consumption in asthmatic and non-asthmatic children: a national cohort study

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INTRODUCTION

Antibiotic therapy is not recommended in the treatment of viral-induced asthma exacerbations involving cough, fever and wheeze. The objective of this study was to compare the use and type of antibiotics in children with and without asthma.

METHODS

This is a retrospective cohort study performed between January 2013 and December 2017 using the EGB (Echantillon Généraliste de Bénéficiaires) which is the 1/97th random permanent representative sample of the French national healthcare insurance system database (SNDS). Claims data for all individuals aged from 5 to 18 years' old were retrieved. Children were defined as asthmatic when delivered at least 2 different classes of antiasthmatic drug (R03) over 12 consecutive months and without any delivery in the previous 24 months, and were subsequently matched to 4 non-asthmatic controls on age, sex and area of residence. The rate of antibiotic use during the 2 years following matching was compared between asthmatic and non-asthmatic children using an adjusted Poisson regression model.

RESULTS

Overall, 3,964 asthmatic children were matched to 15,838 non-asthmatic controls. Asthmatic children had a lower socio-economic status and have had more medical consultations and hospitalizations in the year preceeding the matching than the controls. During the 2 years of follow-up, asthmatic children were more likely to receive antibiotics with a relative risk (RR) of 1.81 [95%CI 1.74-1.89] for any antibiotic use and a RR of 1.98 [1.85-2.12] for wide-spectrum antibiotics. Most frequently prescribed antibiotic was amoxicillin in both asthmatic and non-asthmatic children.

CONCLUSIONS

Asthmatic children and adolescents are being prescribed antibiotics more frequently than their non-asthmatic peers.

ABSTRACT NUMBER 30

Development of a comprehensive search query for an in-depth study of scientific literature on paediatric drug use

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INTRODUCTION

Many drugs are used off-label in pediatrics and for the development of off-label evidence-based dose recommendations, scientific literature is essential. As the amount of scientific literature on drug use in pediatrics is growing exponentially, it is a challenge to keep up. Artificial Intelligence (AI)/Machine Learning (ML) software can be used to screen large datasets in an efficient and transparent manner. In this project, we aimed to develop a general search query to create such large datasets of all relevant scientific literature on a specific drug in the pediatric population.

METHODS

Sensitive search queries were created for both PubMed and Embase. We first created a template search term for the drug of interest. Next, we developed a pediatric search term based on predefined search blocks (https://blocks.bmi-online.nl/catalog/58) and a search term to exclude animal studies.

RESULTS

Our final search queries consisted of three parts: 1) drug of interest, 2) pediatrics and 3) exclusion of animal studies. The template search term for the drug contained MeSH or EMTREE terms, for PubMed and Embase, respectively, and titles and abstracts were screened for generic drug names, brand names, and synonyms. The pediatric part contained terms from the search blocks, with the title/abstract search field tag, and MeSH or EMTREE terms for pediatrics and child-specific diseases. To exclude animal studies, we used MeSH or EMTREE terms.

CONCLUSION

We created two search queries to find all relevant scientific literature on drugs used in children. Our next step is to combine, deduplicate and then screen these search results with AI/ML software for their relevancy to support pediatric off-label dose recommendations.
This abstract is based on research funded by Radboud AI.

ABSTRACT NUMBER 31

Prescribing pattern of anti-asthma medication and antibiotics among asthmatic children and adolescents in Manitoba

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INTRODUCTION
Asthma is a chronic heterogeneous condition of the airway and is prevalent in large number of Canadian children and adolescents. Despite the existence of evidence-based treatment strategies, the management of asthma remains suboptimal, and many patients continue to experience 'uncontrolled' asthma. The aim of this study was to describe the prescribing pattern of asthma-related drugs among asthmatic children and adolescents in the province of Manitoba.

METHODS
A retrospective longitudinal cohort study spanning 2013-2017 was conducted using health administrative data from the Manitoba Centre for Health Policy (MCHP). Claims data for individuals, 5-17 years old, having physician confirmed asthma diagnosis and receiving at least one anti-asthma prescription during the study period without its delivery in previous 24 months were analyzed with 2 years follow up.

RESULTS
Among 15030 children and adolescents (8958, 5-11 years; 6072, 12-17 years), 7890 of them were 'occasional users' with only one anti-asthma drug dispensing in first year. Of the remaining moderate (2 dispensing) and frequent users (≥3 dispensing) in first year, 45.53% of them did not receive asthma medication in second year. Short acting β2-agonists (89.3%) and inhaled corticosteroids (50.95%) were the mostly prescribed asthma drug classes among all users in first year. Antibiotic prescriptions particularly broad-spectrum antibiotics was common among moderate and frequent users (70.6%) and mainly for upper respiratory infections.

CONCLUSIONS
Needs for asthma medications are low in first year following asthma diagnosis in children and adolescents and half of them do not use any controller medication. Even among those who do need, almost half don't receive any anti-asthma medication in second year.

ABSTRACT NUMBER 32

Inspiration to mRNA-Based COVID-19 Vaccination: Acute Myocarditis associated with Hepatitis B Vaccine

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INTRODUCTION
There are few reports of human serious adverse events (SAE) after Hepatitis B vaccination.

METHODS
The authors searched the Chinese legal documents database for all SAE with Hepatitis B vaccination from January 2010 to January 2022.

RESULTS
All patients received yeast-derived recombinant hepatitis B vaccine. A total of 7 cases of SAE were documented, including 3 cases of myocarditis (resulted in death), 2 cases of interstitial pneumonia (resulted in death), 2 cases of encephalitis (resulted in a disability). The mean time of onset of SAE was 8.3 ± 4.3 hours after vaccination.

CONCLUSIONS
Patients need to be aware that the second dose of the hepatitis B vaccine is associated with a higher risk of SAE than the first dose. Based on the experience of adverse events of hepatitis B vaccine, we present new insights into the mechanism of myocarditis induced by mRNA-Based COVID-19 vaccine.

ABSTRACT NUMBER 33

First preliminary pharmacokinetic and pharmacodynamic data on alpelisib use in TIE-2 mutated venous malformations

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INTRODUCTION
Extensive venous malformations (VM) are highly morbid (pain, coagulopathy, altered functionality). 10% are resistant to sirolimus (standard care). 70% of VM are due to a TEK mutation encoding TIE2 receptor on venous endothelial cells. This leads to a dysregulated expression of angiogenic factors and altered vascular development. In vitro data suggests that PIK3CA inhibition may be effective in reversing TIE2 overactivation. We hypothesized that alpelisib could improve the condition of patients with refractory VM. We determined PK of alpelisib to guide dosing.

METHODS
Three patients with extensive lower limb VM were treated with alpelisib (Novartis Managed Access Program). Daily oral doses were 50mg in patients <50kg and 100mg in those >50kg. After 6 months , we performed:

- MRI
- Area under the curve (AUC sampling times: 0,0.5,1,1.5,2,3,6 and 8h post-dose).

Non-compartmental PK analysis was performed.

RESULTS
Patients experienced, pain control, improved functionality, dramatic improvement of localized intravascular coagulation and decreased size of the venous lakes on MRI.
Despite relatively similar weight adjusted dosing (1.1-1.7mg/kg/day), high interindividual variability in clearance drives highly variable AUC (5774-22968 ng*h/mL)
The patient with dramatic improvement had an AUC 2.6-4 times higher than the other suggesting a concentration-effect relationship.

CONCLUSIONS
Alpelisib is a promising treatment of VM with TEK mutation. Currently recommended fixed dosing strategy irrespective of weight (2-18 years old: 50 mg daily oral dose) should be changed for individualized dosing.

ABSTRACT NUMBER 34

The impact of age on intestinal CYP3A activity, assessed with the Ussing methodology

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Little is known about the effect of age on intestinal drug metabolizing enzymes (DMEs) in pediatric patients. Many oral prescribed drugs are absorbed into the intestinal barrier where they can be metabolized by CYP3A4. Previous studies suggest that metabolism differs across the age range. The Ussing chamber is an ex vivo system to study metabolism in tissue barriers. Its use for pediatric intestinal pharmacokinetic studies is promising.
This study aims to elucidate intestinal midazolam metabolism by CYP3A4 across the age range.

Fresh small intestinal leftover tissues from both children and adults were collected during surgery. The mucosal layer is used as a barrier inside the Ussing chamber. Midazolam was dosed either on the mucosal or serosal side of the tissue. Metabolism of midazolam was determined by the production of 1OH-midazolam (pmol/cm2). Statistics was performed to compare the pediatric drug metabolism to adults and explore the impact of age. Intestinal samples from 10 pediatric donors (median age: 41 weeks (range: 14 weeks to 5 years) and 5 adults were studied.

In both age groups, more 1OH-midazolam was excreted to the luminal side of the tissue when midazolam was dosed on the mucosal side compared to dosing at the serosal side ($p<0.001$). The total amount of 1OH-midazolam at t=90 min shows an increased trend in pediatric patients compared to adults, however does not show a significant difference (M>S: $p=0.20$, S>M: $p=0.49$). This might indicate higher metabolic activity of CYP3A4 in pediatrics.
We show that it is possible to study CYP3A4 activity in pediatric tissues. In infants and children ex vivo intestinal CYP3A activity appears higher than in adults. More insight into intestinal DME activity can support drug dosing.

ABSTRACT NUMBER 35

Microdosing/microtracer based pediatric drug development

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INTRODUCTION
An overview is given on the use of microdosing/microtracing studies for the safer and faster development of drugs in children. In a microdosing study a very small amount of radiolabelled (often 14C) drug is administered to a human volunteer. Using accelerator mass spectrometry extremely low amounts of the drug and metabolites can be traced and quantified.

METHODS
Several publications show the feasibility of microdose/microtrace studies in the pediatric population, providing insight into the ontogenic differences between all age groups. So far well-known drugs have been used for these studies in children, such as midazolam and paracetamol. Information was generated on the absolute bioavailability, mass balance and metabolite profiles.

RESULTS
In pediatric drug development especially metabolic pathways raise a challenge, as between age groups the expression levels and activity of metabolizing enzymes can differ significantly. In 2019 the FDA released a draft of the “General Clinical Pharmacology Considerations for Neonatal Studies for Drugs and Biological Products Guidance for Industry”. This document includes the recommendation to perform microdosing studies in neonates to assess ontogenic differences in the metabolic pathways compared to older populations.

CONCLUSIONS
The classic approach of developing a drug for the pediatric population is time consuming, as each age class, starting from human adults down to neonates is investigated consecutively. Using a microdosing approach information in all age groups could be generated in parallel without increasing safety risks, when dose linearity for the drug of interest is shown adults. Thereby providing the most accurate “prediction model” for drug behavior at therapeutic levels.

ABSTRACT NUMBER 36

In vitro investigation of Vancomycin-Induced Kidney Injury: Development of a 2D cellular model

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INTRODUCTION
Vancomycin is a glycopeptide antibiotic that targets gram-positive bacteria and is the recommended treatment against MRSA infections. However, it is known to cause kidney injury in children. Vancomycin accumulates in proximal tubule cells but relatively little is known regarding the mechanism of this. We conducted a multiparameter assessment of vancomycin toxicity in a novel human renal cell line, Conditionally immortalised proximal tubule epithelial cells (ciPTECs), to determine if these cells recapitulate vancomycin-induced kidney injury (VIKI) in vitro.

METHODS
Three ciPTEC lines were used (parent ciPTEC, and ciPTECs with upregulated expression of organic anion transporters 1 (ciPTEC OAT1) or 3 (ciPTEC OAT3), to assess the respective involvement of these transporters in vancomycin accumulation. ciPTECs were cultured at 33°c and seeded in 96-well plates at 1×104 cells/well. Vancomycin stocks were prepared in distilled water and administered between 1mM and 10mM for 24hr incubations before cell viability (ATP) and cell cytotoxicity (LDH) assays were performed.

RESULTS
ATP data showed a dose-dependent increase in vancomycin toxicity with 17% cell viability observed at10mM. (EC50=5.6mM) Membrane permeabilization was only observed at 10mM (60% LDH retention), with no change observed at lower concentrations administered. There was no difference in vancomycin toxicity observed between each cell type.

CONCLUSIONS
Our results suggest that ciPTECs recapitulate the nephrotoxicity induced by vancomycin and indicates that OATs are not involved in vancomycin uptake. Here, we established a proof of concept for the use of ciPTECs as a 2D cellular model for VIKI as toxicity was observed after vancomycin administration.

ABSTRACT NUMBER 37

The Inflammation in the Pathology of Patients with Mucopolysaccharidosis

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INTRODUCTION
Mucopolysaccharidoses (MPS) are a group of rare lysosomal storage diseases caused by different enzyme deficiencies that lead to accumulation of glycosaminoglycans (GAGs) in lysosomes and the extracellular matrix. This storage-induced inflammation is a key driver of cytopathology in MPS, and pharmacological immunomodulation can improve brain, cartilage and bone symptoms in rodents. As the approved enzyme replacement therapy cannot stop the progression of CNS involvement and several other symptoms, we develop a rational for personalized treatment to address the unmet clinical need in MPS patients.

METHODS
First, we conducted comprehensive literature reviews on MPS type specific inflammatory immune response and on the safety and efficacy of Adalimumab, Infliximab, Abatacept, Alemtuzumab, Anakinra. Second, by expert consensus top candidates for innovative personalized drug repurposing in MPS patients were identified and ranked.

RESULTS
The key process is the upregulation of toll-like receptor-4 (TLR4) pathway induced by the accumulation of heparan sulfate (HS) in MPS type I, II and III. This and other relevant mechanisms indicate TNF-alpha and IL-1 as most promising targets. Systematic analysis of the clinical pharmacology of all relevant candidates and several expert focus group meetings identified Anakinra, Adalimumab, Cladribine and Abatacept as top candidate's dependent on the individual clinical situation.

CONCLUSIONS
These results provide the rational for individual treatment trials (ITTs) with the aim to evaluate immunomodulatory molecules, repurposed in MPS. Furthermore, they will – together with the results of the ITTs – be utilized for the development of a decision tool for the personalized treatment of unmet clinical needs in these patients.

ABSTRACT NUMBER 38

Prednisolone pharmacokinetics after oral prednisone administration in paediatric patients with kidney transplant

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INTRODUCTION
Glucocorticoids are one of the primary treatments for paediatric kidney transplantation. Dosages remain empirically established while therapeutic drug monitoring could be relevant in terms of efficacy and tolerance. Goals for this study were: 1) to build a population pharmacokinetics (PPK) model of free prednisolone, prednisone active form, in paediatric kidney transplant recipients; 2) to identify covariates accounting for interindividual variability (IIV) of PK parameters; 3) to investigate drug exposure-tolerance relationships.

METHODS
97 samples were obtained from 39 paediatric kidney transplant recipients (aged 3.4 to 17.2 years) in order to investigate prednisone PPK. We selected children receiving oral prednisone as part of their immunosuppressive regimen. A PPK analysis was performed using Monolix.

RESULTS
Large IIV was found as prednisolone was undetectable at H12 for some patients but not at H24 for others. Weight and cyclosporin co-treatment influenced pharmacokinetics. Free prednisolone clearance (CLu) and volume of distribution scaled allometrically for 70 kg were respectively 27.6 L/h and 101 L. Cyclosporin co-treatment decreased CLu by 67%. High blood pressure and new onset diabetes after transplant were associated with free daily prednisolone exposure.

CONCLUSION
This study is the first prednisolone PPK analysis in kidney-transplanted children. Some of the IIV in PK parameters was explained by weight and cyclosporin co-treatment. These data suggest that dosages must be adapted after identifying variability factors to optimize efficiency and limit side effects. A therapeutic drug monitoring in kidney-transplanted children to adjust the dosages may be useful, especially regarding tolerance issues.

ABSTRACT NUMBER 39

Exposure following oral and intravenous amoxicillin in neonates: a population pharmacokinetic analysis

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INTRODUCTION
In neonates, use of oral antibiotics is limited due to lacking evidence on both pharmacokinetics (PK) and adequate exposure after oral administration. Amoxicillin/clavulanic acid covers most causative pathogens of early-onset neonatal sepsis. Adequate therapy with amoxicillin depends on time (T) the free drug concentration (fC) exceeds the minimal inhibitory concentration (MIC) of the pathogen.
Our aim was to describe oral amoxicillin PK in neonates, including bioavailability. Our second aim was to evaluate pharmacodynamics (PD) based on target attainment and to provide dosing recommendations.

METHODS
For this study we combined three datasets on 261 newborns with a median (range) gestational age (GA) of 35.8 weeks (24.9 – 42.4), postnatal age (PNA) of 6.8 days (0 – 55) and bodyweight of 2.6 kg (0.5 – 5). In total 938 plasma samples were used upon 79 oral and 182 intravenous treatments. NONMEM 7.6 was used. A target of 50% fT>MIC was used for dosing recommendations.

RESULTS
A one-compartment model best described amoxicillin PK. An additional non-linear influence of PNA and GA on amoxicillin clearance was identified. For a typical patient the population estimates were 0.046 L/h/kg for Cl, 0.61 L for V and 87% bioavailability. Clearance at a PNA of 5 days was 2.6-fold and 4.7-fold higher in case of a GA of 32 – 37 and >37 weeks, respectively, compared with 24 – 32 weeks. Dosing simulations indicated that the lowest dosage to achieve the target was 50 mg/kg/day (MIC 8 mg/L).

CONCLUSIONS
This first population PK description of oral amoxicillin in (pre-)term neonates provides insights to optimize oral amoxicillin dosing guidelines in neonates. Current oral dosing regimens lead to adequate exposure and may even be reduced and/or administered twice daily.

ABSTRACT NUMBER 40

Predicting Treatment Response to Vancomycin Using Bacterial DNA Load as a Pharmacodynamic Marker in Premature and Very Low Birth Weight Neonates: A Population PKPD Study

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INTRODUCTION
LOS has a high risk of morbidity and mortality among premature and VLBW newborns. Whilst positive blood cultures are the gold standard for the diagnosis and subsequent treatment of sepsis, this is time-consuming and results in suboptimal antibiotic treatment regimens. The objective of the present study was to investigate whether treatment response to vancomycin could be quantified using BDL based on RT-qPCR.

METHODS
VLWB and premature neonates with suspected late-onset sepsis were included in a single-centre, observational study. Serial blood samples were collected for measurement of BDL and vancomycin concentration (t=0, 1, 2, 4, 8, 12, 24 and 48h). BDL were measured with RT-qPCR, whereas vancomycin concentrations were measured using LC-MS. A population PKPD model was developed with NONMEM software.

RESULTS
28 patients with LOS that were treated with vancomycin were included. A total of 94 vancomycin concentrations and 103 BDLs levels were available. A one- compartment model with PMA and serum creatinine was used to describe vancomycin PK. In 12 patients there was no decrease in BDL over time. Close inspection of the clinical records explained the underlying mechanism of the lack of effect. In 16 patients time profiles of BDL were described with a PD turnover model. The relationship between vancomycin concentration and the increase in first-order BDL elimination was described with a linear effect model. The slope of this model increased with rising PMA.

CONCLUSIONS
BDLs determined through RT-qPCR could be predicted with the population PKPD model. Our findings demonstrate that using RT-qPCR, treatment response to vancomycin may be evaluated as early as 4 hours after treatment initiation, allowing early assessment of efficacy of vancomycin in LOS.

ABSTRACT NUMBER 41

Physiologically based pharmacokinetic model to simulate midazolam pharmacokinetics in a paediatric US population

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There has been a lot of academic and regulatory interest regarding bridging clinical trials between different populations. The aims of this study were to:

1. Develop a PBPK model for the US paediatric population (USPP) incorporating demographic and CYP3A5 phenotype frequency of different ethnic groups (White, Hispanic, Black and Asian).
2. Apply the USPP to predict midazolam pharmacokinetics (PK) of a clinical study performed in the US.

Demographic information, height for age and weight for height relationships, and CYP3A5 phenotype frequencies were established for each US ethnic group using NHANES and literature data. Four separate US paediatric PBPK populations were defined within the Simcyp Simulator (v21).

Simulations of IV and oral midazolam PK were made in the USPP and a North European paediatric population (NECP) and compared with the clinical study. The reported trial design was matched as closely as possible and 400 subjects, 0.5 female, age 0.5 to 16y were run for each population.

For a 0.25mg/kg oral dose, the predicted AUC0-inf was 143±109 and 225±136 ng/ml.h and Cmax was 57.4 and 79.4ng/ml for the USPP and NECP, respectively. The observed AUC0-inf and Cmax was 137±86 ng/ml.h and 55.6ng/ml, respectively. The predicted AUC was 195, 115, 150 and 135 ng/ml.h for the White, Black, Hispanic and Asian USPP and Cmax was 72, 48, 58 and 54ng/ml, respectively.

Prediction of midazolam PK was improved by including the different ethnic groups for the USPP. However, significant differences can be observed between these groups for drugs where elimination changes due to phenotypic enzyme expression (e.g. CYP3A5) and it is important that clinical studies present this information.

ABSTRACT NUMBER 42

Favipiravir pharmacokinetics in immunocompromised infants and children with chronic RNA viral infections

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INTRODUCTION
Favipiravir selectively inhibits RNA polymerase responsible for single-stranded viral replication. It is licensed for treating influenza and repurposed to treat other diseases such as Ebola and COVID-19. It is metabolised by hepatic aldehyde oxidase (AO) and is an AO inhibitor with complex pharmacokinetics. We have used favipiravir, in combination with other antivirals, in severely immunocompromised children with life-threatening RNA virus infections. As an unlicensed indication, favipiravir pharmacokinetics were routinely monitored at our institution. Population pharmacokinetic model is used to describe the favipiravir pharmacokinetic properties, drug exposure and sources of variability in these children.

METHODS
Routine favipiravir plasma levels of 9 patients (0.8-11yrs, mean age=5.3yrs; median weight=15kg) were analysed retrospectively (62 samples). All patients received favipiravir 200mg or 400mg tds and had at least one plasma level 45min (peak), 3h and 8h (trough) post-dose. Parameter estimation and model simulation properties (visual predictive check) were assessed using R language (v 4.1.2) and RStudio (2022.02.0+443).

RESULTS
A one-compartment model with weight as covariate best describes the data, with (1) elimination clearance=1L/h and volume of distribution=7.54L, both allometric scaled centring at median weight, and (2) estimated t1/2=5.17h with Cmax = 24µg/mL at 200mg and 41µg/mL at 400mg.

CONCLUSIONS
To our knowledge this is the first report of favipiravir pharmacokinetic parameters in infants and young children. Weight significantly improves the model fit as a covariate. Reported EC50 for norovirus in vitro was 19–39µg/mL and enterovirus 71 was 23µg/mL, indicating higher favipiravir doses or combination with other antivirals are required.

ABSTRACT NUMBER 43

Plasma renin activity in young children with heart failure: Influence of age, disease and ACE inhibitor treatment

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INTRODUCTION
Increased plasma renin activity (PRA) levels may have various causes: PRA has gained importance as prognostic marker for patients with heart failure; age may have an influence on endogenous PRA levels; and ACE inhibitor (ACEi) treatment can also interfere with PRA levels. We aimed to investigate PRA levels in very young children with heart failure, with and without ACEi treatment.

METHODS
As part of a PK-PD study of enalapril for pediatric heart failure (LENA studies), blood samples were collected and analyzed for PRA levels before, 4 hours after and within the first week of enalapril treatment. In addition, a literature search was conducted according to the PRISMA concept in MEDLINE to identify studies on PRA levels in healthy children as well as in children with heart failure in the age range from 1 day up to 2 years. Comparison was performed with LENA study data and with data from 9 healthy volunteers.

RESULTS
Infants from LENA studies with heart failure (n= 35, aged 25 days – 2.1 years) had median PRA levels of 19.7 (n=35) before, 29.0 (n=34, $p>0.05$) 4 hours after enalapril dose, and 89.1 ng/mL/h (n=29, $p<0.01$) after 5 days of treatment. Literature search revealed mean PRA levels in healthy children between 2.3 to 29.8 (n= 14 studies) and 10.0 to 87.1 ng/mL/h in ACEi naïve heart failure children (n= 4 studies). PRA levels of 9 healthy adults ranged between 0.13 to 1.85 ng/mL/h.

CONCLUSIONS
Very young children had higher endogenous PRA levels compared to adults. Heart failure at this age was associated with even higher PRA levels and ACEi treatment further increased PRA levels. These results indicate that patients appear to respond to ACEi treatment but question the value of PRA levels as prognostic marker in this population.

ABSTRACT NUMBER 44

Medical Cannabis for the Treatment of Comorbid Symptoms in Children with Autistic Spectrum Disorder: An Interim Analysis of Biochemical Safety

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INTRODUCTION
Autistic Spectrum Disorder (ASD) is a common neurodevelopmental disorder and no effective treatment for the core symptoms is currently available. The present study is part of a larger clinical trial assessing the effects of cannabis oil on autism co-morbidities.
The aim of the present study was to assess the safety of a CBD-rich oil treatment in children with ASD.

METHODS
Data from 59 children and young adults (ages 5-25 years) from a single-arm, prospective, open-label, one center, phase III study was analyzed. Participants received medical cannabis extract oil with a CBD:THC ratio of 20:1 for six months. Blood analysis was performed before treatment initiation, and after 3 months. Complete blood count, glucose, urea, creatinine, electrolytes, liver enzymes (AST, ALT, GGT), bilirubin, lipid profile, TSH, FT4, thyroid antibodies, prolactin, and testosterone measurements were performed at baseline, prior to starting treatment and at study midpoint, after three months of treatment.

RESULTS
59 children (85% male and 15% female) were followed for 18± 8 weeks (mean ±SD). The mean total daily dose was 7.88±4.24 mg/kg body weight. No clinical or statistically significant differences were found in any of the analytes between baseline and 3 month follow up. A comparison of patients who received additional medications (n=14), to those who solely received medical cannabis (n=45) showed no differences in biochemical tests.

CONCLUSIONS
CBD-rich cannabis oil (CBD: THC 20:1), appears to have a good safety profile. Long-term monitoring with a larger number of participants is warranted.

ABSTRACT NUMBER 45

Antipsychotics use and weight gain in children compared to adults: analysis of spontaneous adverse drug reaction reports

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INTRODUCTION
Weight gain and obesity are common adverse effects of antipsychotics (APs). We aimed to assess AP-induced weight gain in pediatrics compared to adults.

METHODS
In a case-non case study using the WHO global database of individual case safety reports (ICSRs), VigiBase®, we evaluated the existence of disproportionality in weight gain reporting under antipsychotic treatment in children and adolescents compared to adults. Disproportionality of weight gain reporting was evaluated using the reporting odds ratio (ROR) with corresponding 95% confidence intervals (95%CI). Analysis was adjusted for sex, reporting country, year of notification, reporter qualification and concomitant use of antidepressants (ADs) and lithium.

RESULTS
A total of 282,224 ICSRs reported with an AP were retrieved: 6,446 (2.3%) in children, 14,112 (5%) in adolescents and 261,666 (92.7%) in adults. In children, 1,544 (24%) of ICSRs reported weight gain, 1,831 (13%) in adolescents and 13,506 (5.6%) in adults. Most weight gain cases concerned male patients (55%) and were reported by health professionals (47%) in North America (54%) and Europe (27%). Concomitant use of ADs and lithium was reported in 36% and 3.5% of weight gain cases overall. Disproportionality of weight gain reporting associated with APs was found in adolescents (adjusted ROR: 2.3 [95%CI 2.1-2.4]) and in children (aROR: 3.6 [95%CI 3.3-3.8]) compared to adults. Use of risperidone was associated with the highest increase in weight gain reporting in children (aROR 4.9, 95%CI 3.9-6.1) and adolescents (aROR 3.6, 95%CI 3.1-4.1).

CONCLUSIONS
Children and adolescents are at higher risk of reporting weight gain under APs than adults.

ABSTRACT NUMBER 46

Stimulant drug use in children before six years of age and antipsychotic add-on therapy: a population based longitudinal study

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Stimulant drugs, such as methylphenidate and amphetamine, are frequently prescribed to children at early school age for treatment of attention-deficit hyperactivity disorder(ADHD). Stimulant drugs enhance dopaminergic neurotransmission, a major contributing factor in the development of psychosis.

To characterize the pattern of stimulant use in children and adolescents up to the age of 19 years and determine their requirement for antipsychotic drugs in relation to frequency, age at onset and local health area (urban/rural) of stimulant use.

Children having been on stimulants for at least one year and with ADHD diagnosis were identified. We conducted Kaplan Meier estimates of the rates of antipsychotic add-on. The cohort was stratified by their frequency of stimulant use, age at first prescription of stimulants, and by their local health area. Cox regression was fitted for both unadjusted and adjusted models. Hazard ratios and 95% CI were presented for each included covariate.

14,924 patients have met the inclusion criterion in our cohort study. The mean age of starting stimulants is 9.9 years(sd=3.8). While stimulant use remains low under the age of 5, we find a sudden increase before the age of 6 years, at the period when children enter elementary school. After using stimulants, the average time up to antipsychotic add-on is 5.9 years(sd=4.5). In the adjusted Cox regression model, patients who started stimulants close to school age, were 88% more likely to have antipsychotic add-on than those started above 6 years of age.

Children starting stimulant use < 6 years of age are more than 8x more likely to require an antipsychotic medication later on. Rural areas have more antipsychotic add-on, likely due to fewer mental health services available for children.

ABSTRACT NUMBER 47

Point Prevalence Study of Paediatric Polypharmacy

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INTRODUCTION
Paediatric polypharmacy is defined as two or more medicines, which is lower than the definition in adults (>5 medicines). A recent scoping review of paediatric polypharmacy found a mean prevalence of 39.7% with a large range from 0.9% to 98.4%.

METHODS
Prescribing data from 85 active practices across Liverpool Clinical Commissioning Group (CCG), was extracted on the 6th January 2021 to include all patients below 18 years of age. Prescribing data was also obtained for Alder Hey Children's Hospital from the electronic prescribing system, Meditech on the 12th January 2021. Descriptive analysis was performed.

RESULTS
Of the 110,097 CYP registered in primary care, 17,271 (16%) were prescribed >2 medications, 3,507 (3·2%) >5, 715 (0·7%) ≥10, and 202 (0·2%) ≥15. The median number of CYP prescribed ≥10 and ≥15 medications per primary care practice was 7 (range 0-34) and 2 (range 0-11), respectively.
Within Alder Hey Children's Hospital, 139 inpatients were identified, with 126 patients (91%) prescribed two or more medicines. The most frequently prescribed medicine was paracetamol. When 'as required' and 'one off' medicines were removed, omeprazole was the most frequently prescribed medicine.

CONCLUSIONS
Many children within Liverpool CCG meet the definition for paediatric polypharmacy. Further research is required to assess the consequences of paediatric polypharmacy and address its management which is under recognised and underrepresented in the literature to date.

ABSTRACT NUMBER 48

Introduction of the project of the Czech drug database in neonatology and pediatrics in 2022

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INTRODUCTION
Evidence-based (EB) data on various medicaments and safe drug dosing in pediatric population are already available across Europe. However, their systematic translation and clear processing are lacking in daily pediatric clinical practice in the Czech Republic. The purpose of our work is the development of a Czech drug database similar to some already existing internationally based formulary lists.

METHODS
A systematic approach to the processing of recommended dosages of drugs used in the Czech environment, all compiled in the Czech language. The active substances will be arranged according to the ATC classification system. The strategy of the initial focus on the most commonly used drugs is set (the statistical data will be obtained from SÚKL), more rarely used drugs will be approached subsequently. The server-side system will be based on PHP and MySQL technologies, enabling easy scalability and deployment to a wide range of servers, including the ability to deploy to scalable servers with a load balancer front-end server.

RESULTS
In 2022, the Czech team managed to obtain support for the creation of a database called Gama 2 project TP01010040, supported by The Centre for Knowledge and Technology Transfer of Charles University (EudraCT#). As expected, the database will be developed in the most appropriate data processing framework and validated throughout the year.

CONCLUSIONS
The Gama 2 database project aims to extrapolate strictly EB data systematically processed according to ATC groups into the Czech environment, where it will become a unique reference for safe prescribing, dispensing and administration of drugs in pediatric population. When processed in the Czech language, this might be beneficial for healthcare providers in Czech medical facilities.

ABSTRACT NUMBER 49

Risk factors of augmented renal clearance in critically ill children using iohexol clearance for renal function assessment

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INTRODUCTION
Augmented renal clearance(ARC) of hydrophilic drugs is frequent in PICU patients and warrants adjustment of standard dosing regimens to prevent therapeutic failure. Knowledge of patient-, disease- and therapy-related factors associated with ARC, would allow to predict before the start of treatment, which patients would benefit from higher drug doses. We aimed to identify predictors of ARC in critically ill children with normal serum creatinine(Scr) using iohexol plasma clearance (CLiohexol) to quantify renal function.

METHODS
We performed a post hoc analysis of data collected from an interventional study conducted at our academic PICU, which measured glomerular filtration rate (GFR) by CLiohexol in patients with normal Scr. ARC was defined as GFR exceeding normal values for age plus 2 standard deviations. Multivariable logistic regression analysis was performed to identify predictors of ARC.

RESULTS
GFR was measured in 85 patients, median age was 16 [IQR 5;89] months, 59% had a surgical profile. Median CLiohexol was 122[IQR 75;152] ml/min/1.73m2. Fourthy patients out of 85 (47%) expressed ARC. Postoperative status was identified as independent predictor of ARC (p=0.014, OR 4.253, 95%CI 1.338–13.517). However, in patients after cardiac surgery the odds of developing ARC were significantly lower (p=0.010, OR 0.163, 95%CI 0.041 –0.644). There was a trend suggesting more ARC in male patients and in those without need for vaso-active drugs, however, this was not statistically significant.

CONCLUSION
Our findings raise clinicians' awareness about ARC potentially being present in children after major surgery. This knowledge allows to anticipate on enhanced elimination of drugs by using empirically adjusted dosing regimens immediately from the start of treatment.

ABSTRACT NUMBER 50

Off-label, but on-evidence? A review of the evidence of pediatric pharmacotherapy.

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INTRODUCTION
In pediatrics, many drugs are still prescribed off-label. Off-label drug use is related to an increased risk of adverse drug reactions (ADR) , which in turn is inversely related to the level of evidence supporting the off-label prescriptions. However, a systemic overview of the level of evidence pertaining off-label drug use in children is lacking. This study investigates the level of evidence for all dosing recommendations in the Dutch Pediatric Formulary (DPF).

METHODS
For each drug, indication and pre-specified age group combination in the formulary – defined as 'record'–the authorization status was evaluated. Next, for off-label records the highest available level of evidence defined by the evidence-based medicine methodology was scored.

RESULTS
A total of 774 drugs were analyzed comprising a total of 6,426 records. 58% of all records represent authorized use, from 110 records (30%) in preterm neonates to 1,630 records (64%) in adolescents. Overall, the quality of evidence for off-label use is low. Only 14% of all off-label records are supported high quality evidence defined as systematic reviews or RCTs. For 37% of all off-label records, no substantiating studies are available, only consensus of the professional group.

CONCLUSIONS
It is often argued that off-label use of drugs is only justified when it is supported by a high level of evidence. Our study refutes this assumption showing that the underlying level of evidence pertaining off-label drug use in children is low across ages and drug classes. This puts children at an increased risk of therapy failure and toxicity. Our data identify the drugs and therapeutic areas for which clinical evidence is clearly missing and could therefore drive the global research agenda.

ABSTRACT NUMBER 51

Paediatric Medication Error Prevention (PMEP) A tripartite alliance working together

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Prescribing and medication administration errors are common themes in Paediatrics. We observed an increasing trend of errors in our ward and assessment area. We undertook an audit to quantify errors within our department as per the EQUIP criteria suggested by the General medical council. A zero-tolerance approach was undertaken, and all errors from minor to severe were recorded. An alarming 90% of admissions within the audit period had minor to significant errors recorded in the initial audit. With the zero-tolerance approach, minor errors with no harm to life were also recorded.

Previous research has suggested that good quality care depends upon different professions working together. We created a tripartite alliance involving nursing, pharmacy and medical teams. Our primary aim was to reduce medication prescription and administration errors by at least 10%. The small incremental change target was made in line with the quality improvement principles. We placed education at the heart of the change process, and the programme involved no costs apart from the time invested by the team.

As a result, medication errors have been substantially reduced over the last five years, and education has been at the heart of the change process. The group has achieved change that is sustainable and prudent in design. We aligned staff, method and delivery to minimise avoidable harm and promoted co-production with patient involvement in educating staff about the impact of such errors. Working together as a team involving all three disciplines has helped us understand and modify practices that have led to an overall reduction in medication errors. We would like to share our change model that has influenced consistent and reliable results over several audit cycles.

ABSTRACT NUMBER 52

What domains related to medicines were measured in studies of burden of care for paediatric patients? A systematic review

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INTRODUCTION

Medicines are becoming increasingly common for all populations and polypharmacy has been shown to have numerous risks. Although primary studies and reviews have explored the impact of medical conditions on patients and caregivers, there are no known reviews on the impact of medicines on paediatric patients. This systematic review therefore aimed to determine the domains commonly assessed in studies assessing treatment burden in different conditions for paediatric patients and their caregivers.

METHODS

Searches were conducted on Medline, CINAHL, EMBASE, Web of Science and Cochrane Database of Systematic Reviews to find relevant papers. Two reviewers independently screened the papers based on the chosen inclusion and exclusion criteria. The quality of the papers was assessed independently by two reviewers using the Newcastle Ottawa Scale. This review was registered with PROSPERO (PROSPERO registration number: CRD42021285097) and conducted according to PRISMA methodology.

RESULTS

6 papers with 8276 participants were identified in this review. The domains most commonly assessed were the perceived effectiveness of medications (4/6 studies), psychosocial impact (3/6 studies) and the impact on work and school (3/6 studies). Other domains included the ease of use of medicines, side effects from medicines, adherence to medicines, time requirements, costs, using healthcare resources and support from family/friends/organisations.

CONCLUSIONS

Studies assessing the burden of care due to medicines assessed a range of domains related to the impact of medicines on patients and caregivers. The results from this review will be used create a questionnaire for a cohort study that aims to determine the impact of polypharmacy on paediatric patients and their parents.

ABSTRACT NUMBER 53

Utilization of and Barriers to Individual Treatment Trials in Mucopolysaccharidosis – Interim Results of an Expert Survey

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INTRODUCTION
Mucopolysaccharidoses (MPS), comprise a group of rare chronically debilitating metabolic diseases and associated with reduced life expectancy and a substantial unmet clinical need. Current research directs towards a number of new treatment targets and strategies. Individual treatment trials (ITT) could make these options rapidly available to patients. Based on scientific publication, this is hardly used. We assess the utilization of and relevant barriers to ITT in MPS as well as potential solutions.

METHODS
Phase 1 was done with 5 international top experts. After this interim analysis, the survey will be rolled out to a broader group of experts.

RESULTS
Five MPS experts from Austria, Brazil, Germany and Italy have been enrolled. In total these clinicians manage about 350 MPS patients. Only three experts ever ran 1-3 numbers of ITT in MPS patients, solely MPS type II (n=2) and VI (n=1), summing up to a total of five ITTs, which is about 1.4% of their patients. The treatments used in ITTs comprise Montelukast, THC, Curcuma and a viral vector with transgene. As barriers for a wider use of ITTs, the im-practicability for implementation (n=1) and the insufficient training in ITT (n=1) have been indicated. All experts consider it highly likely that a decision analysis tool increases the use of ITT in MPS.

CONCLUSIONS
ITT are used in about 1% of MPS patients. This seems extremely low, considering the commonness of off label use in children with severe conditions, the high unmet medical need in MPS and the number of research results, which indicate various promising repurposing strategies. This interim analysis already demonstrates several relevant barriers and high potential of the planned decision framework tool to overcome this.

ABSTRACT NUMBER 54

The impact of paediatric dose range checking software

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Dosing errors can cause significant harm in paediatric healthcare settings.

Our objective was to investigate the effects of paediatric dose range checking (DRC) clinical decision support (CDS) software on overdosing-related outcomes.

A before-after study and a semi-structured survey of prescribers was conducted across inpatient wards (excluding intensive care) in a regional children's hospital. DRC CDS software linked to a paediatric drug formulary was integrated into an existing electronic prescribing system.

The main outcome measures were; the proportion of prescriptions with overdosing errors; overdosing-related clinical incidents; severity of clinical incidents; and acceptability of the intervention.

The prescription overdosing error rate did not change significantly following the introduction of DRC CDS software: in the pre-intervention period 12/847 (1.4%) prescriptions resulted in prescription errors and in the post-intervention period there were 9/684 (1.3%) prescription overdosing errors (n=21, Pearson X2 value=0.028, p=0.868).

However, there was a significant trend towards a reduction in the severity of harm associated with reported overdosing incidents (n=60, Mann-Whitney U value=301.0, p=0.012).

Prescribers reported that the intervention was beneficial and they were also able to identify factors that may have contributed to the persistence of overdosing errors.

DRC CDS software did not reduce the incidence of prescription overdosing errors in a paediatric hospital setting but the level of harm associated with the overdosing errors may have been reduced. Use of the software seemed to be safe and it was perceived to be beneficial by prescribers.

ABSTRACT NUMBER 55

mHealth Diabetes Apps for the delivery of Pharmaceutical Care and inter-professional point of care communication in adolescent Type 1 Diabetes Mellitus patients

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INTRODUCTION
Adolescents with type 1 diabetes mellitus (T1DM) require interdisciplinary-team monitoring to achieve glucose control and avoid complications. Diabetes apps have shown benefits in T1DM management. Germany recently introduced the mHealth legal framework (DiGA) to allow app-prescribing and reimbursement. For patient´s outcomes and drug safety, mHealth apps should support pharmaceutical care services and to allow inter-professional point of care communication.

METHODS
Pharmacists evaluated 4 digital diabetes apps: Esysta, Diabetes:M, mySugr, and One-Touch Reveal, using four sets of anonymized real T1DM patient data. In total 25 apps-evaluation criteria were defined. Twelve criteria were chosen according to pharmaceutical care services such as insulin dose and adherence, as well as interoperability with other devices or software (8 criteria).

RESULTS
All four diabetes apps fulfilled at least 19 of the 25 selected criteria. Concerning pharmacists' relevant aspects, mySugr and OneTouch Reveal met 11 out of 12, Diabetes: M 10 out of 12, and Esysta 8 out of 12 criteria relevant to pharmaceutical care. Regarding interoperability with other devices or software, Esysta and Diabetes:M met 6 out of 8 criteria, and mySugr and OneTouch Reveal 5 out of 8 criteria. Direct communication between patients and pharmacists was not provided by any app.

CONCLUSIONS
mHealth diabetes apps provide useful features for pharmaceutical care services in diabetes patients. Yet, none of the apps allowed communication by pharmacists to interact directly with patients and/or physicians. To enable patients to benefit from pharmaceutical services and to provide an inter-professional point of care communication, mHealth apps should provide a customized version to include pharmacists.

ABSTRACT NUMBER 56

Rapid drop in midazolam concentration may be linked to paediatric delirium in critically ill children – an observational pilot study

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INTRODUCTION
We sought to detect a relationship between midazolam concentration and development of new delirium in critically ill children who were on continuous midazolam administration.

METHODS
Delirium was detected using the Sophia Observation withdrawal Symptoms - Paediatric Delirium (SOS-PD) score and 104 left-over samples were available to measure midazolam concentrations.

RESULTS
Twenty-five percent of the included patients developed new delirium. Median cumulative midazolam dose was higher in patients who developed delirium compared to those without delirium but lower compared with the day preceding delirium detection, indicative of a rapid decline. Similar findings were made when active metabolites 1-hydroxymidazolam and 1-hydroxymidazolam glucuronide were considered.

CONCLUSIONS
A sudden and significant reduction in midazolam concentration may contribute to the development of a delirium in critically ill children.

ABSTRACT NUMBER 57

Off-label use of drugs in paediatric (specialised) outpatient clinics – what has changed between 2009 and 2019?

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INTRODUCTION
Off-label use is still inevitable for paediatric drug treatment. The aim of this study was to analyse the licensing status of drug prescriptions in German paediatric (specialised) outpatient clinics and to determine changes over a 10-year time course.

METHODS
Cross-sectional, retrospective, monocentric studies were conducted in 2009 and 2019 to assess drug prescriptions regarding their licensing status in 10 (one general and nine specialised) outpatient clinics in Germany. Prevalence and relative frequency of off-label prescriptions were calculated, reasons for off-label prescribing analysed and logistic regression performed to determine influencing factors.

RESULTS
751 prescriptions of 296 patients in 2009 and 1438 prescriptions of 786 patients in 2019 were examined and classified according to their licensing status. Relative frequency of off-label prescriptions was around 45% without significant change over that decade. Prevalence of off-label prescriptions was 60.1% in 2009 and 53.1% in 2019 and therefore significantly higher in 2009 ($p=0.037$). The number of prescriptions per patient was significantly higher in 2009 (2.5 ± 2.3 vs. 1.8 ± 1.5, $p<0.000$), too. Comparison revealed the same high-ranking reasons in every study: off-label use due to indication, overdosing and missing paediatric information.

CONCLUSIONS
Off-label prescribing still plays an important role in clinical daily routine in paediatrics. Despite numerous regulatory efforts and incentives, no substantial reduction in off-label prescribing could be determined since 2009. Further efforts are needed to generate more evidence-based knowledge about paediatric pharmacotherapy and to treat children as best as possible.

ABSTRACT NUMBER 58

Attitudes of children and young people and their parents towards polypharmacy – pilot study

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INTRODUCTION
A recent survey of healthcare professionals found that healthcare professionals concerns about patient and family anxiety was the main barrier to deprescribing. However, the attitudes of families, children and young people (CYP) have not previously been sought.

METHODS
A questionnaire was designed to assess the attitudes of CYP and their parents towards polypharmacy and deprescribing based on a previously validated adult questionnaire (rPATD). Initial review and modification took place following input from a young person patient and public involvement group and a content evaluation panel of experts. Ethics approval was obtained, and a maximum of 22 participants (10% of the total study population) were to be recruited for the pilot. Inclusion criteria were CYP taking >2 for 28 days or more. The questionnaire was completed online using Microsoft Forms. Descriptive analysis was undertaken.

RESULTS
Twenty participants completed the piloting process (12 parents, 5 CYP aged 10-15 years and 3 CYP aged 16-17 years), as saturation was achieved. The mean number of medicines taken was six. Most parents (67%) thought their children were taking many medicines, whereas only 38% of CYP agreed with this. Only one CYP in the 10-15yrs stated they wanted to be involved in decisions about their medicines, whereas all of the CYP in the 16-17yrs cohort, and 92% of parents, said they liked to be involved. Overall, 83% of parents and 63% of CYP stated they would like to try stopping one of their medicines if it was advised by a doctor.

CONCLUSIONS
The pilot data would suggest that CYP and their parents would be happy to consider stopping one of their medicines if advised to do so but data from the full study, which is currently recruiting, and statistically powered is awaited.

ABSTRACT NUMBER 59

What is known about the pharmacology of intramuscular therapeutics in Duchenne Muscular Dystrophy? A Systematic Review

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INTRODUCTION
In 2018 the Centers for Disease Control published updated Standards of Care for Duchenne Muscular Dystrophy – newly included was the recommendation for all patients with DMD who received steroids to receive prescriptions for intramuscular (IM) hydrocortisone for emergency administration at home.
The aim of this systematic review was to assess the current understanding of the pharmacodynamics and kinetics of intramuscular therapies in patients affected by DMD.

METHODS
A systematic review was conducted according to Cochrane methodology. Medline, EMBASE and PubMed databases were searched. Two independent reviewers reviewed the abstract of each identified paper. Where there was any discrepancy in the decision to include or exclude a paper, a third reviewer arbitrated.

RESULTS
The search returned a total of 98 papers. 96 papers were excluded: 61 described animal or in-vitro studies, whilst the remaining studies did not study an intramuscular pharmacological intervention or were review articles.
Of the two included articles, one compared the immunogenicity of intramuscular and subcutaneous administration of influenza vaccination, and the other studied ten patients with DMD who were injected with two different doses of plasmidic DNA. Neither study reported on the pharmacodynamics or kinetics of the interventions.

CONCLUSIONS
There is very limited evidence into the pharmaco-kinetics and -dynamics of IM therapies for children affected by muscular dystrophy. Given the recognised changes in the muscle structure and function, studies to explore if this causes clinically significant changes in boys with DMD are required.

ABSTRACT NUMBER 60

Mapping Variation between National and Local Clinical Practice Guidelines for Acute Paediatric Asthma from the United Kingdom and the Netherlands

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INTRODUCTION
Increasingly, hospitals rely on local clinical practice guidelines (CPGs) alongside national guidance to standardise clinical care. This study examines variation between national and local CPGs, using the example of acute paediatric asthma (APA) CPGs from the United Kingdom and the Netherlands.

METHODS
Fifteen British and Dutch local CPGs were collected with the matching national guidance for the management of APA. The drug sequences, routes and methods of administration recommended for patients with severe APA were represented. Deviations from national guidance were measured. Variation in recommended doses of intravenous salbutamol was examined. CPG quality was assessed using the AGREE II instrument.

RESULTS
British and Dutch national CPGs differed in the recommended drug choices, sequences, routes and methods of administration for severe APA. Local British CPGs diverged from national guidance for 23% of their recommended interventions compared to 8% for Dutch local CPGs. Variation in second-line recommendations was greater than for first-line recommendations across local CPGs from both countries. Recommended starting doses for salbutamol infusions varied by more than tenfold. The quality of the sampled local CPGs was low across five out of six AGREE domains (<60%).

CONCLUSIONS
Local CPGs for the management of severe APA featured substantial variation and frequently diverged from national guidance. Their methodological quality was low. Although limited to one condition, this study suggests that unmeasured variation across local CPGs may contribute to variation of care more broadly, potentially undermining healthcare quality.

ABSTRACT NUMBER 61

Deprescribing long acting beta2 agonists in children and adolescents with stable asthma: a systematic review

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INTRODUCTION
Current guidelines recommend step-down of asthma drugs once stable asthma has been achieved but there is no guidance regarding deprescribing long acting beta2 agonists (LABAs) in the paediatric population.

AIM
To systematically review evidence regarding deprescribing methods of LABAs in the paediatric population.

METHODS
Searches were undertaken in the following databases: EMBASE, Medline, PubMed and CINAHL regarding reports of deprescription or discontinuation of LABAs in children and adolescents with persistent asthma.

RESULTS
The search returned 168 papers following deduplication. 4 papers met the eligibility criteria including 3 randomised control trials and 1 retrospective study. Overall, LABA step down was attempted in 365 children and young people (5-18 years old). The studies had variable follow up durations once deprescribing was undertaken, from 2 to 12 weeks. Effects of withdrawal were measured using parameters such as airway hyperresponsiveness tests (3 studies), asthma control test scores (3 studies), use of rescue medication (3 studies) and lung function tests (FeNO, FEV1, FEF25-75%, peak expiratory flow rate (PEFR), % forced expiratory flow at 50% of vital capacity (%V50)) (all studies). Airway responsiveness was unchanged 2 weeks following LABA withdrawal, however decreases in %PEFR and %V50, FEV1 and asthma control test scores were observed. 2 studies assessed changes in LABA related adverse effects after deprescribing.

CONCLUSION
There is limited and short-term evidence regarding stepping down LABAs in paediatrics. To fully implement national and international guidelines, prospective studies in this area are required.

ABSTRACT NUMBER 62

Innovative High-Fidelity Simulation for vaccination training of pharmacist including emergency cases - a randomised controlled study

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INTRODUCTION
Recently, pharmacists in Germany were allowed to administer influenza and COVID-19 vaccines for people aged 12 years and older in order to increase vaccination coverage rates. To adapt pharmacy curriculum for clinical practice, an innovative, high level vaccination training course comprising clinical skills, techniques required for level of competence was developed with participants interacting either with a high-fidelity simulator or low-fidelity injection pad. Clinical scenarios to manage adverse events were also implemented.

METHODS
A randomized controlled trial using a pre-post-design with pharmacy undergraduates alongside with a theoretical part was performed. The intervention group interacted with a high-fidelity simulator, while the control group was trained with low-fidelity injection pads. Before and after the respective training each participant went through an objective structured clinical examination (OSCE) and each participant completed a self-assessment questionnaire and knowledge quiz.

RESULTS
OSCE Score were raised through an analytical checklist examining skills in anamnesis, patient information, vaccination process, and handling emergency case. Both training methods showed a significant ($p<0,01$) increase of skills but a significant ($p<0,01$) greater increase in the intervention group compared to the control group, particularly in vaccination process ($p=0,007$). Both Groups showed a similar increase of self-assessment score raised through a 6-point-Likert scale, and no significant differences were observed in the quizzes.

CONCLUSIONS
High fidelity simulation proves to be an appropriate tool to train pharmacy students for vaccine administration, as a new pharmaceutical service and enable the students to recognize and manage adverse events.

ABSTRACT NUMBER 63

Inhaled antiasthmatic drugs and the risk of dental caries in children: a pharmacovigilance analysis

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INTRODUCTION
Dental caries are frequent oral injuries in children worldwide. Some data suggested that the use of inhaled corticosteroids (ICS) and anticholinergic agents are associated with the onset of dental caries in childhood. Our objective was to assess the risk of dental caries reporting in children using inhaled antiasthmatic drugs.

METHODS
Through a case–non case study in VigiBase, WHO global safety database, we assessed the association between dental caries reporting and inhaled antiasthmatic drug use in children according to tooth maturation. Dental caries cases were identified using the ad-hoc preferred term in MedDRA. Results are presented as reporting odds ratio (ROR) and their 95% confidence interval.

RESULTS
Of 2,046,160 reports in children up to 2021/10/07, 9,573 were reported with inhaled antiasthmatic drug, including 24 (0.92%) and 32 (0.46%) dental caries cases in 2-5 yo and 6-17 yo children, respectively. Cases mainly originated from the U.S (46%) and all except one were non serious. Cases were in a large extent reported with ICS in 21 (88%) and 30 (94%) patients in young and older children, respectively. In both groups, a significant disproportionate reporting of dental caries was found with all inhaled antiasthmatic drug classes compared to other drug classes. When comparing to other inhaled antiasthmatic drugs, we found an increased dental caries reporting with ICS monotherapy in 2-5 yo children (ROR, 5.3 [1.2-22.7]) but not in 6-17 yo children (ROR, 2.0 [0.8-5.3]). No increased reporting was found for anticholinergic agent and long-acting beta 2-agonist use.

CONCLUSION
Our study suggests a possible safety signal on a cariogenic risk with the use of ICS in 2–5-year-old children. Additional analyses are needed to confirm this risk.

ABSTRACT NUMBER 64

KiDSafe – Improving medication safety for children and adolescents: implementation and evaluation of a new form of care

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INTRODUCTION
Drug therapy in paediatrics is often associated with uncertainties due to the lack of data from clinical trials, and thus the need for off-label use, but also missing paediatric dosage forms. The KiDSafe project aimed to significantly improve the existing shortfall by introducing a structured treatment procedure (PaedPharm).

METHODS
PaedPharm consists of three modules: 1. a digital paediatric drug information system (PaedAMIS), 2. paediatric-pharmacological quality circles (PaedZirk) and 3. a system for reporting of ADRs/MEs in the paediatric population (PaedReport). By using a stepped-wedge design, PaedPharm was implemented in 12 territorial clusters, each involving a children's hospital and surrounding outpatient paediatricians and psychiatrists. The primary aim of the study was to reduce the prevalence of drug-related hospital admissions by one third. In addition, qualitative and quantitative analysis concerning the quality of the implementation and acceptance of the intervention was performed.

RESULTS
A total of 41829 patient cases were recorded in the participating hospitals, of which 5101 admissions could be assigned to the participating doctors (n=152). Under control conditions, a population-based mean of 4.14% of the admissions were due to an ADR or ME. Under intervention, however, it was 3.07% (OR 0.73 (95% CI 0.39 to 1.37), p>0.05). The PaedAMIS database was well accepted and PaedZirk achieved a particular high level of acceptance.

CONCLUSIONS
Structured, evidence-based drug information in combination with teaching may improve the quality of drug therapy in children.
The number of participating paediatricians as well as the COVID pandemic hampered the results of this study. Thus, further studies are needed to confirm our results.

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We are grateful to all of these people for their contributions to this meeting and to organization of the Society.

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