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

17 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.

18 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 1x104 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 permabilization 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.

19 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 mech-anisms 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.

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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.

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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.

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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