Optimization of Vancomycin Therapy in Neonatal Intensive Care Unit (NICU)

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Candidate's declaration

This is to certify that the content of my thesis is my own work. The content has not been submitted for any other degree.

I certified that all the ideological content of this thesis is my own work, and that I acknowledge all the supervision, support, and assistance I received through my PhD journey and thesis preparation.

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Authorship Attribution Statement

This thesis contains three peer-reviewed publications and one to be submitted.

Chapter 2 includes the publication:

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I developed and performed the search strategy, data extraction, data analysis; abstracted the results, interpreted the findings, elaborated the figure and tables, and drafted the manuscript.

Chapter 3 includes the publication:

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I prepared the research protocol, applied for ethics approval, collected the data from the medical records, analysed the data; elaborated figures and tables, and drafted the manuscript.

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I prepared research proposal, collected, screened the data, simulated and analyzed the results; prepared the tables and figures, and drafted the manuscript.

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I developed and performed the search strategy, data extraction, data analysis; abstracted the results, interpreted the findings, elaborated the figure and tables, and drafted the manuscript.

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No content produced by generative AI tools has been used in the preparation of this thesis.

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Abstract

Introduction

Vancomycin is the first-line treatment of staphylococcal infections in infants. Therapeutic drug monitoring (TDM) is required to attain appropriate drug concentrations**.** Due to the lack of clinical data about the effective and safe doses in neonatal group and the large difference between pharmacokinetic and pharmacodynamic properties between adults and neonates, there is a high demand to accommodate TDM in neonatal intensive care unit. To explore this, I conducted my thesis on optimizing TDM practice and vancomycin dosing in neonates.

Methods

- **Systematic review:** I conducted a literature review on vancomycin dosing in neonates, evaluated the therapeutic target attainment, and the clinical toxicity and efficacy outcomes.
- **Retrospective study:** I conducted a retrospective study in Westmead hospital to examine the current TDM practice, vancomycin dosing strategy, and to illustrate how these affected the proportion of target attainment.
- **Model informed precision dosing software:** I conducted a study to select the best pharmacokinetic model to fit my cohort from Westmead hospital to evaluate it as a new tool to optimize vancomycin dosing and TDM practice in the hospital.
- **Scoping review:** I conducted a scoping review to explore the cost and clinical benefits of conventional and Bayesian TDM practices for vancomycin in neonates.

Results

The findings of the thesis highlighted the importance of using model informed precision dosing software to individualize vancomycin dosing in neonates and to monitor the therapy. Across the systematic review (chapter 2), all tested dosing algorithms achieved **less than 80%** target attainment, which further demonstrated the limitations of conventional dosing methods in this population. In the retrospective study of **69 neonates (chapter 3)**, the target trough concentration was achieved in **75%** of courses after the initial dose when TDM was performed appropriately, and this increased to **84%** after TDM-guided dose adjustments. Patients were dosed appropriately in **121 out of 129** courses, and TDM was performed correctly in **51 out of 93** courses; however, a dose adjustment was still required in **18 out of 29** courses to increase target attainment. These findings collectively reinforce the need for more accurate and consistent dosing approaches in routine neonatal practice. traditional dosing methods, model informed precision dosing (MIPD) allows real-time adjustment of therapy by integrating patient-specific variables and pharmacokinetic models, thereby achieving more accurate and individualized dosing. This approach is particularly valuable in neonates, where rapid physiological changes, immature renal function, and high interpatient variability make conventional dosing strategies unreliable. By providing more precise predictions of drug exposure, MIPD supports safer dose adjustments, minimizes the risk of toxicity, and enhances therapeutic effectiveness. This was also evident in the population pharmacokinetic (PopPK) model evaluation, where 25 published models were identified and nine were considered suitable for further assessment. The model of De Cock et al. (2014) was the only clinically acceptable model across *apriori*, *aposteriori*, and Bayesian forecasting approaches, showing strong

predictive performance which was quantified by mean absolute error (MAE) (*apriori* MAE 0.35 mg/L, aposteriori MAE 0.037 mg/L), which further supports the clinical value of MIPD in improving prediction accuracy. In addition, MIPD offers a framework for continuous monitoring, allowing clinicians to evaluate treatment response dynamically rather than relying solely on trough concentrations. Integrating such software into hospital practice could reduce the incidence of subtherapeutic or supratherapeutic dosing, improve antimicrobial stewardship, and contribute to better clinical outcomes. Furthermore, the findings suggest that adopting MIPD in neonatal care has the potential to standardize TDM practices across institutions, creating a more consistent and evidence-based approach to managing vancomycin therapy in this highly vulnerable patient group. Beyond the technological aspect, the results point to a broader structural need within hospitals: investing in clinical pharmacists and expanding their scope of practice to assume a leadership role in TDM. Pharmacists are uniquely positioned to interpret drug exposure, integrate clinical context, and apply MIPD outputs to optimize therapy, yet their potential remains underutilized in many settings. Training programs and institutional support to equip pharmacists with the skills to use MIPD tools effectively will be crucial for embedding this practice into routine care. Such an approach not only improves the precision of vancomycin dosing but also contributes to safer use of antimicrobials, reduced toxicity, and better long-term outcomes for vulnerable neonatal populations. In addition, adopting pharmacist-led MIPD-driven TDM could streamline workflows, reduce clinician burden, and establish a sustainable model for precision dosing practices across hospitals.

Conclusion

The collective findings from the thesis emphasize on the critical need to improve vancomycin dosing and therapeutic drug monitoring in neonates. Across all chapters, significant variability was observed in current practice, leading to inconsistent therapeutic outcomes and potential risk of toxicity. The Bayesian TDM and dosing approach shows promise for individualized and more precise dosing.

Nomenclature

Abbreviations

TDM	therapeutic drug monitoring
MIPD	model informed precision dosing software
PMA	postmenstrual age
PNA	postnatal age
CGA	corrected gestational age
GA	gestational age
AUC_{24}/MIC	area under the curve over minimum inhibitory concentration ratio (h)
NICU	neonatal intensive care unit
RDS	respiratory distress syndrome
PK	pharmacokinetics
CoNS	coagulase-negative staphylococci
Scr	serum creatinine
CL	clearance
MRSA	methicillin-resistant *Staphylococcus aureus*
Vd	volume of distribution

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Preface

The neonatal intensive care units (NICU) is a specialized unit in the hospital which provides critical care for newborn babies with health issues or who were born prematurely. Neonatal mortality is high and mostly attributed in the first 28 days of life [1, 2]. Neonatal deaths were classified into three categories including: 24-hours of birth, early (1-<7 days) and late (7-<28 days) [3]. The leading causes of neonatal deaths are mostly related to complications of birth such as asphyxia, small for gestational age (SGA), low birth weight (LBW), infections, prematurity complication which mainly caused by undeveloped lungs leading to difficulty in breathing which can cause respiratory distress syndrome (RDS) and sometimes apnea. Moreover, intraventricular hemorrhage is common in premature babies [1]. The World Health Organization published that the global number of neonatal deaths in 2022 was 2.3 million during the first 28 days of life [4]. Preterm birth is the leading cause of death in neonates globally. Prematurity is defined as baby born before completion of 37 weeks of gestation. There are three subcategories of prematurity based on the age of birth which are mild preterm (32-36 weeks), very preterm (28-31 weeks) and extremely preterm (<28 weeks) with increasing risk of mortality and morbidity [5]. Preterm births with unfavorable outcomes mostly happen in low-income countries [6]. In high income countries, babies are more likely to survive with a low risk of short term or long-term health complications [7]. Infections [8], and complications during pregnancy, such as preeclampsia, are significant factors that may necessitate preterm delivery prior to the estimated due date and may require early induction or C-section [9]. However, most premature births occur spontaneously without any identifiable cause [10].

It is recommended that midwives, neonatologists, general practitioners, and community health workers are involved in maternal and neonatal care [11] as mothers receiving comprehensive

care are less likely to lose their baby because of short term or long-term complications [12]. Neonates are a vulnerable group of patients prone to colonization and infections mostly by bacterial microorganisms due to their immature immune systems [13]. Common infections often result in sepsis which is a serious infection affecting the bloodstream [14]. It can be caused by bacteria, viruses, or fungi [15]. Around 15.3% of observed morbidity was caused by late sepsis in eight neonatal units in New South Wales, Australia in 2020 [16]. Meningitis is another common infection in NICU affecting cerebrospinal fluid around the brain or spinal cord, and it is mostly caused by bacteria [17]. The most prescribed medicines in NICU are antibiotics used to treat infectious diseases including sepsis, meningitis, and necrotizing enterocolitis (NEC) [18]. Therefore, prolonged use of antibiotics, residence in hospitals, NICU, and exposure to ventilators put infants at risk of infection with multi drug resistant organisms, NEC, late onset sepsis, invasive candidiasis, chronic lung diseases or death [19]. Regular monitoring and follow up of treatment response and adverse effects is the main goal and the collaborative effort of health care team including neonatologists, pharmacists, and nurses. Small size and immaturity of neonates necessitate a high effort to ensure optimal care with careful attention to drug dosing, adverse effects, and drug-drug interactions. To optimize drug dosing therapeutic drug monitoring (TDM) is used. This is a complex process including ordering lab tests, sample collection, laboratory testing, accurate documentation, reporting, and decision making in a multidisciplinary team [20]. Commonly monitored drugs in NICU are antibiotics such as vancomycin and aminoglycosides [21]. Regular assessment is conducted to monitor any potential side effect such as nephrotoxicity and ototoxicity associated with drugs [22].

Chapter 1: Introduction

1.1 Background

1.1.1 Preterm and term neonates

Accurate drug dosing in neonates remains a significant clinical and research challenge, primarily due to the limited availability of robust pharmacological data. This scarcity is influenced by multiple factors, including ethical limitations associated with enrolling neonates in clinical trials, the relatively small number of patients presenting with specific target conditions, and difficulties in designing methodologically sound and ethically acceptable studies. Additionally, there is a general lack of specialized expertise in neonatal pharmacokinetic (PK) and pharmacodynamic (PD) modelling, alongside practical constraints such as the large blood volumes typically required for PK sampling. These challenges collectively hinder the development of evidence-based dosing strategies in this vulnerable population [23]. Historically, drug dosing in neonates has been largely inferred from studies conducted in adult populations. In the absence of age-specific clinical data, these dosing strategies were typically adjusted with subsequent modifications primarily by scaling doses according to body weight considerations [24]. However, this approach might not fully consider the unique physiological and metabolic characteristics of neonates, such as immature organ function, altered drug absorption and distribution, and variable rates of elimination, all of which can significantly influence drug efficacy and safety in this population [25]. Newborns admitted to NICU often receive multiple pharmacological treatments within the first days or weeks of life. On average, an extremely low birth weight infant undergoes approximately 17 courses of medication, with antibiotics accounting for approximately 25% of these drug exposures [26]. Neonates possess distinct

physiological characteristics that significantly influence how medications are processed within the body. Additionally, the presence of comorbid conditions and the use of multiple concurrent therapies can further impact drug absorption, distribution, metabolism, and excretion [27]. In neonates, several physiological factors influence PK of intravenously administered medications, necessitating careful consideration when determining appropriate dosing. One of the most significant differences is the higher total body water content, which can exceed 75–80% of body weight in preterm infants, compared to approximately 60% in adults [28]. Preterm neonates have higher body water content compared to full term neonates [29]. This increased volume of distribution (Vd) particularly affects hydrophilic drugs like vancomycin, often requiring larger weight-based loading doses to achieve therapeutic plasma concentrations [30]. In the early postnatal period, the clearance of fetal lung fluid can lead to a temporary increase in extracellular fluid volume, which is typically followed by a marked diuretic response accompanied by sodium loss through natriuresis [31]. Conditions such as patent ductus arteriosus, renal impairment, or the implementation of extracorporeal membrane oxygenation (ECMO) can significantly expand the Vd. This expansion often leads to reduced peak serum concentrations of administered drugs, potentially impacting therapeutic effectiveness [32]. In comparison to older children and adults, neonates have low plasma proteins concentration such as albumin and α_1-acid glycoprotein. As only the unbound fraction of a drug can cross biological membranes, exerting pharmacological effects, and undergoing elimination, this can significantly influence both the efficacy and clearance of medications in neonates [33].

Moreover, the immaturity of hepatic enzyme systems, especially cytochrome P450 isoenzymes and conjugation pathways, lead to reduced metabolic capacity [34]. This can result in prolonged half-lives and delayed clearance of hepatically metabolized drugs [35]. Similarly, renal function

in neonates is underdeveloped, with glomerular filtration rate (GFR), tubular secretion, and reabsorption all being significantly lower than in older children or adults [36] . The transition from intrauterine to extrauterine life serves as a key trigger for the rapid postnatal maturation of renal function [37]. GFR is influenced by multiple independent physiological factors, including renal blood flow, glomerular perfusion pressure, oncotic pressure, and the developmental progression of cortical nephrons [38]. Following birth, an increase in oxygen tension and a concurrent reduction in systemic vascular resistance leads to a marked rise in renal blood flow from approximately 6% of cardiac output at birth to nearly 10% by the end of the first postnatal week. Renal blood flow continues to increase and typically reaches adult levels, approximately 140 mL/min, by around two years of age [39].

Neonates commence life with a relatively low GFR, ranging from 10–20 mL/min/1.73 m^2, which rises to approximately 30 mL/min/1.73 m^2 within the first two weeks [40]. Adult-equivalent GFR values (approximately 120 mL/min/1.73 m^2) are generally achieved by the age of two years [41]. At birth, serum creatinine levels are elevated (60–70 µmol/L), reflecting not only the transfer of maternal creatinine but also the neonate's low inherent GFR and the reabsorption of creatinine by immature renal tubules [42]. These values typically stabilize by the end of the first postnatal week to around 30–40 µmol/L [43]. These neonatal renal immaturities contribute to slower elimination of renally excreted medications, increasing the risk of drug accumulation and toxicity if dosing intervals are not appropriately adjusted. Collectively, these physiological characteristics underscore the need for individualized dosing and TDM in neonatal populations.

1.1.2 Antibiotics

Excessive use of antibiotics in neonates increases the risk of antibacterial resistance and therefore therapeutic failure and higher health costs [44]. It may also increase the risk of invasive candidiasis and death [45]. Due to substantial variability in PK profiles in neonates it is more challenging to extrapolate antibiotic dosing from adults dosing. Updated dosing guidelines proved that effective dosing in neonates are either lower, the same, or higher than adults dosing [46]. Moreover, PK variability in neonates occurs at different rates and magnitude for each antibiotic. Importantly, PK of drugs is different between neonates at different stages of maturity [47].

Most neonates admitted to NICU received antibacterials that are used empirically or as a precautionary to treat expected infections, such as early sepsis [48]. Which is mainly caused by coagulase-negative staphylococci (CoNS), Escherichia coli and Klebsiella spp and commonly acquired from the mother genital tract during delivery [49]. Or late sepsis which are mainly caused by CoNS, *Staphylococcus aureus*, *enterococcus* species, and *Enterobacteriaceae* acquired because of prolonged antibiotic therapy during hospitalization or delivery [50-52].

A full course of antibiotic is typically administered based on specific bacteria identified through positive blood cultures. However, it is challenging to determine the length of course given to treat suspected sepsis during the presence of a negative blood culture [53]. New bacterial rapid detection techniques can reveal responsible bacteria in blood culture with 48 hr [54]. Even though, obtaining adequate blood samples from preterm neonate is difficult due procedure's invasiveness, and neonatal small total blood volume [55]. The ability to detect causative bacteria is low when small blood samples is collected. As a result, neonates with negative cultures often complete the course of antibiotic [56].

Vancomycin belongs to the class of tricyclic glycopeptide antibiotics and was originally obtained from the bacterium *Streptococcus orientalis* [57]. It is widely utilized for both the treatment and prevention of infections caused by gram-positive bacteria, particularly those that are resistant to methicillin, such as methicillin-resistant *Staphylococcus aureus* (MRSA) [58]. Vancomycin's initial clinical application was limited by a range of adverse effects, notably infusion-related reactions, nephrotoxicity, and potential ototoxicity [59, 60]. Subsequent analyses revealed that these toxicities were largely attributable to impurities present in the early formulations of the drug. As a result, vancomycin usage reduced significantly following the introduction of semisynthetic penicillin, such as methicillin, oxacillin, and nafcillin, which were perceived to have a more favorable safety profile [61]. However, since the emergence and progressive increase of MRSA infections in the 1980s [62, 63], vancomycin has reemerged as a critical therapeutic agent for managing infections caused by this resistant pathogen.

Vancomycin is one of the most extensively studied antibiotics over time. Comprehensive PK research across diverse patient groups has been revealed, along with the development of commercially available assays, have enabled clinicians to maintain serum vancomycin levels within a relatively narrow therapeutic window [64]. This technique has been promoted to reduce the risks of nephrotoxicity and ototoxicity while ensuring adequate drug exposure. Nonetheless, the routine practice of monitoring and adjusting the dose based on serum vancomycin concentrations continues to generate considerable debate within the medical community in neonatal population [65]. Vancomycin is a glycopeptide antibiotic. Its PK profile is characterized by poor oral absorption, necessitating intravenous administration for systemic infections [66]. Once administered, vancomycin exhibits a distribution volume of approximately 0.4–1.0 L/kg and is predominantly eliminated unchanged via renal excretion, with over 90%

excreted in the urine [67]. Pharmacodynamically, vancomycin demonstrates time-dependent bactericidal activity. The efficacy of vancomycin is best correlated with area under the curve over minimum inhibitory concentration ratio (AUC_{24}/MIC). AUC_{24}/MIC ratio of ≥400 is generally considered predictive of clinical success. Achieving and maintaining this target is crucial to optimize therapeutic outcomes and minimize the development of resistance [68]. Given the complexity of vancomycin's pharmacokinetic/pharmacodynamic (PK/PD) parameters and the narrow therapeutic window, pharmacists play a pivotal role in TDM [69].

1.1.3 Therapeutic drug monitoring

TDM is a clinical process that is used to monitor specific drug concentrations usually in plasma or serum to ensure that the levels of drug are within the therapeutic range [70]. TDM criteria include unpredictable pharmacokinetic variability, a narrow therapeutic range and a clear correlation between concentration and effect [71] and is intended to personalize pharmacotherapy [72]. Variations in drug pharmacokinetics are influenced by both interindividual and intraindividual factors. Inter-individual variability refers to variability between patients, often originating from genetic makeup, age, body weight, kidney function, and existing health conditions [73]. These factors can impact drug metabolization and elimination, leading to different drug exposure and therapeutic responses among individuals. On the other hand, Intraindividual variability is the fluctuations within the same patient over time. Such changes can result from differences in disease status, organ function, and concurrent medications [74, 75]. Drugs with a high risk of toxicity such as those with a narrow therapeutic index, where the difference between the exposure required for therapeutic effect and the exposure that can cause toxicity is small [76], necessitate TDM. Therefore, monitoring drug exposure ensures that each patient maintains it within the therapeutic window, optimizing

efficacy while minimizing the risk of toxicity. PK and TDM are closely related, where PK is the study of drug kinetics in the body including absorption, distribution, metabolism and elimination (ADME), it is crucial in NICU to understand how drug is moving into, across, and out of the body to determine the appropriate dosing [77]. TDM is crucial to minimize the risk of nephrotoxicity, or ototoxicity, by performing vancomycin concentration guided dosing to adjust for physiological maturation and changes in this special population.

The ongoing debate originates from inconsistent findings regarding the reliability of serum vancomycin levels as predictors of both drug-related toxicity and therapeutic efficacy as there is no controlled clinical studies have demonstrated a link between serum vancomycin concentration and clinical response or toxicity [78, 79]. In adult patients, AUC_{24}/MIC is widely recognized as the most reliable metric indicating therapeutic exposure of vancomycin [80]. Vancomycin TDM guidelines developed by the Infectious Diseases Society of America (IDSA) and the American Society of Health-System Pharmacists recommends monitoring vancomycin trough levels > 15 mg/l or AUC_{24}/MUC > 400 to prevent bacterial resistance and dosing guidance for vancomycin based on the clinical condition and developmental age of the neonate [80, 81]. However, due to increasing nephrotoxicity associated with vancomycin, more recent guideline recommends the therapeutic target (AUC_{24}/MIC) to be between 400-600 mg hr/ L for MRSA infections with MIC ≤ 1 mg/L [82]. Increased nephrotoxicity incidence has been linked to its coadministration with other nephrotoxic medications such as aminoglycosides [83], neonates with compromised renal function such as such as neonates with perinatal asphyxia who are treated with controlled therapeutic hypothermia because of hypoxic ischaemic encephalopathy [84]. Reversible ototoxicity such as tinnitus have been reported with vancomycin use. And it is usually associated with vancomycin serum concentrations higher than

40 mg/L. On the other hands, irreversible ototoxicity such as permanent deafness is very rare and associated with serum concentrations higher than 80 mg/L and often preexisting renal problems [85]. The main mechanism of vancomycin nephrotoxicity primarily occurs due to the accumulation high drug concentration in the proximal renal tubules where it causes oxidative stress, activation of complement system, inflammation, mitochondrial damage, and programmed apoptosis (cell death) [86]. Although it is rare, but it has been suggested that vancomycin may induce ototoxicity. When high drug concentration is accumulated into inner ear. The mechanism by which vancomycin damage includes disruption of mitochondrial ribosomes, impairing protein synthesis and cellular respiration which may lead to oxidative damage and cellular apoptosis [87].

1.1.4 Pharmacokinetics of vancomycin in neonates

PK of vancomycin in neonates can be described using models that consider one, two, or three compartments. In adult patients, the distribution phase typically lasts between 0.5 and 1 hour. However, in neonates and infants, this phase is notably shorter, with reported durations ranging from approximately 0.05 to 0.49 hours [88]. After distribution, vancomycin is eliminated by first-order elimination. Using this PK principle appropriate dosing is calculated to attain the required vancomycin trough concentration as a surrogate marker for AUC_{24}/MIC ratio [89]. Mostly, when neonates are administered vancomycin, initial trough concentrations are obtained after the third dose, which presumes that drug concentrations are at steady state [90]. Whereas peak concentrations are obtained 1 hr after the end of 1-hr infusion, by this time it is generally believed that drug has been distributed and has entered the first order elimination phase. And one-compartment model can be used to predict appropriate dosing and plasma concentrations. The purpose of measuring the peak concentration isn't for clinical insight, but rather to provide

one of two necessary data points along with a trough or a second post-dose level, and for applying first-order pharmacokinetic calculations. These calculations help determine the most effective dosing regimen to reach the desired steady-state vancomycin concentration, typically aiming for trough levels between 15–20 mg/L, 5–20 mg/L, or no more than 20 mg/L, depending on the clinical goal, or maintaining a steady concentration of 15–20 mg/L with continuous infusion [91].

Vancomycin primarily binds to serum albumin and immunoglobulin A (IgA). Because vancomycin is a hydrophilic drug, it remines in the extracellular fluid, lower protein binding leads to high Vd and high clearance (CL) through glomerular filtration, since only free drug is capable to be filtered [92]. Currently, the PK and PD data that are available rely on measurements of total vancomycin concentrations. However, it is only the unbound portion of vancomycin that produces a therapeutic effect and is subject to elimination from the body. In neonates, free vancomycin fraction is higher due to lower albumin level and immature protein binding capacity compared to adults and paediatrics [92]. A study by Smits et al included neonates to whom vancomycin was administered to explore vancomycin protein binding and its covariates in neonates. Reported that median unbound vancomycin fraction in neonates is 0.9 which is higher than values reported in children (median 0.71-0.81) [93, 94] and adults (mean ± SD) 0.45 ± 0.09 up to 0.73 ± 0.12 [95]. Protein binding affected PK profile of vancomycin in neonates such as Vd and CL as well as affected pharmacodynamic targets. This suggests that caution is necessary when using total vancomycin concentration to precisely estimate free concentration in clinical settings. Therefore, clinical decisions are built based on total drug concentrations and free concentrations could be predicted using population-based protein binding estimates [94].

A possible explanation why unbound drug concentrations are not routinely measured in clinical practice may rely on the complexity of pre-analytical and analytical procedures [96]. Among these, isolating the unbound portion of a drug poses one of the greatest technical challenges, and various techniques have been employed for this purpose [97]. The most used in vitro method is ultrafiltration (UF), with specific pros and cons. UF is quick and easy to use but may be affected by drug binding to the filter material. Additionally, factors like pH and temperature can alter protein binding [19]. In practice, sample handling conditions such as preincubation and centrifugation temperatures are inconsistently regulated, with 4°C, 25°C, and 37°C being the most applied [98].

Vancomycin is one of the medications that are cleared renally and affected by renal function. Neonates have lower renal clearance than adults and even older children due their immature kidneys, which correspond to slower drug elimination resulting in a longer half-life. Body fluids, extracellular fluids and gestational age influence volume of distribution Vd in neonates. Preterm neonates have high water content, so they might have large Vd. Postmenstrual age (PMA) which is combining both gestational age (GA) and postnatal age (PNA), is used to adjust the dose of vancomycin in neonates, because it is accurate measure of maturational changes of kidney function and fluid status. Based on this, serum creatinine (Scr) at baseline and follow up is used to monitor renal function during vancomycin, and dose adjustment is made based on Scr level and vancomycin concentration. Organs and systems in neonates differ in the degree of maturation, as well as there are differences in capabilities of metabolic enzymes because of critical illness and inflammatory status [99]. Dosage guidelines take into account PK factors depending on the newborn (full-term or preterm). Optimizing vancomycin treatment in newborns to reduce the risk of side effects requires the use of TDM and cooperation between

neonatologists, pharmacists, and clinical pharmacologists. Population pharmacokinetic models (popPK) describing the PK of vancomycin in neonates are implemented in dosing software to assist with accurate dose adjustments based on each neonate specific factors and observed concentrations in a process called Bayesian dosing. Bayesian dosing is a model-informed precision dosing (MIPD) approach that combines prior PK knowledge with individual patient data to optimize drug therapy [100]. For vancomycin, a glycopeptide antibiotic with a narrow therapeutic index, Bayesian dosing facilitates individualized dosing regimens by combining population pharmacokinetic models with patient-specific information, such as serum drug concentrations and clinical covariates [101].

Bayesian dosing begins with an initial set of PK parameters derived from population data called *apriori*. As patient-specific data become available, such as measured vancomycin concentrations, the model updates these priors to *aposteriori* distributions that reflect the individual's PK profile. This process allows for real-time adjustments to dosing regimens, aiming to achieve therapeutic targets, such as (AUC_{24}/MIC), which is associated with both efficacy and reduced toxicity [102].

Implementing Bayesian dosing in clinical practice often involves specialized software that can process complex PK models and patient data to provide dosing recommendations. This approach is particularly beneficial in populations with significant PK variability, such as neonates, where standard dosing may not achieve desired therapeutic outcomes [103]. By individualizing therapy according to individual patient characteristics and responses, Bayesian dosing enhances the precision and effectiveness of vancomycin treatment.

1.1.5 Model informed precision dosing software

Bayesian dosing is the utilization of patient specific characteristics such as age, weight, and serum creatinine to individualize drug dosing regimen during TDM [104]. This process is performed using MIPD software [105] . MIPD software uses population PK model and patient's specific factors to calculate vancomycin dosing that is associated with therapeutic target [106]. In neonatal care, the therapeutic target for vancomycin dosing remains a subject of ongoing research and debate. While adult guidelines often recommend (AUC_{24}/MIC) ratio of ≥400 [107]. Neonates exhibit distinct PK profiles influenced by factors such as immature renal function, higher body water content, and variable protein binding [108]. These differences contribute to significant interindividual variability in vancomycin CL and distribution, complicating the establishment of a universal therapeutic target in this population. Recent studies have explored alternative AUC_{24}/MIC thresholds for neonates. For instance, some research suggests that an AUC_{24}/MIC ratio of ≥331 may be sufficient for effective treatment in neonates, which is lower than the adult target [109]. However, these findings are not yet universally accepted, and further research is necessary to validate optimal exposure targets in this demographic. Bayesian forecasting successfully showed advantages in neonates such as reducing blood sampling frequency, accurate initial dosing, earlier target attainment [110]. Several commercial MIPD software tools are available with growing evidence to support the use of AUC_{24}/MIC instead of trough concentration ratio as a therapeutic target in neonates [111]. Software tools available are different from each other including difference in the panel of drugs included, popPK models suitable for specific age groups, cost, user-friendliness, the ability of integrating different pharmacokinetic models (model averaging) and the ability to integrate electronic health

recording [112]. Model averaging refers to a statistical approach that combines multiple PK models to account for model uncertainty and improve predictive performance. Rather than selecting a single "best" model, model averaging assigns weights to a set of candidate models based on their fit to the data, often using criteria like the Akaike Information Criterion (AIC). The final prediction is then a weighted average of the predictions from all considered models. This approach can enhance the robustness of predictions, especially when no single model is clearly superior, and is particularly useful in complex clinical scenarios where patient variability is high [113].

Several PK software tools support model averaging techniques. For instance, the TDMx platform implements automated model averaging to improve individualized dosing recommendations [114]. Similarly, multiple comparisons procedure-modeling (MCP-Mod) is a framework allows model selection and averaging in dose-response analyses, which can be critical in determining optimal dosing strategies in clinical trials [115]. These tools facilitate the integration of model averaging into PK analyses, thereby enhancing the precision and reliability of TDM and dosing decisions.

1.2 Aim of the thesis and research question

Considering the available evidence, clinical interest, and current knowledge on vancomycin dosing in neonates, there is a clear need to optimize vancomycin dosing strategies, TDM and follow up in NICU as there is a lack of consensus on vancomycin dosing in literature. In addition to the presence of two different modes of intravenous administration; intermittent or continuous infusion, different dosing algorithms including age-based dosing, weight-based dosing or renal function-based dosing as well as different therapeutic target measures including

trough concentration, peak concentration, or AUC_{24}/MIC, the overall aim of this thesis is to explore and optimise vancomycin dosing and TDM in neonates, particularly within NICU, where significant variability exists in clinical practice and limited consensus is available in the literature. Specifically, this thesis aims to answer the following questions:

Question 1: How can vancomycin dosing in neonates be optimized using pharmacometrics to achieve therapeutic target attainment, and what are the associations between dosing strategies and clinical efficacy and toxicity outcome?

Question 2: How appropriate is the current practice of TDM and vancomycin dosing in neonates?

Question 3: Which is the best, the most predictive model to be used to individualize vancomycin dosing in neonates?

Question 4: What are the cost and clinical benefits to consider when implementing Bayesian therapeutic drug monitoring?

1.3 Organization of the thesis

This thesis contains six chapters, of which three were published in peer-reviewed journals (chapter 2, 3, 4), and one (chapter 5) which is semi structured review to be submitted.

This thesis is an original achievement to understand pharmacokinetics, dosing, therapeutic drug monitoring and Bayesian dosing of vancomycin in neonates.

Chapter 1 (this chapter) provides background knowledge regarding vancomycin TDM in NICU.

Chapter 2 presents a comprehensive literature review of vancomycin dosing algorithms in

neonates. This chapter qualitatively synthesises the various dosing strategies, TDM practices across institutions, target attainment rates, and associated risks of toxicity. The aim is to provide a broad and meaningful overview of current clinical practices related to vancomycin use in NICU, and to identify gaps in the existing literature and practice

Chapter 3 presents the findings of my retrospective study that I conducted in Westmead hospital to highlight the TDM and vancomycin dosing appropriateness and its effect on target attainment percentage and nephrotoxicity.

Chapter 4 evaluates vancomycin PK models for therapeutic drug monitoring. It aims to evaluate the performance of published popPK models using the available data of our cohort to select a model that can be implemented to individualize vancomycin doses in Westmead hospital.

Chapter 5 This paper aims to describe differences in the cost and clinical benefits related to the use of MIPD and conventional TDM practices for vancomycin.

Chapter 6 is the discussion and conclusion chapter of the existing evidence, and a summary of the main findings, clinical implications, limitations and future directions to optimize vancomycin in NICU.

Chapter 2: Systematic review

This chapter contains the following published manuscript:

Dosing of vancomycin and target attainment in neonates: a systematic review

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2.1 Abstract

Introduction

Neonatal infections caused by Gram-positive bacteria are commonly treated with vancomycin. There is a lack of agreement on the optimal vancomycin dosing regimen and corresponding vancomycin exposure to correlate with efficacy and toxicity.

Objectives

The objective of this review is to evaluate dosing of vancomycin in neonates, therapeutic target attainment and clinical toxicity and efficacy outcomes.

Methods

Two electronic databases, Embase and PubMed (Medline) were systematically searched between (1995-2020). Studies that reported dosing regimens, drug concentrations, toxicity, and efficacy of vancomycin in neonates were eligible for inclusion. Descriptive analysis and narrative synthesis were performed.

Results

The systematic review protocol was registered with the PROSPERO International Prospective Register of Systematic reviews in 2020 (registration number: CRD42020219568). Twenty-four studies were included for final analysis. Overall, the data from the included studies showed a great degree of heterogeneity. TDM practices were different between institutions. Although most studies used trough concentration with a target range of 10-20 mg/L target attainment

was different across the studies. The probability of target attainment was less than 80% in all tested dosing algorithms. Few studies reported on vancomycin efficacy and toxicity.

Conclusion

This is a comprehensive overview of dosing strategies of vancomycin in neonates. There is inadequate evidence to propose an optimal therapeutic regimen in the newborn population based on the data obtained due to the heterogeneity in the design and objectives of included studies. Consistent and homogeneous comparative RCTs are needed to identify a dosing regimen with a probability of target attainment (PTA) of >90% without toxicity.

2.2 Introduction

Vancomycin is a commonly prescribed glycopeptide antibiotic used in NICU. Based on local resistance profiles it is considered one of the therapeutic options to treat late onset sepsis caused by Gram-positive bacteria; CoNS and MRSA [116]. CoNS is one of the most frequently isolated pathogens within the NICU. Comparatively, MRSA infections are found less frequently in neonates but are considered a significant cause of morbidity and mortality in neonates [117]. Vancomycin is commonly administered as an intermittent intravenous infusion, but a loading dose or continuous infusion have been proposed to achieve target concentrations earlier [118, 119].

As a result of changing clinical conditions and rapid growth/maturation in neonates, changes in PK parameters such as CL and Vd may be unpredictable, potentially resulting in toxic or subtherapeutic drug concentrations. Typically, lower CL and higher Vd are observed in neonates compared to adults. Other factors such as concomitant drugs may increase variability in vancomycin concentrations even further [120]. This can affect target attainment and limit the predictability of drug exposure based on the dosing regimens used in neonates [121]. TDM is a powerful tool used to attain therapeutic concentration ranges and to avoid side effects in neonates [122]. There is currently a large diversity in dosing regimens and TDM strategies based on several factors such as Scr, body weight, PNA or PMA [123].

Current guidelines on TDM of vancomycin for MRSA recommend implementing AUC_{24}/MIC to guide vancomycin treatment [82]. However, AUC_{24}/MIC guided dosing requires substantial clinical practice changes before it can replace the current standard of care (i.e. trough level guided dosing) [118]. To facilitate implementation of evidence-based TDM using AUC_{24}/MIC

guided dosing, evaluation of the current evidence on target vancomycin concentrations and dosing strategies in neonates is required. Therefore, the objective of this systematic review was to evaluate dosing of vancomycin in neonates, therapeutic target attainment and their association with toxicity and efficacy.

2.3 Methods

2.3.1 Search strategy

This systematic review protocol was registered with the PROSPERO International Prospective Register of Systematic reviews in 2020 (Registration number: CRD42020219568). In concordance with PRISMA guidelines, a search was conducted in PubMed (MEDLINE) and EMBASE using the following three keywords "vancomycin" AND ("pharmacokinetics OR therapeutic drug monitoring") AND "neonates". Articles from the two databases were imported and duplicate articles were removed using the systematic review management tool Covidence® [124]. Following this, two reviewers (DA and SX) independently performed title/abstract screening, followed by full-text screening of the articles for eligibility. Discrepancies were resolved by consensus. References of the studies included were screened as well for potential identification of additional studies.

2.3.2 Inclusion and Exclusion Criteria

Vancomycin studies in neonates were considered eligible for inclusion if they were: observational (prospective and retrospective) cohort studies or randomised clinical trials; included neonates ≤ 42 weeks gestational age receiving vancomycin IV infusion in a NICU; and had vancomycin plasma concentration measurements. Studies were excluded if they met one of

the following exclusion criteria: mixed population including adults and pediatrics' without specific neonate data, studies in languages other than English, small studies on < 20 patients, conference and poster abstracts and review papers.

2.3.3 Data extraction

Data from the studies included were extracted by the first reviewer (DA) and 10% of the data was verified by the second reviewer (SX). The following data from the included studies were extracted: study design, number of participants, age, weight, type of illness, vancomycin analytical method used in each study and dose regimen. In addition, the TDM strategies used in the studies were recorded, including time of blood sampling, number of samples per patient, dosing advice according to TDM results, and loading and maintenance dose calculations. Information on target attainment, efficacy and toxicity were also collected.

2.3.4 Data analysis

2.3.4.1 Target attainment

Multiple factors, such as weight, age, type of IV infusion (intermittent or continuous), loading dose administration and renal function reflected by Scr can affect vancomycin dose selection and subsequent drug exposure [119]. To aggregate results from the different studies the current review used subgroup analysis based on age, weight and/or Scr, and presented results on trough concentrations and AUC where available. The following subgroups were defined: **A.** Fixed dosing regimen; **B.** Postnatal age ≤60 days; this category covers the dosing regimens for patient's that postnatal age under 60 days of age. Within this category, three subgroups further specify dosing based on age, renal function or weight. **B1.** Age-Directed Dosing: Dosing regimens are calculated based on PMA and PNA. **B2.** Age and/or Renal Function-Based

Dosing: In here dosing were adjusted based on both age and renal function or renal function only. **B3.** Age and/or Weight-Based Dosing: Vancomycin dosing is determined based on age and body weight or body weight only; **C.** Model-based dosing, **D.** Continuous infusion.

2.3.4.2 Efficacy

To determine the efficacy of an antimicrobial drug for blood stream infections, a positive blood culture at baseline with sequential follow-up blood cultures is required. However, frequent collection of blood cultures is unfeasible in neonates; therefore, an explorative strategy was adopted to collect all potentially relevant information on efficacy from the included studies.

2.3.4.3 Toxicity

Scr is frequently used as an indicator of nephrotoxicity during vancomycin therapy [43]. Therefore, information on Scr monitoring, definitions of nephrotoxicity by the original investigator and if they used specific acute kidney injury (AKI) guidelines, and number of cases with renal toxicity were extracted.

2.3.5 Risk assessment

To validate the reliability and overall risk of bias of included studies in this review, the Risk Of Bias In Non-randomised Studies of Interventions (RoBINS-I) tool [125] was used. The tool was used to examine the assessment of nephrotoxicity in studies reporting this outcome. The potential effect of other co-administered nephrotoxic agents was considered a confounder. In addition, baseline Scr measurement and Scr follow up during vancomycin therapy were considered relevant to reduce the risk of bias. Other elements to determine the risk of bias were completeness of the dataset, adherence to treatment protocol and follow-up of patients.

2.4 Results

As shown in the PRISMA chart in (Figure 2-1), 643 articles were retrieved from PubMed (Medline) and Embase. After removal of 130 duplicate articles, 513 articles underwent title and abstract screening. Subsequently, 101 articles underwent full-text screening after exclusion of irrelevant articles. Twenty-two articles were included in the final analysis. Two additional studies were retrieved through screening of the references of the included studies to reach 24 studies in total (Figure 2-1). Of the included studies, 21 of 24 were retrospective cohort studies with a median number of 102 patients (range 32–265). In these studies, the probability of target attainment was defined as the percentage of patients reaching the target concentration trough, peak and trough concentrations, or AUC_{24}/MIC. TDM and target attainment were based on trough levels in 16 of 24 studies [126-141]. Peak and trough concentrations were measured in five of 24 studies [89, 142-145]. Trough concentration blood samples were drawn 30 minutes prior to a dose or just before the second, third or fourth dose. Peak concentration samples were collected 45–60 minutes after 0.5–2 hour of vancomycin infusion. Only one study has specifically defined AUC_{24}/MIC as a therapeutic target measure [146]. Vancomycin dosing data were presented in each study based on different variables such as PMA, PNA, body weight and Scr to individualize doses.

2.4.1 Quality of studies reporting on nephrotoxicity

One study had a low risk of bias, and six studies were considered as having a high risk of bias. The results of the risk of bias assessment are explained in detail in (Table 2-1) and (Table S1 in the appendix for more details).

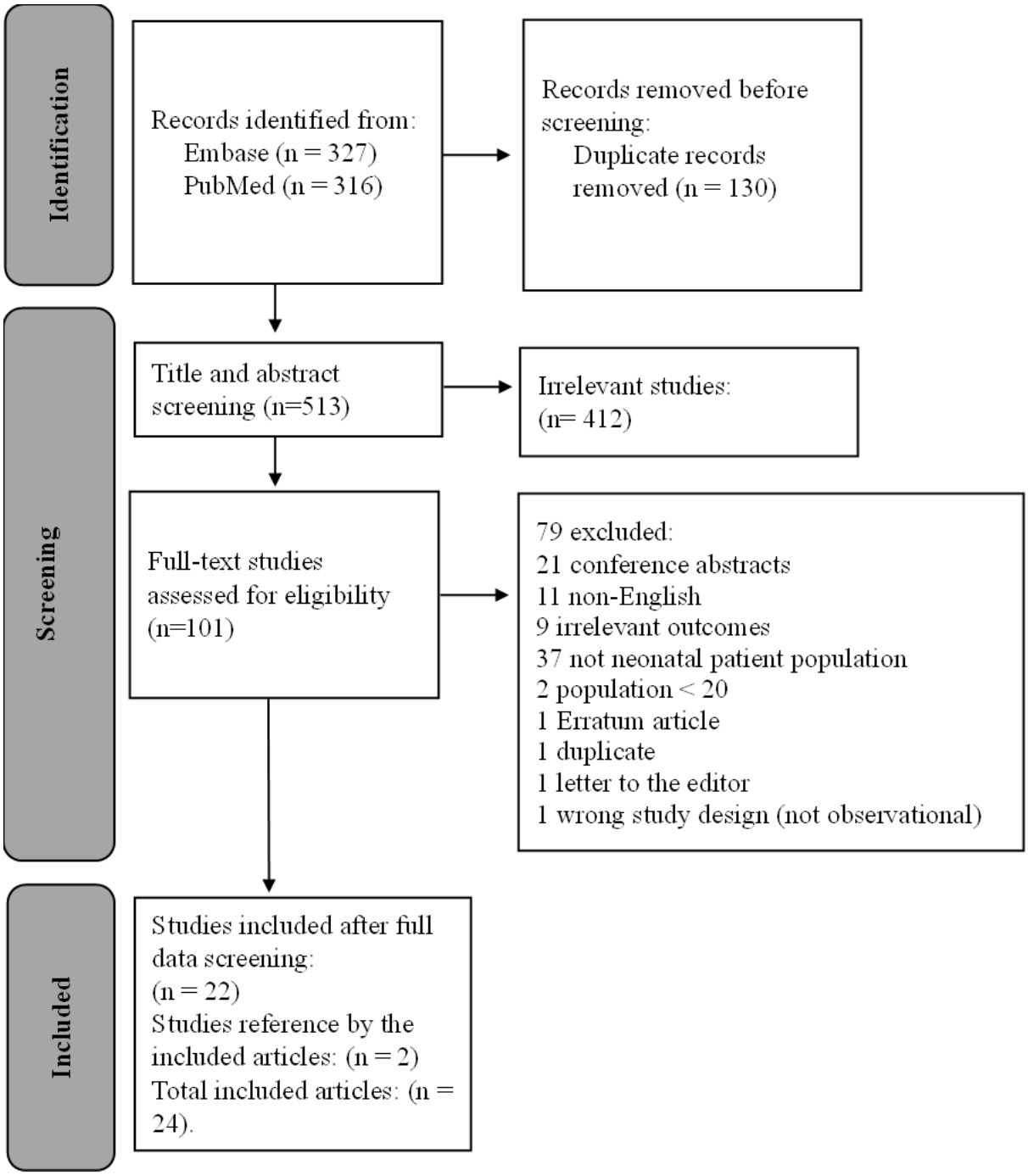

Figure 2-1: Flowchart of the inclusion criteria

2.4.2 Target attainment

(Table 2-2) provides an overview of the main findings from all the included studies, together with reported target attainment.

2.4.2.1 A. Fixed mg/kg dosing regimen

Three studies used fixed 15 mg/kg dosing for all neonates irrespective of their age, weight, or renal function [118, 119, 136]. In a multicenter study such as that by Tauzin et al. [118] two hospitals administered vancomycin as a continuous infusion (30 mg/kg/day) preceded by a loading dose (15 mg/kg), whilst a loading dose was not administered in the third hospital. Low trough concentrations were observed in patients who were not administered a loading dose [119]. Madigan et al. evaluated the proportion of neonates reaching the target trough concentration after the administration of an intermittent fixed dose [136].

2.4.2.2 B. Dosing in patients with PNA ≤ 60 days

B1. Age-based dosing

Ten articles reported PMA and PNA age-based dosing strategies for empirical dosing using intermittent infusion [126-129, 131, 146-149]. Nine of these studies specified trough concentration ranges as a target to be attained [126-129, 131, 139, 147-150]. One study specified their target to be AUC_{24}/MIC > 300 or 400 [70]. Vancomycin dosing and frequency according to PNA in all four studies reporting GA-based and PNA-based dosing, and most of the included neonates were preterm [119, 138-140].

In two studies, corrected gestational age (CGA) and PNA-based dosing had a slightly higher target attainment probability compared with GA-based and PNA-based dosing [138, 139].

Table 2-1: ROBINS-I Risk of Bias in Non-randomized studies of interventions tool.

Study	Ref.	Bias due to confounding	Bias due to participants	Bias in classification of intervention	Bias due to deviation from intended interventions	Bias due to the missing data	Bias in measurement of outcome	Bias in selection of the reported results	Overall
V.Bhargava 2017	[151]	H	L	L	L	L	L	L	H
Ringenberg 2015	[131]	M	L	H	L	M	H	L	H
Leroux 2016	[135]	L	H	H	L	M	H	L	H
Irikura 2011	[133]	S	H	L	M	H	H	M	S
Madigan 2015	[136]	L	H	L	M	H	H	M	H
Sosnin 2019	[137]	S	H	H	M	H	H	M	S
Viel-Theriault 2020	[148]	L	L	L	L	M	L	L	L

L: low; M: moderate; H: high; S: serious.
Overall risk reflects the highest risk in any domain; one high-risk domain can make the study high overall even if most items are low.

CGA, PNA, PMA, PCA (postconceptional age) or GA-based regimens were used for empirical dosing in five different studies [137, 140, 142, 145, 152, 153]. Sosnin et al. showed that the empirical dose was insufficient to achieve target attainment [137]. In the study by Vandendriessche et al. [154], 70% of trough observations were < 10 mg/L upon using a PMA- and PNA-based dosing regimen.

B2. Age and/or renal function-based dosing

Five studies evaluated renal function-based vancomycin dosing regimens [126, 129, 132, 133, 149]. One study evaluated target attainment before and after using Scr-based dosing. A higher probability of target attainment was demonstrated after using the renal function-based dosing regimen [133]. Chung et al. compared renal function-based dosing with two other dosing regimens (age-based dosing and age-weight-class based dosing); a high dose of 15 mg/kg was required to attain therapeutic levels [126]. Furthermore, target trough concentration attainment was affected by the Scr level, as Scr <0.5 mg/dL correlated with subtherapeutic concentrations [126]. In a prospective study of two groups of premature infants, both groups received two different dosing continuous infusions based on Scr measurements and most of the participants in both groups had their trough concentrations within target range after 48 h trough concentration [132]. To identify the effect of Scr covariate on vancomycin trough concentration, Scr-based dosing was used, which resulted in significantly higher trough concentrations compared with PMA- and PNA-based doing [149].

Table 2-2: Summary of dosing regimen and target attainment in the included studies

Author	Ref	Year	Design	(n)	Group	Age (w)	weight (kg)	Dose based on:	Dose	Vancomycin analytical method	Target (mg/L)	PTA (%)
Chung	[126]	2019	R	74		GA 27.6±3.9	1.09±0.73*	PMA and PNA	10-15 mg/kg q 6, 8, 12, 18h	NR	Trough: 10-20	61
								Renal function	10-20 mg/kg q 12, 24, 48h			60
								Weight	10-15 mg/kg q 6, 8, 12, 24h			50
Reilly	[127]	2019	R	182	G1 63	PMA 32 ± 5	1.59 ± 0.93*	PMA and PNA	5-20 mg/kg q 8, 12, and 24h	PIA	Trough: 10-20	29
					G2:119	PMA 29 ± 4	1.10 ± 0.58*		10-15 mg/kg q 6, 8, 12h			62
Ywaya	[128]	2019	R	78		GA 30 (24–42)	1.2 (0.4- 4.3)*	PMA and PNA	10 mg/kg q 8, 12 h	NR	Trough: 5-15	75
Radu	[129]	2018	R(MC)	265	G1:158	GA 28 (26.0–31.9)	1.5 ± 0.84[#]	PMA and PNA	15 mg/kg q 6,8,12 and 18h	NR	Trough: 10-20	34
					G2:118	GA 28.4 (26.3–34.3)	1.8 ± 0.96[#]	PNA and Scr	15 mg/kg q 8,12 and 24 h			53
Padari	[146]	2016	R	76		CA 30.9±4.8	1.3 ± 0.84[#]	PMA and PNA	13–40 mg/kg/d q 6, 8, 12, and 18h	FPIA	AUC/MIC >400 AUC/MIC >300	<25 40
Crumby	[147]	2009	CR	174	G1:108	CA 28(23-42)	1.3 (0.4-4.9)[#]	PMA and PNA PMA	10–15 mg/kg q 6–18 h 20 mg/kg q 12–24 h	FPIA	Peak: 20–40 Trough: 5–15	69 50

				G2: 39	CA 29 (23-40)	1.1(0.5-4.0) #	ABW	20 mg/kg q 12h		Peak: 20–40 Trough: 5–15	77 82
Viel-Thériault	[148]	2020	R	120		GA 28 (26–35)	NR	PMA and PNA	10 mg/kg q 6,8,12 h LD 15 mg/kg (severe sepsis)	CMIA	Trough: 10–15 15–20 (deepest infections)	64
Ringenberg	[131]	2015	R(MC)	141		GA 28.2 ± 4.1	1.6 ± 1.01 #	PMA and PNA (Neofax)	30 (40–45 mg/kg/day) q 8h	NR	Trough: 10-20	25[d] 45[e]
Dersch-Mills	[134]	2014	R	153		NR	NR	PNA and weight (Empirical)	15 mg/kg q 8, 12, 18, 24 h	NR	Trough 10-20	34
								PMA and PNA (Revised)	10 mg/kg q 6, 8, 12 h			72
Leroux	[135]	2016	R	190		GA 30 (24–42)	1.3 (0.5–4.1)*	model–based dosing	LD 11.1 (9.9–12.6) mg/kg/d MD 25.4 (13.0–61.0) mg/kg/d	FPIA	Trough 15-25	72
Tauzin	[118]	2019	R	75		GA 27 (26–30.5)	0.8 (0.7–1.2)*	Continuous infusion fixed dosing	LD 15 mg/kg MD 30 mg/kg/d	NR	Css 20-30	31[b]
Madigan	[136]	2015	R	57	G1: 28	GA 26(24.0–30.1)	0.8 (0.5–1.5)*	Fixed doing	15 mg/kg q 18, 24 h	NR	Trough 10-20	4
					G2: 29	GA 25.9 (22.9–31.6)	0.8 (0.5–1.6)*	PNA and Weight	15 mg/kg q 8, 12, 24, 18 h			35
Sosnin	[137]	2019	R	53[a]		CGA 38.1 (25.3–43.4)	NR	CGA	Empirical dose:15-45 mg/kg/d	NR	Trough: 10-20	39[b]
Hartman	[155]	2020	R(MC)	102		GA 29 (23.9–42.3)	1.2 [0.9–2.1]*	GA and PNA	20, 30 mg/kg/d q 8, 12 h 20 – 48 mg/kg/d q 6,8,12 h	PETINIA	Trough: 10-15	NR 39
Rajon	[139]	2014	R	32		PNA 16 d (1-66 d)	2.7 (0.7-4.0)*	GA and PNA CGA and PNA	20–22 mg/kg q 12,18,24 h 20–22 mg/kg q 8, 12 h	NR	Trough: 5-20	89
Sinkeler	[140]	2014	R	112		GA 28 (24-41)	0.9 (0.4-4.1)*	PMA GA and PNA	15 mg/kg q 24 h 20 – 40 mg/kg q 12h	NR	Trough: 10-15	33[d] 60[e]

Zhao	[141]	2013	R(MC)	116	Hospital 1	PMA 32.7 (24.4–49.4)	1.0 (0.5- 3.9)*	GA and PNA	Continuous infusion: LD 10 mg/kg 20 –35 mg/kg/d (IRF 15-30 mg/kg/d)	FPIA	Trough 15-25	41[c]
					Hospital 2			Fixed dose	LD 15 mg/kg MD 30 mg/kg/d	PETINIA		NR
					Hospital 3			Fixed dose	MD 30 mg/kg/d (IRF 20 mg/kg/d)	FPIA		NR
Irikura	[133]	2011	R	54	G1: 33	GA 33.1 ± 5.94	1.8 ± 0.9 *	PNA and weight	NR	FPIA	Trough: 5–15	49
					G2: 21	GA 29.65 ± 5.27	1.3 ± 0.9 *	Scr	10 –20 mg/kg q 12,24,48 h			82
Badran	[142]	2011	R	151		GA <28 = 26.9 ± 0.4 GA 28 -34 = 30.3 ± 1.7 GA 34-term = 36.7 ± 1.8	2.1 ± 0.9 *	GA (Neofax empirical dosing)	5 – 40 mg/kg q 8,12,18,24,48 h	FPIA	Peak: 20-40 Trough: 5-10	51 66
Pawlotsky	[152]	1998	R	53	G 1: 24	GA 29.2 ± 2.9	1.1 ± 0.3 *	PCA	Continuous infusion: G1: 10 – 30 mg/kg/d	EMIT	Css: 10–30	56
					G2: 29	GA 30.5 ± 3.7	1.5 ± 0.9 *		continuous infusion G2: LD 7 mg/kg MD 10 – 40 mg/kg/day			88
Tan	[145]	2002	R	101		GA 28 (23–41) PNA 10 d (4–99) d	NR	PNA	15 mg/kg q 12, 18 h	FPIA	Range A Trough 5–10 Peak 20–40 Range B Trough 5–12 Peak 15–60	 46 83 55 99

McDougal	[153]	1995	P	44		PMA (27-44) PNA (2-63) d	(0.7 - 3.8) *	PMA	18, 16, 18, 15 mg/kg q 36, 24, 18 or 12 h	FPIA	Trough: 5-10 Peak: 25-35	25 75
O plan	[132]	2008	P	145	G1: 73	PMA 28 (26-29)	1.0 (0.8-1.2) *	Scr	Continuous infusion: 15 or 25 mg/kg/d	EMIT	Trough: 10-25	74
					G2: 72	PMA 27.5 (26-29)	0.9 (0.8-1.2) *		20 or 30 mg/kg/d			75
Vandendriessche	[149]	2014	R	223	G1:193[f]	PMA 35.1 (25.1-56)	1.9 (0.4-4.9)	PMA and Scr	15 mg/kg q 8-24 h	PETINIA or EMIT	Trough: 10	33.7
					G2:101[f]			PMA and PNA	10 mg/kg q 8-18 h			23.8

Numbers are presented as median (range) [IQR] or mean ± SD. Abbreviations: R: Retrospective, R(MC): multicenter retrospective, CR: comparative retrospective, P: Prospective, GA: Gestational age; PNA: postnatal age; PMA: postmenstrual age; PCA: postconceptional age, CGA: corrected gestational age, IRF: impaired renal function, NR: not reported, LD: loading dose, ABW: actual body weight, CW: current weight, CA: current age, G1: group 1, G2: group 2, a: number of courses, b: PTA% of courses, c: Target attainment results for each hospital were not provided in the article, d: initial trough, e: random trough),f: number of concentration measurements, PIA: photometric immunoassay, FPIA: fluorescence polarization immunoassay, CMIA: chemiluminescent magnetic immunoassay, PETINIA: particle enhanced turbidimetric inhibition immunoassay, EMIT: enzyme linked immunoassay (* Birth weight, #: Current weight)

B3: Age and/or weight-class-based dosing

Three studies presented data on dosing regimen and frequency based on weight class, which was grouped as < 1.2 kg, 1.2–2.0 kg and > 2.0 kg [126, 134, 136]. Madigan et al. analyzed the vancomycin concentrations among preterm neonates with very low birth weight (< 1.5 kg) in the intervention group after implementing weight standardized dosing [136]. They observed a significant difference in trough concentration-based target attainment compared with the previously used fixed dosing regimen in the control group [136]. Chung et al. standardized dosing by weight, irrespective of PNA, and the percentage of patients who reached the target was lower than those who received age-based or sCr-based dosing [126].

2.4.2.3 C. Model-based dosing:

Two studies reported model-based dosing, in which PK parameters were used to calculate and individualize the dosing regimen [135, 156]. Leroux et al. calculated the loading dose and maintenance dose based on target trough concentration, CL and Vd, and evaluated the clinical utility and safety of vancomycin model-based dosing [135]. In contrast, Hartman et al. evaluated the target attainment before and after using model-based dose individualization based on CGA and PNA and found that most of the neonatal group had a supratherapeutic concentration [157].

2.4.2.4 D. Continuous infusion:

Of the included studies, in four studies continuous infusion were reported [118, 119, 132, 152]. Zhao et al [119] compared doses administered by continuous infusion in three different hospitals based on renal function, variations in loading dose used and therapeutic outcomes were observed. Low vancomycin serum concentrations were noticed in the group were loading dose not given. While high vancomycin serum concentrations were observed in group that

received a uniform weight-based dose with a loading dose. In addition, greater variability in serum vancomycin concentration were noticed in preterm neonates. In a study by Tauzin et al [118] to determine proportion of target attainment at the first time of vancomycin assay, vancomycin administered by continuous infusions loading dose of 15 mg/kg and 30 mg/kg/d maintenance dose, 44% of patients achieved therapeutic target concentration range between 20-30mg/L in the initial assay. Pawlotsky et al [152] determined probability of target attainment in two groups of patients where vancomycin administered by continuous infusions. Continuous infusion was administered at 10–30 mg/kg/day in Group 1 and target attainment was 56%, while Group 2 reported target attainment of 88% after receiving a loading dose of 7 mg/kg followed by a maintenance dose of 10–40 mg/kg/day. O Plan et al [132] in a prospective study evaluated two periods of continuous infusion in preterm neonates with suspected or confirmed gram positive infections. Vancomycin dosage began with 25 mg/kg/day or 15 mg/kg/day (period 1) and 30 mg/kg/day or 20 mg/kg/day (period 2) depending on whether serum creatinine was below or above 90 μmol/l. Serum levels was higher in period 2 compared to period 1.

2.4.3 Vancomycin assay

Immunoassays are widely used to quantify vancomycin in plasma or serum and are preferred in scenarios that demand quick turnaround and routine application [158]. Because of low molecular weight of vancomycin, its competition immunoassay is the most commonly used method to detect vancomycin blood sample. Immunoassays are classified according to the label type; radioimmunoassay (RIA), fluorescent immunoassay (FIA or FPIA) and enzyme immunoassay (EIA). Labels include radioactive isotopes, fluorescent compounds, or enzymes. Labelled and unbound vancomycin are competed to attach to corresponding antibodies in the

blood sample. When the unbound (free) vancomycin concentration is high, fewer labelled molecules can bind to the antibodies. Among these techniques, bonds between vancomycin and its antibodies are measured. The immunoassay used for TDM must be selective to differentiate between active metabolite, inactive metabolites or other substances. RIA is 0.04 ng/mL sensitive to vancomycin compared to biological methods with 0.8 ng/mL sensitivity. It is not routinely used in laboratory due to multiple disadvantages including radio wastes which is hazardous to humans, it is required to dilute sample, it is required to separate antibody-bound and free fractions before the test, and it is expensive method [159]. FPIA and EIA are the most used immunoassay in the hospitals. Compared to other immunoassays, they offer a simpler and faster procedure, making it well-suited for clinical application [160]. FPIA for vancomycin is known for its high precision; however, it tends to yield slightly elevated results in comparison to other methods. Overestimation of vancomycin concentrations by fluorescence polarization immunoassay (FPIA) has important clinical implications for TDM. Because the assay may cross-react with vancomycin metabolites or degradation products such as crystalline degradation products CPD-1 [161], particularly in patients with impaired renal function or in preterm neonates, measured levels can be higher than the true parent drug concentration determined by reference methods such as liquid chromatography–mass spectrometry (LC-MS/MS). This positive bias can lead clinicians to inappropriately reduce or withhold vancomycin doses under the assumption of excessive exposure, thereby increasing the risk of subtherapeutic concentrations, treatment failure, and potential development of resistance. Moreover, falsely elevated results may give an inaccurate impression of nephrotoxicity risk, further influencing dosing decisions, consequently [162-164].

EIA displayed cross-reactivity and falsely elevated vancomycin concentration results [165]. It sometimes can cross-react to biological substances such as rheumatoid factor, heterophilic

antibodies, paraproteins, C-reactive protein, or unexplained substances affecting enzyme activity. This indicates that immunoassays are fewer specific techniques as they may detected other related substances in addition to the parent drug. Particularly, when compared to more precise techniques such as high-performance liquid chromatography (HPLC) [158] or LC-MS/MS [166]. Same is true for sensitivity where the lowest level of quantitation is often higher than with LC-MS/MS. In clinical practice, immunoassays can be adequately used to measure vancomycin concentrations despite their variability in precision, selectivity and specificity but in case of odd results healthcare professionals should be aware of these issues.

2.4.4 Efficacy

None of the included studies reported clinical outcomes. The systematic review identified 24 studies which evaluated target attainment of vancomycin in neonates. Of these studies only five studies evaluated clinical efficacy [127, 129, 133, 140, 157]. Irikura et al. aimed to evaluate vancomycin efficacy in their study but were unsuccessful because of the ambiguous standards to determine efficacy; they could not find a range that would be considered effective and safe for vancomycin [133]. Sinkeler et al. showed that 47% of initial vancomycin concentrations were subtherapeutic, and the second trough concentrations remained subtherapeutic in 40% of the cases [140]. Radu et al. considered trough levels < 10 mg/L to be subtherapeutic [129]. Reilly et al. were unable to correlate trough concentrations and clinical efficacy because many courses were only administered for 48 hours as empirical therapy [127]. Hartman et al. grouped their patients into three groups therapeutic, subtherapeutic and supratherapeutic based on the pharmacodynamic target concentrations of a trough level 10–15 mg/L as a surrogate marker for AUC in adults: 39.2% of patients had therapeutic trough concentrations, whereas 28.4% and 32.4% of patients had subtherapeutic and supratherapeutic concentrations, respectively [138].

2.4.5 Toxicity

Seven studies evaluated the risk of nephrotoxicity associated with vancomycin administration [131, 133, 136, 137, 148, 151, 167]. It was low in all studies (range 0.03–6%). Different definitions of acute kidney injury (AKI) were used in the included studies (Table 2-3). Nephrotoxicity was frequently observed in neonates with high baseline Scr and low GA and PMA, as reported by Viel-Thériault et al. [130]. Bhargava et al. [151] found a significant association between trough concentration and Scr concentration. Two patients experienced reversible nephrotoxicity with 50% increase in sCr in the study by Ringenberg et al. [131]. Leroux et al [135] reported two patients who experienced nephrotoxicity due to their clinical condition and hemodynamic instability, both in the control group, potentially related to the severity of illness [136]. In addition, when concomitant use of nephrotoxic agents in five studies was evaluated, at least one concomitant nephrotoxic agent was administered to patients experiencing nephrotoxicity [131, 135-137, 151]. It was not described in any of the included studies how the dosing regimen was adjusted in case of supra- or subtherapeutic levels of vancomycin.

Table 2-3: Overview of nephrotoxicity of vancomycin in the literature

Author/ Year	Ref.	Study population (N)	Dose (mg/kg)	Trough concentration (mg/L) (n)	Baseline Scr (mg/dl)	AKI cases	AKI incidence	AKI definition	Nephrotoxic medication	Post-vancomycin Scr (mg/dl)
V. Bhargava 2017	[151]	110	15-20 mg/kg q 12, 18, 24h	<10 (n=72) 10-15 (n=27) 15 (n=11)	0.525 (0.19-1.46)	1 0 2	1.39% 0% 18.18%	pRIFLE criteria (Increase by 0.5 mg/dl or 100% from the baseline Scr)	Yes	0.4(0.2-1.5)
Ringenberg 2015	[168]	141	30 (40-45) mg/kg/day	<10 >10	0.44 (0.3–0.64) 0.5 (0.31–0.8)	2	1.12%	a doubling of the baseline SCr	Yes	0.51±0.28
Leroux 2016	[135]	190	LD 11.1 (9.9–12.6) mg/kg/day MD 25.4 (13.0–61.0) mg/kg/day	NR	0.52 (0.16–1.41)	2	1.05%	2-fold increase or increase by 0.6 mg/dl from the baseline Scr	Yes	0.35 to 1.62 0.52 to 1.22
Irikura 2011	[133]	54	PNA and BW based dosing. Scr based dosing: 10 - 15 mg/kg q 12,24,48 h	NR	NR	2 1	6.06% 4.76%	NR	No	NR
Madigan 2015	[136]	57	15 mg/kg q 18, 24 h PNA and Wt:15 mg/kg q 8, 12,18, 24h	NR	G1 0.65 (0.2-1.4) G2 0.50 (0.2-1.49)	0 2	0% 7.14%	NR	Yes	NR

Sosnin 2019	[137]	53[a]	Empirical dos 15 - 45 mg/kg/day	NR	NR	3	6%	1.5 times increase of baseline Scr	Yes	NR
Veil-Theriault 2020	[130]	120	10 mg/kg q 6,8, 12 h (15 mg/kg LD in severe sepsis)	< 10 10 -20 > 20	0.39 (0.18–1.02) 0.51 (0.10–1.97) 0.55 (0.10–0.76)	6	6%	1.5 times increase of baseline Scr	No	0.38 (0.23–0.45) 0.48 (0.37–0.71) 0.52 (0.38–0.64)

Numbers presented as median (range) or mean ± SD. a: number of courses

Abbreviations: LD: loading dose; MD: maintenance dose; pRIFLE: paediatric risk, injury, failure, loss, end stage renal disease; AKI: acute kidney injury.

2.5 Discussion

This systematic review evaluated dosing of vancomycin in neonates, therapeutic target attainment, and associations with toxicity and efficacy. A high degree of heterogeneity was observed between the included studies, making it difficult to aggregate the data. It also found that sampling times were inconsistent across studies for TDM practice and trough vancomycin concentration. In some institutions, the sampling time occurred before three half-lives of vancomycin, which is before steady state, potentially resulting in the assumption that levels were too low [118, 127, 129, 131, 135, 137, 142, 145].

A vancomycin trough concentration was the main endpoint of target attainment in most studies, highlighting the lack of research on AUC_{24}/MIC in neonates as compared with adults [82]. Most studies focused on evaluating the probability of target attainment as a percentage of patients who reached the target trough concentration. A minority of the studies evaluated Scr during the treatment and reported on nephrotoxicity. In the absence of official guidelines for AKI diagnosis in neonates, due to the lack of standard definitions, clinicians determined the level of kidney injury through a combination of clinical assessments such as urine output, signs of edema and review of the trend in serum creatinine [169]. Clinically according to different practices, neonatal AKI is mostly defined as a Scr greater than 1.5 mg/dl, an increment of at least 0.2 to 0.3 mg/dl per day from a previous value or 0.5 to 2 times increase from baseline [170]. The presence of maternal Scr in the first days of life after birth make the percentage change of baseline Scr a challenging biomarker to diagnose AKI in neonates, which is under estimating AKI prevalence [171], however Scr based definitions are used because urine output is difficult to be captured in medical records [172]. Accurate renal function evaluation during vancomycin

administration is essential for individualizing drug dosing and dosing adjustments [173]. Cystatin C has been suggested as a promising biomarker for evaluating renal function in neonates as it offers some advantages over Scr such as minimal transplacental transfer, high analytical sensitivity, and relatively short serum half-life. And unlike creatinine, its levels are not influenced by body weight, gender, infection, inflammatory status or race [174]. Cystatin C is synthesized at a consistent rate and is exclusively filtered by the glomeruli without undergoing tubular secretion. Additionally, it occupies the extracellular fluid compartment, whereas Scr is distributed more broadly throughout the body. Consequently, reductions in GFR are reflected more promptly by elevations in serum Cystatin-C than by changes in SCr levels [175]. Nonetheless, certain clinical conditions such as respiratory distress, perinatal asphyxia, concurrent nephrotoxic medications, and neonatal sepsis may alter its concentrations. Cystatin C glomerular filtration rate-based equations used to precisely evaluate renal function and early detection of renal injury. Recently published studies suggested Cystatin C to be used as a covariate of vancomycin CL. [176, 177]. In a longitudinal cohort study conducted in Queensland, Australia to measure serial Cystatin C in a group of neonates born preterm until two years. 58 preterm neonates were recruited with mean GA 26.2 weeks and mean birth weight 917 g. The analysis showed no significant difference in Cystatin C levels between 28, 32 and 37 weeks despite the significant increase in body weight [178]. In a retrospective study analyzed the laboratory data for 50 preterm neonates who received vancomycin therapy to compare the usefulness of Cystatin C for predicting vancomycin CL. The study reported a stronger correlation between vancomycin clearance and the inverse of Cystatin C than the inverse of Scr. In addition, glomerular filtration rate based on Cystatin C has a significant correlation with vancomycin clearance than creatinine clearance (CLcr), and regression analysis confirmed glomerular filtration rate based on Cystatin C as the only independent predictor of

vancomycin clearance [173]. In a study of over 52,000 hospitalized neonates in China, Cystatin C levels were found to remain stable regardless of gestational age or birth weight. Using the CyNA criteria, which define AKI based on elevated or rising Cystatin C, 9.8% of neonates had AKI, 0.8% by Kidney Disease Improving Global Outcomes (KDIGO)which define AKI based on Scr, and 0.8% by both. Neonates with AKI identified by CyNA only had a nearly threefold increased risk of in hospital death, while those meeting both criteria faced an even higher risk [175].

Based on the heterogeneity of studies, there is a potential benefit in performing an individual patient data analysis to create a large data set that answers questions about the effective and safe dose of vancomycin in neonates. This can be done by incorporating data from investigators including original deidentified data for each participant such as age, weight, gender and treatment received and its outcome rather than summarized pooled data [179]. Flexible data analysis, investigating the effect of participant level covariate on vancomycin treatment outcome, and the ability to evaluate the effect of therapeutic drug monitoring practice on vancomycin efficacy and toxicity making this approach highly recommended [180]. Combining data sets would resolve issues concerning sample size of different dosing regimens and the effect of multiple variables (age, weight or Scr) on vancomycin dosing and target attainment. Most of the current studies compare different dosing regimens in groups without appropriate age-matching and weight-matching. The use of different target trough concentration ranges (5-15, 10-15 and 10-20 mg/L) made it difficult to determine the target attainment of vancomycin in neonates across the different studies [126, 127, 129, 147]. As can be observed from the included studies, continuous and intermittent administration of vancomycin showed similar target attainment and efficacy. To reach therapeutic trough concentration more rapidly, a

loading dose is required before continuous IV infusion, as shown in different hospitals in Zhao et al. [119]. Continuous infusion required less frequent blood sampling compared with intermittent infusion, especially in preterm infants with a gestational age of < 29 weeks, in addition a fewer adverse related drug effects, making it well-tolerated [181]. The effect of continuous IV infusion on clinical outcome in neonates has not been studied but is likely to be associated with potentially increased target attainment compared with intermittent dosing.

Immunoassays implemented in vancomycin TDM were different between practices and substantially led to the diversity in vancomycin trough concentrations [182]. In the reviewed studies, clinicians did not take into account the effect of immunoassay methods on drug concentration. In addition, there was a lack of studies revealing the inter-assay variability in neonates due to their small blood volume.

Most studies of vancomycin dosing in neonates were not adequately powered to enable observation of correlation between vancomycin exposure and clinical outcomes such as efficacy and toxicity [127, 129, 133, 183]. Studies in neonates were limited by lack of individual patient data due to infrequent TDM sampling, blood cultures and Scr monitoring. Studies that could not observe statistical significances in their results often had a low number of blood samples or a short course (< 48 h) of vancomycin [127, 133, 136, 139, 147]. Therefore, data from observational studies presenting dosing regimens with high target attainment should be pooled and analyzed using population pharmacokinetic modelling to establish more precise dosing algorithms likely to result in high target attainment in neonates. MIPD can subsequently be compared with standard of care in randomised clinical trials. In addition, various methods of vancomycin concentration calculations were used: for example, one study extrapolated trough from two serum samples, which were drawn ≤30 minutes before the third dose [134], whereas in

another study, multiple samples were obtained during therapy, 24, 48, and 72 hours after the first dose, with steady state concentration (Css) calculated from the last two concentrations [152].

Another complicating factor to assess vancomycin outcome was the diversity of clinical indications of vancomycin, severity of infections, unpredictable symptoms of sepsis, and concomitant drugs used. Clinical outcomes related to the vancomycin dosing regimens were not reported. This was mainly because many of the included studies were retrospective and focused on pharmacokinetic targets rather than treatment response. In neonatal practice, it is also difficult to assess outcomes directly, as infants are usually treated with several antibiotics concomitantly, and clinical improvement may not always be linked to vancomycin alone. As a result, many studies did not provide enough information to determine whether the patient actually responded to the dosing regimen. Different target trough concentration ranges were used, with a higher concentration range of 15-20 mg/L for serious infections such as meningitis and endocarditis, and a lower target range for suspected sepsis of 10-15 mg/L [130]. A higher dose of 15 mg/kg/dose was recommended to treat patients with serious infections following a loading dose of 10 mg/kg. A lower dose of 10 mg/kg/dose was used to treat bacteremia in other studies [126, 130].

Among the reviewed studies, patient characteristics such as weight, PMA, PNA, GA or Scr level were considered determinants of trough concentration of vancomycin. Younger age neonates with PMA ≥29 weeks were most at risk of subtherapeutic levels [129, 134]. PNA and weight-based dosing regimens frequently resulted in sub-therapeutic levels with a low target attainment of < 50% of patients reaching the therapeutic target [133, 134, 136]. It appeared from the studies that using PMA-based dosing resulted in a higher target attainment, reflecting

the stronger association with maturational development in neonates, and thus vancomycin clearance [126, 128, 184]. It is worrisome that some of the empirical dosing regimens based on PMA and PNA demonstrated a target attainment < 40% [50]. In addition, due to lack of severity of illness classifications or absence of positive blood cultures, none of the studies were able to correlate vancomycin concentrations with clinical outcomes such as cure or mortality. Although several definitions of vancomycin-induced nephrotoxicity were found in the literature, there was no standard approach for diagnosing AKI in neonates receiving vancomycin. Toxicity was found to be significantly associated with high trough vancomycin concentration (> 15 mg/L) [185] taking into account gestational age [186]. Although vancomycin- induced nephrotoxicity is infrequent and reversible [187], a large-scale study with long term follow up would be necessary to determine the effect of nephrotoxicity on renal function at later age.

Among the limitations of the included observational studies, it was highlighted that free drug concentrations were not measured in any of the included studies, although this is the effective concentration to fight the pathogen.

Several opportunities for future research related to TDM of vancomycin in neonates have been identified. One of the most important debates is about appropriate exposure targets in neonates. Only vancomycin AUC_{24}/MIC targets for MRSA in adults have been defined. Data on targets for other pathogens are lacking, and it is unclear whether the same exposure should be targeted in neonates. From a toxicity point of view there is an urgent need to better define vancomycin-induced AKI in neonates; as mentioned earlier, Scr may not be the most appropriate measure. Fortunately, new biomarkers are being studied, potentially better reflecting renal injury [188]. What has been demonstrated is that model informed precision dosing is better suited to effectively achieve target concentrations [189]; however, due to lacking skills or staff shortages,

clinicians often rely on traditional dose calculators. To convince hospital administrators to invest in a specialized dosing service for drugs with a narrow therapeutic window like vancomycin, cost-effectiveness studies based on robust randomised controlled trials including efficacy and toxicity endpoints rather than target attainment are needed [190]. This means that although the tools to provide optimal TDM are available, few neonates benefit from such a service at the moment. Therefore, large-scale studies should be established by international collaborative initiatives [191] to provide the evidence needed to change practice.

2.6 Conclusion

This systematic review provides a heterogeneous picture of target attainment and vancomycin dosing strategies in neonates. Unfortunately, data were unsuitable to make consistent recommendations with respect to dosing, target attainment and efficacy or toxicity. A potential solution is to perform an individual patient data meta-analysis. Results from such a study could guide a prospective multicenter study to define vancomycin dosing regimens in neonates, resulting in an adequate clinical response without nephrotoxicity.

Chapter 3: TDM practice evaluation

This chapter contains the following published manuscript:

An Audit to evaluate vancomycin therapeutic drug monitoring in a Neonatal Intensive Care Unit

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3.1 Abstract

Background

TDM is used routinely for optimization of vancomycin therapy due to exposure-related efficacy and toxicity, and significant variability in pharmacokinetics leading to unpredictable drug exposure.

Objective

The aim of this study was to evaluate target attainment and TDM of vancomycin in neonates.

Method

The authors conducted a retrospective study and collected data from medical records of all neonates who received vancomycin therapy in the neonatal intensive care unit between January 2019 and December 2019. The primary outcome was the proportion of vancomycin courses that reached target trough concentrations of 10–20 mg/L based on appropriate TDM samples collection. Secondary outcomes included proportion of courses with appropriate dose and dose frequency, and proportion of patients who achieved target concentrations after the first dose adjustment.

Results

In total, 69 patients were included, with 129 vancomycin courses. The median initial vancomycin trough concentration was 12 (range: 4–36) mg/L. The target trough concentration was achieved in 75% of courses after the initial dose with appropriate TDM, and 84% of

courses after TDM-guided dose adjustments. Patients were dosed appropriately in 121/129 courses and TDM was performed correctly according to protocol in 51/93 courses. A dose adjustment was performed in 18/29 courses, to increase target attainment.

Conclusion

This study found that most neonates did not achieve the recommended vancomycin exposure with the current dosing regimens, and higher doses may be needed to improve target attainment. It also showed that relying on trough concentrations alone is not sufficient, highlighting the need for more effective TDM strategies to guide dosing in this population.

3.2 Introduction

Vancomycin is used in the treatment of infections caused by gram-positive bacteria such as MRSA, CoNS, and *Enterococcus* species [192]. These pathogens are common causes of serious systemic infections in the NICU. Moreover, increasing global prevalence of *Enterococcus* species in the NICU is of concern, especially because of the factors contributing to increased risk for colonization, such as catheterization, mechanical ventilation, treatment with antimicrobial agents, low birth weight, and immunosuppression [193]. Vancomycin is considered one of the empirical therapies to treat these infections in neonates [134, 194].

Vancomycin displays a significant interindividual and intraindividual variability in concentrations, due variability in renal clearance (with a mean of 30%) and volume of distribution (with a mean of 23%) in the neonatal group [195, 196]. Because concentrations that are too low result in treatment failure and high concentrations are associated with renal toxicity, different vancomycin dosing strategies have been proposed for neonates, based on body weight, age [e.g. GA, PMA, and/or PNA], and/or renal function [based on Scr)], to increase the likelihood of achieving therapeutic concentrations. Despite the use of different dosing categories, significant variability in vancomycin concentration indicates that there is a need for dose individualization to achieve a therapeutic vancomycin concentration in neonates. In addition, the increase in antimicrobial resistance, as indicated by elevated minimum inhibitory concentration (MIC) values [186, 197], has necessitated increased vancomycin doses and target trough concentrations, thus complicating vancomycin management even further [65]. TDM of vancomycin is, therefore, an important part of clinical decision-making, which helps improve clinical responses and reduce adverse effects [122, 198].

Currently, there is a lack of consensus on vancomycin dosing guidelines for neonates. Empirical dosing recommendations range between 10 and 20 mg/kg every 8, 12, 18, or 24 hours, based on age, weight, or renal function [107, 199]. Previous studies have supported the use of dosage regimen guidelines, where dose and dosing intervals are based on different categories of chronological age [126-128, 146, 148], Scr [132, 133], or weight [133, 136] Clearly, consideration of other factors that affect vancomycin target attainment and evaluation of local practice is also important to optimize the routine care. The objective of our study was to evaluate target attainment and TDM practice of vancomycin in neonates.

3.3 Method

A retrospective study was conducted in neonates treated with vancomycin in the NICU at Westmead Hospital over a period of 12 months (from January 2019 to December 2019). The study was approved by the local Human Research Ethics Committee (approval number: 2008-05 QA). Need for informed consent was waived because of the retrospective nature of the study. Neonates were included if they had received a vancomycin treatment course in this period, as demonstrated by documentation of relevant data in the medical record. In cases where a patient had received multiple courses of vancomycin, data on all courses were included. Vancomycin was administered via intermittent intravenous infusion over one hour, at a dosage of 15 mg/kg per dose for each patient, with dosing frequency based on corrected GA (CGA) and PNA, followed by TDM to individualize the dose (Table 3-1); adherence to TDM was tested in our study and defined as the percentage of blood samples obtained at the right time specified by the hospital protocol, according to CGA and PNA.

The guideline allowed for consideration of a loading dose of 20 mg/kg per dose, if there was suspected severe sepsis, for example, MRSA, meningitis, endocarditis, or bone infection. The dosing guideline followed took CGA into consideration as the primary determinant of dosing interval, with PNA as the secondary qualifier. Both are strongly correlated with renal function and drug elimination. For neonates who are <37 weeks of age, CGA dose changes would only be performed in case TDM has been performed, which informs the clinician about the actual drug exposure under the current renal clearance. To avoid toxicity, trough concentrations were obtained in the youngest age group (CGA ≤29 weeks, PNA <14 days) before the second dose; however, this does not reflect the steady state concentration. Hence, we excluded this group of neonates from the primary analysis of appropriate trough attainment due to high variability in pharmacokinetics and challenges in defining steady-state levels in this population. However, this cohort was included in secondary analyses, such as those shown in (Table 3-1) and discussed in Section 3.4.2 and (Figure 3-2), to explore proportion of doses administered appropriately, and to provide context for dose adjustment considerations in clinical practice.

The therapeutic target of vancomycin was defined as trough concentration between 10-20 mg/L. Dose adjustment was based on the trough level, as shown in (Table 3-1). According to the hospital protocol, nephrotoxicity was defined as an increase in SCr of 17–27 μmol/L per day from a previous lower value or a Scr greater than 133 μmol/L.

Table 3-1: Vancomycin dosing, TDM protocol, and dosing adjustment

Dose selection of vancomycin					**TDM**	
CGA (weeks)	PNA (days)	Dose (mg/kg)	Dosing interval (hr)	Collection of trough sample	Trough concentration (mg/L)	Dose adjustment based on measured trough sample independent of original dose
≤ 29	0-14	15	18	Before 2nd dose*	≤ 5	Increase the daily dose 50-75%
	>14		12	Before 4th dose	0-6	Increase the daily dose 25-50%
30-36	0-14	15	12	Before 4th dose	10-20	No change required
	>14		8			
37-44	0-7	15	12	Before 4th dose	21-30	Reduce the daily dose 10-30%
	>7		8			
≥ 45	ALL	15	6	Before 4th dose	≥ 30	Withhold treatment and repeat level when level 10-20mg/L restart at reduced daily dose (50%)

*to avoid toxicity trough concertation in the youngest age groups of CGA <= 29 weeks were obtained before 2nd dose which did not reflect the steady state concentration and could not be extrapolated because of treatment caseation.

Data collected included GA, CGA, PNA, birth weight, Apgar scores (a measure at 1 and 5 minutes of age of tone, heart rate, reflex irritability, colour, and respiration), weight at birth, length at birth, first Scr (<24 hours after birth), vancomycin indication, pathogen, treatment dose, frequency, duration, weight on day of treatment, cumulative dose, vancomycin trough concentrations, time of measurement of vancomycin concentration, time of last dose before measurement of vancomycin concentration, C-reactive protein concentration, procalcitonin, and sodium level. Scr concentrations within 24 hours of neonatal birth and follow-up measurements throughout the vancomycin course were collected, in addition to concurrent nephrotoxic medications. The primary outcome was the proportion of courses that reached target trough concentrations based on appropriate TDM collection according to the hospital protocol. Secondary outcomes included **(1)** proportion of courses dosed appropriately according to the hospital protocol, where adherence to the dosing protocol was defined as the percentage of courses dosed appropriately, reflected in mg/kg and frequency based on age and weight; **(2)** proportion of courses with a therapeutic level after the first dose adjustment; **(3)** proportion of patients that achieved target attainment based on TDM sampling; and **(4)** vancomycin renal toxicity was described when observed and related to the measured concentrations.

3.4 Results

A total of 69 neonates were included in this study, with none excluded for incomplete documentation. All patients were pre-term, with median GA of 28 (24.4–33.3) weeks, as shown in (Table 3-2). The most common indication for initial vancomycin therapy was risk of sepsis, and 37 cases were confirmed sepsis based on positive cultures. The responsible pathogens included *Staphylococcus epidermis* (coagulase-negative staphylococcus), *Enterococcus* species,

MRSA, and methicillin-susceptible *Staphylococcus aureus* (MSSA) (Table 3-2). A total of 129 courses of vancomycin were given in the NICU during the study period. One hundred courses were administered for ≤48 hours, 21 courses were administered for 2–5 days, and 8 courses were administered for >5 days.

Among vancomycin concentrations, 10 (7.8%) courses had no TDM sampling, whereas a total of 125 vancomycin trough concentrations were available, and the proportion of blood samples drawn for trough measurements was: 1 sample in 96 (74.4%) courses, 2 samples in 10 (7.8%) courses, and 3 samples in 3 (2.4%) courses. Overall, 119 initial trough concentrations were drawn, trough concentrations were measured before the 4th dose in all neonates, except for infants with corrected gestational age ≤29 weeks and postnatal age ≥14 days, as described in section 3.3.

Fifty one samples (55%) were drawn appropriately according to the hospital protocol, as shown in (Table 3-3). Forty-two (42%) deviations were observed in TDM practice, 20 courses had first blood sampling before the fifth dose, and 22 courses before the third dose. Thirty-eight (75%) of the 51 initial concentrations collected appropriately reached the target.

Table 3-2: Patient characteristics

Patient demographics	
Gender (Male/Female)	69(40/29)
Vancomycin courses	129
GA (weeks)	28 (24.4-33.3)
CGA (weeks)	31.1 (25.1-42)
PNA (days)	19 (1-91)
Weight at birth (g)	975 (495-2142)
APGAR score	
1 min	5 (0-9)
5 min	7 (1-9)
C-reactive protein (mg/L)	4 (<3-143)
Procalcitonin (μg/L)	0.28 (0.06-62.31)
Serum creatine (umol/L)	67(44-105)
Sodium level (mEq/L)	136(118-144)
Positive blood culture N (%)	
Coagulase-negative staphylococcus	15 (40.5)
Enterococcus species	10 (27)
Staphylococcus epidermis	7 (18.9)
MRSA	4 (10.8)
MSSA	1 (2.7)

Demographics are presented as median (range). GA; gestational age, CGA; corrected gestational age, PNA; postnatal age, APGAR; Appearance, Pulse, Grimace, Activity, Respiration, MRSA; methicillin resistant *staphylococcus aurous*; MSSA; methicillin sensitive *staphylococcus aurous.* Serum creatinine represents baseline values measured before vancomycin therapy.

Table 3-3: Therapeutic drug monitoring and dosing practice evaluation and therapeutic drug target according to each neonatal group

CGA (weeks)	PNA (days)	Interval (hrs)	Courses n:	Appropriate dose n (%)	Appropriate TDM n (%)	Initial trough levels					First dose adjustment		Trough levels after first dose adjustment		
						n:	Trough level mg/L	Subtherapeutic levels n (%):	Therapeutic levels n (%):	Therapeutic levels based on appropriate TDM n(%)	Supra-therapeutic levels n (%):	n (%)	Dose adjust-ment in %:	n (%)	Therapeutic n (%):	Non-therapeutic in mg/L:
<= 29	**0-14**	**18**	**28**	**27 (96.4)**	**16 (67)**	**26**	**7 (3-15)**	**22 (88)**	**4 (15.4)**	**4(25)**	**0**	**17/22 (77.2)**	**100 (25 to 200)**	**7 (20)**	**4 (57.1)**	**6, 9, 25**
	>14	12	16	14 (87.5)	10 (71)	14	11 (6-16)	5 (38.4)	8(61.5)	6(60)	1 (7.1)	3/6 (50)	41.5(-66 to 50)	2 (6)	1 (50)	9
30-36	0-14	12	24	22 (91.7)	14 (64)	23	13 (4-26)	5 (21.7)	16 (69.6)	6(43)	2 (8.7)	4/7 (57)	35 (20 to 50)	2 (6)	1 (50)	22
	>14	8	49	46 (93.9)	21 (45)	46	15 (4-36)	5 (10.9)	34 (73.9)	17(81)	7 (15.2)	7/12(58)	-20 (-75 to 50)	3 (9)	1 (0.33)	0.3, 8
37-44	0-7	12	0	0	0	0	0	0	0	0	0	0	0	0	0	-
	>7	8	12	12 (100)	6 (50)	10	12 (5-16)	4 (40)	6 (60)	5(42)	0	4/4 (100%)	50 (40 to100)	2 (6)	2 (100)	NA
>=45	ALL	6	0	0	0	0	0	0	0	0	0	0	0	0	0	-
TOTAL			129	121 (93.8)	51 (55)[#]	119	13 (3-36)[#]	19 (22%)[#]	64 (68)[#]	38 (75)	10 (8.4)[#]	18/29 (62)[#]	50 (-75 to 100)[#]	9 (31)[#]	5 (55.5) [#]	-

Row with bold values indicates the trough concentrations obtained before the second dose. And excluded from target attainment proportion calculations, Trough concentrations obtained before the 4th dose were included in the total calculations

(Figure 3-1) shows the dosing protocol, therapeutic targets achieved, and dosing adjustments performed in our cohort.

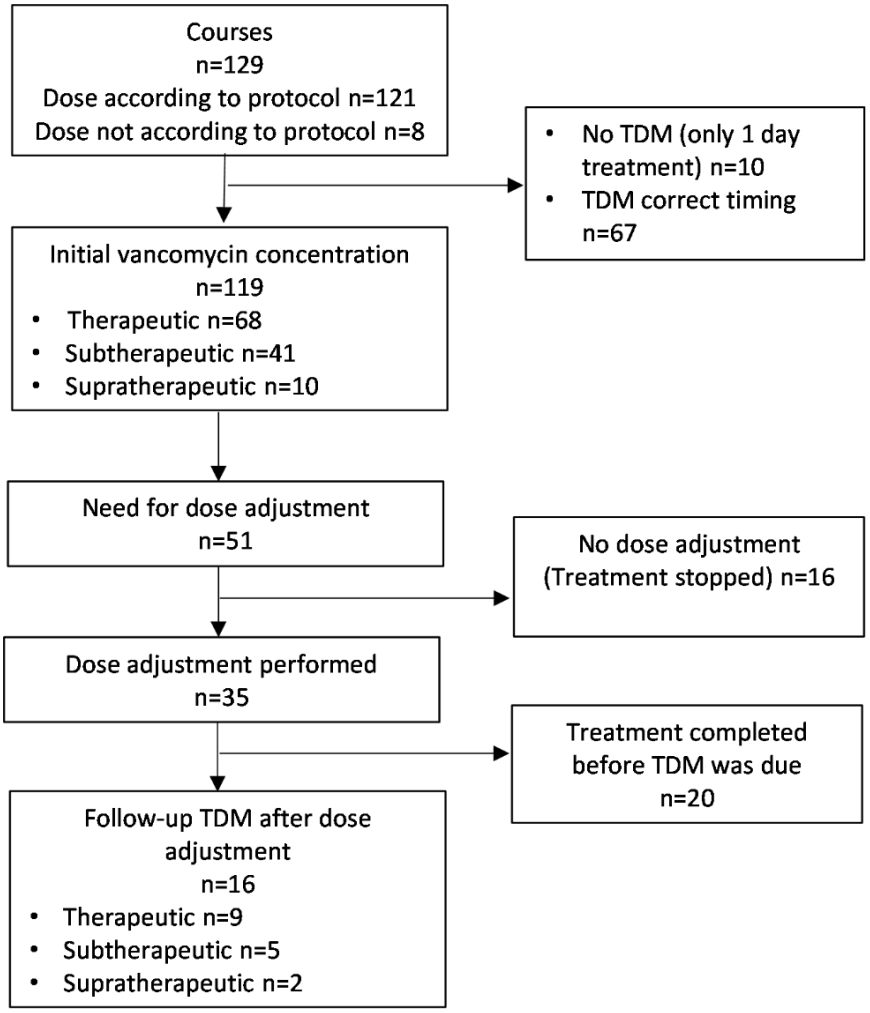

Figure 3-1: A flowchart of therapeutic drug monitoring and dosing practice evaluation of included courses.

3.4.1 Proportion of courses dosed appropriately, according to the hospital protocol

A dose of 15 mg/kg per dose was administered to all the neonates, as an initial dosing regimen, and 121 (93.8%) courses were dosed appropriately according to the hospital protocol, as described in detail in (Table 3-3). Of the 8 courses that were dosed inappropriately, 6 were given as 15 mg/kg every 12 hours, instead of the scheduled 8 hours, one was given as a scheduled dose every 12 hours, instead of the scheduled 18 hours, whereas in another, the dose calculation was based on the birth weight, instead of the current weight.

3.4.2 Proportion of courses with a therapeutic level based on the initial dose

In the cohort, 64/93 (68%) of the initial concentrations were within the target trough range of 10–20 mg/L (Table 3-3), whereas 19/93 (22%) trough concentrations were <10 mg/L. Only 3 patients had trough concentrations < 3 mg/L, after having received the initial dose of 15 mg/kg per dose. The youngest age group (CGA 29 weeks, PNA 0–14 days) had the highest proportion of patients with subtherapeutic concentrations. Samples were all collected before the second dose. This early sampling explains the low concentrations, rather than differences in blood collection timing between subjects. However, in the group of neonates with CGA 30–36 weeks and PNA > 14 days, the highest proportion of courses (15.2%) were supratherapeutic (> 20 mg/L). The vancomycin trough concentrations after initial doses are shown (Figure 3-2).

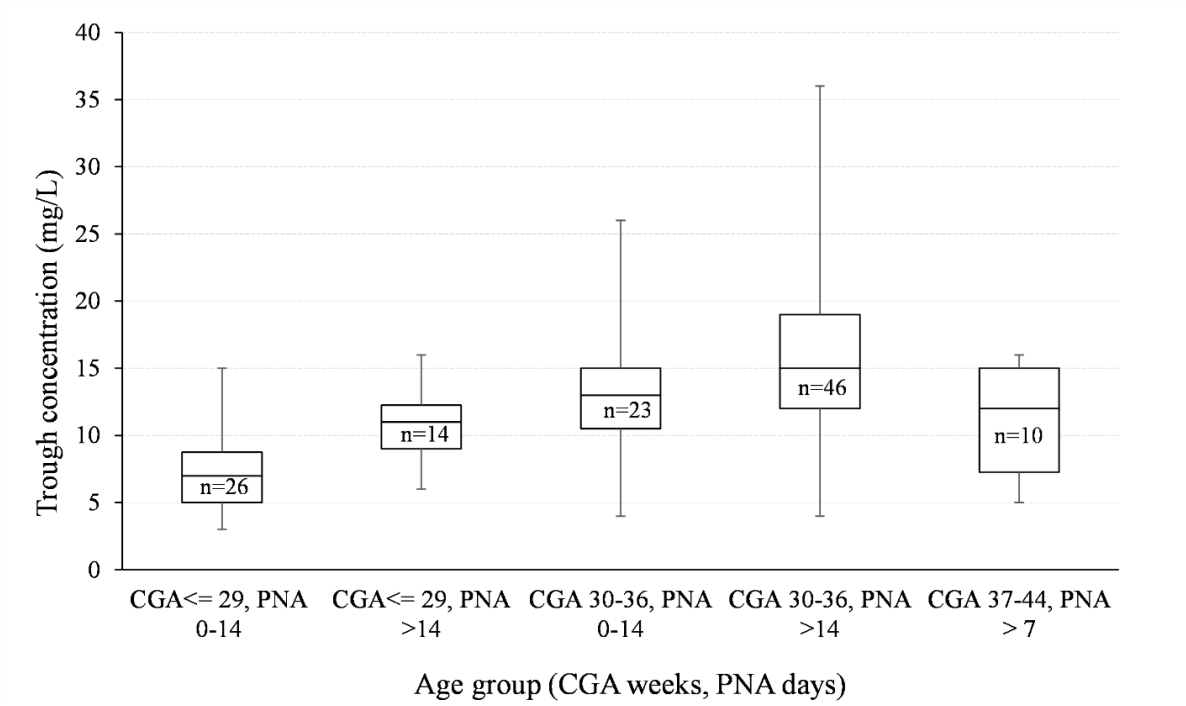

Figure 3-2: Distribution of vancomycin plasma concentrations in the different age groups after treatment initiation.

3.4.3 Proportion of courses that reached a therapeutic level after first dose adjustment

Of the 29 concentrations that were not within the target trough range, 18/29 doses were adjusted to achieve target concentrations, as shown in (ch) . Median dose adjustment was a 50% increase of initial doses (range −75% to 100%). Neonates in the youngest age group (CGA ≤29 weeks) required the highest median daily dose increase (median of 100% dose increment, n = 16 courses), whereas patients in the fourth age group (CGA 30–36 weeks, PNA >14 days) required a median of a 20% dose decrease (n = 4 courses). Post dose adjustment vancomycin concentrations were available for 16 courses, because 20 courses were ceased before their next vancomycin level was due. Therapeutic concentrations were achieved in 5/9 (55.5%) courses after first dose adjustment. In 4 courses, vancomycin concentrations remained subtherapeutic

even after the first dose adjustment, with median trough concentration of 8 (0.3–9) mg/L. One of these had a second dose adjustment, with a dose increase of 25%, resulting in increased vancomycin concentration from 9 mg/L to 17 mg/L, whereas other courses were ceased without any further dosing adjustments. However, in 2 courses, the concentrations became supratherapeutic after one dose adjustment of daily dose increase [22 and 25 mg/L for the age group (CGA ≤29 weeks, PNA 0–14 days)], and the courses were ceased afterward without dose adjustment.

3.4.4 Proportion of patients that achieved target attainment based on TDM sampling.

Of the overall vancomycin concentrations, 43 were between 10 and 20 mg/L, resulting in a probability of target attainment of 84% (43/51) in the cohort. As presented above, 43 courses reached the therapeutic target based on the appropriate TDM. Of the concentrations that did not achieve target attainment, 5 courses (out of the 9 available samples) reached the target after the first dose adjustment.

3.4.5 Renal toxicity

Baseline SCr and follow-up SCr were available in 71 courses. In 9 courses, baseline SCr were missing, whereas in 49 courses, no follow-up was available, and another 43 courses were short (≤48 hours). The incidence of nephrotoxicity in our cohort was 1.6%: 2 patients developed nephrotoxicity, where one patient received gentamicin and furosemide, and the other patient received gentamicin and indomethacin concomitantly with vancomycin. Renal function was found to be increasing in 55% of neonates (Figure 3-2) indicating kidney development with age.

3.5 Discussion

Our study evaluated vancomycin treatment and routine TDM in the setting of empirical treatment. Clear evaluation of routine care is a continuous process to ensure quality of care and detect opportunities for improvement. Wherever possible, it should include not only adherence to guidelines, but also the outcome of patients, to demonstrate clinical relevance.

In our study, adherence to dosing guidelines was high, whereas adherence to TDM practice was moderate, thus demonstrating that TDM is a complex procedure. Furthermore, accurate TDM timing is very difficult in a busy clinical environment, because it involves the steps of collecting, sending, testing, and reporting on the sample, amidst changing shifts between clinical staff. Some studies [200] report limitations in data analysis and results interpretation because of missing or incorrect blood samples [201]. A multicenter nonblinded randomized controlled trial recommended the timing of TDM to be before the fourth dose, instead of the third dose, to ensure that the vancomycin level is within the steady state concentration [202].

Audits on vancomycin dosing in neonates have assessed the effectiveness of their empirical dosing regimen and probability of target attainment without evaluating the percentage of doses administered appropriately according to their practice [203-205]. Our study reveals that vancomycin doses were administered appropriately according to the hospital's protocol, which indicates that all neonates in each age group had the same dose and frequency, and thus, it can be said with confidence that the trough concentrations and probability of target attainment were estimated precisely.

In target attainment based on the initial dose, 43% of initial concentrations were outside the therapeutic target range. Most subtherapeutic concentrations were found in the neonates of the

youngest age group (CGA ≤29 weeks and PNA <14 days). In this group, longer dosing intervals of 18 hours were used, because of anticipated low renal function, indicating that there may be the requirement of a loading dose to achieve the target concentration earlier. Lower postmenstrual age is a risk factor for suboptimal dosing after empirical therapy [134]. Although shorter dosing intervals were used in older neonates, subtherapeutic concentrations were still observed. The fourth age group (CGA 30–36 weeks, PNA >14 days) presented the highest percentage of individuals in the target range. We also observed the highest proportion of supratherapeutic concentrations in this group, whereas vancomycin concentration >25 mg/L was predominant. Our dosing protocol of 15 mg/kg per dose was effective in achieving initial target trough concentrations and it resembles a dose regimen used in a study by Anaïs et al, which used a lower dose of 10 mg/kg per dose [149]. Radu et al. [129] also used a 15 mg/kg per dose protocol, similar to that in our study. In both studies, target attainment was achieved in more than 50% of the participants. However, the youngest age group consistently displayed subtherapeutic levels in both the studies.

Because of the short period of courses, doses were adjusted in several courses where trough concentrations were outside the therapeutic range, but few courses had TDM after dose adjustment, thereby increasing the difficulty in interpretation of results. This explains the shortage of studies exploring target attainment after dosing adjustment. Subtherapeutic concentrations in the youngest age group (CGA ≤29 weeks, PNA 0–14 days) required the highest median dose increase of 100%, whereas the age group (CGA 30–36 weeks, PNA >14 days) required a lower median dose increase of 20%. Radu et al recorded the first steady state vancomycin concentration that did not reach the target range and used this for dose adjustment. They found that the youngest group required the highest mean dose increase (9 patients, 50.4%), whereas the eldest group required an average dose reduction (4 patients, −26.6%) [129].

The TDM protocol included a large dose increase (>50%), in case levels were <5 mg/L; this could potentially result in a supratherapeutic concentration, if the adjustment is made before steady state. Fortunately, we did not find any of such cases in our study; however, the sample size in this patient category was also small (n = 10 courses). The use of dosing software could prevent this, because it facilitates personalized dose adjustments. Through dose adjustments guided by TDM, the probability of target attainment was increased by 9% in the present study, thus taking the probability of target attainment to 84% overall therapeutic levels in our cohort. This supports the need for Bayesian software to individualize TDM practice in the hospital protocol. Although, the whole picture of target attainment could not be interpreted because of short treatment courses, upon looking at courses >48 hours, a small percentage of them (7/27, 25%) remained outside the range of therapeutic trough levels after first dose adjustment.

In our study, AKI incidence was 7.4% for patients who continued treatment >48 hours (2 cases out of the 27 courses that were continued for >48 hours); only 2 patients had Scr elevation, according to the AKI definition in the hospital protocol. Both patients were on 2 nephrotoxic agents concomitantly with vancomycin. The renal toxicity was reversible in these patients, as demonstrated by the declining Scr level after vancomycin cessation. Apparent renal Scr level decrease from baseline was observed in our cohort, indicating kidney function maturation and improvement in neonates after birth. Because of the high number of courses of duration ≤48 hours (102 courses, 79%), neonates did not have time to develop nephrotoxicity, and thus, we could not analyze the nephrotoxic effect in our study. It is known that vancomycin causes nephrotoxicity, especially in the presence of other nephrotoxic drugs; however, the extent of association between nephrotoxicity and vancomycin trough serum concentration has not yet been established in neonates. No specific definition of nephrotoxicity in neonates is found in the literature [187]. Because of the large difference between PK parameters in adults and neonates,

where kidney function is immature in the neonatal group, the adverse effects associated with high initial vancomycin trough concentration are unknown and need more investigation and follow-up. In a study by Bhargava et al, the overall AKI incidence was 2.71%. The study also showed a statistical significance between AKI and vancomycin trough concentration [151]. In a study by Ringenberg et al., although 47.2% of patients were on concomitant nephrotoxic drug with vancomycin, no patient experienced nephrotoxicity [131]. Sosnin et al. revealed that AKI incidence in their cohort was 3% and renal function required between 1 and 18 days to return to normal, without renal replacement therapy [137].

There are a few limitations associated with our study. First, the study is a small-scale retrospective analysis. Second, the data were comprised primarily of short treatment courses (1-2 days), which limited our ability to analyze clinical outcomes related to vancomycin treatment, such as efficacy and toxicity, in addition to TDM follow-up after dosing adjustment. Moreover, the audit was performed to explore target attainment and toxicity in neonates, but unfortunately dosing software is not available in our hospital. Therefore, there is a need for larger prospective studies with comprehensive follow-up, to validate target attainment at steady state using dosing software, instead of fixed time-point sample collection.

Vancomycin was started as an empirical treatment in most cases and short courses of less than 48 hours are, therefore, common. Our data indicated that higher dosages, or a loading dose should be trialed, because we observed low target attainment. With empirical treatment, there is a need for a dose resulting in adequate exposure, to effectively treat infections, especially those caused by a pathogen with MICs close to the breakpoint [206]. When results come back from the microbiology lab at around 48 hours, a decision can be made to stop or continue treatment. Within the short time frame of 48 hours, it is not expected that significant toxicity would result

from exposure to a higher level of dose, but in case of treatment continuation, offering of an effective treatment for the first 48 hours is likely to result in better treatment outcomes. Delaying effective antimicrobial treatment in neonates will increase the risk of mortality and morbidity. Therefore, biomarkers such as plasma procalcitonin concentration or C-reactive protein could serve to be useful, in addition to vancomycin TDM. A rapid decline in infection parameters could show that the treatment is effective, whereas no change in these parameters could show that it is not. If the infection parameters are not declining while vancomycin concentrations are in the so-called therapeutic range, it should trigger further evaluation [207]. Switching to collecting a sample at the time decision is made to continue treatment, in combination with dosing software, may be a potential solution to prevent unnecessary collection of trough samples in patients who discontinue vancomycin.

We acknowledge the limitations of trough level-guided dosing for attaining a therapeutic range of 10–20 mg/L, because it may not adequately reflect the recommended AUC_{24}/MIC target in every patient. Traditionally, C_{min} targets have been considered to calculate the AUC, for practical reasons in the absence of dosing software. A study by Gwee et al determined an AUC_{24} of ≥300 mg/L·h in the first 24 hours or ≥ 424 mg/L·h between 24 and 48 hours of treatment as target for vancomycin, to treat staphylococcus infections in neonates [208].

Because of the significant interindividual variability in CL and Vd of distribution, there is a need for a subsequent dosing adjustment based on TDM results, to individualize dosing of vancomycin and attain therapeutic target concentrations; however, no study has previously reported about dosing adjustment. In our study, the first dose was adjusted in several courses, to reach the target concentration; however, only a small number of courses had blood sampling following dose adjustment, because of treatment cessation. Target attainment percentage

increased after dosing adjustment, which shows that the hospital's TDM protocol was successful in dose individualization. However, 33% of the concentrations remained subtherapeutic after daily dosing increment, with a median of 50%. Therefore, using a Bayesian TDM tool will increase the accuracy of dose adjustments and enable target attainment without the need for a second dose adjustment. Different MIPD software are used to individualize vancomycin dosing in neonates [209]. Clinical pharmacists could serve as local supporters to facilitate the use of MIPD in critical care. They are valued members of the multidisciplinary team who have the skills set to conduct TDM using more advanced dosing software and make appropriate dose recommendations [210]. To implement this in clinical settings, there is a need for developing an institutional guideline and making resources available for pharmacists. When applied to the right patient population, MIPD could serve to be cost-effective, although there is a need for more studies to achieve the same [211]. In a study by Tasa et al. used a web-based dosing adjustment tool which characterized the dose to maximize the target attainment in subsequent concentrations [212].

3.6 Conclusion

In conclusion, the current practice and protocol in Westmead Hospital needs further revision and adjustment, especially in cases of very young neonates (CGA <29 weeks). For this purpose, a personalized dosing application depending on pharmacokinetic variables would be valuable to increase the proportion of neonatal patients who attain vancomycin target trough concentrations.

Chapter 4: Model Selection

This chapter contains the following published manuscript:

Bayesian vancomycin model selection for therapeutic drug monitoring in neonates

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4.1 Abstract

Background and Objective

PK models can inform drug dosing of vancomycin in neonates to optimize therapy. However, the model selected needs to describe the intended population to provide appropriate recommendations. Our study aims to identify the PopPK model(s) with the best performance to predict vancomycin exposure in neonates in our hospital.

Method

Relevant published PopPK models for vancomycin in neonates were selected based on demographics and vancomycin dosing strategy. The predictive performance of the models was evaluated in Tucuxi using a local cohort of 69 neonates. Mean absolute error (MAE), relative bias (rBias) and relative root mean square error (rRMSE) were used to quantify the accuracy and precision of the predictive performance of each model for three different approaches: a priori, a posteriori, and Bayesian forecasting for the next course of therapy based on the previous course predictions. A PopPK model was considered clinically acceptable if rBias was between ± 20 and 95% confidence intervals included zero.

Results

A total of 25 PopPK models were identified and nine were considered suitable for further evaluation. The model of De Cock et al. 2014 was the only clinically acceptable model based on a priori [MAE 0.35 mg/L, rBias 0.8 % (95% confidence interval (CI) - 7.5, 9.1%), and rRMSE 8.9%], a posteriori [MAE 0.037 mg/L, rBias - 0.23% (95% CI - 1.3, 0.88%), and

rRMSE 6.02%] and Bayesian forecasting for the next courses [MAE 0.89 mg/L, rBias 5.45% (95% CI - 8.2, 19.1%), and rRMSE 38.3%) approaches.

Conclusions

The De Cock model was selected based on a comprehensive approach of model selection to individualize vancomycin dosing in our neonates.

Key Points

- Pharmacokinetic model selection based on population, disease and treatment characteristics can help to reduce the workload for model evaluation
- Pharmacokinetic model evaluation using local population data should used to choose the appropriate model.
- A vancomycin trough concentration in neonates does not have to be higher than 15 mg/L to achieve AUC_{24}/MIC ratio > 400 h

4.2 Introduction

Despite the use of vancomycin in neonatal intensive care units to treat infections for more than four decades [213], a lack of consensus remains on optimal dosing. Dosing decisions are particularly challenging in neonates, because patient characteristics such as age [GA and PNA], body weight, and maturation of organ function contribute to rapid changes in vancomycin pharmacokinetics. Vancomycin is predominantly renally cleared, and its renal elimination depends mainly on glomerular filtration, which increases as a function of PNA as renal function matures [214]. Although vancomycin pharmacokinetics have been extensively studied, empiric dosing based on either fixed, body weight, serum creatinine, and/or age-based dosing frequently fail to achieve the exposure targets [65]. Trough concentrations between 10 and 20 mg/L and AUC_{24}/MIC of 400–600 h have both been considered as exposure targets in adults [215]. However, it remains unclear whether these exposure targets can be extrapolated to neonates. Previously, we have shown that vancomycin dose adjustments were required in 62% of courses of therapy of greater than 3 days [216]. Hence, better vancomycin dosing strategies and more effective TDM practices are needed to achieve vancomycin exposure targets in neonates.

MIPD software, a computational tool, has grown to use mathematical models, patients' information, and observed concentrations to optimize therapy [217]. MIPD proved its benefit to predict the required dose to reach target attainment, and broad implementation is limited due to lack of understanding of its benefit and skills, costs, and regulatory issues [218]. Such software has shown benefits in reducing incidence and/or rate of adverse effects and improving clinical outcomes. Also, it proved its benefits in reducing the costs of treating infections [219].

To fully prevail these benefits, we have to select the best model to describe the local patient population, as an inaccurate prediction of drug exposure can lead to inappropriate dose recommendations [220].

Therefore, the aim of our study is to identify vancomycin PopPK models in neonates from literature and evaluate the predictive performance of the selected models using data from our local NICU population. Literature indicated that PK in both preterm and full-term neonates are quite similar, and there is no real difference between term and preterm models, as vancomycin PK models consist of various combinations of significant covariates, such as PNA, PMA, and weight, which indicates growth and maturation [214]. Vancomycin AUC_{24}/MIC, rather than trough concentration, is the PK parameter used to inform dosing decisions for vancomycin in adults [221]. Recent studies have revealed that an AUC_{24}/MIC ratio 400–600 h is highly predictive of efficacy and toxicity of vancomycin in neonates [221, 222]. However, AUC_{24}/MIC calculation is practically limited in individuals due to the need of collecting more than one trough concentration. In adults, a trough concentration range between 15 and 20 mg/L is expected to reach an AUC_{24}/MIC ratio > 400 h, but in the case of neonates, lower trough concentration ranges could be sufficient to reach an AUC_{24}/MIC > 400 h [222]. As a secondary outcome, the correlation between AUC_{24}/MIC and posteriori trough concentrations was evaluated using the best possible model.

4.3 Methods

4.3.1 Model selection

To identify vancomycin PopPK models, a systematic literature search was performed using the PubMed database from its inception to 7 April 2022. The search terms were “vancomycin” and “neonates” and “pharmacokinetics”. Titles and abstracts were independently reviewed by two researchers (DA and RV) before full text articles were retrieved for assessment. The reference lists of included articles were manually screened to identify additional studies. PopPK models were included based on matching local demographic characteristics such as gestational age 28 (24.4–33.3) weeks, postnatal age 19 (1–91) days, postmenstrual age 31.1 (25.1–42) weeks, weight 975 (495–2142) g, and dosing regimen 15 mg/kg intermittent intravenous (IV) infusion [216]. Studies on neonates on ECMO were excluded. PopPK models lacking relevant details on model parameters preventing replication were also excluded. Data on model structure, population pharmacokinetic parameter values, covariate relationships, interindividual variability, residual variability, and patient cohorts’ demographic characteristics were extracted from eligible studies. As the babies in our cohort were born as a preterm, and some of them stayed in the hospital for a long time, the median (range) of hospital stay was 27 (7–90) days, and they received more than one vancomycin course during their hospital stay at different occasions at PMA < 37 or > 37 weeks, we included studies with preterm and term neonates. For studies presenting more than one model with two different settings or populations we chose the best model reflecting our cohort and situation. Out of the models reflecting the same population, we choose the model with the lowest objective function value (OFV) [223]. Extracted data (DA) were independently verified by a second reviewer (TN).

4.3.2 Vancomycin validation dataset

We used a previously published dataset from Westmead Hospital (Sydney, Australia) NICU, which included vancomycin dosing and concentration data from 69 neonates between January–December 2019 [216]. This study was approved by the local Human Research Ethics Committee (approval number 2008-05 QA). Vancomycin dosing and TDM practices were at the discretion of the treating physician. In brief, vancomycin was administered intermittently at 15 mg/kg/dose in a frequency based on patient's CGA and PNA. TDM was performed after the fourth dose in neonates age CGA > 29 weeks and before the second dose in neonates of CGA ≤ 29 weeks. The vancomycin dose was adjusted in both under and overexposure based on the hospital's protocol. A trough concentration between 10 and 20 mg/L was considered the therapeutic target according to the hospital guidelines. All samples included in this study were trough concentrations.

4.3.3 Model predictive performance evaluation

The predictive performance of each selected model was evaluated in Tucuxi [224] using the vancomycin validation dataset. While Tucuxi offers a user-friendly graphical user interface, its core computing engine can also be run as a command line tool. To automate the tests and reduce the human error factor, we designed Python scripts for getting all the data from an Excel file, running the command line tool, and extracting the data. It also offered a way to detect errors in the dataset, allowing a better check of the initial data. The computations were run for all the patients in three different modes: *apriori* prediction which rely only on using patient's covariates to predict concentrations, *aposteriori* prediction (intra-course Bayesian forecasting) Using observed concentrations during a current course to predict future concentrations in the same course (e.g., after dose a adjustment), and Bayesian forecasting for next course (inter-

course Bayesian forecasting) Using individual PK estimates derived from a previous course to predict concentrations in a new, subsequent course before new levels are available. Covariates considered significant in each model such as PNA, CGA, gender, birth weight, weight at initiation of the vancomycin course of therapy, and Scr were used for *apriori* prediction without any vancomycin concentrations. Although, each model has its own structure, whether it is 1 or 2 compartment model and various significant covariates, Tucuxi allows users to upload any model via an online drug editor and select a Bayesian prior based on the study cohort. Afterwards, using parameters and a structural model, Tucuxi will predict concentrations, which can be compared with the observed concentrations. The observed serum vancomycin concentration for each patient was used for a posteriori estimation of individual PK parameters, which in turn is used to predict concentrations. For patients with more than one course of vancomycin therapy during their hospital admission, the first course of therapy was used to predict the concentrations in the next course, considering interaction between interindividual variability and residual variability for prediction of subsequent serum vancomycin concentrations (Bayesian forecasting). Mean absolute error [MAE, (Equation 1)], relative bias [rBias, (Equation 2)] and relative root mean squared error [rRMSE, precision (Equation 3)] were calculated to quantify the accuracy and precision of PopPK models, respectively:

Equation 1 MAE = $\frac{1}{N}\sum_{i}^{n}|predicted_i - observed_i|$

Equation 2 $rBias = \frac{1}{N}\sum_{1}^{i}\frac{predicted_i - observed_i}{(observed_i + predicted_i)/2} X\ 100$

Equation 3 $rRMSE = \sqrt{\frac{1}{N}\sum_{1}^{i}\frac{(predicted_i - observed_i)^2}{((observed_i + predicted_i)/2)^2}}\ X\ 100$

Where N is the number of concentrations

A model was considered clinically acceptable when rBias ranged between − 20 and 20% and when the 95% confidence interval (CI) included zero [225, 226]. All models were compared based on bias and rRMSE, and we selected those models with the lowest values because there are no established thresholds for bias and rRMSE in literature; more research is needed to specify the precision acceptability threshold for vancomycin predictions in neonates [226]. The goodness of fit plots was used to assess the correlation between predicted and observed concentrations.

4.3.4 The relationship between trough vancomycin concentrations and AUC_{24h}

The relationship between daily vancomycin AUC_{24} values and predicted trough concentrations using the best performing model in *aposteriori* approach was determined by linear regression correlation constant [227].

4.4 Results

4.4.1 Model selection

Overall, 25 vancomycin PopPK models for neonates were identified, of which 9 models were evaluated [143, 150, 192, 195, 228-232], the overall description of the model is in (Table 4-1). Sixteen models were excluded for the following reasons: study included mixed populations other than neonates such as older children and infants [220, 233, 234], vancomycin administration was a continuous infusion [119, 235, 236], essential details of the PopPK model description such as model structure, variability, PK parameters, and covariate relationships were lacking [79, 237-240], or patients were receiving extracorporeal membrane oxygenation [241] or positive ventilation pressure [242]. Lastly, one model was excluded, as it was specifically

designed to investigate the effect of amoxicillin and spironolactone coadministration on vancomycin clearance and volume of distribution [243]. In the study of De Cock et al [244] two models were identified. One of these models was excluded as it included ibuprofen coadministration in the covariate model and used an Amikacin covariate model to predict vancomycin clearance which is not reflective of our cohort [245]. The flowchart in (Figure 4-1) summarizes the model selection criteria.

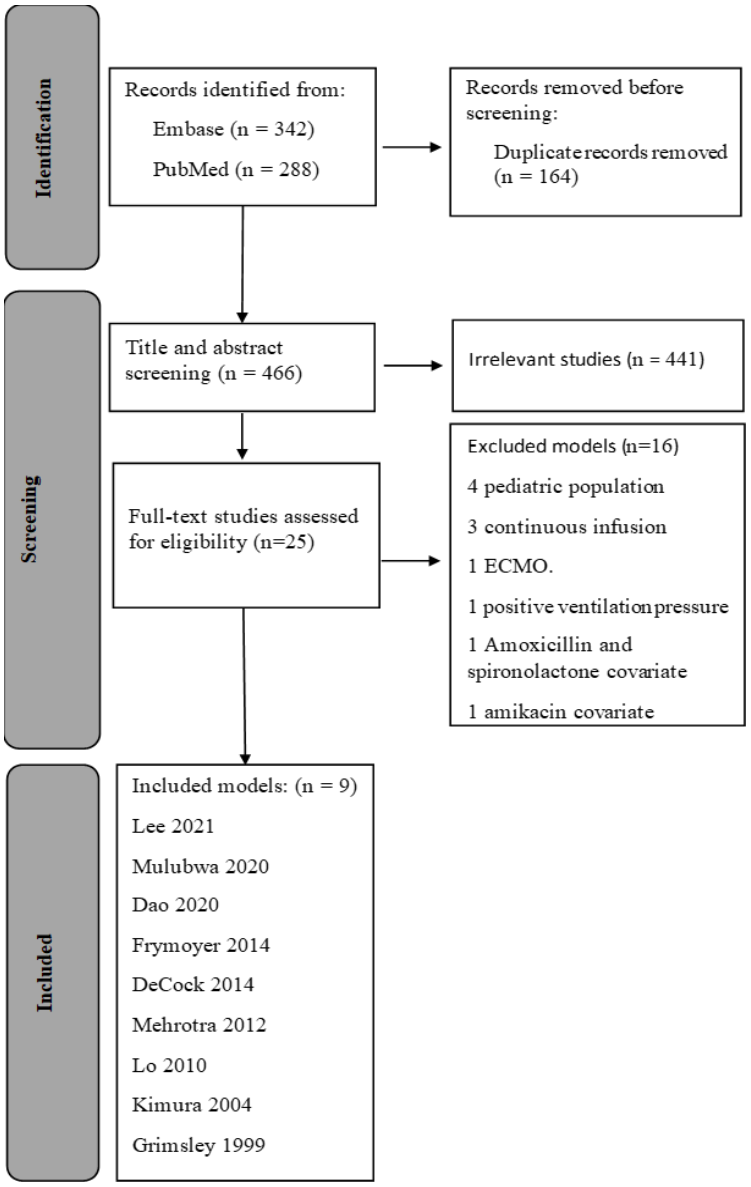

Figure 4-1: Flowchart shows the model selection.

Table 4-1: Description of the population pharmacokinetic models for vancomycin in neonates.

Ref	year	Neonate (n)	Sample (n)	PNA (days) [Median (Min-max)]	GA (weeks) [Median (Min-max)]	Weight (kg) [Median (Min-max)]	Model structure/ modelling software	Pharmacokinetic parameters and covariate relationship	BSV (std)	RUV	Model evaluation
Lee [192]	2021	207	900	2.3 (0-16.4)	31.5 (23.3 - 41.5)	1.5 (0.5 - 5.4)	1 CMT/ NONMEM®	**CL** = 2.09 * $(WT/70)^{0.75}$ * (PMA/31.7) * $(CLcr/50.3)^{0.741}$ **V**=45.6*(WT/70)	CL: 0.123 V: 0.26	Add: 2.015 mg/L Prop: 0.583	Bootstrap
Mulubwa [230]	2020	19	45	14 (3-58)	31 (23-34)	1.27 (0.63-2.69)	1CMT/ Monolix 2018R2	**CL**= 0.102* $(WT./1.48)^{0.75}$ *e^{n} **V**=0.884*$(WT/1.48)^{1}$*e	CL: 0.071 V: 0.107	Exp: 0.284	GOF, (IWRES) and visual predictive checks (VPC).
Dao [195]	2020	405	1831	12.3 (5-14)	29 (26.7-34.9)	1.05 (0.79-2.17)	1 CMT/ NONMEM®	**CL** = θ1 * $(WT/WT_{median})^{\theta 2}$ * $(SCr_{median}/SCr)^{\theta 3}$ * $(PMA^{Hill} / (PMA^{Hill} + T50^{Hill}))$ **V**= θ4 * WT	CL = 0.226 V = none	Add: 1.98 mg/L Prop: 0.236	GOF, bootstrap, pcVPC and NDPE
Frymoyer [229]	2019	492	1702	19 (10-42)	34 (27-39)	2.9 (1.6 - 3.7)	1CMT/ NONMEM®	**CL**(L/h) = 0.345 $(WT/2.9)^{0.75}$*1/(1+ $[PMA/34.8]^{-4.53}$* $(1/SCR)^{0.267}$ **V**(L)=1.75*(WT/2.9)	Exp: 0.216	Add: 1.3 mg/L Prop: 0.205	Bootstrap and NDPE
DeCock [228]	2014	273	689	14 (1-28)	29 (29-34)	1.14 (0.38-2.55)	2 CMT/ NONMEM®	**CL** = CLp × $(bBW/median)^{m}$ × (1 + n × (PNA/median)) **V1** = Vp × $(cBW/median)^{q}$	CL = 0.103	Prop 0.0938 mg/L	GOF and NPDE
Mehrotra [150]	2012	134	267	(26.8 ± 24.3)[a]	(32.7 ± 5.7)[a]	(2.5 ± 1.1)[a]	1CMT/ NONMEM®	**CL**=0.18*$(weight/2.5)^{0.75}$ *0.42/Scr)$^{0.7}$ *PMA/37)$^{1.4}$ **V**=1.7 $(WT/2.5)^{1.0}$	CL = 0.249 V= 0.215	Add: 1.5 mg/L Prop: 0.16	Predictive check
Lo [232]	2010	116	835	6.6 ± 1.6	27.5 ± 1.1	0.97 ± 0.09	1 CMT/ NONMEM®	**CL** = 1.0*$(WT/70)^{0.75}$ * $(PMA/30)^{3.16}$ *[0.83 *SGA 1 1.03 * (1-SGA)] **V** = 36.6 * (WT/70)	CL: 0.202 V: 0.125	Add: 1.5 mg/L Prop: 0.229	VPC and Bootstrap
Kimura [231]	2004	19		(3–71) [b]	(24.1 - 41.3) [b]	710 - 5,200	1 CMT/ NONMEM®	**CL**= 0.0323* WT/SCr, if PCA >=34 **CL**= 0.025* WT/SCr, if PCA<34 **V**=39.4*(WT/70) * 1.19 (L/70 kg)	CL: 0.226 V: 0.205	Add: 3.22 mg/L	Bootstrap
Grimsley and Thomson [143]	1999	59	347	19 (2-76)	29 (25-41)	1.52 (0.57-4.23)	1 CMT/ NONMEM®	**CL**=3.56* WT/SCr [c] **V**=0.669*WT (L/kg) **Q** = r * CL V2 = V1	CL: 0.217 V: 0.178	Add: 4.53 mg/L	Diagnostic plots

Add RRE, additive residual random error; BSV, between-subject variability, BW, birth weight (kg); CL, clearance (L/h); CMT, compartment; CLcr, creatinine clearance (mL/min), calculated with Schwartz equation; GA, gestational age (weeks); GOF, goodness of fit;; NPDE, normalized prediction distribution errors; pcVPC, prediction-corrected visual predictive check; PCA: postconceptional age ; PNA, post-natal age (days); Prop RRE, proportional residual random error; Q, inter-compartmental clearance (L/h); RUV, residual unexplained variability; SCr, serum creatinine (µmol/L); c, serum creatinine in mmol/L. SGA, small for gestational age; V, volume of distribution (L); V_1, central volume of distribution (L); V_2, peripheral volume of distribution (L); VPC, visual predictive check; IWRES; individual weighted residuals, a, mean ± SD; b, range; c, Serum creatinine in mmol/L.

4.4.2 Validation vancomycin dataset

The validation dataset included data on 69 preterm neonates, all admitted to the NICU with a median (range) age of 28 (24.4–33.3) weeks and body weight of 975 (495–2142) g. They received an intermittent IV course of vancomycin with a median (range) daily vancomycin dosage of 18 (9–56) mg/day for 1–8 days, and 118 vancomycin concentrations were available for model validation and simulations. The demographics and baseline clinical characteristic of the population are detailed in (Table 3-2) chapter 3, the simulation parameters were derived from previously collected data.

4.4.3 Overall model evaluation

4.4.3.1 *Apriori* approach

Apriori analysis for all 69 neonates using only patient's covariates showed that models by Frymoyer et al., Grimsley et al., and Mulubwa et al. [143, 229, 230] had rBias values between (− 20 and 20%), but they were considered biased as their 95% CI did not cross through zero (see Figure 4-2 a). Predicted and observed concentrations for Kimura et al., Lee et al., Lo et al., Mehrotra et al., and Dao et al. [150, 192, 195, 231, 232] had a significant difference (> 20%), and their rBias was outside the clinically acceptable range. As such these models were not considered further. On the other hand, the De Cock model [244] had a clinically acceptable rBias. Additionally, De Cock had a precision higher than 90%, whereas all the other models had a precision < 61% (Figure 4-2 b).

4.4.3.2 Intra-course Bayesian forecasting

Using the *aposteriori* approach for the first observed concentration and the patient's covariates, the accuracy and precision of all models improved compared to the *apriori* approach (Figure 4-2 c and d). For example, the precision of the best fit model (De Cock) increased by 2.88% using the *aposteriori* approach compared with the *apriori* approach. A similar conclusion can be reached using the goodness of fit between predicted concentrations using *apriori* and *aposteriori* approaches (Figure 4-3 and Figure 4-4 respectively) for all selected models.

The solid line shows the ideal situation of the perfect model, where observed concentrations equal predicted concentrations. The gradient line shows the trendline of the model's prediction. Using the *apriori* approach, an ideal correlation factor, due to using one factor of the patient's data (patients' covariates), as such in (Figure 4-4) shows that the *aposteriori* approach enhanced the correlation results for all models as it used the recent observed concentrations as well as the patients' covariates. The goodness fit plot in (Figure 4-4) also suggested that the De Cock model was the best fit for the observed data using the a posteriori approach. The difference between (Figure 4-3) and (Figure 4-4) mainly comes from the type of predictions being assessed. In (Figure 4-3), the models were assessed using *apriori* predictions, which rely only on the population model and baseline patient characteristics. Whereas in (Figure 4-4), the evaluations included aposteriori predictions, where the model incorporates each patient's measured vancomycin concentration in addition to their baseline characteristics

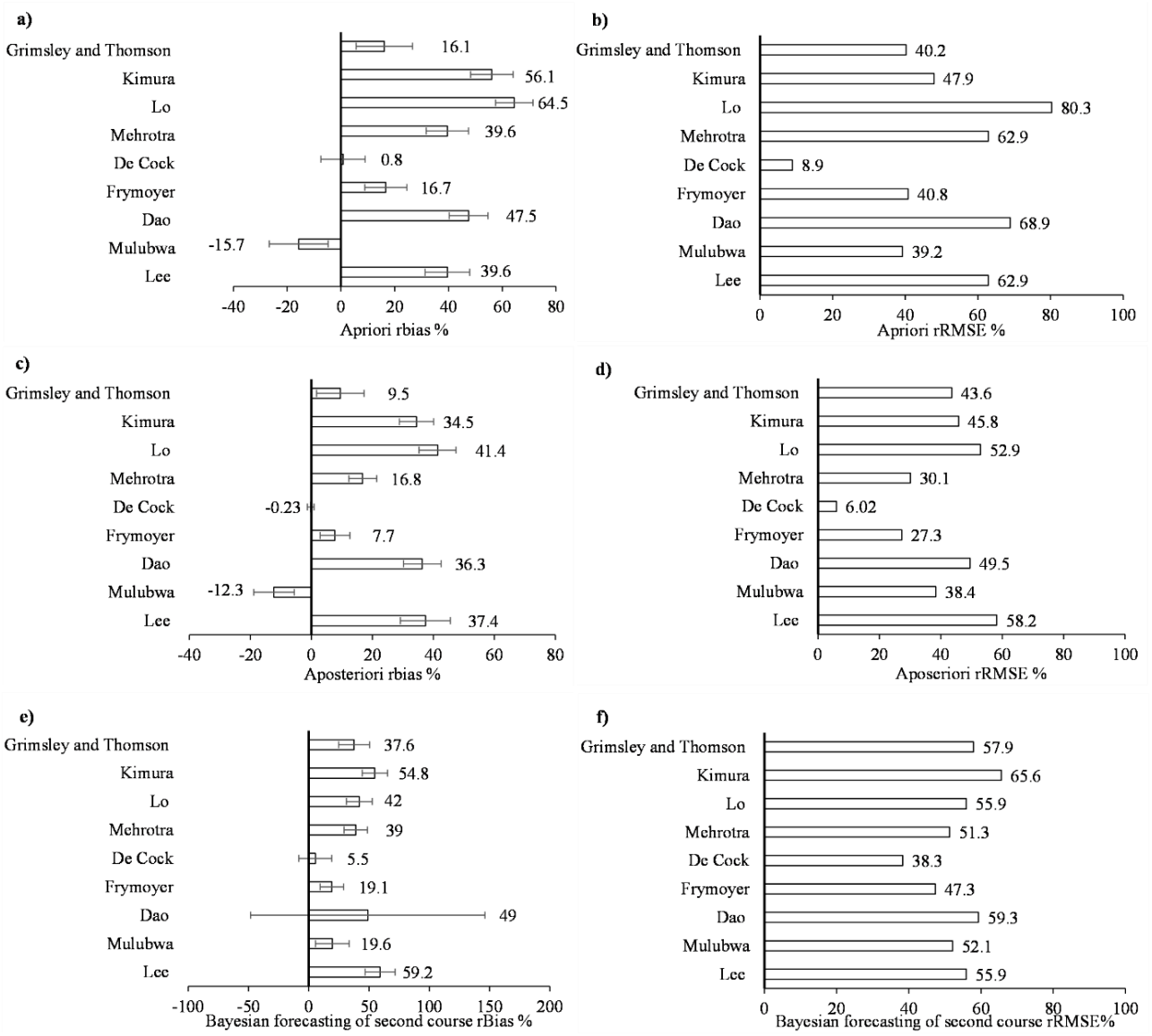

Figure 4-2:Models rBias (a) and rRMSE (b) for apriori prediction, Models rBias (c) and rRMSE (d) for aposteriori prediction, and Models rBias (e) and rRMSE (f) for Bayesian forecasting of second course predictions.

Data labels adjacent to each bar are shown for rBias and rRSME. error bars; 95% CI of rBias%. For the clinically acceptable model the rBias was between (-20, 20%) and 95% CI pass through zero. rBias; relative bias (accuracy), rRMSE; relative root mean square error (precision).

4.4.3.3 Inter-course Bayesian forecasting:

Overall, 27 neonates had 2-5 courses of vancomycin during their hospital stay and were used to assess the Bayesian forecasting approach using the previous course's observations. In (Figure 4-2 e) the De Cock rBias did not improve compared with the former two approaches. Furthermore, precision reduced to less than 62% for all models, as illustrated in (Figure 4-2 f). The De Cock model was the only clinically acceptable model using all approaches. Renal changes over time in newborn were modelled using age indicator (PNA) and the ratio between observed and predicted concentrations, as in (Figure 4-5). It shows that predictions in neonates with age range between 15–30 days was adequate with a ratio close to 1. The trend to lower ratios in some of the models can be explained by change in renal function with PNA. Glomerular filtration maturation changes in premature babies with PMA < 37 weeks is slower than in babies with PMA > 37 weeks. This was because nephrogenesis is not accomplished before 34–35 weeks gestational age [41, 246].

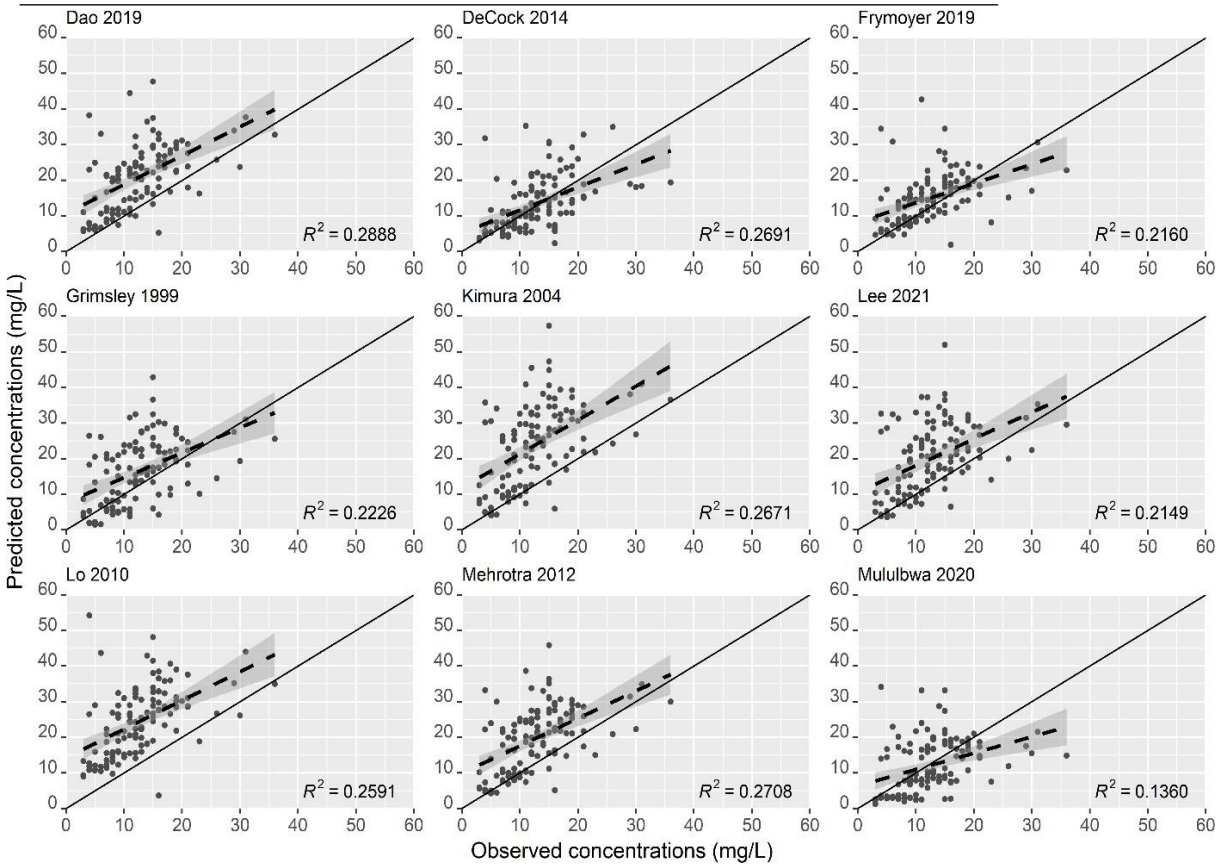

Figure 4-3: Goodness of fit plot, portraying the predicted concentrations using a priori approach for all selected models.

The solid line shows the ideal situation of the perfect model, where observations equal predictions. The gradient line shows the trendline of the model's prediction.

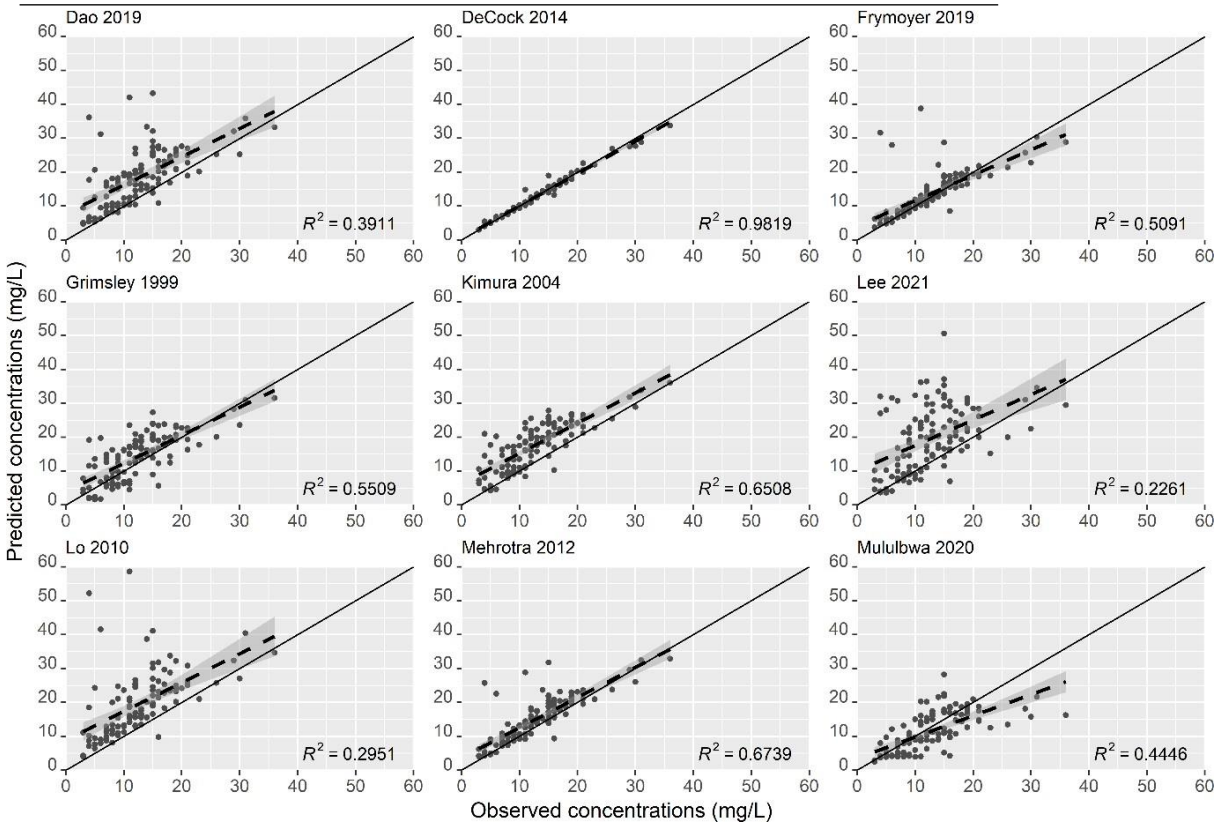

Figure 4-4: Goodness of fit plot, portraying the predicted concentrations using aposteriori prediction approach for all selected models.

The solid line shows the ideal situation of the perfect model, where observations equal predictions. The gradient shows the trendline of the model's prediction.

4.4.3.4 Trough concentration and AUC_{24h} relationship

The De Cock et al [244] model was used to compare the predicted vancomycin trough concentrations and AUC_{24} values. In (Figure 4-6) the regression line shows that a trough concentration range between 10-15 mg/L correlates with an AUC_{24}/MIC ratio of 400-600 h assuming a MIC of 1 mg/L. It showed a high correlation constant for aposteriori prediction (r^2=0.9807). The relationship between predicted trough concentrations and AUC/MIC ratios presented in this section is a property of the pharmacokinetic model used in the analysis. Both trough concentrations and AUC values were derived from model-based simulations and are therefore inherently linked through the structure and parameters of the model. This association

illustrates how the model predicts changes in AUC_{24}/MIC based on variations in trough levels under different covariate conditions. However, it is important to note that this is not a representation of a correlation between measured trough and measured AUC_{24} values in real-world clinical data. Previous studies have demonstrated that such correlations are often weaker and subject to greater variability, emphasizing the need for caution when interpreting trough concentrations as surrogate markers for AUC_{24} in clinical decision-making [247-249].

Vancomycin clearance in neonates is highly variable and depends on factors such as body size, postmenstrual age, and renal function, rather than being constant. Different population pharmacokinetic models use different combinations of these covariates, which can lead to systematic over- or under-prediction in specific age groups. In our study, the observed/predicted ratios being below one for some models likely reflects under-prediction by the model in certain postnatal age groups, rather than actual differences in renal function. This pattern has been reported in previous studies, which show that empirical dosing regimens often fail to achieve target concentrations in neonates, highlighting the need for individualized dosing strategies that account for maturational changes and interpatient variability [250, 251].

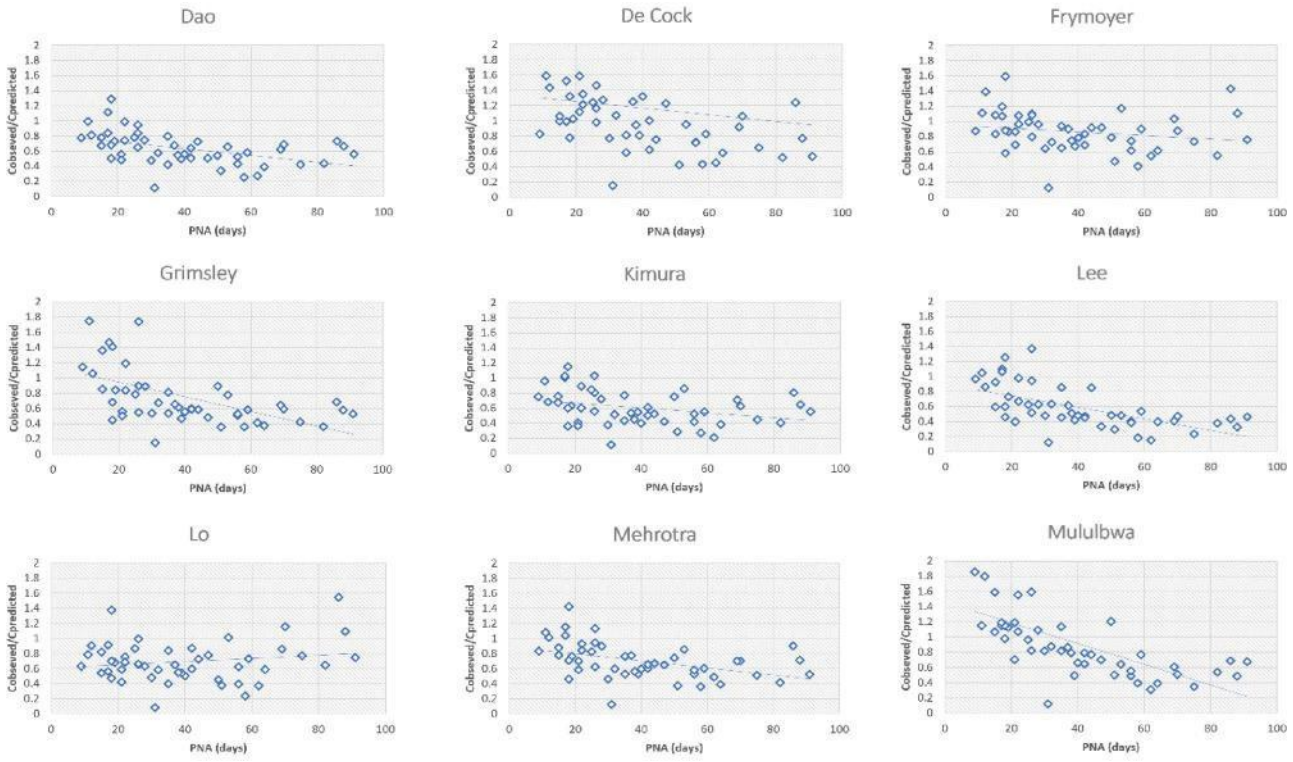

Figure 4-5: Overall performance of concentration prediction for vancomycin using the prediction of a next course approach using postnatal age (PNA) and ratio between observed and predicted concentrations in all models.

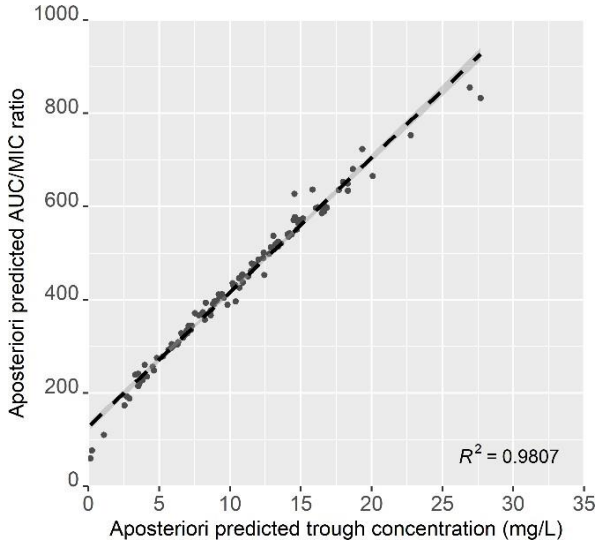

Figure 4-6: AUC/MIC and trough concentration correlation using De Cock model in aposteriori approach.

4.5 Discussion

The predictive performance of nine PopPK models for vancomycin in neonates were evaluated in a cohort of 69 preterm neonates (Table 4-2). In our study, we informed on the most appropriate model to be used in dosing software to calculate vancomycin dosing in NICU. All models used trough concentration (one reading) to predict concentration, but no peak concentration was collected in our cohort; this was one of our study limitations. For neonates < 29 weeks gestational age, blood sampling was done before the second dose, which could not be extrapolated to steady state concentration. However, It is important to note that no data were excluded based on gestational age or the attainment of steady-state concentrations. One of the key advantages of Bayesian MIPD is its ability to estimate PK parameters without requiring steady-state conditions. The model integrates the entire dosing history and available concentration data to generate accurate estimates of exposure (e.g., AUC_{24}/MIC), even in early treatment phases.

All neonates, including those <29 weeks gestation, were included in the analysis, and the model appropriately accounted for their individual pharmacokinetic profiles. The De Cock model was the best performing model based on the lowest rBias, bias, and rRMSE using all approaches, and it shows minimal data spread around the linear regression between predicted and observed concentration. As shown in (Figure 4-2), RMSE values were low for the De Cock model in the first two approaches, and *apriori* and *aposteriori* approaches 8.9 and 6.02%, respectively; on the other hand, the RMSE value was not low in case of the third approach (38.3%). This can be explained by the fact that the maturation of renal function in neonates, which is highly related to PNA, is expected to affect volume status and clearance and, therefore, change vancomycin pharmacokinetic in the next course. The higher RMSE for the De Cock model in this approach

also may be partly due to changes in body weight as the neonates grow. Because the model includes weight and postnatal age as predictors, rapid growth can lead to differences between observed and predicted vancomycin concentrations.

In Figure 4-4 using a Bayesian method and trough only concentrations, observed concentrations are very close to predicted concentrations. Unfortunately, no peak concentration was collected in our cohort, and this was one of our study limitations. For neonates < 29 weeks gestational age, blood sampling was done before the second dose. There were cases with more than one trough concentration in our cohort, ten babies had two trough samples, and three babies had three samples during their treatment course. For patients with multiple courses of vancomycin, the accuracy and precision of all the model's predictions did not improve when using vancomycin concentrations from a previous course of therapy. This highlights the importance of obtaining vancomycin concentration during the current course of therapy in preterm neonates and the use of it to guide dosing. This may in part reflect the rapid organ maturation in neonates [252] and/or dynamic changes in physiology related to their critical/unstable conditions [253]. Hence, timely collection of new vancomycin concentration in the ongoing course will provide the most accurate and precise information on drug exposure and is best suited to guide the dose.

Table 4-2: The overall model bias and precision for Bayesian predicted vancomycin concentrations.

	Apriori			**Aposteriori Bayesian forecasting**			**Aposteriori Bayesian forecasting for the next course**		
Model	MAE	rBias Mean (95%CI)	rRMSE	MAE	rBias Mean (95% CI)	rRMSE	MAE	rBias Mean (95% CI)	rRMSE
Lee [192]	0.848	39.6 (31.3, 47.9)	62.9	0.804	37.4 (29.2, 45.6)	58.2	0.557	59.2 (46.8, 71.6)	55.9
Mulubwa [230]	0.566	-15.7 (-26.6, -4.8)	39.2	0.284	-12.3 (-18.9, -5.6)	38.4	0.290	19.6 (5.6, 33.6)	52.1
Dao [195]	0.896	47.5 (40.3, 54.7)	68.9	0.638	36.3 (30.2, 42.5)	49.5	0.382	49 (-48.2, 146.2)	59.3
Frymoyer [229]	0.494	16.7 (8.9, 24.5)	40.8	0.240	7.7 (2.9, 12.6)	27.3	0.199	19.1 (9.5, 28.8)	47.3
De Cock [244]	0.426	0.8 (- 7.5, 9.1)	8.9	0.035	-0.23 (-1.3, 0.88)	6.02	0.172	5.5 (-8.2, 19.1)	38.3
Mehrotra [150]	0.796	39.6 (31.7, 47.4)	62.9	0.289	16.8 (12.3, 21.4)	30.1	0.299	39 (29.3, 48.7)	51.3
Lo [232]	1.285	64.5 (57.6, 71.4)	80.3	0.762	41.4 (35.3, 47.4)	52.9	0.358	42 (31.3, 52.7)	55.9
Kimura [231]	1.135	56.1 (48.2, 64.0)	47.9	0.544	34.5 (28.9, 40.1)	45.8	0.456	54.8 (44.3, 65.3)	65.6
Grimsley and Thomson [143]	0.681	16.1 (5.7, 26.6)	40.2	0.414	9.5 (1.7, 17.3)	43.6	0.373	37.6 (24.8, 50.4)	57.9

These values represent the Bayesian predictive performance of the tested models for apriori, aposteriori and bayesian forecasting for the next course. A model had a clinically acceptable bias if rBias was between -20% and 20%, and the 95% confidence interval passed through 0. The model with the lowest rRMSE has a high predictive precision. MAE, mean absolute error; rBias, relative bias; rRMSE, relative root mean square error.

Neonates are a diverse group, ranging from extremely premature infants to full-term newborns, and factors such as GA, birth weight, ethnicity, and postnatal age can significantly affect the PK and PD of vancomycin. Herein, many factors could affect the process of model building and evaluation, such as study settings, population characteristics, sample size used to build the model, and analytical model. Ethnicity can significantly impact vancomycin PK as it is eliminated renally, inter-ethnic differences in renal transporter expression, protein binding (e.g., α1-acid glycoprotein levels), and renal function may contribute to observed variability in drug exposure [254]. African Americans had a higher incidence of AKI. In a study of 501 patients 45.5% were African Americans, they had higher baseline serum creatinine and history of comorbid disease such as diabetes and renal diseases [255]. Another retrospective study conducted on 1130 adults who were administered vancomycin to determine if the incidence of AKI affected by race. The study shown that black individuals (10.1%) had a higher incidence of AKI compared to white patients (6.5%) [256]. Elevated vancomycin trough levels were strongly linked to AKI. When broken down by race, the likelihood of developing AKI was greater in blacks than in Whites. A study in adult patients showed that a race-based based estimated glomerular filtration rate (eGFR) equation performed better to predict vancomycin clearance in Thai population [257]. This has not yet been confirmed in neonates, likely due to underpowered studies [258]. Therefore, model built using a wide range of neonatal populations may exhibit a great variability and could be generalized, as it is not restricted to one category of population. For example, our dataset had a diverse ethnicity, as the catchment area of our hospital has the largest ethnic diversity in Australia [259]. As such, models built based on a specific ethnic group of population may not be adequate to predict PK parameters in a more general population, such as the model by Lo et al., which was built using data from Malaysian preterm neonates. Moreover, differences in study design could affect model building and

evaluation process, such as retrospective versus prospective studies. Retrospective studies rely on medical records and may have limited control over data collection and patient management. Prospective studies, on the other hand, allow for standardized data collection, more rigorous monitoring, and controlled dosing regimens, reducing some sources of variability. Furthermore, models built using a smaller population size may not give a complete description of patient's population pharmacokinetics of vancomycin. This may result in biased or imprecise Bayesian estimation of vancomycin exposure, such as what we noticed in the Mulubwa and Kimura models, which were built using only 19 neonates, which might be the reason that those two models did not perform well in our dataset. Although small sample size can contribute to poor model performance, models developed from large datasets, such as Dao and Frymoyer, may still show imperfect predictions in our cohort. Both the Frymoyer and Dao models were developed in neonatal populations that were generally older, heavier, and more physiologically stable than the infants in our study. For example, the Frymoyer cohort had a median postmenstrual age around 36 weeks and a median weight of about 2.4 kg, which is quite different from our median GA of 28 weeks and birth weights median 0.975 kg. Similarly, the Dao model was built using data from several hundred neonates whose ranges of age, size, and renal function were broader than some earlier studies but still did not reflect the degree of prematurity and clinical variability seen in our group. In contrast, our cohort included extremely preterm infants with wide variation in postnatal age, serum creatinine, and inflammatory markers, along with a diverse set of infections.

These differences matter because PK models rely heavily on assumptions about how clearance and volume of distribution mature with age, weight, and kidney function. When a population lies beyond the typical ranges used to build a model as is the case with many of the very small and clinically unstable infants in our dataset predictions are more likely to drift from observed

values. This mismatch in maturity, weight, renal function, and overall clinical status provides a practical explanation for why the Dao and Frymoyer models, despite being developed from large and well-structured datasets, did not perform as accurately when applied to our patient population. Variations in laboratory techniques, calibration standards, and quality control procedures can introduce variability in measured drug concentrations across studies, as such, affecting model building and evaluation. Inter-study differences across vancomycin concentrations may also arise from methodological variability, including differences in assay sensitivity and specificity, sampling schedules (e.g., timing and frequency), and the population pharmacokinetic modelling approaches employed [260].

There are multiple possible reasons why the De Cock model performed well with our data. First, vancomycin exposure after IV infusion is generally described by a two-compartment model [244]. The original model by De Cock et al. is a two-compartment model. Two-compartment model can better account for the initial distribution phase and subsequent slower elimination phase of vancomycin, which is particularly relevant in neonates due to their unique and dynamic physiology [89]. By incorporating a peripheral compartment, the De Cock model may offer enhanced accuracy in predicting concentration-time profiles, especially when using sparse or non–steady-state sampling data. This characteristic may explain its robustness in diverse clinical scenarios and supports its potential utility in model informed precision dosing in neonatal populations.

Clinicians commonly use the one-compartment model for vancomycin dosing, but since the drug follows a multi-compartment pattern, this approach requires carefully timed post-distribution samples, which can be hard to obtain accurately. In contrast, the two-compartment model offers more reliable predictions of vancomycin peak and trough levels, with reduced bias

and greater precision [261]. The De Cock two-compartment model demonstrated superior predictive performance in this study. This can be attributed to its robust development using a large and diverse neonatal dataset, inclusion of physiologically relevant covariates such as weight and age, and its ability to better capture interindividual variability. When applied within a Bayesian forecasting framework, the De Cock model provided more accurate individualized concentration predictions, outweighing the structural simplicity of one-compartment models and highlighting the importance of model selection based on predictive accuracy rather than compartment structure alone.

De Cock model was built based on a large dataset of 689 neonates, where all neonates were preterm with a birth weight range between 385 and 2550 g and a PNA of 1–28 days. In our cohort, all neonates were born prematurely (< 28 weeks gestation) and started a vancomycin course within a median (range) of 20 (1–91) days of their life. Comparable neonatal populations (i.e., GA and birth body weight) between the model building dataset of De Cock and our validation dataset might explain the good performance of the De Cock model compared with other models. The good performance of the De Cock model in our study is likely could be due to the similarity between our patient population and the one used to develop the model. In other neonatal populations with different characteristics, such as gestational or postnatal age, body weight, or renal function, the model may not perform as well. This highlights the importance of validating population pharmacokinetic models in each specific neonatal cohort before applying them broadly.

AUC_{24}/MIC is an important pharmacokinetic parameter used to evaluate the efficacy of vancomycin therapy in adults. For most infection caused by susceptible Gram-positive bacteria, a target AUC_{24}/MIC ratio of 400–600 h is considered optimal [117]. In this study, an AUC_{24}/MIC

ratio of 400–600 h correlated well with a trough concentration of 10–15 mg/L, with a high correlation coefficient close to one that is consistent with the high correlation factor found by other studies, which used a large number of neonates, such as Tseng et al [262] It was found that the trough concentration does not have to be higher than 15 mg/L in neonates to achieve AUC_{24}/MIC ratio > 400 h [263]. Also, a recent study revealed a significant correlation between trough concentration and AUC_{24}/MIC at different dosing and dosing intervals [222]. The PMA of our cohort ranged from 25 to 42 weeks, with a weight of 495– 2142 g, which can be considered heterogeneous. The vancomycin dosing regimen of our hospital [65] includes dosing according to PMA and PNA, bodyweight, and renal function, which are likely corrected for this heterogeneity, as shown in (Figure 4-6).

Our study also has some limitations. We applied a predefined criterion developed with the aim of selecting a model suitable for clinical practice in our patient population. Use of this criterion may have resulted in the exclusion of models that could have performed well. This was seen earlier in a study by Colin et al. [264] which included a greater age range than considered appropriate for our intended population. In our study, we did not exclude outliers, as bias due to outliers may have impacted model performance. However, in our opinion, the current number of patients in the validation dataset was fit for the purpose in selecting the best model for the local patient population suitable for clinical implementation. Models used for ECMO patients and positive ventilation pressure were excluded, as it was not representative of our cohort.

4.6 Conclusion

The De Cock model was the most precise and accurate in predicting vancomycin exposure (with and without including a vancomycin concentration) in neonates. Using a recent vancomycin concentration improved the predictive performance of all models evaluated. Also, a trough concentration 10–15 mg/L is adequate to reach AUC_{24}/MIC > 400 h in neonates.

Chapter 5: TDM cost aspects

This chapter contains the following manuscript to be submitted:

Therapeutic drug monitoring: understanding costs with various approaches

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5.1 Abstract

Background

Therapeutic drug monitoring (TDM) is a critical practice in optimizing medication dosing. There is indeed a growing trend toward Bayesian dosing in clinical settings, particularly for medications with narrow therapeutic windows like vancomycin.

Objective

The cost and clinical benefits were compared for both conventional TDM and Bayesian TDM of vancomycin. In addition to an overview of the role of healthcare professionals in TDM practices, especially clinical pharmacists.

Methods

A semi-structured search was performed focused on (**1**) identifying key aspects of both practices, including associated costs, clinical outcomes, adverse effects, and implementation challenges, and (**2**) providing future directions for comparing Bayesian to conventional approaches.

Results

The cost and clinical benefits were compared for both conventional TDM and Bayesian TDM. Conventional TDM were considered more affordable in terms of immediate resource utilization. However, the long-term costs related to longer hospital stay due to nephrotoxicity and laboratory cost for higher number of blood samples. On the other hand, Bayesian TDM can

significantly enhance patient outcomes and lower long-term healthcare costs. However, it requires a more significant initial financial commitment due to the high license cost of the Bayesian software. The cost depends on the hospital's size, number of models, modules and users. The initial cost is also related to the training required to allow easy use of the software. On the other hand, in long-term use, the software can save costs related to nephrotoxicity, which is the main side effect of vancomycin, by reducing the cost related to labor for management of nephrotoxicity, laboratory and the length of hospital stay due to these complications. In addition, Bayesian TDM can likely reduce the frequency of blood sampling needed during TDM and thus reduce laboratory costs.

Conclusion

The adoption of Bayesian TDM can optimize vancomycin treatment in neonates, leading to improved efficacy and safety, although the initial costs outlaid are usually more significant. The improvements associated with Bayesian TDM compared with non-Bayesian approaches need to be carefully weighed against the costs of implementing them over time (and if extra costs are avoided, such as reduced length of hospital stay) by healthcare providers to determine value for money.

5.2 Introduction

Drug dosing in newborns is challenging due to the rapid maturational and functional development resulting in drug exposure variability [265]. This is particularly relevant for empirical dosing of antimicrobial drugs as sepsis in neonates is very common due to their immature immune system [47]. Sepsis is often caused by pathogens like coagulase-negative staphylococci, enterococci, and MRSA [266]. Despite the long history of vancomycin being used to treat these infections, there is still debate on the most effective dose or dosing regimen due to the large variability in drug exposure between and within individuals [65].

Therapeutic Drug Monitoring (TDM) is a clinical process designed to optimize medication therapy by measuring the concentrations of drugs in the bloodstream and adjusting the dose to achieve a concentration in the target range [20]. TDM is a multidisciplinary service involving clinicians, nurses, pharmacists and laboratory specialists. Clinicians evaluate the clinical situation of patients and infection severity, initiate therapy, check response to medication, and interpret side effects. Pharmacists are often considered experts on pharmacokinetics, drug dosing, and drug interactions to ensure the appropriateness of therapy. TDM is especially critical in neonates, where developmental changes can significantly influence drug absorption, distribution, metabolism, and excretion (collectively known as pharmacokinetics). For drugs with a narrow therapeutic window like vancomycin, effective monitoring is essential to ensure therapeutic benefits while minimizing potential side effects [23].

TDM is recommended to reduce the likelihood of complications related to underdosing (which may lead to treatment failure) or overdosing (which can cause toxicity) by maintaining drug exposure within the therapeutic range [70].

In general, for all patients ages and groups, research using Bayesian dosing software incorporating pharmacokinetic (PK) models to individualize therapy has increased over the last 30 years primarily due to its role in achieving therapeutic range quicker than conventional TDM practice [205]. Several studies have shown that Bayesian dosing individualization improved patient outcomes, such as clinical response to antibiotics and reduced side effects such as nephrotoxicity and ototoxicity [267]. Patients' prior specific data, such as age, sex, weight and serum creatinine, are used to individualize population PK models in conjunction with the measured drug concentration after one or multiple doses to guide dose adjustment and maintain the drug concentration within the therapeutic window. When used correctly, Bayesian TDM requires fewer blood samples than the routinely used trough-based TDM, reducing invasiveness and healthcare costs [100]. In addition, it was reported that utilizing Bayesian software is associated with better target attainment, reduction in side effects and improved treatment outcomes compared to conventional TDM [268]. Despite these benefits, uptake in hospital care, especially in NICU, is limited, as was reflected by only 29.7% of hospitals across the United States [269] and only 51% of hospitals across Australia have access to dose monitoring software [270]. The lack of implementation of Bayesian TDM has been studied by Drennan et al. [271], who mentioned the lack of evidence, funding, regulatory approval, time availability, and user opinions as important reasons. Therefore, this study aimed to conduct a scoping review of the key features of two TDM approaches—conventional TDM and Bayesian TDM—including cost considerations, required end-user training, and future directions for optimising vancomycin therapy in neonatal intensive care units (NICUs) using Bayesian methods.

5.3 Method

An initial structured literature search was undertaken in PubMed and Embase using the keywords: *"vancomycin"* AND *"therapeutic drug monitoring"* AND *"cost"* AND *"economic evaluation"* AND *"pharmacist"*. The search was limited to publications between [inception-2024]. Due the absence of eligible studies from database searches, an additional search was carried out using Google and Google Scholar. Broader search terms were used, including *"Therapeutic drug monitoring cost", "Bayesian TDM cost", "model informed precision dosing cost", "model informed precision dosing software licence cost", "nephrotoxicity cost", "hospital stay cost", "pharmacist role in TDM"*. Relevant articles and reports that discussed the economic aspects of TDM, Bayesian dosing, or pharmacist involvement were selected.

5.4 Results

The total number of studies included was 30 studies. From the search relevant studies were identified across several areas. Seven studies were evaluating the implications of conventional TDM and five studies for bayesian TDM. Three publications exploring closed loop system were considered relevant and fifteen studies examined the economic implications of TDM approaches, and the role of healthcare professionals, especially clinical pharmacists in TDM practices were examined in six studies. While the semi-structured review highlighted potential cost benefits of Bayesian or model-informed precision dosing (MIPD), most evidence comes from adult populations or general estimates, and there is limited literature evaluating cost-effectiveness specifically in neonates. Available studies suggest that Bayesian TDM can reduce hospital stay, laboratory testing, and the incidence of

vancomycin-associated AKI, which collectively may lower healthcare costs [272-274]. However, the actual cost savings depend on local healthcare settings, patient characteristics, and infrastructure. Future studies in neonatal populations should include real cost data, including software, training, and hospital stay, to quantify the potential financial and clinical benefits of implementing model-based dosing strategies.

5.4.1 Conventional therapeutic drug monitoring

TDM is a tool for dose optimization to attain therapeutic concentration ranges and avoid side effects in neonates [20]. Although TDM of vancomycin is considered standard of care, the actual process can differ from hospital to hospital. Practical issues like blood sampling in neonates can result in delayed or too early sampling [8], which limits its performance. Dosing and TDM strategies in neonates generally include factors such as renal function (reflected by serum creatinine), body weight, and postnatal or postmenstrual age [65] irrespective of vancomycin being administered intermittently, or as continuous infusion [275].

Practice guidelines of vancomycin TDM recommended using the ($AUC_{0–24}$/MIC) ratio between 400-600 μg·h/mL as a therapeutic target. Although the AUC_{24}/MIC ratio is the recommended pharmacodynamic target for vancomycin therapy, the MIC is often not measured for individual patients in routine clinical practice. Therefore, an MIC value of 1 mg/L is commonly assumed, based on clinical guidelines and local susceptibility data. This assumption facilitates AUC-based dosing but may introduce variability when actual MIC values differ significantly [276]. An accurate prediction of the (AUC_{24}/MIC) requires blood sampling at several time points at steady state [221]. As this is burden to staff and patients peak concentration (C_{max}) and trough concentration (C_{min}) have been measured routinely in some hospitals for vancomycin TDM

[277]. Some hospitals have implemented further reductions in sampling to rely solely on trough concentrations, as these were historically considered a modest surrogate for AUC_{24}/MIC and were once thought to provide a reasonable estimate of drug exposure and treatment efficacy [82, 278]. However, this approach has limitations and is now increasingly being replaced or supplemented by AUC-based monitoring strategies, particularly considering updated guideline recommendations [279].

The conventional TDM process of vancomycin is a well-established procedure (Figure 5-1) and captured in hospital protocols and national or international guidelines [71]. The hospital protocols help ensure the decision-making process's consistency and reliability [70]. At the same time, the clinical guidelines provide the relevant scientific context to ensure that individual patient factors, such as age, weight, gestational age, and clinical condition, are considered [280].

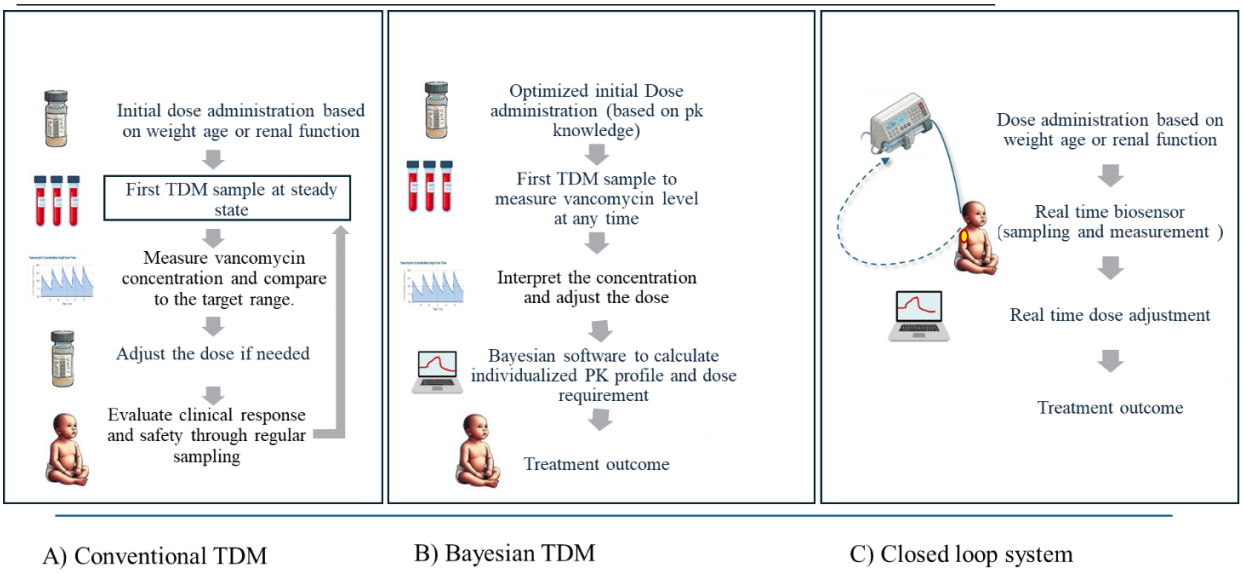

Figure 5-1: Different TDM approaches.

A) Conventional TDM relies on nomogram or dose calculator to adjust the dose. B) Bayesian TDM integrates patient's specific pharmacokinetic data, predictive pharmacokinetic model to optimize the dose. C) Closed loop system integrates real time data detected by the biosensor and monitored by Bayesian software to adjust the dose automatically.

Monitoring vancomycin levels throughout the course helps to ensure their safety and efficacy, especially in neonates, because of their rapid maturation and development [70]. This harmonizes with regular monitoring of renal function and allows for a timely dosing adjustment, particularly in critically ill neonates where drug clearance due to fluctuating renal function is highly variable [234]. Hence, TDM allows for personalized dosing to reduce the risk of subtherapeutic drug concentrations, which is an important cause of treatment failure [72]. Conventional TDM heavily relies on collecting blood samples at predetermined intervals. The timing of these samples is crucial and is based on the clearance of vancomycin and dosing schedule. Incorrect timing of blood sampling, either collecting samples not at a steady state on missing trough levels, can lead to inaccurate results and the need for repeated sampling or, worst-case, inaccurate dosing adjustment resulting in complications [216, 281].

5.4.2 Bayesian therapeutic drug monitoring

Bayesian TDM is a more advanced approach to TDM (Figure 5-1). The foundation of Bayesian software relies on the population pharmacokinetic model, which is developed using modelling approaches such as non-linear mixed effect modelling, which includes three components: i) the structural model, which outlines the overall PK characteristics of the medication, ii) the covariate model which is considered how patients' characteristics affect PK parameters, and iii) variability model which outlines the variability in PK parameters and residual variability between predicted and observed concentrations [282]. Developed pharmacokinetic models are typically incorporated in Bayesian dosing software and are suitable for routine care use. Clinicians and pharmacists can use the Bayesian dosing software and select the most appropriate model for an individual patient to predict the drug concentration in that individual patient, allowing for a more precise approach to dosing. Using existing information, such as patient clinical data (gender, weight, and renal function) combined with the best predictive pharmacokinetic model and antibiotic-specific data (such as target attainment and the minimum inhibitory concentrations (MIC) of the causative pathogen [283] can allow the software to predict future drug concentrations precisely reducing the need for frequent blood sampling and earlier target attainment [284]. Using Bayesian dosing software has resulted in a high percentage of patients achieving the therapeutic target compared to patients treated using fixed dosing approaches [283]. It has been shown that Bayesian software improved clinical outcomes by reducing the toxicity risk associated with a high drug concentration [100]. It is especially beneficial in reducing the blood sampling needed to calculate the optimum dose. Moreover, sampling time is more flexible as Bayesian TDM does not necessitate blood sampling after the steady-state concentrations have been reached [285]. Various software tools are available, and

different criteria are applied to calculate individualized doses. Most software packages have specific PK models for specific drugs, including antibiotics. Additional PK models can be added to some software packages (see Table 5-1).

5.4.3 Closed loop system

One of the systems that are using bayesian dosing software is closed-loop target-controlled infusion (TCI) systems (Figure 5-1), though still largely experimental, represent a newer advancement that enables clinicians to adjust drug delivery by aiming at specific target concentration [286]. In comparison to manually controlled infusions these systems show potential benefits. Specifically, they automatically modify the drug's target concentration and infusion rate by continuously analysing the patient's PD responses, thereby creating a feedback loop [287]. Ideally monitoring of antimicrobial agent should be continuous and through minimally invasive procedures. In TCI, drug concentration is measured within dermal interstitial fluids (ISF) through microneedles biosensors. As the free antimicrobial concentration in ISF is generally in equilibrium with plasma levels, this approach allows near real-time monitoring of ISF concentrations and estimation of plasma drug levels without direct blood sampling [288]. Data generated by these sensors is then linked to the closed loop system. Which offers the ability to adjust both continuous and intermittent dosing to achieve pre-specified therapeutic target such AUC_{24}/MIC [289]. Electrochemical sensors developed for antimicrobial monitoring are relied on aptamers, antibodies, or enzyme-linked sensors [290]. Which characterized by its high sensitivity, often within the physiological concentration ranges expected in interstitial fluid (ISF) [291]. Whereas the traditional way of TDM requires the administration of loading dose followed by maintenance dose to ensure reaching the steady state target concentration, these systems ensure easy dosage individualisation through incorporating

the population pharmacokinetic model and the covariates into the computer system.

Clinical studies suggest that TCI technology could also be adapted for more accurate antibiotic dosing in ICU settings [287]. A simulation model designed for piperacillin TCI demonstrated improved target attainment, along with a 30% decrease in total daily drug consumption. In comparison to continuous infusion or intermittent bolus methods, TCI for piperacillin appears to be a safe, cost-effective approach with added clinical benefits [292]. More recently, in the in-silico study, researchers have evaluated vancomycin dosing by comparing the traditional therapeutic drug monitoring (TDM) regimen with an adaptive TCI (aTCI) approach. This adaptive system, which is based on the Thomson model, integrates TCI with limited TDM sampling. Results indicate that aTCI provides better PK/PD target attainment and reduces the risk of toxic concentration spikes during vancomycin treatment [293].

5.4.4 Cost Considerations

5.4.4.1 Infrastructure costs:

When evaluating resource utilization in conventional TDM versus Bayesian TDM it is essential to consider infrastructure costs, which include software expenses or dose calculation tools, personnel time required for TDM procedures, and the frequency and timing of blood sampling. Software costs vary widely depending on licensing models (free access, subscription, or commercial licenses), ease of use, training requirements, and platform availability (web-based, desktop, or mobile). Regulatory-approved software generally incurs higher costs due to validation and registration processes [294]. For example, DoseMeRx is the only Bayesian dosing software registered as a medical device with the Australian Register of Therapeutic Goods Administration (ARTG), contributing to its higher implementation cost [295]. Other

Bayesian software packages such as BestDose, PrecisePK, and Tucuxi, although widely used, may lack formal regulatory approval [224, 296, 297] (Table 5-1) presents a full description of the main characteristics of the selected Bayesian software, chosen based on factors such as regulatory approval status, clinical usage prevalence, and availability for neonatal dosing.

5.4.4.2 Personnel and procedural costs

Conventional TDM typically requires multiple clinical consultations for dose adjustments, increasing workload for clinicians, pharmacists, nurses, and laboratory staff. Blood sampling in neonates is most commonly performed via capillary heel pricks, which take approximately 10 to 15 minutes per sample and require skilled nursing personnel [298]. The cumulative burden of frequent blood sampling, laboratory analysis, result interpretation, dose adjustment, and documentation can contribute significantly to resource consumption, administrative workload, as well as efficacy and accuracy in clinical decision making. Individualised PK/PD parameters can be estimated using just a single serum drug concentration measurement. This approach has the potential to reduce the number of blood samples needed for therapeutic drug monitoring, thereby enhancing patient comfort and minimising the burden of blood draws [299]. In a study were Bayesian approach implemented to individualize busulfan in paediatric and adolescent patients demonstrated that TDM of busulfan using Bayesian software could achieve accurate and precise exposure targets with only two optimally timed blood samples, compared to the conventional approach that typically requires six to nine samples. This represents a significant reduction in sampling burden—by approximately 70–80%—without compromising dosing accuracy, thereby improving patient comfort and clinical efficiency in paediatric settings [300].

5.4.4.3 Economic Consequences and Clinical Outcomes

Economic consequences reflect the downstream costs related to clinical outcomes influenced by TDM strategies, including management of adverse drug reactions such as nephrotoxicity, length of hospital stay, and the need for specialized interventions or readmissions due to treatment complications [301]. Figure (5-2) describes these relevant cost considerations under TDM approaches in more detail. Conventional TDM has been associated with longer hospital stays owing to adverse drug reactions or suboptimal dosing, whereas Bayesian TDM facilitates precise targeting of vancomycin exposure, measured as (AUC_{24}/MIC), resulting in reduced nephrotoxicity incidence [299, 302].

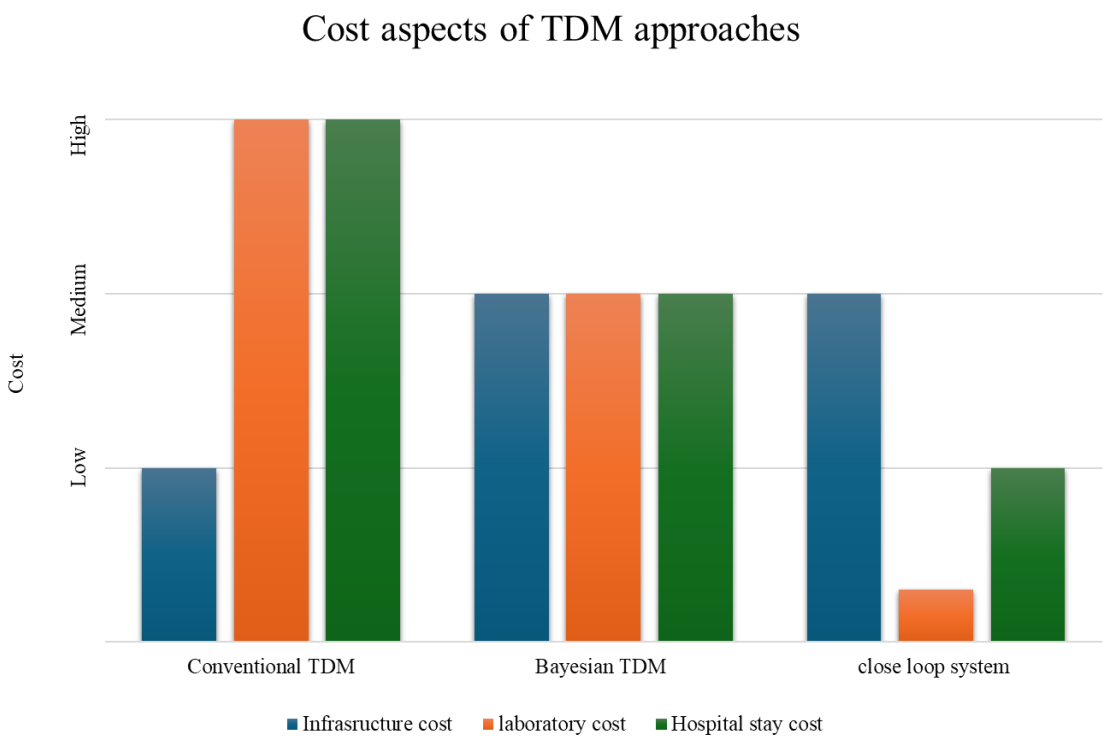

Figure 5-2: Estimated comparison of implementation costs for three TDM approaches, shown on a relative scale from low to high.

Conventional TDM involves low initial costs, mainly limited to staff training. In contrast, Bayesian TDM and closed-loop systems have higher upfront costs due to software licensing fees, training, and, in the case of closed-loop systems, additional system expenses. However, these approaches may offer overall cost savings by reducing labor and laboratory expenses, as well as shortening hospital stays related to therapeutic failure or toxicity management. Notably, closed-loop system shows minimal laboratory costs entirely.

In neonatal intensive care units (NICUs), extended hospital stays not only elevate healthcare costs but may also negatively impact patient outcomes. Key cost drivers include the need for respiratory support, prolonged hospitalisation, and the management of complications arising from vancomycin toxicity [299]. In neonates, such complications frequently necessitate specialised care, potential readmissions, and additional resources. Vancomycin-induced acute kidney injury (AKI) further burdens healthcare systems through increased requirements for nursing care, specialist consultations, and other support services [303]. Despite its potential, there is limited literature evaluating the cost-effectiveness of Bayesian TDM in vancomycin therapy.

Several studies have demonstrated the cost-effectiveness of Bayesian TDM. A comprehensive review evaluating acute cost of sepsis and meningitis treatment in neonates across countries with various income levels revealed that the average expense per patient for a hospital stay range from $55 in India to $129,632 in US [304]. This large contrast explains the importance of investigating local economic situation when evaluating the financial impact of advanced dosing strategies. Interventional studies further support the benefits of bayesian guided TDM and dosing. A prospective multicentre study was conducted across three adults ICU and one paediatric ICU in Australia, evaluated the cost of hospital stay in two phases. Phase 1 was for patients received standard antibiotics dose as determined by clinician and phase 2 antibiotic dose was based on MIPD software. The intervention's cost per patient was estimated at $71.13. Notably, the use of ID-ODS™ was associated with a reduction in ICU length of stay by 2.13 days. This decrease translated into a potential cost savings of $12,324.28 per patient, with a 95% confidence interval ranging from $9,520.93 to $15,127.62, due to the averted ICU stay

[305]. The projected financial benefits from reducing ICU stays are general estimates and can differ significantly across countries. These variations are influenced by factors such as the diversity of patient conditions and the specific costs associated with healthcare services in each country. Therefore, while MIPD use that decrease hospital stay may lead to costs savings, the actual saved amount depends on the local economic settings and infrastructure [306].

Moreover, bayesian guided TDM has shown laboratory cost reduction which might be linked to lower blood sampling frequency. Neely et al. conducted a prospective observational study over a three-year period involving 252 adult patients receiving vancomycin therapy. The study demonstrated a reduction in the mean number of blood samples per patient for vancomycin concentration measurement from 3.6 with conventional TDM in the first year, to a mean number of 2.0 in the second year following the implementation of Bayesian TDM. On the other hand, the mean number of blood samples per patient of combined Bayesian TDM with optimally timed sampling strategies was 3.0 [299]. One cost-benefit analysis involving 206 adult patients demonstrated a 60% reduction in laboratory testing costs when switching from trough-based monitoring to Bayesian AUC-based dosing. This reduction was largely attributed to a decrease in the number of required blood samples from five to two per patient—with each laboratory assay costing approximately US$10 [307]. Altogether, these findings emphasize that bayesian approaches reduces both workload and direct test.

Another driver of cost minimization effect of bayesian TDM approach is the prevention of vancomycin associated AKI. A cost-minimisation analysis by Patel et al. [308] reported a median hospital stay of 12 days (interquartile range: 7–17 days) in patients with vancomycin-associated AKI compared to 7 days (IQR: 5–10 days) in those without AKI. The treatment cost

per course in the absence of AKI was US$1,214. In contrast, treatment costs for AKI ranged from US$9,379.36 without specialist consultation to US$13,395.18 when including both specialist consultation and acute dialysis. In a separate retrospective study of 49 adult patients receiving vancomycin for at least seven days across five hospitals in Kuwait, Alghanem et al. [309] reported 18% incidence of vancomycin-associated AKI, with average treatment costs per course of US$2,379 and a total institutional cost exceeding US$370,000 for all included patients. Notably, Lee et al. [310] found that single-sample Bayesian TDM offered significant cost savings in the context of AKI prevention. Their institutional cost-benefit analysis, using a decision tree model to evaluate vancomycin-associated AKI outcomes over treatment durations ranging from 48 hours to over 21 days, demonstrated that Bayesian AUC dosing saved an average of US$2,065 per patient encounter. These savings were attributed to reductions in AKI incidence, length of hospitalisation, and the need for additional medical consultations [310]. These findings underscore the potential benefits of bayesian TDM in improving patient safety and reduce the cost associated with drug toxicity.

Table 5-1: General characteristics of Bayesian software tools. [114]

	BestDose RX	**PrecisePK**	**DoseMeRX**	**Tucuxi**
Developer	R.W. Jelliffe	Philip Anderson	Robert McLeay	Yann Thoma
Cost (US$/year)	Free	Subscription model	Subscription model	Free
Company/institution	Laboratory of Applied Pharmacokinetics and Bioinformatics	Healthware Inc	Tabula Rasa Healthcare Company	School of management and engineering of Vaud and The University Hospital of Lausanne
Location of company/institution	USA	USA	USA	Switzerland
Date of first version	2018	1986 (Desktop) 2019 (Web-based)	2014	2013
Commercially available	No	Yes	Yes	No
Platform	Web-based	Desktop and Web-based	Web-based and mobile application	Desktop
User-friendliness	Need extensive training	Need moderate training	Easy to use, require minimal training	Easy to use, require minimal training
Clinical manual	No	Yes	Yes	No
Interfacing	Interfaces is less user-friendly	modern interface where the path to run a simulation was easily identifiable	modern interface where the path to run a simulation was easily identifiable	modern interface where the path to run a simulation was easily identifiable
Electronic health record	Stand alone	Integrated	Integrated	Integrated
Drug classes	Antibiotics, digoxin	Antiarrhythmic anti-asthmatic, antibiotics, antiepileptics, antifungals, antineoplastics, antipsychotics, immunosuppressants (drugs for transplants)	Antibiotics, anticoagulants, anticonvulsants antifungals, antineoplastics, antithrombotic, immunosuppressants (drugs for transplants), digoxin, warfarin	Antibiotics, anticoagulants, antivirals, antineoplastics, immunosuppressants (drugs for transplants), kinase inhibitors
New drug model addition	No	Yes	Yes	Yes
PK plot generation	Yes	Yes	Yes	Yes
Website	lapk.org/bestdose.php	precisepk.com	doseme-rx.com	tucuxi.ch

5.4.5 End users

Pharmacists have the required knowledge and skills regarding pharmacokinetic and pharmacodynamic properties of the medication and personalized dosing. Such knowledge is helpful when working with Bayesian dosing software as it requires understanding interindividual and intraindividual variability between patients and selecting the most

appropriate model [section 1.1.3 (chapter 1)]. An effective and efficient TDM service relies on strong collaboration among nurses, phlebotomists, physicians, pharmacists, and laboratory personnel. Phlebotomists play a key role in sample collection, timing, and communication of relevant clinical information [311]. Laboratory staff are essential for accurate sample analysis and timely reporting of drug concentrations. Furthermore, Clinical Pharmacologists and other specialist physicians playing a pivotal role in interpreting TDM results, guiding individualized dosing decisions, and supporting complex clinical scenarios including infectious diseases, immunosuppressants and anticonvulsants. Clinicians enter TDM plan through electronic medical records and requesting drug concentration analysis. Afterward, clinical decisions guided by overall conditions of the patient including laboratory results. Clinicians use TDM for different reasons including diagnosis and treatment guidance, overdose monitoring, reduce toxicity, and drug-drug interactions [312].

TDM serves as a critical role to assist clinicians in identifying drug overdose and tracking therapeutic response over time e.g. a case presented by Unal et al [313] for a neonate weighing 1380g and age 29 weeks GA. The baby developed apnea after two doses of 10-fold of the recommended dose per weight was given. The patient's serum vancomycin concentration measured at 10-hour post-infusion was 84 mg/L. Such elevated plasma level may contribute to the toxicity noticed in this patient. Clinicians request drug exposure monitoring to reduce the risk of adverse drug reactions, particularly in drugs with narrow therapeutic index where small changes outside the therapeutic range can lead to undesirable outcome. Moreover, clinicians may request TDM to try to administer the lowest dose with maximum therapeutic outcomes. Some drugs may interact with each other increasing the risk of toxicity [314]. For example, vancomycin, which is eliminated renally, may have increased toxicity when administered with

other nephrotoxic agents such aminoglycosides, loop diuretics and amphotericin products [315]. Clinical pharmacists play a crucial rule in guiding medical team on appropriate TDM timing based on pharmacokinetic principles and application of TDM. They also have expertise in interpreting drug concentrations results. In addition, they are assisting in dosage individualization [316]. In Australia it has been suggested to expand the role of the pharmacist in TDM where there role is restricted to providing advice about the time to collect blood samples and TDM results interpretation [317]. In countries like New Zealand, prescribing pharmacists are permitted to request and interpret laboratory tests as part of a collaborative healthcare team, although limited research is available on how widely this practice is implemented [318]. In the United Kingdom, pharmacists with independent or supplementary prescribing rights are allowed to order lab tests, and a recent survey found that half of the pharmacists surveyed routinely requested pathology tests for therapeutic drug monitoring [319]. In the United States, most primary care pharmacists can order lab investigations under collaborative practice agreements with physicians, or they conduct point-of-care testing and provide patient education in clinical or pharmacy settings [320]. Within the U.S. hospital system, a survey conducted by the American Society of Health-System Pharmacists (ASHP) revealed that 97.3% of hospitals reported pharmacists routinely monitored serum drug exposure or related markers, 85.5% permitted pharmacists to order initial drug level tests, and 84.5% allowed pharmacists to adjust medication dosages based on monitoring results [321].

5.4.6 Future Directions

Economic considerations associated with TDM particularly within specific healthcare system such as in Australia including cost are related to workflows, laboratory expenses and analytical platform such as (immunoassays and liquid chromatography) [322]. The primary purpose of

evaluating health economic status of TDM is to inform decision-makers if TDM and other comparators provides good value for money, with the goal of making the most efficient use of healthcare resources [219]. To achieve this, a rigorous evaluation must consider all relevant factors that could influence the decision to adopt or reject it. This involves clearly defining the framework of the study such as the perspective taken, the intervention and its comparator, the target population, the setting, and the time horizon. It also requires careful identification, measurement, and valuation of both health outcomes and resource utilization. Moreover, selecting an appropriate analytical approach and addressing uncertainty are essential steps in ensuring robust results. Finally, the findings must be clearly summarized and interpreted to guide evidence-based decisions [323].

In the setting of precision dosing of vancomycin in neonates, the intervention involves TDM guided by MIPD, and the comparator is TDM guided dosing. The target population are neonates undergoing treatment with vancomycin to treat infections. When conducting economic evaluation alongside with clinical studies, it is generally recommended to include cost and healthcare outcomes with certain period to reflect short term costs. And extend the analysis to reflect long term cost. For instance, overdose or underdose may subject a longer hospital stay due to disease progression or toxicity.

In Australia, many diagnostic laboratories routinely measure drug concentrations for clinical use. However, delivering a comprehensive TDM service involves more than just analytical testing it also requires robust pre and postanalytical support to ensure that drug concentration results are clinically meaningful and tailored to individual patient care. While TDM is applied to a broad spectrum of medications, there are concerns about the continued use of suboptimal

assay techniques, even in situations where existing guidelines advocate for more accurate alternatives such as LC-MS/MS, however its organic solvent is toxic [324]. Therefore, there is rigorous research for more accurate alternatives collecting the advantages of easy, fast, accurate, economic and not harmful to the environment. Furthermore, the interpretive component of TDM services was often limited in scope and quality. There is a notable gap in the quality of TDM services, particularly in assay selection and the provision of clinical interpretation. The findings underscore the need for enhanced guidance on best practices and the establishment of professional standards in TDM. Such improvements would benefit from structured professional development initiatives and stronger collaboration among the diverse healthcare professionals involved in TDM. Additionally, incorporating measures that assess the clinical impact of TDM practices particularly their influence on clinical decision-making will be critical for advancing the quality and effectiveness of these services. Some of the recommendations identified may also have relevance beyond the Australasian context [325].

Ongoing research into the cost-effectiveness of Bayesian-guided TDM compared to traditional methods is critical for understanding its long-term benefits. This analysis focuses on the impact on healthcare resource utilization, patient outcomes, and overall financial sustainability. TDM protocols showed a significant cost benefit for patients treated with vancomycin as it reduced the risk of nephrotoxicity and, thus, the length of hospital stay [326]. On the other hand, there is a shortage of research analyzing the cost of Bayesian TDM. In addition to cost-benefit analysis studies, it is important to gather insights from clinicians and pharmacists about their preferences and decision-making processes regarding vancomycin TDM in neonatal care. This information will help improve neonatal care through evidence-based practices and collaborative research. It is important to note that this assumes the findings from studies predominantly

conducted in adult populations are transferable to neonates. Given the distinct pharmacokinetic and pharmacodynamic profiles in neonates such as differences in drug clearance, volume of distribution, and organ maturity caution should be exercised when extrapolating adult data to neonatal care. Further research specifically targeting neonatal populations is essential to validate these findings and ensure safe and effective therapeutic strategies.

A strategy to gather such information is via a Discrete Choice Experiment (DCE). This research method is used to understand preferences by asking participants to choose between sets of hypothetical scenarios [327] and is a quantitative method to provoke participants' perspectives on the scenarios presented [328, 329]. This method have been used by a wide range of clinical guidelines studies, such as a tool to measure clinical response to therapy in uncontrolled asthma [330] and neuroendocrine tumor treatment preferences [327], as well as COVID-19-related studies [331]. But DCE is still not used in TDM related studies yet. It could be employed to understand the preferences of key stakeholders, such as pharmacists, physicians, and potentially patients or caregivers, regarding various TDM approaches. For instance, participants might be asked to choose between TDM strategies that differ in attributes like frequency of monitoring, accuracy, cost, and potential impact on patient outcomes

Blood sampling in neonates is challenging because of their small blood volume and is a painful procedure [280]. Therefore, there is an interest in non-invasive methods like electrochemical sensors to measure vancomycin concentration in real-time. These minimally invasive devices penetrate the skin's outer layer to access interstitial fluid, which reflects plasma drug concentrations. By detecting vancomycin levels in interstitial fluid, these sensors can provide real-time data that closely correlates with serum concentrations, facilitating timely and precise

dosing adjustments [332]. The sensor consists of an aptamer which can measure drug concentration in ISF. Aptamer is a single strand DNA or RNA molecule engineered to bind specifically to the drug, which is attached to the electrode surface. Furthermore, the signal reporter is a redox-active molecule attached to the aptamer. It produces electrochemical signals detected by the sensor. The sensor will continuously measure the vancomycin concentration, allowing for real-time monitoring [333]. Combining real-time monitoring and Bayesian TDM may offer a powerful synergy to optimize vancomycin therapy in neonates. Real-time measured drug concentrations can be directly linked to the Bayesian model software deployed in target-controlled infusion systems [334]. Such a closed-loop system (Figure 5-1) has excellent potential to remove any delays due to the logistical process of TDM and laboratory tests [335, 336]. What increases Bayesian dosing adoption complexity is the need for manual data entry, which is time-consuming. Most of the software is stand-alone and needs moderate to extensive training to be friendly user software. An automated system or integrated electronic health record (EHR) allows data to be imported directly without risk of mistakes. Some of the software has EHR integration capabilities. It provides real-time dosing recommendations such as DoseMeRX, PrecisePK and Tucuxi (Table 5-1) [218, 337].

5.5 Discussion

This review compared conventional and Bayesian TDM strategies of vancomycin, showing the favorable effect of Bayesian TDM due to its impact on vancomycin safety and efficacy. Initial implementation costs of Bayesian TDM are higher than those for conventional TDM methods mainly due to the former method requiring the purchase of the software license and staff training. Currently, there are very limited data on the actual costs associated with implementing

model-informed precision dosing, including software, training, or potential reductions in hospital stay. While the potential economic benefits are suggested in the literature, numerical cost comparisons between conventional and Bayesian dosing are not available. Future studies should aim to collect real cost data to quantify the value of implementing model-based dosing, including effects on hospital admission duration, drug-related toxicity, and overall treatment efficiency. The quality system regulations for Bayesian software is different between countries. Bayesian software that provides information to be used in clinical decision making is called "medical device" by (ARTG). On the other hand, the United States Food and Drug Administration (FDA) classifies Bayesian software based on its use, Software that aligns its recommendations with FDA-required labelling is classified as "non-device clinical decision support software." However, there are no regulations yet for software that suggests off-label dosing regimens [294]. Although regulatory-approved software may entail higher initial costs, it offers verified safety and compliance. In contrast, freeware options, lacking regulatory approval, might be more affordable upfront but pose potential risks. Consequently, hospitals and healthcare professionals face challenging decisions when balancing cost considerations against the imperative for patient safety and regulatory adherence. Utilizing reliable, even non-regulatory-approved dosing software may be preferable to not employing any dosing software at all. Effective dosing strategies can lead to quicker recovery times, shorter hospital stays, and decreased healthcare costs. While Bayesian TDM offers several advantages, including improved safety, the challenges associated with its implementation, mainly cost and complexity, remain significant barriers for many hospitals. Addressing these challenges through education, training, and a clear demonstration of long-term benefits could facilitate broader acceptance and integration of Bayesian dosing in clinical practice.

This study provides an overview of the costs' aspects associated with various TDM strategies. By comparing conventional TDM with Bayesian-guided TDM strategies, we aimed to evaluate each approach's economic and practical implications. The findings highlighted the need for cost analysis studies comparing all TDM protocols and addressing the implementation cost, time efficiency, improved patient outcomes, and the long-term cost associated with AKI incidence, length of hospital stay, and clinical workload.

Our results underscore the potential for integrating Bayesian-guided models into routine practice. And to include pharmacists in planning and adoption stages which inform local policy and protocol development in neonatal intensive care units, fostering improved cost-efficiency and enhanced care quality. Further research is recommended to validate these findings across healthcare settings and evaluate long-term clinical outcomes.

5.6 Conclusion

The investments that come with the implementation of TDM differ by approach. Upfront costs associated with Bayesian TDM approach adoption in hospitals are higher than conventional TDM; these costs may be offset by long-term benefits such as reducing adverse effects, achieving optimal drug exposure and potentially decreasing the length of hospitalization. To determine the overall value of this approach, it is important to consider the financial investment required for implementation and the potential cost savings and clinical benefits it offers over time. Conducting comprehensive cost-benefit analyses will be essential to assess whether adopting Bayesian TDM provides a sustainable and impactful improvement in neonatal care.

Chapter 6: Discussion

6.1 Overview

In this chapter I will summarize the key findings of this thesis, examining them in the context of previously published literature and exploring their implications for clinical practice. Through a comprehensive review of literature and analysis of clinical data from a neonatal intensive care unit several important findings have emerged.

The primary objective of this thesis was to evaluate TDM practice of vancomycin in neonates. With a particular focus on optimizing TDM using model informed precision dosing MIPD software to improve therapeutic outcomes and reduce adverse effects. It was structured to achieve these aims. This thesis consists of four studies that investigated TDM, and pharmacokinetics of vancomycin in neonates. Three studies have been published in peer reviewed journals while the fourth is in the process of submission.

6.2 Key findings

Vancomycin is the commonly prescribed antimicrobial in NICU to treat Gram positive infections. TDM is essential to ensure that therapeutic concentration is attained with no adverse effects. As highlighted in Chapter 2, there is a wide range of dosing regimens and TDM strategies influenced by pharmacokinetic properties such as serum creatinine (sCr), body weight, postnatal age (PNA), and postmenstrual age (PMA). For instance, preterm neonates have underdeveloped renal and hepatic functions, which can result in slower drug clearance and the need for lower doses to avoid toxicity. Low birth weight neonates may require different

dosing due to their reduced body mass and altered drug distribution. In addition, renal maturity and function vary significantly among neonates, especially in the first weeks of life. This can lead to wide differences in how quickly vancomycin is cleared from the body, necessitating frequent dose adjustments. Due to this significant variability, achieving consistent target attainment is challenging.

Inconsistent target attainments were reported across studies leading to suboptimal treatment outcomes or increased risk of toxicity [107]. Therefore, it is crucial to individualize vancomycin dosing and monitoring according to the individual needs of each neonate, based on their unique pharmacokinetics characteristics. In addition to the importance of TDM in managing vancomycin therapy in neonates, the frequency and timing of TDM varied widely in the literature, contributing to inconsistent target attainment. Some studies recommended earlier and more frequent monitoring for preterm neonates [200, 216] to adjust dosing promptly. Although practically challenging such information should find its way into dosing guidelines which could improve the consistency of target attainment and enhance the overall efficacy and safety vancomycin in neonates. Safety concerns, particularly the risk of nephrotoxicity, is prevalent with the use of nephrotoxic drugs such as vancomycin where a trough concentration > 15 mg/L is associated with an increased risk of nephrotoxicity [77]. Guidelines derived from adult's studies recommended the use of (AUC_{24}/MIC) of 400-600 to monitor vancomycin efficacy and safety. However, these recommendations need further investigation in neonates due to pharmacokinetic variabilities in this age group [338]. In chapter 2, studies reported rates of nephrotoxicity ranging from 1.05- 7.18%. It is important to realize that between studies different definitions for nephrotoxicity were used linked to e.g. higher Scr level and clinical signs such as low oliguria, anuria, and or oedema which complicated the analysis.

The variability of TDM practice for vancomycin in NICU was also highlighted in Chapter 3. TDM is commonly implemented in hospitals while the frequency and timing of blood sampling is different among patients based on their PMA and PNA. The aim of this study was to assess the proportion of neonates achieving the therapeutic target as defined in the hospital protocol. Significant number of neonates either had subtherapeutic or supratherapeutic concentrations, proposing issues with dose adjustment and TDM practice. Several factors were explored to affect the attainment of therapeutic target such as GA, birth weight, renal function and TDM timing, which also contributed to the variability of observed concentrations. The adherence to the constituted TDM protocol was tested. Inconsistencies were found including some patients not receiving TDM as recommended by the hospital protocol, and timing of drug administration and blood sampling. Inadequate TDM practice was associated with increased risk of low therapeutic target attainment. The chapter underscored the need for more consistent TDM practice and blood sampling to ensure optimal vancomycin therapy. It provided several recommendations to optimize vancomycin therapy in neonatal population including standardizing TDM protocols, staff education and training on vancomycin pharmacokinetics, and using appropriate TDM technology such as introducing MIPD software.

Bayesian guided TDM can improve dosing accuracy because it uses models incorporating patient specific characteristics such as age, weight and renal function [111]. In chapter 4, I aimed to identify the most effective population pharmacokinetic (PopPK) model for predicting vancomycin exposure in neonates at Westmead Hospital. After evaluating 25 published population pharmacokinetic models, nine models were included in the analysis. De Cock 2014 model demonstrated the best predictive performance. It showed low bias and high predictive accuracy before and after incorporating observed concentrations. It consists of key covariates relevant to maturational changes in neonates including weight and postnatal age. These factors

are markers of neonatal rapid physiological changes affecting drug kinetics [339]. Combining the best predictive model and Bayesian forecasting software promising for individualized dosing and reduce the need for frequent blood sampling, improve target attainment and reduce risk of toxicity [77]. They can be integrated in clinical practice to support TDM in neonates ensuring better clinical outcomes while minimizing risk of adverse effects [104]. Conventional TDM is the routinely used approach in hospitals [340]. The main problem in conventional TDM is the need to collect blood samples at the steady state and at specific time points [100]. As the process is not very accurate it often involves multiple frequent blood sampling and laboratory analysis accompanied by dose adjustments [311]. It may require more time to reach therapeutic target, and because of its low accuracy it may result in suboptimal outcomes and increased risk of side effects [341]. All of which may contribute to increasing the cumulative long-term cost of conventional TDM. On the other hand, Bayesian TDM requires lower blood sampling frequency which can contribute to lower laboratory costs. Accurate dosing calculation and adjustment, and achieving therapeutic target faster, minimizing the risk of adverse nephrotoxicity, therefore reducing the length of hospital stay and the associated cumulative cost. In chapter 5, I used semi-structured search to explore the pros and cons of conventional TDM and Bayesian TM approaches regarding costs reviewed. The cost aspects for both practices included the initial implementation requirement cost, and the long-term cost saving resulted from precise dosing, TDM, and reduction of side effects incidence. It also addressed the pharmacist role to facilitate easy and effective Bayesian TDM adoption. Nourishing pharmaceutical knowledge through training workshops is essential to ensure safe and effective use of Bayesian TDM [342]. They can collaborate with clinicians to use Bayesian software and the best predictive model to calculate the initial dose, interpreting drug concentrations and adjusting the dose based on the readings. In addition to monitoring and minimizing risk of nephrotoxicity, pharmacists have a pivotal role;

they can provide training and support to other health care professionals to facilitate smooth and proper integration of Bayesian software in hospitals. Therefore, there is a need to determine the cost saving contributed to pharmacist role intervention [343].

In addition, the chapter suggested future direction to optimize TDM practice and vancomycin in NICU. Besides the need to evaluate cost-effectiveness of TDM approaches there is a need to understand the barriers of implementing Bayesian TDM in hospitals. One suggestion is to understand clinicians and pharmacists' preferences through discrete choice analysis making use of real-world scenarios.

6.3 Limitations

Despite all efforts the studies included in the thesis had some limitations. The literature review showed highly heterogenous studies using various methodologies, population, and clinical settings. The lack of homogenous target attainment evaluation made it challenging to combine the data and draw conclusions about the optimal vancomycin dosing in neonates. The literature lacked information on the long-term effects of vancomycin use in neonates, particularly regarding its impact on renal function and neurological development. Additionally, the included studies were mostly performed retrospectively which provide weaker evidence than prospective or randomized controlled trials. Intervention studies are difficult to perform on neonatal population due to the ethical concerns and practical challenges. Neonates are vulnerable and interventions cannot be applied or controlled as rigorously as in other populations [344]. It requires informed consent from parents or carers which can be difficult, especially in critical situations. Simple procedures like an additional blood sampling are a considerable risk which could be critical in fragile neonates. Prospective studies require well-defined protocols and plans, specialized staff, intervention, funding and infrastructure which is often not available in

neonatal settings due to lack of funding [345].

The retrospective nature of chapter 3 could have limited the accuracy and comprehensiveness of its findings since the data were collected from medical records. It was a single center study conducted in NICU, which in turn limited the generalizability of the results to other clinical settings such as TDM practices, protocols and populations can vary significantly between institutions.

Chapter 4 focused on finding the best predictive model for a local NICU with certain characteristics who received vancomycin under a specific protocol or practice. Systematic errors were evaluated using rBias. It measured the mean deviation of the difference between predicted and observed concentrations in percentage. RBias closing to zero indicates higher accuracy of prediction and the clinical acceptable range was between (-20% to 20%). RRMSE were used to evaluate models' precision and reliability [346]. It accounts for both systematic and random errors. Lower value indicates higher precision of prediction. These metrics focus on the accuracy and precision of prediction and could be affected by outliers [347, 348]. The accuracy and precision of the included models in the chapter might be affected by the quality of the data used in model building or validation. If the datasets are not representative of the target population it may not provide accurate individualized dosing or dosing adjustment [138]. A prospective study could be designed to standardize data collection and reduce the risk of missing data. It allows for real-time monitoring of neonates and clinical outcomes. Additionally, implementation of Bayesian model in clinical settings may be challenging due to the need for specialized software and staff training. These challenges were not fully addressed in the chapter which could limit the adoption of Bayesian models to guide TDM in neonatal population.

In Chapter 5 we performed a review using a semi structured search to explore costs and benefits of TDM approaches. This study adopts a semi-structured review approach, which systematically identifies and synthesizes literature on a specific topic, albeit without the exhaustive search and strict inclusion criteria characteristic of a systematic review. Unlike a narrative review, which offers a broad, descriptive summary of existing research without predefined protocols, the semi-structured approach provides a more focused synthesis while maintaining flexibility in study selection and analysis. This method allows for a comprehensive understanding of the topic, incorporating diverse expert-perspectives and findings, yet may be more susceptible to bias due to its less stringent methodology.

6.4 Future directions

Several key areas to optimize vancomycin treatment in neonates need to be focused on in the future. There is a need to understand the relationship between drug concentration and clinical outcomes or adverse effects [198]. In Australia there is a need to standardize evidence-based dosing protocols and TDM practice guidance of vancomycin specifically for neonates [270]. Unique pharmacokinetic and pharmacodynamic characteristics of neonates should guide these protocols. Large scale multicenter studies should be performed in the future, collect more generalizable data on vancomycin dosing and TDM in neonates. Such studies should include the use of PK/PD modelling to improve individualized dosing regimens validating these models in diverse neonatal populations and integrate them into routine clinical practice. There is also a need to integrate user-friendly software into hospitals and address logistical challenges associated with software. In addition to training the healthcare providers to use this technique and familiarize them with its purpose, capabilities and how it interacts with clinical practice. Public private partnerships between a company (software developers or owners) and hospitals

would enhance the accessibility and functionality of the software and ensure the adaptability of the software to various clinical needs and users. Exploring new surrogate markers to monitor vancomycin could be helpful for better TDM of vancomycin and reduce the invasiveness of blood sampling for neonatal population. This could include urinary biomarkers which may help in better predicting vancomycin induced kidney injury [349], salivary vancomycin TDM [350], or the use of non-invasive biosensor for continuous monitoring of drug exposure [351].

Cost-effectiveness studies should be conducted to analyze the financial implications of introducing Bayesian models in clinical settings compared to traditional dosing and TDM methods including possibility of savings resulted from reduced adverse effects, reduced hospital stays and improved therapeutic outcomes. Conducting these directions can help optimize the use of Bayesian TDM of vancomycin in neonatal populations and ensure more effective, personalized and safe therapy for neonates.

6.5 Conclusion

The collective findings from the thesis emphasizes the critical need to improve vancomycin dosing and therapeutic drug monitoring in neonates. Across all chapters, significant variability was observed in current practice, leading to inconsistent therapeutic outcomes and potential risk of toxicity. The Bayesian TDM and dosing approach shows promise for individualized and more precise dosing. However, challenges prevent generalization and integration of Bayesian models into routine clinical settings. Overall, this thesis highlights the importance of developing evidence based, standardized protocols and advanced software such as Bayesian dosing software along with ongoing staff training and education to optimize vancomycin therapy in neonates.

Future work could focus on developing and validating a new population pharmacokinetic model of vancomycin specifically for neonates in Australia. Such a model should take into account local patient characteristics, including gestational and postnatal age, body weight, and renal function, as well as clinical practices and dosing protocols used in Australian NICUs. Validation of the model in real-world clinical settings would help ensure accurate predictions of vancomycin exposure and improve target attainment. Additionally, integrating this model with model-informed precision dosing software could support individualized dosing, reduce the risk of toxicity such as AKI, and potentially optimize resource use, including reducing hospital stay and laboratory costs. Collecting cost and outcome data alongside model implementation would provide valuable evidence for the benefits of adopting such approaches in neonatal care.

APPENDIX

6.6 Appendix

Table S 1 ROBINS-I: Risk of Bias in Non-randomized studies of interventions tool.

Author	Bias due to confounding					Bias due to participants			Bias in classification of intervention		Bias due to deviation from intended interventions			Bias due the missing data			Bias in measurement of outcome			Bias in selection of the reported results		
	Potential effect of nephrotoxic agent, hemodynamic stability status	Baseline SCr measured before the start of therapy	Vancomycin therapy discontinued or switched due to nephrotoxicity	Age and weight variables controlled e.g.: (age groups)	Appropriate TDM during vancomycin therapy and SCr monitoring (sampling time)	Participant's selection based on renal function, and hemodynamic stability	Follow up of patients coincide for most participants	Trough conc entration known per group of AKI incidence	Total datasets of vancomycin treatment (Clearly defined, at the start of the treatment)	Nephrotoxicity affected by knowledge of concurrent nephrotoxic medications	Vancomycin dose administered successfully to all patients (defined duration of treatment)	Vancomycin therapy adherence measurement (according to the study protocol in all patients)	Appropriate Scr and analysis (adhering to vancomycin therapy)	Outcome data (baseline Scr and after vancomycin) available for all, nearly all patients	Patient's excluded to the missing data on vancomycin therapy	Patient's excluded due to missing data on (Scr, age, or weight)	Nephrotoxicity affected by the knowledge of vancomycin administration	Nephrotoxicity dassessment method comparable across all patients	Any systematic error in nephrotoxicity measurement related to treatment	Reported results based on multiple analyses of vancomycin-toxicity relationship	Reported results based on multiple analyses of vancomycin-toxicity relationship	Reported results based on differed subgroups (age, weight, renal function)
V. Bhargava 2017	Yes	Yes	No	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	PY	No	Yes	No	No	Yes	PN
Ringgenberg 2015	Yes	Yes	No	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No	Yes	No

Leroux 2016	Yes	Yes	No	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Irikura 2011	NI	NI	Yes	NI	NI	No	No	No	Yes	No	Yes	Yes	NI	No	No	No	Yes	NI	NI	No	No	No
Madigan 2015	Yes	Yes	NI	NI	NI	No	No	No	Yes	NI	Yes	Yes	NI	No	NI	NI	Yes	NI	NI	No	NI	No
Sosnin 2019	Yes	No	No	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	NI	No	NI	No	Yes	NI	NI	Yes	Yes	Yes
Veil-Theriault 2020	No	Yes	No	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	NI	No	Yes	No	No	Yes	Yes

NI: no information, PY: partially yes, PN: partially no

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