A DESCRIPTIVE STUDY OF VANCOMYCIN USE AT RED CROSS WAR MEMORIAL CHILDREN'S HOSPITAL, CAPE TOWN

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Objectives:

To document the use, prescribing practices and monitoring of intravenous vancomycin and the spectrum of bacteria isolated on microbiological culture in children treated with intravenous vancomycin during a 12-month period at Red Cross War Memorial Children's Hospital (RCWMCH).

Methods:

A retrospective audit of intravenous vancomycin use in children admitted to RCWMCH during 2019.

Results:

All 158 vancomycin prescription episodes for 143 children were included. Overall usage of intravenous vancomycin was 63 days of therapy/1000 patient days (IQR 38–72). The median starting dose was 15 mg/kg/dose (IQR 14− 15) and median daily dose was 45 mg/kg/day (IQR 43–60). Vancomycin was prescribed as empiric (127/158, 80%) and directed (31/158, 20%) treatment. The median duration of treatment for the directed group was longer than the empiric group (p=0.001). Only 65/98 (66%) episodes where vancomycin treatment exceeded three days had vancomycin serum trough concentrations performed, and only 16/65 (25%) of these samples were obtained before the fourth dose. Prolonged antibiotic treatment of 14 days or more was not associated with gram positive bacteria on culture (OR 1.02, 95% CI 0.17−4.2,).

Conclusion:

Prolonged empiric treatment and inappropriate vancomycin monitoring were problems associated with paediatric vancomycin prescriptions in this patient population.

Contribution:

Our study identified multiple opportunities for improved vancomycin prescribing and monitoring. Further research and implementation of improved prescribing practices could contribute to the preservation of vancomycin as an effective antibiotic.

Acknowledgements, format and contributions

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Format

This dissertation is submitted in a publication ready format and has not been submitted to any journal or publication.

Contributions

Leonore Greybe was responsible for study design, data collection, data analysis and writing of the manuscript. James Nuttall, Brian Eley and Hafsah Tootla assisted with study design, manuscript review, editing and supervision. Wisdom Basera assisted with statistical analysis. Anna Botha provided the pharmacy data. All authors read and approved the final manuscript.

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Abbreviations

ADE – Adverse drug events

AMS – Antimicrobial stewardship

AST – Antimicrobial susceptibility testing

AUC_{24} – Area under the concentration-time curve from 0 to 24 hours

BSI – Blood stream infection

CAI – Community-acquired infection

CI – Confidence interval

CLSA – Clinical and Laboratory Standards Institute

CONS – Coagulase-negative *Staphylococcus*

DOT/1000 PD – Days of therapy per 1000 patient days

HAI – Hospital-acquired infection

HAP – Hospital-acquired pneumonia

HREC – Human Research Ethics

Committee

IDSA – Infectious Diseases Society of America

ICU – Intensive care unit

IPC – Infection prevention and control

IQR – Interquartile range

LMICs – Low- and middle-income countries

MIC – Minimum inhibitory concentration

MRSA – Methicillin-resistant *Staphylococcus aureus*

NEC – Necrotising enterocolitis

NHLS – National Health Laboratory Service

OR – Odds ratio

PD – Peritoneal dialysis

RCWMCH − Red Cross War Memorial Children's Hospital

REDCAP − Research Electronic Data Capture

SSTI − Skin and soft tissue infection

TDM − Therapeutic drug monitoring

TN − Tennessee

USA − United States of America

VAP − Ventilator-associated pneumonia

VPS − Ventriculo-peritoneal shunt

WHO − World Health Organization

Chapter 1 – Publication ready manuscript

Title page

A Descriptive Study of Vancomycin Use at Red Cross War Memorial Children's Hospital, Cape Town

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Contribution:

Our study identified multiple opportunities for improved vancomycin prescribing and monitoring. Further research and implementation of improved prescribing practices could contribute to the preservation of vancomycin as an effective antibiotic.

Introduction

Children in low- and middle-income countries (LMICs) are significant recipients of antibiotics globally (1), and little progress has been made in mitigating the risk of antimicrobial resistance by improving stewardship in this setting (2). The World Health Organization (WHO) has classified 35 antibiotics used in human health into *Access*, *Watch* and *Reserve* categories. This classification is based on spectrum of activity, frequency of use and resistance potential. Vancomycin is classified as a *Watch* antibiotic and should be prioritised for stewardship and surveillance for resistance (3). Vancomycin's mechanism of action against Gram-positive bacteria is by inhibition of bacterial cell wall synthesis. It remains the treatment of choice for infection caused by β-lactam-resistant Gram-positive bacteria such as *Enterococcus faecium*, β-lactam-resistant *Streptococcus pneumoniae* and methicillin-resistant *Staphylococcus aureus* (MRSA) (4,5).

A pharmacist-led, multicenter, antimicrobial stewardship (AMS) initiative, across 47 private hospitals in South Africa showed that one in every 15 antibiotic prescriptions required intervention, commonly for inappropriate dosing or excessive duration of treatment (6). An audit on the impact of stewardship on vancomycin use in children indicated non-approved indications for prescription, dosing errors, and prolonged duration of treatment were problems (7). Real time intervention and feedback on prescriptions of vancomycin have reduced overall vancomycin use and improved the safety and quality of care in tertiary hospitals (8, 9).

Adequate plasma and tissue concentrations of vancomycin are essential for an optimal clinical response. The effectiveness of vancomycin in the treatment of invasive infections due to Gram-positive bacteria, is associated with the area under the concentration-time curve from 0 to 24 hours divided by the minimum inhibitory concentration (AUC_{24}/MIC ratio) of the organism being targeted. For MRSA with a vancomycin MIC of 1 mg/L, an AUC_{24}/MIC ratio >400 is recommended (10). The 2011 Clinical Practice Guidelines produced by the Infectious Diseases Society of America (IDSA) recommended targeting vancomycin trough concentrations of 15–20 mg/L, which correlates with an AUC_{24}/MIC ratio >400, in adults with severe bacterial infections. The effectiveness and safety of targeting trough concentrations of 15–20 mg/L in children were not established at the time and a dose of 15 mg/kg administered intravenously six-hourly was recommended (11). Pharmacokinetic modelling subsequently suggested that a trough concentration of 7−10 mg/L may be sufficient to achieve an AUC_{24}/MIC of >400 in more than 90% of children with MRSA infection (12). Although optimal dosing and the role of therapeutic drug monitoring (TDM) in paediatric practice remains uncertain (11, 13), current IDSA guidelines recommend individualised targeting of an AUC_{24}/MIC ratio of 400–600 (assuming a vancomycin MIC of 1 mg/L) to achieve clinical efficacy while improving safety (5). Individualised AUC_{24}/MIC targeting is not readily available in LMICs but has been successfully used as an entry point for stewardship elsewhere (14).

Paediatric prescribing practices of vancomycin have not been evaluated in South Africa. Therefore, the aims of this study were to document the use, prescribing practices and monitoring of intravenous vancomycin and describe the spectrum of bacteria isolated on microbiological culture and their antibiotic susceptibility profile in children treated with intravenous vancomycin during a 12-month period at Red Cross War Memorial Children's Hospital (RCWMCH) in Cape Town, South Africa. With this information, we hope to identify potential AMS intervention opportunities, thereby contributing to better patient outcomes and the preservation of vancomycin as an effective antibiotic at our institution, and possibly beyond.

Methods

Study design, setting and identification of study participants:

A retrospective descriptive study of intravenous vancomycin use in children admitted to RCWMCH during 2019 was performed. The RCWMCH is a 272-bedded referral hospital that serves children aged 13 years and below from the Western Cape province and occasionally from surrounding provinces. All children treated with intravenous vancomycin during the study period were eligible for inclusion. Study participants were primarily identified from the RCWMCH pharmacy database. In addition, the intensive care unit (ICU) discharge summary database was searched since vancomycin used to treat children admitted to the ICU is obtained from ICU medication stock and not issued directly from the pharmacy on an individual patient basis.

Data collection:

Demographic details, clinical information, and vancomycin prescription data on the enrolled participants was extracted from the medical records obtained from the RCWMCH medical records department and entered into Redcap (Research Electronic Data Capture, Vanderbilt University, Nashville, TN, USA). Details of each vancomycin prescription episode were obtained from the paper-based antibiotic prescription chart (a separate prescription chart from that used for other medication) that is currently in use at RCWMCH. This chart prompts the prescriber to send appropriate cultures prior to antibiotic prescribing and to indicate the suspected clinical diagnosis, source of infection, and an indication as to whether the antibiotic is for empirical or directed treatment. The route, dose, dosing frequency, duration, and start date and time is also captured (*Supplementary data, Figure 1)*. Prescription data was collected directly from this antibiotic chart where available, multiple prescription episodes were collected within a single admission.

All microbiological cultures were performed at the National Health Laboratory Service (NHLS) microbiology laboratory at Groote Schuur Hospital in Cape Town. Bacterial identification and antibiotic susceptibility testing (AST) were performed using the Vitek®2 automated system (bioMérieux,

France), biochemical or antigen-detection methods, and disc or gradient diffusion antibiotic susceptibility testing methods where appropriate. Results of AST were interpreted using the Clinical and Laboratory Standards Institute (CLSI) guidelines (15).

Data analysis:

Data was analysed using Microsoft Excel (version 2111) and Stata statistical software, version 15.0 (Stata Corp., College Station, Texas, USA). Categorical variables were described using absolute values and percentages with the associated 95% confidence intervals (CIs); continuous variables were described using median and interquartile range (IQR) for non-normally distributed data. Comparison of the association between the treatment groups and vancomycin usage days and treatment groups and daily dose was done using the Wilcoxon rank sum test. Odds ratio was calculated using the STATA immediate command. A p-value of less than 0.05 was used to denote statistical significance.

Study definitions:

An infection episode was considered a community-acquired infection (CAI) if vancomycin was started within 48 hours of admission to hospital and considered a hospital-acquired infection (HAI) if vancomycin treatment was started more than 48 hours after hospital admission or within 30 days of discharge from a previous admission (16).

A vancomycin prescription was considered empiric treatment if treatment commenced before culture and antibiotic susceptibility results were available, and all prescriptions for which cultures remained negative or no cultures were submitted to the laboratory. A vancomycin prescription was considered directed treatment when an organism susceptible to vancomycin was identified by culture and AST, and vancomycin was considered the preferred treatment option.

Vancomycin usage was expressed as days of therapy per 1000 patient days (DOT/1000 PD) defined as the number of days that study participants were treated with intravenous vancomycin (regardless of the dose) per 1000 inpatient days including all patients admitted in the hospital during the study period (17).

A vancomycin dose of 15 mg/kg administered intravenously 6 hourly or 60mg/kg/day, was considered the recommended dose (10).

Vancomycin TDM was considered appropriate if a serum trough level was performed before the fourth dose for patients with vancomycin prescriptions episodes exceeding three days (18) and a trough level of 10−20 mg/L was considered therapeutic based on guidelines followed within the study period (18).

Ethical considerations

Ethical approval was obtained from the University of Cape Town Human Research Ethics Committee (approval number HREC Ref: 498/2020) and the RCWMCH research committee (RCC 241 /

WC_202008_114). The HREC granted a waiver of informed consent on the basis that the study only used archived data which was anonymised. The study was done in accordance with the Declaration of Helsinki.

Results

A total of 158 vancomycin prescription episodes for 143 children were included (Figure 1), of which 67 (47%) were male and 76 (53%) were female. The median age at admission was seven months (IQR 1−77), with 36 (25%) neonates included, and the median weight was 7 kg (IQR 3−19).

Vancomycin usage:

The overall usage of intravenous vancomycin during the study period was 63 DOT/1000 PD (IQR 38–72). The monthly usage ranged from 1–104 DOT/1000 PD and the monthly usage stratified by use in and outside of the ICU is illustrated in Figure 2.

Vancomycin prescription episodes occurred in the following wards: ICU (81/158, 51%), transplant (23/158, 15%), surgical (19/158, 12%), haematology/oncology (19/158, 12%) and general paediatric (16/158, 10%).

Vancomycin prescribing practices:

a. Diagnosis and indications for vancomycin

All vancomycin prescription episodes met the definition of a HAI. The majority (127/158, 80%) started vancomycin treatment more than 48 hours after admission. For those who started vancomycin treatment before 48 hours (31/158, 20%), 19/31 (61%) were transferred in from other hospitals where they were admitted for more than 48 hours, and 13/31 (39%) where discharged within 30 days prior to current admission. Vancomycin was prescribed as empiric treatment for 127/158 (80%) prescription episodes and directed treatment for 31/158 (20%). Suspected clinical diagnoses and indications for vancomycin use are summarised in Table 1.

b. Dose

A starting dose of 15 mg/kg/dose was identified in 83/158 (53%) prescription episodes, with the median starting dose also being 15 mg/kg/dose (IQR 14−15). A total daily dose of 60 mg/kg/day was identified in 34/158 (22%) prescription episodes, with 109/158 (69%) receiving less and 15/158 (9%) more than 60 mg/kg/day. The median daily dose was 45 mg/kg/day (IQR 43–60) and there was no significant difference between the total daily dose in the definitive (IQR 40−60) versus empiric treatment (IQR 43−60) groups ($z=0.3$, $p=0.8$).

c. Dosing frequency

Dosing frequencies included six-hourly dosing in 42/158 (27%) and eight-hourly dosing in 89/158 (56%) prescription episodes. Other frequencies included: 12-hourly dosing in 11/158 (7%) of which ten (10/11, 90%) frequencies were based on prematurity and gestational age, and one (1/11, 10%) had renal dysfunction; three (3/158, 2%) episodes of 24-hourly dosing in which one (1/3, 33%) was based on gestation, and two (2/3, 67%) had renal dysfunction. In both episodes (2/158, 1%) where vancomycin was prescribed 48-hourly, renal dysfunction was present. A single dose was given in 11/158 (7%) episodes with ten (10/11, 90%) stopped after a single dose and one (1/11, 10%) episode where the vancomycin was re-prescribed eight-hourly.

d. Duration of treatment

The median duration of vancomycin treatment was five days (IQR 3−7). There was a significant difference between directed and empiric vancomycin treatment groups (z=3.2, p=0.001) with duration of treatment longer in the former [seven days (IQR 4−10) versus four days (IQR 2−7) respectively]. In 15/158 (9%) prescription episodes, the duration of vancomycin treatment was14 days or more. These prescriptions included empiric treatment of suspected meningitis or ventriculitis (4/15, 26%), skin and soft tissue infections (SSTI) (2/15, 13%), post-surgical intra-abdominal infection and typhlitis (2/15, 13%), ventilator-associated pneumonia (VAP) (1/15, 7%), febrile neutropaenia (1/15, 7%), a spinal abscess (1/15, 7%), and suspected toxic shock syndrome (1/15, 7%). One episode of necrotising enterocolitis (NEC) and coagulase-negative staphylococci (CONS) on blood culture (1/15, 7%) and two episodes of directed treatment for confirmed MRSA BSI (2/15, 13%) from wound sepsis after cardiac surgery and hospital-acquired pneumonia (HAP) in an episode of flame burns. In 3 of 15 episodes (20%) where vancomycin was prescribed for 14 days or more, Gram-positive organisms were cultured. Similarly, in episodes where vancomycin was prescribed for less than 14 days, 28/143 (20%) isolated Gram-positive bacteria from culture. Thus, the odds of having a Gram-positive organism on culture when treated with vancomycin for 14 days or more compared to the odds when treated for less than 14 days were similar [odds ratio (OR) 1.02, 95% confidence interval (CI) 0.17−4.2, p=0.59].

Therapeutic drug monitoring (TDM):

TDM was performed in 95/158 (60%) vancomycin prescription episodes. Vancomycin treatment exceeded three days in 98/158 (62%) prescription episodes and of these, 65/98 (66%) had vancomycin serum trough concentrations performed. Only 20/95 (21%) samples were obtained before the fourth dose, 44/95 (46%) before the second or third dose, and 31/95 (33%) after the fourth dose.

Dosing strategies in relation to vancomycin serum trough concentrations:

For samples obtained before the fourth dose, the median vancomycin serum trough concentration was 14 mg/L (IQR 6–18).

In total, there were 37/95 (39%) serum trough concentrations <10 mg/L. Irrespective of the timing of serum trough concentration measurements, prescription adjustments based on trough concentrations below 10 mg/L included an increase in dose (20/37, 54%), dose frequency (13/37, 23%), or both (5/37, 14%). Nine (9/37, 24%) prescriptions were not adjusted. Trough concentrations greater than 20 mg/L occurred in 21/95 (22%) of all prescription episodes where a trough concentration was performed. The dose (6/21, 29%), frequency (9/21, 43%), or both (1/21, 4%) were adjusted respectively. Vancomycin was stopped in three (3/21, 14%) and continued without any adjustments in two (2/21, 10%) episodes.

Microbiology:

Cultures were done before initiating 146/158 (92%) vancomycin prescription episodes. Culture results and antibiotic susceptibility of isolates from positive cultures are detailed in Table 2. A high proportion of culture positive episodes had an indwelling device present (39/58, 67%). These included indwelling venous catheters (31/58, 53%), urinary catheters (4/58, 7%), intracranial monitors (2/58, 3%), a ventriculoperitoneal shunt (VPS) (1/58, 2%) and a peritoneal dialysis catheter (1/58, 2%).

Vancomycin MICs were performed in 21/38 (55%) Gram-positive isolates including all seven MRSA isolates. All MICs were ≤ 1 mg/L.

Antibiotic de-escalation practices following culture and antibiotic susceptibility results:

Cultures were negative in 88/146 (60%) episodes and the median vancomycin treatment duration in these episodes was five (IQR 3−6) days. Vancomycin was stopped within three days for 36/88 (41%), within three to five days for 28/88 (32%) and continued for a median of seven (IQR 6–10) days for 24/88 (27%) prescription episodes.

Positive cultures were obtained in 58/146 (40%) vancomycin prescription episodes and the median vancomycin treatment duration in these episodes was six (IQR 2–8) days. Vancomycin was the appropriate antibiotic choice and prescribed as directed treatment in 22/58 (38%) prescription episodes and 9/58 (15%) episodes where CONS were identified, of which the clinical significance is uncertain. For 19/58 (33%) episodes, vancomycin was stopped within five days as culture either identified an organism for which vancomycin was not the appropriate antibiotic choice or the organism was not deemed clinically significant.

Vancomycin was continued beyond five days in 8/58 (14%) prescription episodes where the organism identified was either not susceptible to vancomycin or vancomycin was not considered the preferred treatment option. These included the following: 3/8 (37%) episodes where Gram-negative bacteria were isolated from blood and pus in suspected NEC (2) and from a tracheal aspirate in febrile neutropaenia (1); 3/8 (37%) episodes where methicillin-susceptible *S. Aureus* was identified from sputum in one episode of VAP, from a pus swab in wound infection after cardiac surgery, and from blood culture in

febrile neutropaenia respectively; one (1/8 (13%) episode in which *Candida albicans* was isolated from blood culture in an episode of VAP; and one (1/8, 13%) episode in which *Streptococcus agalactiae* was isolated from blood culture in an episode of NEC.

Adverse events:

Only four adverse drug events (ADE) were documented in the clinical records. One episode was associated with a hypersensitivity reaction; three had acute kidney injury attributed to vancomycin of which all had pre-existing chronic kidney disease, including advanced membranous nephropathy, lupus nephritis, and hepatorenal syndrome respectively. Vancomycin was stopped in two (50%) episodes, and continued despite the ADE in two (50%) episodes.

Discussion

To the best of our knowledge, this is the first description of vancomycin usage and prescribing practices in South African children. Intravenous vancomycin prescription occurs throughout our hospital with ICU unsurprisingly accounting for most of the usage (51%) during 2019. Comparable vancomycin usage has not been published from healthcare facilities treating children in South Africa.

Vancomycin was prescribed exclusively for HAI and mostly as empiric treatment (80%) and less often as directed treatment (20%) with cultures routinely obtained prior to prescriptions (92%). Clinical indications for inclusion of vancomycin at initiation of empiric antibiotic treatment included intra-abdominal infection and NEC (26%), HAP including VAP (24%) and SSTI (19%). For directed treatment, indwelling venous catheter-associated infection (24%), HAP (including VAP) (19%), and intra-abdominal infection and NEC (23%) was common. Vancomycin prescription for inappropriate or non-approved indications was less frequent than what has been described in other settings (7).

Dosing of vancomycin was variable with only 53% of prescriptions adhering to a starting dose of 15 mg/kg/dose and only 22% adhering to a total daily dose of 60 mg/kg/day as recommended (16). More than two-thirds of prescriptions were for <60 mg/kg/day. Dosing frequency was most often eight-hourly (56%) or six-hourly (27%) with dosing less frequently than eight-hourly due to prematurity or renal dysfunction. The significant difference in treatment duration detected between empiric and directed treatment episodes suggests that vancomycin is stopped sooner once cultures are negative than in cases where cultures and AST confirm an infection for which vancomycin is the appropriate treatment. However, among the 15 episodes (9%) where vancomycin treatment continued for 14 days or more, empiric treatment accounted for 80% of prescription episodes. These findings are in keeping with studies from other countries indicating that inappropriate prescribing and prolonged empiric treatment is common, with differences amongst age groups contributing to dosing complexity (19,20, 21).

The optimal dosing of vancomycin and the role of TDM in paediatric practice remains uncertain (11, 12) and may soon be replaced with model-informed precision dosing where available (22). IDSA guidelines (5) recommend AUC_{24}/MIC targeting whereas guidelines aiming for vancomycin serum trough levels of 10 – 20 mg/L are still followed at our institution (16). Serum trough concentration monitoring was only performed in 60% of prescription episodes overall and in 66% of episodes where treatment continued for > three days. Only 21% of samples were obtained before the fourth dose as recommended (16). This is lower adherence than the 40% reported by Matthieu et al. (23). With the very variable dosing found in our study overall, it is surprising that the median vancomycin serum trough concentration in the 20 episodes with samples obtained before the fourth dose was 14 mg/L (recommended range 10−20 mg/L (16)) although the variability was wide (IQR 6−18). Due to wide range of sampling times in relation to doses, it was difficult to interpret the serum trough concentration that were <10 or >20 mg/L as well as the appropriateness of dose adjustments done in response to these results. Although AUC_{24}/MIC monitoring is not currently available, its future utilization as an AMS tool may improve vancomycin dosing and safety, which is particularly important as ADE are likely underreported at our hospital (14).

The microbiological results revealed that approximately two-thirds of positive cultures occurred where an indwelling device were present. This finding suggests that improved compliance with infection prevention and control (IPC) could reduce the need for vancomycin prescription. Although blood culture yielded MRSA in 47% of isolates, it is reassuring that none of the isolates were non-susceptible to vancomycin. The rate of MRSA in our study was lower than the 72% and 65% in hospital-acquired BSI due to *S. aureus* recorded in previous paediatric studies done in Cape Town (24, 25).

Like many others in LMIC settings, our institution lacks the capacity to implement prospective audit and real-time feedback to prescribers, and discontinuation or de-escalation to narrower spectrum antibiotics based on culture and AST results where appropriate are important AMS interventions. Among episodes with negative cultures, vancomycin was discontinued in 41% within three days and 73% within five days of starting treatment. However, among 58 episodes with positive cultures, 8 (14%) continued vancomycin treatment despite the identification of an organism that was not susceptible to vancomycin or vancomycin is not the preferred treatment option.

Our study has several limitations. Firstly, paper-based medical record review with lost documents resulted in a high exclusion rate (23%). Uniform local guidance on vancomycin prescribing is limited and variable, and the appropriateness of vancomycin treatment based on the documented clinical syndrome could not be assessed. Furthermore, clinical indications were only collected at the time when vancomycin was initiated as information on indications for continued prescribing was not available. Due to the diversity in prescribing practices among different institutions, results may not be applicable elsewhere.

Monitoring antimicrobial use and instituting effective AMS interventions remain a challenge in areas where electronic prescribing is not yet feasible. Our study emphasises the need to develop and implement uniform guidelines for the prescription and monitoring of vancomycin along with appropriate de-escalation practices as urgent AMS interventions. Ongoing training and monitoring of prescribers and compliance with IPC practices is essential. Future research should focus on defining methods to improve prescribing practices and evaluate future AMS interventions.

Conclusions

Dosing errors, prolonged empiric treatment and inappropriate vancomycin monitoring were problems associated with vancomycin prescriptions identified in our study. AMS interventions targeting uniform prescribing and monitoring guidance and concurrently improving IPC compliance, may contribute to the preservation of vancomycin at our institution and others treating children.

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Data availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

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References

1. Allwell-Brown G, Hussain-Alkhateeb L, Kitutu FE, Strömdahl S, Mårtensson A, Johansson EW. Trends in reported antibiotic use among children under 5 years of age with fever, diarrhoea, or cough with fast or difficult breathing across low-income and middle-income countries in 2005-17: a systematic analysis of 132 national surveys from 73 countries. Lancet Glob Health. 2020;8(6):e799-e807. doi:10.1016/S2214-109X(20)30079-6
2. Porter GJ, Owens S, Breckons M. A systematic review of qualitative literature on antimicrobial stewardship in Sub-Saharan Africa. Glob Health Res Policy. 2021;6(1):31. Published 2021 Aug 20. doi:10.1186/s41256-021-00216-0
3. Hsia Y, Lee BR, Versporten A, et al. Use of the WHO Access, Watch, and Reserve classification to define patterns of hospital antibiotic use (AWaRe): an analysis of paediatric survey data from 56 countries. Lancet Glob Heal. 2019;7(7):e861-e871. doi:10.1016/S2214-109X(19)30071-3
4. Rossiter D, editor. South African Medicines Formulary. 13th edition. South African Medical Association; 2020
5. Rybak MJ, Le J, Lodise TP, et al. Executive Summary: therapeutic monitoring of vancomycin for serious Methicillin-Resistant Staphylococcus aureus infections: a revised consensus guideline and review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of A. Pharmacotherapy. 2020;40(4):363-367. doi:10.1002/phar.2376
6. Brink AJ, Messina AP, Feldman C, et al. Antimicrobial stewardship across 47 South African hospitals: an implementation study. Lancet Infect Dis. 2016;16(9):1017-1025. doi:10.1016/S1473- 3099(16)30012-3
7. Di Pentima MC, Chan S. Impact of antimicrobial stewardship program on vancomycin use in a pediatric teaching hospital. Pediatr Infect Dis J. 2010;29(8):707-711. doi:10.1097/INF.0b013e3181d683f8
8. Gillon J, Xu M, Slaughter J, Di Pentima MC. Vancomycin use: room for improvement among hospitalized children. J Pharm Pract. 2017;30(3):296-299. doi:10.1177/0897190016635478
9. Moise-Broder PA, Forrest A, Birmingham MC, Schentag JJ. Pharmacodynamics of vancomycin and other antimicrobials in patients with Staphylococcus aureus lower respiratory tract infections. Clin Pharmacokinet. Published online 2004. doi:10.2165/00003088-200443130-00005

10. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children. Clin Infect Dis. 2011;52(3). doi:10.1093/cid/ciq146
11. Frymoyer A, Guglielmo BJ, Hersh AL. Desired vancomycin trough serum concentration for treating invasive methicillin-resistant staphylococcal infections. Pediatr Infect Dis J. 2013;32(10):1077-1079. doi:10.1097/INF.0b013e318299f75c
12. Oskarsdottir K, Haraldsson A, Thorkelsson T, Oskarsdottir T, Gunnarsson P, Thors V. Children may need higher vancomycin doses to achieve therapeutic levels. Acta Paediatr. 2021;110(11):3077-3082. doi:10.1111/apa.16025
13. Suryadevara M, Steidl KE, Probst LA, Shaw J. Inappropriate vancomycin therapeutic drug monitoring in hospitalized pediatric patients increases pediatric trauma and hospital costs. J Pediatr Pharmacol Ther. 2012;17(2):159-165. doi:10.5863/1551-6776-17.2.159
14. Kreitmeyr K, Pecar A, Mikolajczyk R, von Both U, Huebner J. Pediatric Antibiotic Stewardship: optimization of vancomycin therapy based on individual pharmacokinetics. Pediatr Infect Dis J. 2021;40(6):556-562. doi:10.1097/INF.0000000000003058
15. CLSI. Performance standards for antimicrobial susceptibility testing. 29th ed. CLSI supplement M100. Wayne, PA: Clinical and Laboratory Standards Institute; 2019
16. The National Department of Health, South Africa: Essential Drugs Programme. Hospital level paediatrics standard treatment guideline and essential medicine list. 4th ed. South African National Department of Health; 2017. Available at https://www.knowledgehub.org.za/system/files/elibdownloads/2022-07/Paediatric%20Hospital%20Level%20STGS%20and%20EML_4th_2017.pdf
17. Stanić Benić M, Milanič R, Monnier AA, et al. Metrics for quantifying antibiotic use in the hospital setting: results from a systematic review and international multidisciplinary consensus procedure. J. Antimicrob. Chemother.2018; 73(6): vi50–vi58. doi:10.1093/jac/dky118
18. Martin JH, Norris R, Barras M, et al. Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society Of Infectious Diseases Pharmacists. Clin Biochem Rev. 2010;31(1):21-24.
19. Di Pentima MC, Chan S, Eppes SC, Klein JD. Antimicrobial prescription errors in hospitalized children: role of antimicrobial stewardship program in detection and intervention. Clin Pediatr (Phila). 2009 Jun;48(5):505-12. doi:10.1177/0009922808330774.
20. Jones DA, Pulver L, Tai B, Nourse C. Glycopeptide prescribing in an Australian tertiary paediatric hospital. J Paediatr Child Health. 2001 Aug;37(4):342-7. doi:10.1046/j.1440-1754.2001.00662.

21. Abanyie-Bimbo F, O'Leary E, Nadle J, et al. Evaluation of vancomycin prescribing quality in hospitalized pediatric patients. Open Forum Infect Dis. 2018 Nov 26;5(Suppl 1):S114. doi: 10.1093/ofid/ofy210.286.
22. Frymoyer A, Schwenk HT, Zorn Y, et al. Model-informed precision dosing of vancomycin in hospitalized children: implementation and adoption at an academic children's hospital. Front Pharmacol. 2020 Apr 29;11:551. doi:10.3389/fphar.2020.00551.
23. Roustit M, François P, Sellier E, et al. Evaluation of glycopeptide prescription and therapeutic drug monitoring at a university hospital. Scand J Infect Dis. 2010 Mar;42(3):177-84. doi:10.3109/00365540903413614.
24. Dramowski A, Cotton MF, Rabie H, Whitelaw A. Trends in paediatric bloodstream infections at a South African referral hospital. BMC Pediatr. 2015;15(1):1-11. doi:10.1186/s12887-015-0354-3
25. Naidoo R, Nuttall J, Whitelaw A, Eley B. Epidemiology of Staphylococcus aureus bacteraemia at a tertiary children's hospital in Cape Town, South Africa. PLoS One. 2013;8(10):1-9. doi:10.1371/journal.pone.0078396

Table 1: Clinical classification associated with each vancomycin prescription episode

Clinical classification*	Empiric (N=127$)		Directed (N=31$)	
	n (%)	95% CI	n (%)	95% CI
Infection without a clinical focus				
Fever[1]	4 (3)	1 - 8	1 (3)	0 - 17
Neutropaenia[2]	7 (6)	2 - 11	2 (6)	1 - 21
Infection with a clinical focus				
Hospital acquired pneumonia	13 (10)	6 - 17	2 (6)	1 - 21
Ventilator associated pneumonia	18 (14)	9 - 21	4 (13)	4 - 30
Shunt infection[3]	3 (2)	0 - 7	-	-
Subdural empyema	1 (1)	0 - 4	-	-
Ventriculitis	3 (2)	0 - 7	-	-
Meningitis	6 (5)	2 - 10	-	-
Intra-ocular infection	-	-	1 (3)	0 - 17
Intra-abdominal infection[4]	20 (15)	10 - 23	4 (13)	4 - 30
Necrotizing enterocolitis	14 (11)	6 - 18	3 (10)	2 - 26
Typhlitis	2 (2)	0 - 6	-	
Skin and soft tissue infection[5]	24 (19)	12 - 27	2 (6)	1 - 21
Toxic shock syndrome	1 (1)	0 - 4	-	
Osteitis	-	-	1 (3)	0- 17
Spinal Abscess	1 (1)	0 - 4	-	
Urinary tract infection	3 (2)	0 - 7	3 (10)	2 - 26
Infective endocarditis	2 (2)	0 - 6	-	
Line infection	5 (4)	1 - 9	7 (24)	10 - 41
Blood stream infection	-	-	1 (3)	0 - 17

** Includes any clinical diagnosis supplied at vancomycin initiation*
$ N=denominator unless otherwise specified
[1] Body temperature > 38 °C at the time of prescriptions
[2] Absolute neutrophil count < 1.5 X 10^9/l
[3] Includes ventriculoperitoneal and ommaya shunts
[4] Includes all post-surgical intra-abdominal infections and peritonitis
[5] Includes skin abscesses, burn wound infections and wound sepsis

Table 2: Microbiological profile of organisms isolated from positive cultures

Sample type: (N=58[$]) n (%)	**Organisms identified: (N=61[$])**	**n (%)**	**Number and proportion of Gram-positive organisms susceptible to selected antibiotics**	
Blood 46[*] (79)	*Staphylococcus aureus*	13 (21)	Cloxacillin Vancomycin	7 (53) 13 (100)
	Coagulase negative *Staphylococcus*	8 (13)	Cloxacillin Vancomycin AST not performed	0 6 (100) 2
	Enterococcus faecalis	2 (3)	Ampicillin Vancomycin	2 (100) 2 (100)
	Enterococcus faecium	10 (16)	Ampicillin Vancomycin	0 10 (100)
	Streptococcus mitis	2 (3)	Penicillin Ceftriaxone Vancomycin	0 2 (100) 2 (100)
	Streptococcus viridans	2 (3)	Penicillin Ceftriaxone Vancomycin	0 2 (100) 2 (100)
	Streptococcus agalactiae [1]	1 (2)	Penicillin Vancomycin	1 (100) 1 (100)
	Gram-negatives [2]	6 (10)	-	-
	Candida species [3]	4 (7)	-	-
Pus swabs 4 (8)	*Staphylococcus aureus*	2 (3)	Cloxacillin Vancomycin	1 (50) 2 (100)
	Enterococcus faecium	1 (2)	Ampicillin Vancomycin	0 1 (100)
	Klebsiella pneumoniae	1 (2)	-	-
Respiratory samples 3 (5)	*Staphylococcus aureus*	2 (3)	Cloxacillin Vancomycin	1 (50) 2 (100)
	Serratia marcescens	1 (2)	-	-
Peritoneal fluid 2 (3)	Coagulase negative *Staphylococcus*	1 (2)	AST not performed	
	Enterococcus faecium	1 (2)	Ampicillin Vancomycin	0 1 (100)
Urine 2 (3)	*Enterococcus faecium*	1 (2)	Ampicillin Vancomycin	0 1 (100)
	Enterococcus species [4]	1 (2)	AST not performed	
Vitreous fluid 1 (2)[#]	*Streptococcus salivarius*	1 (2)	Penicillin Ceftriaxone Vancomycin	0 0 1 (100)
	Streptococcus mitis	1 (2)	Penicillin Ceftriaxone Vancomycin	0 1 (100) 1 (100)

**Total pathogens isolated from blood culture includes two isolates identified in two cultures (48 pathogens from 46 samples), including a mixed growth of Klebsiella pneumoniae and Escherichia coli and Staphylococcus aureus and Streptococcus mitis*

$ N = denominator unless otherwise stated

1 Group B Streptococcus

2 Klebsiella pneumoniae, Citrobacter freundii, Serratia marcescens, Pseudomonas aeruginosa, Klebsiella oxytoca, Escherichia coli

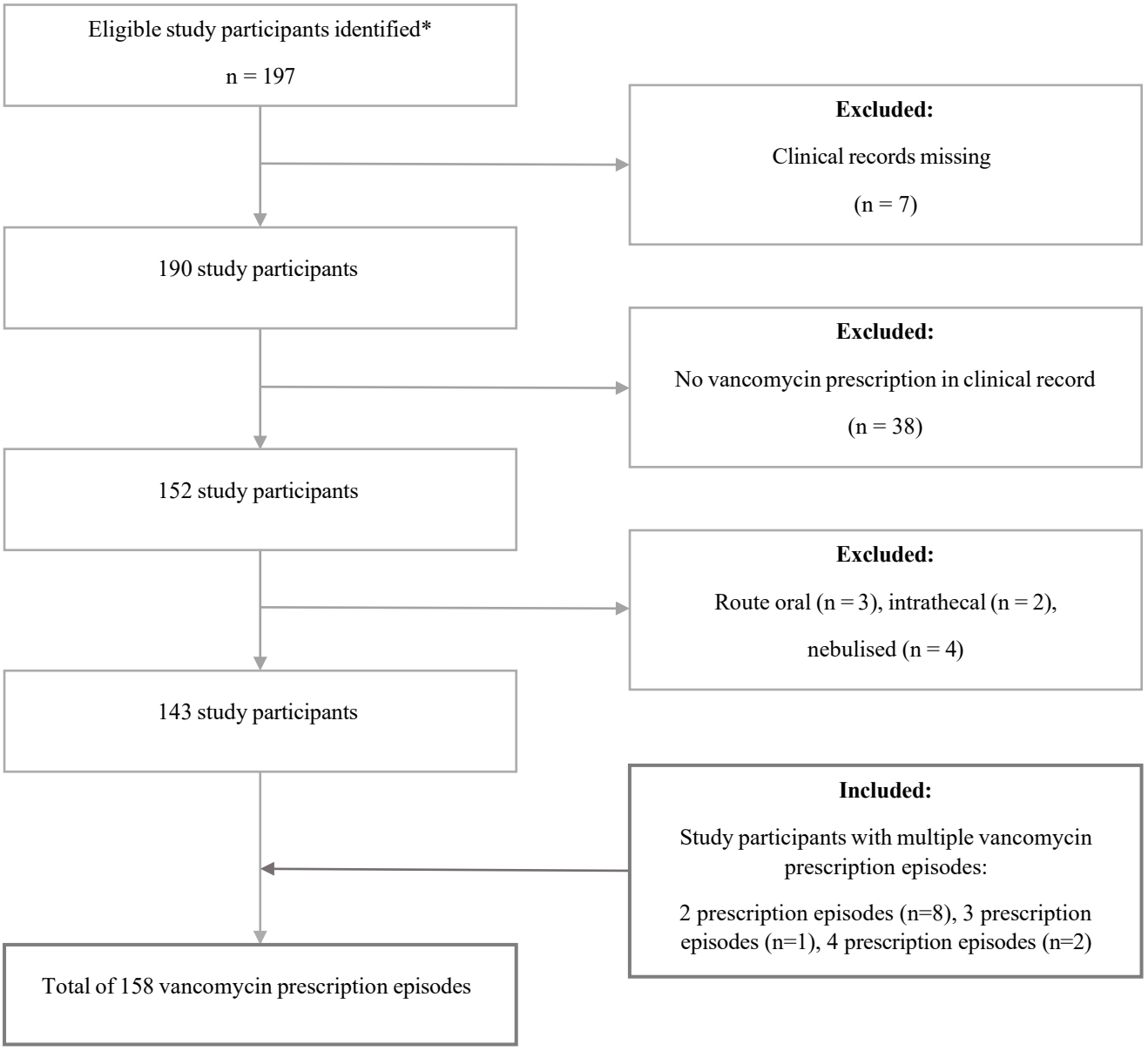
3 Candida albicans, Candida parapsilosis

4 Only identified up to genus

 # Two pathogens isolated from one vitreous fluid sample

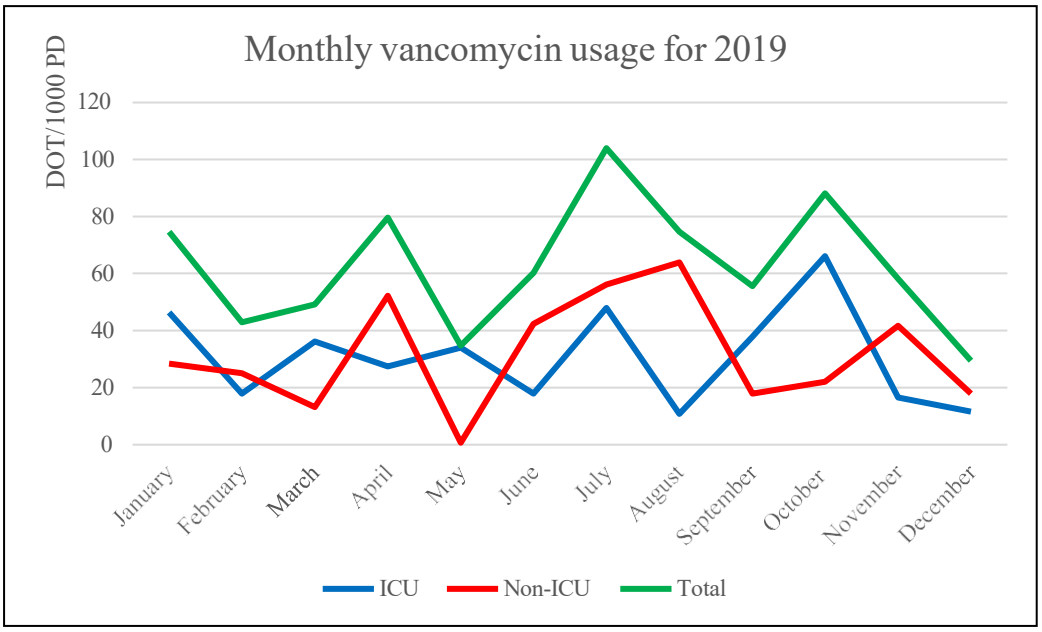
Abbreviations AST, Antimicrobial susceptibility

Figure 1: Participants and vancomycin prescription episodes included in the study



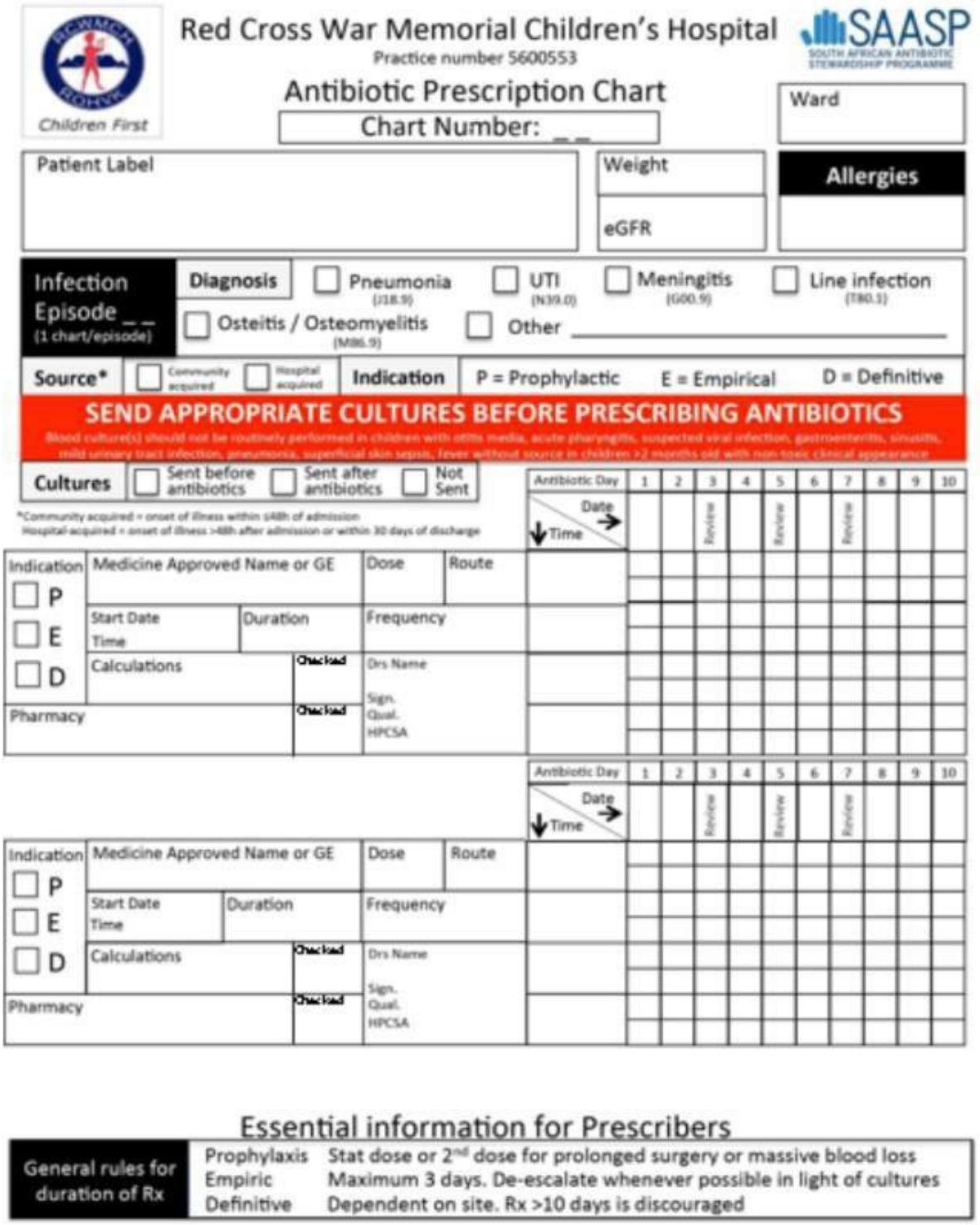
***** *Identified via the Red Cross War Memorial Children's Hospital (RCWMCH) Pharmacy database or from the RCWMCH intensive care unit discharge summary database*

Figure 2: Monthly usage of vancomycin over the study period (2019) in ICU & non-ICU wards at Red Cross War Memorial Children's Hospital.



DOT/1000 PD, days of therapy per 1000 patient days; ICU, intensive care unit.

Supplementary figure 1: The antibiotic prescription chart currently in use for the exclusive prescription of antibiotics at Red Cross War Memorial Children's Hospital



Red Cross War Memorial Children's Hospital

Practice number 5600553

Antibiotic Prescription Chart

Chart Number: _ _

Children First

SAASP

SOUTH AFRICAN ANTIBIOTIC STEWARDSHIP PROGRAMME

Ward

Patient Label

Weight

eGFR

Allergies

Infection Episode _ _ (1 chart/episode)

Diagnosis: Pneumonia (J18.9); UTI (N39.0); Meningitis (G00.9); Line infection (T80.1); Osteitis / Osteomyelitis (M86.9); Other _____

Source*: Community acquired; Hospital acquired

Indication: P = Prophylactic; E = Empirical; D = Definitive

SEND APPROPRIATE CULTURES BEFORE PRESCRIBING ANTIBIOTICS

Blood culture(s) should not be routinely performed in children with otitis media, acute pharyngitis, suspected viral infection, gastroenteritis, sinusitis, mild urinary tract infection, pneumonia, superficial skin sepsis, fever without source in children >2 months old with non-toxic clinical appearance

Cultures: Sent before antibiotics; Sent after antibiotics; Not Sent

*Community acquired = onset of illness within ≤48h of admission
Hospital-acquired = onset of illness >48h after admission or within 30 days of discharge

Antibiotic Day	1	2	3	4	5	6	7	8	9	10
Date → / Time ↓			Review		Review		Review			

Indication: P / E / D

Medicine Approved Name or GE | Dose | Route

Start Date Time | Duration | Frequency

Calculations | Checked | Drs Name Sign. Qual. HPCSA

Pharmacy | Checked

Antibiotic Day 1 2 3 4 5 6 7 8 9 10

Date → / Time ↓ Review Review Review

Indication: P / E / D

Medicine Approved Name or GE | Dose | Route

Start Date Time | Duration | Frequency

Calculations | Checked | Drs Name Sign. Qual. HPCSA

Pharmacy | Checked

Essential information for Prescribers

General rules for duration of Rx		
	Prophylaxis	Stat dose or 2nd dose for prolonged surgery or massive blood loss
	Empiric	Maximum 3 days. De-escalate whenever possible in light of cultures
	Definitive	Dependent on site. Rx >10 days is discouraged

Appendices

Appendix 1 − Study protocol

RESEARCH PROTOCOL

A DESCRIPTIVE STUDY OF VANCOMYCIN USAGE AT RED CROSS WAR MEMORIAL CHILDREN'S HOSPITAL, CAPE TOWN

Investigator: Dr L Greybe[1]
Supervisors: Dr JJC Nuttall1, Prof BS Eley[1]
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3Red Cross War Memorial Children's Hospital.

Introduction

Vancomycin is a glycopeptide antibiotic active against Gram-positive bacteria by inhibiting bacterial cell wall synthesis. It is generally reserved for the treatment of infections due to cloxacillin-resistant staphylococci and penicillin-resistant enterococci or Clostridioides difficile infections.Vancomycin-resistant staphylococci and enterococci have been widely reported internationally but there is a lack of recent published paediatric data from South Africa. Paediatric prescribing practices have not been recently evaluated in South Africa.[1] Vancomycin was originally discovered in the 1950's when Eli Lilly and company initiated a programme aimed at finding alternative antibiotics for the treatment of penicillin-resistant staphylococcal infections. It is derived from an organic substance called "compound 05865" produced by Streptomyces orientalis and found in a sample of dirt sent to the laboratory by a missionary in Borneo.[2] In its first therapeutic trial, vancomycin cured 8/9 patients suffering from penicillin resistant staphylococcal infections and was quickly approved and distributed to treat patients where other treatments failed. The ototoxicity and nephrotoxicity of vancomycin was documented soon after its distribution and it was quickly overshadowed by the discovery of equally efficient and less toxic antibiotics. The increased use of vancomycin would not occur until almost three decades later, when the emergence of pseudomembranous enterocolitis called for an antibiotic that would be effective against Clostridioides difficile and not absorbed via the gastrointestinal tract. An outbreak of methicillin-resistant Staphylococcus aureus (MRSA), first described in Detroit and later found throughout the world, directed the attention to vancomycin. The accelerated use of vancomycin in the following decades has inevitably led to resistance and the emergence of vancomycin-resistant enterococci (VRE) as a virulent pathogen.[2]

Vancomycin has a narrow therapeutic index and adequate concentrations are essential for clinical response. The

efficacy of vancomycin is associated with the area under the plasma concentration-time curve from 0 to 24 hours (AUC0-24) over minimum inhibitory concentration (MIC) and for MRSA with an MIC of 1mg/L an AUC/MIC ratio >400 is recommended.[3] The 2011 Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA) previously suggested that vancomycin trough levels at a target range of 15–20 mg/L in adults with severe bacterial infections could be used as a surrogate marker for AUC/MIC. The efficacy and safety of targeting trough concentrations of 15–20 mg/L in children were not established at the time and a dose of 15 mg/kg 6 hourly was recommended in lieu of evidence.[4] Simulation data of vancomycin pharmacokinetics in children subsequently showed that 90% of simulated children achieved AUC/MIC >400 at trough concentrations of 7 -10 mg/L.[5] Furthermore, a recent meta-analysis showed that nephrotoxicity at vancomycin trough levels >15 mg/L occurs more commonly in the paediatric population, especially in critically ill children where hypovolaemia and the concurrent use of other nephrotoxic drugs may aggravate vancomycin's toxic effects.[6] Current IDSA guidelines no longer advise trough monitoring, but rather advocate for individualised targeting of the AUC:MIC ratio of 400–600 (assuming a vancomycin MIC of 1mg/L) to achieve clinical efficacy while improving safety.[7]

A 3-month audit at Tygerberg hospital in Cape Town found that >60% of trough concentration samples of both paediatric and adult patients were outside of the therapeutic range.8 This was attributed to difficulty in predicting dose adjustments in response to previously abnormal trough concentrations. A computerized therapeutic drug monitoring (TDM) system was implemented as an intervention to estimate AUC 0-24 based on trough samples. After implementation of the computerised system, 71% of serum vancomycin concentrations included in the study, irrespective of dosing method, achieved an AUC0-24/MIC > 400.[8] Computerised TDM is not readily available in resource-limited settings. A global surveillance study of antimicrobial resistance (AMR) among blood-borne pathogens published in 2018 found that AMR was predominantly found in isolates from Africa, Latin America and Asia. Extended spectrum beta-lactamase-producing Enterobacteriaceae (ESBL-PE) and other Gram-negatives resistant to carbapenems and tigecycline were the most common isolates, followed by Gram-positive cocci, which included staphylococci and enterococci.[9] The proportion of MRSA isolates from Africa (32.6%) was similar to the proportion of MRSA isolates globally (33%). Resistant bacteria have also been documented elsewhere in African literature. A systematic review of AMR by Tadesse et al. only found MRSA reported in 8.9% of studies reviewed. The median prevalence of MRSA was 10.4% (interquartile range 12.6 – 33.8%), but as cefoxitin is typically used to screen for MRSA, the rate is likely underestimated. AMR surveillance data was only available for 60% of African countries.[10] Ameta-analysis on the aetiology of serious bacterial infections in neonates indicated that antimicrobial resistance is a major concern with Staphylococcus aureus (S. aureus), as this organism was identified as the leading Gram-positive organism causing infection.[11] Another specific review of the aetiology and resistance patterns of community-acquired bloodstream infections (BSI) in African children in studies published between 1990 and 2019 found that 29.5% of S. aureus BSI were caused by MRSA.[12] This is higher than the reported 9.5% of MRSA found in S. aureus isolates in community-acquired BSI in neonates and children in a study published in 2018 by Crichton et al. at a district hospital in Cape Town,[13] and 4.8% of S. aureus isolates in community-acquired BSI from a study at Red Cross War Memorial Children's Hospital (RCWMCH) published in 2013.[14] Reporting on the aetiology and resistance patterns of

hospital-acquired BSI in African children have been published from cohorts in South Africa, Tanzania and Kenya. In a prospective cohort from Kenya, the risk of hospital-acquired BSI was 5.9/1000 admissions and S. aureus was identified as the causative organism in 16%, but no susceptibility results were reported.[15] In a Tanzanian cohort, S. aureus was the most common Gram-positive organism causing HAI and 12% were resistant to cloxacillin. All MRSA isolates were noted to be sensitive to vancomycin.[16] The prevalence of MRSA in all public and private hospitalised patients as reported from 4 regions in South Africa, showed a decrease in MRSA prevalence from 53% in 2010 to 40% in 2012 with the Western Cape MRSA prevalence, the lowest in the country (37%).[17] A study on BSI in children from birth to 14 years of age between 2008 and 2013, conducted at a tertiary hospital in Cape Town, showed that hospital-acquired infections (HAI) account for 47% of all BSI, with AMR present in 70% of hospital-acquired isolates. MRSA and ESBL-PE are among the most commonly isolated resistant organisms.[18] MRSA accounted for 26% of all cases of staphylococcal BSI in children from 2007 - 2011 in a study by Naidoo et al. done at RCWMCH.14 In another study, conducted at the same institution from 2011-2012, MRSA accounted for 21.4% of positive blood cultures during the study period, while 16% of the MRSA cultures were attributed to HAI and accounted for 5% of total HAI.[19] Furthermore, an adult study from Groote Schuur Hospital (GSH) published in 2018, documented an MRSA prevalence of 24%, suggesting that the rate of MRSA is relatively stable.[20] MRSA BSI without an identified source is associated with a high case fatality rate.[14] The risk factors for AMR include infancy, malnutrition, duration of hospital admission, previous exposure to antimicrobials and human immunodeficiency virus (HIV).[21] The emergence of VRE in the South African paediatric setting has only been described in a single outbreak at the haematology and oncology unit of RCWMCH. The incidence of VRE at RCWMCH remains very low and the specific incidence of VRE in paediatrics remains unknown. [22] In 2019, the World Health Organisation (WHO) declared antimicrobial resistance one of the ten most pressing threats to global health, emphasising the importance of stewardship programmes in the ongoing monitoring of AMR and education around antimicrobial consumption. The WHO Essential Medicines List Access, Watch, and Reserve (AWaRe) classification was developed and global paediatric AWaRe antibiotic use puplished in order to facilitate stewardship interventions globally.[23] The WHO also developed a priority pathogens list of antibiotic resistant bacteria to guide research and discovery of new antibiotics in accordance with global public health priorities. S. aureus is classified as a high priority resistant pathogen.[24] South Africa is part of the Global Resistance Partnership that in accordance with the WHO, urges the optimisation of antimicrobial use in humans through antibiotic stewardship programmes, research and ongoing surveillance. Although paediatric prescribing practices have not recently been evaluated in South Africa, an antimicrobial stewardship implementation study in 47 hospitals showed that 1 out of every 15 antibiotic scripts required intervention of which dosing and excessive duration were the most common problems.[25] Stewardship programmes specifically aimed at the optimal use of vancomycin in paediatric practice have been well established internationally. An audit on the impact of stewardship on vancomycin use, showed that non-approved indications for prescription, dosing errors, and prolonged duration of therapy were among the most common problems associated with vancomycin prescription.[26] The impact of stewardship programmes specifically aimed at real time intervention and feedback on prescriptions of vancomycin, has improved overall vancomycin use,

defined as days of therapy per thousand patient days, and improved the safety and quality of care in tertiary hospitals.[26,27]

Justification for the study

Children are amongst the most frequent consumers of antibiotics globally, and yet little progress has been made to improve stewardship in the paediatric setting. Increasing AMR poses a significant risk to individual and public health. Resistant Gram-positive bacteria, especially MRSA, have been identified as important pathogens in African children.Vancomycin, a Watch antibiotic according to the WHO Essential Medicines List AWaRe classification, is the treatment of choice for drug-resistant Gram-positive enterococci and MRSA, and the prescribing practices of vancomycin in this paediatric population in middle- and low- income countries have not been described. We therefore intend to describe the use of vancomycin at our institution. Our aim is to identify areas for improvement and possible targets for future stewardship interventions. The monitoring of antibiotic prescribing practices can identify further stewardship opportunities to successfully reduce inappropriate use and contribute to the preservation of vancomycin effectiveness.

Defining the research

Hypothesis:

A review of vancomycin use in a tertiary paediatric hospital will identify opportunities for future antibiotic stewardship interventions.

Aim:

To describe the usage, prescribing practices and microbiological profile of children treated with vancomycin at Red Cross War Memorial Children's Hospital (RCWMCH), Cape Town in 2019.

Objectives:

1. To describe the aggregated monthly use of vancomycin at RCWMCH as a whole and by different clinical units measured in days of therapy per thousand patient days (DOT/1000 PD) during the study period
2. To describe the following factors related to the prescription of vancomycin

a. Clinical indication

b. Prophylaxis, empirical or definitive treatment

c. Route of administration

d. Dosage (mg/kg/day and mg/kg/dose)

e. Dosing frequency

f. Therapeutic drug monitoring (TDM)

g. Variable dosing strategies in relation to plasma trough concentration levels

h. Dose adjustment based on TDM results

i. De-escalation practices following culture and antibiotic susceptibility results

j. Duration of treatment

3. To describe adverse events associated with vancomycin usage

4. To describe the microbiological profile including antibiotic susceptibility pattern of bacteria cultured from children receiving treatment with vancomycin during the study period

5. To describe the usage of repeat blood cultures to document culture conversion after initiation of appropriate antibiotic therapy and the proportion of repeat cultures that are negative

6. To describe the clinical outcome of children treated with vancomycin

Definitions:

1. HIV status:

a) HIV-infected: a child < 18 months old with a positive HIV DNA PCR result confirmed by either a quantitative HIV RNA PCR or repeat HIV DNA PCR test, or a child ≥ 18 months old with 2 positive serological test results (HIV ELISA or HIV Rapid test) or a positive HIV DNA PCR result confirmed by either a quantitative HIV RNA PCR or repeat HIV DNA PCR test

b) HIV-uninfected: a child with a negative HIV serological or HIV DNA PCR result

c) Unknown HIV status: a child with unknown maternal HIV status and who was not tested for HIV infection.

2. Prophylaxis, empirical and definitive treatment refers to the indicators as selected by the treating physician on the antibiotic prescription chart.

3. Infection present on admission (IPOA)[28] : An infection is considered Present on Admission (POA) if the date of event of the site-specific infection criterion occurs during the POA time period, which is defined as the day of admission to an inpatient location (calendar day 1), the 2 days before admission, and the calendar day after admission.

4. Healthcare-associated Infection (HAI)[28]: An infection is considered a Healthcare-associated Infection (HAI) if the date of event of the site-specific infection criterion occurs on or after the 3rd calendar day of admission to an inpatient location where day of admission is calendar day 1.

5. Bloodstream infection episode: An identical pathogen cultured from repeat blood cultures within 14 days of the initial blood culture, is considered part of the same bloodstream infection episode.

6. Effective treatment: Treatment is considered effective when the cultured organism is susceptible to the prescribed antimicrobial agent.

7. Therapeutic vancomycin level [29]:

a. With intermittent dosing: trough level (just before next dose): 10-20 mg/L (6.9-13.8umol/L)

b. In complicated infections, or when vancomycin MIC is >1mg/L, trough level: 15-20mg/L (10.4-13.8 umol/L)

c. With constant infusion: steady-state concentration: 20-25 mg/L (13.8-17.3 umol/L)

8. Complicated infection: pneumonia, bacteraemia, endocarditis, meningitis, and osteomyelitis.[29]

9. Adverse events

a. ‘Red man’ syndrome: Histamine realease resulting in hypotension, palpitations, erythematous rash with intense pruritis over the face, neck and upper body, urticaria, chills and nausea

b. Hypersensitivity: any skin rash or eosinophilia

c. Acute kidney injury 30: acute drop in glomerular filtration rate resulting in an increase in serum creatinine

(i) Stage 1 : increase in serum creatinine > 0.3 mg/dL (26.5 μmol/L) or a 150 – 200% increase during a period of 48 hours

(ii) Stage 2 : increase in serum creatinine > 200 – 300%

(iii) Stage 3 : increase in serum creatinine > 4 mg/dL (353.65 μmol/L) or > 300% increase or estimated GFR > 35ml/min/1.73 m2 or dialysis

Study methods

Study setting:

Red Cross War Memorial Children's Hospital is a dedicated 272-bed tertiary paediatric hospital and offers specialist paediatric and surgical services to children referred from within the Western Cape and neighbouring provinces. Dedicated maternal and neonatal care is offered at alternative institutions but neonates requiring immediate surgical intervention, and medical or intensive care services outside of the first seven days are frequently admitted to RCWMCH. The hospital provides all levels of multidisciplinary care that can be offered in a middle-income country.

Study design:

This is a retrospective descriptive case series of all patients who received vancomycin at RCWMCH from the first of January to the thirty-first of December 2019.

Study population:

Children managed at RCWMH come from urban, peri-urban and outlying farming communities with a high density of low income households who are burdened by poverty and subsequent high rates of malnutrition, HIV and invasive bacterial infections.

Inclusion criterion:

All patients treated with vancomycin at RCWMCH during the study period are eligible for inclusion.

Exclusion criterion:

Any patient whose clinical records relevant to the study cannot be reasonably obtained.

Sample size and power:

According to pharmacy records, 3664 vials of vancomycin were issued during 2019. For convenience, the sample size will include all patients whose records can reasonably be obtained over the study period and will not be specifically powered. We estimate that at least 150 -200 participants will be included in the study.

Data sources:

Eligible study subjects will primarily be identified via the RCWMCH pharmacy database, but vancomycin issued as ward stock in the paediatric intensive care unit (ICU) and vials shared in the wards are not captured by the pharmacy database.The ICU discharge summary database will be searched for subjects who received vancomycin while in ICU or neonatal high care and the Division of Clinical Pharmacology at the University of Cape Town will provide a list of patients who had vancomycin trough levels performed during the study period in order to identify subjects not captured through prior mentioned methods. Clinical records of study subjects will be obtained through medical records at RCWMCH and a review of treatment charts will be conducted. Laboratory data including haematology, biochemistry, pharmacology and microbiology results pertaining to the treatment period only, will be accessed from the National Health Laboratory Service (NHLS), Division of Clinical Pharmacology and Division of Medical Microbiology at Groote Schuur Hospital (GSH).

Data collection:

Names, dates of birth, and hospital folder numbers will be used to identify the clinical records of eligible canditates. Relevant clinical data will then be extracted retrospectively from hospital folders and entered manually into an electronic case record form (CRF). The patient identifiers obtained from all sources will be used to extract laboratory data including vancomycin levels and culture and antibiotic susceptibility results of specimens submitted from all cultures of study subjects during the study period.

Data management:

An electronic CRF will be used for data collection. Each study subject will be allocated a unique study number and each prescription episode will be documented and counted separately. The data will be entered into an electronic CRF and stored on the Redcap® database. All identifiers will be removed when data is entered into the electronic database, but may be accessed by the study investigators through a master list. All paper documents will be stored securely in the Centre for Childhood Infectious Diseases at RCWMCH.

Data analysis:

The data will be exported to a statistical software programme (Stata) for analysis. A descriptive analysis of the study data will be expressed as means ± standard deviations or medians ± interquartile ranges as appropriate, frequencies and percentages. Associations between variables will be analysed using the chi-square test and differences between means assessed using the Student's t-test. Factors associated with in-hospital mortality of patients treated with vancomycin will be assessed using a multivariate stepwise logistic regression model. A confidence interval of 95% and $p \leq 0.05$ will be considered statistically significant.

Communication and dissemination:

The results of the study will be presented to the RCWMCH and the Western Cape Antimicrobial Stewardship Committees and published in a peer-reviewed scientific journal.

Ethical considerations:

The study protocol will be submitted to the Department of Paediatrics & Child Health Research Committee and the Human Research Ethics Committee (HREC) of the University of Cape Town as well as to the RCWMCH administration for approval. The study will be carried out in accordance with the Declaration of Helsinki. Anonymity and confidentiality of participants will be protected by allocating a study number to each enrolled participant. Study numbers (but not names or hospital folder numbers) will be entered into the electronic study database for anonymous analysis and reporting.

Informed consent:

Since the data is being collected retrospectively, the privacy of patients will not be infringed upon and a request for informed consent to be waivered will be included in the HREC application.

Risks to the participants:

There are no risks to the participants in this study. Data will be collected retrospectively and analysed anonymously.

Benefits to the participants:

There are no direct benefits to participants. More appropriate utilisation of vancomycin and effective antibiotic stewardship will benefit the entire community served by RCWMCH in the future.

Anticipated gain in scientific knowledge:

This study will contribute to understanding the usage of vancomycin at RCWMCH and the identification of antibiotic stewardship opportunities that may lead to improved prescribing practices thereby limiting the emergence of antibiotic resistance to vancomycin.

Strengths and limitations

Strengths:

The data for the study is easily obtainable and the completion of the study over a short period of time is feasible.

Limitations:

Retrospective data collection is limited by the availability of clinical records and selection bias occurs naturally. The availability of specific and relevant information may also impact on the quality of the data. There are no controls and no gold standard for comparison and conclusions can not be extrapolated and applied to the general population.

Regulatory aspects

An electronic regulatory file will be kept and updated.

References

1. Division of Clinical Pharmacology, Faculty of Health Sciences, University of Cape Town, and the Health and Medical Publishing Group publishers for the SAMA. The South African Medicines Formulary.

2. Levine DP. Vancomycin : A History. 2006;42(Suppl 1):5-12.

3. Moise-Broder PA, Forrest A, Birmingham MC, Schentag JJ. Pharmacodynamics of vancomycin and other antimicrobials in patients with Staphylococcus aureus lower respiratory tract infections. Clin Pharmacokinet. Published online 2004. doi:10.2165/00003088-200443130-00005

4. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children. Clin Infect Dis. 2011;52(3). doi:10.1093/cid/ciq146

5. Frymoyer A, Guglielmo BJ, Hersh AL. Desired vancomycin trough serum concentration for treating invasive methicillin-resistant staphylococcal infections. Pediatr Infect Dis J. 2013;32(10):1077-1079. doi:10.1097/INF.0b013e318299f75c

6. Fiorito TM, Luther MK, Dennehy PH, LaPlante KL, Matson KL. Nephrotoxicity With Vancomycin in the Pediatric Population: A Systematic Review and Meta-Analysis. Pediatr Infect Dis J. 2018;37(7):654-661. doi:10.1097/INF.0000000000001882

7. Rybak MJ, Le J, Lodise TP, et al. Executive Summary: Therapeutic Monitoring of Vancomycin for Serious Methicillin-Resistant Staphylococcus aureus Infections: A Revised Consensus Guideline and Review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of A. Pharmacotherapy. 2020;40(4):363-367. doi:10.1002/phar.2376

8. Abulfathi AA, Chirehwa M, Rosenkranz B, Decloedt EH. Evaluation of the Effectiveness of Dose Individualization to Achieve Therapeutic Vancomycin Concentrations. J Clin Pharmacol. 2018;58(9):1134-1139. doi:10.1002/jcph.1254

9. Zhang Z, Chen M, Yu Y, Pan S, Liu Y. Antimicrobial susceptibility among gram-positive and gram-negative blood-borne pathogens collected between 2012-2016 as part of the Tigecycline Evaluation and Surveillance Trial. Antimicrob Resist Infect Control. 2018;7(1):1-13. doi:10.1186/s13756-018-0441-y

10. Tadesse BT, Ashley EA, Ongarello S, et al. Antimicrobial resistance in Africa: A systematic review. BMC Infect Dis. 2017;17(1):1-17. doi:10.1186/s12879-017-2713-1

11. Okomo U, Akpalu ENK, Le Doare K, et al. Aetiology of invasive bacterial infection and antimicrobial resistance in neonates in sub-Saharan Africa: a systematic review and meta-analysis in line with the STROBE-NI reporting guidelines. Lancet Infect Dis. 2019;19(11):1219-1234. doi:10.1016/S1473-3099(19)30414-1

12. Droz N, Hsia Y, Ellis S, Dramowski A, Sharland M, Basmaci R. Bacterial pathogens and resistance causing community acquired paediatric bloodstream infections in low- And middle-income countries: A systematic review and meta-analysis. Antimicrob Resist Infect Control. 2019;8(1):1-12. doi:10.1186/s13756-019-0673-5

13. Crichton H, O'Connell N, Rabie H, Whitelaw AC, Dramowski A. Neonatal and paediatric bloodstream infections: Pathogens, antimicrobial resistance patterns and prescribing practice at Khayelitsha District Hospital, Cape Town, South Africa. South African Med J. 2018;108(2):99-104. doi:10.7196/SAMJ.2018.v108i2.12601

14. Naidoo R, Nuttall J, Whitelaw A, Eley B. Epidemiology of Staphylococcus aureus Bacteraemia at a Tertiary Children's Hospital in Cape Town, South Africa. PLoS One. 2013;8(10):1-9. doi:10.1371/journal.pone.0078396
15. Aiken AM, Mturi N, Njuguna P, et al. Risk and causes of paediatric hospital-acquired bacteraemia in Kilifi District Hospital, Kenya: A prospective cohort study. Lancet. Published online 2011. doi:10.1016/S0140-6736(11)61622-X
16. Blomberg B, Manji KP, Urassa WK, et al. Antimicrobial resistance predicts death in Tanzanian children with bloodstream infections: a prospective cohort study. BMC Infect Dis. 2007;7(1):1-14. doi:10.1186/1471-2334-7-43
17. Perovic O, Iyaloo S, Kularatne R, et al. Prevalence and trends of staphylococcus aureus bacteraemia in hospitalized patients in South Africa, 2010 to 2012: Laboratory-based surveillance mapping of antimicrobial resistance and molecular epidemiology. PLoS One. Published online 2015. doi:10.1371/journal.pone.0145429
18. Dramowski A, Cotton MF, Rabie H, Whitelaw A. Trends in paediatric bloodstream infections at a South African referral hospital. BMC Pediatr. 2015;15(1):1-11. doi:10.1186/s12887-015-0354-3
19. Lochan H, Pillay V, Bamford C, Nuttall J, Eley B. Bloodstream infections at a tertiary level paediatric hospital in South Africa. BMC Infect Dis. Published online 2017. doi:10.1186/s12879-017-2862-2
20. Steinhaus N, Al-talib M, Ive P, et al. The management and outcomes of Staphylococcus aureus bacteraemia at a South African referral hospital: A prospective observational study. Int J Infect Dis. 2018;73:78-84. doi:10.1016/j.ijid.2018.06.004
21. Dramowski A, Whitelaw A, Cotton MF. Burden, spectrum, and impact of healthcare-associated infection at a South African children's hospital. J Hosp Infect. 2016;94(4):364-372. doi:10.1016/j.jhin.2016.08.022
22. Lochan H, Moodley C, Rip D, et al. Emergence of vancomycin-resistant Enterococcus at a tertiary paediatric hospital in South Africa. South African Med J. 2016;106(6):562-566. doi:10.7196/SAMJ.2016.v106i6.10858
23. Hsia Y, Lee BR, Versporten A, et al. Use of the WHO Access, Watch, and Reserve classification to define patterns of hospital antibiotic use (AWaRe): an analysis of paediatric survey data from 56 countries. Lancet Glob Heal. 2019;7(7):e861-e871. doi:10.1016/S2214-109X(19)30071-3
24. WHO. Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics. Who. Published online 2017.
25. Brink AJ, Messina AP, Feldman C, et al. Antimicrobial stewardship across 47 South African hospitals: an implementation study. Lancet Infect Dis. 2016;16(9):1017-1025. doi:10.1016/S1473-3099(16)30012-3
26. Di Pentima MC, Chan S. Impact of antimicrobial stewardship program on vancomycin use in a pediatric teaching hospital. Pediatr Infect Dis J. 2010;29(8):707-711. doi:10.1097/INF.0b013e3181d683f8
27. Gillon J, Xu M, Slaughter J, Di Pentima MC. Vancomycin Use: Room for Improvement among Hospitalized Children. J Pharm Pract. 2017;30(3):296-299. doi:10.1177/0897190016635478
28. CDC - Center for Disease Control and Prevention. Identifying Healthcare-associated Infections (HAI) for NHSN Surveillance. http://www.cdc.gov/nhsn/PDFs/pscManual/2PSC_IdentifyingHAIs_NHSNcurrent.pdf. 2015;2015(April):1-14.
29. Jh M. TDM for Vancomycin-Induced Nephrotoxicity Definition: A minimum of two or three consecutive.

Clin Biochem Rev. Published online 2010.
30. Selewski DT, Cornell TT, Heung M, et al. Validation of the KDIGO acute kidney injury criteria in a pediatric critical care population. Intensive Care Med. Published online 2014. doi:10.1007/s00134-014-3391-8

Appendix 2 – Data capturing instrument

Demographics

Record ID	_____
Gender	◯ male ◯ female
DOB	_____ ◯
Weight	_____
Premature	◯ Yes No
CGA	_____
HIV status	◯ infected ◯ uninfected ◯ exposed ◯ unknown
Admission date	_____
Age at admission	_____
Discharge date	_____
Admission from	◯ home ◯ primary health care ◯ district health service ◯ regional hospital ◯ referral within hospital ◯ other tertiary hospital
Admission to	◯ PICU ◯ NHC ◯ G1 ◯ E1/2 ◯ D1/2 ◯ B1/2 ◯ S11/12 ◯ burns
Outcome	◯ d/c ◯ died ◯

Location of death	◯ PICU ◯ NHC ◯ GI ◯ EI/2 ◯ DI/2 ◯ BI/2 ◯ SII/I2 ◯ burns
Date of death	_____
Cause of death	_____

Vancomycin Prescription

Record ID	_____
Antibiotic chart complete?	◯ Yes ◯ No
Start date	_____
Stop date	_____
Vancomycin use (days)	_____
Indication	◯ empiric ◯ definitive ◯ prophylaxis ◯ not indicated
Route	◯ IV ◯ po ◯ IT ◯ intraperitoneal ◯ lock therapy
Suspected source	◯ meningitis ◯ pneumonia ◯ BSI ◯ bone/joint ◯ UTI ◯ line ◯ endocarditis ◯ GIT ◯ not specified ◯ other
Infection type	◯ Healthcare-associated infection ◯ Infection present on admission
First Vancomycin dose documented	◯ Yes ◯ No
First vancomycin dose	_____ (mg/kg/dose)

Frequency	◯ single dose ◯ 72 hourly ◯ 48 hourly ◯ daily ◯ twice daily ◯ 8 hourly ◯ 6 hourly
Vancomycin level	◯ Yes ◯ No
Vancomycin level after 1st dose given	◯ Yes ◯ No
Time before first level	◯ < 24 hours ◯ 24-48 hours ◯ >48 hours (hours)
The time between documented dose and level	◯ < 24 hours ◯ 24-48 hours ◯ >48 hours
Doses before first level	◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ Unknown
Level	_____ (mg/L)
Date of level	_____
Therapeutic	◯ Yes ◯ No
Dose adjusted?	◯ Yes ◯ No
Adjusted dose	_____ (mg/kg/dose)
Frequency adjusted?	◯ Yes ◯ No
Frequency	◯ omit dose ◯ 72 hourly ◯ 48 hourly ◯ daily ◯ twice daily ◯ 8 hourly ◯ 6 hourly

More levels performed?	◯ Yes ◯ No
How many levels?	◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5 ◯ >5
How many levels before therapeutic?	◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5 ◯ >5 ◯ no therapeutic level
How many dose adjustments?	◯ no repeat dose ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5 ◯ >5
Initial antibiotic choice	☐ Ampicillin ☐ Co-amoxiclavulanic acid ☐ Cloxacillin ☐ Piperacillin + Tazobactam ☐ Cephalosporin ☐ Aminoglycoside ☐ Macrolide ☐ Fluoroquinolone ☐ Co-trimoxazole ☐ Colistin ☐ Linezolid ☐ Carbapenem ☐ Vancomycin
What happened to the vancomycin?	◯ stopped ◯ completed ◯ de-escalated ◯ toxic ◯ death
Can you calculate time to effective therapy?	◯ Yes ◯ No
Time to effective therapy	_____

Adverse Events

Record ID	_____
Adverse event documented	◯ Yes ◯ No
Type of adverse event	☐ Red man syndrome ☐ Hypersensitivity reactions ☐ Acute kidney injury ☐ Other ☐ Unknown
Renal function monitored?	◯ Yes ◯ No
Baseline serum creatinine	_____
Highest creatinine on vancomycin	_____
Additional nephrotoxic drugs?	◯ Yes ◯ No
Specify	_____
Presence of shock at the time of vancomycin administration	◯ Yes ◯ No

Microbiology

Record ID	_____
Culture done	◯ Yes ◯ No
Date	_____
Site	_____
Positive culture?	◯ Yes ◯ No
Organism cultured	☐ Staphylococcus Aureus ☐ Enterococcus Faecium ☐ CONS ☐ Gram-negative ☐ Clostroides Difficile ☐ Other
Specify organism	
PCR result	◯ Positive ◯ Negative
Toxin result	◯ Positive ◯ Negaitive
Was sensitivity testing done?	◯ Yes ◯ No
What was the sensitivity of the Staph Aureus?	☐ MSSA ☐ MRSA
Was the clearance of Staph documented?	◯ Yes ◯ No
Organism Sensitivity	☐ Penicillin ☐ Cloxacillin ☐ Ceftriaxone ☐ Linezolid ☐ Vancomycin
Organism resistant	☐ Penicillin ☐ Cloxacillin ☐ Ceftriaxone ☐ Linezolid ☐ Vancomycin

Vancomycin MIC	_____
Antibiotics adjusted after the result	◯ Yes ◯ No
Ajustment	◯ De-escalation ◯ Stopped ◯ Continued appropriately
Repeat culture	◯ Yes ◯ No
Culture outcome	◯ Positive ◯ Negative
Date	_____

Appendix 3 − Human research ethics approval letter

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room GSO- Old Main Bulldlng
Groote Schuur Ho■pltal
Obaervatory 7925
Telephone [021] 406 6492
Emall: hrec-enguirjes@uct.ac.za **Weblllte:**
www.health.uct.ac.za/fhs/research/humanethlcs/forms

20 August 2020

HREC REF: 498/2020

Dr J Nuttall
Division of Paediatrics & Child Health
ICH Bulldlng-
Red Cross War Memorial Children's Hospital
Rondebosch
Email: james.nuttall@uct.ac.za
Student: GRYLE0002@myuct.ac.za

Dear Dr Nuttall

PROJI!CT TITLE: A DESCRIPTIVE STUDY OF VANCOMYCIN USAGE AT RED CROSS WAR MEMORIAL CHILDRENrs HOSPITAL, CAPE TOWN (MPHIL DEGREE - DR LEONORE GREYBE)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It Is a pleasure to Inform you that the HREC has **formally approved** the above-mentioned study.

This approval Is aubject to strict adherence to the HREC recommendations regarding research Involvlng human participants during COVID -19, dated 17 March 2020 & 6 July 2020.

Approval Is granted for one year untll the 30 August 2021.

Please submit a progress form, using the standardised Annual Report Form If the study continues beyond the approval period, Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethlcs/forms)

The HREC acknowledge that the student: Dr Leonore Greybe will also* be *Involved in this study.

Pl•••• quote the HREC REF In all your correspondence.

Yours sincerely

PROFESSOR M &LOCKMAN
CHAIRPERSON. FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board **(IRB)** number: IRB00001938
NHREC-reglstratlon number: REC-210208-007

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Cllnlcal Research with a new drug In patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Councll for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Cllnical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines **(ABPI),** and Declaration of Helslnkl (2013) guldellnes. The Human Research Ethics Committee granting this approval is in compllance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

Appendix 4 – Human research ethics annual progress report

HUMAN RESEARCH ETHICS COMMITTEE
01 OCT 2021
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

UNIVERSITY OF CAPE TOWN | FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938) This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30.9.22
☐ Not approved	See attached comments		
Signature Chairperson of the HREC/ Designee		Date Signed	2/11/21

Note: Please email this form and supporting documents (if applicable) in a combined pdf-file to hrec-enquiries@uct.ac.za.
Please clarify your plan for research-related activities during COVID-19 lockdown.
Please use the latest form found on our website:
http://www.health.uct.ac.za/fhs/research/humanethics/forms

Comments to PI from the HREC

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	05/08/2021		
HREC REF Number	498/2020	Current Ethics Approval was granted until	30/09/2021
Protocol title	A Descriptive Study Of Vancomycin Usage At Red Cross War Memorial Children's Hospital, Cape Town		
Protocol number (if applicable)			
Are there any sub-studies linked to this study?		☐ Yes	✓ No
If yes, could you please provide the HREC Reference number for all sub-studies? **Note:** A separate FHS016 must be submitted for each sub-study.			
Principal Investigator	Dr J Nuttall		

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

Department / Office Internal Mail Address	James.nuttall@uct.ac.za

1.1 Does this protocol receive US Federal funding?	☐ Yes	✓ No
1.2 If the study receives US Federal Funding, does the annual report require full committee approval? **Note:** Any annual approvals for **Full Committee** review MUST be submitted on the monthly HREC submission dates. (Please send electronic copy for full committee review to hrec-submission@uct.ac.za)	☐ Yes	☐ No

If yes in 1.2 please complete section 1.3 below for invoicing purposes

1.3 Ethics Renewal Fee

Please (tick ✓)appropriate box for billing purposes:

Submission Type	***Description***	***New fee (Vat Incl.)***	***tick ✓***
Research funded solely from UCT departmental/ divisional/group budget	Annual evaluation of research progress report for re-certification	**R0,00**	☐
Non-sponsored student research for degree purposes at UCT/Other Universities & Colleges	Annual evaluation of research progress report for re-certification	**R0,00**	✓
Annual re-certification / Progress report (FHS016 Form)	Clinical Trial & International Grant Funded Research - Annual evaluation of research progress report for re-certification for Full Committee Approval	**R7000,00**	☐
Annual re-certification / Progress report (FHS016 Form)	Clinical Trial & International Grant Funded Research - Annual evaluation of research progress report for re-certification for Expedited review	**R3 710.00**	☐
Annual re-certification / Progress report (FHS016 Form)	National grant funded research - Annual evaluation of research progress report for re-certification for Full Committee Approval	**R6000.00**	☐
Annual re-certification / Progress report (FHS016 Form)	National Grant funded research for Annual evaluation of research progress report for re-certification for Expedited review	**R1 500,00**	☐

NB: Protocols funded by UCT (e.g. departmental funding / student research) and by certain grant funding organizations (e.g. MRC, NRF, CANSA,) are exempt from these charges.

Please provide details for invoicing, either complete section 1 or 2 :

1. Invoice billing – Directly to Sponsor

Sponsor's name	
Billing Address of Sponsor:	
Vat Number:	

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

Contact person	
Telephone number	
Email Address	
2. Internal Journal Billing:	
Fund Number:	
Cost Centre Number:	
Account Holder Name:	
Division of Account Holder:	

2. List of documentation for approval

3. Protocol status (tick ✓)

☐	Open Enrolment
☐	Closed to enrolment (tick ✓)
✓	Research-related activities are ongoing
☐	Research-related activities are complete, long-term follow-up only
☐	Research-related activities are complete, data analysis only
☐	Main study is complete but sub-study research-related activities are ongoing
☐	Study is closed → Please submit a Study Closure Form (FHS010)

4. Enrolment

Number of participants enrolled to date	135
Number of participants enrolled, since last HREC Progress report (continuing review)	
Additional number of participants still required	70

5. Refusals

Total number of refusals (participants invited to join the study, but refused to take part)	N/A

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

6. Cumulative summary of participants

Total number of participants who provided consent	**N/A**
Number of participants determined to be ineligible (i.e. after screening)	N/A
Number of participants currently active on the study	N/A
Number of participants completed study (without events leading to withdrawal)	N/A
Number of participants withdrawn at participants' request (i.e. changed their mind)	N/A
Number of participants withdrawn by PI due to toxicity or adverse events	N/A
Number of participants withdrawn by PI for other reasons (e.g. pregnancy, poor compliance)	N/A
Number of participants lost to follow-up. Please comment below on reasons for loss of follow-up.	N/A
Number of participants no longer taking part for reasons not listed above. Please provide reasons below:	N/A

7. Progress of study

Please provide a brief summary of the research to date including the overall progress and the progress since the last annual report as well as any relevant comments/issues you would like to report to the HREC:
Data collection for the first 135 participants complete, collection for the remaining 70 participants and analysis in progress.

8. Protocol violations and exceptions (tick ✓ all that apply)

✓	No prior violations or exceptions have occurred since the original approval
☐	Prior violations or exceptions have been reported since the last review and have already been acknowledged or approved
☐	Unreported minor violations that have occurred since the last review, as well as significant deviations not yet reported, are attached for review

9. Amendments (tick ✓ all that apply)

✓	No Prior amendments have been made since the original approval
☐	Prior amendments have been reported since the last review and have already been approved

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

☐	New protocol changes/ amendments are requested as part of this continuing review (See note below)

Note: If new protocol changes are being requested in this review, please complete an amendment form (FHS006).
Specific changes in the amended protocol and consent/assent forms must be **bolded**, *italicised* or tracked and all changes must include a rationale.

10. Adverse events

10.1 Please provide below or attach a narrative summary of serious adverse events and/ or unanticipated problems since the last progress report. Please indicate changes made to the protocol and informed consent document(s) as a result (if not already reported to the HREC). Please comment on whether causality to any study procedure or intervention could be established.
N/A

10.2 Have participants received appropriate treatment/ follow-up/ referral when indicated (e.g. in the case of abnormal or incidental clinical findings, distress or anxiety)?		
☐ Yes	☐ No	✓ Not applicable
If yes, please describe:		

11. Summary of Monitoring and Audit Activities (tick ✓)

11.1 Was this study monitored or audited by an external agency (e.g. SAHPRA, FDA)?		
☐ Yes	☐ No	✓ Not applicable

11.2 Did a Data and Safety Monitoring Board publish a report?		
☐ Yes	☐ No	✓ Not applicable

11.3 If yes, please identify the agency and attach a summary of the findings.					
Agency Name		Report attached	☐ Yes	☐ No	☐ Not applicable
		DSMB report attached	☐ Yes	☐ No	☐ Not applicable

11.4 Has there been any agency, institutional or other inquiry into non-compliance in this study, or any finding of non-compliance concerning a member of the research team?	
☐ Yes	✓ No
If yes, please explain:	

12. Level of risk (tick ✓)

12.1 In light of your experience of this research, please indicate whether the level of risk to participants has:	
☐	Increased
☐	Decreased
✓	Shown no change
If there has been a change, please explain:	

12.2 Please provide a narrative summary of recent relevant literature that may have a bearing on the level of risk.

13. Insurance

Please confirm that valid no fault insurance is still in place? (tick ✓)			
☐ Yes		✓ No	
If yes, please complete the following:			
Insurer's name:			
Policy no.		*Coverage Period:	
For UCT sponsored studies please liaise the insurance office via fhs.sponsorship@uct.ac.za regarding the required documentation and information required obtain a renewed UCT No-fault Insurance Certificate.			

14. Statement of conflict of interest

Has there been any change in the conflict of interest status of this protocol since the original approval? (tick ✓)	
☐ Yes	✓ No
If yes, please explain and if necessary, attach a revised conflict of interest statement (Section #7 in the New Protocol Application Form FHS013):	

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

15. Signature

My signature certifies that the above is complete and correct.			
Signature of PI		Date	30 September 2021

Appendix 5 – Hospital research review committee approval letter

Western Cape Government
Health

DR AN PARBHOO
Manager: Medical Services
Red Cross War Memorial Children's Hospital
Email: Anita.Parbhoo@westerncape.gov.za
Tel: +27 21 658 5430 Fax: +27 21 658 5006/5166

08 September 2020

Dr L Greybe
Paediatric Infectious Diseases

Dear Greybe,

RESEARCH: RXH: RCC 241 / WC_202008_114

PROJECT TITLE: A descriptive study of vancomycin usage at Red Cross War Memorial Children's Hospital, Cape Town

It is a pleasure to inform you that the hospital Research Review Committee has approved your application to conduct above-mentioned study at Red Cross War Memorial Children's Hospital.

Kindly note that this approval is subject to strict adherence to the HREC recommendations regarding research involving participants during COVID-19, dated 17 March 2020 (UCT HREC notice attached).

Yours sincerely,

DR AN PARBHOO
MANAGER: MEDICAL SERVICES

Appendix 6 – Instructions to the author

SAJID Submission Guidelines

Overview

The author guidelines include information about the types of articles received for publication and preparing a manuscript for submission. Other relevant information about the journal's policies and the reviewing process can be found under the about section. The **compulsory cover letter** forms part of a submission and must be submitted together with all the required **forms.** All forms need to be completed in English.

Original Research Article

An original article provides an overview of innovative research in a particular field within or related to the focus and scope of the journal, presented according to a clear and well-structured format.

Submission status	open
Word limit	3500 words (excluding the abstract, tables, figures, graphs, and references)
Abstract	maximum: 250 words requires structural headings: Background, Objectives, Method, Results, Conclusion and Contribution
Main text	requires structural headings, refer to the full structure 'Ethical considerations' is a sub-section in the manuscript and must include: • Name of the ethical review committee • Study approval number • Manner of consent (written, oral) for human participants • Description of measures taken to maintain the confidentiality of data • If the study was not human or animal research or the study was determined to be non-human subjects research or exempt, the authors must provide a statement with those details in this section.
References	60 or less, adhere to the **Vancouver referencing style**
Tables, figures and graphs	7 or less, adhere to the Illustrations requirements found in the AOSIS House style guide
Formatting requirements	apply the guidelines located on the **Formatting requirements page** and the **AOSIS house style guide**
Compulsory supplementary file(s)	the **Authorship, disclosure statements, copyright, and license agreement form**, **Ethical Clearance/Waiver Documentation** and any other relevant form applicable to your submission
Ethical clearance/waiver documentation	evidence of ethical clearance for the study, such as the study approval letter or certificate from the Institutional Review Board (IRB), a waiver from the IRB et cetera

Review Article

Review articles provide a comprehensive summary of research on a certain topic, and a perspective on the state of the field and where it is heading. These articles are often meta-analyses comparing and combining findings of previously published studies. **See the full structure of the review articles below.**

Submission status	open
Word limit	3500-5000 words (excluding the abstract, tables, figures, graphs, and references)
Abstract	maximum: 250 words requires structural headings: Background, Aim, Setting, Method, Results, Conclusion and Contribution
Main text	requires structural headings, refer to the full structure

	'Ethical considerations' is a sub-section in the manuscript and must include: • Name of the ethical review committee • Study approval number • Manner of consent (written, oral) for human participants • Description of measures taken to maintain the confidentiality of data • If the study was not human or animal research or the study was determined to be non-human subjects research or exempt, the authors must provide a statement with those details in this section.
References	60 or less, adhere to the **Vancouver referencing style**
Tables, figures and graphs	7 or less, adhere to the Illustrations requirements found in the AOSIS House style guide
Formatting requirements	apply the guidelines located on the **Formatting requirements page** and the **AOSIS house style guide**
Compulsory supplementary file(s)	the **Authorship, disclosure statements, copyright, and license agreement form**, and any other relevant form applicable to your submission

Brief Reports

Brief Reports present complete studies that are narrower in scope than those described in Original Research Articles or that present new developments. Manuscripts that are descriptive or primarily methodological, or that describe in vitro chemotherapeutic studies should, in general, be submitted as Brief Reports.

Submission status	open
Word limit	2000 words (excluding the tables, figures, graphs, and references)
Abstract	maximum: 100 words requires structural heading: Contribution
Main text	structural headings are not required, but authors are encouraged to use them to help guide readers when necessary
References	15 or less, adhere to the **Vancouver referencing style**
Tables, figures and graphs	2 or less, adhere to the Illustrations requirements found in the AOSIS House style guide
Formatting requirements	apply the guidelines located on the **Formatting requirements page** and the **AOSIS house style guide**
Compulsory supplementary file(s)	the **Authorship, disclosure statements, copyright, and license agreement form** and any other relevant form applicable to your submission

Correspondence

They may be subjected to the peer-review process and their eventual placement is at the discretion of the editorial team. Kindly include a correspondence address. Correspondence must be submitted referring to a previous publication in the journal (within the prior 12 months) or relate to a topical matter in line with the interests of the journal.

Submission status	open
Word limit	750 words (excluding the tables, figures, graphs, and references)
Abstract	none
Main text	structural headings are not required, but authors are encouraged to use them to help guide readers when necessary
References	10 or less, adhere to the **Vancouver referencing style**
Tables, figures and graphs	1 or less, adhere to the Illustrations requirements found in the AOSIS House style guide
Formatting requirements	apply the guidelines located on the **Formatting requirements page** and the **AOSIS house style guide**
Compulsory supplementary file(s)	the **Authorship, disclosure statements, copyright, and license agreement form** and any other relevant form applicable to your submission

Commentary

Commentaries are by invitation only and are intended to provide expert comments on relevant topics within the focus and scope of the journal.

Submission status	open
Word limit	800 words (excluding the tables, figures, graphs, and references)
Abstract	none
Main text	structural headings are not required, but authors are encouraged to use them to help guide readers when necessary
References	10 or less, adhere to the **Vancouver referencing style**
Tables, figures and graphs	2 or less, adhere to the Illustrations requirements found in the AOSIS House style guide
Formatting requirements	apply the guidelines located on the **Formatting requirements page** and the **AOSIS house style guide**
Compulsory supplementary file(s)	the **Authorship, disclosure statements, copyright, and license agreement form** and any other relevant form applicable to your submission

Case Reports

A venue to document their experience with testing, diagnosis and treatment of a patient, animal or group.

Submission status	open
Word limit	1500 words (excluding the abstract, tables, figures, graphs, and references)
Abstract	maximum: 75 words requires structural headings: Contribution
Main text	structural headings are not required, but authors are encouraged to use them to help guide readers when necessary 'Ethical considerations' is a sub-section in the manuscript and must include: • Name of the ethical review committee • Study approval number • Manner of consent (written, oral) for human participants • Description of measures taken to maintain the confidentiality of data • If the study was not human or animal research or the study was determined to be non-human subjects research or exempt, the authors must provide a statement with those details in this section.
References	60 or less, adhere to the **Vancouver referencing style**
Tables, figures and graphs	7 or less, adhere to the Illustrations requirements found in the AOSIS House style guide
Formatting requirements	apply the guidelines located on the **Formatting requirements page** and the **AOSIS house style guide**
Compulsory supplementary file(s)	the **Authorship, disclosure statements, copyright, and license agreement form**, and any other relevant form applicable to your submission

Editorials

Editorials are by invitation only and are intended to provide expert comments on relevant topics within the focus and scope of the journal.

Submission status	by invitation only
Word limit	800 words (excluding the tables, figures, graphs, and references)
Abstract	none
Main text	structural headings are not required, but authors are encouraged to use them to help guide readers when necessary
References	10 or less, adhere to the **Vancouver referencing style**
Tables, figures and graphs	2 or less, adhere to the Illustrations requirements found in the AOSIS House style guide

Formatting requirements	apply the guidelines located on the **Formatting requirements page** and the **AOSIS house style guide**
Compulsory supplementary file(s)	the **Authorship, disclosure statements, copyright, and license agreement form** and any other relevant form applicable to your submission

Conference Proceedings

This allows the author to submit a report on a national or international conference relevant to the focus and scope of the journal.

Submission status	open
Word limit	1500 words (excluding the tables, figures, graphs, and references)
Abstract	none
Main text	structural headings are not required, but authors are encouraged to use them to help guide readers when necessary
References	6 or less, adhere to the **Vancouver referencing style**
Tables, figures and graphs	1 or less, adhere to the Illustrations requirements found in the AOSIS House style guide
Formatting requirements	apply the guidelines located on the **Formatting requirements page** and the **AOSIS house style guide**
Compulsory supplementary file(s)	the **Authorship, disclosure statements, copyright, and license agreement form** and any other relevant form applicable to your submission

Book Reviews

Book reviews are brief articles providing insights or opinions on new books within the research field of the journal.

Submission status	typically invited, authors are encouraged to before submission to express their interest or ideas for reviews of a particular book **contact the editors**
Word limit	1000 words (excluding the tables, figures, graphs, and references)
Abstract	none
Main text	structural headings are not required, but authors are encouraged to use them to help guide readers when necessary
References	10 or less, adhere to the **Vancouver referencing style**
Tables, figures and graphs	2 or less, adhere to the Illustrations requirements found in the AOSIS House style guide
Formatting requirements	apply the guidelines located on the **Formatting requirements page** and the **AOSIS house style guide**
Compulsory supplementary file(s)	the **Authorship, disclosure statements, copyright, and license agreement form** and any other relevant form applicable to your submission

State-of-the-Art Article

State-of-the-Art articles are by invitation only and should be on important topical issues and interest in the infectious disease profession. The articles should reflect the author's knowledge and expertise in the field and include relevant and pertinent literature. State-of-the-Art articles should be on topical issues that are of relevance to the profession in South Africa as well as internationally. They may be invited by the editor or spontaneously submitted. State-of-the-Art articles may discuss ideas, and controversies, raise or generate new questions for future research; draw attention to current research findings and future directions of a specific topic; provide insightful and actionable ideas; add context or discuss the 'doing' of research in this area, or may pick up on issues or give alternative perspectives allowing for an open dialogue between researchers and clinicians. Authors must note that submissions under this section need to be coherently argued, engaging and thought-provoking.

Submission status	open
Word limit	3500-5500 words (excluding the tables, figures, graphs, and references)
Abstract	maximum: 250 words requires structural headings: Background, Objectives, Method, Results, Conclusion and Clinical Implications
Main text	structural headings are not required, but authors are encouraged to use them to help guide readers when necessary
References	10 or less, adhere to the **Vancouver referencing style**

Tables, figures and graphs	2 or less, adhere to the Illustrations requirements found in the AOSIS House style guide
Formatting requirements	apply the guidelines located on the **Formatting requirements page** and the **AOSIS house style guide**
Compulsory supplementary file(s)	the **Authorship, disclosure statements, copyright, and license agreement form** and any other relevant form applicable to your submission

Opinion Papers

Short opinion pieces or personal perspectives (not research papers) personal viewpoints on infectious diseases. With rare exceptions, these essays are meant to express a personal viewpoint and should have no more than two authors.

Submission status	open
Word limit	2000 words (excluding the abstract, tables, figures, graphs, and references)
Abstract	maximum: 250 words requires structural heading: Contribution
Main text	structural headings are not required, but authors are encouraged to use them to help guide readers when necessary
References	15 or less, adhere to the **Vancouver referencing style**
Tables, figures and graphs	2 or less, adhere to the Illustrations requirements found in the AOSIS House style guide
Formatting requirements	apply the guidelines located on the **Formatting requirements page** and the **AOSIS house style guide**
Compulsory supplementary file(s)	the **Authorship, disclosure statements, copyright, and license agreement form**, and any other relevant form applicable to your submission

Photo Quiz

This format will allow authors to submit interesting cases to the Journal, with appropriate figures depicting the disease process and including a question and answer format to allow readers to test their clinical and diagnostic skills.

Submission status	open
Word limit	800 words (excluding the tables, figures, graphs, and references)
Abstract	none
Main text	structural headings are not required, but authors are encouraged to use them to help guide readers when necessary
References	10 or less, adhere to the **Vancouver referencing style**
Tables, figures and graphs	3 or less, adhere to the Illustrations requirements found in the AOSIS House style guide
Formatting requirements	apply the guidelines located on the **Formatting requirements page** and the **AOSIS house style guide**
Compulsory supplementary file(s)	the **Authorship, disclosure statements, copyright, and license agreement form** and any other relevant form applicable to your submission

Guidelines

A guideline provides evidence-based recommendations that will influence clinical research and practice. These can be consensus-based statements of reporting standards or clinical practice guidelines.

Submission status	open
Word limit	3000 words (excluding the tables, figures, graphs, and references)
Abstract	none
Main text	structural headings are not required, but authors are encouraged to use them to help guide readers when necessary
References	10 or less, adhere to the **Vancouver referencing style**
Tables, figures and graphs	2 or less, adhere to the Illustrations requirements found in the AOSIS House style guide
Formatting requirements	apply the guidelines located on the **Formatting requirements page** and the **AOSIS house style guide**
Compulsory supplementary file(s)	the **Authorship, disclosure statements, copyright, and license agreement form** and any other relevant form applicable to your submission

Corrections

A correction provides the platform to communicate important, scientifically relevant errors or missing information in a published article. Any changes after publication that affect the scientific interpretation (e.g., changes to a misleading portion of an otherwise reliable publication, an error in a figure, error in data that does not affect conclusions or addition of missing details about a method) are announced using a Correction. Read our submission procedure for **corrections** and **publishing policies**.

Compulsory title	The title of the submission should have the following format: 'Corrigendum: Title of original article'.
Submission File	completed **Correction Submission Form** (required)
Compulsory supplementary file	any supporting documents or emails, **Author Change Request Form** (if applicable), **Corresponding Author Change Request Form** (if applicable)

Cover Letter

The authorship, disclosure statements, copyright, and license agreement form is our compulsory cover letter which needs to form part of your submission. Kindly download and complete, in English, the provided **form**.

Anyone that has made a significant contribution to the research and the paper must be listed as an author in your cover letter. Contributions that fall short of meeting the criteria as stipulated in our policy should rather be mentioned in the 'Acknowledgements' section of the manuscript. Read our **authorship** guidelines and **author contribution** statement policies.

Original Research Article full structure

Title: The article's full title should contain a maximum of 95 characters (including spaces).

Abstract: The abstract, written in English, should be no longer than 250 words and must be written in the past tense. The abstract should give a succinct account of the objectives, methods, results and significance of the matter. The structured abstract for an Original Research article should consist of five paragraphs labelled Background, Methods, Results, Conclusion and Contribution.

- Background: Summarise the social value (importance, relevance) and scientific value (knowledge gap) that your study addresses.
- Methods: Clearly express the basic design of the study, and name or briefly describe the methods used without going into excessive detail.
- Results: State the main findings.
- Conclusion: State your conclusion and any key implications or recommendations.
- Contribution: What practical, scientific or theoretical gap did your research filled? How do these insights link to the focus and scope of the journal? It should be a concise statement of the primary contribution of the manuscript; and how it fits within the scope of the journal.

Do not cite references and do not use abbreviations excessively in the abstract.

Introduction: The introduction must contain your argument for the social and scientific value of the study, as well as the aim and objectives:

- Social value: The first part of the introduction should make a clear and logical argument for the importance or relevance of the study. Your argument should be supported by the use of evidence from the literature.
- Scientific value: The second part of the introduction should make a clear and logical argument for the originality of the study. This should include a summary of what is already known about the research question or specific topic and should clarify the knowledge gap that this study will address. Your argument should be supported by the use of evidence from the literature.
- Conceptual framework: In some research articles it will also be important to describe the underlying theoretical basis for the research and how these theories are linked together in a conceptual framework. The theoretical evidence used to construct the conceptual framework should be referenced from the literature.

- Aim and objectives: The introduction should conclude with a clear summary of the aim and objectives of this study.

Research methods and design: This must address the following:

- Study design: An outline of the type of study design.
- Setting: A description of the setting for the study; for example, the type of community from which the participants came or the nature of the health system and services in which the study is conducted.
- Study population and sampling strategy: Describe the study population and any inclusion or exclusion criteria. Describe the intended sample size and your sample size calculation or justification. Describe the sampling strategy used. Describe in practical terms how this was implemented.
- Intervention (if appropriate): If there were intervention and comparison groups, describe the intervention in detail and what happened to the comparison groups.
- Data collection: Define the data collection tools that were used and their validity. Describe in practical terms how data were collected and any key issues involved, e.g. language barriers.
- Data analysis: Describe how data were captured, checked and cleaned. Describe the analysis process, for example, the statistical tests used or steps followed in qualitative data analysis.
- Ethical considerations: Approval must have been obtained for all studies from the author's institution or other relevant ethics committee and the institution's name and permit numbers should be stated here.

Results: Present the results of your study in a logical sequence that addresses the aim and objectives of your study. Use tables and figures as required to present your findings. Use quotations as required to establish your interpretation of qualitative data. All units should conform to the **SI convention** and be abbreviated accordingly. Metric units and their international symbols are used throughout, as is the decimal point (not the decimal comma).

Discussion: The discussion section should address the following four elements:

- Key findings: Summarise the key findings without reiterating details of the results.
- Discussion of key findings: Explain how the key findings relate to previous research or to existing knowledge, practice or policy.
- Strengths and limitations: Describe the strengths and limitations of your methods and what the reader should take into account when interpreting your results.
- Implications or recommendations: State the implications of your study or recommendations for future research (questions that remain unanswered), policy or practice. Make sure that the recommendations flow directly from your findings.

Conclusion: Provide a brief conclusion that summarises the results and their meaning or significance in relation to each objective of the study.

Acknowledgements: Those who contributed to the work but do not meet our authorship criteria should be listed in the Acknowledgments with a description of the contribution. Authors are responsible for ensuring that anyone named in the Acknowledgments agrees to be named. Refer to the acknowledgement structure guide on our *Formatting Requirements* page.

Also provide the following, each under their own heading:

- Competing interests: This section should list specific competing interests associated with any of the authors. If authors declare that no competing interests exist, the article will include a statement to this effect: *The authors declare that they have no financial or personal relationship(s) that may have inappropriately influenced them in writing this article.* Read our **policy on competing interests**.
- Author contributions: All authors must meet the criteria for authorship as outlined in the **authorship** policy and **author contribution** statement policies.
- Funding: Provide information on funding if relevant
- Data availability: All research articles are encouraged to have a data availability statement.

- Disclaimer: A statement that the views expressed in the submitted article are his or her own and not an official position of the institution or funder.

References: Authors should provide direct references to original research sources whenever possible. References should not be used by authors, editors, or peer reviewers to promote self-interests. Refer to the journal referencing style downloadable on our *Formatting Requirements* page.

Review Article full structure

Title: The article's full title should contain a maximum of 95 characters (including spaces).

Abstract: The abstract should be no longer than 250 words and must be written in the past tense. The abstract should give a concise account of the objectives, methods, results and significance of the matter. The abstract can be structured and should consist of six paragraphs labelled Background, Aim, Method, Results, Conclusion and Contribution.

- Background: Why is the topic important to us? State the context of the review
- Aim: What is the purpose of your review? Describe the aim or purpose of your review.
- Method: How did you go about performing the review? Describe the methods used for searching, selecting and appraising your evidence.
- Results: What are the findings? What are the main findings of your literature review?
- Conclusion: What are the implications of your answer? Briefly summarise any potential implications.
- Contribution: What practical, scientific or theoretical gap did your research filled? How do these insights link to the focus and scope of the journal? It should be a concise statement of the primary contribution of the manuscript; and how it fits within the scope of the journal.

Introduction: Present an argument for the social and scientific value of your review that is itself supported by the literature. Present the aim and objectives of your literature review.

Methods: Although this is not a systematic review (see instructions on original research for this type of article) it is still necessary to outline how you searched for, selected and appraised the literature that you used. Discuss any methodological limitations.

Review findings: Present your review of the literature and make use of appropriate sub-headings. Your review should be a critical synthesis of the literature.

Implications and recommendations: Discuss the findings of your review in terms of the implications for policy makers and clinicians or recommendations for future research.

Conclusion: This should clearly state the main conclusions of the review in terms of addressing the original aim and objectives.

Acknowledgements: Those who contributed to the work but do not meet our authorship criteria should be listed in the Acknowledgments with a description of the contribution. Authors are responsible for ensuring that anyone named in the Acknowledgments agrees to be named. Refer to the acknowledgement structure guide on our *Formatting Requirements* page.

Also provide the following, each under their own heading:

- Competing interests: This section should list specific competing interests associated with any of the authors. If authors declare that no competing interests exist, the article will include a statement to this effect: *The authors declare that they have no financial or personal relationship(s) that may have inappropriately influenced them in writing this article.* Read our **policy on competing interests**.
- Author contributions: All authors must meet the criteria for authorship as outlined in the **authorship** policy and **author contribution** statement policies.
- Funding: Provide information on funding if relevant
- Data availability: All research articles are encouraged to have a data availability statement.

- Disclaimer: a statement that the views expressed in the submitted article are his or her own and not an official position of the institution or funder.

References: Authors should provide direct references to original research sources whenever possible. References should not be used by authors, editors, or peer reviewers to promote self-interests. Refer to the journal referencing style downloadable on our *Formatting Requirements* page.