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# Measuring and improving the timeliness of vancomycin therapeutic drug monitoring and potential patient safety impacts

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ABSTRACT

*Background:* Timely vancomycin therapeutic drug monitoring (TDM) enables prompt dose adjustments and safe treatment. Local incidents prompted an investigation into the reasons for prolonged reporting times.
*Objectives:* To investigate the variation in reporting times of vancomycin concentrations between hospitals with and without on-site TDM processing, and patient safety implications.
*Methods:* Vancomycin concentration results for Hospital 1 (off-site monitoring), Hospitals 2 and 3 (both on-site monitoring) from June to December 2021 were retrospectively analysed. Retrospective data collection was repeated for Hospital 1 three months post on-site TDM commencement for comparison. Vancomycin clinical incidents at Hospital 1 were reviewed to identify examples of when delays in reporting of results potentially contributed towards adverse patient outcomes.
*Results:* Hospital 1 had a median reporting time of 11.13 h compared with Hospital 2 and Hospital T3 (1.73 h and 1.70 h respectively). Following the commencement of on-site TDM at Hospital 1, the reporting time reduced to 1.33 h ($p < 0.001$). Several incidents at Hospital 1 during the period of off-site monitoring involved delays to TDM results.
*Conclusions:* Off-site processing of TDM introduced significant delays in reporting of vancomycin concentrations, which was significantly improved by transitioning to onsite availability of testing. This study also highlights the impact of accurate problem identification in improving patient safety.

## 1. Introduction

Vancomycin is a high-risk antibiotic used to treat serious infections where bacteria may be resistant to alternative first line antibiotics.[1] Therapeutic drug monitoring (TDM) is required to ensure infections are treated effectively whilst minimising risk of serious adverse effects such as nephrotoxicity.[2] Whilst reversible in the majority of cases, vancomycin associated nephrotoxicity can lead to increased hospital length of stay, increased requirement for TDM monitoring and interpretation, and in rare cases, patients may require dialysis.[3] Timely processing and reporting of vancomycin concentrations by pathology laboratories is crucial, however not all laboratories in hospitals have the ability to process TDM (hereafter referred to as on-site monitoring). In such cases, blood samples need to be transported to another facility (hereafter referred to as off-site monitoring), prolonging the time to reporting and potentially delaying time critical dose adjustments. 'Point-of-care' testing, where results are made available rapidly and often at the bedside, as is common for blood glucose testing is not yet widely available for vancomycin.[4]

Intermittent dosing frequency of vancomycin is dependent upon the patient's renal function measured by Creatinine Clearance. Patients with adequate renal function will be prescribed doses every 12 h. Evidence based guidelines recommend performing TDM by one of 2 methods.[1] Calculating the area under the concentration-time curve (AUC) requires two samples to be taken at differing times before and after dose administration and used in complex calculations to determine further dose adjustments. This method is best performed by experienced clinicians with the support of dose optimisation software. Where this is not

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available, a specifically-timed trough (up to 60 min prior to next dose) plasma concentration must be obtained, where a result of between 15 and 20 mg/L is considered in therapeutic range in most cases. Ideally, results are available for review prior to the next prescribed dose to allow for dose adjustments if required.

Vancomycin TDM is complex in nature with multiple themes that may contribute to its suboptimal management.

A recent study across Australian hospitals published that one of the major barriers to performing TDM of various antimicrobials is the lack of timely processing and reporting of drug concentrations.[5]

A widely experienced issue is the incorrect timing of drawing a trough blood sample with a study from 2012 reporting that 4 in 10 vancomycin concentrations were not able to be interpreted as a true trough.[6] A theme identified in a qualitative study of prescribers in a large tertiary teaching hospital was difficulty achieving timely orchestration of vancomycin trough concentrations,[7] with many participants describing a lack of time due to workload pressures.

There is presently a paucity of literature evaluating the contribution of location of TDM processing to differences in reporting times of vancomycin concentrations and medication related outcomes or incidents.

Anecdotal evidence from clinicians at Hospital 1 highlighted that delays in reporting time was a local issue due to samples being sent to another hospital for processing.

This risk was escalated to executive leaders at Hospital 1 and the proposed intervention of on-site processing of vancomycin TDM was approved and commenced in June 2022.

The aim of this study was to investigate the variation in reporting times of vancomycin concentrations between hospitals with and without on-site TDM processing and consider the patient safety implications of this variation.

## 2. Methods

This was a mixed methods quality improvement study involving 3 hospitals in the same hospital and health service (HHS) as detailed in Table 1.

### 2.1. Setting

Hospital 1, a major secondary hospital did not have access to on-site processing of vancomycin TDM during the retrospective period of June to December 2021. Blood samples were sent via courier to Hospital 2, a tertiary hospital for processing. The logistics of the off-site monitoring process involved four courier departure times across the day with prolonged transit times of up to 5 h between sites. The courier service reduced in frequency to once a day on weekends and public holidays. Delivery of individual samples were at times expedited upon medical officer request.

All sites included in this study employed the same method of turbidimetric inhibition immunoassay (PETINIA) technique using the Siemens Atellica® Platform to perform vancomycin TDM.[8]

#### 2.1.1. Data collection - Quantitative

Retrospective data was extracted from the AUSCARE Pathology result portal using convenience sampling. All vancomycin concentration assays performed from June to December 2021 for the 3 hospital sites were initially reviewed.

Data collection included:

- patient unique record number (URN)
- ward the patient was admitted to
- time from collection to registration of blood sample (in minutes)
- time from registration to validation of vancomycin concentration (in minutes) and;
- the total time from collection to validation (in minutes).

Results for patients admitted under Hospital in the Home (HITH) arrangements, and results identified as quality control samples were excluded.

Results for each hospital were reported using descriptive statistics as the calculated median time from blood sample collection to validation of the result, reported in hours (to 2 decimal points).

Data collection was repeated for Hospital 1 only from June to September 2022 to calculate the median reporting time for the 3 months after implementation of on-site vancomycin TDM processing.

#### 2.1.2. Data collection - Qualitative

All clinical incidents involving vancomycin at Hospital 1 submitted to RiskMan® (a statewide clinical incident management system) for the initial retrospective period were independently reviewed by the chief investigator (BC) and collaborating author (BS) to conduct a thematic analysis. The incidents were initially reviewed to gain familiarity and codify by incident type. Incidents identified as relating to timing were further reviewed to establish timelines of vancomycin administration, monitoring and result availability in each case to generate, review and name themes.

To further the learning opportunity from this study, a reflective mapping of the process of problem identification and implementation was also undertaken.

### 2.2. Statistical analysis

Continuous data for each hospital was tested for normality using the Shapiro Wilk test. Results for Hospital 1 were compared with Hospitals 2 and 3 using either a Student's *t*-test (for normally distributed data) or a Wilcoxon rank sum test (for not normally distributed data). *P* values of $<0.05$ were considered statistically significant.

This study is reported in keeping with the SQUIRE 2.0 guidelines.[9]

**Table 1**
Demographic characteristics of hospitals.

| | Inpatient bed numbers | Location | On-site processing of vancomycin TDM |
|---|---|---|---|
| Hospital 1 (secondary) | Approximately 290 | Approximately 45kms from Hospital 2 | No |
| Hospital 2 (tertiary) | Approximately 1000 | Near CBD of major city | Yes |
| Hospital 3 (secondary) | Approximately 250 | Approximately 35kms from Hospital 2 | Yes |

CBD = central business district.

**Table 2**
Median reporting time of vancomycin concentrations for each hospital.

| | | Number of assays | Median time (hours) | Interquartile range (hours) | *p*-value* |
|---|---|---|---|---|---|
| Hospital 1 | Off-site monitoring | 114 | 11.13 | 7.83–17.97 | |
| | On-site monitoring | 33 | 1.33 | 0.93–1.58 | <0.001 |
| Hospital 2 | On-site monitoring | 1302 | 1.73 | 1.27–2.61 | <0.001 |
| Hospital 3 | On-site monitoring | 260 | 1.70 | 1.19–2.31 | <0.001 |

* Compared to Hospital 1 during period of off-site monitoring.

## 3. Results

### 3.1. Quantitative data

A total of 1676 results were collected for the 3 hospitals from June to December 2021 with results and analysis summarised in Table 2. Hospital 1 had a significantly longer median reporting time (11.13 h) than other sites (1.73 h, 1.7 h).

A total of 33 reporting times were available for analysis from the 3 months following implementation of on-site processing of TDM at Hospital 1, with median reporting times significantly improving following this change (11.13 h reduced to 1.33 h).

### 3.2. Qualitative data

Eight clinical incidents involving vancomycin at Hospital 1 were entered into the RiskMan® system from June to December 2021.

Incident types were coded as relating to overdosage (2 incidents), underdosage (2 incidents) and timing (4 incidents). Only incidents coded as relating to timing were further analysed and generated the following themes: timing of blood test, timing of result availability. These themes, in which prolonged reporting times may have contributed to adverse patient outcomes, are detailed in Table 3 and accompanied by a clinical incident example.

The authors identified in reflection that the change to introduce the improvement of on-site monitoring to assist in the safe management of vancomycin therapies was not linear, with different pieces of information, incidents, and stakeholders becoming involved at different times. Fig. 1 has been included to explore the barriers and enablers to problem identification and improvement in this instance.

**Table 3**
Incident themes in vancomycin clinical incidents affected by prolonged reporting times.

| Themes Identified | Count | Incident Example Description |
|---|---|---|
| Theme 1: Incorrect time of drawing trough samples resulting in withheld doses | 1 of 8 clinical incidents reported | A patient was prescribed vancomycin to treat a Methicillin resistant *Staphylococcus Aureus* (MRSA) post-surgical wound infection.<br><br>The first vancomycin concentration was supratherapeutic at 40 mg/L. There was suspicion this may not have been a true trough concentration. The vancomycin order was withheld and another blood sample was sent for TDM processing.<br><br>A subtherapeutic concentration of 4 mg/mL was reported at 18.45 h leading to 3 vancomycin doses not being administered. This resulted in undertreatment of a serious infection and a longer time to reach the target therapeutic range. |
| Theme 2: Reporting of vancomycin concentration results outside of standard hours delaying review of results prior to administration of additional doses | 3 of 8 clinical incidents reported | A patient was prescribed vancomycin for sepsis from a suspected skin source.<br><br>A supratherapeutic trough vancomycin concentration of 44 mg/L was reported at 9:56 pm, 12.5 h after collection. The patient received 2 further doses of vancomycin before the result was identified and escalated by a pharmacist the following day.<br><br>A decline in renal function was also identified with a two-fold increase in serum creatinine. Vancomycin was ceased due to the supratherapeutic concentration and blood culture results also confirming sensitivity to a first line antibiotic. The patient required ongoing close monitoring of renal indices which slowly recovered. |

## 4. Discussion

The off-site processing of vancomycin TDM required by Hospital 1 appeared to be the reason for significantly longer median reporting time when compared to hospitals with this service on-site. After on-site processing of vancomycin TDM was implemented at Hospital 1, the median reporting time reduced by almost 10 h, aligning with results from Hospital 2 and 3.

Incorrect timing or site of drawing blood samples is one commonly reported issue which can result in the repeating of TDM if the error is recognised, or incorrect dose adjustments if not recognised.[6] This type of issue was described as 'Theme 1' in Table 3. Had the repeat vancomycin concentration been available within 2 h (approximate median time to reporting for on-site monitoring) instead of 18.45 h, the incorrect timing of the initial sample could have been confirmed and prevented the need to withhold multiple doses.

Staff availability, or the availability of results for interpretation within regularly staffed hours was described as 'Theme 2' in Table 3. Had the initial vancomycin concentration been available within 2 h instead of 12.5 h, the results would have been available within the standard working hours for the treating team to review and adjust. This could have avoided 2 unadjusted doses being administered to a patient with already declining renal function.

The median reporting time of 11.13 h for Hospital 1 during the pre-implementation time period meant that the majority of vancomycin TDM could be impacted by Theme 2. With results being reported outside of the standard working hours and the usual twice daily dosing times of 8 am and 8 pm, the implications of this delay would most often mean 2 further doses would proceed either unadjusted or potentially be withheld unnecessarily. Exploring this aspect of incidents which had occurred helped to highlight that the first problem with vancomycin that needed to be addressed was not one of a staff knowledge deficit requiring education (as initially recommended, see Fig. 1), but one of having timely access to information required for decision-making to occur.

TDM can be utilised for a variety of drug classes. It can be performed to measure clinical effect, monitor for toxicity, confirm medicine adherence or ingestion after a suspected polypharmacy overdose. Irrespective of the indication for TDM, results must be provided promptly and accurately to be clinically relevant and useful.[4]

The example incidents, and the results demonstrated in this study show that the median time to reporting can be significantly influenced by whether processing of vancomycin TDM is conducted on-site, and that prolonged time to reporting can have significant impacts on clinical management. As such, the median reporting times and potential reasons for delay should be given consideration where challenges in vancomycin (or other drug) management have been identified as a local issue. This study showed the significance of on-site TDM processing in improving timeliness, however at other sites, reasons for delay may differ and should be explored on a case-by-case basis to ensure the correct problem is being addressed.

A strength of this study was identifying the need for a systems change by implementing on-site TDM processing at Hospital 1. An

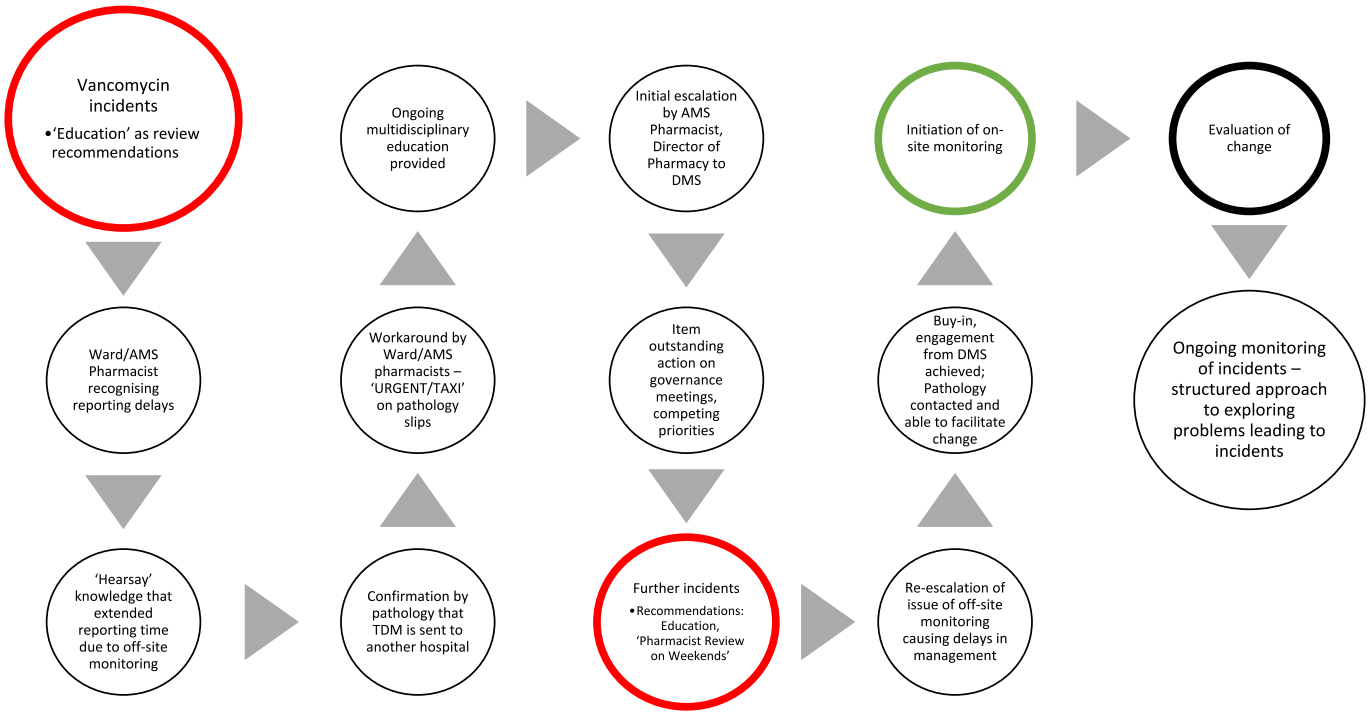


**Fig. 1.** Process of problem identification and implementation.

understanding of 'work as done' versus 'work as imagined' was instrumental in identifying an effective and sustainable intervention,[10] though in this particular instance it occurred somewhat by chance due to the persistence of individual clinicians in escalating and challenging the status quo. In future, the investigators plan to use Implementation Science Tools, such as Normalisation Process Theory[11] or COM-B,[12] in the development and implementation phase of complex interventions to more consistently identify critical steps in processes which may not be initially apparent and continue improvement in an iterative manner.

There is a limitation in the generalisability of the off-site monitoring results as it is greatly dependent upon the location of the hospital and its proximity to the designated hospital with on-site monitoring to which samples are sent. As this study's results are reflective of a metropolitan setting, more pronounced variation would be expected for rural and remote settings. Further to this, data and examples included relating to the qualitative aspect of this study rely on subjective and often self-initiated clinician incident reporting and should not be used as an absolute representation of incident rates.

## 5. Conclusions

Clinical incident examples have shown that prolonged reporting times can be an additional barrier to the safe and effective management of vancomycin, and reasons for reporting delays should be explored. This study showed that access to on-site vancomycin TDM can substantially reduce reporting times compared to off-site monitoring, enabling more consistent patient care. Furthermore, the problem identification and intervention described in this study offers a learning opportunity and example for other clinicians and managers to use Implementation Science tools to consider critical steps and accurate solutions in the clinical challenges and safety issues faced in practice.

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## Ethics

Exemption from Human Research Ethics Committee (HREC) review was granted by the deputy chair of the Metro South HREC (2022/QMS/88629). Data custodian approval was obtained for access the data from Pathology Queensland and RiskMan.

## CRediT authorship contribution statement

**Belinda Chappell:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Validation, Visualization, Writing – original draft, Writing – review & editing. **Benita Suckling:** Conceptualization, Methodology, Visualization, Writing – review & editing. **Champika Pattullo:** Writing – review & editing.

## Declaration of Competing Interest

None.

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