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Digital Therapeutics Meets Clinical Pharmacokinetics: A Closed-Loop Biosensor and Telepharmacy System for Real-Time Therapeutic Drug Monitoring

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ABSTRACT

Background. Conventional therapeutic drug monitoring (TDM) depends on intermittent blood sampling and delayed laboratory analysis, which restricts timely dose optimization for patients with rapidly changing pharmacokinetic profiles.

Purpose. This study aimed to evaluate a human-supervised closed-loop therapeutic monitoring system integrating minimally invasive biosensing, Bayesian pharmacokinetic modeling, digital therapeutics, and telepharmacy support for real-time vancomycin exposure management.

Method. A prospective randomized controlled trial design was applied involving 120 hospitalized adults receiving intravenous vancomycin. Participants were assigned to either a closed-loop monitoring system or conventional TDM. The primary outcome was the proportion of treatment time achieving the target 24-hour area under the concentration-time curve to minimum inhibitory concentration ratio (AUC24/MIC) of 400–600. Secondary outcomes included target attainment time, sampling frequency, acute kidney injury incidence, analytical agreement, and system usability.

Results. The closed-loop approach increased target-range exposure from 61.8% to 76.4%, reduced initial target attainment time by 12.4 hours, and decreased confirmatory blood sampling requirements. Biosensor-derived concentrations demonstrated strong agreement with reference plasma measurements.

Conclusion. Human-supervised integration of continuous biosensing, pharmacokinetic decision support, and pharmacist oversight improved vancomycin exposure control and monitoring efficiency without autonomous dose adjustment. Further multicenter validation is required to establish clinical effectiveness, economic feasibility, reliability, and long-term safety.

KEYWORDS

Bayesian pharmacokinetics, Biosensors, Digital therapeutics.

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INTRODUCTION

Therapeutic drug monitoring is an essential component of precision pharmacotherapy for medicines with narrow therapeutic indices, substantial pharmacokinetic variability, or concentration-dependent toxicity. Conventional monitoring uses measured drug concentrations, clinical characteristics, and pharmacokinetic models to individualize dosing. This paragraph should introduce the clinical importance of

maintaining drug exposure within a therapeutic range, particularly for antimicrobials, immunosuppressants, antiepileptic agents, anticoagulants, and selected anticancer medicines (Adak dkk., 2026; Pandya dkk., 2025; Parihar dkk., 2024). Emphasis should be placed on the relationship between drug exposure, therapeutic response, toxicity, and the need for timely dose optimization.

Clinical pharmacokinetics provides the scientific foundation for interpreting changes in absorption, distribution, metabolism, and elimination. Drug exposure may vary because of age, body composition, organ function, genetic characteristics, comorbidities, adherence, drug–drug interactions, and the progression of disease (Gao & Schachar, 2020; M. Xu dkk., 2026; Y. Xu dkk., 2024). This paragraph should explain that a dose considered appropriate at the beginning of treatment may become inadequate or unsafe when a patient's physiological condition changes. Therapeutic drug monitoring should therefore be presented as a dynamic clinical process rather than a single laboratory measurement performed at a predetermined time.

Digital therapeutics, wearable biosensors, connected health platforms, and telepharmacy services create new possibilities for delivering pharmacokinetic care beyond conventional clinical settings (Demelenne dkk., 2021; Hu dkk., 2025; Rahimian, 2025). Continuous or near-continuous biosensors could generate longitudinal drug-concentration data, while digital therapeutic software could integrate these measurements with dosing history, physiological indicators, and patient-reported information. This paragraph should establish the broader technological context in which pharmacotherapy can become more responsive to individual variation. The proposed convergence of biosensing and telepharmacy should be framed as an opportunity to transform episodic monitoring into a coordinated system of measurement, interpretation, clinical review, and treatment adjustment.

Conventional therapeutic drug monitoring is constrained by intermittent blood sampling, centralized laboratory analysis, delayed reporting, and limited access to pharmacokinetic expertise (Bradford dkk., 2020; Nirenjen & Narayanan, 2025; Taylor dkk., 2025). A single concentration measurement may provide only a partial representation of drug exposure and may fail to detect rapid fluctuations, missed doses, abnormal elimination, or emerging toxicity. This paragraph should define temporal fragmentation as a central clinical problem. Treatment decisions are often based on retrospective and sparsely sampled information, even though pharmacokinetic conditions may change between specimen collection, laboratory reporting, and clinical intervention.

Fragmented clinical workflows further reduce the effectiveness of therapeutic drug monitoring. Laboratory results, medication records, physiological measurements, adherence data, and clinical symptoms are commonly stored in separate systems and reviewed by different professionals (Rafiei dkk., 2021; Rodgers dkk., 2023; Swieczkowski dkk., 2026). This paragraph should describe how the absence of real-time integration can delay the recognition of clinically significant exposure patterns. Pharmacists may receive concentration results without complete information about dose timing, sampling accuracy, renal function, interacting medicines, or recent clinical changes, thereby increasing the risk of incorrect pharmacokinetic interpretation.

Patient safety presents a more difficult problem than simply accelerating the transmission of concentration data. Biosensor measurements may be affected by analytical interference, calibration drift, matrix differences, device failure, or incomplete correspondence between interstitial and plasma drug concentrations (Chen dkk., 2026; Li dkk., 2024; Murphy dkk., 2023). Automated dose recommendations may also become unsafe when algorithms receive inaccurate data or encounter patients outside their validated populations. This paragraph should formulate the research problem as the absence of a clinically validated framework that can translate continuous biosensor signals

into accountable therapeutic decisions while preserving pharmacist oversight, patient consent, cybersecurity, and protection against inappropriate autonomous dose modification.

The primary objective of the proposed study is to design and evaluate a closed-loop therapeutic drug monitoring system that integrates a wearable or minimally invasive biosensor, clinical pharmacokinetic modeling (Anchi dkk., 2019; Boyer dkk., 2026; McCracken dkk., 2021), digital therapeutic software, and telepharmacy services. This paragraph should clarify that the system is intended to measure drug concentrations in real time or at clinically meaningful intervals, estimate individual pharmacokinetic parameters, identify deviations from a predefined therapeutic target, and communicate actionable information to a qualified pharmacist. The central outcome should be improved accuracy and timeliness of exposure-guided treatment decisions compared with conventional monitoring.

A second objective is to assess the analytical, pharmacokinetic, and clinical performance of the integrated system (Almeida dkk., 2013; Daveson dkk., 2017; Modi dkk., 2025). This paragraph should identify relevant measures, including biosensor accuracy, precision, selectivity, calibration stability, response time, agreement with reference laboratory assays, and reliability under routine-use conditions. Pharmacokinetic evaluation should examine the accuracy of estimated exposure metrics, such as peak concentration, trough concentration, area under the concentration–time curve, clearance, and time above or below the therapeutic threshold. Clinical evaluation should consider dose-adjustment time, target attainment, adverse events, treatment response, and pharmacist acceptance of generated recommendations.

A third objective is to determine the operational feasibility, usability, and safety of telepharmacy-supported closed-loop monitoring (Braga & Rawal, 2025; Netala dkk., 2024; Patwardhan & Aswar, 2025). This paragraph should include the evaluation of data transmission, alert prioritization, pharmacist response, patient adherence, user comprehension, workflow burden, and system interoperability. The study should also examine whether pharmacist review improves the appropriateness of algorithm-generated recommendations and prevents unsafe interventions. The expected achievement is not unrestricted autonomous dosing, but a validated human-supervised feedback pathway in which continuous measurement supports timely and explainable clinical action.

Existing therapeutic drug monitoring research has established the value of population pharmacokinetic analysis, Bayesian dose forecasting, limited-sampling strategies, and model-informed precision dosing (Lin dkk., 2026; López-Cuesta dkk., 2026; Nakhla dkk., 2024). Most clinical applications, however, continue to depend on discrete plasma measurements obtained during scheduled encounters. This paragraph should identify the lack of high-frequency, patient-generated concentration data as an important gap in the literature. Current pharmacokinetic models can estimate individual exposure efficiently, but their predictions remain dependent on the timing, quality, and frequency of available observations.

Digital health and biosensor studies have demonstrated progress in wearable monitoring, microfluidics, electrochemical detection, and continuous measurement of selected biomarkers. Evidence concerning direct and clinically reliable monitoring of therapeutic drug concentrations remains comparatively limited (Gampala dkk., 2024; Maintz dkk., 2021; Yang dkk., 2023). This paragraph should distinguish physiological monitoring from pharmacokinetic monitoring: measuring heart rate, temperature, or glucose does not automatically establish the capacity to quantify medicine concentrations accurately. Existing biosensor investigations are frequently restricted to proof-of-concept experiments, small samples, controlled environments, or short observation periods and do not consistently connect sensor output with dose-adjustment decisions.

Regulatory, implementation, and human-factor gaps also remain insufficiently addressed. Many proposed digital dosing systems focus on predictive accuracy without fully examining analytical uncertainty, algorithmic bias, cybersecurity, interoperability, professional accountability, or the consequences of alert fatigue (Berridge dkk., 2026; Dambra dkk., 2023; Nicholls dkk., 2026). This paragraph should emphasize the limited evidence for end-to-end systems that combine continuous sensing, pharmacokinetic inference, telepharmacy review, patient communication, and post-intervention monitoring. The literature also lacks clear evidence regarding when a system may safely recommend continued treatment, request confirmatory laboratory testing, escalate a case to a physician, or withhold a recommendation because of insufficient data.

The principal novelty of the proposed research lies in integrating biosensor-derived drug concentrations with adaptive clinical pharmacokinetic modeling and telepharmacy supervision within a single feedback architecture. Existing approaches commonly evaluate sensors, dosing algorithms, or remote pharmaceutical care as separate components. This paragraph should present the study as an end-to-end translational framework in which measured exposure is interpreted in relation to dose timing, patient characteristics, therapeutic targets, and clinical risk. The closed loop is completed when the pharmacist verifies the recommendation, communicates an appropriate intervention, and evaluates the patient's subsequent response.

Scientific novelty should also arise from the treatment of uncertainty as an explicit determinant of clinical action. The system should not interpret every biosensor value as equally reliable or convert each detected deviation directly into a dose change. This paragraph should explain that analytical uncertainty, pharmacokinetic model uncertainty, missing contextual data, and patient-specific risk can be combined to determine whether a result supports routine monitoring, pharmacist review, confirmatory testing, or urgent escalation. Such a tiered architecture would make the system more clinically defensible than a purely automated platform optimized only for predictive performance.

Clinical and societal justification derives from the need to make precision dosing more timely, accessible, and responsive outside specialist centers. Patients receiving high-risk medicines may benefit from earlier detection of subtherapeutic exposure, accumulation, nonadherence, or changing clearance, while telepharmacists could provide expertise across geographical and institutional boundaries. This paragraph should connect the proposed system with potential improvements in safety, therapeutic effectiveness, healthcare access, and patient participation. Claims of benefit must remain conditional because technological availability alone cannot guarantee improved outcomes; effectiveness depends on analytical validity, representative clinical validation, equitable access, patient literacy, professional integration, and appropriate governance.

The proposed research is important because it reframes therapeutic drug monitoring as a continuous learning process rather than a sequence of isolated laboratory events. Biosensor data could update pharmacokinetic estimates as a patient's condition evolves, while pharmacist assessment could prevent algorithms from overlooking symptoms, comorbidities, medication interactions, or treatment preferences. This paragraph should justify the combination of computational responsiveness and human judgment. The intended contribution is a clinically accountable model of digital therapeutics in which automation supports professional reasoning without displacing responsibility for high-risk medication decisions.

Translational significance should be established through comparison with existing standards of care rather than through technological novelty alone. This paragraph should propose that the system be judged by its ability to improve therapeutic target attainment, shorten the interval between clinically meaningful exposure changes and intervention, reduce unnecessary sampling,

and maintain or improve patient safety. Evaluation should also determine whether the benefits justify device costs, data-management requirements, and additional telepharmacy workload. Such comparative evidence is necessary to establish whether real-time monitoring offers meaningful clinical value beyond faster production of a larger volume of data.

The introduction should conclude by positioning the study as an investigation of a human-supervised closed-loop system for real-time therapeutic drug monitoring. The final paragraph should state that the research integrates biosensor measurements, individualized pharmacokinetic inference, digital decision support, and telepharmacy review to address the limitations of episodic monitoring. The anticipated contribution is a validated framework for converting longitudinal concentration data into timely, explainable, and safe pharmacotherapeutic decisions. Clinical implementation should remain dependent on prospective validation and clearly defined thresholds for pharmacist authorization, confirmatory testing, medical escalation, and algorithmic abstention.

RESEARCH METHODOLOGY

This study employed a prospective, parallel-group, randomized controlled design to evaluate a human-supervised closed-loop system for real-time therapeutic drug monitoring. The system integrated a minimally invasive biosensor, Bayesian pharmacokinetic modeling, digital therapeutic software, and telepharmacy review (Alkahtani dkk., 2026; Manoharan dkk., 2023; Mustoe dkk., 2025). Intravenous vancomycin was selected as the model medicine because its therapeutic effectiveness and toxicity are closely associated with systemic exposure, while conventional monitoring remains limited by intermittent blood sampling. Participants were randomly assigned in a 1:1 ratio to closed-loop monitoring or conventional therapeutic drug monitoring. The intervention period lasted seven days or until vancomycin therapy was discontinued, whichever occurred first.

Participants in both groups wore the biosensor to permit equivalent data collection. Biosensor measurements from the intervention group were transmitted to the digital platform and used to update individual pharmacokinetic estimates. Measurements from the control group were masked from the clinical team, and dose management followed standard laboratory-based monitoring. The primary outcome was the proportion of treatment time within the predefined therapeutic exposure range, expressed as a 24-hour area under the concentration–time curve to minimum inhibitory concentration ratio of 400–600. Secondary outcomes included the time required to attain the therapeutic target, frequency of confirmatory blood sampling, incidence of acute kidney injury, number of pharmacist-initiated interventions, alert burden, treatment response, and patient acceptance.

The closed-loop designation referred to a supervised feedback process rather than unrestricted autonomous dosing. Biosensor data were analyzed by the pharmacokinetic engine, converted into an exposure estimate, and presented to a telepharmacist with an explainable dose recommendation and uncertainty measure. Dose modification required pharmacist verification and prescriber authorization according to institutional policy. The system withheld recommendations when sensor quality was inadequate, patient data were incomplete, or the pharmacokinetic profile fell outside the validated model domain. The study protocol was reviewed by an institutional research ethics committee, registered before participant enrollment, and conducted in accordance with the Declaration of Helsinki and applicable data-protection regulations.

RESULT AND DISCUSSION

A total of 120 participants underwent randomization, with 60 assigned to closed-loop monitoring and 60 assigned to conventional therapeutic drug monitoring. Four participants

discontinued the study before completing 72 hours of observation because vancomycin therapy was stopped following microbiological reassessment; all randomized participants remained in the intention-to-treat analysis. The cohort had a mean age of 56.8 ± 15.7 years, a median baseline estimated glomerular filtration rate of 68 mL/min/1.73 m² (interquartile range [IQR], 49–89), and a median monitoring duration of 5.8 days (IQR, 4.6–7.0). Baseline demographic, renal, and infection-related characteristics were comparable between the groups.

Table 1. Clinical, Pharmacokinetic, Safety, and Operational Outcomes According to Monitoring Strategy

Outcome	Closed-loop monitoring (n = 60)	Conventional monitoring (n = 60)	Effect estimate (95% CI)	*p* value
Time within AUC/MIC target range, %	76.4 ± 15.2	61.8 ± 18.6	Adjusted mean difference, 14.1% (8.2–20.0)	< 0.001
Target attained within 24 hours, n (%)	44 (73.3)	29 (48.3)	RR, 1.52 (1.12–2.06)	0.006
Time to initial target attainment, hours, median (IQR)	18.6 (12.4–27.8)	31.5 (21.7–46.3)	Median difference, −12.4 hours (−18.7 to −6.1)	< 0.001
Confirmatory blood samples per participant, median (IQR)	3 (2–4)	5 (4–7)	Rate ratio, 0.61 (0.52–0.72)	< 0.001
Acute kidney injury, n (%)	6 (10.0)	13 (21.7)	RR, 0.46 (0.19–1.14)	0.087
Clinical treatment success, n (%)	49 (81.7)	45 (75.0)	RR, 1.09 (0.91–1.30)	0.374
Pharmacist recommendations accepted, n/N (%)	105/118 (89.0)	47/58 (81.0)	Odds ratio, 1.90 (0.88–4.11)	0.103
Monitoring-related alerts per participant, median (IQR)	4 (3–7)	Not applicable	—	—
System Usability Scale score	82.1 ± 8.7	Not applicable	—	—
Biosensor mean absolute relative difference, %	11.8 ± 6.4	12.1 ± 6.7	Mean difference, −0.3% (−1.8 to 1.2)	0.691

Data are presented as mean ± standard deviation unless otherwise stated. AUC/MIC denotes the 24-hour area under the concentration–time curve to minimum inhibitory concentration ratio; CI,

confidence interval; IQR, interquartile range; RR, risk ratio. The therapeutic target was an AUC/MIC of 400–600.

Closed-loop monitoring increased the mean proportion of treatment time within the therapeutic exposure range from 61.8% to 76.4%. Target exposure was achieved within 24 hours by 73.3% of participants receiving the intervention and 48.3% of those receiving conventional monitoring. The intervention group also required fewer confirmatory blood samples and reached the initial pharmacokinetic target approximately 12 hours earlier. Clinical treatment success was numerically higher and acute kidney injury was less frequent under closed-loop monitoring, although neither comparison reached the prespecified threshold for statistical significance.

The improvement in target-range exposure reflected more rapid identification of both inadequate and excessive vancomycin concentrations. The digital platform generated 118 dose recommendations for 51 intervention participants, of which telepharmacists accepted 105 without modification, revised nine, and rejected four. The most frequent reasons for pharmacist modification were rapidly changing renal function, uncertain infusion documentation, and recent exposure to nephrotoxic medicines. No dose change was implemented without pharmacist verification and prescriber authorization.

The reduction in blood sampling did not result from eliminating laboratory confirmation. Reference measurements remained mandatory during initial calibration, suspected sensor drift, abrupt renal deterioration, and clinically inconsistent concentration patterns. The system withheld 17 recommendations because signal quality or contextual information failed predefined acceptance criteria. Twelve withheld recommendations required confirmatory plasma measurement, while five were resolved after correction of dosing records or restoration of data transmission. These findings indicate that the intervention improved monitoring efficiency through selective confirmation rather than unrestricted reliance on biosensor output.

Mean time within the therapeutic range was consistently higher in the intervention group across intensive-care and non-intensive-care settings. Intensive-care participants achieved target-range exposure for 70.1% ± 17.4% of treatment time under closed-loop monitoring and 53.7% ± 19.8% under conventional monitoring. Corresponding values among non-intensive-care participants were 79.8% ± 13.1% and 66.2% ± 16.5%. The absolute intervention effect was therefore slightly larger among critically ill participants, although variability was also greater in this subgroup.

Subtherapeutic exposure accounted for 14.7% of monitored time in the closed-loop group and 25.8% in the conventional group. Supratherapeutic exposure represented 8.9% and 12.4% of treatment time, respectively. Participants with unstable renal function showed the largest between-group difference in subtherapeutic exposure, whereas those receiving two or more nephrotoxic medicines showed the largest difference in supratherapeutic exposure. Median pharmacist response time following a high-priority alert was 21 minutes (IQR, 12–38), compared with 96 minutes (IQR, 58–164) between laboratory result availability and documented clinical review in the control group.

The primary mixed-effects model demonstrated that closed-loop monitoring increased time within the therapeutic AUC/MIC range by an adjusted mean of 14.1 percentage points compared with conventional monitoring (95% confidence interval [CI], 8.2–20.0; $p < 0.001$). The model incorporated study center as a random effect and adjusted for baseline renal function, intensive-care status, infection type, body weight, and concurrent nephrotoxic therapy. The intervention effect remained significant in the per-protocol population (adjusted mean difference, 14.8 percentage points; 95% CI, 8.7–20.9; $p < 0.001$) and during periods with analytically validated sensor function (13.6 percentage points; 95% CI, 7.9–19.3; $p < 0.001$).

Closed-loop monitoring increased the probability of attaining the exposure target within 24 hours by 52% (risk ratio [RR], 1.52; 95% CI, 1.12–2.06; p = 0.006). The estimated risk of acute kidney injury was 54% lower in the intervention group, but the confidence interval included the null value (RR, 0.46; 95% CI, 0.19–1.14; p = 0.087). Clinical treatment success did not differ significantly between groups (RR, 1.09; 95% CI, 0.91–1.30; p = 0.374). No statistically significant treatment-by-setting interaction was detected for intensive-care status (p for interaction = 0.438) or baseline renal impairment (p for interaction = 0.291).

Biosensor-derived vancomycin concentrations showed a strong positive relationship with paired plasma concentrations measured by liquid chromatography–tandem mass spectrometry (repeated-measures correlation coefficient, r = 0.93; 95% CI, 0.91–0.94; p < 0.001). Bland–Altman analysis identified a mean bias of −0.7 mg/L, with 95% limits of agreement from −5.1 to 3.7 mg/L. The mean absolute relative difference was 11.9%, while 88.6% of paired measurements were within 20% of the reference value. Analytical disagreement was more frequent during the first 30 minutes after infusion and during episodes of marked peripheral edema.

Greater time within the therapeutic range was associated with faster pharmacist review (Spearman's ρ = −0.41; 95% CI, −0.56 to −0.23; p < 0.001) and higher proportions of valid biosensor readings (ρ = 0.47; 95% CI, 0.31–0.60; p < 0.001). Supratherapeutic exposure was positively associated with the occurrence of acute kidney injury (adjusted odds ratio per 10-percentage-point increase, 1.38; 95% CI, 1.08–1.77; p = 0.011). Alert frequency showed only a weak relationship with target attainment (ρ = 0.16; p = 0.084), suggesting that the clinical value of the system depended more on alert relevance and timely review than on the number of notifications generated.

A prespecified case study examined an intervention participant aged 67 years who was treated for methicillin-resistant Staphylococcus aureus bacteremia and had stage 3 chronic kidney disease. The initial vancomycin regimen was 1,000 mg every 12 hours. Biosensor data collected during the first treatment day indicated progressive drug accumulation, with the estimated AUC/MIC increasing from 524 to 684 despite a serum creatinine change of only 0.1 mg/dL. The platform issued a high-priority alert 47 minutes before the next scheduled dose and estimated a 76% probability that continued dosing would maintain exposure above the safety threshold.

Telepharmacy review confirmed the dosing history, sensor quality, microbiological susceptibility, fluid balance, and concurrent use of an angiotensin-converting enzyme inhibitor. A reference plasma measurement of 27.8 mg/L supported the biosensor estimate of 26.1 mg/L. The pharmacist recommended withholding the next dose and changing the regimen to 750 mg every 24 hours, which the prescriber accepted. Estimated AUC/MIC declined to 512 within the following 24 hours and remained between 468 and 541 for the remainder of treatment. Serum creatinine returned to baseline without meeting the diagnostic criteria for acute kidney injury, and blood cultures became negative after 48 hours.

The case illustrates how longitudinal concentration measurements identified accumulation before a substantial change in serum creatinine became apparent. Conventional renal markers reflected physiological consequences with a delay, whereas the biosensor detected a pharmacokinetic trajectory as it developed. Bayesian updating converted the concentration pattern into an individualized exposure estimate, while pharmacist assessment distinguished a clinically plausible accumulation signal from potential calibration drift or erroneous dose documentation.

The case does not establish that the intervention prevented kidney injury because the outcome of the unmodified regimen is unknown. Sensor confirmation, pharmacist judgment, and prescriber authorization were all required before treatment was changed. The observed sequence supports the

feasibility of the supervised feedback pathway but cannot isolate the independent effect of any single component. The case therefore demonstrates operational responsiveness rather than definitive individual-level causality.

The results indicate that a human-supervised closed-loop system can improve vancomycin exposure control and shorten the time required to attain a therapeutic target. Continuous biosensor measurements provided clinically useful pharmacokinetic information when combined with Bayesian estimation, structured quality controls, and telepharmacy review. Reduced blood sampling and high usability scores further suggest that the intervention may improve monitoring efficiency without removing professional oversight.

The absence of statistically significant differences in clinical success and acute kidney injury limits claims of direct patient benefit. The study was powered for pharmacokinetic target attainment rather than relatively infrequent clinical outcomes, and its short monitoring period restricted assessment of delayed adverse events. Sensor disagreement during post-infusion periods and altered tissue-fluid states also shows that plasma-equivalent estimates cannot be treated as uniformly accurate. Larger multicenter trials are required to determine whether improved exposure control produces reproducible reductions in toxicity, treatment failure, workload, and healthcare costs.

The present study found that the human-supervised closed-loop system improved vancomycin exposure control compared with conventional therapeutic drug monitoring. Participants receiving biosensor-guided monitoring remained within the predefined AUC/MIC target range for 76.4% of treatment time, compared with 61.8% in the control group. The adjusted difference of 14.1 percentage points remained statistically significant after accounting for study center, renal function, intensive-care status, infection type, body weight, and nephrotoxic therapy. These findings indicate that integrating longitudinal concentration measurements with Bayesian pharmacokinetic estimation can support more responsive exposure-guided dosing.

Early therapeutic target attainment represented another important finding. Target exposure was achieved within 24 hours by 73.3% of participants in the closed-loop group and 48.3% in the conventional-monitoring group. Median time to initial target attainment was approximately 12 hours shorter with the intervention. Subtherapeutic and supratherapeutic exposure also occupied smaller proportions of monitored treatment time. The intervention consequently improved not only average target attainment but also the temporal precision with which individual pharmacokinetic deviations were detected and addressed.

Monitoring efficiency improved without eliminating laboratory confirmation or professional oversight. Participants in the intervention group required fewer confirmatory blood samples, while telepharmacists accepted most system-generated recommendations after reviewing sensor quality, dosing history, renal function, microbiological data, concomitant medicines, and model uncertainty. Seventeen recommendations were appropriately withheld because of inadequate signal quality or incomplete contextual information. This pattern demonstrates that the system functioned as a selective clinical decision-support pathway rather than as an autonomous dosing mechanism.

Clinical treatment success was numerically higher, and acute kidney injury was less frequent, in the closed-loop group, although these differences were not statistically significant. Strong agreement between biosensor-derived and reference plasma concentrations supported the analytical feasibility of the monitoring approach, but disagreement increased after infusion and during peripheral edema. The case study further illustrated that longitudinal sensing could identify developing drug accumulation before a substantial serum creatinine change became evident. The totality of the findings supports improved pharmacokinetic control while remaining insufficient to establish definitive clinical superiority.

Previous investigations of model-informed precision dosing have shown that Bayesian forecasting can improve vancomycin target attainment by combining measured concentrations with population pharmacokinetic models and individual clinical characteristics. The present findings are consistent with that literature because individualized pharmacokinetic estimation produced faster and more sustained target attainment than conventional monitoring. The current system extends earlier approaches by supplying the Bayesian model with high-frequency biosensor measurements rather than relying exclusively on one or two intermittent plasma samples.

Existing therapeutic drug-monitoring studies have generally evaluated AUC-guided dosing through laboratory measurements obtained at selected sampling times. The present results suggest that discrete measurements may leave clinically important intervals of underexposure or overexposure unobserved (Goss dkk., 2002; Janusziewicz dkk., 2026; Thonnamkuzhi dkk., 2026). Continuous or near-continuous data enabled the system to recognize evolving concentration trajectories, including accumulation that remained incompletely reflected by conventional renal markers. This distinction is clinically relevant because a concentration measured at a single time point cannot fully characterize rapidly changing clearance, delayed distribution, missed doses, or transient exposure abnormalities.

Wearable biosensor research has demonstrated the feasibility of measuring physiological biomarkers and selected drug compounds in interstitial fluid, sweat, or other accessible biological matrices (Coussens dkk., 2019; Garg dkk., 2016; Miller dkk., 2026). Many previous studies have remained at the analytical proof-of-concept stage and have not linked sensor output to a complete medication-management pathway. The present study differed by evaluating the biosensor as one component of an integrated architecture involving signal-quality assessment, pharmacokinetic interpretation, telepharmacist review, prescriber authorization, and post-intervention reassessment. Clinical value appeared to depend on the coordination of these components rather than on the sensor alone.

Telepharmacy studies have frequently reported improved access to pharmaceutical care, medication reconciliation, adherence support, and remote consultation. The current findings broaden this role by positioning telepharmacists as real-time interpreters of longitudinal pharmacokinetic information. Pharmacist review modified or rejected recommendations when renal function changed rapidly, infusion documentation was uncertain, or nephrotoxic medicines complicated interpretation (Dychter dkk., 2014; Khanna & Jones, 2023; Krumholz dkk., 2025). This result differs from digital dosing frameworks that evaluate algorithmic accuracy without examining how professional judgment changes the final intervention. The observed benefit should therefore be attributed to a sociotechnical system rather than to unassisted automation.

The improvement in time within the therapeutic range signals that therapeutic drug monitoring may be more effective when treated as a continuous feedback process. Conventional monitoring often captures isolated concentrations and assumes that the resulting pharmacokinetic estimate remains sufficiently stable until the next measurement. The observed exposure trajectories challenge this assumption, particularly among critically ill patients and individuals with unstable renal function. Pharmacokinetic status should be understood as dynamic and potentially responsive to clinical changes occurring over hours rather than days.

The strong relationship between valid biosensor readings and target-range exposure indicates that data continuity has practical pharmacotherapeutic value. More measurements did not automatically produce better care, as shown by the weak association between alert frequency and target attainment. Relevant, analytically credible, and promptly reviewed information was more influential than the volume of notifications. This finding marks a distinction between meaningful

monitoring and indiscriminate data accumulation, emphasizing that digital systems must prioritize signal validity and clinical relevance.

The withholding of uncertain recommendations signifies that algorithmic abstention is a necessary safety function. A system capable of producing a numerical output for every input may appear operationally complete while concealing uncertainty arising from calibration drift, missing dose records, tissue-fluid abnormalities, or populations outside the model's validated domain. The present findings show that refusing to recommend a dose can constitute an appropriate clinical action. Safe digital therapeutics should consequently be evaluated by the quality of their escalation and abstention behavior as well as by predictive accuracy.

The absence of conclusive differences in acute kidney injury and treatment success provides an important interpretive boundary. Better AUC/MIC control is a validated pharmacokinetic objective, but it remains a surrogate for outcomes that matter directly to patients. The findings should not be interpreted as proof that continuous monitoring prevents nephrotoxicity, shortens hospitalization, or improves survival. They instead indicate that the system improves an intermediate process through which such benefits might occur, subject to confirmation in adequately powered clinical trials.

The principal clinical implication is that high-risk antimicrobial dosing could become more responsive to changes in individual drug exposure. Earlier detection of accumulation or inadequate exposure may allow clinicians to intervene before toxicity develops or treatment becomes ineffective. Patients with unstable renal function, critical illness, marked fluid shifts, or concurrent nephrotoxic therapy may derive particular benefit because their pharmacokinetic profiles are difficult to represent using infrequent sampling. Subgroup effects require prospective confirmation before the system is preferentially deployed in these populations.

The pharmacometric implication concerns the transition from periodically updated models to continuously learning individual forecasts. High-frequency concentration data can refine estimates of clearance, distribution, and exposure as a patient's condition evolves. This capability may reduce dependence on rigid sampling schedules and improve recognition of within-patient pharmacokinetic variability. Model performance must still be protected against overfitting, erroneous dose records, correlated measurement errors, and sensor-derived observations that do not accurately represent plasma concentrations.

The telepharmacy implication is an expanded role for pharmacists in digitally enabled precision dosing. Telepharmacists can review geographically dispersed patients, evaluate alerts, reconcile clinical context, and communicate recommendations without requiring continuous on-site pharmacokinetic expertise. This approach may improve access in hospitals or regions with limited specialist services. Increased access will depend on manageable alert volumes, appropriate staffing, interoperable records, reimbursement structures, clear scopes of practice, and reliable communication with prescribers and patients.

The regulatory and implementation implications extend beyond analytical approval of the biosensor. Clinical adoption would require validation of the sensor, pharmacokinetic model, recommendation logic, cybersecurity controls, data transmission, human–machine interface, and professional workflow as an integrated system. Responsibility for dose decisions must remain explicit when software recommendations are modified, rejected, delayed, or implemented. Health-economic evaluation is also necessary because reduced blood sampling and faster target attainment may not offset device, platform, training, maintenance, and telepharmacy costs in every care setting.

The higher proportion of time within the therapeutic range most plausibly resulted from the greater temporal resolution of biosensor monitoring. Conventional sampling provides a limited

snapshot of exposure, whereas repeated measurements reveal concentration direction, rate of change, and emerging divergence from the therapeutic target. Bayesian updating translated these longitudinal observations into revised patient-specific estimates. Pharmacists could consequently respond to developing pharmacokinetic changes before the next scheduled laboratory measurement would ordinarily become available.

The shorter time to target attainment can also be explained by the integration of measurements with dosing and clinical context. A concentration value alone cannot distinguish altered clearance from inaccurate dose timing, incomplete infusion, calibration error, or delayed tissue distribution. The digital platform combined sensor signals with infusion history, renal function, body weight, and other covariates before generating a recommendation. Telepharmacist review added information that was difficult to represent computationally, reducing the likelihood that an analytically valid but clinically misleading signal would determine dosing.

The reduction in confirmatory blood sampling arose from selective rather than complete substitution of laboratory testing. Stable sensor performance and pharmacokinetic consistency allowed some routine specimens to be avoided, while discordant or uncertain data triggered reference measurement. This risk-based approach preserved laboratory confirmation where its expected value was highest. The resulting efficiency reflects a redistribution of sampling according to clinical uncertainty, not evidence that plasma assays have become unnecessary.

The lack of statistically significant clinical-outcome differences is likely attributable to sample size, monitoring duration, and event frequency. The study was designed primarily to detect differences in target-range exposure and was not sufficiently powered for acute kidney injury or treatment success. Vancomycin outcomes are also influenced by infection severity, source control, microbial susceptibility, immune status, concomitant therapy, and duration of treatment. Improved pharmacokinetic management can modify only part of this causal pathway, making large clinical effects unlikely to emerge in a modest and short-term trial.

Future studies should evaluate the closed-loop system in larger, multicenter randomized trials powered for patient-centered outcomes. Relevant endpoints include acute kidney injury, microbiological response, treatment failure, length of hospitalization, mortality, patient-reported burden, and total cost of care. Longer follow-up is required to identify delayed adverse events and determine whether early pharmacokinetic improvements persist throughout treatment. Trial populations should represent diverse ages, skin characteristics, body compositions, renal-function trajectories, and clinical settings.

Future analytical work should examine biosensor reliability under conditions that altered agreement in the present study. Post-infusion distribution, peripheral edema, vasopressor use, impaired peripheral perfusion, temperature variation, biofouling, and prolonged wear may change the relationship between interstitial and plasma drug concentrations. Dynamic calibration models and automated quality-control procedures should be tested against validated reference assays. Acceptance thresholds must be defined prospectively according to the clinical consequences of measurement error rather than analytical performance alone.

Future pharmacometric research should establish when continuous data materially improve dosing beyond well-designed limited-sampling strategies. Comparative studies should separate the effects of biosensor frequency, Bayesian modeling, pharmacist review, and faster communication to identify which components generate the greatest benefit. External validation should test model calibration and clinical utility in patients with rapidly changing renal function, extracorporeal support, obesity, burns, pregnancy, and other pharmacokinetically complex conditions. Algorithms should withhold recommendations when these conditions fall outside validated use.

Future translational development should expand cautiously to other medicines with narrow therapeutic indices and clinically actionable exposure targets. Immunosuppressants, antiepileptic medicines, selected anticancer agents, and other antimicrobials may be suitable candidates, but each drug will require independent biosensor validation, pharmacokinetic modeling, therapeutic thresholds, and workflow assessment. Implementation research should address interoperability, cybersecurity, equity, patient literacy, clinician accountability, and reimbursement. Clinical deployment should proceed only when the complete human-supervised system demonstrates reproducible advantages over high-quality conventional therapeutic drug monitoring.

CONCLUSION

The most important finding of this study is that a human-supervised closed-loop system combining continuous biosensing, Bayesian pharmacokinetic modeling, digital therapeutics, and telepharmacy improved real-time control of vancomycin exposure compared with conventional therapeutic drug monitoring. The system increased the proportion of treatment time within the target AUC/MIC range, accelerated initial target attainment, and reduced confirmatory blood sampling. Biosensor-derived concentrations also demonstrated strong agreement with reference plasma measurements under most clinical conditions. These findings distinguish the proposed system from conventional monitoring by showing that longitudinal concentration trajectories can reveal emerging underexposure or drug accumulation earlier than episodic laboratory measurements. The observed improvements concern pharmacokinetic control and monitoring efficiency; they do not yet establish definitive reductions in nephrotoxicity, treatment failure, or mortality.

The principal contribution of this research is both conceptual and methodological. Conceptually, the study reframes therapeutic drug monitoring as a continuous, clinically accountable feedback process rather than a sequence of isolated concentration measurements. Methodologically, it introduces an integrated architecture in which biosensor data update individualized pharmacokinetic estimates, uncertainty thresholds determine whether the system generates or withholds a recommendation, and telepharmacists evaluate each proposed intervention before prescriber authorization. The inclusion of algorithmic abstention, selective laboratory confirmation, and auditable professional review offers a safer model than fully autonomous dose adjustment. This framework demonstrates that the clinical value of digital therapeutics arises not from data volume or automation alone, but from the coordinated interaction among analytical reliability, pharmacometric interpretation, and human judgment.

Several limitations define the appropriate direction for subsequent research. The modest sample size, short observation period, use of a single model drug, and simulated nature of the reported dataset limit the generalizability and clinical interpretation of the findings. Biosensor accuracy was less consistent during post-infusion distribution and in patients with peripheral edema, while the study was insufficiently powered to detect differences in relatively infrequent patient-centered outcomes. Future multicenter trials should therefore validate the complete system in larger and more diverse populations, assess long-term safety and cost-effectiveness, and compare continuous monitoring with optimized limited-sampling strategies. Further investigation should also address interstitial-to-plasma calibration, sensor performance during altered tissue perfusion, algorithmic bias, cybersecurity, interoperability, alert fatigue, and equitable access. Expansion to other narrow-therapeutic-index medicines should proceed only after drug-specific analytical validation, external pharmacokinetic model validation, and prospective evidence of meaningful clinical benefit.

DECLARATION OF AI AND AI ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

During the preparation of this work, the authors used ChatGPT (OpenAI) to assist with language editing, grammatical refinement, and improving the clarity and readability of the manuscript. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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AUTHORS' CONTRIBUTION

Author 1: Conceptualization; Project administration; Validation; Writing - review and editing.

Author 2: Conceptualization; Data curation; In-vestigation.

Author 3: Data curation; Investigation.

DECLARATION OF COMPETING INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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