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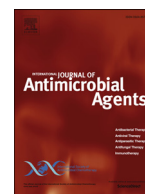
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## Short Communication

## Antimicrobial therapeutic drug monitoring in critically ill adult patients – An international perspective on access, utilisation, and barriers



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**Abbreviations:** ESCMID, European Society of Clinical Microbiology and Infectious Diseases; ESGCIP, ESCMID Study Group for Infections in Critically Ill Patients; ESICM, European Society of Intensive Care Medicine; HIC, high-income country; ICU, intensive care unit; ID, infectious diseases; LIC, low-income country; LMIC, lower-middle-income country; MIC, minimum inhibitory concentration; PK, pharmacokinetics; TDM, therapeutic drug monitoring; UMIC, upper-middle-income country.

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## ABSTRACT

**Background:** Therapeutic drug monitoring (TDM) is an effective method for individualising antimicrobial therapy in critically ill patients. The 2021 ADMIN-intensive care unit survey studied a wide range of intensive care unit clinicians worldwide to gain their perspectives on antimicrobial TDM. This article reports the responses from this survey relating to TDM access, utilisation, and barriers.

**Methods:** An online survey consisted of multiple-choice questions and 5-point Likert scales. The survey examined respondent's access to minimum inhibitory concentration (MIC) results, drug assays, and dosing software, as well as barriers to TDM.

**Results:** The survey included 538 clinicians from 409 hospitals in 45 countries, with 71% physicians and 29% pharmacists. Despite most respondents having access to assays, 21% and 26% of respondents lacked access to vancomycin and aminoglycosides, respectively. In lower-income countries, almost 40% reported no access. Delayed drug assay turnaround time was the most significant barrier to TDM, particularly in lower-income countries. Routine access to MIC results was unavailable for 41% of respondents, with 25% of lower-income country respondents having no access to MIC or susceptibility reports.

**Conclusions:** This global survey indicated that consistent TDM usage is hindered by assay access in some sites and the timeliness of assay results in others. Addressing barriers to TDM, particularly in low-income countries, should be a priority to ensure equitable access to affordable TDM.

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## 1. Introduction

Treating critically ill patients in the intensive care unit (ICU) with serious infections can be complex, with persisting poor outcomes, especially in patients with septic shock [1]. These patients commonly demonstrate altered pharmacokinetics (PK), which risks suboptimal antimicrobial exposures (concentrations) [2]. Since product-information-derived antimicrobial dosing often results in under-exposure, it is unsurprising that traditional antimicrobial dosing strategies risk an inadequate therapeutic response [3]. Clinicians face the challenge of tailoring dosing strategies to account for PK variability, aiming to achieve positive patient outcomes.

Therapeutic drug monitoring (TDM) offers a more individualised approach to optimise antimicrobial dosing. The goal is to employ precision dosing that achieves patient-specific antimicrobial exposure targets that give the best probability of cure while minimising toxicity [2]. To date, the use of antimicrobial TDM in critically ill patients has been shown to improve the attainment of therapeutic drug concentrations [4,5], is recommended in consensus guidelines [6–8], and may improve patient outcomes [9,10], however, future work is required to quantify patient outcome benefits and cost-effectiveness.

International surveys have been conducted to measure the translation of antimicrobial optimisation research into clinical practice [11,12]. In 2015, Tabah et al. [11] published an international survey of antibiotic dosing and monitoring in ICUs (ADMIN-ICU 2015), with respondents describing large variations in clinical practice relating to antibiotic dosing, administration, and monitoring. As more evidence for TDM has accumulated over recent years, our group conducted a follow-up to the 2015 survey, a new survey termed 'ADMIN-ICU 2021' [12], which described the incorporation into clinical practice of more evidence-based antibiotic dosing and monitoring strategies used to treat serious infections. From this follow-up survey, we found increased use of vancomycin and beta-lactam loading doses, administration of beta-lactams via prolonged infusions, and increasing utilisation of TDM in clinical practice.

Therefore, using data from the ADMIN-ICU 2021 survey, the aim of this report is to describe access, utilisation, and barriers of antimicrobial TDM in the treatment of adult ICU patients with serious infections.

## 2. Material and methods

An online survey was developed by a panel of international experts based upon relevant literature and expert opinion [6,7,11,13]. The survey recorded respondent demographic details and included multiple choice questions and 5-point Likert scales. It was designed to describe the utilisation and barriers of antimicrobial TDM in critically ill patients, exploring access to pathogen minimum inhibitory concentration (MIC) results, drug assays, and dosing software.

Drug assay access and availability of subsequent results were assessed for vancomycin, voriconazole, linezolid, teicoplanin, and the aminoglycoside and beta-lactam classes. The 2020 Antimicrobial TDM in Critically Ill Adult Patients Position Paper recommended TDM for these agents [6], hence their selection in the survey. We assessed both individual responses and unit responses. A unit response was considered concordant if at least half of the individual responses from the same unit agreed. Non-concordant responses were excluded.

Respondents were presented with a selection of potential TDM barriers and a 5-point Likert scale was used to rate the significance of the barrier. The full text of the survey is presented in eTable 1. The country in which respondents worked was categorised by region and economy according to the World Bank criteria [14]. Ethics approval was granted by the University of Queensland, Human Research Ethics Committee (2020/HE002747).

An open invitation to participate in the online survey (hosted on the REDCap platform), was accessible to respondents between August and December 2021. The invitation was distributed to members of professional societies as listed in the acknowledgements, and via local networks through national coordinators. A reminder email was sent after one and 3 months. A cross-sectional representation of clinicians involved in the treatment of critically ill infections was the target of this survey. No incentive was offered to respondents to complete the 15-min survey.

The data was pulled from REDCap into Microsoft Excel. Investigators (P.W. and J.A.R.) conducted a consensus review of all data entered. Data was excluded from the final analysis when  $\geq 50\%$  of the respondent's answers were missing, when respondents did not certify their response as complete, when duplicate survey submissions existed (only the final submitted survey was included), or when respondents were not formally credentialed health professionals (e.g., unlicensed students).

**Table 1**  
Respondent demographics<sup>a</sup>.

Characteristic	Total	HIC	UMIC	LMIC	LIC
Position	<i>n</i> = 534	<i>n</i> = 288	<i>n</i> = 122	<i>n</i> = 100	<i>n</i> = 24
<b>Physicians</b>	377 (71)	183 (64)	73 (60)	98 (98)	23 (96)
Physician in training (ICU)	69 (13)	14 (5)	27 (22)	18 (18)	10 (42)
Physician in training (ID)	31 (6)	4 (1)	11 (9)	10 (10)	6 (25)
Specialist in intensive care medicine	187 (35)	134 (47)	12 (10)	41 (41)	0 (0)
Specialist in infectious diseases	30 (6)	22 (8)	4 (3)	4 (4)	0 (0)
Other physician	59 (11)	9 (3)	19 (16)	25 (25)	7 (29)
<b>Pharmacists</b>	153 (29)	103 (36)	48 (39)	2 (2)	0 (0)
ICU pharmacist	96 (18)	63 (22)	31 (25)	2 (2)	0 (0)
ID pharmacist	20 (4)	18 (6)	2 (2)	0 (0)	0 (0)
AMS pharmacist	28 (5)	18 (6)	10 (8)	0 (0)	0 (0)
Other pharmacist	9 (2)	4 (1)	5 (4)	0 (0)	0 (0)
<b>Others</b>	4 (1)	2 (0.5)	1 (1)	0 (0)	1 (4)
Experience in ICU	<i>n</i> = 533	<i>n</i> = 288	<i>n</i> = 121	<i>n</i> = 100	<i>n</i> = 24
<5 y	258 (48)	93 (32)	80 (66)	64 (64)	21 (88)
5–10 y	131 (25)	85 (30)	28 (23)	16 (16)	2 (8)
>10 y	144 (27)	110 (38)	13 (11)	20 (20)	1 (4)
Type of hospital	<i>n</i> = 529	<i>n</i> = 288	<i>n</i> = 122	<i>n</i> = 95	<i>n</i> = 24
General	188 (36)	85 (30)	70 (57)	21 (22)	12 (50)
Rural	13 (2)	10 (3)	1 (1)	2 (2)	0 (0)
University	199 (38)	111 (39)	23 (19)	57 (60)	8 (33)
University affiliated	123 (23)	82 (28)	22 (18)	15 (16)	4 (17)
Other	6 (1)	0 (0)	6 (5)	0 (0)	0 (0)
ICU type	<i>n</i> = 528	<i>n</i> = 286	<i>n</i> = 122	<i>n</i> = 96	<i>n</i> = 24
Cardiac	9 (2)	3 (1)	4 (3)	2 (2)	0 (0)
Medical	99 (19)	47 (16)	21 (17)	26 (27)	5 (21)
Medical-surgical	342 (65)	193 (67)	77 (63)	56 (58)	16 (67)
Surgical	48 (9)	20 (7)	17 (14)	9 (9)	2 (8)
Other	30 (6)	23 (8)	3 (2)	3 (3)	1 (4)
Open or closed ICU	<i>n</i> = 532	<i>n</i> = 284	<i>n</i> = 125	<i>n</i> = 99	<i>n</i> = 24
Closed	339 (64)	245 (86)	45 (36)	46 (46)	3 (13)
Open	193 (36)	39 (14)	80 (64)	53 (54)	21 (88)

HIC, high-income country; UMIC, upper-middle-income country; LMIC, Lower-middle-income country; LIC, low-income country; ICU, intensive care unit; ID, infectious diseases; AMS, antimicrobial stewardship; TDM, therapeutic drug monitoring; *n*, number; %, percentage.

<sup>a</sup> eTable 4 presents demographics according to region.

Data was expressed as numbers and/or percentages (categorical variables), and descriptive summary statistics were produced using IBM SPSS Statistics v27. A sub-group analysis was conducted to determine any differences in the availability of MIC or susceptibility test results, assay availability, and barriers to TDM between respondents from a high-income country (HIC) or upper-middle-income country (UMIC) and respondents from a lower-middle-income country (LMIC) or low-income country (LIC). This determination was made using a Chi-square test, and a two-sided *P* value of  $\leq 0.05$  was considered statistically significant.

### 3. Results

#### 3.1. Demographics

Nine hundred and twelve respondents participated in the survey, providing at least one response. eTable 2 presents the exclusion criteria and frequency of exclusions. Five hundred and thirty-eight respondents were included in the study. Most respondents were from an HIC (54%, 288/538), followed by a UMIC (23%, 125/538), with 23% (125/538) from either a LIC or LMIC (see eTable 3). Respondents from 409 hospitals in 292 cities across 45 countries were represented (see eTable 3). Table 1 and eTable 4 present respondent demographics, with 71% physicians and 29% pharmacists; most of which were ICU specialists.

#### 3.2. TDM candidate availability

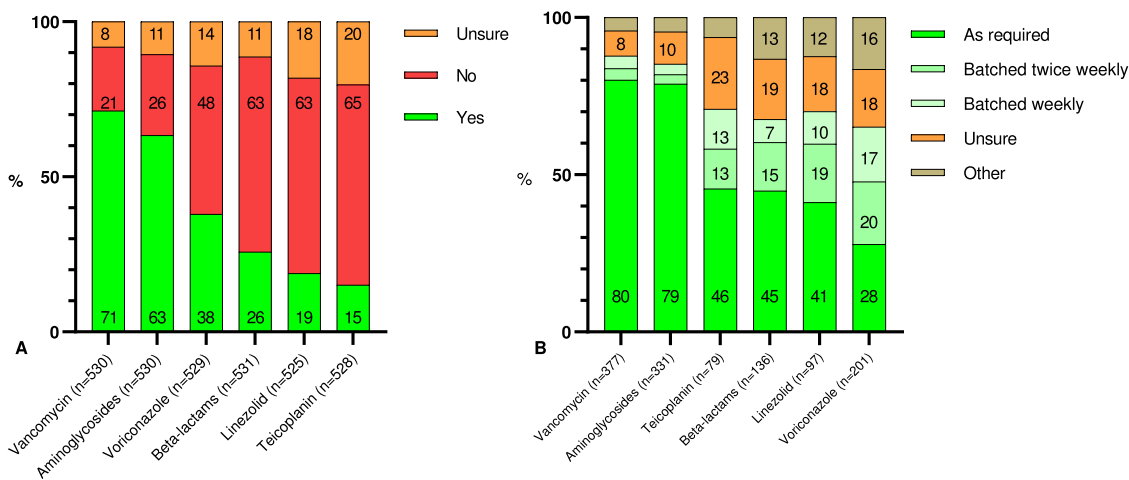
Most respondents had access to vancomycin and aminoglycoside assays (71%, 378/530, and 63%, 336/530, respectively), with only 15% (80/528) having access to a teicoplanin assay (see Fig. 1).

Among respondents who had access to specific drug assays, only vancomycin and aminoglycoside assays were performed as required, with results reported on the same day for most respondents (80%, 302/377, and 79%, 261/331, respectively) (see Fig. 1). Respondents from HICs had greater drug assay access and were more likely to receive timely assay results (see eTable 5). There was a statistically significant increase in the availability of drug assays for most TDM candidates to respondents from an HIC or UMIC, except for linezolid and teicoplanin (see eTable 6). eTable 7 presents these results on a 'unit' level and demonstrated similar results to the responses of individuals.

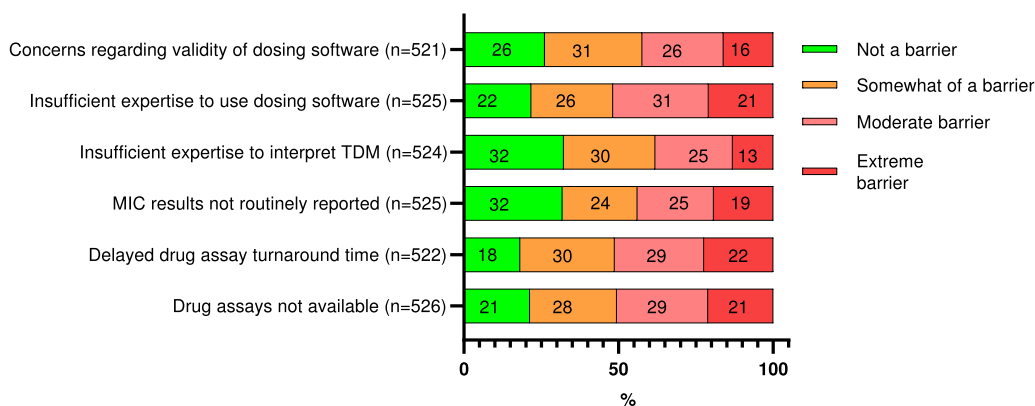
#### 3.3. TDM utilisation, and barriers

In most countries, the ICU physician was primarily responsible for ordering TDM (79%, 403/512) and subsequent dose adjustments (69%, 354/512) (see eTable 8). In HICs, the ICU pharmacist had increased TDM ordering and dose adjustment responsibility compared to lower-income countries. In North America, the ICU Pharmacist was primarily responsible for TDM ordering and dose adjustments (90%, 60/67, and 93%, 62/67, respectively) (see eTable 8).

Numerous barriers to TDM in clinical practice were identified (see Fig. 2 and eTable 9). The most significant barrier (based on 'extreme barrier' ranking) was delayed drug assay turnaround time (22%, 117/522), followed by drug assays not available (21%, 111/526). Conversely, the least significant barrier was insufficient expertise to interpret TDM results (13%, 69/524). Respondents from LMICs and LICs considered all potential barriers to TDM to be more of an issue than respondents from HICs or UMICs. This difference was statistically significant (see eTable 6).



**Figure 1.** TDM drug assay (A) access and (B) results availability<sup>a</sup>. TDM, therapeutic drug monitoring; n, number; %, percentage. <sup>a</sup>eTable 5 presents responses according to region and economy.



**Figure 2.** In your ICU, rate the following in terms of being a barrier to performing TDM ± dosing software<sup>a</sup>. TDM, therapeutic drug monitoring; n, number; %, percentage. <sup>a</sup>eTable 8 presents responses according to region and economy.

### 3.4. Dosing software utilisation, and barriers

Dosing software was rarely used in clinical practice (12%, 62/528). It was most frequently used in East Asia and Pacific regions (16%, 14/90) and in HICs (16%, 45/284) (see eTable 8). Respondents used a wide range of dosing software programs, with specific regions preferring specific programs (see eTable 8). When dosing software was used in clinical practice, it was commonly performed by a Pharmacist (ICU Pharmacist 49%, 28/57, AMS Pharmacist 42%, 24/57), followed by an ICU physician (44%, 25/57), noting that multiple clinicians could be involved in this task (see eTable 8). In total, 78% (411/525) of respondents identified 'insufficient expertise to interpret dosing software results' as a TDM barrier. Furthermore, 74% (385/521) of respondents classed 'concerns regarding the validity of dosing software' as a TDM barrier (see Fig. 2). At least 40% of respondents from East Asia and Pacific, Europe and Central Asia, North America, and HICs were satisfied with the expertise to interpret dosing software results. Additionally, respondents from HICs were least concerned with the validity of dosing software programs (see eTable 9).

### 3.5. MIC access and clinical value

MIC determination methods and reporting frequency available to respondents are presented in eTable 10. MIC results were not routinely reported according to 41% (221/534) of respondents, however, 28% (150/534) had access to the antimicrobial-pathogen

susceptibility or resistance profiles (without the MIC value reported). A total of 33% (174/534) of respondents had all ICU MIC results reported, and 22% (118/534) of respondents had access to MIC results only when requested by the ICU team or infectious diseases physician. Respondents from lower-income countries were least likely to have access to either MIC or susceptibility reports, with 25% of LMICs or LICs having no access as compared to 10% of HICs or UMICs ( $P \leq 0.0001$ ), (see eTable 6).

Most respondents agreed that knowledge of the actual MIC, suspected MIC, and worst-case scenario MIC were valuable for clinical decision-making when aiming for a specific PK-pharmacodynamic target (see eTable 10). The actual MIC was considered the most important MIC descriptor by respondents, with 31% strongly agreeing that this parameter was of clinical value. Most respondents (68%, 358/525) recognised MIC results not routinely reported as a barrier to performing TDM (see eTable 9). This result was more pronounced in respondents from an LMIC or LIC (83%, 99/119) compared to those from an HIC or UMIC (64%, 259/406);  $P \leq 0.0001$ , (see eTable 6).

## 4. Discussion

This international cross-sectional survey reveals significant global insights in the use and challenges of antimicrobial TDM in ICUs from a clinician's perspective. Timely access to drug assays for a selection of TDM candidates was not routinely available and delayed drug assay results were significant barriers to TDM utili-

sation, especially in lower-income countries. Dosing software was rarely used in clinical practice, and concerns regarding the validity of dosing software were identified as a barrier that requires future consideration. MIC results were not routinely accessible.

#### 4.1. TDM barriers and TDM candidate availability

Numerous barriers to TDM utilisation were identified in our study, with delayed drug assay turnaround times being the most significant. This finding aligns with national cross-sectional literature from Australia and France [15,16], although to the best of our knowledge, this is the first international survey exploring TDM barriers in this cohort of patients. Unsurprisingly, TDM barriers were more prominent in lower-income countries.

With the exception of vancomycin and aminoglycosides, we found that most respondents either did not have access to drug assays for the selected antimicrobial TDM candidates, or same-day turnaround was not available. A TDM approach to guide therapy for vancomycin and aminoglycosides is well-established and is routinely recommended in clinical guidelines [6,7]. It was, therefore, unexpected that 21% of respondents did not have the ability to measure vancomycin concentrations, and 26% could not measure aminoglycoside concentrations. The availability of TDM in LMICs and LICs is reduced further, with almost 40% of respondents unable to perform vancomycin or aminoglycoside TDM. Our findings highlight that evidence and guidelines supporting TDM are slow to translate into clinical practice, especially in resource-limited settings. Our results demonstrate the disparity in TDM access on a global level and suggest that equitable access to TDM remains a challenge, with economic and technical barriers likely contributing to this finding. In the short term, the use of other more feasible dosing interventions such as population-specific dosing guidelines could be considered.

#### 4.2. Dosing software utilisation

Evidence supporting a dosing software strategy that includes TDM to guide antimicrobial therapy in patients with serious infections is emerging. Improved vancomycin and beta-lactam target attainment and reduced vancomycin nephrotoxicity have previously been demonstrated [5,17]. However, a recent randomised controlled trial of model-informed dosing of beta-lactam and ciprofloxacin demonstrated no improvement in clinical outcomes, although this study was not able to improve the achievement of target concentrations [18]. Contemporary guidelines for vancomycin and aminoglycoside therapy recommend a dosing software approach [6,7], however, in our study, respondents rarely used dosing software in clinical practice. Drug assay inaccessibility and delayed drug assay turnaround likely contribute to this finding. In addition, dosing software validity and insufficient expertise to interpret dosing software results were identified as barriers. Given the large variability in antimicrobial dosing software characteristics [19], it is not surprising that dosing software interpretation was identified as a barrier in our study. The need for increased dosing software accessibility and training, as well as clinical expertise to utilise dosing software, have recently been identified as key requirements [15].

#### 4.3. MIC results

When performing TDM, knowledge of the pathogen's MIC value or MIC surrogate value is considered valuable, as these parameters form the denominator for the desired PK-pharmacodynamic target (e.g., 100% time above MIC) [20]. In our study, MIC results were not routinely reported and were thus identified as a barrier to performing TDM. Of note, a quarter of respondents from LMICs

and LICs had no access to MIC results or susceptibility reports. Antimicrobial susceptibility testing is a critical component of effective antimicrobial stewardship programs and is likely to minimise the emergence of antimicrobial resistance. This result highlights the international disparity in MIC access, and broader access must be a priority.

In our study, most respondents were in agreement that all MIC data were important for clinical decision-making. This finding suggests that most clinicians are considering the MICs of both the suspected pathogen and that of the worst-case pathogen when dosing empirically. Respondents also value knowing the individual MIC measurement for directed therapy.

There are limitations to our study we would like to declare. First, the electronic survey was voluntary, with no means to measure the response rate. Therefore, response bias may be present, potentially skewing results. Second, generalising the results is difficult given the weighting of global regions represented. To mitigate this limitation, we ensured the survey was distributed widely via professional bodies and national coordinators, with results presented according to region and income. Finally, results are presented on an individual level as opposed to on a 'unit' level which may influence the results presented. To address this, we also examined TDM availability at a 'unit' level, which yielded similar results.

## 5. Conclusions

In this international survey, we observed significant variability of antimicrobial TDM access and utilisation and identified barriers that can inform future efforts to allow more equitable availability. Although an antimicrobial TDM approach is advocated by key clinical guidelines, our results showed that TDM use was limited to a narrow number of drugs and was challenged by economic disparity in clinician access to MIC values and timely drug assay results. Significant barriers to implementing TDM programs were identified, especially in lower-income countries. Efforts to ensure equitable access to affordable essential TDM should be a priority on a global level.

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## Declarations

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**Competing Interests:** None to declare for all authors.

## Appendix

National Coordinators: Alexander Brinkmann, Mahesh Ramanan, Despoina Koulenti, Mohan Gurjar, Helmi Sulaiman, Gentle S. Shrestha, Andrea Cortegiani, Monica Crespo, Lowell Ling, Khalid Abidi, and Peter Schellongowski.

## Supplementary materials

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