Optimizing antimicrobial use: challenges, advances and opportunities

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Abstract | An optimal antimicrobial dose provides enough drug to achieve a clinical response while minimizing toxicity and development of drug resistance. There can be considerable variability in pharmacokinetics, for example, owing to comorbidities or other medications, which affects antimicrobial pharmacodynamics and, thus, treatment success. Although current approaches to antimicrobial dose optimization address fixed variability, better methods to monitor and rapidly adjust antimicrobial dosing are required to understand and react to residual variability that occurs within and between individuals. We review current challenges to the wider implementation of antimicrobial dose optimization and highlight novel solutions, including biosensor-based, real-time therapeutic drug monitoring and computer-controlled, closed-loop control systems. Precision antimicrobial dosing promises to improve patient outcome and is important for antimicrobial stewardship and the prevention of antimicrobial resistance.

Antimicrobial resistance
The development of resistance to the effects of an antimicrobial drug that once was effective against a bacterium, fungus or other microorganism.

Antimicrobial stewardship
An approach to optimize antimicrobial use to ensure optimal therapeutic outcomes while minimizing the harmful consequences of therapy on the individual (toxicity) and the wider population (antimicrobial resistance).

Pharmacokinetics
The movement of a drug into, through and out of the body (what the body does to a drug). Pharmacokinetics can be described by, for example, concentration over time.

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Antimicrobial resistance (AMR) is a global threat to human health and well-being[1]. The complexity of AMR means that a range of different approaches are required to address this problem, including the development of new antimicrobials, better, cheaper and more rapid diagnostics, and novel strategies to make the use of existing drugs more precise.

Improving the precision of current antimicrobial use is crucial. Precision use can involve better selection (start, choice and combination), dosing and duration of antimicrobial therapy. Improving the precision with which antimicrobials are used, also termed antimicrobial stewardship, can lead to better clinical outcomes of infections, reduce the risk of toxicity and reduce the emergence of drug resistance[2–4]. In vitro data demonstrate that optimization of the antimicrobial dose is an important mechanism through which the development of AMR may be slowed, for example, by delivering optimal doses of drug to suppress resistant subpopulations, understanding drug exposures that prevent the emergence of AMR and exploring optimal durations of treatment[5,6]. In addition to affecting patient outcome, suboptimal antimicrobial therapy can have important economic consequences. A focus on optimization of antimicrobial dosing as part of precision prescribing may support the use of less expensive drugs, shorter durations of therapy and reductions in the rate of development of AMR[7–9].

An important aspect of antimicrobial dose optimization is ensuring that the regimen selected is effective and appropriate to treat the infection of the individual patient, while minimizing the risk of toxicity for that individual and minimizing the development of drug resistance. It is possible to address these requirements by optimization of individual antimicrobial pharmacokinetics and pharmacodynamics[10].

In this Review, we summarize the requirements and challenges for the optimization of antimicrobial dosing. We review state-of-the-art technologies under development that may support the delivery of optimized antimicrobial dosing with the aim of providing adequate drug exposure to achieve a clinical response, while minimizing toxicity and the emergence of drug resistance. We highlight the remaining gaps in the implementation of such dosing approaches. This Review is limited to biosensor and computing technologies to support antimicrobial therapeutic drug monitoring (TDM) and dose optimization for the treatment of bacterial infections. The Review will not focus on laboratory-based diagnostics such as mass spectroscopy or point-of-care laboratories, which have been reviewed elsewhere[11–13].

The importance of dose optimization

Antimicrobial pharmacokinetics–pharmacodynamics is influenced by patient, microbial and drug factors[14]. Many factors that influence therapy are difficult to quantify and determine in vivo, such as host immune responses, size of the bacterial inoculum, biofilm formation and hetero-resistance (FIG. 1). However, it is possible to measure and adjust the dose of an antimicrobial drug to optimize the exposure of drug (pharmacokinetics)

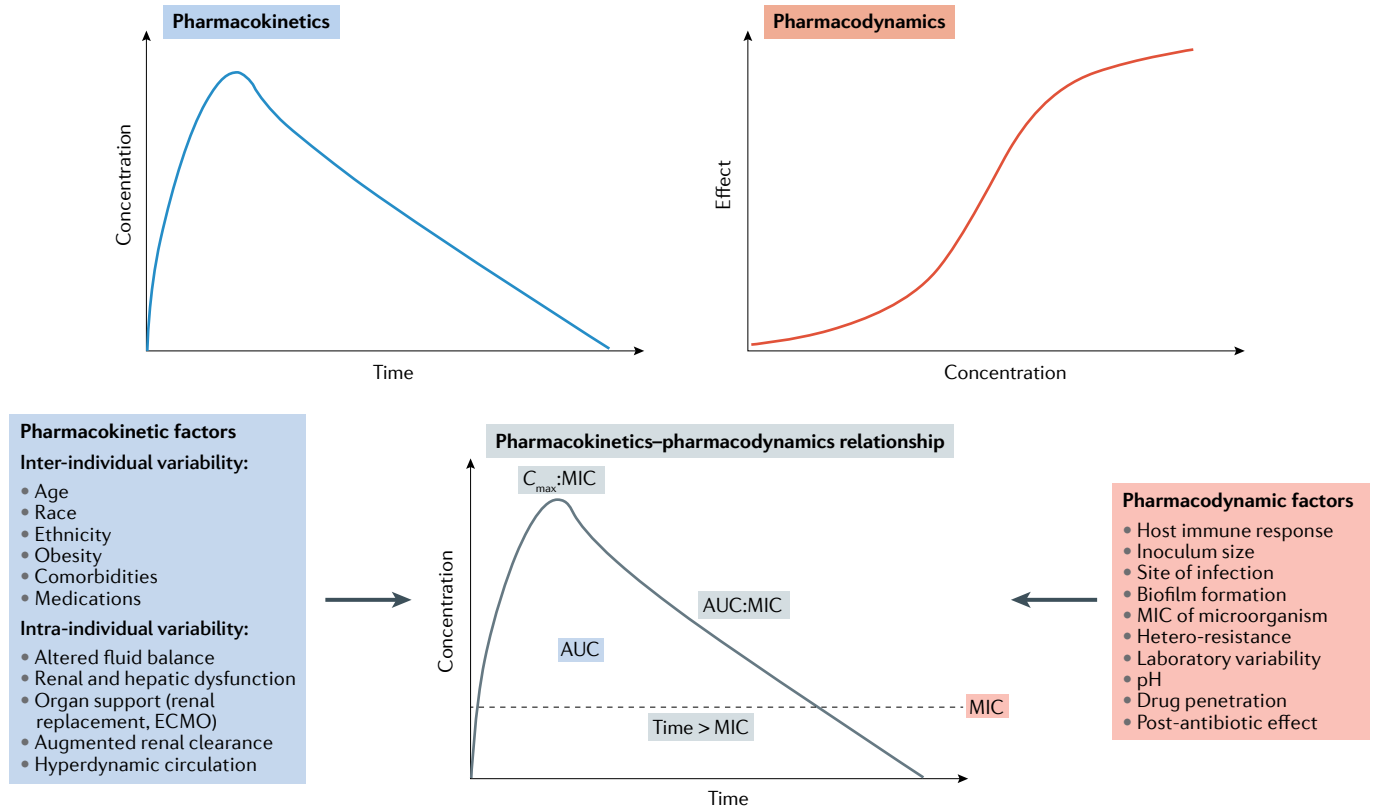

Fig. 1 | **Antimicrobial pharmacokinetics, pharmacodynamics and factors driving variation.** Pharmacokinetics describes the influence of the body on a drug after administration, and can be described by the change in drug concentration over time. Pharmacodynamics describes the effect of the drug on an end target, which for antimicrobials includes treatment of an infection or development of toxicity in host cells, and can be described in terms of the observed effect at changing concentration. To understand the effect of antibiotic exposure (pharmacokinetics) on bacterial killing (pharmacodynamics), antimicrobials can be assigned pharmacokinetic–pharmacodynamic indices. These can be time-dependent such as the time the drug concentration remains above the minimum inhibitory concentration of the microorganism (time > MIC), concentration-dependent such as the maximum concentration of the drug compared with the MIC (C_{max}:MIC) or a mix of both, such as the ratio of the area under the concentration–time curve to the MIC (AUC:MIC). Antimicrobial pharmacokinetics–pharmacodynamics is influenced by factors between individuals (inter-individual variability), factors that change within the individual during the course of treatment (intra-individual variability) and pharmacodynamic factors associated with the host immune response, microbial characteristics and the site of infection. EMCO, extracorporeal membrane oxygenation.

Pharmacodynamics
The relationship between drug concentration and an observed effect (what the drug does to the body).

and, thus, the response of the individual to treatment (pharmacodynamics).

Pharmacokinetic variability. Antimicrobials are generally administered using a one-size-fits-all approach. In reality, antimicrobial pharmacokinetics and pharmacodynamics are highly variable. Antimicrobial pharmacokinetics can vary widely between individuals (inter-individual) and within the same individual (intra-individual) over time. Variability can be defined as explained (fixed) or unexplained (residual). Fixed sources of variability are measurable and predictable. For example, the effect of augmented renal function on the clearance of piperacillin–tazobactam (a combination of β-lactam and β-lactamase inhibitor) in patients who are critically ill resulted in suboptimal drug exposure with usual doses[15,16]. Sources of residual variability are impossible to definitively identify. Whatever the reason for pharmacokinetic variability, it must be quantified, the impact on clinical care must be defined and there must be approaches to mitigate any detrimental effects.

Inter-individual pharmacokinetic variation is well described in certain settings, including critical care, chronic renal disease, obesity and extremes of age[17–21]. Most antimicrobials show pharmacokinetic variation, not only drugs with a narrow therapeutic index. Even within antimicrobial classes, considerable variability is the norm. Monitoring and controlling for this variability is clinically important to optimize outcomes and reduce the harmful consequences of therapy, including toxicity and development of drug resistance (FIG. 1).

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Biofilm
A collection of microorganisms in which the cells stick to each other and/or a surface. The adherent cells are protected by an extracellular matrix of polymeric substances.

Hetero-resistance
Resistance to an antimicrobial occurring in a subset of an otherwise susceptible microbial population.

Therapeutic index
A relative measure of drug safety. Defined as a ratio between the amount of drug that causes toxicity and the amount of drug that leads to a therapeutic effect. A narrow therapeutic index (low ratio) therefore has a small window between therapeutic success and toxicity.

Volume of distribution
A theoretical volume that would be required to contain the total amount of an administered drug at the concentration that is observed in the plasma.

Minimum inhibitory concentration
(MIC). The minimum antimicrobial concentration required to prevent the visible growth of bacteria in vitro. Measurement is performed under standardized conditions.

C-reactive protein
(CRP). An acute-phase response protein produced by the liver in response to inflammation, including that caused by infection.

Galactomannan
A polysaccharide component of the cell wall of certain fungi, such as *Aspergillus* spp.

Breakpoints
Chosen concentrations (milligrams per litre) of antimicrobial that define whether an organism is sensitive or resistant based on the minimum inhibitory concentration. Defined based on the highest drug concentration that can likely be achieved in a patient.

Area under the concentration–time curve
(AUC). The total integrated area under a drug concentration–time curve.

EC_{50}
The concentration of drug that gives a half-maximal response.

For example, for drugs such as vancomycin, a glycopeptide antibiotic that causes nephrotoxicity, TDM can improve clinical outcome and reduce toxicity[22]. In vitro data for levofloxacin, a fluoroquinolone used to treat *Pseudomonas aeruginosa* infections, identified a pharmacokinetic–pharmacodynamic target that can prevent the emergence of resistant subpopulations upon antimicrobial exposure[6]. Delivering optimal doses to achieve pharmacokinetic–pharmacodynamic targets designed to suppress resistance emergence both prevents initial mechanisms of resistance, such as upregulation of efflux pumps, and reduces the frequency of secondary mutational events[6]. Clinical studies have also observed this relationship of reduced emergence of drug resistance when pharmacokinetic–pharmacodynamic targets are achieved for ciprofloxacin and *P. aeruginosa*[23,24]. Achievement of pharmacokinetic–pharmacodynamic targets that consider emergence of resistance may reduce the development of decreased susceptibility and hetero-resistance in many other microorganisms[25]. For drugs with lower risks of toxicity, such as β-lactams, adjustment of dosing in critical care patients is an important factor influencing clinical outcome and development of drug resistance[26–28].

Intra-individual variation in antimicrobial pharmacokinetics is driven by numerous factors during the course of infection, many of which are not immediately obvious. Factors driving intra-individual pharmacokinetic variation include renal dysfunction and augmented renal clearance, fluid shifts owing to inflammatory response and the requirement for organ support, such as renal replacement therapy[17]. For example, in patients who are critically ill receiving linezolid therapy for methicillin-resistant *Staphylococcus aureus*, dose by dose variations have been observed in the volume of distribution, clearance and, thus, plasma and tissue pharmacokinetics[29]. This variation is driven by numerous factors that make determining optimal dosing strategies for individual patients challenging[29].

Pharmacodynamic variability. Optimal antimicrobial pharmacodynamics provides drug exposure that is sufficient to deal with the invading microorganism. Sufficient drug exposure can be assessed in several ways, for example, through determination of the minimum inhibitory concentration (MIC) of the microorganism, using biomarkers such as C-reactive protein (CRP) and galactomannan (in antifungal therapy), the rate of decline of bacterial colony-forming units per millilitre and measures of the host response, such as the white cell count or temperature[30–34].

The MIC is an in vitro measure of the lowest concentration of an antibiotic required to inhibit the visible growth of a microorganism[30]. Interpretation of MIC results may be variable based on different organizational classification of selected breakpoints[35,36]. The challenges of using the MIC to guide individualized dosing include the accuracy of intra-laboratory variation in MIC determination and observed intra-sample variations, which must be accounted for when determining pharmacokinetic–pharmacodynamic targets for the individual patient[30]. Pharmacokinetic–pharmacodynamic indices describe the exposure–response relationship for a specific antimicrobial class. They aim to form a quantitative relationship between drug exposure (pharmacokinetics) and the effect this exposure has on a microorganism (pharmacodynamics). As an in vitro measure, the MIC fails to provide information on in vivo microbial characteristics and host factors, such as immune response[37]. Hetero-resistance in a bacterial population also means that the MIC can only provide an average target concentration, with subpopulations having higher and lower MICs than the average[38,39]. MIC breakpoints also do not take into account the site of infection and drug penetration, biofilm formation, inoculum load and local factors, such as pH[10,14].

In many situations, the MIC is unknown — in particular, when the invading pathogen is not detected or identified, for example during the empirical phase of antimicrobial therapy and in a substantial proportion of cases of sepsis that remain culture-negative throughout the treatment period[40,41]. In vivo measures of antimicrobial pharmacodynamics aim to link drug exposure to the response of a biomarker, such as CRP or galactomannan[31–33]. It has been demonstrated that the area under the concentration–time curve (AUC) of teicoplanin, a glycopeptide antibiotic used for Gram-positive infections, to EC_{50} ratio ($AUC:EC_{50}$) could predict response to therapy in paediatric critical care patients[32]. The teicoplanin AUC was compared with the EC_{50} value, which describes the concentration of drug required to cause a half-maximal response (that is, decline) in CRP, in the individual patient[32]. This was determined using individual Bayesian posterior estimates from a pharmacokinetic–pharmacodynamic model fitted to patient data[32]. The use of CRP to predict the response to glycopeptide therapy has also been explored in adult patients, with the $AUC:EC_{50}$ demonstrating good predictive ability when compared with the traditional AUC:MIC for vancomycin[33]. The pharmacokinetic exposure of voriconazole, a triazole antifungal that is widely used in the treatment of invasive fungal infections, was linked to individual galactomannan–time profiles using the $AUC:EC_{50}$ to predict the outcome of treatment in patients with invasive aspergillosis[31].

Comorbidities and polypharmacy. In addition to individual pharmacokinetic–pharmacodynamic variability, the treatment of patients for infection is becoming ever more complex. Multi-morbidity and polypharmacy are globally prevalent, providing serious challenges to health care[42–44]. In many countries, HIV infection and tuberculosis, as well as their associated opportunistic infections, are prevalent[45], which can increase the risk of polypharmacy substantially[42–44] and are associated with higher risk of adverse events and drug–drug interactions than in patients without these co-infections. These factors may drive residual variation in antimicrobial pharmacokinetics–pharmacodynamics. In some cases, drug–drug interactions may be beneficial to optimize antimicrobial dosing, whereas they may be detrimental in other cases. For example, probenecid, a uricosuric drug commonly used for the treatment of gout, inhibits the clearance of β-lactam antibiotics, increasing

Bayesian posterior estimate
An estimate that enables the inference of a value (for example, drug concentration at a certain time), derived using a prior assumption and a likelihood function, forming a statistical model for observed data.

drug exposure[46,47], which can be used to optimize target attainment in the treatment of central nervous system infections, such as syphilis[48]. Conversely, rifampicin is known to induce cytochrome P450 enzymes in the liver and upregulate *p*-glycoprotein in the intestine, increasing drug metabolism and reducing absorption, respectively[49,50]. This often requires close monitoring of co-administered drugs, such as antiretrovirals, anticancer treatment, cardiac medications and oral contraceptives.

Certain comorbidities are associated with increased risk of infection and unpredictable antimicrobial pharmacokinetics. For example, obesity and malnutrition are important comorbidities in high and low-income settings[51–54]. Obesity is associated with large inter-individual variability and failure to obtain pharmacokinetic–pharmacodynamic targets for a range of antimicrobials including vancomycin, linezolid and β-lactams[55–57]. Immunosuppressive therapy is an important comorbidity when considering antimicrobial dose optimization. Not only do patients with immunosuppression, such as those receiving chemotherapy for solid organ or haematological malignancy, tend to have highly variable pharmacokinetics, but they are also at risk of substantial drug–drug interactions and may require different pharmacokinetic–pharmacodynamic targets compared with individuals who are immune-competent[58]. These factors can make dose optimization challenging using routine antimicrobial regimes.

Impact of suboptimal dosing. To describe the relationship between exposure and response, pharmacokinetic–pharmacodynamic indices have been determined for most antimicrobial classes[10] (TABLE 1). Three targets are commonly applied. Drugs, such as β-lactams, display time-dependent mechanisms of bacterial killing. The time that the free serum concentration of drug spends above the MIC of the target organism ($fT > MIC$) has been demonstrated to be the optimal target for β-lactams[10]. In general, spending at least 40% of the dosing interval above the MIC of the microorganism (40% $fT > MIC$) is associated with better outcomes for patients[27,59,60]. Drugs such as aminoglycosides (for example, amikacin) are associated with concentration-dependent killing. For concentration-dependent killing, the ratio of the maximum concentration of the drug compared with the MIC is the relevant index[10,59,60]. Other drugs such as vancomycin demonstrate concentration-dependent and time-dependent killing[10,59,60]. The AUC:MIC is the optimal pharmacokinetic–pharmacodynamic index for these agents. For example, vancomycin success has been associated with AUC:MIC > 400 mg h l^{-1} for many Gram-positive infections[10,59,60].

A better understanding of drug exposure within the individual can predict toxicity. For example, a vancomycin AUC greater than 700 mg h l^{-1} has been associated with increased risk of nephrotoxicity[22]. Linezolid, an oxazolidinone with activity against Gram-positive bacteria, is associated with numerous exposure-related toxicities, including thrombocytopenia and hyperlactataemia. These effects can be reduced through TDM and dose adjustment to AUC or minimum drug concentration targets[61]. Understanding and characterizing exposure-related toxicity can help guide the upper limits of dosing and support decisions on the appropriateness of initiating treatment when combined with targets for efficacy and the emergence of drug resistance.

The development of drug resistance during treatment is closely linked to antimicrobial pharmacokinetics–pharmacodynamics[5,6]. Approaches to suppress resistance differ from those that focus on optimal treatment outcomes or avoiding toxicity. Therefore, different antimicrobial pharmacokinetic–pharmacodynamic targets may be required if we wish to achieve both therapeutic success and suppression of drug resistance during treatment[5,6]. The emergence of resistant mutants within a bacterial population can be thought of as in 'inverted U', with low drug exposure having little selective pressure and only limited amplification of resistance in a bacterial population. As drug exposure increases, so does the amplification of drug resistance in the population. Once a sufficient exposure of drug is obtained, resistant mutants are suppressed[5,6]. This concept builds on traditional views of the mutant prevention concentration. The mutant prevention concentration describes the minimum concentration of an antimicrobial required to prevent the growth of resistant mutants under standardized in vitro conditions[62]. This concept has guided recommendations for the dosing of β-lactam antibiotics at higher targets of $fT > 100\%$ up to $fT > 4$ to $6 \times 100\%$ MIC to prevent the emergence of drug resistance, particularly in critical care patients[63,64]. These observations have been supported by clinical data that demonstrate that higher drug exposure than is currently recommended may be required to suppress the emergence of drug-resistant populations during the treatment of Gram-negative infections[65]. One study examined the emergence of drug resistance during treatment of lower respiratory tract infections in patients who are critically ill receiving one of five antimicrobial regimes[23].

Table 1 | **Pharmacokinetic and pharmacodynamic targets for antimicrobials**

Antimicrobial	Time above minimum inhibitory concentration ($T > MIC$)	Ratio of maximum concentration to minimum inhibitory concentration (C_{max}:MIC)	Ratio of area under the concentration–curve to minimum inhibitory concentration (AUC:MIC)
β-Lactams	✓	–	–
Aminoglycosides	–	✓	–
Glycopeptides	–	–	✓
Fluoroquinolones	–	✓	✓
Oxazolidinones	✓	–	✓
Glycylcycline	–	–	✓
Lipopeptide	–	✓	✓
Polymyxins	–	–	✓
Triazoles	–	–	✓
Echinocandines	–	✓	✓
Polyene	–	✓	–

Table 2 | **Approaches for antimicrobial optimization**

Approach	Currently applied	Targets PK–PD indices[a]	Delivery of individualized dosing	Addresses fixed variables	Addresses residual variables	Evidence of improved clinical outcomes	Evidence of impact on antimicrobial resistance	Evidence of cost saving
Variable (e.g. weight or clearance)	Routine practice[b]	Yes[c]	Population-based adjustment[d]	Single variables[d]	No	Yes[c]	Unknown	Yes[c]
Nomogram	Routine practice[b]	Yes[c]	Population-based adjustment[d]	Single variables[c]	No	Yes[c]	No	No
Therapeutic drug monitoring	Narrow therapeutic index drugs (focus on toxicity)[c]	Yes[c]	Population-based adjustment[d]	Yes[b]	Partially[d]	Yes[b]	Yes[c]	Yes[b]
Advanced therapeutic drug monitoring	Specialist centre[c]	Yes[b]	Population or individualized[c]	Yes[b]	Yes[b]	Yes[b]	To be determined	Yes[b]
Dose optimization software	Specialist centre[c]	Yes[b]	Individualized[c]	Yes[b]	No	Yes[b]	To be determined	Yes[b]
Invasive biosensors	Animal models[d]	Yes (artificial targets)[c]	Individualized[c]	Yes[b]	Yes[b]	To be determined	To be determined	To be determined
Minimally invasive biosensors	Studies in healthy volunteers[d]	To be determined	Individualized[c]	Yes[b]	Yes[b]	To be determined	To be determined	To be determined
Closed-loop control systems	In silico and/or animal models[d]	Yes[b]	Individualized[c]	Yes[b]	Yes[b]	To be determined	To be determined	To be determined
Artificial intelligence	No[d]	To be determined	To be determined	Yes[b]	To be determined	To be determined	To be determined	To be determined

If no evidence level is indicated, it remains to be determined or is unknown. PK–PD pharmacokinetic–pharmacodynamic. [a]Includes therapeutic or toxicity targets. [b]Good evidence. [c]Some evidence. [d]Little evidence.

Across all antimicrobials studied, higher antimicrobial exposure, determined by estimation of the AUC:MIC, was associated with a significant reduction in the emergence of drug resistance during the study period[23]. However, the balance between adequate exposure and toxicity must be considered. Obtaining optimal exposure when there is risk of toxicity may be achieved through combination therapy instead of dose escalation of a single antimicrobial drug[5,6].

The wider impact of antimicrobial drug exposure on the microbiome and the development of AMR also requires consideration. Antimicrobial exposure is known to drive substantial, and sometimes long-lasting, changes in the microbiome[66,67]. This includes the emergence of drug-resistant strains. Emerging in vitro and preclinical evidence supports the importance of dose optimization in reducing the impact of antimicrobial therapy on the microbiome[68,69], including directly suppressing the selection of resistance mutants, but also indirectly, through narrow-spectrum antimicrobials and shortening durations of antimicrobial exposure. Optimal selection of antimicrobial dosing will be an important factor in limiting the impact of therapy on the microbiome.

Current approaches and barriers

Several approaches to antimicrobial dose optimization are currently in use (TABLE 2). One common method is a pharmacokinetic dosing nomogram[70–73], which is developed from pharmacokinetic models for the drug in question. Nomograms describe the effect of a covariate, such as weight, on achieving a drug exposure target (for example, concentration)[74]. For example, one study reported the development of a dosing nomogram to guide the dosing of continuous infusion of meropenem in patients with variable renal function[74]. The use of the nomogram successfully achieved optimal pharmacokinetic–pharmacodynamic targets (set at 8 mg l^{-1}, which is four times the break-point MIC)[74]. Dosing nomograms have been developed and implemented for a wide range of antimicrobials, including β-lactams, glycopeptides and aminoglycosides delivered in both continuous and intermittent dosing regimens[70–74]. The benefits of nomograms are that they are simple, can be combined with routine TDM and are an easy way of translating important variables determined through population pharmacokinetic modelling into clinical practice. However, nomograms use population-level estimates for dose optimization based on single variables. The covariate that nomograms rely on, such as weight or height, is not always accurately available in practice[75]. Nomograms also do not account for residual variability. Therefore, nomograms do not provide a truly individualized approach to dose optimization.

For individualized dose adjustment of antimicrobials, we rely on the ability to monitor antimicrobial concentrations in the individual patient using TDM. TDM routinely consists of taking a single time-point sample of plasma, normally before a dose is given (a trough concentration). The trough concentration can then guide subsequent doses. For vancomycin, routine TDM is

Nomogram
A diagram that represents the relationship between three or more variables, designed so that one variable can be estimated, for example, by drawing a straight line intersecting the other variables at measured values.

often used for dose optimization in acute care[76]. A target range for trough drug concentrations is set (either 10–15 mg l^{-1} or 15–20 mg l^{-1}) and then dose adjustments of ±500 mg are made based on whether the level achieved is above or below the defined target range[76]. This method of dose adjustment aims to ensure that AUC:MIC targets are achieved for vancomycin, while avoiding doses that can potentially lead to renal toxicity[76].

Current TDM approaches have several barriers to wider adoption in clinical practice (FIG. 2). Barriers include ensuring the accurate recording of drug dosing and sampling times, concerns about drug degradation following sampling or freeze–thawing, the requirement to have validated assays available to perform drug monitoring, the potential need to measure unbound plasma drug, delays in returning results due to laboratory facilities being off site and difficulty interpreting delayed results when there is considerable intra-individual pharmacokinetic variability. Moreover, when TDM is implemented, dose adjustments are commonly made by rounding up and down (for example, ±500 mg increments), meaning that truly individualized therapy is not delivered. Single time-point trough concentrations are a useful clinical measurement, but may not always correlate with more relevant measures of drug exposure, such as AUC[22]. The application of pharmacokinetic–pharmacodynamic target-guided dosing with the support of dosing software helped to reduce nephrotoxicity, shorten the length of therapy and help improve TDM in patients dosed using either routine TDM or AUC-targeted approaches[77].

Advanced TDM, including AUC-targeted approaches, requires multiple plasma samples (≥2 samples) to be taken during the dosing interval. This approach is often supported by the use of dose optimization software. Dose optimization software has been extensively reviewed elsewhere[78,79]. A common approach involves Bayesian forecasting, which uses individual patient data and a model-derived population prior probability to estimate individual pharmacokinetic parameters. These individual parameters are then used to define dose adjustments, in order to ensure optimal pharmacokinetic–pharmacodynamic targets are achieved[78,79]. To support advanced TDM, near-patient mass spectroscopy and newer optical sensing techniques, such as surface-enhanced Raman spectroscopy, have been used to improve turnaround times for sample analysis[80]. Despite the potential benefits of Bayesian forecasting and advanced TDM, there are numerous challenges and potential limitations. Software can be difficult to use or requires technical skill to interpret. Many of the population pharmacokinetic models used in dose optimization software have been developed based on small, targeted populations and are not validated for large, diverse groups. Finally, although dose optimization software provides recommendations for single antimicrobials, it often does not take into consideration drug–drug interactions, patient comorbidities and combination therapies.

An additional challenge to the wider adoption of antimicrobial optimization is the failure to incorporate optimization strategies into regulatory approval and licensing for current and new antimicrobials. Despite evidence for better outcomes, reduced toxicity and potential reductions in the emergence of drug resistance when dose optimization is applied, arguments for dose adjustment are usually not presented to regulatory authorities. Therefore, most dose adjustment is 'off-licence'. For drugs that are licensed, there is little appetite to pursue new authorizations and approvals. For new drugs undergoing licensing approval, agreement is still required on frameworks to address this challenge.

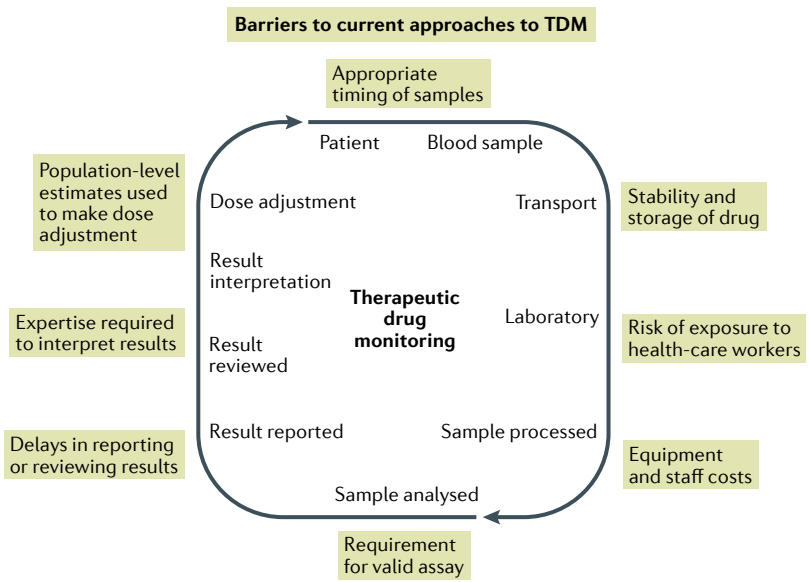

Fig. 2 | **Barriers to implementation of therapeutic drug monitoring of antimicrobials.** The process of therapeutic drug monitoring (TDM) and current barriers to wider implementation and adoption in clinical practice. TDM is a complex process that requires appropriate timing of sample taking, specimen transport to a laboratory, processing and then analysis using approaches such as high-performance liquid chromatography. The results of analysis must then be reported, reviewed by the clinician and interpreted in the clinical context. Currently, dose adjustments will normally be made based on population-level data, meaning that truly individualized dose adjustments are not performed. Each step in the process has potential barriers to the wider implementation of TDM in clinical practice. Major barriers include the few commercially available assays for antimicrobials, the inability to routinely analyse the concentration of unbound antimicrobials, delays in reporting diminishing the clinical usefulness of results and a paucity of expertise to interpret results.

Technological solutions

A role for biosensors in drug monitoring. The application of biosensor technology to support advances in TDM, and thus dose optimization, offers potential solutions to some of the hurdles to implementation. Biosensors provide a method for detecting and quantifying a substrate or analyte. This occurs typically in a continuous fashion in situ or ex vivo using a minimally pretreated biological fluid. Biosensors have been reviewed extensively for their use in medicine, agriculture and the environment[81–85]. They often can be miniaturized, facilitating the development of portable, easy to use, point-of-care devices that do not require expensive analytical machinery, laboratories or technical ability to operate[81,82]. This means that biosensors can be applied to support TDM as point-of-care, single time-point assays or as part of devices developed to facilitate real-time antimicrobial monitoring[37].

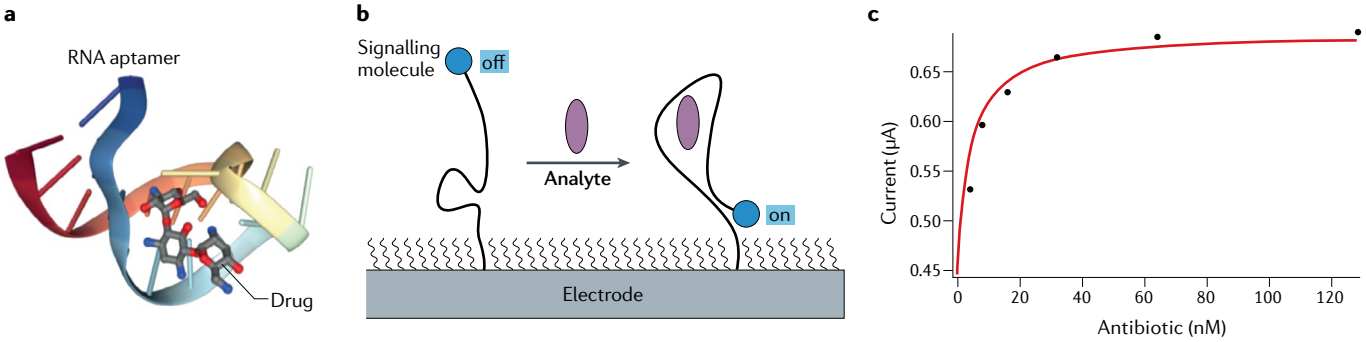

Fig. 3 | **Aptamer-based antimicrobial detection.** Several different methods can be used to detect antimicrobials in biosensors. **a** | For example, binding of the target antibiotic induces a conformational change in the structure of an RNA aptamer. **b** | If the aptamer is fixed to an electrode at one end and labelled with a signalling molecule, such as methylene blue, at the other end, this conformational change can be detected as a change in signal across the electrode. **c** | The amount of change in a signal can be calibrated to the concentration of drug, with increasing concentration of antibiotic (nanomolar) leading to a non-linear increase in current across the electrode.

Electrochemical biosensors convert a biological response into a quantifiable and processable signal[83–85]. They can be applied to a large variety of samples, including body fluids, cells, foods and environmental material[83–85]. Methods of molecular recognition vary but can be classified into two broad categories depending on the nature of the interaction between the recognition molecule and the substrate: biocatalytic sensors driven by enzymatic reactions[86], and bio-affinity sensors using aptamer or antibody-based sensing that involve binding of the receptor and substrate[83,87].

Electrochemical biosensors for the detection of antimicrobials in the environment, agriculture and humans have been reported[37,88,89] using aptamer, antibody-linked and enzyme-based methods of molecular recognition[90–92]. A major advance in biosensor technology has been the development of aptamer-based biosensors. Aptamers are nucleic acid sequences that are highly specific for a target molecule. Aptamer-based biosensors for antimicrobial monitoring have been developed for a wide range of drugs and have been extensively reviewed[88,90,93,94]. They are engineered using an in vitro selection process called systematic evolution of ligands by exponential enrichment (SELEX). They have a high sensitivity for detection of molecules in the range of picomoles[90]. On target binding, a conformational change in the structure of the aptamer occurs (FIG. 3), which can be detected through attachment of a signalling molecule (for example, methylene blue) to the aptamer. Upon substrate binding to the aptamer there is a conformational change that causes a change in rate of oxidation–reduction occurring at the sensor interface (redox reaction).

Real-time drug monitoring. Real-time monitoring can help response to residual antimicrobial pharmacokinetic variability and facilitate optimized dosing. Real-time antimicrobial sensing requires the use of sensor devices directly in vivo, which presents a range of technical challenges. These challenges are substantial compared with the development of point-of-care, near-patient tests[81,95]. Although the challenges of sensor implantation are broad, many arise from the foreign body responses to the sensor[81,95,96].

There is no 'magic bullet' for overcoming all of these challenges, but knowledge is increasing on issues such as material selection[96], electrode materials[96] and the characterization of adsorbed biofilms[97,98]. There have been several recent reviews surveying these challenges and potential technological solutions[99–101]. Although biosensor measurements in vivo are undoubtedly difficult, it is important to note that none of the current techniques is completely non-invasive. For example, some fluorescent indicators that are described as non-invasive methods of biological detection can function as drugs and inhibit Na^+/K^+-ATPase[102].

The use of a biosensor in vivo exposes the sensor to contamination and biofouling, electrical interference and mechanical artefacts, as well as potentially low patient acceptance of devices[81,95,103–106]. Continuous or almost continuous measurement with little or no sample preparation can offer important biological or clinical information, as recently shown for luteinizing hormone oscillations, for which biosensors can offer an economically viable route to obtain relevant data[107]. For antimicrobial monitoring, several approaches are currently being explored. The two most advanced approaches are invasive monitoring directly in the bloodstream and minimally invasive approaches through wearable sensors, such as microneedle-based technologies[92,108–111].

A proof of concept for invasive monitoring of aminoglycoside concentrations has been shown in awake rats with an aptamer-based biosensor that was inserted into the central venous system[92,108]. The sensors provided rapid, real-time monitoring of kanamycin, an aminoglycoside antibiotic, with high sensitivity and specificity[92,108]. However, the authors reported challenges of blood biofouling, requiring development of a filter that protected the sensor. There are other potential limitations to central venous antibiotic biosensing that must be considered, including the need for insertion of a central venous catheter, which in humans would limit use of this device to critical care.

An alternative approach to real-time antimicrobial monitoring is microneedle-based, wearable technology[109–111] (FIG. 4). As foreign body responses are the cause

Aptamer
An oligonucleotide or peptide molecule that is selected to bind to a specific target molecule.

Square wave voltammetry
An electrochemical technique that is a type of linear potential sweep voltammetry, using combined square wave and staircase potentials applied to a stationary electrode.

Chronoamperometry
An electrochemical technique that involves stepping the potential of an electrode. The step in potential results in a current that can be monitored as a function of time.

of most in vivo measurement problems, implantation in the skin, which is less reactive, offers important advantages. Interstitial fluid (ISF) has a similar composition to plasma regarding small molecules and a surprising number of larger peptides and proteins, but albumin (a significant cause of sensor failure) is ~25% of the plasma concentration[112,113]. The absence of blood vessels further reduces sensor fouling, reduces risk of complications, such as infection or bleeding, and improves patient acceptability. Such technologies have the potential to overcome many of the barriers to antimicrobial TDM (see above and FIG. 2).

In humans, solid microneedle array biosensors that enzymatically detect penicillin provided accurate measurements of ISF penicillin concentration in real time[111]. Measuring in ISF bypasses the challenges that central venous access presents and opens the technology to a range of clinical scenarios, including outpatient clinics and paediatrics. However, potential limitations for this technology include the inhibition of the sensor by β-lactamase inhibitors and the need for broader characterization of ISF pharmacokinetics within different compartments beyond those that can currently be measured[109–111]. Linking real-time drug monitoring to automatic control of antimicrobial dosing (closed-loop control) opens up a range of potential clinical applications, including supporting the wider use of continuous infusions and the ability to individualize the timing and delivery of antimicrobials to obtain ideal pharmacokinetic–pharmacodynamic targets.

Additionally, although current enzymatic sensors need to be calibrated individually, microneedles can be used as a base for several alternative technologies, including aptamers[114], which opens the possibility for numerous calibration-free methods such as square wave voltammetry[115] or chronoamperometry[114].

With the development of such technologies and generation of further clinical evidence, numerous potential regulatory and financial barriers remain to be addressed. First, optimal pharmacokinetic–pharmacodynamic targets for dose optimization must be defined, including the incorporation of emergence of drug resistance into accepted targets. Second, clinical trial data must include both efficacy and economic benefit. Third, the implementation and licensing of these technologies must be directly linked to their intended antimicrobial targets, which will require support from industry and regulatory authorities and demonstration of the economic benefit of prolonging the use of antimicrobial therapies that they are designed to optimize.

Closed-loop control. Closed-loop control systems are used for a range of clinical applications, including blood glucose control of patients with diabetes mellitus through automated insulin delivery[116], control of anaesthesia during operation[117] and the treatment of refractory epilepsy[118]. Continuous biosensing linked to closed-loop control systems has the potential to deliver truly individualized antimicrobial therapy[37,119]. Closed-loop systems for automated drug delivery (FIG. 5) work on the principle of feedback, in which a target signal (for example, target drug concentration or pharmacokinetic–pharmacodynamic target) is compared with a real-time measurement (for example, determined through biosensing). The difference between these two readings is used to generate a corrective control action (for example, increase or decrease in the rate of drug delivery from an infusion pump) to reduce the difference between the current measurement and the target value[119,120].

Three closed-loop control techniques that have been successfully applied to automated drug delivery may have a role in automated continuous antimicrobial therapy: proportional–integral–derivative (PID) control[121], model predictive control (MPC)[122] and reinforcement learning[123]. If the feedback and/or control action are intermittent dosing (for example, a dose every 6 h), another

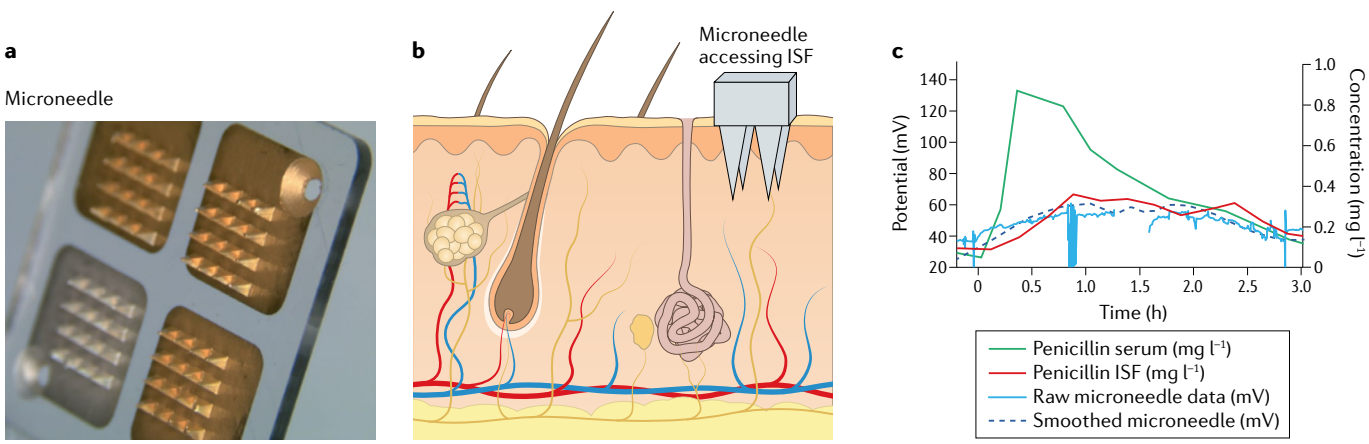

Fig. 4 | **Microneedle-based biosensors for real-time drug monitoring in humans. a** | Biosensor contains microneedles attached to a base. **b** | Microneedles penetrate the epidermis to access interstitial fluid (ISF) of the skin. This approach has numerous advantages including the presence of reduced concentration of albumin compared with serum (that can contribute to biofouling of sensors), no blood vessels and no nerve endings in this layer of the skin. **c** | Comparison of unbound penicillin concentration in serum (green) and corresponding ISF penicillin concentration (red) from a single healthy volunteer after a dose of 500 mg penicillin V. The individual also wore a microneedle biosensor with the raw, real-time output (millivolts) from the individual shown in light blue. The measurement can then be smoothed (dark blue dash) to remove noise from the read-out. Calibration of the microneedle data to ISF drug concentration can then be performed, showing good correlation in outputs. Part **a** reproduced from REF.[111], CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

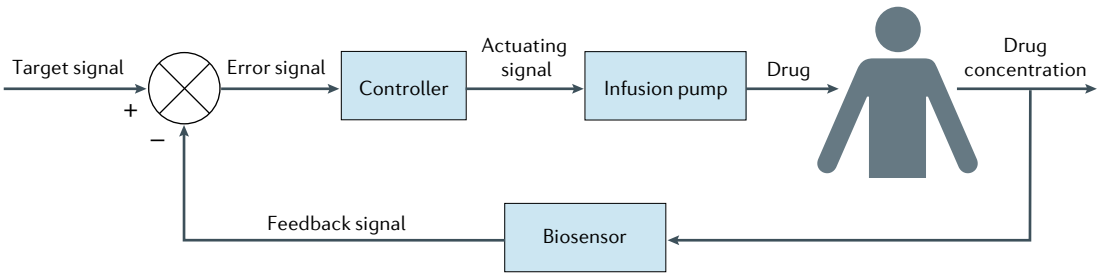

Fig. 5 | **Closed-loop control for automated, precision drug delivery.** Automated, precision drug delivery can be achieved with a closed-loop control system that incorporates a biosensor, a feedback controller and an infusion pump for drug delivery to the patient. Biosensor provides real-time in vivo measurements of the drug concentration in the patient, which is then compared with a predefined target (set point) to produce an error signal that is fed to the feedback controller. The feedback controller computes a corrective action to reduce the error signal and sends an actuating signal to the infusion pump, which delivers the corresponding drug dose to the patient.

type of controller may be applied: iterative learning control, repetitive control and run-to-run control[122].

The PID controller is by far the most popular controller in industrial applications and is often favoured given its simple implementation and effectiveness. PID control has already been demonstrated in silico and in awake rats to be able to deliver antibiotics with a narrow therapeutic window at predetermined concentrations[121,124].

In contrast to PID control, MPC has a built-in predictive ability owing to its model-based nature, which means that it can predict the effect of changes made to drug delivery on future target attainment and act upon them. This feature can be useful when dealing with delays in the sensing of biomarkers and drug delivery. Furthermore, MPC can deal with multiple input and output variables (for example, sensing multiple molecules and delivering multiple antibiotics), handle constraints (for example, drug infusion constraints) and better cope with potential non-linearities of system dynamics than more traditional methods, such as PID control. MPC is currently one of the preferred choices for automatic insulin delivery in diabetes mellitus and is commercially available.

The artificial intelligence technique of reinforcement learning sequentially interacts with its environment, and receives rewards for performing correctly and penalties for performing incorrectly. Reinforcement learning is particularly useful when controlling systems in which rewards and penalties have a substantial delay and it is difficult to obtain a reliable model of the system to be controlled. Reinforcement learning has already been applied for drug delivery in different healthcare settings, such as cancer therapy dosing and control of blood glucose in diabetes mellitus[125,126].

Iterative learning control, repetitive control and run-to-run control have an important role in controlling repetitive processes such as automated batch production in the chemical and semiconductor industries. In medicine, these techniques have been successfully applied for insulin delivery in diabetes mellitus[127,128]. Their application to antimicrobial dosing is still at the proof of concept stage, but they have great potential to support intermittent dosing, including with oral antimicrobials using traditional TDM or continuous or intermittent biosensor-based sensing. In the case of precision drug delivery, these techniques attempt to improve pharmacokinetic–pharmacodynamic target attainment by adjusting the dose based on the deviation of observed drug exposure after past doses[127]. In many cases, the optimal pharmacokinetic–pharmacodynamic index and target value still require exploration and characterization.

Artificial intelligence and decision support systems. So far, decision support for optimization of antimicrobial regimens has focused predominantly on implementation of Bayesian forecasting and mobile applications containing traditional dose optimization software[78,79,129]. To promote the wider adoption of optimized therapy, future approaches must focus on greater integration and connectivity with other aspects, such as diagnostics, electronic health records and surveillance systems[130]. With advances in artificial intelligence, connected data may be rapidly used to support real-time decision-making for individualized treatment[131–133]. Artificial intelligence has been applied to optimization of insulin delivery in diabetes[128], and closed-loop control techniques, such as reinforcement learning, have been demonstrated to support individualized therapy[134]. Future work must explore connecting novel tools for optimization of antimicrobial dosing to wider decision support for antimicrobial therapy, which requires integration with electronic health records and other aspects of decision support for precision antimicrobial therapy. Integration will increase adoption and provide individualized decision support at different points of antimicrobial management[135]. For example, artificial intelligence systems that support personalized antimicrobial selection have been developed to incorporate dose optimization packages for individual drugs[132].

A major question for antimicrobial dose optimization is whether data generated by individual institutions and networks can be used for wider dosing recommendations in the population. With large variation in practice and reporting, improved curation and analysis of such data are required. Artificial intelligence may provide a mechanism to facilitate this, for example, by analysing whether pooled population data can be applied to individualized dosing when TDM and biosensing technologies are not available in an area or data are lacking for the

Artificial intelligence
The theory and development of computer systems that can perform tasks that normally require human intelligence.

population in question. Through the pooling of individual data in large artificially curated data sets, the inference of optimal treatment strategies for the individual within this population may be possible in the future.

Concluding remarks

Optimized antimicrobial dosing may improve patient outcomes, including reduced drug-related toxicity, and help maintain antimicrobial efficacy in the face of AMR. With increasing rates of AMR and complex infections in comorbid patients, state-of-the-art technologies — including real-time biosensing, closed-loop control and artificial intelligence-driven decision support tools — have the potential to address current barriers and support wider implementation of precision antimicrobial dosing. Data generated by such technologies may further support determination of optimal treatment recommendations, even in areas in which application of such technologies remains challenging. Future work must focus on addressing current barriers to implementation of optimized antimicrobial use and support greater connectivity with other developments in the field of antimicrobial prescribing.

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