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Challenges for global antibiotic regimen planning and establishing antimicrobial resistance targets: implications for the WHO Essential Medicines List and AWaRe antibiotic book dosing

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SUMMARY The World Health Organisation's 2022 AWaRe Book provides guidance for the use of 39 antibiotics to treat 35 infections in primary healthcare and hospital facilities. We review the evidence underpinning suggested dosing regimens. Few (n = 18) population pharmacokinetic studies exist for key oral AWaRe antibiotics, largely conducted in homogenous and unrepresentative populations hindering robust estimates of drug exposures. Databases of minimum inhibitory concentration distributions are limited, especially for community pathogen-antibiotic combinations. Minimum inhibitory concentration data sources are not routinely reported and lack regional diversity and community representation. Of studies defining a pharmacodynamic target for ß-lactams (n = 80), 42 (52.5%) differed from traditionally accepted 30%–50% time above minimum inhibitory concentration targets. Heterogeneity in model systems and pharmacodynamic endpoints is common, and models generally use intravenous ß-lactams. One-size-fits-all pharmacodynamic targets are used for regimen planning despite complexity in drug-pathogen-disease combinations. We present solutions to enable the development of global evidence-based antibiotic dosing guidance that

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provides adequate treatment in the context of the increasing prevalence of antimicrobial resistance and, moreover, minimizes the emergence of resistance.

KEYWORDS antimicrobial pharmacodynamics, population pharmacokinetics, pharmacodynamic targets, global health, antimicrobial resistance, WHO

INTRODUCTION

Antimicrobial resistance (AMR) is a major threat to global health—4.95 million deaths worldwide were associated with bacterial AMR in 2019 (1). The World Health Organisation (WHO) introduced the AWaRe antibiotic classification into the Essential Medicines List (EML) in 2017 (2). AWaRe divides antibiotics into Access, Watch, and Reserve groups based on their propensity to generate AMR. "Access" antibiotics should be readily available to treat a wide range of clinical infections. "Watch" antibiotics are more likely to select for resistance, and their use should be discouraged unless clearly clinically indicated. "Reserve" antibiotics are important/novel classes and/or combinations indicated only to treat multidrug-resistant (MDR) infections (2).

The AWaRe Book (December 2022) (3) provides advice on the optimal use of the antibiotics on the EML (39 on the 2021 EML) (4), providing recommendations for the first and second choice antibiotic regimens for around 35 clinical infections, including guidance on the dose and duration. There is a strong focus on primary healthcare (PHC), which accounts for over 90% of global antibiotic use (3, 5). Dosing recommendations are based on existing WHO and regional guidance, literature evidence, and expert opinion (3). All of the oral AWaRe antibiotics on the EML are off patent older generic antibiotics, and dosing strategies for these oral agents vary globally (6–8).

AMR has multiple definitions (e.g., mechanistic, laboratory, clinical)—however, at its core, it refers to a situation where antibiotics are not optimally clinically effective. Modern pharmacodynamics provides a framework for understanding and quantifying AMR. At the center of this construct is the interplay of drug exposure (i.e., dose and schedule of an antibiotic), some measure of potency of an antibiotic for its microbiological target (invariably the minimum inhibitory concentration, MIC) and the magnitude of drug exposure relative to MIC that is required to secure a favorable therapeutic response for any given disease (pharmacodynamic target). Through systematic and database reviews, we examine the evidence that underpins current AWaRe Book PHC antibiotic dosing guidance and consider approaches to ensure future global recommendations are more evidence-based and robust.

KEY CONCEPTS FOR PK-PD AND AMR

Defining the impact of AMR on pharmacodynamics: the "triple lock"

Modern pharmacodynamic theory defines AMR as resulting from insufficient drug exposure relative to the MIC of the invading pathogen. The response to an antibiotic (and by corollary the probability of resistance) is determined by the interplay of regimen, MIC, and pharmacodynamic target. We have developed a new term for the interplay of these factors—the triple lock, which is a name that alludes to their interdependent nature. A change in any one element has a resultant impact on the other two. The triple lock is central to all antimicrobial chemotherapy—ranging from modern antibiotic development programs through to determining the optimal regimens for community or hospital antibiotics as recommended in the AWaRe Book (Fig. 1).

The triple lock (Fig. 2A) consists of (i) the *antibiotic exposure* (e.g., area under the concentration time curve [AUC]) at the site of infection, which is dependent on the antibiotic regimen (i.e., the dose, schedule/frequency, and duration of drug administration) (Fig. 2B); (ii) the *MIC distribution* that needs to be covered in clinical settings—being able to cover the wild-type distribution (i.e., those strains that do not carry a resistance mechanism to the antibiotic) is critical (Fig. 2C); and (iii) the *pharmacodynamic target* (i.e., magnitude of drug exposure relative to the MIC of the target pathogen that is

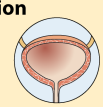
Community infection	Causative (bacterial) pathogens	Recommended (1st line) antibiotic(s)	Challenges
Bronchitis 	• Bacterial causes unlikely	• Antibiotics not recommended	• N/A
Acute otitis media 	• *S. pneumoniae* • *H. influenzae* • *M. catarrhalis* • *S. pyogenes*	• Amoxicillin	• Spatial PK in middle ear • Middle ear immune activity • Limited culture and MIC surveillance
Pharyngitis 	• Group A *Streptococcus* • Group C/G *Streptococci*	• Amoxicillin • Phenoxymethylpenicillin	• Immune activity in pharyngeal tissue • Limited culture and MIC surveillance
Acute sinusitis 	• *S. pneumoniae* • *H. influenzae*	• Amoxicillin • Co-amoxiclav	• Spatial PK of sinuses • Immune activity in sinuses • Limited culture and MIC surveillance
Oral and dental infections 	• *Streptococcus* spp. • *Lactobacillus* spp. • *Actinomyces* spp. • *Capnocytophaga* spp. • *Prevotella* spp. • *Aggregatibacter* spp. • *Porphyromonas* spp.	• Amoxicillin • Phenoxymethylpenicillin	• Spatial PK in dental abscess • Limited culture and MIC surveillance
Community Acquired Pneumonia 	• *S. pneumoniae* • *H. influenzae* • *M.catarrhalis* • *S. aureus*	• Amoxicillin • Phenoxymethylpenicillin	• Limited ELF PopPK • Limited culture and MIC surveillance • High bacterial density
Exacerbation of COPD 	• *H. influenzae* • *M. catarrhalis* • *S. pneumoniae* • Gram-negative bacteria (e.g. *Pseudomonas* spp.)	• Amoxicillin	• Spatial PK in emphysema • Limited culture and MIC surveillance
Acute infective diarrhoea/ gastroenteritis 	• *Cholera* (endemic areas) • *Shigella* spp. • *Campylobacter* spp. • Non-typhoidal *Salmonella* • Enterotoxigenic *E.coli*	• Ciprofloxacin – Bloody diarrhoea, immunocompromise, enteric fever (low fluoroquinolone resistance) • Azithromycin – Cholera, enteric fever (high fluoroquinolone resistance) • Doxycycline – Cholera	• Inadequate regional surveillance for fluoroquinolone resistance in dysentery causing organisms
Skin and soft tissue infection (mild) 	• *S. pyogenes* • *S. aureus* • *Enterobacterales* • *Pseudomonas spp.* • *Anaerobes*	• Co-amoxiclav • Cefalexin • Cloxacillin	• Limited soft tissue PopPK • Limited PK in community populations at hight risk (e.g. diabetes, obesity) • Limited culture and PHC MIC surveillance
Lower urinary tract infection 	• Enterobacterales (mostly *E. coli*) • Coagulase negative *Staphylococci* • *Enterococcus* • *P. aeruginosa* • *A. baumannii*	• Co-amoxiclav • Nitrofurantoin • Trimethoprim • Co-trimoxazole	• Limited urinary PopPK • Minimal relevant PopPK data for 1st line agents e.g. nitrofurantoin, trimethoprim • Different typical causative organisms than in SSTI/sinusitis and may therefore not be suitable for same dosing regimen

FIG 1 The 10 most common primary healthcare infections, their common causative bacterial pathogens and recommended first line treatments, and key barriers to generating an evidence base for AWaRe Book dosing.

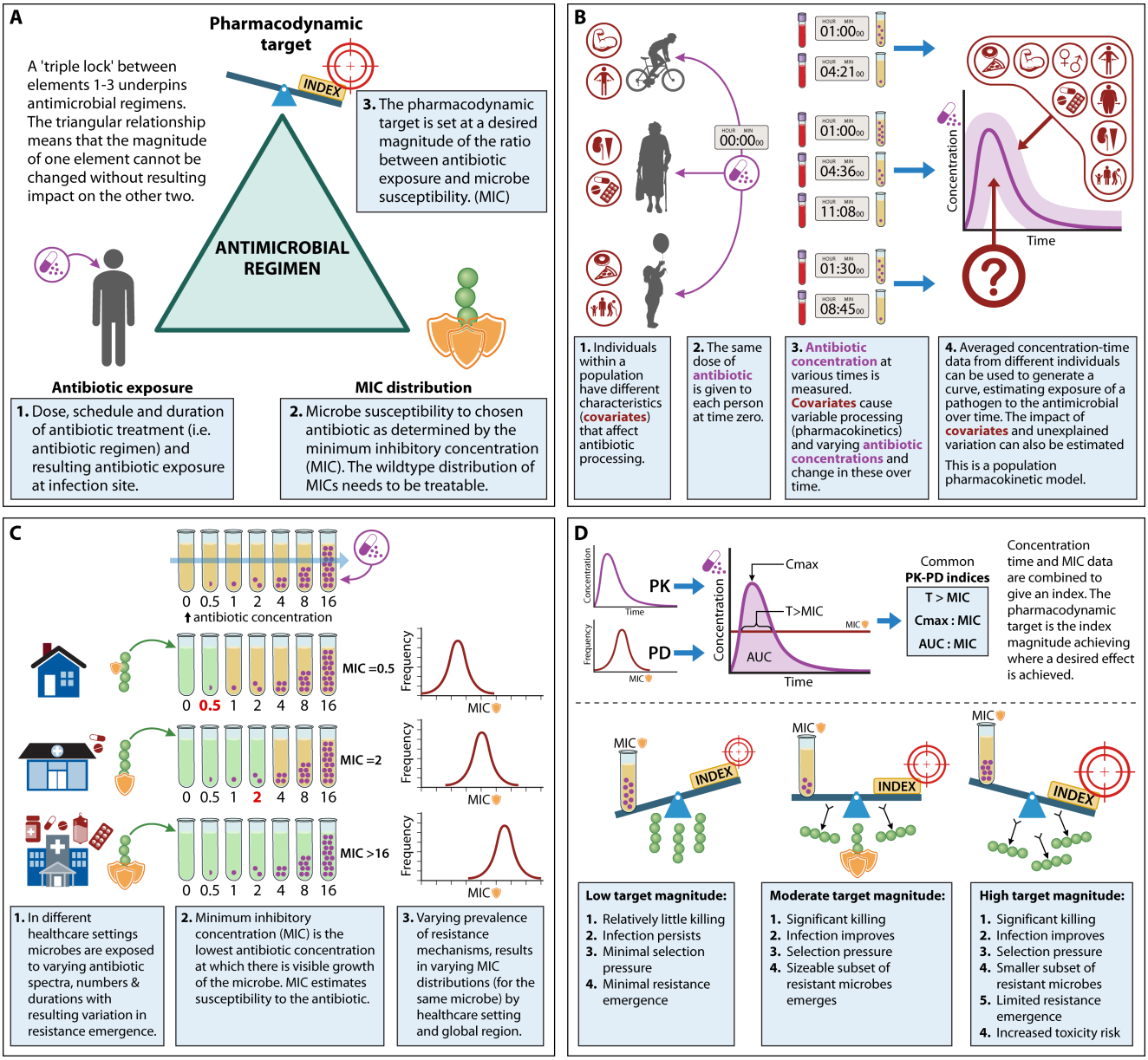


FIG 2 (A) The "triple lock" triangular relationship underpinning dose-exposure response relationships of modern pharmacokinetic-pharmacodynamic theory. (B) Population pharmacokinetics provides an estimate of central tendency and between-patient variance. (C) MICs measure the susceptibility of a pathogen to a given antibiotic and the distribution of MIC values differs with clinical setting. (D) Pharmacodynamic targets are set magnitudes of a given index deemed to result in an outcome of interest such as clinical efficacy and/or resistance mitigation.

required to secure a favourable therapeutic outcome for a given drug-pathogen-disease combination; Fig. 2D).

Changing any of these factors has an immediate impact on the others (e.g., the requirement to cover a higher MIC requires higher drug exposure; the treatment of pneumonia, which may require a higher pharmacodynamic target, requires higher drug exposure), meaning that a full understanding of all three factors is required to assess the adequacy of any given antibiotic regimen.

Antibiotic regimen and drug exposure

An antibiotic regimen includes the dose, schedule, and duration of antibiotic treatment. For a chosen antibiotic, a variety of regimens may be appropriate dependent on the clinical infection and the nature of the host. In this review, we focus on the dosing aspect of an antibiotic regimen. The planned dosing regimen is designed to achieve adequate drug exposure (relative to MIC) to ensure a favorable therapeutic outcome for most of the population. The regimen must generate sufficient drug exposure for (i) the target patient population (e.g., children); (ii) the most common causative bacteria for that specific infection (Fig. 1); and (iii) overcome the considerable pharmacokinetic variability that is typically present in those receiving antibiotics. For effective global antibiotic guidance, regimens must also consider the practicality of prescribing in limited-resource settings and strategies to ensure adequate access to key antibiotics at a program level (e.g., dose/ schedule harmonization across multiple infections) (9) and to facilitate compliance with antibiotic treatment (e.g., minimizing doses per day).

The behavior of any drug in a population of patients is described using population modeling approaches. Population pharmacokinetic (PopPK) models estimate average values of key pharmacokinetic parameters for the population (e.g., volume of distribution, clearance) and additionally estimate the degree of variability and contributing factors to true inter-individual differences (Fig. 2B) (10). PopPK models are mathematical stores of past experiences of a drug within a population—they enable the consequences of pharmacokinetic (PK) variability to be estimated and mitigation strategies to be designed. For antibiotics on the EML, this means understanding how much variability can be expected from a single dosing regimen given in the AWaRe Book.

Antibiotic potency and MIC distribution

The MIC is an *in vitro* measure of antibiotic potency and is estimated using standardized and well-characterized methodologies (11, 12). The absolute value of the MIC is a function of the experimental conditions that are ultimately used—it does not necessarily have any direct intrinsic biological relevance. Rather, the MIC serves as scalar in all pharmacodynamic (PD) indices and calculations—for example, a pathogen with twice the MIC requires twice the drug exposure to generate the same pharmacological effect. Importantly, increasing antibiotic drug exposure as means to treat pathogens with significantly elevated MICs correlating to high-level resistance may not be practically possible because of limitations of solubility and/or safety.

Just as human diversity affects antibiotic drug exposure, pathogen diversity has a comparable effect on the attainment of pharmacodynamic targets—the distribution of MICs is a critical determinant of estimates of the adequacy of a given antibiotic regimen (Fig. 2C). The distribution of MICs for any drug-pathogen combination is affected by context (e.g., PHC versus hospital, case mix, infection site, antibiotic usage, geography, etc.).

Pharmacodynamic targets

There are characteristic patterns of antibiotic efficacy, which vary according to the specific drug-pathogen combination—concentration-dependent killing, time-dependent killing, or a combination of both. Which of these patterns is relevant is determined experimentally using dose fractionation studies and can be described using one of three PK-PD indices (Fig. 2D). These are (i) the ratio of free drug peak antibiotic concentration to MIC (fC_{max}:MIC); (ii) the fraction of the dosing interval that free drug concentrations are above the MIC (fT>MIC); and (iii) the ratio of the area under the free drug concentration-time curve, to MIC (fAUC:MIC) (10).

A magnitude of the relevant PK-PD index to achieve a desired effect (e.g., bacterial logarithmic killing, survival, clinical response) can then be defined in non-clinical and/or clinical settings–— these values are disease specific and a central component of regimen planning for new antibiotic agents and those in the AWaRe book.

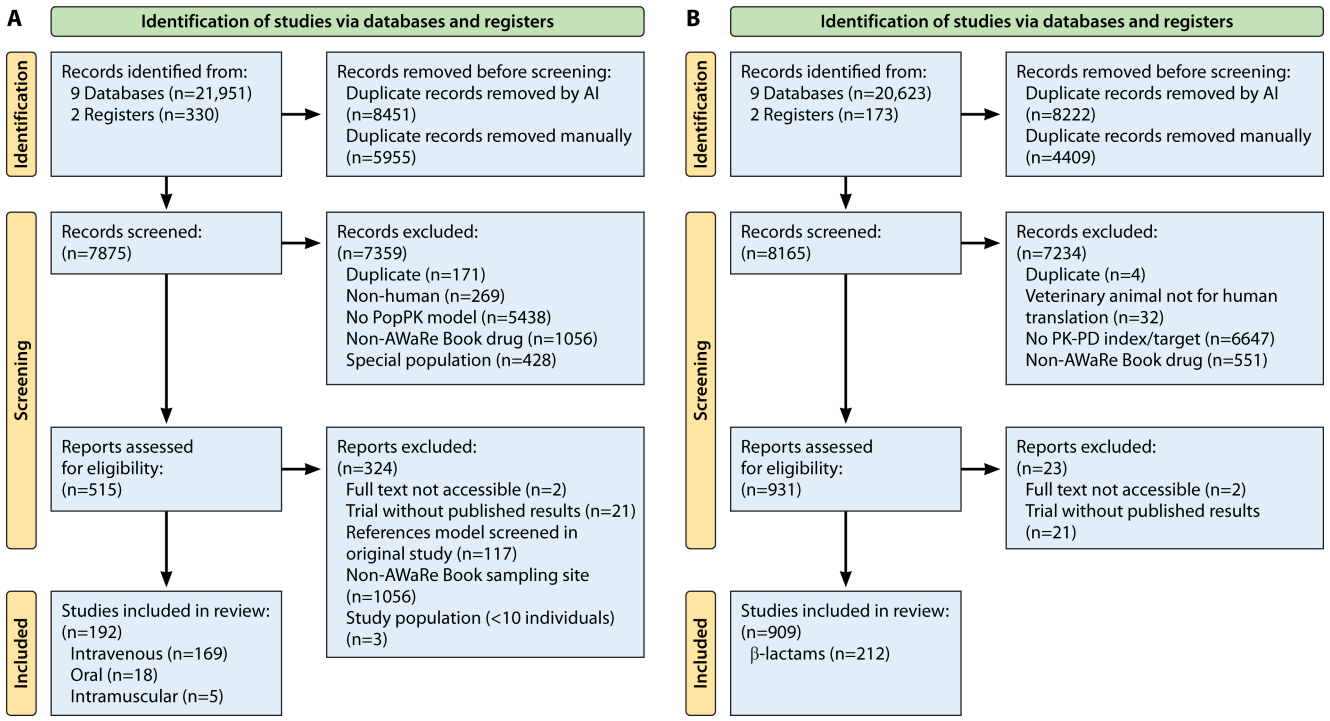


FIG 3 PRISMA flow-charts detailing: (A) results of systematic review of population pharmacokinetic studies for AWaRe Book PHC agents and (B) results of systematic review of pharmacodynamic targets for AWaRe Book PHC agents.

PK-PD LITERATURE SEARCH STRATEGY AND SELECTION CRITERIA

Studies reporting population pharmacokinetic models

Population pharmacokinetic (PopPK) studies of antibiotics administered via routes specified in the PHC section of the AWaRe Book (*n* = 29, 20 Access, 9 Watch) published from database inception until 20/01/2022 were systematically reviewed in line with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (13). In line with Cochrane guidance (14), 10 databases encompassing general bibliographic databases, trial registers, and gray literature were searched. These included Cochrane Central, Clinicaltrials.gov, EMBASE, MEDLINE, medRxiv, SciFinder, Scopus, Web of Science, WHO ICTRP portal, and WorldCat databases.

The search terms used were as follows:

((population AND (pharmacokinetic* OR PK)) OR "population pharmacokinetic*" OR popPK) AND (model* OR simulat* or analys* OR study OR studies) AND (<ANTIBIOTIC SEARCH TERMS>)

Table S1 details search terms used for individual antibiotics. After automatic and manual deduplication using Rayyan (Qatar Computing Research Institute, Doha, Qatar), 7,875 records were screened against selection criteria, fully outlined in Fig. 3A. Excluded special populations are listed in Table S2. A total of 192 studies were included after screening, of which only 18 were conducted in oral AWaRe Book PHC antibiotics (Fig. 3A).

The 18 PopPK models for oral AWaRe agents were reviewed in more detail. A grading system for quality (Table S3) was developed based primarily on the European Medicines Agency reporting guidance for PopPK studies in conjunction with previously published grading criteria for other PK study types (15–17). Included oral PopPK studies were then scored based on this. Further analysis was conducted using R (v.4.2.0).

Studies reporting optimal pharmacodynamic target magnitude

Utilizing the same databases listed above, articles published on the same 27 PHC AWaRe Book antibiotics (antibiotic search terms found in Table S1) from database inception until 05/03/23 meeting the search criteria below were compiled.

The search terms used were as follows:

("pharmacokinetic/pharmacodynamic" OR "pharmacokinetic-pharmacodynamic" OR "PK/PD" OR "PK-PD" OR pharmacodynamic OR PD) AND (target OR index OR indices) AND (<ANTIBIOTIC SEARCH TERMS>)

Automatic and manual deduplication using Rayyan and subsequent screening against selection criteria yielded 880 unique articles on any PHC oral AWaRe Book antibiotic (Fig. 3B). Studies were reviewed in Rayyan and tagged with the appropriate antibiotic agent or class. A subset of these articles (n = 10) (Table S4), consisting of only those featuring ß-lactam antibiotics, published in the years 2022 or 2023, was used as a starting corpus to establish pharmacodynamic target magnitudes within the literature and trace their experimental sources through review of citations. This subset was selected both due to the strategic importance of ß-lactam antibiotics in treating PHC infection, and additionally, given the immediacy of these articles, it was expected that these would cover publications that may not yet have been referenced elsewhere, while still generating a tree of historical publications where a pharmacodynamic target was derived. A Python algorithm (v.3.11.4) was then used to graphically demonstrate connections between articles featuring a pharmacodynamic target magnitude. All articles within the tree-like network where a pharmacodynamic target magnitude was experimentally or clinically determined were then reviewed in full and their methodology and results were tabulated (Table 2).

RESULTS OF SYSTEMATIC AND DATABASE REVIEWS

Systematic review of PopPK studies

A total of 192 PopPK studies met the inclusion criteria (Fig. 3A). Amoxicillin and amoxicillin-clavulanate (co-amoxiclav) were the most frequently used antibiotics in most countries (18)—however, only two studies for oral amoxicillin met the inclusion criteria for this review (19, 20). Nitrofurantoin and trimethoprim (without sulfamethoxazole), both of which are recommended first line agents (Fig. 1), had no published PopPK models. Intravenous agents constituted the majority of included studies (n = 169) and were primarily conducted in vancomycin (n = 110) and gentamicin (n = 48).

Only 18 PopPK studies had been conducted for the 16 oral PHC AWaRe antibiotics (Table 1) (19–36). All included studies were conducted using serum or plasma antibiotic concentrations irrespective of the infection site for which the agents were primarily indicated.

The grading of oral PHC studies, which scored the methodology and results reporting of these studies (Table S3), ranged from 15 (31.9%) to 35 (74.5%) out of 47 (mean 44.9%), indicating that many of these studies did not comply with the European Medical Agency guidance for PopPK reporting (15). The domains with lowest scores included model generation data (with studies typically using single centre data sets alone, [mean = 0.17/2]), ethnic diversity (commonly unreported or skewed [mean = 0.44/2]), and representative population [mean = 0.55/4, mode = 0/4]).

The PopPK studies conducted in patients were largely in hospitalized populations who may have different PK parameters compared with generally less ill patients treated in PHC settings. Conversely, 12 of the 18 studies were conducted partially (n = 2) or entirely (n = 10) in healthy individuals (19–25, 28–31, 35) (Table 1). The included studies, especially those conducted in healthy volunteers, disproportionately represent young adult males. Four studies were conducted exclusively in males (19, 21, 24, 31) and a further nine had a minority of females (23, 26–28, 30, 32, 33, 35, 36) (Table 1). There were striking regional imbalances with the Middle East and North Africa (MENA), Sub-Saharan Africa, Southeast Asia, and South America being underrepresented (Fig. 4B).

TABLE 1 Summary of 18 literature published population pharmacokinetic studies for WHO AWaRe Book PHC oral antibiotic[a]

Authors	Regimen	Combination agent	Participants	Sample type(s)	Sampling (total/per person)	Sampling strategy	Region	Ethnic diversity	Sex ratio (%M:%F)	Age mean ± SD/med (range)	Infection syndrome	Covariates	Grading (/47)
Amoxicillin													
De Velde et al., (19)	875 mg q12, 500 mg q12	Clavulanic acid	28	Plasma	1428 Tot	I	Netherlands	Unknown	100:0	34 ± 7	Healthy	None	31
Li et al., (20)	500 mg, 2,000 mg STAT	Cranberry juice	18	Blood (serum), urine	8 PP	I	USA	Unknown	0:100	28 ± 5	Healthy	TBW, juice, dose	23
Azithromycin													
Pene-Dumitrescu et al., (21)	500 mg q24	NA	12	Blood, plasma	9 PP	I	Unknown	Unknown	100:0	29 (19–47)	Healthy	None	22
Muto et al., (22)	2,000 mg STAT	NA	559	Serum	4310 Tot	S	Japan	Japanese, Western	36:64	36 (16–90)	Healthy (six studies), RTI (three studies)	Age, TBW	25
Sampson et al., (23)	250 mg, 1,000 mg STAT	NA	20	Blood, mononuclear cells, neutrophils	269 Tot	I	UK	Caucasian, Other	60:40	48.5 (21–63)	Healthy	None	26
Idkaidek et al., (24)	250 mg STAT	NA	46	Plasma	26 PP	I	Jordan	Unknown	100:0	Unknown	Healthy	None	17
Zhao et al., (25)	30 mg/kg q24, 500 mg q24	Chloroquine	219	Serum	1,198 Tot	I/S	sub-Saharan Africa/USA	Unknown	Unknown mix	<5 (123), 5–12 (56) and adults (40)	Healthy adults (40), children with malaria (179)	TBW	24
Cefalexin													
Gwee et al., (26)	Unknown	NA	12	Blood	53 Tot	I	Australia	Unknown	58:42	7.6 (1.2–16.7)	MSSA bone & joint infection	TBW	26
Ciprofloxacin													
Zahr et al., (27)	500 mg-3,000 mg q24	Rifampicin	92	Plasma	397 Tot	I	France	Unknown	63:38	67.1 (18.9–87.7)	Osteoarticular infection	FFM/TBW, modified renal diet, rifampicin	27
Knippenberg et al., (28)	500 mg STAT	NA	10	Plasma, dried blood spots	6 PP	I	Australia	Unknown	70:30	28 (26–47)	Healthy	None	28
Clarithromycin													
Morozov et al., (29)	1,000 mg STAT	NA	24	Plasma, urine	11 PP	I	Argentina	Unknown	Unknown mix	(20–60)	Healthy	None	15
Abduljalil et al., (30)	500 mg q12	NA	12	Plasma	624 Tot	I	Moldova	Caucasian	58:42	28 ± 8	Healthy	TBW	23
Co-amoxiclav													
De Velde et al., (31)	875/125 mg q12, 500/125 mg q8	NA	29	Plasma	1,479 Tot	I	Netherlands	Unknown	100:0	33 ± 7	Healthy	Dosing time	29
Co-trimoxazole													

(*Continued on next page*)

TABLE 1 Summary of 18 literature published population pharmacokinetic studies for WHO AWaRe Book PHC oral antibiotic[a] (*Continued*)

Authors	Regimen	Combination agent	Participants	Sample type(s)	Sampling (total/per person)	Sampling strategy	Region	Ethnic diversity	Sex ratio (%M:%F)	Age mean ± SD/med (range)	Infection syndrome	Covariates	Grading (/47)
Wu et al., (32)	TMP med 4.5 mg/kg	NA	20	Plasma	121 Tot	I	USA	Caucasian/Other	60:40	4.4 (0.23–15)	Bacterial infection	Post-natal age, creatinine	33
Alsaad et al., (33)	960 mg q24	Rifampicin, Ethambutol, Isoniazid, Pyrazinamide	12	Plasma	9 PP	I	Netherlands	European, African, Middle Eastern, Western Pacific, American	83:17	30 (25–50)	TB	None	29
Autmizguine et al., (34)	TMP med 4.6 mg/kg/day, SMX med 23 mg/kg/day	NA	153	Plasma	240 Tot	S	USA	Caucasian, Other	54:46	7.9 (0.055–20)	Bacterial o-amoxiclavinfection	Albumin, maturation half-life, serum Cr	35
Doxycycline													
Hopkins et al., (35)	100 mg, 120 mg q24	NA	178	Plasma	7,093 Tot	I	Australia	Caucasian, Black, Asian, American native, Hispanic	67:33	28 (18–73)	Healthy	Sex, fasting/fed	33
Flucloxacillin													
Drennan et al., (36)	1,000 mg q8	Probenecid	56	Serum	1 PP/10 PP	I/S	New Zealand	European, Maori, Pacific Islander	73:27	48.8 (19.8–73.7)	Staphylococcal infection	Probenecid, fasting, FFM	26

[a]NA, not applicable; I, intensive; S, sparse; MSSA, methicillin sensitive *Staphylococcus aureus*; TB, tuberculosis; TBW, total body weight; FFM, fat free mass; serum Cr, serum creatinine.

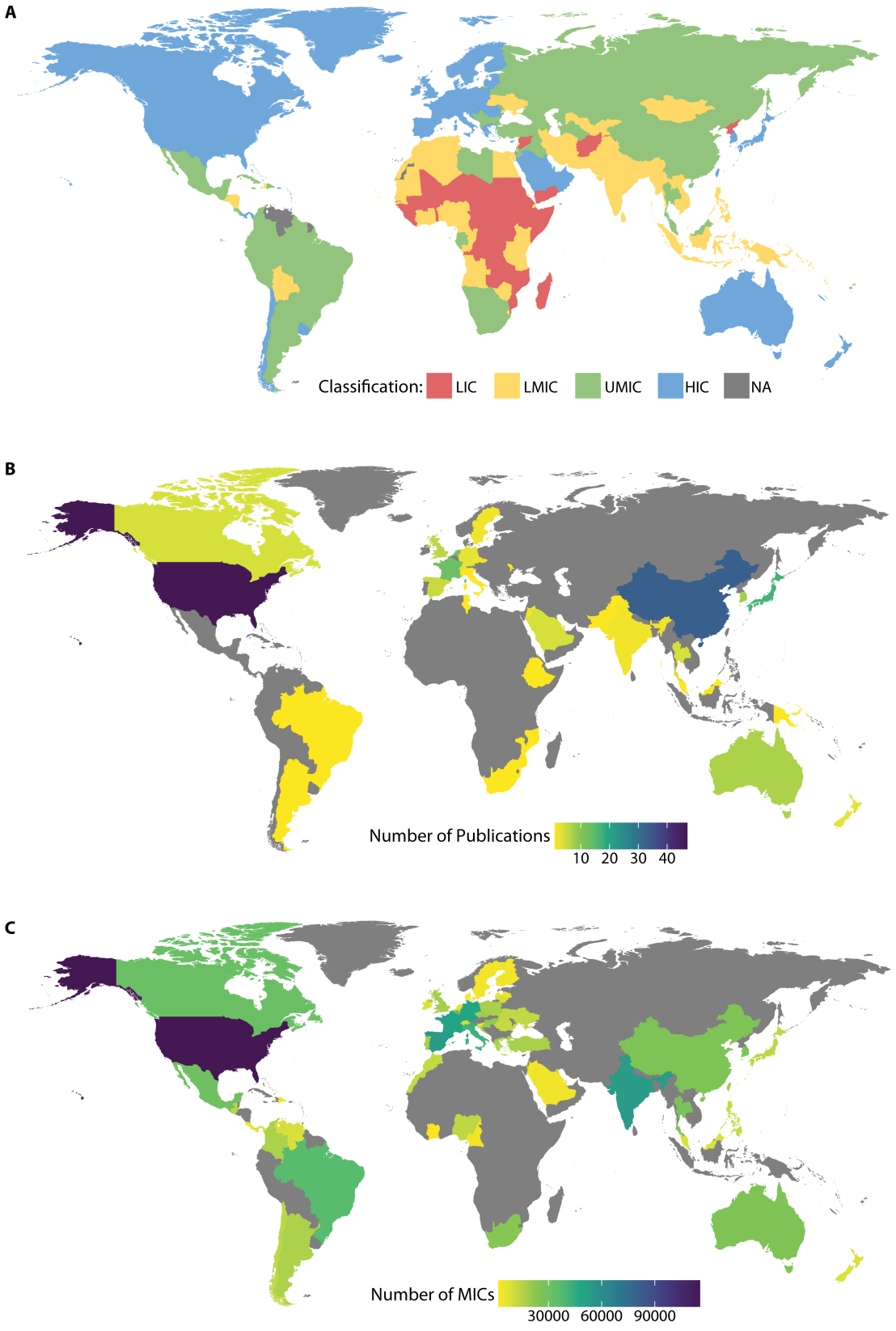


FIG 4 (A) Countries by World Bank Income Classification; (37) (B) Published PopPK studies for AWaRe Book PHC antibiotics (all routes) meeting the systematic review inclusion criteria by participant country(ies) of origin; (C) Individual MIC datapoints (all organism and antibiotic combinations) within the ATLAS database added in 2016–2020 by country of origin. LIC, low-income country; LMIC, lower-middle income country; UMIC, upper-middle income country; HIC, high income country; NA, unclassified.

Moreover, ethnicity was often not reported or investigated by studies—where ethnicity was reported, Europeans or Caucasians represented a majority of participants (33–35).

Body composition, malnutrition, and obesity may affect PK (38–43). In low- and middle- income countries (LMICs) (Fig. 4A), malnutrition is persistently prevalent and obesity rates are rising (42, 43)—however, only two of the included studies were conducted in LMICs (24, 25). AWaRe Book recommendations apply to children and over-65s, but these age groups are even scarcer in existing data sets. Only four studies were conducted at least, in part, in pediatric populations (25, 26, 32, 34). There were only four studies where participant age extended above 65 years, and only two studies where it extended above 80 years (22, 27, 35, 36) despite the increasing global prevalence of these age groups (44). Age-related physiological changes, multi-morbidity, and polypharmacy have a well-recognised impact on PK and vary globally (45, 46).

Database review of antibiotic susceptibility testing and MIC distributions

Most surveillance databases only report sensitive vs resistant (S/R) susceptibility data that is based on currently recommended breakpoints from the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and/or the Clinical and Laboratory Standards Institute (CLSI)—this includes the WHO Global Antimicrobial Resistance and Use Surveillance System (GLASS) (5, 47, 48). GLASS reports AMR rates for *Streptococcus pneumoniae*, the most common causative pathogen of community infections (Fig. 1), and notes generally very low penicillin resistance rates (<5%) in the context of bloodstream infection (5). However, the GLASS Report (2022) highlights that despite increasing enrolment in the programme, convenient selection, and therefore, representativeness of AMR surveillance is a limitation in the global interpretation of resistance data. Additionally, there was limited antimicrobial susceptibility test (AST) reporting for key PHC pathogen-antibiotic combinations (e.g., *Streptococcus pneumoniae* vs penicillins [<80%], *Salmonella* spp. and fluoroquinolones [<80%], *Escherichia coli* and sulfonamides/trimethoprim [<50%]—see Fig. 1) (5). Furthermore, due to periodic revision of breakpoints by EUCAST and CLSI, the same MIC value can result in variation between S and R within GLASS and other S/R data sets over time (49).

Established open-access databases of MIC distributions for key drug-pathogen combinations include EUCAST, the Centers for Disease Control and Prevention (CDC), and the Antimicrobial Testing Leadership and Surveillance (ATLAS) published by the Wellcome Trust and Open Data Institute. Only EUCAST and ATLAS include global data sources (50, 51). ATLAS has been repurposed from Pfizer/AstraZeneca surveillance of tigecycline and ceftazidime/avibactam resistance (49, 51)—the MICs are, therefore, limited to just 10 of the common pathogen-antibiotic combinations (Fig. 1), and MICs for amoxicillin, which is the key agent for treatment of many PHC diseases (Fig. 1), are not captured. Compared to GLASS, *Streptococcus pneumoniae* sensitivity to penicillin is significantly less frequent in ATLAS (62.5%) even when stratified for community samples (59.0%) and respiratory tract infection (59.2%).

Despite the reported global provenance of ATLAS and EUCAST data, the specific regional/healthcare setting(s) and time periods used to generate EUCAST MIC distributions are not reported (50). This may result in geographical regions being over- or under-represented in data sets. Data in repositories may be old and out of date. Geographical sources are specified in ATLAS, but the database only contains MIC values for 70 nations—data from parts of Asia, MENA, and sub-Saharan Africa are sparse (Fig. 4C) (51). Similar to PopPK studies, MIC values are primarily generated from hospital settings, potentially skewing MIC distributions to less susceptible values (Fig. 2C). In the ATLAS database, 4.1% of all isolates values are from PHC settings—this may account for MIC values within ATLAS that more frequently correspond to breakpoint definitions of AMR compared to other databases, where the same drug-pathogen combinations have been found to be sensitive (49, 51).

Systematic review of pharmacodynamic targets and citation tracing

A second systematic review evaluating pharmacodynamic targets for AWaRe Book PHC antibiotics yielded 880 results meeting the inclusion criteria (Fig. 3B); however, at screening, most articles did not determine a target magnitude within their study. Ten of these studies were conducted for ß-lactam antibiotics from January 2022 to present. When values for a pharmacodynamic target were manually traced back through serial citations to establish their origins, the network (Fig. 5) generated from these 10 articles yielded 567 articles citing a target magnitude, of which 80 defined a target magnitude within (Table 2) (52–131). The most frequently cited article within the network was cited 82 times and cited a target magnitude from another article (132). Of the 25 most cited articles, 9 (36%) did not define a target magnitude.

From the 80 studies defining a target magnitude (Table 2), only 10 (12.5%) were conducted using an oral PHC AWaRe agent (e.g., amoxicillin, co-amoxiclav) with the vast majority using an i.v. administered β-lactam. A total of 34 articles included an *in vitro*

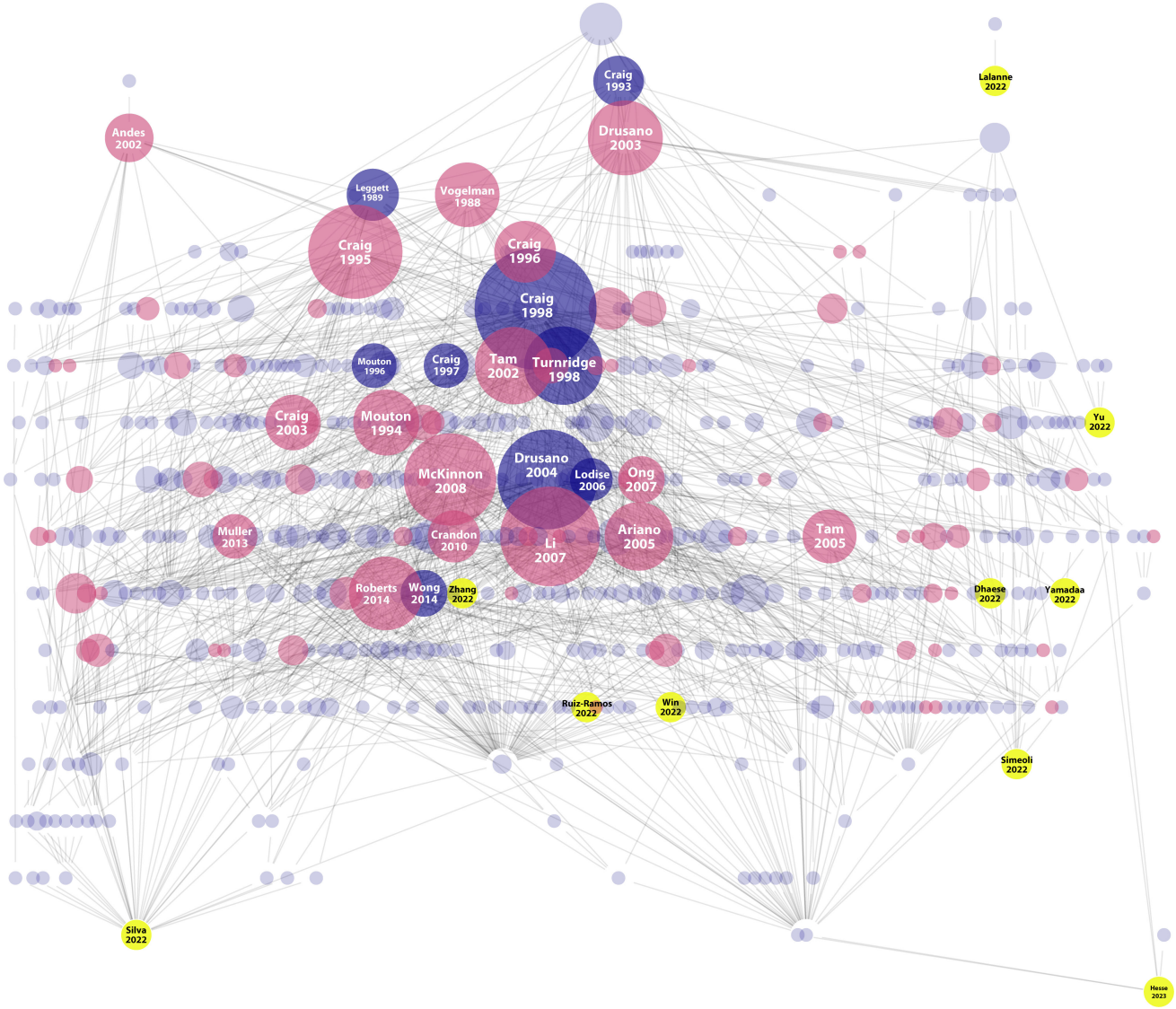


FIG 5 Graphic representation of the network of citation links between literature articles specifying a PK-PD target magnitude for ß-lactam antibiotics derived from an original corpus of 10 articles published 2022/2023 (Table S4). Yellow labeled nodes (n = 10) represent the original corpus. Red nodes (n = 80) represent articles which define a target *in vitro*, *in vivo* or from clinical studies. Blue nodes (n = 477) represent studies citing target(s) from preceding literature evidence. The 25 most cited nodes (cited 10–82 times within the network) are labeled in white (Table S5).

TABLE 2 Summary of 80 published studies defining a pharmacodynamic target for any ß-lactam antibiotic[a]

Author	Year	Antibiotic	Study type	Organism(s)	Animal model	Infection syndrome	Regimen	Target	Outcome
Abodakpi et al. (52)	2019	Piperacillin/ Tazobactam	*In vitro* (HFIM)	*Klebsiella pnuemoniae*	N/A	N/A	4 g Piperacillin q8 +1.5 g Tazobactam q8	55.1% fT>MIC	Regrowth suppression
				Escherichia coli			4 g Piperacillin q8 +1.0 g Tazobactam q8	60.0% fT>MIC	
Aitken et al. (53)	2015	Cefepime	Clinical	*Acinetobacter, Aeromonas, Citrobacter, Enterobacter, Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Serratia marcescens*	N/A	Bacterial pneumonia	1 g IV q12, 1 g IV q6, 1 g IV q8, 2 g IV q12, 2 g IV q8	fCmin/MIC >= 2.1	Clinical response
Alou et al. (54)	2005	Ceftazidime	*In vitro*	*Pseudomonas aeruginosa* (susceptible, intermediate, and resistant strains)	N/A	N/A	6 g CI, 2 g q8	50% T>MIC	Regrowth suppression
Andes et al. (55)	1998	Amoxicillin, Co-amoxiclav	*In vivo*	*Streptococcus pneumoniae*	Murine (neutropenic)	Thigh	7 mg/kg Amoxicillin q8, 7 mg Amoxicillin + 1.75 mg Clavulanic acid/kg q8	40% T>MIC	Survival
								20% T>MIC	Bacterial stasis
								50-60% T>MIC	Maximum bacterial killing
Andes et al. (56)	2002	Penicillins, Carbapenems, Cephalosporins	*In vivo*	*Streptococcus pneumoniae, Staphylococcus, Gram-negative bacilli*	Murine (neutropenic)	Lung, thigh	Unspecified	25-50% T>MIC	1–2 log bacterial kill
		Ceftazidime	*In vivo*	*Klebsiella pneumoniae*	Murine (neutropenic)	Lung	Unspecified	40% T>MIC	Stasis
Andes et al.(57)	2006	Ceftaroline	*In vivo*	*Streptococcus pneumoniae*	Murine (neutropenic)	Lung, thigh	0.20–14.3 mg/kg/24 h	39% T>MIC	Stasis
							0.29–22.2 mg/kg/24 h	43% T>MIC	One log bacterial killing
							0.41–34.0 mg/kg/24 h	50% T>MIC	Two log bacterial killing
				Methicillin-resistant *Staphylococcus aureus*			2.57–9.88 mg/kg/24 h	26% T>MIC	Stasis
							7.23–22.0 mg/kg/24 h	33% T>MIC	One log bacterial killing
							14.8–64.1 mg/kg/24 h	45% T>MIC	Two log bacterial killing

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TABLE 2 Summary of 80 published studies defining a pharmacodynamic target for any ß-lactam antibiotic[a] (*Continued*)

Author	Year	Antibiotic	Study type	Organism(s)	Animal model	Infection syndrome	Regimen	Target	Outcome
				Klebsiella pneumoniae, *Escherichia coli*			22–234 mg/kg/24 h	28% T>MIC	Stasis
							51–1040 mg/kg/24 h	41% T>MIC	One log bacterial killing
							154–992 mg/kg/24 h	54% T>MIC	Two log bacterial killing
Ariano et al. (58)	2005	Meropenem	Clinical	*Staphylococcus epidermidis*, *Streptococcus mitis*, *Streptococcus sanguis*, *Staphylococcus haemolyticus*, Coagulase-negative *Staphylococcus*, *Staphylococcus aureus*, *Enterococcus faecalis*, *Enterobacter cloacae*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Escherichia coli*	N/A	Febrile neutropenia with bacteraemia	500 mg IV q6, 1 g IV q8	83% T>MIC (mean)	Clinical response
Azoulay-Dupuis et al. (59)	2004	Ceftobiprole	*In vivo*	*Streptococcus pneumoniae*	Murine (leukopenic)	Lung	25 mg/kg	9-18% T>MIC	Survival
		Ceftriaxone					400 mg/kg	30-50% T>MIC	
Bakker-Woudenberg et al. (60)	2006	Ceftazidime	*In vivo*	*Klebsiella pneumoniae*	Rat (immunocompetent)	Lung	6.3–1600 mg/kg/24 h	60-70% T>MIC	Maximum bacterial killing
Bergen et al. (61)	2016	Piperacillin	*In vitro* (HFIM)	*Pseudomonas aeruginosa*	N/A	N/A	4 g q8, 4 g q6, 4 g q4	fCmin >5xMIC	3–4 log bacterial killing and regrowth suppression
Bergen et al. (62)	2017	Meropenem	*In vitro* (HFIM)	*Pseudomonas aeruginosa*	N/A	N/A	0.5 g q8, 1 g q8, 2 g q8	>= 82% fT>5 xMIC, fCmin/MIC >= 2	Regrowth suppression
Berkhout et al. (63)	2015	Ceftazidime/ Avibactam	*In vivo*	*Pseudomonas aeruginosa*	Murine (neutropenic)	Lung, thigh	Ceftazidime q2 +Avibactam q2, Ceftazidime q2 +Avibactam q8	0 - 29.6% fT>MIC	Stasis
Bhavnani et al. (64)	2015	Ceftaroline	Clinical	*Staphylococcus aureus*	N/A	Bacterial skin and skin structure infection	600 mg q12	>55% fT>MIC	Microbiological response
				All organisms (others unspecified)				54.2% fT>MIC (90.4% in diabetics, 82.5% in age >55)	

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TABLE 2 Summary of 80 published studies defining a pharmacodynamic target for any ß-lactam antibiotic[a] (*Continued*)

Author	Year	Antibiotic	Study type	Organism(s)	Animal model	Infection syndrome	Regimen	Target	Outcome
Bulik et al. (65)	2012	Ceftolazone (± Tazobactam)	*In vivo*	*Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae*	Murine (immuno-competent)	Thigh	1000 mg q8, 100 mg Ceftolazone +500 mg Tazobatam q8	37.5% fT>MIC	1–3 log bacterial kill
		Piperacillin/ Tazobactam					4.5 g q6	40% fT>MIC	Stasis to one log bacterial kill
Craig et al. (66)	1995	Cefotaxime	*In vivo*	*Klebsiella pneumoniae*	Murine (neutropenic)	Lung	Unspecified	40% T>MIC	Stasis
								60-70% T>MIC	Maximum bacterial killing
		Cefotaxime, Ceftriaxone		*Staphylococcus aureus*	Murine (neutropenic)	Thigh	Unspecified	40%T>MIC	Maximum bacterial killing
		Cefotaxime, Ceftriaxone, Ceftazidime, Cefpirome		*Streptococcus pneumoniae, Staphylococcus aureus, Enterobacteriaceae*	Unspecified	Unspecified	Unspecified	35-40% T>MIC	Stasis
								60-70% T>MIC	Maximum bacterial killing
Craig et al. (67)	1996	Penicillins, Cephalosporins	Clinical	*Streptococcus pneumoniae, Haemophilus influenzae*	N/A	Otitis media	Unspecified	40% fT>MIC	85-100% bacteriological cure
Craig et al. (68)	1996	Penicillins, Cephalosporins	*In vivo*	*Streptococcus pneumoniae*	Unspecified	Unspecfied	Unspecified	40% T>MIC	Survival
Craig et al. (69)	2002	Ceftazidime	*In vivo*	*Klebsiella pneumoniae*	Murine (neutropenic)	Thigh	Unspecified	40% fT>MIC	Stasis
		Penicillins, Cephalosporins	*In vivo*	*Streptococcus pneumoniae*	Unspecified	Unspecified	Unspecified	20-40% T>MIC	Survival
		Penicillins, Cephalosporins, Carbapenems	*In vivo*	*Streptococcus pneumoniae*	Unspecified	Unspecified	Unspecified	25-35% fT>MIC (Penicillins), 35-45% fT>MIC (Cephalosporins), 10-20% fT>MIC (Carbapenems),	Stasis
		β-Lactams	Clinical	*Streptococcus pneumoniae, Haemophilus influenzae*	N/A	Acute otitis media, acute maxillary sinusitis	Unspecified	>40% fT>MIC	Microbiological response
Craig et al. (70)	2003	Ceftazidime	*In vivo*	*Pseudomonas aeruginosa*	Murine (neutropenic)	Thigh	q2, q4, q6, q8, q12	>40% T>MIC	Stasis

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TABLE 2 Summary of 80 published studies defining a pharmacodynamic target for any ß-lactam antibiotic[a] (*Continued*)

Author	Year	Antibiotic	Study type	Organism(s)	Animal model	Infection syndrome	Regimen	Target	Outcome
		Penicillins, Cephalosporins, Carbapenems	*In vivo*	Unspecified	Murine (neutropenic)	Thigh	q1-2, q3-4, q6-8, q12-24	29-34% fT>MIC (Penicillins), 35-53% fT>MIC (Cephalosporins), 20-26% fT>MIC (Carbapenems),	Stasis
		Ceftazidime, Cefepime, Cefpirome, Cefotaxime, Ceftriaxone, Cefonicid	*In vivo*	*Streptococcus pneumoniae*	Murine (neutropenic)	Thigh	q6	30-40% fT>MIC	Stasis
		Amoxicillin, Cefpodoxime	*In vitro*	*Streptococcus pneumoniae*	N/A	N/A	Unspecified	25-35% fT>MIC (Amoxicillin), 35-45% fT>MIC (Cefpodoxime)	Stasis
		β-Lactams	Clinical	Penicillinsusceptible/intermediate/resistant *Streptococcus pneumoniae, Haemophilus influenzae*	N/A	Acute otitis media, acute maxillary sinusitis	Unspecified	>40% T>MIC	85-100% bacteriological cure
Craig et al. (71)	2008	Ceftobiprole	*In vivo*	*Streptococcus pneumoniae*	Murine (neutropenic and immunocompetent)	Lung, thigh	10 mg/kg, 40 mg/kg, 100 mg/kg	18.8% T>MIC	Stasis
								25.8% T>MIC	Two log bacterial kill
				Staphylococcus aureus				21.1% T>MIC	Stasis
								29.3% T>MIC	Two log bacterial kill
				Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae				40.8% T>MIC	Stasis
								64.5% T>MIC	Two log bacterial kill
				Pseudomonas aeruginosa				46.7% T>MIC	Stasis
								98.8% T>MIC	One log bacterial kill
Craig et al. (72)	2013	Ceftolazone	*In vivo*	*Pseudomonas aeruginosa*, wild-type Enterobacteriaceae	Murine (neutropenic)	Thigh	q6	25.2% T>MIC	Stasis
								31.5% T> MIC	One log bacterial kill

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TABLE 2 Summary of 80 published studies defining a pharmacodynamic target for any ß-lactam antibiotic[a] (*Continued*)

Author	Year	Antibiotic	Study type	Organism(s)	Animal model	Infection syndrome	Regimen	Target	Outcome
		Ceftolazone/ Tazobactam		ESBL Enterobacteriaceae			400 mg/kg Ceftolazone or 800 mg/kg Ceftolazone and 2:1, 4:1, or 8:1 Tazobactam q6	31.1% T >MIC	Stasis
								24.8% T>MIC	One log bacterial kill
Crandon et al. (73)	2010	Cefepime	Clinical	*Pseudomonas aeruginosa*	N/A	Pneumonia, skin and skin structure infections, bacteremia	1 g q24, 1 g q12, 1 g q8, 2 g q12, 2 g q8, 2 g q8 extended infusion	60% fT>MIC	Microbiological response
Crandon et al. (74)	2016	Doripenem, Imipenem, Meropenem	Clinical	*Pseudomonas aeruginosa*	N/A	Ventilator associated pneumonia	Doripenem: 0.25 g q8 4 h, 0.5 g q8 4 h/q8 1 h/q12 4 h, 1 g q8 4 h/q12 4 h; Imipenem 0.25 g q6 1 h/q12 1 h, 0.5 g q6 1 h/q8 1 h/q12 1 h, 1 g q8 1 h; Meropenem 0.5 g q24 1 h, 1 g q24 1 h/q12 1 h/q8 1 h	19.2% fT>MIC	Clinical response
								47.9% fT>MIC	Survival
Drusano et al. (75)	2003	Meropenem	*In vivo*	*Escherichia coli*	Murine	Thigh	Unspecified	20-35% T>MIC	Stasis
								40% T>MIC	Maximum bacterial killing
				Pseudomonas aeruginosa				20-30% T>MIC	Stasis
								40% T>MIC	Maximum bacterial killing
Drusano et al. (76)	2011	Meropenem	*In vivo*	*Pseudomonas aeruginosa*	Murine (neutropenic)	Pneumonia	2.4–150mg/kg	31.7% T>MIC (ELF)	Two log bacterial kill
								49.6% T>MIC (ELF)	Three log bacterial kill
								49.8% T>MIC (ELF)	Resistance suppression
Erlendsdottir et al. (77)	2001	Benzylpenicillin	*In vivo*	*Streptococcus pneumoniae*	Murine (immuno-competent)	Lung	1, 10, 50, 100 mg/kg	65% T>MIC	Bactericidal activity
					Murine (immuno-competent)	Thigh	1, 10, 50, 100 mg/kg	65% T>MIC or Cmax > 15xMIC	Bactericidal activity
					Murine (immuno-competent)	Peritoneum, bacteraemia	1, 10, 50, 100 mg/kg	65% T>MIC or Cmax > 15xMIC	Bactericidal activity

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TABLE 2 Summary of 80 published studies defining a pharmacodynamic target for any ß-lactam antibiotic[a] (*Continued*)

Author	Year	Antibiotic	Study type	Organism(s)	Animal model	Infection syndrome	Regimen	Target	Outcome
					Rabbit	Tissue cage	4, 7.5, 15, 75, 150 mg/kg	35% T>MIC, Cmax >5 xMIC, AUC/MIC 25	Maximum bacterial killing
Fantin et al. (78)	1994	Cefpirome, Ceftazidime (± Amikacin)	*In vivo*	*Pseudomonas aeruginosa*	Rabbit	Endocarditis	Cefpirome 50 mg/kg q12 or 100 mg/kg q10, Ceftazidime 50 mg/kg q12 or q18	>61% T>MIC	Resistance suppression
Felton et al. (79)	2013	Piperacillin/ Tazobactam	*In vitro* (HFIM)	*Pseudomonas aeruginosa*	N/A	N/A	q8 30 m bolus	Cmin/MIC > 3.4	Resistance suppression
							q8 4 h extended infusion	Cmin/MIC > 10.4	
Firsov et al. (80)	2012	Doripenem	*In vitro*	*Pseudomonas aeruginosa*	N/A	N/A	unspecified	AUC24/MIC > 170	Resistance suppression
		Imipenem						AUC24/MIC > 140	
Gustafsson et al. (81)	2001	Cefotaxime	*In vitro*	*Streptococcus pyogenes*	N/A	N/A	unspecified	>50% T>MIC	Maximum bacterial killing
				Escherichia coli				> 80% T>MIC	Maximum bacterial killing
		Amoxicillin		Penicillin susceptible *Streptococcus pneumoniae*				>50% T>MIC	Maximum bacterial killing
				Penicillin intermediate *Streptococcus pneumoniae*				>60% T>10xMIC	Maximum bacterial killing
Keil et al. (82)	1997	Imipenem	*In vitro*	*Pseudomonas aeruginosa*	N/A	N/A	1 g q8	Css 2–3ug/mL	Resistance suppression
		Meropenem						Css 2.5 ug/mL	
Kim et al. (83)	2008	Doripenem	*In vivo*	*Pseudomonas aeruginosa*	Murine (neutropenic)	Thigh	500 mg q8 IV 1 h or 4 h	20% fT>MIC	Stasis
								>40% fT>MIC	Maximum bacterial killing
Knudsen et al. (84)	2003	Benzylpenicillin	*In vitro*	*Streptococcus pneumoniae*	Murine	Thigh	0.12/2/31 mg/kg q3/q2/q1	40-50% T>MIC and Cmax/MIC >10	Maximum bacterial killing
			In vivo		Murine	Peritoneum			
					Rabbit	Tissue cage	3/15/30/75 mg/kg		
Kuti et al. (85)	2018	Meropenem	Clinical	*Pseudomonas aeruginosa, S. maltophilia, Enterobacter cloacae, Inquilinus limosus*	N/A	Cystic fibrosis acute pulmonary exacerbation	40 mg/kg q8	>65% fT>MIC	Clinical response (FEV1 improvement)
Lamp et al. (86)	1998	Ampicillin/ Sulbactam	*In vitro*	*Escherichia coli*	N/A	N/A	1.5 g q6, 3 g q6	>27% T>MIC	Bactericidal activity

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TABLE 2 Summary of 80 published studies defining a pharmacodynamic target for any ß-lactam antibiotic[a] (*Continued*)

Author	Year	Antibiotic	Study type	Organism(s)	Animal model	Infection syndrome	Regimen	Target	Outcome
Lee et al. (87)	2007	Cefepime	Clinical	*Klebsiella pneumoniae, Klebsiella oxytoca, Escherichia coli*	N/A	Pneumonia, bacteraemia	1 g q12, 1 g q 24, 2 g q12	50% fT>MIC or Cmin/MIC >7.6 or AUC/MIC >1654	Microbiological response
Lepak et al. (88)	2014	Ceftolazone	*In vivo*	*Streptococcus pneumoniae*	Murine (neutropenic)	Thigh	0.39 mg/kg-800 mg/kg q6	18.1% T>MIC	Stasis
								23.8% T>MIC	One log bacterial kill
								26.7% T>MIC	Two log bacterial kill
				Pseudomonas aeruginosa				31.2% T>MIC	Stasis
								39.4% T>MIC	One log bacterial kill
								42.0% T>MIC	Two log bacterial kill
Li et al. (89)	2007	Meropenem	Clinical	*Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae, Klebsiella pneumoniae, Escherichia coli, Pseudomonas aeruginosa*	N/A	LRTI	500 mg/1 g q8/q12	fCmin/MIC > 5	Clinical and microbiological response
								54% fT>MIC, fCmax/MIC >383	Microbiological response
Li et al. (90)	2014	Meropenem	*In vitro* (HFIM)	*Acinetobacter baumanii*	N/A	N/A	0.5/1.0/2.0 g q8 0.5 h/3 h	>=20% T>MPC and T >MPC/TMSW >= 0.25	Maximum bacterial killing and resistance suppression
Louie et al. (91)	2010	Meropenem (± Levofloxacin)	*In vitro* (HFIM)	*Pseudomonas aeruginosa* (wild-type PA01)	N/A	N/A	1 mg/1.5 mg/2 mg/3 mg Meropenem q8 +/-750/1000/1250/1500 mg Levofloxacin q24	Cmin/MIC > 3.09 (meropenem alone), Cmin/MIC > 0.92 (meropenem and levofloxacin)	Three log bacterial kill and resistance suppression
				Pseudomonas aeruginosa (MexAB pump-overexpressed mutant)				Cmin/MIC > 1.88 (meropenem alone), Cmin/MIC > 0.822 (meropenem and levofloxacin)	
Lutsar et al. (92)	1997	Ceftriaxone	*In vivo*	*Streptococcus pneumoniae*	Rabbit	Meningitis	150 or 400 mg/kg q24/q12	95-100% T>MBC (CSF)	CSF sterilisation

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TABLE 2 Summary of 80 published studies defining a pharmacodynamic target for any ß-lactam antibiotic[a] (*Continued*)

Author	Year	Antibiotic	Study type	Organism(s)	Animal model	Infection syndrome	Regimen	Target	Outcome
MacGowan et al. (93)	2008	Tomopenem	*In vitro*	*Staphylococcus aureus* 10^6 CFU	N/A	N/A	750 mg q8, 1500 mg q8	8% T>MIC	Stasis
								12% T>MIC	One log bacterial kill
								16% T>MIC	Two log bacterial kill
								21% T>MIC	Three log bacterial kill
								32% T>MIC	Four log bacterial kill
								24.9% T>MIC	Maximum bacterial killing
				Staphylococcus aureus 10^8 CFU				6.4% T>MIC	One log bacterial kill
								13.4% T>MIC	Two log bacterial kill
								20.9% T>MIC	Three log bacterial kill
								30.1% T>MIC	Four log bacterial kill
								20-30% T>MIC	Resistance emergence
MacGowan et al. (94)	2015	Ceftolazone/ Tazobactam	*In vitro*	*Escherichia coli*	N/A	N/A	q8	27.8% fT>MIC	Stasis
								33% fT>MIC	One log bacterial kill
								39.6% fT>MIC	Two log bacterial kill
								>40% fT>8xMIC	Resistance suppression
				Pseudomonas aeruginosa				24.9% fT>MIC	Stasis
								26.6% fT>MIC	One log bacterial kill
								31.2% fT>MIC	Two log bacterial kill
								20-30% fT>MIC	Resistance emergence

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TABLE 2 Summary of 80 published studies defining a pharmacodynamic target for any ß-lactam antibiotic[a] (*Continued*)

Author	Year	Antibiotic	Study type	Organism(s)	Animal model	Infection syndrome	Regimen	Target	Outcome
MacVane et al. (95)	2014	Ceftazidime, Cefepime	Clinical	*Pseudomonas aeruginosa*, Enterobacteriaceae	N/A	Ventilator associated pneumonia	Ceftazidime: 2 g IV q8 Il, 3 g IV 24 h CI, Cefepime: unspecified	53% fT>MIC	Microbiological response
Maglio et al. (96)	2004	Cefepime	*In vivo*	ESBL *Escherichia coli* 10^7 CFU	Murine (neutropenic)	Thigh	25/75/300 mg/kg	6% T>MIC	Bactericidal activity
				ESBL *Escherichia coli* 10^5 CFU				26% T>MIC	
Maglio et al. (97)	2005	Ertapenem	*In vivo*	*Klebsiella pneumoniae*, *Escherichia coli*	Murine (neutropenic)	Thigh	10, 40, 100 mg/kg IM	19% fT>MIC	Stasis
								33% fT>MIC	80% maximum bactericidal activity
Manduru et al. (98)	1997	Ceftazidime	*In vitro*	*Pseudomonas aeruginosa*	N/A	N/A	2–96ug/l	Cmax/MIC 6.6	90% maximum bactericidal activity
McKinnon et al. (99)	2008	Cefepime, Ceftazidime	Clinical	*Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Staphylococcus aureus, Providencia*	N/A	UTI, skin/soft tissue, respiratory, bacteraemia	3.71 Ceftazidime per patient, 1.1 Ceftazidime per patient q8, q12, q24	AUIC 24 > 250, 100% T>MIC	Clinical and microbiological response
Mikamo et al. (100)	2008	Meropenem, Biapenem	Clinical	Unspecified	N/A	Pelvic inflammatory disease	Unspecified	35% T>MIC	Clinical and microbiological response
Mouton et al. (101)	1994	Ceftazidime	*In vitro*	*Pseudomonas aeruginosa*	N/A	N/A	Unspecified	100% T>4–5xMIC	Stasis
Mouton et al. (102)	2007	Ceftazidime	*In vitro*, *In vivo*, Clinical	*Pseudomonas aeruginosa*	Murine	Unspecified	35–38mg/kg (mice), q2/3/4/6/8/12	35-38% T>MIC	Stasis
								45-50% T>MIC	Two log bacterial kill
Muller et al. (103)	2013	Ceftazidime	Clinical	*Acinetobacter baumannii, Klebsiella pneumoniae, Pseudomonas aeruginosa, Escherichia coli, Enterobacter cloacae, Serratia marcescens, Haemophilus influenzae, Stenotrophomonas maltophilia*	N/A	Nosocomial pneumonia	Ceftazidime 2 g IV q8 +Linezolid 600 mg q12	>45% fT>MIC	Clinical and microbiological response
Muller et al. (104)	2014	Ceftobiprole	Clinical	*Acinetobacter* spp., *Citrobacter* spp., *Enterobacter* spp., *Escherichia coli*,	N/A	Nosocomial pneumonia	Ceftobiprole 500 mg q8IV, or Linezolid 600 mg	51.1% fT>MIC	Clinical response

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TABLE 2 Summary of 80 published studies defining a pharmacodynamic target for any ß-lactam antibiotic[a] (*Continued*)

Author	Year	Antibiotic	Study type	Organism(s)	Animal model	Infection syndrome	Regimen	Target	Outcome
				Haemophilus influenzae, Klebsiella spp., *Pseudomonas* spp., *Proteus* spp., Serratia spp., *Stenotrophomonas maltophilia*, *Miscellaneous* spp., *Corynebacterium* spp., *Enterococcus* spp., *Staphylococcus aureus*, *Staphylococcus* spp. (excluding *S. aureus*), *Streptococcus pneumoniae*, *Streptococcus* spp. (excluding *S. pneumoniae*)			q12 IV + Ceftazidime 2 g q8 IV		
								62.2% fT>MIC	Microbiological response
Nakamura et al. (105)	2019	Cefiderocol	*In vivo*	Enterobacteriaceae	Murine (neutropenic)	Thigh	4/40/400/600 mg/kg	62.5% fT>MIC	Stasis
								73.3% fT>MIC	One log bacterial kill
				Pseudomonas aeruginosa				63.0% fT>MIC	Stasis
								77.2% fT>MIC	One log bacterial kill
				Acinetobacter baumannii		Lung		88.1% fT>MIC	One log bacterial kill
				Stenotrophomonas maltophilia				53.9% fT>MIC	One log bacterial kill
				Enterobacteriaceae				64.4% fT>MIC	One log bacterial kill
				Pseudomonas aeruginosa				70.3% fT>MIC	One log bacterial kill
Navas et al. (106)	2004	Cefepime (± Tobramycin)	*In vivo*	*Pseudomonas aeruginosa*	Rabbit	Endocarditis	10/25/40/200 mg/kg Cefepime CI 24 h, 25 mg/kg Cefepime CI 24h + 3 mg/kg Tobramycin	LESCC 3–4xMIC	Two log drop in vegetations
		Imipenem (± Tobramycin)					10/15/25/100 mg/kg Imipenem CI 24 h, 15 mg/kg Imipenem CI 24h + 3 mg/kg Tobramycin	LESCC 0.25xMIC	Two log drop in vegetations
Nicolau et al. (107)	2000	Cefprozil	*In vivo*	*Streptococcus pneumoniae*	Murine (neutropenic)	Thigh	6 mg/kg PO q12	50% T>MIC	Survival

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TABLE 2 Summary of 80 published studies defining a pharmacodynamic target for any ß-lactam antibiotic[a] (*Continued*)

Author	Year	Antibiotic	Study type	Organism(s)	Animal model	Infection syndrome	Regimen	Target	Outcome
								20-30% T>MIC	Stasis
								40-50% T>MIC	Maximum bacterial killing
Nielsen et al. (108)	2011	Benzylpenicillin	*In vitro*	*Streptococcus pyogenes*	N/A	N/A	1000 mg q4	29% fT>MIC	Stasis
								38% fT>MIC	Three log bacterial kill
		Cefuroxime					750 mg q8	30% fT>MIC	Stasis
								41% fT>MIC	Three log bacterial kill
Ong et al. (109)	2007	Meropenem, Imipenem, Cefepime	*In vivo*	*Pseudomonas aeruginosa*	Murine (neutropenic)	Thigh	50/150/300 mg/kg Meropenem or 25/50/100 mg/kg Imipenem/Cilastatin	40% T>MIC	2.74 log kill
							25/75/200 mg/kg Cefepime	70% T>MIC	2.19 log kill
Rhodes et al. (110)	2015	Cefepime	Clinical	Gram negative blood stream infection	N/A	Bacteraemia	2 g q12, 2 g q8, 1 g q 12, 500 mg q12	68-74% T>MIC	Survival
Roberts et al. (111)	2014	Co-amoxiclav, Ampicillin, Cefazolin, Cefepime, Ceftriaxone, Doripenem, Meropenem, and Piperacillin/ Tazobactam	Clinical	*Pseudomonas aeruginosa, Escherichia coli*, others unspecified	N/A	Prophylaxis, treatment for lung infection/intra-abdominal infection/bacteraemia	Unspecified	50%/100% fT>MIC	Clinical response
Roosendaal et al. (112)	1989	Ceftazidime	*In vivo*	*Klebsiella pneumoniae*	Rat (leukopenic)	Pneumonia, bacteraemia	0.3/1/3/9 mg/kg q6	100% T>MIC	Bactericidal activity
Schentag et al. (113)	1991	Cefmenoxime	*In silico*	*Pseudomonas, Staphylococcus*	N/A	N/A	1000 mg q6	AUIC>MIC = 125	Clinical outcome
Soubirou et al. (114)	2015	Temocillin	*In vivo*	*Escherichia coli*	Murine (immuno-competent)	UTI, skin/soft tissue, respiratory, bacteraemia	200 mg/kg q2/q4/q6	80% fT>MIC	Maximum bacterial killing
Stearne et al. (112)	2007	Ceftizoxime	*In vivo*	*Bacteroides fragilis* and *Enterobacter cloacae*	Murine	Abscess	6–1536 mg/kg q2/4/6/8	fAUC/MIC >1000 and at least 100% T>MIC	Resistance suppression
Takata et al. (115)	2004	Biapenem, Imipenem/ Cilastatin,	*In vivo*	*Pseudomonas aeruginosa*	Murine	Thigh	300 mg BD Biapenem	17% fT>MIC	Clinical response

(*Continued on next page*)

TABLE 2 Summary of 80 published studies defining a pharmacodynamic target for any ß-lactam antibiotic[a] (*Continued*)

Author	Year	Antibiotic	Study type	Organism(s)	Animal model	Infection syndrome	Regimen	Target	Outcome
		Meropenem, Ceftazidime							
							500 mg/500 mg BD Imipenem/Cilastatin	17% fT>MIC	
							500 mg BD Meropenem	23% fT>MIC	
							1 g Ceftazidime BD	33% fT>MIC	
Tam et al. (116)	2002	Cefepime	Clinical	Gram negative blood stream infection	N/A	Bacteraemia	2 g q12, 2 g q24, 1 g q24	>100% T >MIC, Cmin/MIC > 5.8, T>4.3xMIC	Microbiological response
Tam et al. (117)	2005	Meropenem	*In vitro* (HFIM)	*Pseudomonas aeruginosa*	N/A	N/A	0.125 to 128 mg/liter	fCmin/MIC > 6.2	Resistance suppression
Tam et al. (118)	2007	Meropenem	*In vitro* (HFIM)	*Pseudomonas aeruginosa*	N/A	N/A	64 mg/L	100% T>MIC and Cmin/MIC >= 4	Resistance suppression
Tannous et al. (119)	2020	Piperacillin/ Tazobactam	Clinical	*Pseudomonas aeruginosa*	N/A	Bacteraemia	4.5 g q6/q8	>60.68% T>MIC	Survival
Thomas et al. (120)	1998	Cefmenoxime, Imipenem, Ceftazidime, Piperacillin	Clinical	*Pseudomonas, Enterobacter cloacae, Enterobacter aerogenes, Serratia marscesens, Citrobacter* spp., *Morganella morganii, Proteus vulgaris, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Haemophilus influenzae, Staphylococcus aureus,* Streptococcus pneumoniae	N/A	LRTI	Cefmenoxime 1 g/2 g q4/q6, Imipenem 1 g q8, Ceftazidime 1/2 g q8/q12, Piperacillin - unspecified	AUC/MIC < 100	Resistance emergence
Vanscoy et al. (121)	2013	Ceftolazone/ Tazobactam	*In vitro*	*Escherichia coli*	N/A	N/A	0.01, 0.05, 0.1, 0.25, 0.5, 0.75, and 1 µg/mL	35% T> threshold	Stasis
								50% T> threshold	One log bacterial kill
								70% T> threshold	Two log bacterial kill
Vogelman et al. (122)	1988	Ticarcillin (100% *Pseudomonas spp.*), penicillin (100% *S. pneumoniae*), Cefazolin (20% *S.*	*In vivo*	*Pseudomonas aeruginosa*	Murine (neutropenic)	Thigh	q1/2/3/4/6/8/12/24	100% T>MIC	One log bacterial kill

(*Continued on next page*)

TABLE 2 Summary of 80 published studies defining a pharmacodynamic target for any ß-lactam antibiotic[a] (*Continued*)

Author	Year	Antibiotic	Study type	Organism(s)	Animal model	Infection syndrome	Regimen	Target	Outcome
		aureus, 60% *E. coli*)							
		Benzylpenicillin		Streptococcus pneumoniae			q1/2/3/4/6/8/12/24	100% T>MIC	
		Cefazolin		Staphylococcus aureus			q3-q24	20% T>MIC	
		Cefazolin		*Escherichia coli*			q1-q12	60% T>MIC	
White et al. (123)	1996	Meropemen, Imipenem	*In vitro*	Pseudomonas aeruginosa	N/A	N/A	Imipenem: 64, 32, 16, 8,4, 2, 1, 0.5, 0.25, 0.125 mg/mL, Meropenem: 8, 4,2, 1, 0.5, 0.25, 0.125, 0.063, 0.031, 0.016 mg/mL	C >4xMIC	Three log bacterial kill
Wong et al. (124)	2020	Cefepime, Ceftazidime, Ceftriaxone, Piperacillin/ Tazobactam, Meropenem	Clinical	Acinetobacter baumannii, Citrobacter koseri, Enterobacter aerogenes, Enterobacter cloacae, *E. coli*, Klebsiella oxytoca, *K. pneumoniae*, *Klebsiella* spp., Morganella morganii, P. aeruginosa, Proteus mirabilis, Proteus vulgaris, Serratia liquefaciens, Serratia marcescens	N/A	Bacteraemia	Unspecified	fCmin/MIC > 1.3 (fCmin/MIC > 4.95 for Meropenem, Ceftriaxone)	Clinical outcome
Woodnutt et al. (125)	1999	Amoxicillin, Co-amoxiclav	*In vivo*	*Streptococcus pneumoniae*	Murine (neutropenic)	Lung	2.5/1280 mg/kg/day, q4/q6/q8/q12	35-40% T>MIC	Three log bacterial kill
Woodnutt et al. (126)	1999	Co-amoxiclav	*In vivo*	*Streptococcus pneumoniae*	Rat	Lung	45/6.4 mg/kg/day q12, 90/6.4 mg/kg/day q12	>34% T>MIC	One log bacterial kill
Xuan et al. (127)	2002	Ertapenem	*In vivo*	*Streptococcus pneumoniae*	Murine (neutropenic)	Thigh	20, 50, 100 mg/kg	6% fT>MIC	Stasis
								30% fT>MIC	Maximum bacterial killing
Zelenitsky et al. (128)	2016	Piperacillin/ Tazobactam	*In vitro*	*Pseudomonas aeruginosa*	N/A	N/A	8 mg/L, 16 mg/L	27% fT>MIC	Stasis
								75% fT>MIC	Three log bacterial kill
Zhou et al. (129)	2011	Meropenem	Clinical	Gram negative bacilli	N/A	LRTI	0.5 g/1 g q8/q12	76% T>MIC	Clinical response
Zinner et al. (130)	2013	Doripenem	*In vitro*	*Pseudomonas aeruginosa*	N/A	N/A	TDS	T in MSW >= 45%, AUC24/MIC < 170	Resistance emergence

[a]CFU, colony forming units; ESBL, extended spectrum β-lactamase; HFIM, hollow fibre infection model; OD, once daily dosing; BD, twice daily dosing; TDS, three times daily dosing; IV, intravenous administration; PO, oral administration; CI, continuous infusion; AUIC, area under the inhibitory curve; fCMIN, minimum free drug concentration; CSS, steady state drug concentration; LESCC, lowest effective steady-state concentration; MBC, minimum bactericidal concentration; MPC, mutant prevention concentration; MSW, mutant selection window.

component, 35 included an animal model, and 23 were conducted using clinical data. 26/35 (74.3%) of animal studies were conducted only in murine thigh or lung models.

A total of 42/80 (52.5%) articles determined the optimal target magnitude to be something other than 30%–50% *f*T>MIC. 100% *f*T>MIC and 100% *f*T>4×MIC were both frequently cited target magnitudes (101, 111, 112, 118, 119, 123). Variability in target magnitudes occurred based on study type (e.g. *in vitro* vs animal model vs clinical) and the pharmacodynamic endpoints/outcomes used. For example, for meropenem, 40%T > MIC correlated with logarithmic and maximal bacterial killing in two neutropenic murine models (75, 109), which was similar to the 35% T>MIC required for clinical cure in pelvic inflammatory disease patients (100); however, a much larger magnitude of 82%–83% T>MIC was determined for regrowth suppression and in treatment of bacteraemic neutropenic patients (58, 62). Conversely, similar target magnitudes were at times derived from different endpoints (e.g., for *Pseudomonas aeruginosa* and ceftazidime in animal models, 40%–50% *f*T>MIC was determined optimal for stasis, logarithmic killing, and regrowth suppression) (54, 69, 72, 101). Infecting pathogen (especially Gram-positive vs Gram-negative) (71, 81, 97), the bacterial inoculum (96), and different strains (91) were all shown to cause variability in targets within studies. Few studies (18/80, 22.5%) used resistance or regrowth suppression as a pharmacodynamic endpoint, and for these studies, 50% utilized an alternative index to *f*T>MIC.

DISCUSSION: CHALLENGES AND OPPORTUNITIES

Antibiotic regimen and drug exposure

The key concept that underpins PopPK studies is that robust estimates of variability are central to estimating the likely treatment effects for any given antibiotic regimen. Studying homogenous patient populations generally results in measures of central tendency that approximate the true population value but the coefficient of variation (CV%) is much lower. For example, the CV% for antibiotic clearance (and hence, area under the concentration time curve [AUC]) for human volunteers is generally 40%–50% but typically doubles in patients and may be >100% in those with extreme physiology (e.g., in critical care) (33). Using unrepresentative patient groups (and, therefore, models) for regimen planning generally results in underestimating variance by a factor of approximately two, which translates to being able to treat a pathogen with one doubling dilution lower MIC (e.g., for a volunteer population, an MIC of 4 mg/L can be covered; for a patient population, only an MIC of 2 mg/L can be adequately treated—this is the cost of increased variability) (Fig. 6A).

There is a marked inequity in current PopPK data sets for key AWaRe agents (Fig. 4); the lack of data from LMIC settings may underestimate true variance. Malnutrition and chronic infections may result in higher pharmacokinetic variability. In particular, regions with a high prevalence of HIV and tuberculosis may have altered pharmacokinetics due to the disease itself (e.g., secondary to altered body composition, reduced renal function) or drug-drug interactions (DDIs). A study of ciprofloxacin PopPK that met the inclusion criteria of our systematic review determined rifampicin treatment as a significant covariate; indeed, rifampicin is well established to increase the metabolism of several key oral antibiotic classes recommended for community used within the AWaRe Book, including quinolones, macrolides, and sulfonamides (27, 133). Another quinolone PopPK model found efavirenz to be a significant covariate, which is also well recognized to be responsible for clinically relevant DDIs (134). The co-administration of AWaRe Book antibiotics with any agents that reduce the magnitude of or alter the duration of antibiotic drug exposure may have a significant impact on the expected effect and resistance liabilities.

The systematic review shows there is a striking paucity of high-quality population PK data for amoxicillin ± clavulanic acid. One of the studies was in healthy European men (19), who are poorly representative of the extensively diverse global populations that rely on amoxicillin to treat the diseases shown in Fig. 1. At the present time, there is little

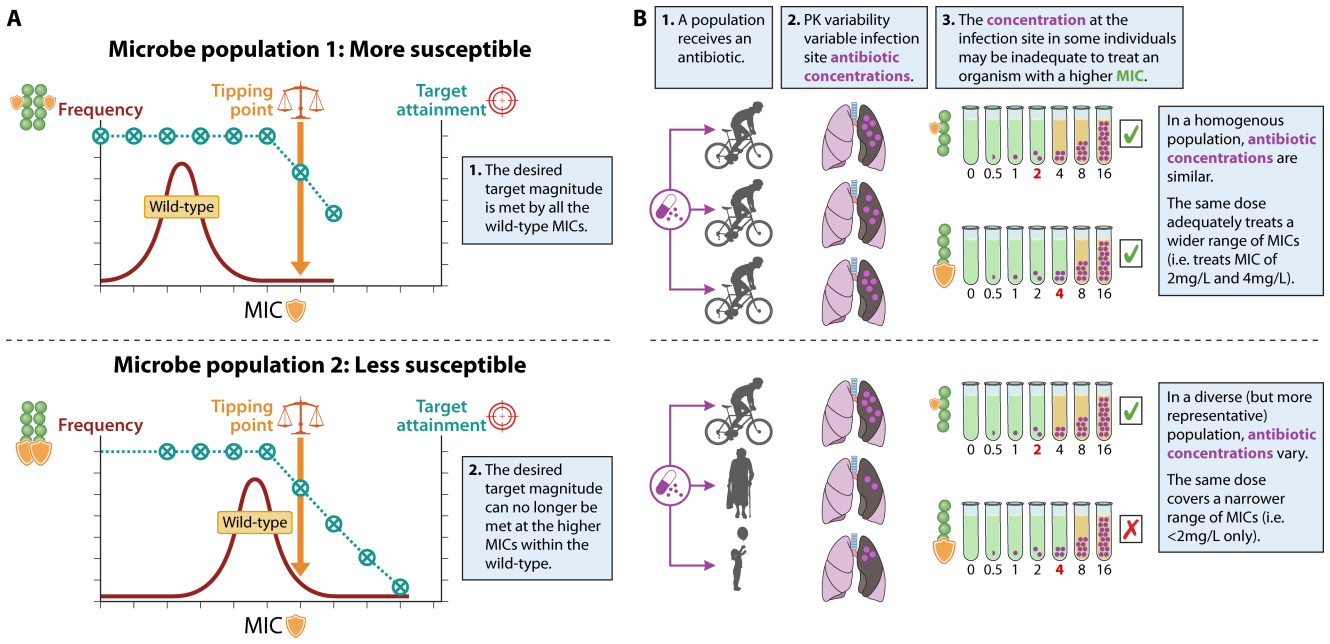

FIG 6 Interdependent elements of the triple lock: (A) Increased PK variability results in an antibiotic dose being inadequate to treat the whole population at higher MICs; (B) When the MIC distribution shifts to the right, the PD target is not met at higher wild-type MICs.

understanding of the potential impact of malnutrition, comorbidity, body size, or illness on the absorption, distribution, and clearance of the world's most widely used antibiotic (18) —this needs to be urgently rectified.

Antibiotic potency and MIC distribution

As with PopPK data, AST data show inadequate representation of diverse global community settings. Regions previously determined to have a high burden of AMR are poorly represented in databases (1). For regions where AST data are reported, sampling strategies may skew available results. The disparity between reported penicillin resistance for *Streptococcus pneumoniae* in ATLAS and GLASS highlights the need for widened surveillance with sampling representative of the global burden of disease. Community pathogens and infections and their corresponding antibiotic treatments are inadequately reported in existing data sets.

Databases containing complete, representative and unbiased MIC distributions are significantly more useful for regimen planning than a simple S/R classification; however, these resources are scarcer. Knowledge of the distribution of MICs enables overall target attainment rates for drug-pathogen combinations to be calculated (see Fig. 6B). Probability of target attainment (PTA) plotted with the MIC distribution provide an indication whether the regimen is potentially close to a tipping point (see Fig. 6B), which may prompt closer surveillance and monitoring. Ultimately, without open-access MIC databases encompassing a range of populations, clinical infections, geographical and healthcare settings, comprehensive MIC distributions cannot be described, which limits detailed regimen planning.

Even where surveillance data are available, laboratory antibiotic susceptibility testing, regimen guidance, and prescribing practice are all slow to reflect right-shifts in MIC distributions and impact of alterations in breakpoints. The AWaRe Book could provide a useful role to integrate these changes if provided with a sufficient evidence-base.

There are well understood limitations of the MIC and, therefore, its role in establishing the adequacy of a given regimen. While MIC is a standard measure of antibiotic susceptibility, it may not account for many of the progressive dynamic changes that occur with longer antibiotic exposures. As such, the MIC may not predict the potential for

rapid emergence of resistance that is characteristic of some drug-pathogen combinations.

Pharmacodynamic targets

Defining pharmacodynamic targets that are relevant for clinical care is challenging. For antibiotic drug development, the drug exposure that is associated with stasis or orders of logarithmic killing in murine models of infection is used to define regimens of new drugs for complicated urinary tract infection (cUTI) and pneumonia, respectively. Most articles meeting systematic review criteria (Fig. 3B) utilized a target magnitude defined in another study. Citation tracing (Fig. 5) demonstrates that old studies are repeatedly cited leading to widely held and self-propagating constructs such as *f*T>MIC of 30%–50% of the dosing interval is required for efficacy for the β-lactam antibiotics. While this is likely to be a reasonable estimate for most patients, there are clearly circumstances where this "one-size-fits-all" target may not be appropriate. For example, little is known about drug exposure targets that counter-select emergence of resistance in global settings (as opposed to treatment of pathogens with established resistance mechanisms), appropriate pharmacodynamic targets for sequestered disease (e.g., sinusitis) and disease entities where drug partitioning may be compromised by anatomical constraints (e.g., ear and acute otitis media) or intense inflammation (e.g., pneumonia, complex ear disease). Current targets are entirely reliant on serum pharmacokinetics despite known differences in tissue partitioning and further within-tissue spatial distributions of antibiotic affected by pathogenesis (135, 136).

The systematic review revealed that the pharmacodynamic evidence for targets is not as homogenous as might be believed (Table 2), largely contributed to using different pharmacodynamic endpoints and model systems but also possibly due to organism, strain, and bacterial load. This inconsistency is more evident when target magnitudes for AMR mitigation are considered. Clearly such wide differences in these targets have significant implications for regimen planning with extreme estimates potentially producing contradictory and unrealistic predictions. Further insight and agreement as to pharmacodynamic targets that are relevant for regimen planning for agents in the AWaRe Book would be a significant advance for the global AMR agenda.

Pharmacodynamic targets for widely used β-lactam antibiotics (e.g., amoxicillin, phenoxymethylpenicillin, flucloxacillin/cloxacillin/dicloxacillin, and cefalexin) are primarily extrapolated from data from i.v. formulations. For these agents, a total of four PopPK and eight PD target studies were included within the systematic reviews. Importantly, there were no studies establishing pharmacodynamic targets for cefalexin or the anti-staphylococcal penicillins. The dangers of poorly defined pharmacodynamic targets are clear: when the traditional target of 30%–50% *f*T>MIC is used for a regimen of 1,000 mg cefalexin administered eight hourly, the PTA falls below 90% at MICs of 4–8 µg/mL (137); however, if a target of >70% *f*T>MIC is used, the "tipping point" (Fig. 6A) occurs at an MIC of 2 µg/mL. Within the EUCAST MIC database, 30% (when inferred from cefoxitin)–50% (when directly cefalexin tested) of *Staphylococcus aureus* isolates had an MIC > 2 µg/mL. Concerningly, when AWaRe Book cefalexin doses of 500 mg three times daily are used, drug exposure may be insufficient to adequately treat skin and soft tissue infection (SSTI) caused by *Staphylococcus aureus*.

The systematic review also demonstrated that other than UTI, pneumonia, and SSTI there was no specific consideration for the pharmacodynamics of diseases considered in AWaRe Book. The pharmacodynamic field currently depends largely on the murine thigh infection model (a surrogate for cUTI and SSTI), murine pneumonia model (surrogate for pneumonia), and hollow fiber infection models (surrogate for high density infections to address emergence of resistance). These model systems have been largely tuned for the study of new antibiotic agents against multiple and extremely drug-resistant (MDR, XDR) Gram negative pathogens rather than the Gram-positive pathogens (e.g., Group A *Streptococcus*, *Staphylococcus aureus*, *Streptococcus pneumoniae*) that are relevant to the PHC settings of the AWaRe Book. Furthermore, available model systems are typically

conducted on a profoundly neutropenic background and may, therefore, be a poor mimic of diseases and patients seen in PHC settings. Development of new model systems and disease constructs that adequately reflect both the pathogen and host is an urgent priority to help define and plan regimens that are safe, effective, and resilient. Given the challenges in developing experimental models that fully represent the complexity of the interplay between the pathogen, pathogenesis, comorbidity, and host immune defects on therapeutic outcomes alternative approaches are required. The increased use of *in silica* tools to combine evidence from multiple sources may be one way this can be achieved.

Conclusions

Currently, evidence from our systematic and database reviews shows that all elements of the "triple lock" are lacking in adequate, diverse, and representative evidence to support the AWaRe Book recommended PHC oral antibiotic dosing strategies (Fig. 1 [column 4]) or, indeed, other dosing strategies used in current national or regional guidance. Pharmacokinetic and pharmacodynamic data are significantly lacking in regions where the burden of resistant infections may be highest. Available data are not generated in the PHC settings where most antibiotics are used. One-size-fits all targets do not reflect the nuances for drug-pathogen-disease combinations described in the AWaRe Book. As a result of these deficits, there is uncertainty about the resilience of the recommended treatment regimens in minimising AMR emergence.

In line with the WHO Global Research Agenda for AMR (138), we propose several recommendations to enable optimization of empirical antibiotic dosing in community settings, outlined in Box 1. Our recommendations emphasize the need for equitable generation of regional data sets, collaborative open-access data-sharing, the development of cost-effective novel technologies, and the need for models that are representative of the breadth of human infection and focus on AMR counter-selection.

BOX 1. POSSIBLE SOLUTIONS TO GENERATE THE NECESSARY PHARMACOLOGIC EVIDENCE-BASE TO IMPLEMENT MORE EVIDENCE-BASED GLOBAL ANTIBIOTIC DOSING RECOMMENDATIONS.

Challenge 1: Lack of diversity and underrepresentation of PHC and LMICs in data sets

Possible Solutions:

a. Development of novel methodologies for PopPK sampling and MIC determination that limit costs, reduce the need for personnel and laboratory infrastructure, and allow for the acceptability of sampling across diverse populations.
b. Encourage data pooling through the generation of open-access repositories of PopPK and MIC data, with reporting of raw data and their sources.

Challenge 2: Inadequate model systems for PHC infection

Possible Solutions:

a. Development of laboratory animal infection models that are relevant to PHC diseases (e.g., upper respiratory tract) to allow generation of site- and disease-specific pharmacodynamic targets.
b. Development of novel techniques to investigate antibiotic distribution in key PHC infection anatomical sites in laboratory animal models and clinical studies and to facilitate PopPK sampling from effect sites.

c. Encourage the use of *in silico* technologies that can help model spatial PK, sequence of mutational events, and other dynamic phenomena.

Challenge 3: Current antibiotic dosing regimens rarely include strategies to mitigate the development of future AMR associated with their use

Possible Solutions:

a. Pharmacodynamic analyses of older generic AWaRe agents, their resistance liabilities, and the dose and scheduling strategies required to subvert these processes.
b. Exploration of the role of combination Access antibiotics in both counter-selecting for AMR and adequately treating emerging AMR over the course of clinical infection.
c. Encourage clinical studies that can better correlate pharmacodynamic targets with AMR emergence in patients.
d. Optimise drug delivery strategies to allow improved antibiotic exposures at the relevant infection site that can be assessed according to improved understanding of site-specific PK-PD.

A total of only 12 oral antibiotics are being recommended to treat the most common infection presentations in community settings, where most antibiotics are administered. These antibiotics are older generic agents that are already widely recommended by multiple international agencies with billions of courses used annually despite inadequate data to underpin their optimal dosing. For some of these agents, there is no data on which to base regimen planning. Many of these essential, well-established antibiotics are administered at current commonly used doses due to existing labels and literature that characterize their safety. An overhaul of existing formulations may be neither feasible nor cost-effective on a global scale and may, indeed, hinder access to essential antibiotics. However, there remains disagreement within international guidance on the regimens of existing agents/formulations required for the treatment of the most common community infections, e.g., community acquired pneumonia. With very few novel oral antibiotics in development, it is critical that the use of existing key antibiotics is optimized, to ensure evidence-based dosing regimens that optimize clinical efficacy in the context of AMR, reduce the selection of resistance, and minimize toxicity.

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Nada Reza, Conceptualization, Data curation, Formal analysis, Methodology, Software, Visualization, Writing – original draft | Alessandro Gerada, Software, Writing – review and editing | Katharine E. Stott, Conceptualization, Writing – review and editing | Alex Howard, Writing – review and editing | Mike Sharland, Conceptualization, Writing – review and editing | William Hope, Conceptualization, Supervision, Writing – review and editing

ADDITIONAL FILES

The following material is available online.

Supplemental Material

Supplemental tables (CMR00139-23-s0001.docx). Tables S1 to S5.

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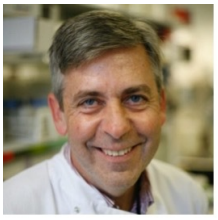

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