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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Running Head: Challenges for global antibiotic regimen planning

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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 non-community 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 provides adequate treatment in the context of the increasing prevalence of antimicrobial resistance and moreover, minimises the emergence of resistance.

# 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 for 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 often used 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 centre 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 favourable 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 & 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 (Figure 1).

***Figure 1.*** *The ten 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.*

The triple lock (Figure 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) (Figure 2b); (ii) the *MIC distribution* that needs to be covered in clinical settings—being able to cover the wildtype distribution (i.e., those strains that do not carry a resistance mechanism to the antibiotic) is critical (Figure 2c); and (iii) the *pharmacodynamic target* (i.e., magnitude of drug exposure relative to the MIC of the target pathogen that is required to secure a favourable therapeutic outcome for a given drug-pathogen-disease combination; Figure 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.

***Figure 2a.*** *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.*

## Antibiotic regimen & drug exposure

An antibiotic regimen includes the dose, schedule, and duration of antibiotic treatment. For a chosen antibiotic a variety of regimens maybe 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 favourable 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 (Figure 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 harmonisation across multiple infections), (9) and to facilitate compliance with antibiotic treatment (e.g., minimising doses per day).

The behaviour of any drug in a population of patients is described using population modelling 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 (Figure 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 & MIC distribution

The MIC is an *in vitro* measure of antibiotic potency and is estimated using standardised and well characterised 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 (Figure 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 (Figure 2d). These are: (i) the ratio of free drug peak antibiotic concentration to MIC (*f*Cmax:MIC), (ii) the fraction of the dosing interval that free drug concentrations are above the MIC (*f*T>MIC), and (iii) the ratio of the area under the free drug concentration-time curve, to MIC (*f*AUC: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.

# PK-PD literature search strategy & 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) ten databases encompassing general bibliographic databases, trial registers and grey 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), 7875 records were screened against selection criteria, fully outlined in Figure 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 (Figure 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).

***Figure 3*** *PRISMA flow-charts detailing:* ***a.*** *results of systematic review of population pharmacokinetic studies for AWaRe Book PHC agents,* ***b.*** *results of systematic review of pharmacodynamic targets for AWaRe Book PHC agents.*

## Studies reporting optimal pharmacodynamic target magnitude

Utilising 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 (Figure 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, whilst 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 & database reviews

## Systematic review of PopPK studies

A total of 192 PopPK studies met the inclusion criteria (Figure 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 (Figure 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 datasets 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 hospitalised populations who may have different PK parameters compared with generally less ill patients treated in PHC settings. Conversely, twelve 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 (Figure 4b). 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 (37–42). In low- and middle- income countries (LMICs) (Figure 4a), malnutrition is persistently prevalent and obesity rates are rising (41, 42)– 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 datasets. Only four studies were conducted at least in part in paediatric 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 (43). Age-related physiological changes, multi-morbidity and polypharmacy have a well-recognised impact on PK and vary globally (44, 45).

*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*

***Table 1.*** *Summary of eighteen literature published population pharmacokinetic studies for WHO AWaRe Book PHC oral antibiotic.*

*LIC = low income country, LMIC = lower-middle income country, UMIC = upper-middle income country, HIC = high income country, NA= unclassified*

***Figure 4a.*** *Countries by World Bank Income Classification;*(46)***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.*

## 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 (Figure 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* versus penicillins (<80%), *Salmonella* spp. *and fluoroquinolones* (<80%), *Escherichia coli* and sulfonamides/trimethoprim (<50%) – see Figure 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 datasets 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 ten of the common pathogen-antibiotic combinations (Figure 1), and MICs for amoxicillin , which is the key agent for treatment of many PHC diseases (Figure 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 datasets. 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 (Figure 4c) (51). Similar to PopPK studies, MIC values are primarily generated from hospital settings, potentially skewing MIC distributions to less susceptible values (Figure 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 (Figure 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 (Figure 5) generated from these ten 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, nine (36%) did not define a target magnitude.

***Figure 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 ten articles published 2022/2023 (Table S4). Yellow labelled 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 labelled in white (Table S5).*

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 ß-lactam. A total of 34 articles included an *in vitro* 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 > 4xMIC 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% utilised an alternative index to *f*T>MIC.

*CFU = colony forming units, ESBL = extended spectrum ß-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, 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*

***Table 2.*** *Summary of 80 published studies defining a pharmacodynamic target for any ß-lactam antibiotic.*

# Discussion: Challenges & opportunities

## Antibiotic regimen & 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 generally 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) (Figure 6a).

There is a marked inequity in current PopPK datasets for key AWaRe agents (Figure 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 recognised 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 Figure 1. At the present time, there is little 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.

***Figure 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.*

## Antibiotic potency & MIC distribution

As with PopPK data, AST data shows 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 is 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 datasets.

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 Figure 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 Figure 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 this 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, at 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 (Figure 3b) utilised a target magnitude defined in another study. Citation tracing (Figure 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 ß-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 ß -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 1000mg 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’ (Figure 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 fibre 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 (Figure 1 [column 4]) or indeed other dosing strategies used in current national or regional guidance. Pharmacokinetic and pharmacodynamic data is significantly lacking in regions where the burden of resistant infections may be highest. Available data is 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 optimisation of empirical antibiotic dosing in community settings, outlined in Panel 1. Our recommendations emphasise the need for equitable generation of regional datasets, 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.

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 characterise 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 optimised, to ensure evidence-based dosing regimens that optimise clinical efficacy in the context of AMR, reduce the selection of resistance and minimise toxicity.

**Challenge 1: Lack of diversity and underrepresentation of PHC and LMICs in datasets**

**Possible Solutions:**

1. 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.
2. 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:**

1. 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.
2. 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.
3. 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:**

1. Pharmacodynamic analyses of older generic AWaRe agents, their resistance liabilities, and the dose and scheduling strategies required to subvert these processes.
2. 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.
3. Encourage clinical studies that can better correlate pharmacodynamic targets with AMR emergence in patients.
4. 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.

***Panel 1.*** *Possible solutions to generate the necessary pharmacologic evidence-base to implement more evidence based global antibiotic dosing recommendations.*

# Acknowledgements

NR holds an Academic Clinical Fellowship awarded by NIHR. KES holds an Academic Clinical Lectureship awarded by NIHR. MS is CI for the Wellcome Trust grant of ADILA [222051/Z/20/Z]. AH & AG are funded in part by the Wellcome Trust [grant ref: 226691/Z/22/Z]. For the purpose of open access, the author has applied a CC BY public copyright licence to any Author Accepted Manuscript version arising from this submission. This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Contributor roles: NR– conceptualisation, data curation, formal analysis, methodology, visualisation, writing - original draft; AG– methodology, writing - review & editing; KES– conceptualisation, writing - review & editing; AH – writing - review & editing; MS – conceptualisation, writing - review & editing; WH – conceptualisation, supervision, writing - review & editing

# Conflicts of Interests

AH declares consulting work for Pfizer outside the submitted work. MS is Chair of the WHO Essential Medicine List Antibiotic Working group. WH holds or has held research grants with UKRI, EU, F2G, Spero Therapeutics, Antabio, Pfizer, Bugworks, Phico Therapeutics, BioVersys, Global Antibiotic Research & Development Partnership (GARDP), and NAEJA- RGM. WH is or has been a consultant for Appili Therapeutics, F2G, Spero Therapeutics, NAEJA-RGM, Centauri, Pfizer, Phico Therapeutics, Pulmocide, Amplyx, Mundipharma Research, and VenatoRx. WH is a member of the Specialist Advisory Committee for GARDP and the Specialty National co-lead for Infectious Diseases for the National Institute of Health Research.

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**Katharine Stott** is an NIHR Academic Clinical Lecturer in Antimicrobial Pharmacology at the University of Liverpool, UK. In addition to academic work, she is also a specialist medical registrar at the Royal Liverpool University Hospital. Her academic work focusses on immunocompromised medicine and optimisation of antimicrobial therapy, with a particular interest in mycology and antifungal pharmacodynamics.

She completed a Wellcome Trust clinical PhD fellowship studying the pharmacodynamics of antifungal drugs in HIV-associated invasive fungal disease. She ran a clinical pharmacodynamic study of cryptococcal meningitis (CM) in Blantyre, Malawi. Her current research continues to seek to optimise pharmacodynamics in CM and also aims to improve the treatment of invasive candida disease.

Dr Stott has established an infection pharmacology teaching network between the UK, Malawi and South Africa. She has additional teaching roles at the University of Liverpool, the University of Exeter and the Schools of Tropical Medicine in Liverpool and London.

**Alex Howard** graduated from University of Liverpool Medical School in 2011 and took up a post as Consultant in Medical Microbiology at Liverpool University Hospitals NHS Foundation Trust in 2019. He has previously held posts as Antimicrobial Stewardship Lead and Tuberculosis Laboratory Lead at the same Trust, and Infection Control Doctor at the Clatterbridge Cancer Centre. He currently leads the haemato-oncology and bone marrow transplant infection MDTs at the Clatterbridge Cancer Centre and is undertaking a PhD in Pharmacology. He has an interest in medical informatics and data science applied to antimicrobial regimens and resistance.

**Mike Sharland** is an expert in antimicrobial prescribing, resistance and healthcare associated infection (APRHAI) in children. Professor Sharland graduated from medical school and is since 2011 Professor in Paediatric Infectious Diseases at St George’s University of London. He is the lead clinical advisor for the neonatal and paediatric programme of the Global Antibiotic Research and Development Partnership (GARDP) and Vice-Chair and AMR lead of the Penta Foundation, a global Paediatric Infectious Diseases research network. He has Chaired the Department of Health’s National Expert Advisory Committee of APRHAI from 2011 to 2018. He is a frequent advisor to the WHO, including as member of the Expert Committee on the Selection and Use of Essential Medicines and the Chair of the Antibiotic Working Group of the EML/EMLc, which developed the Access/Watch/Reserve grouping of antibiotics. He leads numerous clinical projects globally with active funding from EDCTP, EU H2020, GARDP, NIHR, MRC, Wellcome Trust.

**William Hope** (BMBS, FRACP, FRCPA, PhD), is Dame Sally Davies Chair of AMR Research at the University of Liverpool in the UK. Professor Hope is a Fellow of the Royal Australasian College of Physicians and a Fellow of the Royal College of Pathologists of Australasia.  Areas of special interest and research are antimicrobial pharmacokinetics and pharmacodynamics, antimicrobial drug development and individualisation of antimicrobial therapy. He is a Fellow of the American Academy of Microbiology and European Society of Clinical Microbiology and Infectious Diseases.