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1 **Methodological features of clinical pharmacokinetic (PK)-pharmacodynamic (PD)**
2 **studies of antibacterials and antifungals: a systematic review**

3

4 *Running title: Systematic review of clinical PK-PD studies*

5

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23

24 **Synopsis**

25 **Background:** Pharmacokinetic (PK)- pharmacodynamic (PD) indices relate measures of drug
26 exposure to antibacterial effect. Clinical PK-PD studies aim to correlate PK-PD indices with outcomes
27 in patients. Optimisation of dosing based on pre-clinical studies mean that PK-PD relationships are
28 difficult to establish, therefore studies need to be designed and reported carefully to validate pre
29 clinical findings.

30 **Objectives:** To describe the methodological features of clinical antibacterial and antifungal PK-PD
31 studies that reported the relationship between PK-PD indices and clinical or microbiological
32 responses.

33 **Methods:** Studies published between 1980 and 2015 were identified through systematic searches.
34 Methodological features of eligible studies were extracted.

35 **Results:** We identified 85 publications containing 97 PK-PD analyses. Most studies were small, with
36 fewer than 100 patients. Around a quarter were performed on patients with infections due to a
37 single specific pathogen. In approximately one third of studies, patients received concurrent
38 antibiotics/antifungals, and in some other studies patients received other treatments that may
39 confound the PK-PD – outcome relationship. Most studies measured antimicrobial concentrations in
40 blood/serum, and only four measured free concentrations. Most performed some form of
41 regression, time to event analysis or used the Hill/ E_{max} equation to look at the association between
42 PK-PD index and outcome. Target values of PK-PD indices that predict outcomes were investigated in
43 52% of studies. Target identification was most commonly done using recursive partitioning or logistic
44 regression.

45 **Conclusions:** Given the variability in conduct and reporting, we suggest that an agreed set of
46 standards for the conduct and reporting should be developed.

47 Introduction

48 Pharmacokinetics (PK) and pharmacodynamics (PD) are central to an understanding of how best to
49 employ anti-infective medications. PK and PD considerations ensure that patient outcomes are
50 optimised, since they inform the choice, dose and frequency of appropriate anti-infectives, the
51 potential use of combinations, decisions about duration of treatment, and definitions for
52 categorising the infecting pathogen as susceptible or resistant to therapy.

53 The PK and PD properties of antimicrobials are often considered simultaneously to form PK-PD
54 indices, for example, the ratio of peak concentration of the antimicrobial (C_{max}) to the MIC
55 (C_{max}/MIC).

56 Knowledge of the PK-PD index that best predicts treatment efficacy, and the magnitude of that index
57 that is associated with optimal outcomes, can be used to guide antimicrobial treatment. This can
58 maximise the possibility of both successful clinical outcome and pathogen eradication, which in turn
59 may help to prevent the development of drug resistant pathogens.

60 The study of PK-PD is an iterative process whereby pre-clinical (*in vitro* and *in vivo*) experiments,
61 population PK models, and *in silico* simulations are used to investigate potential dosing regimens and
62 PK-PD targets. These studies can be used to inform regimen selection for clinical studies.

63 Numerous clinical PK-PD studies of antimicrobials have been performed. They generally aim to
64 investigate the relationship between PK-PD indices and either clinical or microbiological response (or
65 some element of these outcomes, or both) in patients. In some cases, they have sought to
66 determine the target magnitude of a PK-PD index to increase the probability of successful outcome
67 during therapy. Relationships between PK-PD indices and response, and PK-PD targets for efficacy
68 may be difficult to find in clinical PK-PD studies if pre-clinical development has been performed well.

69 Clinical PK-PD studies are required to confirm conclusions from pre-clinical studies and to provide
70 information for future use to calibrate pre-clinical systems more closely to clinical circumstances. In
71 addition, there are concerns that many of these clinical PK-PD studies have limitations including:
72 small size (<100 patients), not limiting analyses to populations with similar pathogens and sites of

73 infection, not measuring free drug concentration, not being designed with a primary
74 pharmacodynamic end point in mind, and not adjusting analyses for confounders such as source
75 control or comorbidities. There is also uncertainty over how results should be analysed and how PK-
76 PD index targets for efficacy should be identified. In addition, there may be a bias in the literature
77 towards reporting positive results.

78 It is therefore timely to perform a systematic review of the methodological features of clinical PK-PD
79 studies of antibacterials and antifungals. Here we review articles published between 1980 and 2015
80 that reported the relationship between PK-PD indices and some form of clinical or microbiological
81 response. In addition to summarising the methodological features of these studies, we had a
82 secondary goal of finding examples of good practice that might be used to inform future PK-PD
83 analyses.

84 **Materials and methods**

85 **Inclusion and exclusion criteria**

86 We sought clinical PK-PD studies that related a calculated PK-PD index to the probability of clinical or
87 microbiological cure (or some element of either of these outcomes).

88 We included nested case-control, cohort studies and randomised controlled trials (RCTs) published
89 since 1980 in English. We excluded conference abstracts, due to the lack of methodological detail,
90 and case reports, due to the inability to link a PK-PD index with outcome. Participants had to have a
91 bacterial or fungal infection, although we excluded studies on patients with mycobacterial
92 infections. We included studies of combination therapy, and studies that pooled patients treated
93 with different antimicrobials of the same class when performing analyses, but we excluded studies
94 that pooled different classes of antimicrobials as PK-PD indices and targets are class-specific.

95 Eligible studies had to measure the concentration of an antimicrobial in a biological material for all
96 patients in the analysis and use this concentration in the calculation of the PK-PD index (directly, by
97 creating a population PK model, or by using the concentrations in conjunction with a previously

98 constructed PK model). We excluded studies that estimated PK parameters using only values of
99 covariates in a population PK model to which the included patients did not contribute concentration
100 measurements. We excluded studies that did not measure microbial susceptibility of an isolated
101 causative pathogen and instead used, for example, breakpoints for susceptibility or the distribution
102 of MICs for a particular pathogen. We excluded inhibitory/bactericidal titres in either urine or serum
103 due to the methodological problems with these assays.

104 Eligible outcomes were any measure of treatment response or failure. We included studies that
105 analysed statistically or described the association between PK-PD index and outcome. We excluded
106 studies that had only development of resistance as an outcome.

107

108 **Search strategy**

109 We searched MEDLINE, Embase, Web of Science and BIOSIS up to 22 July 2015 using a combination
110 of MeSH headings and free-text search terms for PK-PD indices, antibiotics and antifungals, and
111 treatment outcome. Full search strategies for each database are presented in the Supplementary
112 data. In addition, we tried to find full journal articles corresponding to relevant conference abstracts
113 that had been identified in the search, we hand-searched reference lists of included studies, and
114 PGA, SMB, GLD, WH and JWM ratified the list of included studies and provided any missing studies
115 that met our inclusion criteria.

116

117 **Selection of studies**

118 One author (Alexandra McAleenan [AM]) sifted the titles and abstracts. At title and abstract stage
119 conference abstracts and foreign language papers were not excluded as they were used to identify
120 English language versions or additional studies. Potentially relevant studies were obtained and full-
121 texts were assessed for eligibility by one author (AM).

122

123 **Data extraction**

124 We extracted data on study characteristics including population, antibiotic analysed, how PK
125 parameters were derived, how bacterial susceptibility was determined, PK-PD indices calculated,
126 outcomes and timing of outcome assessment, methods used to explore the relationship between
127 PK-PD index and outcome, industry funding, and results of the study. Study characteristics were
128 extracted from each publication without recourse to other cited references. The full list of items
129 extracted is given the Supplementary data.

130 When a single publication included studies performed on different groups of patients, data on each
131 cohort were extracted as a separate PK-PD analysis, providing no analysis had been performed on all
132 patients combined. If patients received therapy with different antimicrobials and separate PK-PD
133 analyses were performed per antimicrobial, these were also extracted as separate PK-PD analyses.

134 One author (AM) extracted the data. In all situations, if numbers were not reported they were
135 calculated from available data where possible.

136 ***Role of the funding source***

137 The funders had no role in data collection and analysis, decision to publish, or preparation of this
138 manuscript.

139 **Results**

140 ***Study selection and description***

141 We identified 6096 records after deduplication. Of the 348 full-text studies assessed, we included 85
142 publications. Ten publications included multiple analyses (studies).¹⁻¹⁰ In total, 97 PK-PD analyses
143 were included in the review. The flow chart for study inclusion is shown in Figure 1. Features of the
144 included analyses are presented by class in Table 1, and study level details are presented in the
145 Supplementary data, Tables S1-S5.

146 The 97 included analyses comprised 88 analyses of antibacterials and nine analyses of antifungals.

147 The most studied class of antimicrobial were the quinolone (21 studies). For several classes of

antimicrobials (polymyxins, macrolides, and polyenes) only one study was identified. The antimicrobial with the most studies was vancomycin (nine studies). Five studies examined a mix of antibiotics of the same class: four on aminoglycosides (gentamicin or tobramycin [two studies],^{11,12} gentamicin, tobramycin or amikacin [two studies]),^{13,14} and one on β -lactams (ceftriaxone, cefepime or piperacillin).¹⁵

Overall, 38 studies (39%) reported at least some industry/commercial funding, 39 (40%) reported that they had no funding or were funded by a non-industrial source, and the funding source was not reported in 20 studies (21%). It was clear that some PK-PD analyses were performed on the same patients, although this was not investigated systematically. There was overlap in the populations used in Peloquin *et al.*,¹⁶ Forrest *et al.*,¹⁷ and Goss *et al.*,⁷ in Meinel *et al.*¹⁸ and Forrest *et al.*,¹⁹ in Passarell *et al.*,²⁰ and Bhavnani *et al.*,²¹ and in Ambrose *et al.*²² and Bhavnani *et al.*²³

Population characteristics, site of infection and infecting organisms

Most PK-PD analyses were small, containing 59 patients on average (range 2 to 404).^{24,25} Only 15 analyses (15%) studied more than 100 patients. Only two of the included studies made any comparison between the patients included in the study and patients excluded.^{26,27}

The analyses included patients with a wide range of infections. Most investigated patients with a single type of infection, but 19 studies (20%) included patients with a variety of different infections (categorised as “multiple” infections in Table 1). In general, inclusion into the studies was based solely on both having an infection (sometimes limited by pathogen) and being treated with a particular antibiotic. Some studies addressed classes of infection, such as complicated intra-abdominal infections (cIAI) or complicated skin and skin structure infections (cSSSI), which encompass several different infections. One study split their analyses by site of infection after finding in multivariable analyses that differences in outcome were due to site of infection in addition to antibiotic exposures and PK-PD indices.²⁸

In 24 studies (25%), analyses were performed on patients with infections due to a particular pathogen. *Staphylococcus aureus* was the most studied pathogen (13 studies). The other studies of

individual pathogens investigated infections due to *Coxiella burnetii*,²⁹ *Haemophilus influenzae*,⁵ *Pseudomonas aeruginosa* (six studies),^{3,30-33} and *Streptococcus pneumoniae* (three studies).^{5,6,34} PK-PD analyses of glycopeptides were most likely of all the antimicrobial classes to be performed on patients with infection due to a particular pathogen. Other studies only included patients infected with a restricted number of pathogens (for example infections with *S. pneumoniae* and/or *H. influenzae*³⁵ or *P. aeruginosa* and/or *Acinetobacter baumannii*),³⁶ or limited the analysis to patients infected with a single genus, (for example *Aspergillus*,¹ *Candida*,^{37,38} *Haemophilus*,³⁹ or Enterobacteriaceae).²¹ Several studies subdivided their cohort depending on infecting pathogen, but were not categorised as being monomicrobial as the subcohorts were subsequently re-combined in the analyses.^{20,40,41} Two studies sequentially combined the subcohorts they had created based on the infecting pathogen, and found statistically significant relationships between PK-PD indices and outcomes when certain combinations of patients were pooled, but that these relationships disappeared when additional patients were added to the analyses.^{20,41} They attributed this to the infecting pathogen becoming so heterogeneous that the relationship between PK-PD indices and outcomes was occluded.

We did not extract specific eligibility criteria for each study, but we observed that several studies used infection with a resistant organism as an exclusion criterion. Although it would be regarded as ethical to administer antibiotics with a high probability of successfully treating an infection, if all patients are infected with susceptible organisms, MICs (or equivalent) will be low and it is therefore likely that PK-PD indices will be high for all patients. This makes it unlikely that a relationship between PK-PD index and outcome will be observed.

Because microbiological and clinical cure are associated with eradication of pathogens, receipt of effective antimicrobials in addition to the antimicrobial under investigation may obscure the PK-PD – outcome relationship of interest. In 20 studies (21%), it was explicitly reported that no patients received concurrent antibiotics/antifungals or that the receipt of concomitant antibiotics/antifungals was an exclusion criterion. However, in 33 studies (34%), some patients received concurrent

200 antibiotics or antifungals, and in the remaining 44 studies (45%) it was unclear or not reported.
201 Some studies included receipt of concurrent antimicrobials as a potential confounder in
202 multivariable analyses (discussed below).
203 Depending on the type of infection and on patients' comorbidities, patients could have received
204 other treatments concurrently with the antimicrobials. Concurrent treatments may also confound
205 the PK-PD - outcome relationship. Some studies reported that patients had the source of the
206 infection removed by surgery. This is important for some infections, for example complicated skin
207 and skin structure infections, complicated intra-abdominal infections, endocarditis, and
208 bacteraemia/sepsis secondary to central line infection. In some cases it was reported that non-
209 infectious treatment was "standardised"³¹ or that a "standard treatment protocol"³⁰ was used.
210 Other studies included concomitant pharmacotherapy and surgery (or probability of a surgical or
211 radiological procedure being successful in controlling the source of infection) as potential covariates
212 in multivariable models.
213 Study level data are presented in Table S1.

214 ***Determination of PK-PD indices***

215 Details of how studies determined PK-PD indices, summarised by antimicrobial class, are presented
216 in Table 2. We included studies only if they measured antimicrobial concentration in at least one
217 matrix and these concentrations enabled an estimate of the pharmacokinetics. Nearly all studies (95
218 [98%]) measured antimicrobial concentration in blood, serum or plasma. In the remaining two
219 studies the biological source was not reported.^{22,40} Antimicrobial concentration was also measured
220 in sputum (three studies);^{33,42,43} bronchoalveolar lavage⁴⁴ (using it to calculate PK-PD indices in
221 epithelial lining fluid); middle ear effusion;³⁵ urine (two studies^{32,33}- which developed population PK
222 models to characterise the serum concentration and urinary excretion data simultaneously); and
223 sinus aspirate (two studies^{34,45}- in which the plasma and sinus aspirate concentrations were
224 modelled simultaneously).

225 Most antimicrobials are protein bound to some degree, but only the unbound (free) fraction is
226 considered active, since antimicrobial binding to serum albumin and other proteins may affect
227 penetration and the ability of a drug to bind at its site of activity. It has been recommended that all
228 PK-PD indices should be calculated relative to the unbound fraction of the drug.⁴⁶ Four studies
229 measured free concentrations, using ultrafiltration to isolate unbound drug.⁴⁷⁻⁵⁰ A further 23 studies
230 adjusted for protein binding by proportionate scaling of the concentrations measured. However,
231 proportionate scaling assumes that the fraction of antimicrobial that is protein bound is constant
232 (i.e. not patient specific). However, changes in a patient's condition may change protein and albumin
233 levels and alter the free fraction of the drug. One study compared total and free concentrations of
234 vancomycin.⁴⁸ It found that the correlation between free and total concentrations was adequate at
235 the population level, but the free/total ratio varied between different samples.

236 A population PK model was used in 62 (64%) of the studies. We categorised the population PK
237 models according to the population from which they were constructed. Eight studies used a
238 population PK model constructed only from the participants in the analysis. Twenty-two studies used
239 a population PK model that was constructed from patients from the same cohort or randomized
240 controlled trial (i.e. treated for the same infection with the same antimicrobial over the same time
241 period), but not all patients were in the analysis associating the PK-PD index with the outcome
242 (because, for example, some patients did not have pathogen susceptibility data or outcome data).

243 Eleven studies used a population PK model that was constructed from patients in the analysis but
244 also patients with different infections and/or healthy volunteers. Two studies used population PK
245 models constructed from different populations. Eighteen studies referenced the population PK
246 model, but the population used to construct the PK model was not described adequately to
247 categorise it. One study did not describe the population PK model, and it was not referenced.⁵¹

248 Some studies used the population PK model for some analyses, but not for all. For example,
249 Okusanya *et al.*³³ constructed a population PK model for serum and urinary excretion data, and used

250 it to calculate serum AUC, but the sputum AUC on days one and 14 was calculated using the linear
251 trapezoidal rule. These studies were classified as using a population PK model.

252 Study level data are presented in Table S2.

253 Approximately half of studies reported the strategy adopted if more than one strain/pathogen was
254 identified. Strategies included excluding patients with polymicrobial infections, calculating PK-PD
255 indices on a per pathogen basis, using the least susceptible pathogen for calculation of the PK-PD
256 index, and choosing the pathogen deemed most likely to be responsible for the infection. In many
257 cases the source of the pathogen and the exact timing of collection were not reported, but we
258 presumed that pathogens were isolated prior to therapy and from an appropriate source.

259 Study level data are presented in Table S3.

260 Further detail regarding determination of antimicrobial drug concentrations in biological matrices
261 and determination of antimicrobial drug susceptibility is given in the Supplementary data.

262

263

264 ***PK-PD indices determined***

265 The types of PK-PD indices calculated are presented in Table 3. The PK-PD index that was most
266 commonly calculated was a ratio of AUC to some measure of microbial susceptibility, but this varied
267 by antimicrobial class. Of the antimicrobial classes with more than ten studies identified, a ratio of
268 C_{max} to some measure of microbial susceptibility was the most common PK-PD index calculated for
269 aminoglycosides, a ratio of AUC to some measure of microbial susceptibility was the most common
270 PK-PD index calculated for glycopeptides and quinolones, and time that the concentration exceeded
271 ($T >$) some measure of microbial susceptibility was the most common PK-PD index calculated for β -
272 lactams. Just under half of the identified studies ($n=45$ [46%]) calculated more than one index. We
273 did not observe any particular trend over time in the choice of PK-PD index calculated for each class
274 of antimicrobial (data not shown). A number of studies investigated other PK-PD indices. The other
275 PK-PD indices calculated included a ratio of pre-dialysis concentration to MIC,¹¹ ratio of average

276 concentration to MIC (two studies),^{13,25} ratio of concentration at steady state to MIC,⁴⁹ intensity
277 index (AUC above MIC) (two studies),^{14,15} and ratio of concentration to MIC or to MBC (three
278 studies).^{24,29,39}

279 Study level data are presented in Table S3.

280 **Outcomes**

281 The outcomes assessed are presented in Table 4. The two most common outcomes were clinical
282 response (n=48 [49%]) and bacteriological response (n=41 [42%]). We did not examine in detail how
283 these terms were defined in the individual studies. However, we note the possibility of some
284 misclassification: for example, in one paper clinical cure was defined as a composite of clinical and
285 bacteriological cure.⁵² Some studies examined specific outcomes that could contribute towards
286 “clinical cure”.

287 Clinical PK-PD studies of glycopeptides were most likely to assess the relationship of a PK-PD index
288 with undesirable outcomes, such as treatment failure or mortality.

289 In 12 studies, at least one outcome was time to some event, such as time to clinical success or time
290 to bacterial eradication. Of the 91 studies that assessed non time-to-event outcomes, 64 studies
291 (70%) reported clearly the timing of the outcome assessment. Of the studies which assessed
292 outcomes at fixed timepoints, just over one third (33 studies) of studies reported assessing at least
293 one outcome at the end of therapy. Other outcome assessment timing included during therapy, at
294 test-of-cure (at various time points), and at the end of the study. Some outcomes had timing as part
295 of the outcome, for example 30-day mortality, or recurrence within 60 days of discontinuation.

296 Study level data are presented in Table S3.

297 **Statistical analyses**

298 The statistical approaches used to link PK-PD index with outcome are presented in Table 5, with
299 study level data in Table S4. Only three studies (from two publications) reported performing a
300 sample size calculation,^{10,53} although in only one of these publications (two studies)¹⁰ was the

301 calculation based on estimating the association of PK-PD index and outcome (in the other it was
302 based on the estimated association between MIC and treatment outcome).⁵³ In addition, in two
303 studies sample size was a consideration in whether to combine data across cohorts separated by
304 pathogen, though specific details were not reported.^{20,41}

305 Sixty-one studies (63%) performed some form of regression, time to event analysis or used the
306 Hill/ $E_{\max}$ equation to look at the association between PK-PD index and outcome. The most common
307 form of analysis was logistic regression, performed in 51 studies. We categorised analyses according
308 to whether linear or non-linear relationships were assumed, and on whether the models were
309 adjusted for additional variables. Most of the analyses were based on linear models (n=58; we
310 considered models in which one of the variables was log transformed to be linear), with a non-linear
311 model being assumed in only seven studies.

312 Linear models may not adequately characterize the relationship between the PK-PD index and the
313 outcome. For example, Rayner *et al.* examined a variety of linear and non-linear regression models
314 and found that $E_{\max}$ -type functions (modified Hill equations) best described the relationship between
315 AUC/MIC and the probability of microbiological eradication and clinical cure at particular sites of
316 infection.²⁸ Step functions, in contrast, better described the association between %T>MIC and
317 probability of microbiological eradication and clinical cure at particular sites of infection. In contrast,
318 one study explored the possibility of nonlinearity using splines and quadratic functions, but found
319 that the relationship between the average concentration/MIC ratio versus response was best
320 described using a linear term.²⁵ Several other studies explored the relationship between PK-PD
321 index and outcome using a number of different types of analysis.^{17,19} One the papers we included
322 focussed on whether frequentist or Bayesian logistic regression may impact on the magnitude of the
323 treatment effect.²²

324 Many factors may influence the outcome of an infection. For example, general host factors such as
325 inflammatory response, antibody response, phagocyte function, underlying disease; site of infection
326 factors such as abscess drainage, sequestrum formation, presence of a foreign body such as an

intravascular catheter or a prosthetic cardiac value; and pathogen factors including toxin production or other virulence factors, evasion of the host inflammatory response or of antibiotic by entry into a protected site e.g. an intracellular location. However, fewer than half of the studies (42 studies) performed or planned a multivariable analysis. The covariates included varied among studies. Thirty-nine studies examined demographic factors such as age or sex as potential covariates. Thirty-four studies examined clinical and physiological patient characteristics such as underlying disease and comorbidities. Thirty studies examined potential covariates related to infection, such as infecting organism and site/type of infection. Twenty-seven studies examined covariates relating to anti-infection treatment, such as receipt of concurrent antibiotics and surgery/removal of the infection focus.

Of the 73 studies in which analyses were not performed on a per-pathogen basis, 11 studies examined the infecting organism as a potential covariate (15%). Of the 33 studies where at least some proportion of the population received concurrent antimicrobials, 11 studies considered this as a potential covariate (33%). It was unclear in how many studies surgery was performed, but only four studies considered surgery, probability of the primary surgical or radiological procedure being successful in controlling the source of infection, or removal of eradicable focus as a potential covariate.

Eighteen studies did not report planning or performing any form of statistical analysis to examine the association between PK-PD index and outcome.^{8,34,35,42,43,45,49-51,54-62} In these studies there was either some form of descriptive analysis, for example in one study the AUC/MIC values of strains that were eradicated and strains that were not eradicated were described,⁵¹ and/or PK-PD indices and outcomes were tabulated (often per patient or per pathogen).

Study results

Study results are presented in Table S5. Of the studies that performed some sort of statistical analysis, 56 studies (71%) reported a statistically significant relationship between a PK-PD index

(either analysed as a continuous variable or categorised) and at least one of the outcomes investigated.

Over half the studies (n=51, 52%) looked at target values of the PK-PD indices that might be used to link to clinical outcome. Target values in each study are reported in Table S5. In 20 studies (21%) a pre-specified target was examined, in 34 studies (35%) a *de novo* target was identified, and three studies investigated both. The two most common techniques to identify *de novo* targets were variations on recursive partitioning and logistic regression. Twenty-six studies used a form of recursive partitioning. The most common method was classification and regression tree (CART) analysis, which derives optimal ‘splits’ of the continuous exposure variables in an iterative process. The split point determined for the PK-PD index is interpreted as a ‘target’ or ‘breakpoint’. When logistic regression was implemented, it was used to identify the PK-PD value that corresponded to 80% or 90% or 95% probability of cure (four studies). Further techniques for identifying *de novo* targets included identifying the AUC above dynamic response concentration that achieved eradication in four days or less based on cohort of patients observed,⁸ visual inspection,⁶³ and receiver operating characteristic (ROC) curve analysis.⁶⁴ In three studies the method used to identify targets was unclear or not reported.^{18,42,65} Two studies identified targets using two different techniques (CART and logistic regression).^{12,66}

Many of the studies identified multiple targets by identifying targets for multiple PK-PD indices for multiple outcomes. In some cases, multiple targets were identified for the same PK-PD index for the same outcome, resulting in the population being divided into three or more. Some studies reported infection site-specific or organism-specific targets.

Only a few studies reported uncertainty around the PK-PD targets identified, for example using 95% confidence intervals around the identified target,² or 95% confidence intervals around the probability of being above or below the target.⁶⁷ Several studies analysing time-to-event outcomes reported measures of variability.^{28,40,68}

377 Among studies reporting probabilities of a successful outcome above or below a target (or
378 information sufficient to calculate this probability), the probability of a successful outcome among
379 individuals with PK-PD index values exceeding the identified target varied. The lowest probability
380 above a recursive partitioning identified target was 39%, and the highest was 100%. The probability
381 of a successful outcome above the target was greater than 90% for 36 of the targets identified by
382 recursive partitioning. In some studies, the probability of the outcome was lower above the CART
383 identified target than below it. For example, Lodise *et al.* found a probability of a favourable
384 outcome (not failure, where failure was defined as 30-day mortality, microbiological failure or
385 recurrence of infection) to be 57% above the target of $C_{\min 0-24h}/MIC$ (determined by broth
386 microdilution) ≥ 14.9 and 71% below the target.⁶⁹ This may have arisen due to increasing
387 administration of antimicrobial or change in PK parameters in the sickest patients with the poorest
388 prognosis. These recursive partitioning-based probabilities among individuals above and below an
389 identified target are averages across values of the PK-PD index. In contrast, logistic regression
390 estimates the probability of an outcome for each specific value of the index. For instance, Kashuba *et*
391 *al.* used both CART and logistic regression, finding a target of $C_{\max}/MIC = 4.7$ using CART, with
392 success rate of 89% above this threshold. In logistic regression, a $C_{\max}/MIC$ of 4.7 corresponded to a
393 68% probability of response while a $C_{\max}/MIC$ of 23.6 (the highest seen) corresponded to a 99%
394 probability of response: the value of 89% is the average probability across this range.¹²
395 Graphical representations of the relationship between PK-PD index and probability of outcome
396 facilitate judgements by clinicians and policy makers about reasonable targets. Several studies
397 provided graphs. For example, several studies plotted the probability of success versus a PK-PD index
398 based on the results of logistic regression, with confidence intervals around the regression
399 line.^{5,23,25,27} Twenty-two studies reported relative risks or odds ratios for outcome, either above and
400 below a pre-specified target or with increasing levels of PK-PD index.

401 As mentioned above, in 20 studies (21%) a pre-specified target was examined, for example by
402 seeking to confirm targets identified in another cohort⁸ or another outcome.⁷⁰ Independent
403 confirmation of targets is important if targets are going to be used to guide therapy.

404 **Discussion**

405 In a systematic review of clinical PK-PD studies of antimicrobials performed between 1980 and 2015
406 we found wide variability in conduct and reporting. Many of the concerns that have been voiced
407 about these studies, such as small size (<100 patients), not limiting analyses to populations with
408 similar pathogens and sites of infection, not measuring free drug concentration, and not adjusting
409 analyses for the effect of surgery, appear to be justified. For many of the items we tried to examine,
410 there were studies which did not report the item or provided descriptions that were unclear.

411 We believe this is the first systematic review of the methods employed in clinical PK-PD studies. We
412 searched comprehensively for studies reported over a period of over 35 years and examined many
413 features of their conduct and reporting. Our review has limitations, however. We excluded studies
414 that did not measure the concentration of an antimicrobial in a biological material for all patients in
415 the analysis, or which did not use this concentration in the calculation of the PK-PD index, and
416 therefore we have only reviewed a subset of the clinical PK-PD literature. We did not extract
417 detailed information on the PK methods used, as we did not aim to assess the PK aspects of the
418 studies, and we have assumed that these were performed appropriately. We did not extract detailed
419 information on the definitions of outcomes used in all the papers. Our search did not contain terms
420 for disease-specific outcomes (for example, improvement in forced expiratory volume in one
421 second). We therefore may have missed studies with these outcomes if they were not indexed
422 under the 'Treatment outcome' MeSH heading. Finally, due to resource constraints we excluded
423 foreign language studies, and sifting of titles and abstracts and extracting the data was performed by
424 one reviewer. In addition, limiting the review to published, peer reviewed studies introduces the

possibility of bias due to non-reporting, where studies with undesirable results are less likely to be written up by researchers and/or published.

Future studies of associations between a PK-PD index and a clinical or microbial response may struggle to identify informative relationships because optimum dosing regimens can often be derived using pre-clinical data. However, when they are undertaken, they should be designed and reported carefully so that findings can be attributed to genuine relationships (or lack of a relationship) rather than to poor conduct, and so that the pre-defined PK-PD indices can be validated through high clinical success rates. In Table 6 we offer some recommendations for future clinical PK-PD studies, informed by our deliberations over what we observed while undertaking the review. We also identified a need for improved reporting of methodology. Studies might consider reporting all the items that we aimed to extract. In addition, we suggest that studies should compare features and outcomes of patients included in the PK-PD analysis (because there are data for PK parameters and MICs for pathogens) and other eligible patients (same infection, same pathogen, same antibiotic but for some reason do not have PK data or MICs of pathogens) to ensure that there are no material differences; and that PK-PD studies should plot PK-PD index versus probability of outcome or amount of improvement so that the exposure-response relationship is clear. Such plots, possibly with exposures divided into quantiles (an option when regression methods are used) can also allow individuals to determine their own targets.

The results of clinical PK-PD – response studies should be considered in conjunction with results from pre-clinical PK-PD studies. Obtaining a response rate that correlates with the expectation operation over the probability of target attainment relationship is powerful evidence.

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734 *Figure 1: Flow chart for study inclusion. Reasons for exclusion at full text are given in the Supplementary data.*

Table 1: Features of the included clinical PK-PD studies, by antimicrobial class.

Antimicrobial class	Number of studies	Industry funded, n (%)	Specific antibiotic (number of studies)	Average number of people (range)	Number of studies with ≥100 participants, number of studies (%)	Infections (number of studies)	Single pathogen, number of studies (%)	Concomitant antibiotics or antifungals, number of studies (%)*
Aminoglycoside ^{3,4,10-14,31-33,59,72-74}	16	2 (13%)	Amikacin (5), Arbekacin (2), Gentamycin (1), Isepamicin (1), Tobramycin (3), Multiple aminoglycosides (4)	52 (13-236)	1 (6%)	Bacteraemia (1), Infections in cystic fibrosis (5), Multiple (4), Nosocomial pneumonia (including intensive care unit acquired and ventilator associated pneumonia) (3), Sepsis (3)	7 (44%)	11 (69%)
Cyclic lipopeptide ^{52,55,75}	3	0 (0%)	Daptomycin (3)	27 (6-41)	0 (0%)	Cardiovascular implantable electronic device endocarditis (1), Multiple (2)	0 (0%)	1 (33%)
Cyclic peptide/ polymyxin ⁴⁴	1	0 (0%)	Colistin (1)	20 (20-20)	0 (0%)	Ventilator associated tracheobronchitis (1)	0 (0%)	0 (0%)
Echinocandin (Antifungal) ^{1,9,37}	5	5 (100%)	Anidulafungin (4), Caspofungin (1)	44 (11-100)	1 (20%)	Invasive aspergillosis (1), Candidiasis (1), Oesophageal candidiasis (1), Invasive candidiasis, including candidemia (1), Mucosal candidiasis (1)	0 (0%)	1 (20%)
Glycopeptide ^{2,48,53,68,69,76-81}	12	4 (33%)	Norvancomycin (2), Oritavancin (1), Vancomycin (9)	73 (20-139)	3 (25%)	Bloodstream infections/bacteraemia (5), Complicated bacteraemia; Infective endocarditis (1), Concomitant MRSA bacteraemia and MRSA osteomyelitis (1), Infective endocarditis (1), Multiple (4)	9 (75%)	8 (67%)
Ketolide ^{5,70}	4	3 (75%)	Telithromycin (4)	85 (22-115)	2 (50%)	Community acquired pneumonia (4)	3 (75%)	0 (0%)
Macrolide ⁶³	1	1 (100%)	Azithromycin (1)	101 (101-101)	1 (100%)	Respiratory tract infections (1)	0 (0%)	0 (0%)
Oxazolidinone ^{24,28,58}	3	1 (33%)	Linezolid (3)	83 (2-239)	1 (33%)	Endocarditis (1), Multiple (2)	1 (33%)	1 (33%)
Polyene (Antifungal) ⁸²	1	0 (0%)	Amphotericin B (liposomal) (1)	9 (9-9)	0 (0%)	Multiple (1)	0 (0%)	0 (0%)
Quinolone ^{6,7,16-19,26,34,39,42,45,47,50,51,61,65,67,83-85}	21	8 (38%)	Ciprofloxacin (4), Garenoxacin (3), Gatifloxacin (3), Grepafloxacin (3), Levofloxacin	58 (4-216)	3 (14%)	Chronic bronchitis (1), Multiple (3), Nosocomial lower respiratory tract infections (1), Nosocomial	2 (10%)	3 (14%)

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Antimicrobial class	Number of studies	Industry funded, n (%)	Specific antibiotic (number of studies)	Average number of people (range)	Number of studies with ≥100 participants, number of studies (%)	Infections (number of studies)	Single pathogen, number of studies (%)	Concurrent antibiotics or antifungals, number of studies (%)*
			(6), Sitafloxacin (1), Sparfloxacin (1)			pneumonia (including ventilator associated pneumonia) (3), Otitis media (1), Respiratory tract infections (5), Secondary infections of chronic respiratory diseases (1), Acute exacerbation of chronic bronchitis (3), Intraabdominal infections (1), Acute maxillary sinusitis (2)		
Tetracycline ^{20-23,29,40,41}	7	6 (86%)	Doxycycline/hydroxychloroquine (1), Tigecycline (6)	62 (15-123)	1 (14%)	Community acquired pneumonia (1), Complicated skin and skin-structure infections (1), Hospital acquired pneumonia (2), Q fever endocarditis (1), Complicated intra-abdominal infections (2)	1 (14%)	1 (14%)
Triazole (Antifungal) ^{1,25,38}	3	2 (67%)	Cyclodextrin/Itraconazole (1), Voriconazole (2)	151 (23-404)	1 (33%)	Invasive aspergillosis (1), Oropharyngeal candidosis (1), Invasive fungal infections (1)	0 (0%)	1 (33%)
β-lactam ^{7,8,10,15,27,30,35,36,43,49,54,56,57,60,62,64,66,86,87}	20	6 (30%)	Amoxicillin/clavulanic acid (1), Cefaclor advanced formulation (1), Cefazedone (1), Cefepime (1), Cefmenoxime (3), Cefoperazone/sulbactam (1), Ceftazidime (2), Ceftobiprole (1), Ertapenem (1), Imipenem (or imipenem/cilastatin) (2), Meropenem (3), Piperacillin/tazobactam (1), Tebipenem pivoxil (1), Multiple beta-lactams (1)	42 (6-309)	1 (5%)	Acute otitis media (1), Acute pulmonary exacerbations of cystic fibrosis (1), Community acquired pneumonia (1), Complicated skin and skin-structure infections (1), Febrile neutropenia (1), Lower respiratory tract infections (1), Meningitis (1), Multiple (3), Nosocomial pneumonia (including ICU acquired and ventilator associated pneumonia) (6), Respiratory tract infections (1), Sepsis (1), Ventilator associated pneumonia and signs of severe sepsis or septic shock	1 (5%)	6 (30%)

737
738

Antimicrobial class	Number of studies	Industry funded, n (%)	Specific antibiotic (number of studies)	Average number of people (range)	Number of studies with ≥100 participants, number of studies (%)	Infections (number of studies)	Single pathogen, number of studies (%)	Concurrent antibiotics or antifungals, number of studies (%)*
						(1), Acute exacerbation of chronic bronchitis (1)		
Total	97	38 (39%)		59 (2-404)	15 (15%)		24 (25%)	33 (34%)

* Concurrent antibiotics when antibiotic under investigation; concurrent antifungals when antifungal under investigation.

Table 2: Data used to determine PK-PD indices in clinical PK-PD studies, by antimicrobial class.

Antimicrobial class	Number of studies	Pharmacokinetics							Antimicrobial susceptibility			
		Biological material sampled (number of studies)	Mean number of samples (range)*	Sample collection timing reported, number of studies (%) [†]	Method for determining drug concentration reported, number of studies (%)	Free-drug concentration measured, number of studies (%) [‡]	Protein binding adjustment, number of studies (%) [§]	Population PK model used, number of studies (%) ^{**}	Measure of antimicrobial susceptibility (number of studies)	Method of measurement reported, number of studies (%)	Measurement in accordance with guidelines/ recommendation, number of studies (%) ^{††}	Strategy if more than one pathogen/ strain, number of studies (%)
Aminoglycoside	16	Blood/serum (16), Sputum (1), Urine (2)	7 (1 to 24)	14 (88%)	14 (88%)	0 (0%)	2 (13%)	10 (63%)	MIC (16)	14 (88%)	5 (31%)	8 (50%)
Cyclic lipopeptide	3	Blood/serum (3)	4 (2 to 9)	2 (67%)	3 (100%)	0 (0%)	0 (0%)	1 (33%)	MIC (3), MBC (1)	1 (33%)	0 (0%)	1 (33%)
Cyclic peptide/ polymyxin	1	Blood/serum (1), BAL fluid (1)	7 (7 to 7)	1 (100%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)	MIC (1)	1 (100%)	0 (0%)	0 (0%)
Echinocandin (Antifungal)	5	Blood/serum (5)	6 (3 to 9)	4 (80%)	1 (20%)	0 (0%)	0 (0%)	5 (100%)	MIC (5)	4 (80%)	4 (80%)	1 (20%)
Glycopeptide	12	Blood/serum (12)	2 (1 to 11)	5 (42%)	5 (42%)	1 (8%)	3 (27%)	7 (58%)	MIC (12)	11 (92%)	8 (67%)	8 (67%)
Ketolide	4	Blood/serum (4)	2 (1 to 3)	3 (75%)	4 (100%)	0 (0%)	0 (0%)	4 (100%)	MIC (4)	4 (100%)	3 (75%)	4 (100%)
Macrolide	1	Blood/serum (1)	8 (8 to 8)	1 (100%)	1 (100%)	0 (0%)	0 (0%)	1 (100%)	MIC (1)	1 (100%)	1 (100%)	1 (100%)
Oxazolidinone	3	Blood/serum (3)	8 (3 to 18)	1 (33%)	2 (67%)	0 (0%)	0 (0%)	1 (33%)	MIC (2), MBC (1)	2 (67%)	0 (0%)	0 (0%)
Polyene (Antifungal)	1	Blood/serum (1)	13 (13 to 13)	1 (100%)	1 (100%)	0 (0%)	0 (0%)	1 (100%)	MIC (1)	1 (100%)	0 (0%)	0 (0%)
Quinolone	21	Blood/serum (21), Sputum (1), Sinus aspirate (2)	6 (1 to 12)	16 (76%)	20 (95%)	2 (10%)	5 (26%)	15 (71%)	MIC (18), MIC midpoint (3)	17 (81%)	11 (52%)	10 (48%)
Tetracycline	7	Blood/serum (5), Not reported (2)	2 (1 to 5)	4 (57%)	2 (29%)	0 (0%)	3 (43%)	5 (71%)	MIC (7)	5 (71%)	3 (43%)	5 (71%)
Triazole (Antifungal)	3	Blood/serum (3)	7 (1 to 16)	1 (33%)	2 (67%)	0 (0%)	1 (33%)	1 (33%)	MIC (3)	2 (67%)	2 (67%)	0 (0%)
β-lactam	20	Blood/serum (20), Middle	5 (1 to 9)	12 (60%)	19 (95%)	1 (5%)	9 (47%)	11 (55%)	MIC (17), MIC midpoint (1),	18 (90%)	4 (20%)	9 (45%)

Antimicrobial class	Number of studies	Pharmacokinetics							Antimicrobial susceptibility			
		Biological material sampled (number of studies)	Mean number of samples (range)*	Sample collection timing reported, number of studies (%) [†]	Method for determining drug concentration reported, number of studies (%)	Free-drug concentration measured, number of studies (%) [‡]	Protein binding adjustment, number of studies (%) [§]	Population PK model used, number of studies (%) ^{**}	Measure of antimicrobial susceptibility (number of studies)	Method of measurement reported, number of studies (%)	Measurement in accordance with guidelines/ recommendation, number of studies (%) ^{††}	Strategy if more than one pathogen/ strain, number of studies (%)
		ear effusion (1), Sputum (1)							Dynamic response (2)			
Total	97		5 (1 to 24)	65 (67%)	75 (77%)	4 (4%)	23 (25%)	62 (64%)		81 (84%)	41 (42%)	47 (48%)

* Mean number of samples taken per patient as reported in results. If range only reported, lower number taken. If number taken not reported but the timing of samples was reported, the number of samples taken was estimated by counting the number of timepoints. If number taken not reported and timing not reported, but it was clear than concentration of antibiotic in biological material had been measured, it was assumed that one sample had been taken. NB If the study created a population PK model, the number of samples was the number of samples per patient who contributed to the population PK model.

[†] Had to report more than just “peak” or “trough”

[‡] Stated that free-drug concentration measured

[§] % of studies which did not measure free-drug concentrations

^{**} Had to explicitly state that a population PK model used or judged by Alasdair McGowan to have used/constructed a population PK model

^{††} For example, Clinical & Laboratory Standards Institute (CLSI), National Committee for Clinical Laboratory Standards (NCCLS), British Society for Antimicrobial Chemotherapy (BSAC) or Japan Society of Chemotherapy guidelines.

Table 3: Type and number of PK-PD indices determined in clinical PK-PD studies, by antimicrobial class.

Antimicrobial class	Number of studies	Number of studies (%) that calculated some form of:				Other PK-PD indices (number of studies)	≥ 2 indices, number of studies (%)	≥ 3 indices, number of studies (%)	≥ 4 indices, number of studies (%)
		AUC/measure of microbial susceptibility	C _{max} /measure of microbial susceptibility	C _{min} /measure of microbial susceptibility	T> measure of microbial susceptibility				
Aminoglycoside	16	10 (63%)	13 (81%)	2 (13%)	3 (19%)	Pre-dialysis concentration/MIC (1), Average concentration/MIC (1), Intensity index (1)	10 (63%)	5 (31%)	0 (0%)
Cyclic lipopeptide	3	2 (67%)	1 (33%)	0 (0%)	0 (0%)	None	0 (0%)	0 (0%)	0 (0%)
Cyclic peptide/polymyxin	1	1 (100%)	1 (100%)	0 (0%)	1 (100%)	None	1 (100%)	1 (100%)	0 (0%)
Echinocandin (Antifungal)	5	5 (100%)	1 (20%)	1 (20%)	0 (0%)	None	1 (20%)	1 (20%)	0 (0%)
Glycopeptide	12	9 (75%)	1 (8%)	4 (33%)	3 (25%)	None	4 (33%)	1 (8%)	0 (0%)
Ketolide	4	4 (100%)	3 (75%)	0 (0%)	0 (0%)	None	3 (75%)	0 (0%)	0 (0%)
Macrolide	1	1 (100%)	0 (0%)	0 (0%)	0 (0%)	None	0 (0%)	0 (0%)	0 (0%)
Oxazolidinone	3	2 (67%)	0 (0%)	0 (0%)	2 (67%)	Concentration/MBC (1)	2 (67%)	0 (0%)	0 (0%)
Polyene (Antifungal)	1	1 (100%)	1 (100%)	0 (0%)	0 (0%)	None	1 (100%)	0 (0%)	0 (0%)
Quinolone	21	20 (95%)	11 (52%)	3 (14%)	6 (29%)	Concentration/MIC (1)	11 (52%)	6 (29%)	3 (14%)
Tetracycline	7	6 (86%)	0 (0%)	0 (0%)	0 (0%)	Concentration/MIC (1)	0 (0%)	0 (0%)	0 (0%)
Triazole (Antifungal)	3	2 (67%)	1 (33%)	1 (33%)	1 (33%)	C _{avg} /MIC (1)	1 (33%)	1 (33%)	1 (33%)
β-lactam	20	10 (50%)	7 (35%)	5 (25%)	19 (95%)	Free concentration at steady state/MIC (1), AUC above MIC (1)	11 (55%)	8 (40%)	3 (15%)
Total	97	73 (75%)	40 (41%)	16 (16%)	35 (36%)		45 (46%)	23 (24%)	7 (7%)

Table 4: Outcomes investigated in clinical PK-PD studies, by antimicrobial class.

Antimicrobial class	Number of studies	Composite measure of treatment failure or success, number of studies (%)	Bacteriological response, number of studies (%)	Time to bacteriological response, number of studies (%)	Clinical response, number of studies (%)	Time to clinical response, number of studies (%)	Mortality, number of studies (%)	Other outcomes (number of studies)	Timing of outcome assessment reported, number of studies (%)*	At least one outcome at the end of therapy, number of studies (%)*
Aminoglycoside	16	2 (13%)	2 (13%)	0 (0%)	6 (38%)	0 (0%)	3 (19%)	SOFA score>3 at day 7 (1), Duration of mechanical ventilation (1), Development of acute kidney injury (1), Improvement/change in pulmonary function tests (including forced expiratory volume in 1s and forced vital capacity) (5), Change in inflammatory parameters (CRP, leukocyte count and IgG) (2), Time (days) to temperature resolution (1), Time (days) to leukocyte count resolution (1), Change in the number of colony forming units (2).	12 (75%)	6 (38%)
Cyclic lipopeptide	3	0 (0%)	0 (0%)	0 (0%)	2 (67%)	0 (0%)	1 (33%)	None	2 (67%)	1 (33%)
Cyclic peptide/polymyxin	1	0 (0%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	None	1 (100%)	1 (100%)
Echinocandin (Antifungal)	5	2 (40%)	0 (0%)	0 (0%)	1 (20%)	0 (0%)	1 (20%)	Global response (1), Endoscopic response (1).	5 (100%)	3 (60%)
Glycopeptide	12	7 (58%)	2 (17%)	1 (8%)	3 (25%)	0 (0%)	3 (25%)	Recurrence of MRSA bacteraemia within 60 days of discontinuation of therapy (1), length of stay (1), infection-related length of stay (1), alteration of therapy from vancomycin (1), recurrent MRSA bacteraemia within 90 days (1), hospital readmission within 30 days (1), Resolving bacteraemia (<3 days of bacteraemia with all subsequent blood cultures documented to be negative after the initial positive blood culture) versus persistent bacteraemia (bacteraemia for ≥7 days while receiving appropriate antibiotic therapy) (1).	6 (55%)	3 (27%)
Ketolide	4	0 (0%)	4 (100%)	0 (0%)	1 (25%)	0 (0%)	0 (0%)	None	1 (25%)	0 (0%)
Macrolide	1	0 (0%)	1 (100%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)	None	1 (100%)	0 (0%)
Oxazolidinone	3	0 (0%)	2 (67%)	1 (33%)	3 (100%)	0 (0%)	0 (0%)	None	1 (33%)	1 (33%)
Polyene (Antifungal)	1	0 (0%)	0 (0%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)	None	0 (0%)	0 (0%)
Quinolone	21	0 (0%)	16 (76%)	5 (24%)	13 (62%)	1 (5%)	0 (0%)	Time to 70% decrease in sputum volume from peak (1), Time to 25% decrease in the percentage of neutrophils in sputum from peak (1), Time to 60% decrease in coughs per day from peak (1), Time to equilibration of sinus aspirate neutrophil elastase, and	11 (61%)	5 (27%)

								myeloperoxidase concentration with that of plasma, and time to postnasal drip resolution (1), Time to clinical resolution of individual signs and symptoms of maxillary sinusitis (sinus pain, dental pain, sinus tenderness, purulent nasal discharge, headache, face pressure, nasal congestion, postnasal drip, sore throat, cough) (1).		
Tetracycline	7	0 (0%)	5 (71%)	0 (0%)	6 (86%)	0 (0%)	0 (0%)	Time to defervescence (fever resolution) (1), Response (if the clinical signs and symptoms had regressed along with a >2-fold decrease in antibody titre (IgG and/or IgA) to phase I antigen at the completion of a yearlong course of treatment) versus patients in whom the regression of clinical signs and symptoms was not associated with a fall in antibody titre to phase I antigen (1).	7 (100%)	0 (0%)
Triazole (Antifungal)	3	0 (0%)	0 (0%)	0 (0%)	1 (33%)	0 (0%)	1 (33%)	Global response (1), Change in oropharyngeal candidiasis score (1).	3 (100%)	3 (100%)
β-lactam	20	2 (10%)	8 (40%)	3 (15%)	10 (50%)	0 (0%)	2 (10%)	SOFA score>3 at day 7 (1), Duration of mechanical ventilation (1), CRP normalisation (1), Number of admission days (1), Time to defervescence (1), Brasfield score (1), Pulmonary function score (1), Clinical score (1), General score (1).	14 (78%)	10 (56%)
Total	97	13 (13%)	41 (42%)	10 (10%)	48 (49%)	1 (1%)	11 (11%)		64 (70%)	33 (36%)

* The fields "timing of outcome assessment reported" and "at least one outcome at the end of therapy" exclude the six studies which exclusively reported time-to-event outcomes.^{8,18,34,45,79}

Abbreviations: CRP, C-reactive protein; IgA Immunoglobulin A; IgG Immunoglobulin G; SOFA, Sequential Organ Failure Assessment.

Table 5: Statistical analyses performed in clinical PK-PD studies, by antimicrobial class.

Antimicrobial class	Number of studies	Sample size calculation performed, number of studies (%)	Analysis of 2x2 tables, number of studies	Comparison of means, number of studies	Correlation, number of studies	Receiver operating characteristic (ROC) curve, number of studies	Recursive partitioning, number of studies	Type of analysis (number of studies)	Standard and/or non-linear (number of studies)	Adjusted and/or unadjusted (number of studies)	No statistical analyses, number of studies
Aminoglycoside	16	1 (6%)	3	4	5	1	4	Logistic regression (9), Time to event analysis (1), Hill equation/E _{max} model (1), Repeated-measures mixed effects (1)	Standard (10), Non-linear (1)	Unadjusted (7), Adjusted (7)	1
Cyclic lipopeptide	3	0 (0%)	1	0	0	0	0	Logistic regression (1)	Standard (1)	Adjusted (1)	1
Cyclic peptide/ Polymyxin	1	0 (0%)	0	0	1	0	0				0
Echinocandin (Antifungal)	5	0 (0%)	0	0	0	0	0	Logistic regression (5)	Standard (5)	Unadjusted (2), Adjusted (4)	0
Glycopeptide	12	1 (8%)	7	8	0	0	7	Logistic regression (9), Poisson regression (1), Time to event analysis (1)	Standard (11)	Unadjusted (2), Adjusted (11)	0
Ketolide	4	0 (0%)	0	0	0	0	4	Logistic regression (4)	Standard (4)	Unadjusted (4), Adjusted (1)	0
Macrolide	1	0 (0%)	0	0	0	0	0	Logistic regression (1)	Standard (1)	Adjusted (1)	0
Oxazolidinone	3	0 (0%)	1	0	0	0	1	Logistic regression (1), Time to event analysis (1), Hill equation/E _{max} model (1)	Standard (1), Non-linear (1)	Adjusted (1)	1
Polyene (Antifungal)	1	0 (0%)	0	1	0	0	0				
Quinolone	21	0 (0%)	2	3	1	1	6	Logistic regression (9), Time to event analysis (4), Hill equation/E _{max} model (3)	Standard (11), Non-linear (3)	Unadjusted (12), Adjusted (8)	6
Tetracycline	7	0 (0%)	4	1	0	2	5	Logistic regression (6), Time to event analysis (1)	Standard (6)	Unadjusted (6), Adjusted (5)	0
Triazole (Antifungal)	3	0 (0%)	0	0	0	0	0	Logistic regression (2), Hill equation/E _{max} model (1)	Standard (2), Non-linear (2)	Unadjusted (3), Adjusted (2)	0
β-lactam	20	1 (5%)	4	3	4	1	4	Logistic regression (4), Linear regression (1), Time to event analysis (1)	Standard (6)	Unadjusted (5), Adjusted (1)	9
Total	97	3 (3%)	22 (23%)	20 (21%)	11 (11%)	5 (5%)	31 (32%)				18 (19%)

Suggested guidelines for conducting studies.

1. Consider sample size calculations to determine whether an exposure-response relationship has a reasonable likelihood of being identified. Conducting analyses on too few patients is unlikely to yield meaningful results.
2. Consider reporting confidence or credible intervals measuring the level of uncertainty in the results to avoid over-interpretation when PK-PD index- response relationships are not identified.
3. Ensure the population is as homogeneous as possible with respect to infection and infecting pathogen, or control for these factors. This will facilitate the detection of PK-PD index- response relationships. Similarly, it may be desirable to standardise concurrent treatments.
4. Derive the PK parameters of the antimicrobial in a robust manner from sufficient samples (the sampling framework may be derived using Stochastic Optimal Design or similar methodology) and using an appropriate population PK model. If free concentrations of antimicrobials are important, then these should be measured rather than adjusting for protein binding using a fixed rate to allow for the fact that protein binding may vary. For some infections, concentration at the site of infection may be important and this should be measured if possible.
5. Perform antimicrobial susceptibility testing of infecting pathogens before the start of therapy, and determine them using standardised methodology. If possible, it may be preferable to store strains to test concurrently in one laboratory.
6. Consider having standardised outcomes and timing of outcomes. The outcomes should be relevant to the patient. PK-PD index-response relationships may be more likely if continuous rather than dichotomous outcomes are used.
7. Follow a pre-specified analysis plan. The most appropriate way of statistically analysing the

relationship between PK-PD indices and outcomes needs to be further investigated. Explicit modelling of the PK-PD index, for example using fractional polynomials,⁸⁸ may be preferable to recursive partitioning, if the sample size is sufficient. It may be advisable to produce a standardised list of covariates that should be assessed to see if they are associated with outcome, for example severity of illness and presence of comorbidities. This list may vary by indication. The investigation of the influence of covariates on the PK-PD relationship for efficacy using multivariable analyses and through the findings of interactions with the PK-PD index may help further the understanding of which subsets of patients are at increased risk of suboptimal drug exposure.

8. The evaluation of PK-PD indices achieved among patients relative to non-clinical PK-PD targets for efficacy is useful. Such information provides dose selection support, especially if PK-PD indices achieved are on the upper plateau of the non-clinical PK-PD relationship for efficacy.