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► To cite this version:

Vincent Aranzana-Climent, Wisse van Os, Amir Nutman, Jonathan Lellouche, Yael Dishon-Benattar, et al.. Integration of individual preclinical and clinical anti-infective PKPD data to predict clinical study outcomes. *Clinical and Translational Science.*, 2024, 17 (7), 10.1111/cts.13870 . hal-04645902

HAL Id: hal-04645902

<https://hal.science/hal-04645902>

Submitted on 12 Jul 2024

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ARTICLE

Integration of individual preclinical and clinical anti-infective PKPD data to predict clinical study outcomes

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Abstract

The AIDA randomized clinical trial found no significant difference in clinical failure or survival between colistin monotherapy and colistin–meropenem combination therapy in carbapenem-resistant Gram-negative infections. The aim of this reverse translational study was to integrate all individual preclinical and clinical pharmacokinetic–pharmacodynamic (PKPD) data from the AIDA trial in a pharmacometric framework to explore whether individualized predictions of bacterial burden were associated with the trial outcomes. The compiled dataset included for each of the 207 patients was (i) information on the infecting *Acinetobacter baumannii* isolate (minimum inhibitory concentration, checkerboard assay data, and fitness in a murine model), (ii) colistin plasma concentrations and colistin and meropenem dosing history, and (iii) disease scores and demographics. The individual information was integrated into PKPD models, and the predicted change in bacterial count at 24 h for each patient, as well as patient characteristics, was correlated with clinical outcomes using logistic regression. The in vivo fitness was the most important factor for change in bacterial count. A model-predicted growth at 24 h of $\geq 2\text{-log}_{10}$ (164/207) correlated positively with clinical failure (adjusted odds ratio, aOR = 2.01). The aOR for one unit increase of other significant predictors were 1.24 for SOFA score, 1.19 for Charlson comorbidity index, and 1.01 for age. This study exemplifies how preclinical and clinical anti-infective PKPD data can be integrated through pharmacodynamic modeling and identify patient- and pathogen-specific factors related to clinical outcomes – an approach that may improve understanding of study outcomes.

Vincent Aranzana-Climent and Wisse van Os contributed equally to this work.

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Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

The AIDA trial found no significant differences in outcomes between colistin monotherapy and colistin–meropenem combination therapy for carbapenem-resistant Gram-negative infections. Subsequent analyses indicated that increasing colistin exposures relative to the infecting pathogens' susceptibility to colistin was associated with increased hazard of death; in vitro meropenem–colistin synergy was not related to clinical outcomes; and high in vivo fitness was associated with clinical failure.

WHAT QUESTION DID THIS STUDY ADDRESS?

We developed a PKPD modeling framework that simultaneously considered individual drug exposures and strain-specific data on antibiotic susceptibility, meropenem–colistin interactions, and in vivo fitness. We aimed to explore whether obtained individualized predictions of bacterial response, together with patient characteristics, were related to the outcomes of the AIDA trial.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

PKPD models developed on preclinical data have been used to optimize antibiotic dosing strategies, but bacterial response predictions have not been linked to clinical outcomes. In this study, model-predicted bacterial growth exceeding 2-log_{10} , together with SOFA score, Charlson comorbidity index, and age, was positively associated with clinical failure in the AIDA trial. More generally, we demonstrated how various types of patient-level preclinical and clinical PK and PD data can be integrated to potentially gain insight into the effects of patient- and pathogen-specific factors on clinical outcomes.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

Application of the integrative (reverse) translational approach presented in this study could offer insights into trial outcomes and advance our understanding of translational antibiotic PKPD.

INTRODUCTION

A randomized clinical trial (the AIDA trial) including 406 patients with severe carbapenem-resistant Gram-negative infections found no significant differences between colistin monotherapy and colistin–meropenem combination therapy in the primary outcome (clinical failure at 14 days after randomization) or in the secondary outcomes, including survival, microbiological cure, and emergence of colistin resistance.¹ The clinical implications of these results are that colistin–meropenem combination therapy should be avoided as it may add to toxicity and the spread of carbapenem resistance without clinical benefit.¹ In a subsequent population pharmacokinetic (PK) study, the predicted average steady-state concentration of colistin-to-minimum inhibitory concentration (MIC) ratio was positively correlated with hazard of death.² This finding illustrates that establishing exposure–response relationships is difficult when patient status and drug exposures are correlated

(e.g., through kidney function), unless patients are randomized to different dose groups. The unexpected direction of the relationship between colistin exposure and patient outcomes motivated us to further elucidate how PK and pharmacokinetics–pharmacodynamics (PKPD) are related to clinical outcomes following colistin treatment. Additional experiments and analyses have been performed with the strains isolated in the AIDA trial. One study evaluated pharmacodynamic drug interactions between meropenem and colistin using checkerboard assays and found that in vitro synergism did not correlate with clinical outcomes.³ Another study with the carbapenem-resistant *Acinetobacter baumannii* isolates found that high bacterial fitness in a mouse thigh infection model was associated with worse clinical outcomes.⁴

PKPD models based on preclinical time-kill data have previously been linked to population PK models to compare antibiotic dosing strategies.⁵ However, predictions by such PKPD models have not been correlated

to clinical outcomes. In this study, we integrated the unique combination of clinical and preclinical data available from patients who participated in the AIDA trial in a PKPD model to obtain individual predictions of bacterial response, based on drug exposures and infecting strain-specific data on fitness, antibiotic susceptibility, and colistin–meropenem interaction. In doing so, we aimed to explore whether predictions based on all these data simultaneously were related to outcomes in the AIDA trial.

METHODS

Patient data and trial information

This PKPD analysis was performed with data from the AIDA randomized controlled trial. The AIDA study was conducted according to the principles expressed in the Declaration of Helsinki, and all participating hospitals obtained ethics approval from their respective ethics committees. Informed consent was obtained from each eligible patient or the patient's representative. Details on inclusion and exclusion criteria, patient and infection characteristics, and outcome measures have been published previously.^{1,6} Briefly, patients with hospital-acquired pneumonia, ventilator-associated pneumonia, bloodstream infections, or urosepsis, caused by Gram-negative bacteria non-susceptible to carbapenems (MIC >2 mg/L) and susceptible to colistin (MIC ≤2 mg/L for *Acinetobacter* spp. and *Enterobacteriaceae* and MIC ≤4 mg/L for *Pseudomonas* spp.),⁷ were randomly assigned to either colistin monotherapy or colistin–meropenem combination treatment. Patients in both treatment arms received 9 million units (MU) loading dose of colistimethate sodium (CMS), followed by 4.5 MU maintenance doses q12h, administered as intravenous infusions over 30 min. Maintenance doses were reduced in patients with creatinine clearance (CrCl) <50 mL/min according to a previously proposed formula.⁸ CMS dosing before randomization was allowed, but no loading dose was administered to patients treated with colistin for >48 h before randomization. Patients in the combination treatment arm additionally received 2 g meropenem q8h as intravenous infusions over 3 h, with dose reductions for patients with renal impairment. The primary outcome, clinical failure on day 14, was defined as a failure to meet a composite of success criteria: patient alive, hemodynamic stability, and improved or stable Sequential Organ Failure Assessment (SOFA) score. In addition, patients with pneumonia should have had stable or improved ratio of partial pressure of arterial oxygen to fraction of expired oxygen, and patients with bacteremia should have had no

microbiological failure on day 14 or later. Microbiological failure, a secondary outcome, was defined as repeat isolation on or after day 7 of bacteria phenotypically identical to the index isolate.

Blood samples were drawn for bioanalysis of CMS and colistin concentrations to allow for the development of a population PK model.² Isolates were sent to a central laboratory, where the infecting species identification was confirmed and the MIC was measured using broth microdilution. In addition, antibiotic interaction studies were performed using checkerboard assays.³

This PKPD analysis considered the data from patients who were included in the dataset for development of the colistin population PK model² and whose infecting pathogen was an *A. baumannii* strain for which checkerboard assay data were available.³ A total of 207 patients met these criteria, of which 115 (55.6%) had been assigned to the colistin monotherapy arm and 92 (44.4%) to the combination treatment arm. Clinical failure and death at day 14 had been observed for 78.7% and 21.3% of the included patients, respectively. Detailed characteristics of patients and isolates included in this analysis are presented in [Table 1](#).

Software

Data processing and visualization were performed with R (v.3.5.2).⁹ NONMEM (v7.4.4)¹⁰ was used for modeling, and NONMEM output was processed using the Xpose4 package (v4.7.0)^{11,12} in R. All scripts used to perform the analyses in this study are available in [Data S1](#) to this article. Files containing representative mock data are also provided; the original data are not freely shareable.

Modeling

PKPD modeling was divided into four parts ([Figure 1](#)), outlined in more detail below. Using population PK models,^{2,13} individual PK profiles were predicted for colistin and meropenem (i). An in vitro PKPD model describing the bacterial killing and interaction between meropenem and colistin against *A. baumannii*¹⁴ was used to estimate isolate-specific drug interaction for patients who had received the combination (ii). The same model was subsequently used to predict individual bacterial response over time, where drug potency parameters were scaled by MICs, and maximum growth was based on in vivo bacterial fitness data (iii). Finally, predicted bacterial densities were linked, together with selected patient characteristics, to trial outcomes using a multivariable logistic regression model (iv).

TABLE 1 Patient and isolate characteristics.

	Median [Standard deviation]	Min–Max
Patient characteristics		
SOFA score	6 [2.95]	0–16
Charlson comorbidity index	2 [2.26]	0–12
Age (years)	0.69 [17.5]	17–94
Hemodialysis ^a	No = 168 (81.2%) Yes = 39 (18.8%)	
Consciousness ^a	Normal = 67 (32.4%) New confusion = 50 (24.2%) Stupor/Coma = 82 (39.6%) Background dementia = 8 (3.8%)	
Site of infection ^a	Bloodstream infection = 71 (34.3%) (Probable) ventilator-associated/hospital-acquired pneumonia = 127 (61.4%) Urinary tract infection = 9 (4.3%)	
Recent surgery ^a	No = 142 (68.6%) Yes = 65 (31.4%)	
Isolate characteristics		
Colistin MIC (mg/L)	0.75 [5.77]	0.5–16
Meropenem MIC (mg/L)	80 [28.9]	1–128
In vivo fitness at 24 h (log ₁₀ CFU/mL)	8.76 [0.616]	5.23–10.1
FICI values	0.531 [0.202]	0.187–1.01

Abbreviations: FICI, fractional inhibitory concentration index; MIC, minimum inhibitory concentration.

^aFor categorical covariates, number of subjects and % of the patients in each category are reported.

PK predictions

Predictions of CMS and colistin PK were performed using the population PK model that had been developed using concentration measurements in the AIDA trial.² Individual PK profiles were predicted using patient-level data on CrCl (the only covariate included in the model), dosing records, and observed CMS and colistin concentrations (i.e., using empirical Bayes estimates to obtain individual PK parameters). For most of the patients, CrCl was determined on multiple occasions during the trial. Between such occasions, CrCl values were imputed with the next observation carried backward method. For timepoints succeeding the last CrCl determination, the last observation carried forward method was used.

Meropenem PK was predicted using a previously published population PK model.¹³ Patient-level information on covariates (age, weight, CrCl) and the dosing records from the AIDA trial were used to predict individual concentration–time profiles. Meropenem dosing records included information on the start and end dates of dosing regimens but lacked exact dosing times. The following assumptions were made: (i) if CMS and meropenem dosing started on the same day, they were assumed to be dosed at

the same time; (ii) if meropenem dosing started after CMS dosing, the start time was assumed to be midnight; (iii) if two meropenem dosing regimens were recorded for the same day (e.g., both 500 mg q8h and 1 g q8h), they were assumed to be switched at noon; and (iv) meropenem dosing records prior to CMS dosing were ignored as meropenem was assumed to be inefficient alone (meropenem MIC >2 mg/L was an inclusion criterion in the AIDA trial) and has a short half-life. CrCl was imputed as described for the colistin PK predictions.

Drug interaction model

A previously published PKPD model by Bian et al.¹⁴ was used to estimate an isolate-specific colistin–meropenem interaction parameter. The model describes the effect of colistin and meropenem alone and in combination based on data from in vitro time-kill experiments with three *A. baumannii* strains, two of which were meropenem-resistant and thus selected for the present study (clinical isolates AB1845 and AB2092).¹⁴ The bacterial model consists of a single bacterial population growing according to a saturable exponential model (Equation 1):

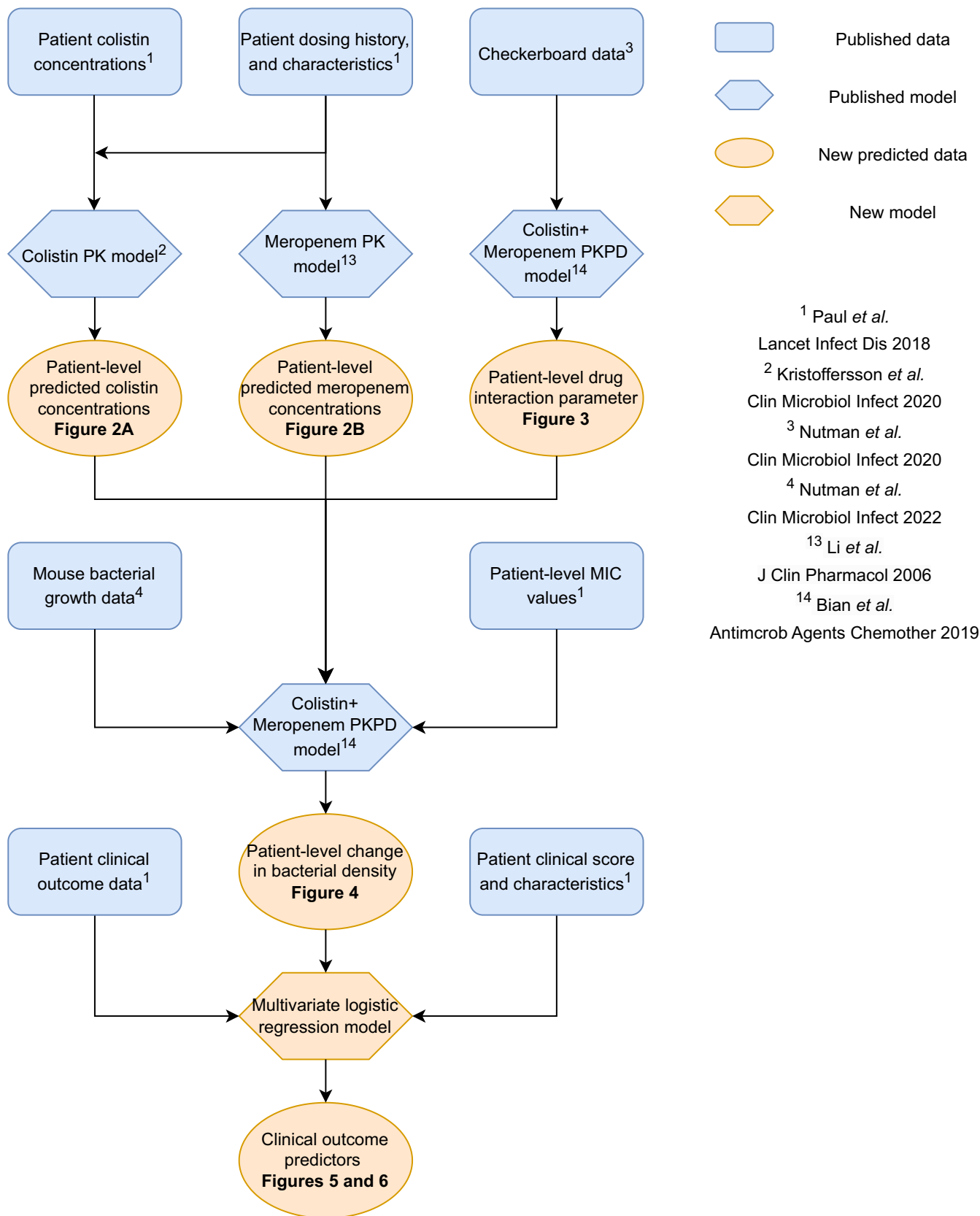


FIGURE 1 Illustration of the inputs and workflow of the analysis. Blue rectangles denote published data used as input for models. Blue diamonds denote published models. Orange ovals denote predicted data from developed models. The orange diamond represents the developed multivariable logistic regression model. Superscripts refer to the source from which data or models were extracted and match the reference number in the bibliography.

$$\frac{dB}{dt} = k_g \times \left(1 - \frac{B}{B_{\max}}\right) \times B \quad (1)$$

where B represents the bacterial density, k_g represents the growth rate constant, and B_{\max} represents the maximal bacterial density. The concentration–effect relationships of meropenem and colistin follow a sigmoidal E_{\max} model (Equations 2 and 3):

$$k_{\text{MER}} = \frac{E_{\max, \text{MER}} \times C_{\text{MER}}^{\gamma_{\text{MER}}}}{EC_{50, \text{MER}}^{\gamma_{\text{MER}}} + C_{\text{MER}}^{\gamma_{\text{MER}}}} \quad (2)$$

$$k_{\text{CST}} = \frac{E_{\max, \text{CST}} \times C_{\text{CST}}^{\gamma_{\text{CST}}}}{\left(\alpha \times EC_{50, \text{CST}}^{\gamma_{\text{CST}}}\right) + C_{\text{CST}}^{\gamma_{\text{CST}}}} \quad (3)$$

where k represents the killing rate of meropenem (MER) or colistin (CST), E_{\max} the maximal effect rate constant, EC_{50} the drug concentration at which the effect is 50% of E_{\max} , γ a sigmoidicity factor, and α an adaptation factor to colistin. The adaptive resistance to colistin follows a function describing a concentration-dependent increase in colistin EC_{50} over time (Equation 4):

$$\alpha = 1 + f \times \left(1 - e^{(-C_{\text{CST}} \times k \times t)}\right) \quad (4)$$

where f is the maximal adaptation factor and k is the rate constant of adaptation. The model includes a strain-specific drug interaction parameter in the combination drug effect function (Equation 5):

$$k_{\text{COMB}} = k_{\text{MER}} \times \left(1 + \frac{k_{\text{CST}}}{k_{\text{CST}} + k_{\text{MER}}}\right)^{\text{INT}} + k_{\text{CST}} \times \left(1 + \frac{k_{\text{MER}}}{k_{\text{MER}} + k_{\text{CST}}}\right)^{\text{INT}} \quad (5)$$

where k represents the killing rate of meropenem (MER), colistin (CST), and the two drugs combined (COMB), and INT is the drug interaction parameter describing drug synergism (INT > 0), antagonism (INT < 0) or additivity (INT = 0). The resulting differential equation for B Equation (6) is

$$\frac{dB}{dt} = \left(k_g \times \left(1 - \frac{B}{B_{\max}}\right) - k_{\text{COMB}}\right) \times B \quad (6)$$

The checkerboard assay data were used to estimate individual values for INT for each isolate. Detailed microbiological procedures for the checkerboard assays have previously been described.³ To be able to use the binary data (visible growth/no visible growth) obtained from checkerboard experiments in the model fitting, we first set the starting inoculum in each well at 5×10^5

colony-forming units (CFU)/mL. Also, we assumed that the limit for visible growth in the wells was 1×10^7 CFU/mL.¹⁵ For each observation (one observation = one well of one plate), the NONMEM likelihood function was impacted as follows:

- When an observation was below the limit (i.e., no visible growth), the likelihood function was set to the probability of being below the limit, similar to the M3 method by Beal for data below the limit of quantification.¹⁶
- When an observation was above the limit (i.e., visible growth), the likelihood function was set to one minus the probability of being below the limit.

Individual INT values were estimated using a population estimate θ_{INT} with an additive variability term (i.e., variability between strains) η_{INT} (Equation 7):

$$\text{INT}_i = \theta_{\text{INT}} + \eta_{\text{INT}} \text{ with } \eta_{\text{INT}} \rightarrow N(0, \omega^2) \quad (7)$$

All other PKPD model parameters were fixed to the estimates reported by Bian et al.¹⁴ Estimation of INT_i was performed using the parameters from both meropenem-resistant strains, resulting in two INT_i estimates per patient isolate. Monte Carlo importance sampling was used as estimation method in NONMEM.

PD predictions

The in vitro PKPD model¹⁴ from which INT_i were estimated was also used to predict individual bacterial response. The PK part of the model was replaced by the individual colistin and meropenem concentrations over time as predicted by the population PK models, multiplied by the unbound drug fraction (0.34¹⁷ and 0.98¹⁸ for colistin and meropenem, respectively) to account for plasma protein binding. For patients in the combination treatment arm, INT_i values were incorporated into the combination drug effect function (Equation 5).

The predictions of bacterial response were further individualized by scaling the colistin and meropenem EC_{50} values by their respective MIC for each isolate (Equation 8):

$$EC_{50i} = EC_{50} \times \frac{\text{MIC}_{\text{mod}}}{\text{MIC}_{\text{isolate}}} \quad (8)$$

EC_{50i} represents the drug concentration at which 50% of the maximum killing rate constant E_{\max} is achieved for isolate i . $\text{MIC}_{\text{isolate}}$ is the MIC of the patient isolate in question, and MIC_{mod} is the MIC of either of the two strains the model had been built on (colistin MIC of 0.5 mg/L

and 1 mg/L, meropenem MICs of 32 mg/L and 128 mg/L, for strains AB1845 and AB2092, respectively¹⁴).

Lastly, predictions were also individualized based on the in vivo fitness of the isolates by fixing the maximal bacterial density (B_{\max}) for each isolate to the bacterial burden at 24 h in the untreated neutropenic mouse thigh infection model, as measured by Nutman et al.⁴

For each patient, bacterial response was predicted over a 24 h period starting from the first CMS dose. The starting inoculum was set to 1×10^6 CFU/mL in all patients, as used in the time-kill experiments by Bian et al.¹⁴ Predictions of bacterial count were performed using the models for both strains, which were subsequently averaged (weighted) using the Akaike Information Criterion (AIC) value obtained for each model in the previous step.¹⁹

Logistic regression model

Predictive models of two trial outcomes (clinical failure and death, both on day 14 after randomization) were developed using multivariable stepwise logistic regression. Potential explanatory variables were added to the prediction model one at a time, and the AIC was computed. Variables were added until no significant improvement in AIC was observed. Then, variables were removed one at a time until a worsening of AIC was observed. The smallest (least number of explanatory variables) model with the best AIC was considered final. Adjusted odds ratios (aOR) were computed.

Several parameterizations of predicted CFU/mL at 24 h after the first CMS dose were evaluated as predictor: predicted Δ CFU/mL (i.e., the difference in CFU/mL between 0 and 24 h), the area under the bacterial (kill) curve over the 0–24 h interval (AUBC/AUBKC²⁰), and binary predictions on whether the predicted \log_{10} Δ CFU/mL was ≥ 0 , ≥ 1 or ≥ 2 . In addition, seven clinical variables, measured at the start of the study, were considered as predictors: SOFA score, Charlson comorbidity index, age, hemodialysis, consciousness, site of infection, and recent surgery.

RESULTS

PK predictions

Predicted plasma concentrations of colistin and meropenem showed high inter-individual variability. The predicted PK profiles for both drugs from the first CMS dose up to 24 h thereafter (i.e., the time period used for PD predictions) are displayed in Figure S1.

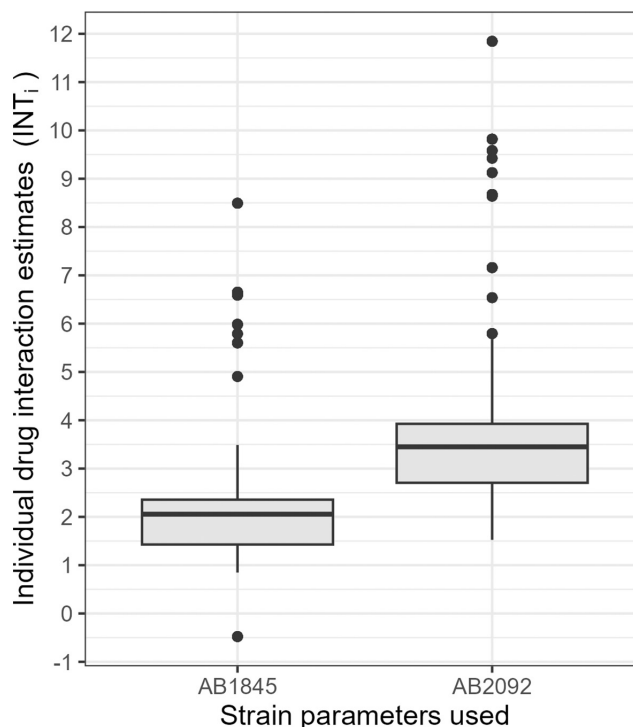


FIGURE 2 Box plot visualizing the distribution of the individual drug interaction (INT_i) estimates. Estimation was performed with parameters for both the AB1845 and AB2092 strains.

Drug interaction model

The distribution of INT_i values estimated with the models for AB1845 and AB2092 based on the checkerboard assay observations are visualized in Figure 2. The median INT value was positive for both PKPD models (2.06 and 3.44 for the AB1845 and AB2092, respectively), that is, typically a synergistic interaction between colistin and meropenem was predicted.

PD predictions

Model-averaged predictions of Δ CFU/mL in response to the corresponding free fractions of predicted drug concentrations are displayed in Figure 3. Many of the isolates in both treatment arms were predicted to reach their maximal bacterial density within 24 h after the first CMS dose. The colistin MIC had limited impact on Δ CFU/mL (Figure 3a), while the maximal change in bacterial density as measured in mice had a strong impact for both treatment arms (Figure 3b).

Logistic regression model

The final model for probability of clinical failure included four significant predictors: SOFA score, Charlson comorbidity index, age at randomization, and Δ CFU/mL

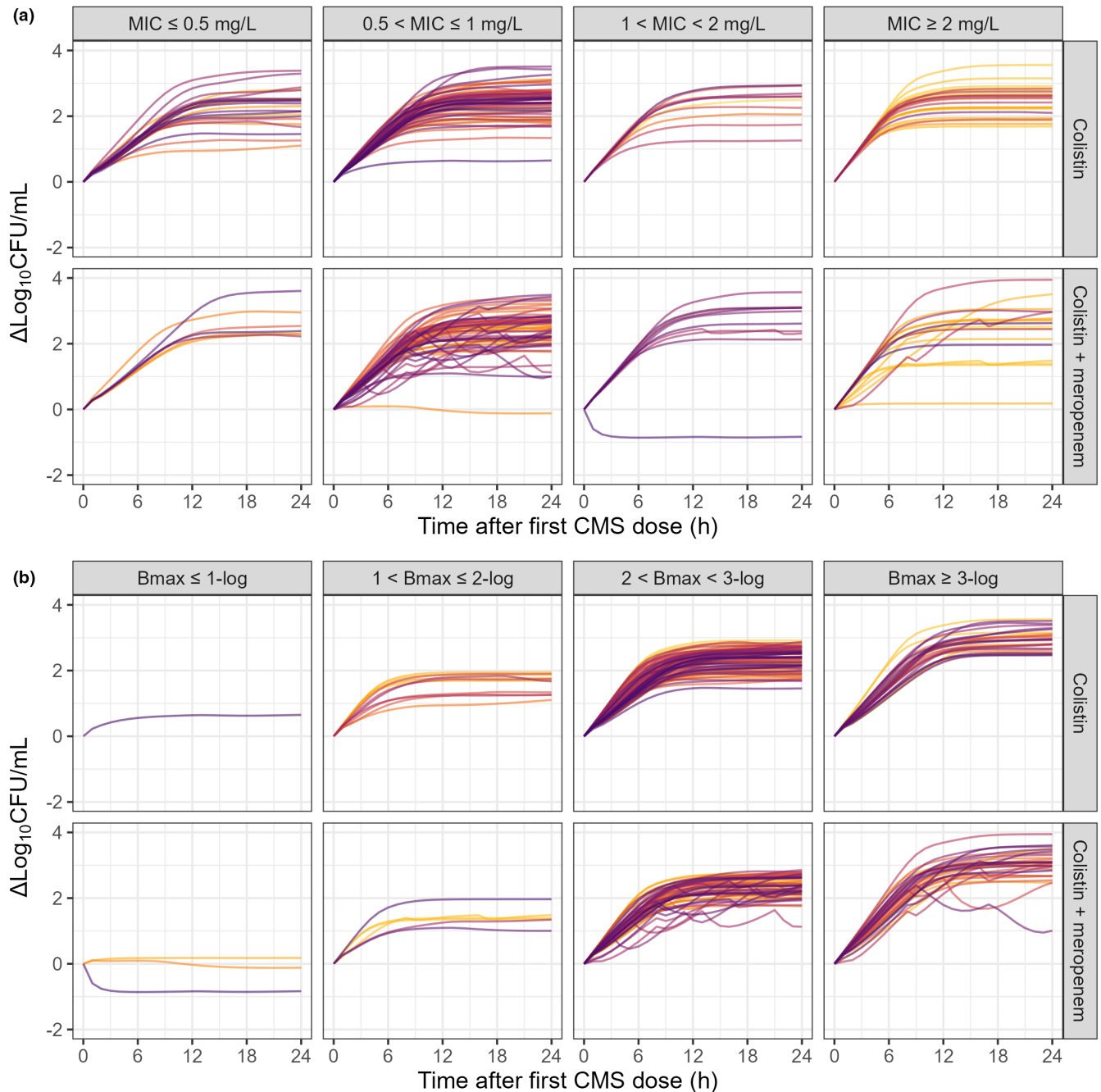


FIGURE 3 Change in bacterial density over time, predicted for patients in the colistin monotherapy arm (top rows) and colistin–meropenem combination therapy arm (bottom rows) using model averaging. (a) Isolates grouped by colistin MIC (columns). (b) Isolates grouped by their fitness (columns) in the mouse thigh infection model, i.e., the change in bacterial density measured at 24 h in untreated mice.

predicted to be $\geq 2\text{-log}_{10}$ at 24 h after the first CMS dose. The most influential variable was SOFA score with a relatively steep increase in the probability of clinical failure as the SOFA score increased (Figure 4). Some significant variables in the model (global test) had their (symmetric) 95% confidence intervals including 1 for the adjusted odds ratio (aOR) (Charlson comorbidity index, age, and $\Delta \text{CFU/mL}$ being $\geq 2\text{-log}_{10}$; Table 2).

The model for probability of death at day 14 included three significant predictors: SOFA score, Charlson comorbidity index, and age at randomization (Figure 5). The most influential variable was Charlson comorbidity index with a steep increase in clinical failure probability as the Charlson comorbidity index increased. The symmetric 95% confidence interval of the adjusted odds ratio (aOR) included 1 for SOFA score (Table 2).

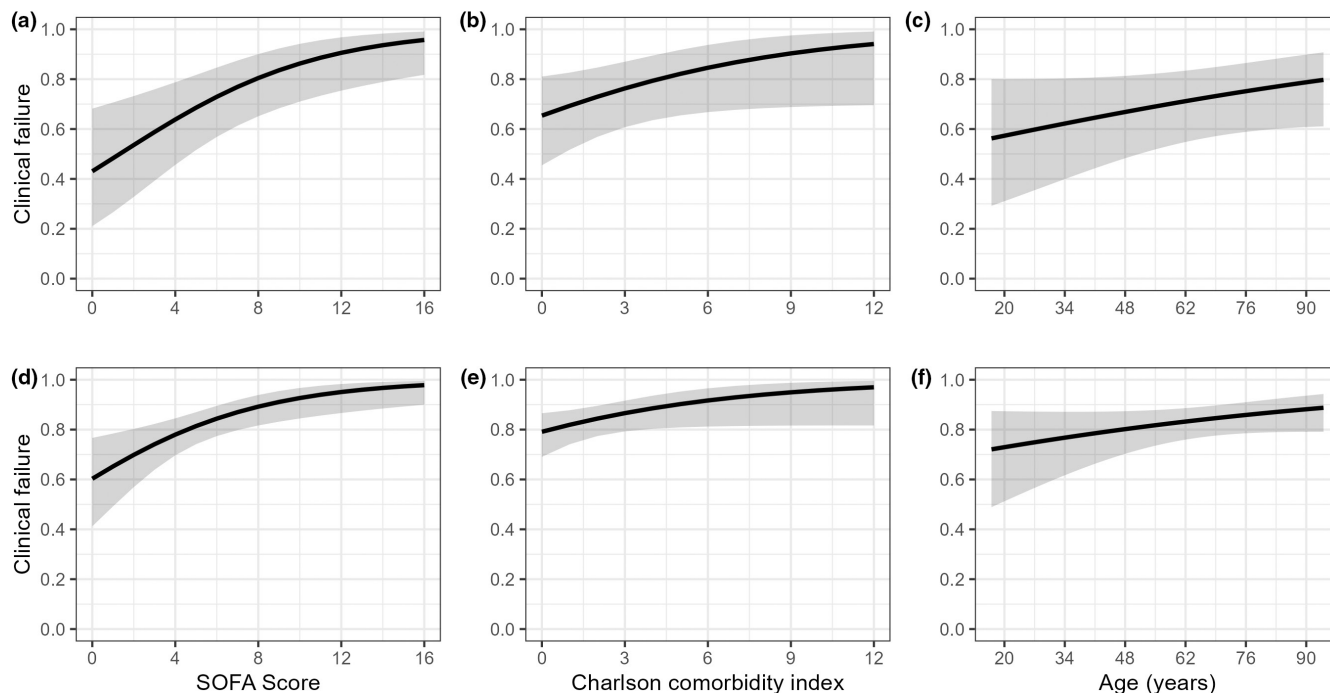


FIGURE 4 Predicted probabilities of clinical failure at day 14 by logistic regression when predicted change in bacterial density at 24 h post first CMS dose was $<2\text{-log}_{10}$ growth (top row) and $\geq 2\text{-log}_{10}$ growth (bottom row). The probabilities of clinical failure at day 14 are plotted against SOFA score (a and d), Charlson comorbidity index (b and e), and age (c and f). The variables that are not illustrated in a panel were set to their median in the population (e.g., SOFA score = 6 and Charlson comorbidity index = 2 in the rightmost panel). The gray areas are the 95% confidence intervals around the prediction.

DISCUSSION

The presented framework is, to our knowledge, the first to integrate individual patient-level data on the infecting pathogens' MIC values, in vitro checkerboard data, in vivo fitness data, as well as individual PK, in a PKPD model of antibiotic effects. The resulting bacterial response predictions for each individual were subsequently evaluated, together with patient health status and demographics, as predictors of survival and clinical cure using logistic regression models.

The analysis showed an increase in odds of clinical failure when the increase in predicted bacterial burden at 24 h exceeded 2 log_{10} CFU/mL. Inclusion of $\geq 2\text{-log}_{10}$ bacterial growth as a predictive factor improved the model fit significantly. It was, however, noted that the symmetric 95% confidence interval included 0 (i.e., included 1 on the aOR scale), but the effect size, here represented by the aOR, is important to consider for exploratory studies,^{21–23} and was 2.01 with a confidence interval upper bound of 4.60, indicating that when underlying patient characteristics such as SOFA score, age, and Charlson morbidity index were accounted for, the predicted bacterial density was related to the outcome.

The proposed framework shows promise for linking individual-level preclinical information, together with

patient demographics and clinical PK data, to clinical outcomes, considering that bacterial burden can most often not be measured in patients. The PKPD model predictions should be seen as a proxy of treatment response related to the outcome, which may also be valuable for comparing treatment strategies based on preclinical data before clinical information, is available. In future studies, measurements of circulating bacterial DNA as a biomarker of bacterial burden²⁴ could be used to connect the PKPD model predictions and clinical outcomes. Other extensions of the pharmacometric framework could include linking the predicted bacterial growth to the transitions in a multi-state model describing clinical and/or microbiological outcomes over time,²⁵ or to a model of repeated measurements of SOFA scores.²⁶

The PKPD modeling methodology that was applied in this study has several strengths. First, it integrates different types of patient-level data in a translational framework. Consideration of all types of data simultaneously can provide insights that would be hard to deduce from evaluating the data sources individually. Second, the model predictions take into account the full time course of PK and PD simultaneously. This is an advantage over using, for example, the PK/PD index approach, in which dynamic PK and PD profiles are separately captured in a single summary value and subsequently linked (e.g.,

AUC/MIC), which cannot readily be applied to drug combinations. Considering the full PKPD time course is particularly important in the context of drug combinations, since the strength of the drug interaction may depend on the concentrations of the two drugs, which fluctuate over time clinically. Third, we used a novel method to estimate

TABLE 2 Parameter estimates and adjusted odds ratios for the logistic regression model linking predicted bacterial density and clinical characteristics to clinical failure and microbiological failure or death. Estimates are reported with standard errors. Adjusted odds ratios were computed as the exponential of the estimated regression coefficients, and their 95% confidence intervals (95%CI) were computed from the standard errors of the estimated regression coefficients assuming they follow a normal distribution.

Parameter	Estimate [standard error]	Adjusted odds ratio [95%CI]
Clinical failure at day 14		
Baseline	−1.62 [0.834]	–
SOFA score	0.212 [0.0702]	1.24 [1.08–1.42]
Charlson comorbidity index	0.178 [0.0936]	1.19 [0.99–1.43]
Age	0.0145 [0.00971]	1.01 [1.00–1.03]
≥2-log ₁₀ bacterial growth predicted 24 h after first CMS dose	0.697 [0.423]	2.01 [0.880–4.60]
Death at day 14		
Baseline	−3.73 [0.845]	–
SOFA score	0.0964 [0.0527]	1.10 [0.990–1.22]
Charlson comorbidity index	0.176 [0.0688]	1.19 [1.04–1.36]
Age	0.0302 [0.0105]	1.03 [1.01–1.05]

a parameter governing the strength and direction of drug interactions. The estimates were based on checkerboard assay data, which, compared to time-kill experiments, are relatively easy to obtain experimentally for a large number of strains. To estimate an interaction factor for each strain, the checkerboard data were handled as categorical data, using the M3 method to estimate the probability of bacterial density in each well being above or below the threshold for visible growth. The strain-specific interaction parameter estimates could be incorporated into the PKPD model to simulate the aforementioned time-varying strength of drug interaction expected to occur clinically due to fluctuating drug concentrations. This is an advantage over the static nature of the interaction metric normally derived from checkerboard experiments, the fractional inhibitory concentration index (FICI), which may explain why the checkerboard FICI data alone were not significantly related to clinical outcomes.³

A limitation of the present work is that the PKPD model parameters have, as is commonly done, been estimated based on time-kill data over 24 h only, and we therefore restricted the predictions to a 24 h time frame, which is not representative of therapy duration in the clinic. It can, however, be argued that the first 24 h is most important for reducing the bacterial burden in critically ill patients²⁷ and is related to outcomes observed later. Second, the predictions of bacterial response were based on strain-specific in vitro data on antibiotic susceptibility and drug interaction as well as in vivo fitness data but lacked information on other strain-specific characteristics such as resistance development rates. Moreover, the PKPD time-kill model used to predict bacterial densities was built with data from two *A. baumannii* strains, which is not representative of the population pharmacodynamics across the infecting

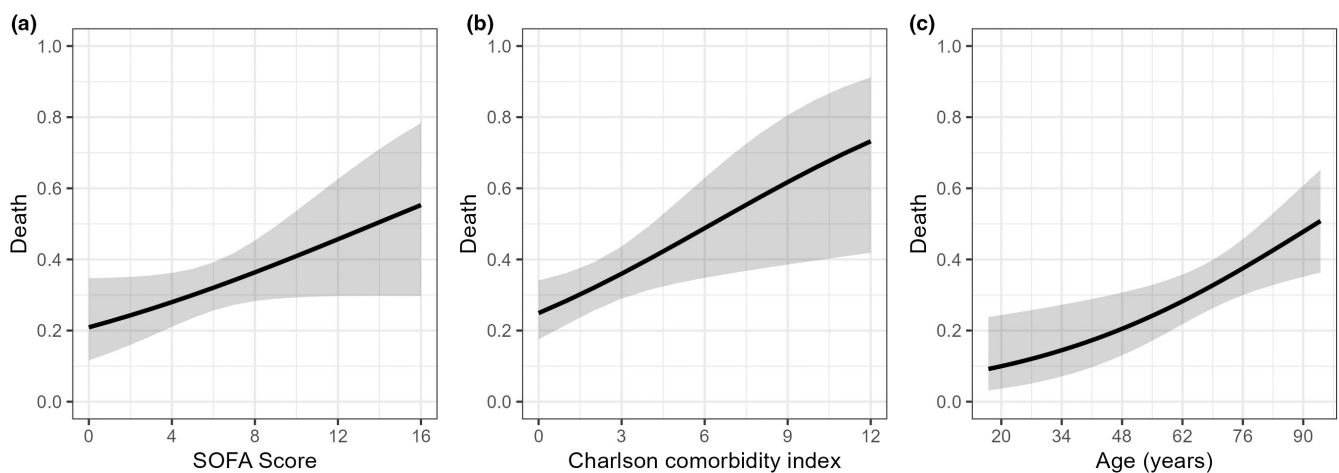


FIGURE 5 Logistic regression predicted probabilities of death at day 14 plotted against SOFA score (a), Charlson comorbidity index (b), and age (c). Variables that are not illustrated in a panel were set to their median in the population (e.g., SOFA score = 6 and Charlson comorbidity index = 2 in the right panel). The gray areas are the 95% confidence intervals around the predictions.

pathogens in the AIDA trial. These limitations could be overcome by generating data from static and/or dynamic time-kill experiments for each isolate and estimate strain-specific pharmacodynamic parameters. High-throughput and low-cost approaches, such as the spotting method,²⁸ should be used for these experiments to maintain feasibility. Alternatively, time-kill experiments could be performed with a subset of isolates, followed by the development of a population PD model. Integration of such data in the presented methodology would be straightforward. The limitations listed above are related to the availability of data used to develop the models within the framework and thus apply to the results of the present analysis using data from the AIDA trial but are not inherent to the applied methodology. Indeed, the developed workflow could be applied to other drugs, bacteria, and sources of in vitro and/or in vivo data that can be linked with bacterial density predictions through semi-mechanistic PKPD models. For example, predictions from PK models describing the unbound concentrations at the site of action may provide a more precise link to outcome,²⁹ and ideally the impact of the immune system on the infecting pathogen could be considered.³⁰ Future research should focus on the contribution of host-related factors to bacterial killing and clinical outcomes, as this will also enhance our understanding of the relative contributions of drug and pathogen-related factors.³¹

To conclude, we developed a reverse translational, model-based approach integrating different types of data from in vitro, in vivo, and clinical sources to explore whether individualized predictions of bacterial response were related to observed clinical outcomes. Based on data from the AIDA trial, we found that a predicted bacterial growth over 24 h exceeding 2-log₁₀ was significantly correlated with an increased risk of clinical failure, together with SOFA score, Charlson comorbidity index, and age. The methodological concepts presented in this study can be applied to other types of data and other clinical trials to explore the explanatory and predictive abilities of such models for various patient populations, infection types, pathogens, and antimicrobial therapies. Moreover, in cases where strong links between individual PKPD and clinical outcomes can be established, these integrative models have the potential to contribute to an improved understanding of translational antibiotic PKPD.

AUTHOR CONTRIBUTIONS

V.A.-C., W.v.O., and L.E.F. wrote the manuscript; V.A.-C., W.v.O., A.N., J.L., Y.D.-B., N.R., G.L.D., A.S., I.P., E.D.-M., U.T., M.P., Y.C., and L.E.F. designed the research; V.A.-C., W.v.O., and L.E.F. performed the research; V.A.-C., W.v.O., and L.E.F. analyzed the data.

ACKNOWLEDGMENTS

A preliminary analysis was presented at the ISAP/EPASG meeting (online) November 2021.

FUNDING INFORMATION

The modeling analyses were funded by the Swedish Research Council grant No 2018–03296 and 2022–00657.

CONFLICT OF INTEREST STATEMENT

Yehuda Carmeli received consultancy fees from MSD, Qpex, Pfizer, Roche, and Enlivex and payment for lectures from Pfizer. Emanuele Durante-Mangoni received grants from Pfizer, Shionogi, Advanz Pharma, Infectopharm, and Angelini, and payment for lectures from Pfizer, Shionogi, Advanz Pharma, Infectopharm, Angelini, Abbvie, and Trx and participated on a data safety monitoring board or advisory board of Roche, Genentech, and Pfizer. George Daikos received honoraria for lectures from Pfizer, MSD and received support to attend meetings from Pfizer and participated on an advisory board of Vitaris, MSD, and Pfizer. All other authors declared no competing interests in this work.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Aranzana-Climent V, van Os W, Nutman A, et al. Integration of individual preclinical and clinical anti-infective PKPD data to predict clinical study outcomes. *Clin Transl Sci*. 2024;17:e13870. doi:[10.1111/cts.13870](https://doi.org/10.1111/cts.13870)