Infectious Disease Practice

Machine learning and clinician predictions of antibiotic resistance in Enterobacterales bloodstream infections

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SUMMARY

Background: Patients with Gram-negative bloodstream infections are at risk of serious adverse outcomes without active treatment, but identifying who has antimicrobial resistance (AMR) to target empirical treatment is challenging.
Methods: We used XGBoost machine learning models to predict antimicrobial resistance to seven antibiotics in patients with Enterobacterales bloodstream infection. Models were trained using hospital and community data from Oxfordshire, UK, for patients with positive blood cultures between 01-January-2017 and 31-December-2021. Model performance was evaluated by comparing predictions to final microbiology results in test datasets from 01-January-2022 to 31-December-2023 and to clinicians' prescribing.
Findings: 4709 infection episodes were used for model training and evaluation; antibiotic resistance rates ranged from 7–67%. In held-out test data, resistance prediction performance was similar for the seven antibiotics (AUCs 0.680 [95%CI 0.641–0.720] to 0.737 [0.674–0.797]). Performance improved for most antibiotics when species identifications (available ~24 h later) were included as model inputs (AUCs 0.723 [0.652–0.791] to 0.827 [0.797–0.857]). In patients treated with a beta-lactam, clinician prescribing led to 70% receiving an active beta-lactam: 44% were over-treated (broader spectrum treatment than needed), 26% optimally-treated (narrowest spectrum active agent), and 30% under-treated (inactive beta-lactam). Model predictions without species data could have led to 79% of patients receiving an active beta-lactam: 45% over-treated, 34% optimally-treated, and 21% under-treated.
Conclusions: Predicting AMR in bloodstream infections is challenging for both clinicians and models. Despite modest performance, machine learning models could still increase the proportion of patients receiving active empirical treatment by up to 9% over current clinical practice in an environment prioritising antimicrobial stewardship.

Introduction

Active and timely antibiotic treatment of severe bacterial infections potentially saves lives and improves patient outcomes.[1] However, it can take 24–48 h or more to obtain microbiology results to guide treatment, and many important infections remain culture negative.[2] Therefore, substantial reliance is placed on antibiotic guidelines that are designed to maximise active empirical treatment of infections before microbiology results are available, while also minimising overuse of broad-spectrum antibiotics to avoid driving antimicrobial resistance (AMR).

Population-level antibiotic recommendations can be refined for individual patients, e.g. considering previous resistance or prior antibiotic exposure. However, this does not happen consistently, e.g. due to limited time available to retrieve earlier results or variable prescriber experience. Therefore, several previous studies have evaluated whether combining electronic healthcare record (EHR)

data with predictive algorithms could improve AMR detection and hence lead to better targeted prescribing (Table 1).[3–18] These studies typically focus on patients with positive microbiology and use machine learning to predict resistance to key antibiotics. Most previous studies focused on urinary tract infections or all infections (likely dominated by urine cultures), in part due to the availability of large datasets for model training.[5–18] Only a minority focus specifically on bloodstream infection despite its clinical importance.[3,4] Several data types have been shown to be potentially informative, including a history of isolates with AMR, population AMR rates, previous personal antimicrobial exposure, past medical history, and demographics. Data are typically obtained from a single hospital or community setting, but occasionally from a whole healthcare network.

In previous studies, predictive performance for detecting AMR has been relatively modest, e.g. area under the receiver operating curve (AUC) values for important pathogen-antibiotic combinations of around 0.65–0.75, but varying between drugs and settings. If species identification is included as a model input performance improves, e.g. AUCs of 0.80–0.88.[8,17] However, species is unknown when starting empirical treatment, becoming available ~24 h later. Most studies use test data from the same setting either randomly chosen from the same period or from shortly after the training period, limiting generalisability over geographic locations and time. Within 16 previous studies identified, only two externally validated their findings using data from a different area/hospital.[14,15] Most approaches do not address how to update models over time. Four studies retrospectively compared model performance to clinical decision-making, showing models could potentially reduce inappropriate antibiotic treatments.[5,9,10,15] Taken together, alongside technical barriers to interfacing with EHR systems and implementing models in healthcare settings, to date, uptake of such predictions into clinical practice has been very limited.

Here we apply machine learning predictions to an important, but only partially studied patient group at particular risk of poor outcomes from AMR, those with Enterobacterales bloodstream infection.[19] Our models are designed to be used in suspected bloodstream infections where Enterobacterales species are the most probable cause, e.g. with urinary or intra-abdominal focus. We use a comprehensive input feature set addressing potential limitations of some earlier studies, by combining data from hospital EHRs with community microbiology results. We also evaluate how performance changes over time and test approaches for updating models as new data emerges. We describe how well clinicians detect AMR and compare the performance of our models to actual prescribing and simulate the impact that a prediction system might have on the number of patients receiving active antibiotic treatment, and the wider impact on use of broad-spectrum antibiotics.

Methods

Study design and population

We used data from Oxford University Hospitals (OUH), four teaching hospitals collectively providing 1100 beds, serving 750,000 residents in Oxfordshire, ~1% of the UK population. The hospitals' microbiology laboratory also provides nearly all community testing for the region. Deidentified data were obtained from Infections in Oxfordshire Research Database, which has approvals from the South Central-Oxford C Research Ethics Committee (19/SC/0403), the Health Research Authority, and the Confidentiality Advisory Group (19/CAG/0144) as a deidentified database without individual consent.

We included all patients aged ≥16 years with a positive blood culture containing a single Enterobacterales species between 01-January-2017 and 31-December-2023. Polymicrobial blood cultures were excluded as these potentially contained non-Enterobacterales species. Patients were included once per positive blood culture episode, i.e. including the first positive blood culture with an Enterobacterales species per 14-day period.

Antimicrobial resistance prediction

We predicted antimicrobial susceptibility results for intravenous treatments for bloodstream infection that were commonly used in our institution with resistance rates > 5%, i.e. amoxicillin, co-amoxiclav (amoxicillin-clavulanate), ceftriaxone, piperacillin-tazobactam, co-trimoxazole (trimethoprim-sulfamethoxazole), and ciprofloxacin. Predictions were not made for meropenem as resistance rates were < 1%. Predicted results were binary, i.e. susceptible (including intermediate/dose-dependent susceptible) or resistant. During the study, hospital empirical antibiotic guidelines recommended co-amoxiclav ± additional single-dose gentamicin for treatment of suspected sepsis of an unknown, urinary, or intra-abdominal source.

We made predictions at two time points, firstly when blood was taken for culture and secondly when the species was identified (typically ~24 h later). Input features included patient demographics, comorbidities, previous hospital-prescribed antibiotics, current clinical syndrome, hour of day the blood culture was taken, counts of the number of recent laboratory blood tests sent, previous hospital and community microbiology results including numbers of samples taken, number culture positive, and presence of antibiotic resistance to specific antibiotics, patient height and weight, previous hospital exposure, previous hospital-based procedures, current specialty, and counts of the number of recent vital sign measurements (Table S1). We also included recent population-level rates of AMR. The species-level analysis additionally included the species identified and any history of AMR in previous isolates of the same species. Overall, there were 152 features in the baseline model, and 182 in the species model.

Model architecture, data partitioning and evaluation

We fitted separate XGBoost models for each antibiotic, aiming to predict subsequently identified phenotypic resistance. We used a temporal training-test split to mimic real-world implementation (training: 01-January-2017 to 31-December-2021; testing 01-January-2022 to 31-December-2022 (Test dataset 1)), reporting performance in the test dataset (see Supplement, Table S2-S3).

Model updating

We used additional test data (Test dataset 2: 01-January-2023 to 31-December-2023) to evaluate if performance changed over time and investigate different approaches for updating models. Three approaches were evaluated, in the first no further model training was undertaken, i.e. the model was based only on data from 2017–2021. In the second we retrained the model from scratch using all available data, i.e. from 2017–2022 inclusive. In the final approach we used on online-training method, where the trained model from the 2017–2021 was updated with data from 2022, using an inbuilt method available within XGBoost.

Comparison with clinical decision-making

To compare our models with clinical practice, we combined both test datasets and considered patients initially treated with a beta-lactam antibiotic. Beta-lactams were the most commonly used antibiotics in our institution and facilitated establishing a hierarchy of antibiotic choices. We included patients empirically treated with amoxicillin, co-amoxiclav, ceftriaxone, piperacillin-tazobactam, or a carbapenem (mostly meropenem; a small number receiving

Table 1
Previous models for predicting antibiotic resistance.

Publication	Population	Infection type	Prediction input contains species information	Antibiotics	Model architecture	Features	Performance-AUC	External validation	Comparison with clinicians	Ref.
Vazquez-Guillamet et al. 2017	US, 2008–2015, single Hospital, 1618 patients	Bloodstream infection	Yes	Piperacillin-tazobactam (PT), cefepime (CE), meropenem (ME)	Logistic regression (LR), decision trees (DT)	Nursing home residence, transfer from an outside hospital, prior antibiotic use, source of infection, bacterial species	LR: 0.68, 0.63, and 0.83 for resistance to PT, CE, and ME; DT: 0.67, 0.61, and 0.80 for resistance to PT, CE, and ME	No	No	3
Sousa et al. 2019	Spain, 2015–2016, single hospital, 448 samples	Gram-negative bacteraemia	No	β-lactamase production	Decision tree	Comorbidities, source of infection, history of infection, antibiotic exposure, previous hospitalisation	0.76	No	No	4
Yelin et al. 2019	Israel, 2007–2017, community health maintenance organization, 315,047 patients	Urinary tract infection	No	Co-trimoxazole, ciprofloxacin, co-amoxiclav, cefuroxime, cephalexin, nitrofurantoin	Logistic regression, gradient-boosted decision trees	Resistance profile, demographics, sample history, drug purchase history, cross-resistance	0.70 (co-amoxiclav) to 0.83 (ciprofloxacin)	No	Yes	5
Fretzakis et al. 2020	Greece, 2017–2018, single hospital, 345 patients	All infections	Partial (Gram stain)	Multiple	Random forest (RF), multi-layer perceptron (MLP)	Demographics, type of sample, Gram stain, antibiotics, previous antibiotic susceptibility testing	RF: 0.70 MLP: 0.73	No	No	6
Hebert et al. 2020	US, 2011–2016, single hospital, ICU patients, 6366 patients	Urinary tract infection	No	Cefazolin, ceftriaxone, ciprofloxacin, cefepime, and piperacillin-tazobactam	Logistic regression	Demographics, comorbidity score, recent antibiotic use, recent antimicrobial resistance, and antibiotic allergies	0.65 (ceftriaxone) to 0.69 (cefazolin)	No	No	7
Lewin-Epstein et al. 2020	Israel, 2013–2015, single hospital, 16,198 samples	All infections	No and Yes	Ceftazidime, gentamicin, imipenem, ofloxacin, sulfamethoxazole-trimethoprim	Logistic regression, neural networks, gradient-boosted decision trees	Bacteria species, previous resistance, demographics, comorbidities, prior hospitalisation, department/ward, previous antibiotics exposure	Without species: 0.73–0.79 With species: 0.80–0.88	No	No	8
Moran et al. 2020	UK, 2010–2016, 3 hospitals, 15,695 admissions	Community-associated bloodstream and urinary tract infections	No	Co-amoxiclav, piperacillin-tazobactam	XGBoost	Comorbidities, demographics, previous resistance, previous antibiotics exposure	0.70	No	Yes	9
Kanjilal et al. 2020	US, 2007–2016, 2 hospitals, 13,682 patients, female, 18–55 years	Urinary tract infection	No	Nitrofurantoin, co-trimoxazole, ciprofloxacin, levofloxacin	Logistic regression, decision tree, random forest	Demographics, comorbidities, previous hospitalisation, previous procedures, lab tests, previous antibiotics use, previous resistance	Full cohort: 0.56–0.64; limit to prior antibiotic resistance or exposure: 0.61–0.77	No	Yes	10
McGuire et al. 2021	USA, 2012–2017, single hospital, 68,472 samples	All infections	No	Carbapenem	XGBoost	Demographics, medications, vital signs, prior procedures, lab tests, billing code, culture, sensitivity	0.846	No	No	11
Pascual-Sánchez et al. 2021	Madrid, Spain, 2004–2020, single hospital, 3500 patients	All infections	No	Multiple, predict multi-drug resistance	Logistic regression, XGBoost, neural network, random forest	Time to culture, previous resistance	0.76	No	No	12

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Table 1 (*continued*)

Publication	Population	Infection type	Prediction input contains species information	Antibiotics	Model architecture	Features	Performance-AUC	External validation	Comparison with clinicians	Ref.
Martínez-Agüero et al. 2022	Madrid, Spain, 2004–2020, single hospital, 3470 patients	All infections	No	Multiple agents	Long short-term memory network	Clinical time-series data	0.67	No	No	13
Rich et al. 2022	US, 2011–2019, multi-centre, 6307 patients	Urinary tract infection	No	Co-trimoxazole (SXT), nitrofurantoin (NIT), ciprofloxacin (CIP), multi-drug resistance	Boosted logistic regression	Demographics, zip code, comorbidities, previous resistance, previous antibiotics exposure, previous hospital stay	0.58 (SXT), 0.62 (NIT), 0.64 (CIP), and 0.66 (MDR)	Yes	No	14
Corbin et al. 2023	US, 2009–2021, multi-centre, 8342 infections from 6920 patients	All infections	No	Vancomycin, piperacillin/tazobactam, cefepime, ceftriaxone, cefazolin, ciprofloxacin, ampicillin and meropenem	Gradient boosted decision tree, random forest	Diagnostic codes, prior procedures, lab tests, medications, respiratory care, previous resistance, vital signs, demographics, insurance, imaging, institution	0.61–0.73	Yes	Yes	15
Lee et al. 2023	Korea, 2020–2021, single hospital, 550 samples	Urinary tract infection	No	Ciprofloxacin (CIP), extended-spectrum beta-lactamases (ESBL)	Gradient-boosted decision trees	Demographics, medical device, infection type, comorbidities, past history, vital signs, lab tests	0.827 for CIP 0.811 for ESBL	No	No	16
Mintz et al. 2023	Israel, 2016–2019, single hospital, 10053 samples	All infections	No and Yes	Ciprofloxacin	Super learner	Demographics, comorbidities, previous resistance, previous antibiotics exposure, department/ward	Without species: 0.737 With species: 0.837	No	No	17
Yang et al. 2023	US, 2007–2016, two hospitals, 101,096 samples	Urinary tract infection (UTI)	No	Nitrofurantoin (NIT), co-trimoxazole (SXT), ciprofloxacin (CIP), levofloxacin (LVX)	TabNet, XGBoost	Department/ward, demographics, previous resistance, previous organism, previous antibiotics exposure, comorbidities, previous procedures, colonisation pressure	Complicated UTI: 0.686 (NIT), 0.701 (SXT), 0.811 (CIP), 0.814 (LVX) Uncomplicated UTI: 0.559 (NIT), 0.591 (SXT), 0.646 (CIP), 0.639 (LVX).	Validated on uncomplicated UTI	No	18

Results shown are from an illustrative literature review.
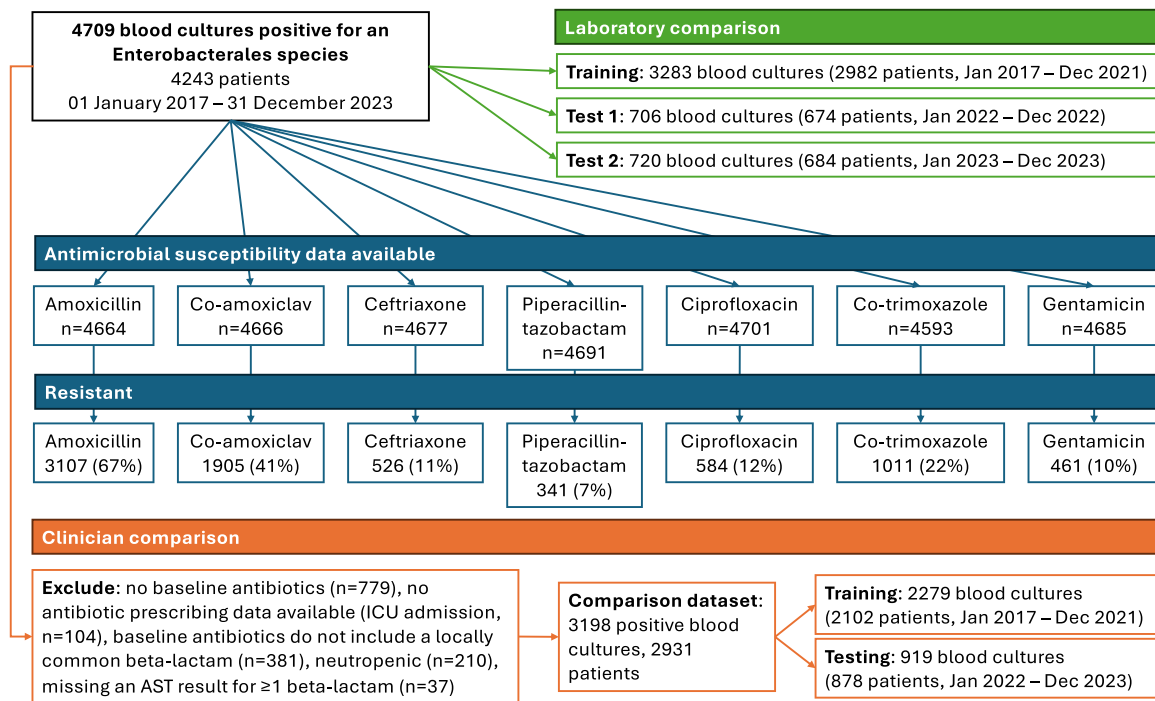Only four studies were identified that have made their code publicly available.[10,15,17,18]

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Fig. 1. Blood cultures studied, and laboratory and clinical comparison groups. Repeat positive cultures from the same patient within the next 14 days after a positive blood culture were excluded. Only 7 blood cultures were resistant to meropenem; in the laboratory comparison 3 were in the training data, 2 in test 1 and 2 in test 2; in the clinical comparison 3 meropenem resistant blood cultures were included, 1 in the training data and 2 in the test data. Not all blood cultures had susceptibility results reported for all antibiotics as shown. Within the 3198 blood cultures studied in the clinical comparison, 2064 (65%) were resistant to amoxicillin, 1225 (38%) to co-amoxiclav, 320 (10%) to ceftriaxone, 190 (6%) to piperacillin-tazobactam, and 3 (< 1%) to meropenem. Rates of resistance to gentamicin, ciprofloxacin and co-trimoxazole were 318/3195 (10%), 379/3196 (12%), and 674/3170 (21%) respectively. Of the 381/4709 (8%) of patients treated with antibiotics other than one of beta-lactams studied, only 74 (2%) received an alternative beta-lactam. These were predominantly (n=49) beta-lactams not active against Enterobacterales, such as flucloxacillin or penicillin, most likely representing diagnostic uncertainty about the initial focus of infection, and therefore situations where even if our model was in use, it might not have been applied.

empirical ertapenem), in order of increasing spectrum of coverage. The most common adjunctive antibiotic in our setting was single-dose gentamicin; however, we excluded it from our main analysis considering only the beta-lactam given, as we have previously shown gentamicin does not rescue patients with beta-lactam (co-amoxiclav) resistance from associated increases in mortality in *Escherichia coli* bloodstream infection.[20] We excluded from the clinical comparison neutropenic patients (as piperacillin-tazo-bactam or meropenem would have been the only appropriate empirical treatments from our beta-lactam hierarchy), patients not started on antibiotics (as there was no clinician antibiotic choice to compare with), patients admitted to an ICU using a different prescribing system not included in the dataset, and blood cultures missing ≥1 susceptibility results for the beta-lactams listed above (further details in supplement). No patient allergy data were available.

To compare clinical practice and model predictions, we evaluated the number of patients who were i) optimally-treated, i.e. received the least broad-spectrum beta-lactam to which their blood culture isolate was sensitive, ii) under-treated, given a beta-lactam with resistance present, and iii) over-treated, given an active beta-lactam, but of broader spectrum than necessary. We also described the relative usage rates of each antibiotic.

We evaluated 4 strategies for applying our machine learning predictions (using models without species information), tuning the prediction thresholds using the training data to: 1) match total antibiotic use to total clinician antibiotic use, but potentially distributing it between patients more optimally, 2) match total use to population antibiotic susceptibility rates, 3) match rates of over-treatment by clinicians, while aiming to increase active treatment, and 4) to quantify how much our models could reduce over-treatment if the default antibiotic policy was switched from using co-

amoxiclav to ceftriaxone first-line (details in Supplement). Thresholds were then applied in the combined test data and performance summarised.

Results

Between 01 January 2017 and 31 December 2023, 252,849 blood cultures were taken. 24,228 (9.6%) were culture-positive, including 6983 (2.8%) with an Enterobacterales species. After removing polymicrobial infections and de-duplicating repeat positive samples within 14 days, there were 4752 Enterobacterales bloodstream infections in 4273 patients; of these 43 blood cultures were excluded because antimicrobial susceptibility testing was not performed, leaving 4709 bloodstream infections in 4243 patients for model training and evaluation (Fig. 1). The median (IQR) patient age was 74 (60−84) years, and 2611 (55%) episodes were in male patients. The median (IQR) Charlson comorbidity score was 1 (0−3). 3631 (77%) bloodstream infections were community-onset (i.e. taken within < 48 h of hospital admission).

The most commonly isolated species were *E. coli* (3094, 66%), *Klebsiella pneumoniae* (545, 12%), *Proteus mirabilis* (203, 4%), *Enterobacter cloacae* (177, 4%), and *K. oxytoca* (153, 3%). Across all species, 3107/4664 (67%) infections were resistant to amoxicillin, 1905/4666 (41%) to co-amoxiclav, 526/4677 (11%) to ceftriaxone, 341/4691 (7%) to piperacillin-tazobactam, 461/4685 (10%) to gentamicin, 1011/4593 (22%) to co-trimoxazole, and 584/4701 (12%) to ciprofloxacin (denominator varied as not all samples were tested for all antibiotics). Resistance to meropenem was uncommon, 7/4689 (< 0.2%).

The most frequently prescribed empirical antibiotics given within 4 h of obtaining blood cultures were co-amoxiclav alone (1194, 25%), no antibiotics (779, 17%), co-amoxiclav+gentamicin (761,

Table 2
Model performance for predicting antibiotic resistance at blood culture sampling (A) and at species identification (B) in held-out test dataset 1, 01 January 2022 – 31 December 2022, Oxfordshire, UK.

(A) Model performance for predicting antibiotic resistance at blood culture sampling

Antibiotic	n	Resistant, n	Resistant, %	AUC (95%CI) at blood culture sampling	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)
Amoxicillin	693	455	66	0.680 (0.641 - 0.720)	62.2 (57.8 – 66.6)	66.4 (60.2 – 72.3)	78.0 (73.9 - 81.9)	47.9 (42.6 – 53.7)
Co-amoxiclav	699	283	40	0.684 (0.642 - 0.722)	60.4 (54.7 – 66.1)	67.8 (63.7 – 71.9)	56.1 (50.5 – 61.3)	71.6 (67.8 – 75.8)
Ceftriaxone	701	78	11	0.737 (0.674 - 0.797)	48.7 (37.5 – 60.2)	83.0 (80.1 – 85.9)	26.4 (19.2 – 34.2)	92.8 (90.6 - 94.9)
Piperacillin-tazobactam	704	64	9	0.708 (0.643 - 0.779)	51.6 (39.6 – 63.8)	79.1 (75.8 – 82.1)	19.8 (14.2 – 26.3)	94.2 (92.2 - 96.0)
Ciprofloxacin	706	86	12	0.726 (0.655 - 0.789)	50.0 (39.2 – 60.6)	88.2 (85.7 – 90.6)	37.1 (28.0 – 45.4)	92.7 (90.6 – 94.8)
Co-trimoxazole	688	123	18	0.698 (0.641 - 0.754)	40.7 (32.7 – 49.6)	91.5 (89.2 – 93.7)	51.0 (41.7 – 60.5)	87.6 (84.8 – 90.3)
Gentamicin	704	75	11	0.700 (0.625 - 0.775)	45.3 (34.2 – 57.1)	85.2 (82.6 – 88.0)	26.8 (19.4 – 35.2)	92.9 (90.6 – 94.8)

(B) Model performance for predicting antibiotic resistance at blood culture species identification

Antibiotic	n	Resistant, n	Resistant, %	AUC (95%CI) with species information	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)
Amoxicillin	693	455	66	0.827 (0.797 - 0.857)	65.1 (60.8 – 69.9)	85.7 (81.3 – 90.0)	89.7 (86.4 – 92.8)	56.2 (51.3 – 61.5)
Co-amoxiclav	699	283	40	0.771 (0.734 - 0.805)	67.1 (61.0 – 72.6)	72.8 (68.3 – 77.1)	62.7 (57.3 – 68.1)	76.5 (72.4 – 80.7)
Ceftriaxone	701	78	11	0.799 (0.745 - 0.846)	64.1 (53.1 – 73.9)	77.5 (74.1 – 80.9)	26.3 (19.8 – 32.4)	94.5 (92.5 - 96.3)
Piperacillin-tazobactam	704	64	9	0.723 (0.652 - 0.791)	64.1 (51.9 – 75.4)	67.3 (63.6 – 71.1)	16.4 (12.1 – 20.8)	94.9 (92.7 - 96.8)
Ciprofloxacin	706	86	12	0.783 (0.724 - 0.840)	47.7 (37.1 – 59.2)	92.7 (90.6 – 94.7)	47.7 (36.6 – 57.8)	92.7 (90.7 – 94.8)
Co-trimoxazole	688	123	18	0.774 (0.726 - 0.821)	49.6 (41.3 – 58.9)	89.7 (87.2 – 92.2)	51.3 (42.6 – 60.2)	89.1 (86.6 – 91.6)
Gentamicin	704	75	11	0.729 (0.654 - 0.794)	41.3 (29.5 – 52.6)	91.7 (89.5 – 93.9)	37.3 (26.8 – 47.4)	92.9 (90.9 – 94.8)

AUC, area under the receiver operating curve. Confidence intervals were generated by bootstrapping with 1000 iterations.

16%), ceftriaxone alone (236, 5%), and piperacillin-tazobactam alone (109, 2%); 82 (2%) patients received a carbapenem with or without another antimicrobial.

Model performance at baseline

In held-out test data from 2022 (Test dataset 1), predictive performance was broadly similar for the seven antibiotics, with AUCs ranging from 0.680 [95%CI 0.641–0.720] for amoxicillin to 0.737 [0.674 - 0.797] for ceftriaxone (Table 2A; Table S4 for training data performance). Jointly optimising sensitivity and specificity, sensitivity ranged from 40.7% (32.7–49.6%) for co-trimoxazole to 62.2% (57.8–66.6%) for amoxicillin, while specificity ranged from 66.4% (60.2–72.3%) for amoxicillin to 91.5% (89.2–93.7%) for co-trimoxazole. Positive predictive values (PPVs) and negative predictive values (NPVs), which are influenced by differences in resistance prevalence, ranged from 19.8% (14.2–26.3%) to 78.0% (73.9–81.9%) and 47.9% (42.6–53.7) to 94.2% (92.2–96.0%), respectively. Alternative values for sensitivity/specificity/PPV/NPV could be obtained by varying the threshold chosen for identifying resistance (e.g. prioritising sensitivity, Table S5).

Model performance following species identification

Performance improved for most antibiotics when species data were included as inputs to the prediction models, i.e., mimicking the point during laboratory work-up of a blood culture when the species is first identified, but susceptibility results remain pending. For example, AUCs increased for amoxicillin (0.680 [95%CI 0.641–0.720] to 0.827 [0.797–0.857]) and co-amoxiclav (0.684 [0.642–0.722] to 0.771 [0.734–0.805]). Performance increases were seen for other antibiotics, but with minimal improvement for piperacillin-tazobactam (Table 2B, Table S6 for training dataset).
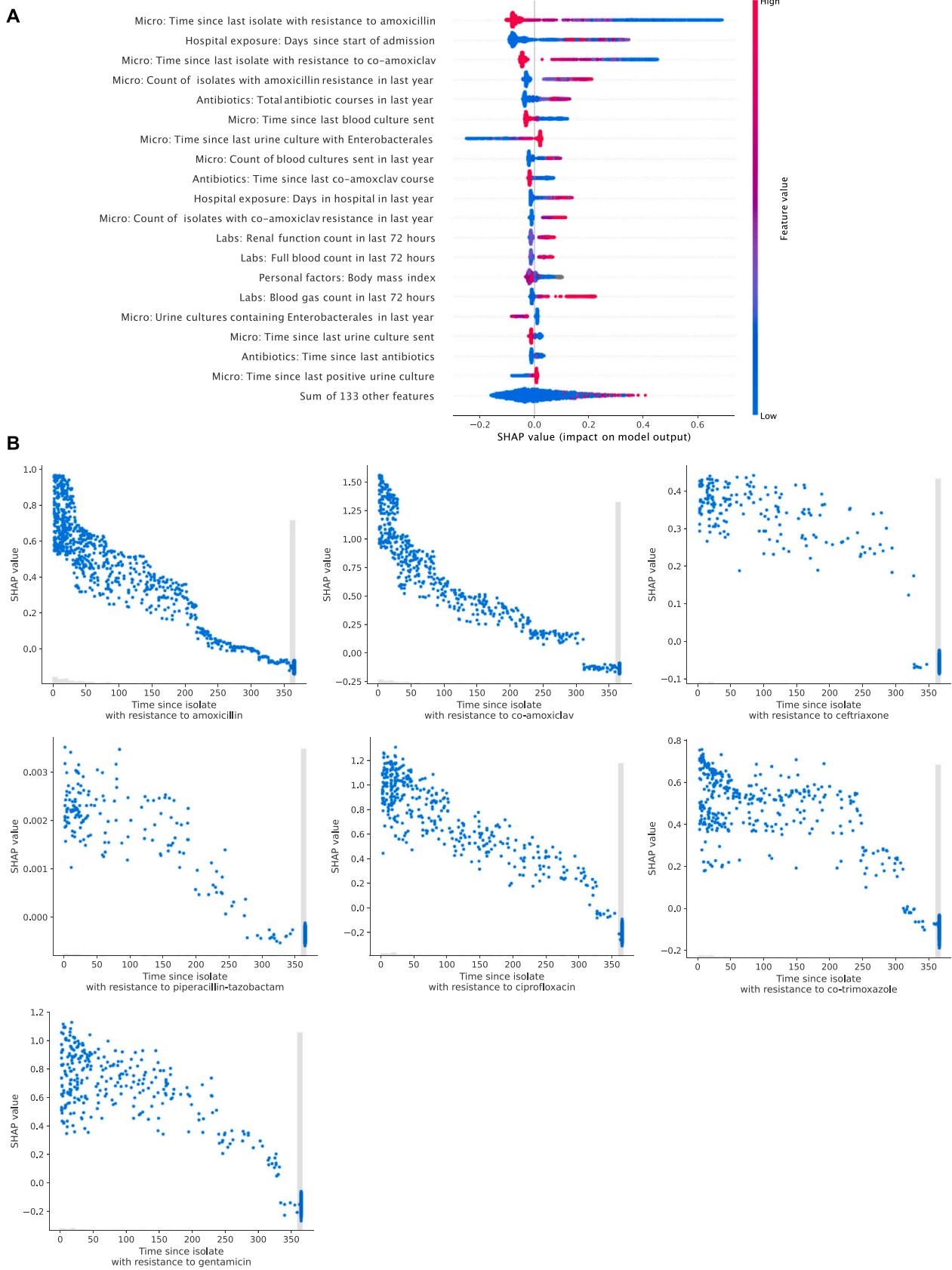
Feature importance

The most important features for making predictions were relatively consistent across different antibiotics (Fig. 2A, Figs. S1-S6). The time since the last isolate from any anatomical site with resistance to the specific antibiotic modelled was the most important feature for all antibiotics except piperacillin-tazobactam. Shorter times contributed most strongly to a prediction of resistance, with the importance of a previous resistant isolate to the same antibiotic typically attenuating over 1 year (Fig. 2B). Other consistently important features included greater time since hospital admission at blood culture sampling, shorter time since a previous resistant isolate to other related antibiotics, increased hospital antibiotic exposure (specifically for the antibiotic of interest, related antibiotics, and total antibiotics), and recent blood and urine cultures being sent.

When adding the species identified as an input, this became an important model feature, particularly for antibiotics where species information improved performance the most, e.g., amoxicillin and co-amoxiclav (Fig. S7-13). In some cases, this reflected information in the data arising from intrinsic resistance (e.g. *Klebsiella spp.* and amoxicillin), and in others reflected different resistance prevenances in different species.

Model updates over time

Observed rates of resistance were relatively stable over time for the 7 antibiotics investigated (Fig. S14). Using held-out test data from 2023 (Test Dataset 2) there was minimal evidence that model performance changed over time compared to 2022. Results in 2023 were similar using the original model, a retrained model, and an incrementally updated model (Fig. 3A). Models were relatively quick to train, taking around a minute on a high-performance personal

Fig. 2. SHAP (SHapley Additive exPlanations) plot showing feature importance and impacts on model output for predicting amoxicillin resistance at blood culture sampling (A) and SHAP plots showing the time since last resistant isolate and impact on model output for predicting resistance to the same antibiotic at blood culture sampling (B). In panel A, positive values on the x-axis indicate contributions towards predicting resistance, and negative values contributions towards predicting susceptibility. Absolute x-axis values reflect the relative importance or contribution of the feature in making a prediction. Colour indicates the value of the feature, red dots indicate higher values and blue dot lower values. For example, the shorter the time since the last isolate with resistance to amoxicillin the more likely a prediction of resistance. See Figs. S1–S6 for other antibiotics. Shorter times since the last urine culture with Enterobacterales were associated with predicting susceptibility, although this might seem surprising, it needs to be interpreted considering also having the time since a resistant isolate in the model, such that given that result, shorter times may represent evidence of a recent susceptible isolate. In panel B, where no resistant isolate was seen in the last year, the value is set to 365, hence when interpreting change over time values exactly equal to 365 days should be ignored. The grey histogram indicates the relative frequency of each observation on the x-axis. The spread of blue points arises from other features also influencing the SHAP value on the y-axis.

computer, such that savings in training time from not updating the models or from incremental updating were minimal (Fig. 3B).

Comparison to clinical practice

Of the 4709 blood cultures positive for an Enterobacterales species, 3198 were treated with a beta-lactam commonly used in our hospitals and were included in the clinical comparison analysis (see Fig. 1 for exclusions).

Antibiotic use by clinicians – over, under and optimal treatment

Of the 3198 Enterobacterales bloodstream infections with antibiotics recorded in the 4 h after blood was taken for culture, 2512 (79%) received at least one active baseline antibiotic, and 686 (21%) did not. Considering the beta-lactam given, 806 (25%) were optimally-treated, 974 (30%) under-treated, and 1418 (44%) over-treated. Most patients were treated with co-amoxiclav (2286, 71%), which also accounted for the greatest proportion of patients under-treated (Fig. 4A). In an ideal scenario where all infections were treated with the narrowest spectrum active antibiotic, more patients would have
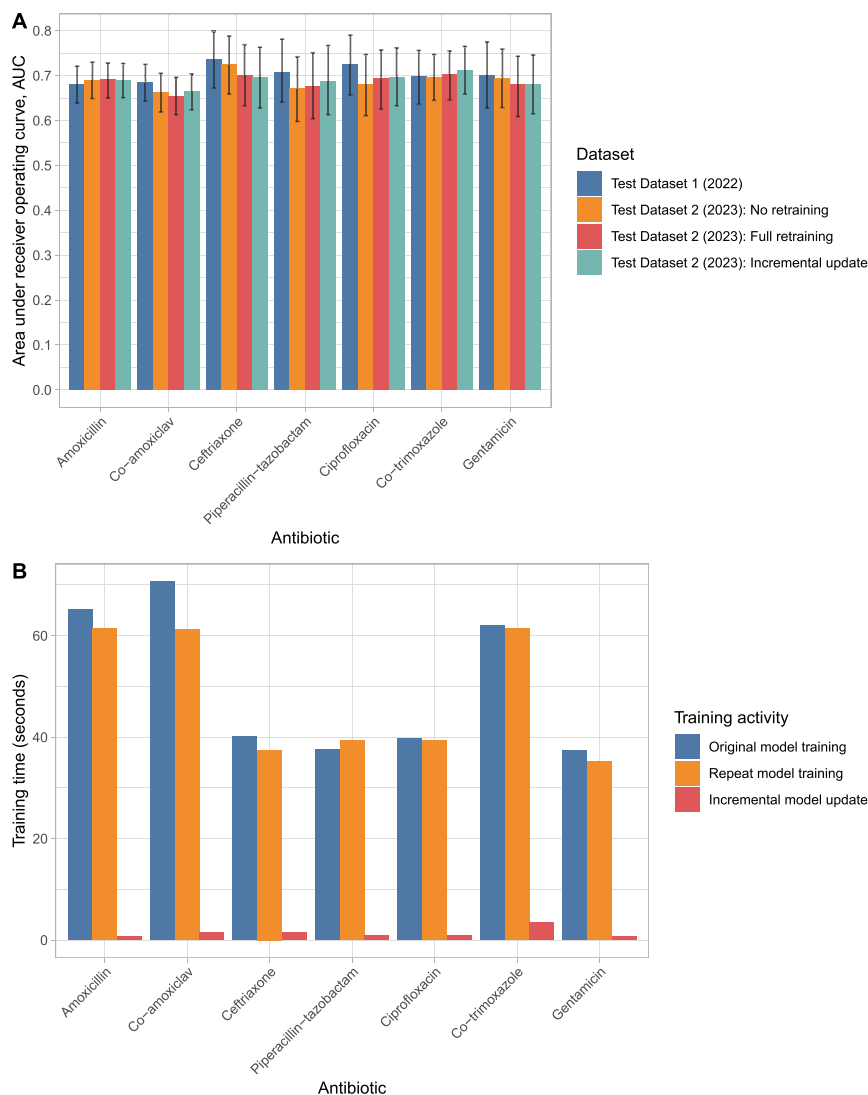

Fig. 3. Model performance for predicting antibiotic resistance at blood culture sampling in held-out test dataset 1 (01 January 2022 – 31 December 2022) and 2 (01 January 2023 – 31 December 2023), panel A and model training, retraining and model updating times, panel B. For test dataset 2 three approaches to updating the model over time are presented – no retraining, full re-training from scratch using data from 2017–2022 inclusive, incremental updating of the original model trained using 2017–2021 data with the data from 2022. AUC, area under the receiver operating curve. Confidence intervals were generated by bootstrapping with 1000 iterations. In panel B, all times are from training using a single Apple M3 Max core. Original and repeat training include hyperparameter optimisation, incremental updates are based on previously obtained hyperparameters from initial training.
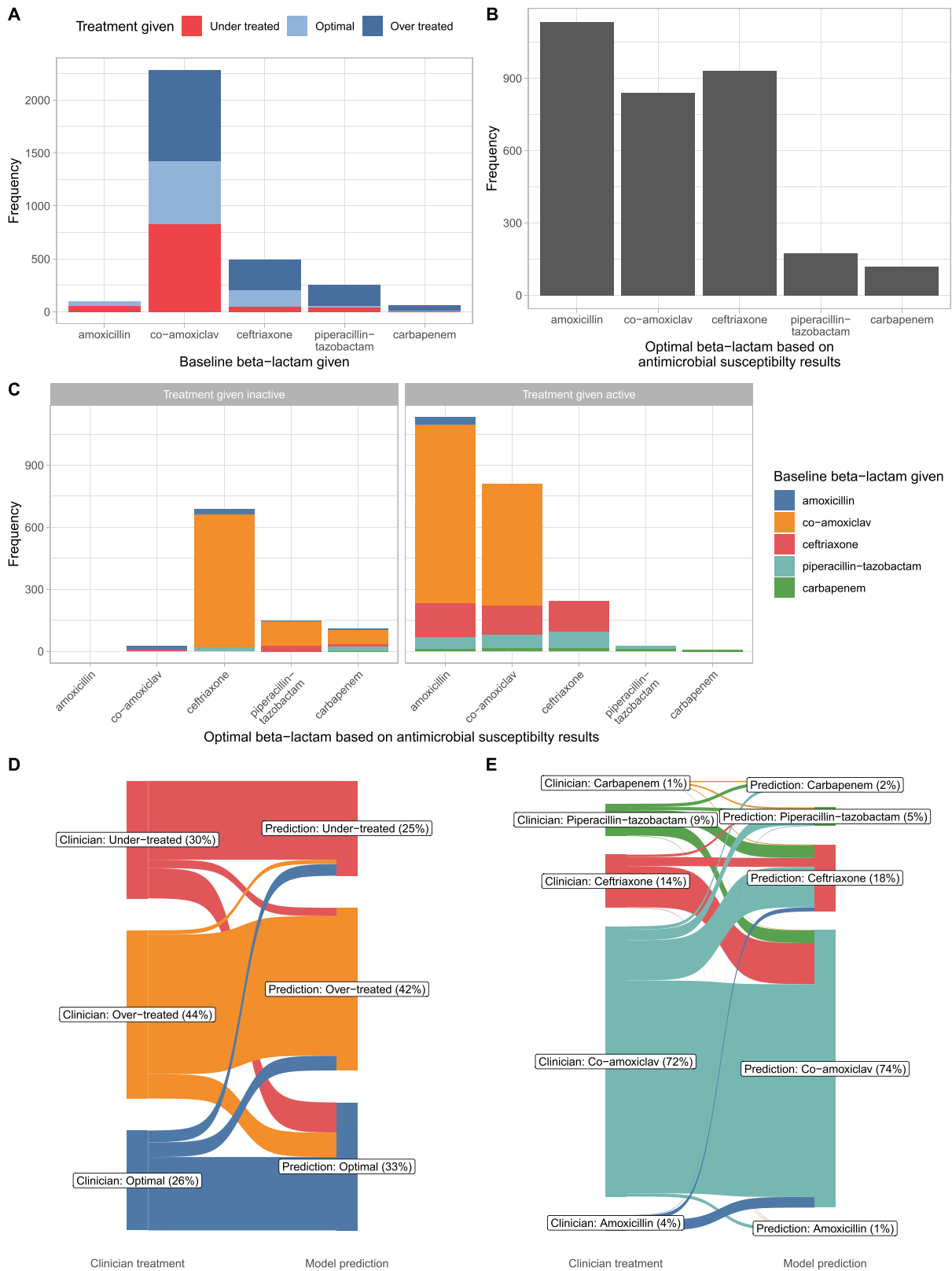
Fig. 4. Clinician prescribing practice in 3198 positive blood cultures (A-C) and percentage of patients receiving optimal, under or over treatment (panel D), and specific antibiotics (panel E) according to clinician prescribing and model predictions under scenario 1. Panel A shows the number of infections treated with different beta-lactams, classified by whether treatment was optimal, broader than necessary ('over-treated'), or had resistance to the beta-lactam used ('under-treated'). Panel B displays the optimal breakdown of antibiotic use, had the narrowest spectrum active agent been used to treat each infection. Panel C shows the distribution of optimal antibiotics by whether the actual beta-lactam treatment given was inactive (left hand sub-panel) or active (right). In panels D-E, predictions in test data from 2022–2023 are shown for a model constrained to match the total use of each antibiotic as closely as possible (scenario 1) (differences in antibiotic use arise from differences between training and test dataset model fit and calibration).

Table 3
Comparison of model predictions to clinician prescribing in test data from 2022–2023 (n=919).

Scenario	Active beta-lactam, n (%)	Under-treated, n (%)	Optimally treated, n (%)	Over-treated, n (%)	Receiving amoxicillin, n (%)	Receiving co-amoxiclav, n (%)	Receiving ceftriaxone, n (%)	Receiving piperacillin-tazobactam, n (%)	Receiving carbapenem, n (%)
Clinician prescribing	639 (70%)	280 (30%)	238 (26%)	401 (44%)	37 (4%)	663 (72%)	130 (14%)	79 (9%)	10 (1%)
Model, strategy 1: matching clinician antibiotic use	693 (75%)	226 (25%)	305 (33%)	388 (42%)	10 (1%)	681 (74%)	164 (18%)	45 (5%)	19 (2%)
Model, strategy 2: matching antibiotic susceptibility rates	655 (71%)	264 (29%)	384 (42%)	271 (29%)	320 (35%)	238 (26%)	301 (33%)	23 (3%)	37 (4%)
Model, strategy 2: matching antibiotic susceptibility rates with 20% leeway	705 (77%)	214 (23%)	374 (41%)	331 (36%)	258 (28%)	194 (21%)	395 (43%)	26 (3%)	46 (5%)
Model, strategy 3: matching clinician over-treatment rates	724 (79%)	195 (21%)	309 (34%)	415 (45%)	0 (0%)	543 (59%)	356 (39%)	16 (2%)	4 (<1%)
Simple comparator: switch first-line antibiotic to ceftriaxone	817 (89%)	102 (11%)	221 (24%)	596 (65%)	0 (0%)	0 (0%)	830 (90%)	79 (9%)	10 (1%)
Model, strategy 4: matching clinician active treatment rates in ceftriaxone first-line comparator	822 (89%)	97 (11%)	282 (31%)	540 (59%)	5 (1%)	59 (6%)	836 (91%)	15 (2%)	4 (<1%)

Patients treated with a beta-lactam were included. Model scenarios are described in more details in the Methods.

received amoxicillin, fewer co-amoxiclav and more ceftriaxone, with small increases compared to actual practice in piperacillin-tazobactam and carbapenem use (Fig. 4B). Most patients given inactive treatment would have been optimally treated with ceftriaxone with a smaller number requiring piperacillin-tazobactam or a carbapenem (Fig. 4C).

The implied sensitivity of clinicians for detecting resistance, i.e., the proportion of patients with resistance to a given antibiotic receiving treatment with any active broader spectrum beta-lactam was 97% (2005/2064) for amoxicillin, 29% (360/1225) for co-amoxiclav, 19% (61/320) for ceftriaxone, and 6% (11/190) for piperacillin-tazobactam.

Strategy 1 – matching clinician antibiotic use

Model performance without species information was compared to clinicians by attempting to constrain the predictions made to result in the same total number of prescriptions for each antibiotic as used by clinicians. Within the combined test data, clinician prescribing resulted in 70% of patients receiving an active beta-lactam: 44% were over-treated, 26% optimally-treated, and 30% under-treated. Model predictions resulted in more patients being actively treated, 75%, fewer being over-treated, 42%, fewer under-treated, 25%, and therefore more being optimally-treated, 33% (Fig. 4D). Due to differences in model fit and calibration between training and test data, despite targeting no change, small variations in antibiotic use relative to clinicians were observed (Fig. 4E, Table 3).

Strategy 2 – matching antibiotic use to susceptibility rates

Using alternative prediction thresholds that matched total antibiotic use to susceptibility rates resulted in more patients receiving optimal treatment compared to clinician's prescribing, 42% (cf. 26% by clinicians) and reduced over-treatment in 29% (cf. 44%). However, overall active treatment was similar, 71% (cf. 70%). In a sensitivity analysis where 20% reductions in amoxicillin and co-amoxiclav use were allowed relative to susceptibility rates, the percentage of patients predicted to receive active treatment increased to 77%, while overtreatment at 36% remained less than with clinicians' prescribing.

Strategy 3 – fixing overtreatment rates, aiming for more active treatment

If prediction thresholds were set by matching clinician over-treatment rates, using the machine learning algorithm 79% of patients would have received an active beta-lactam and 34% would have been optimally-treated, 45% over-treated, and 21% under-treated. This performance was predominantly achieved by moving a subset of patients treated by clinicians with co-amoxiclav to receive ceftriaxone, with fewer given piperacillin-tazobactam or a carbapenem to offset this.

Switching to ceftriaxone as first-line treatment and strategy 4

We also compared performance to a simpler intervention, changing first-line treatment to ceftriaxone, i.e. switching all patients receiving amoxicillin or co-amoxiclav to ceftriaxone. This would reduce the number of under-treated patients to 11%, but also cause 65% to be over-treated. Setting our models to achieve the same level of active treatment allowed over-treatment to be reduced to 59%.

Discussion

Machine learning models can predict resistance to commonly used antimicrobials in Enterobacterales bloodstream infection with moderate accuracy. Despite considering a wide range of input features, including hospital and some community data, model performance was broadly consistent with previous findings for similar tasks.[3–18] This suggests there is a ceiling on the performance of

machine learning in this context that is unlikely to be improved on without further data, e.g. for our models, data on community prescribing. It may also reflect intrinsic stochasticity where bacteria with and without AMR exist within a patient's microbiome, and cause disease with or without AMR with a degree of randomness.

Despite modest performance of machine learning models, detecting resistance is also a highly challenging task for clinicians. In our hospital group antimicrobial stewardship is given a high priority, seeking to minimise over-use of broad-spectrum antibiotics to protect local needs and meet national prescribing incentives.[21,22] However, this also results in a substantial proportion of patients receiving inactive initial treatment, 21% overall, with 30% receiving inactive initial beta-lactam treatment. The implied sensitivity of clinician detection of resistance was low at 29% for co-amoxiclav, 19% for ceftriaxone, and 6% for piperacillin-tazobactam. Prescriptions up to 4 h after blood culture sampling were considered; they represent the practice of clinicians with a range of experiences, e.g., from 1–2 years post-graduation to > 10 years, as senior reviews will not all have been completed for all patients within the time window chosen. However, this is representative of those making antibiotic prescribing decisions.

The challenging nature of antibiotic selection meant clinician's choice of beta-lactam resulted in 30% of patients being under-treated, 44% being over-treated and only 26% being optimally-treated. Several modelling approaches were able to improve on this. The main potential application of our models is helping select which antibiotics to start initially, i.e. using the models that do not use species information. Using these models, if total antibiotic use was kept similar, but redistributed, an additional 5% of patients received active treatment, 75% overall, and optimal treatment rose to 33%. Alternatively, if we matched antibiotic use to rates of antibiotic susceptibility and allowed for some over-prescribing of broader-spectrum agents to offset imperfect model performance, then 79% of patients could be actively treated, 9% more than by clinicians, while still only over-treating 45% (similar to clinicians). A simpler approach of switching all first-line antibiotics to ceftriaxone increased active treatment to 89% but caused 65% to be over-treated; the latter could be reduced to 59% if a model rather than a guideline change was used. Additionally, as our models perform better once a species is identified, they could also potentially be used to screen at this timepoint for patients with a high probability of having been started on inactive empirical therapy.

Model performance was relatively consistent over time and models could be retrained rapidly if needed. The features contributing most to predictions, such as infections with AMR within the last year or antibiotic exposures, are likely to be relatively stable over time. To improve overall performance and facilitate antimicrobial stewardship, better models are particularly needed for the narrower spectrum agents including amoxicillin and co-amoxiclav. Data on community use of these antibiotics and other narrow spectrum agents may help. It is unlikely that other model architectures would have substantially improved performance given the range of approaches tried in other studies without much better performance.[8,12,13,17,18]

This study has several limitations. A fundamental limitation with all studies of this kind is that the data are trained and tested on patients known to have positive blood cultures, and in our models, we specifically focused on cultures with Enterobacterales species. However, < 10% of sampled patients will have positive blood cultures and these results are not known a priori. Hence, we have to assume the predictors of resistance are similar in those with and without positive cultures, and that rates of resistance are similar too. However, this same assumption underlies use of antibiotic resistance patterns in positive cultures to determine population-level institutional or regional antimicrobial guidelines. This assumption may only be partially true though, especially if AMR contributes to blood cultures being positive in patients with prior community antibiotic exposures. By focusing on Enterobacterales we also did not consider infections with other species or polymicrobial infections; future work could consider focusing on predicting AMR in all pathogens causing specific clinical syndromes to improve applicability.

We did not have data available on allergies. Hospital guidelines during the study suggested that in patients with mild penicillin allergy (i.e. a rash), ceftriaxone could be substituted for co-amoxiclav (adding metronidazole where anaerobic cover was required). Patients with severe penicillin allergy were predominantly treated with non-beta-lactam antibiotics. It is therefore possible that some of the model improvements in reducing over-treatment from switching ceftriaxone to co-amoxiclav may not have been possible in reality due to penicillin allergies. However, this is less important for increases in patients receiving active treatment, where the switches were generally to ceftriaxone.

We did not have data on community antibiotic exposures, which may have improved model performance. We did however have data on community microbiology samples as nearly all samples were sent to the single regional hospital laboratory. It is possible that clinician prescribing in Oxfordshire is unusual in the priority given to antibiotic stewardship, but national prescribing data suggest it is not atypical for the UK.[22] In our setting patients receiving inactive initial treatment are typically switched to active treatment within 24–72 h of blood cultures being obtained.[20] Our model was validated on two independent internal validation datasets, but further external validation is required before it can be deployed, for example as a decision support aid for hospital clinicians.

In conclusion, predicting who will have AMR is challenging for clinicians and models alike. Despite relatively modest performance of machine learning models, these could still potentially increase the proportion of patients receiving active treatment by up to 9% over current clinical practice in an environment prioritising antimicrobial stewardship.

Code availability

Codes for model development, analysis and visualisation are available at https://github.com/eyrelab/abx_selection.

Author contributions

DWE and ASW conceived the study. DWE and KY analysed the data. KY, AL and JW performed the literature review. Oversight was provided by DWE, TZ and ASW. DWE wrote the first draft of the manuscript assisted by KY, AL and JW. All authors revised the manuscript.

Data availability

The datasets analysed during the current study are not publicly available as they contain personal data but are available from the

Infections in Oxfordshire Research Database (https://oxfordbrc.nihr.ac.uk/research-themes-overview/antimicrobial-resistance-and-modernising-microbiology/infections-in-oxfordshire-research-database-iord/), subject to an application and research proposal meeting the ethical and governance requirements of the Database. For further details on how to apply for access to the data and for a research proposal template please email iord@ndm.ox.ac.uk.

Declaration of Competing Interest

No author has a conflict of interest to declare.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jinf.2024.106388.

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