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Defining antibiotic use reduction targets for the management of hospital-onset healthcare-associated *Clostridioides difficile* infection: results of the multi-center TARGET-A project in four UK hospitals

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Defining antibiotic use reduction targets for the management of hospital-onset healthcare-associated *Clostridioides difficile* infection: results of the multi-center TARGET-A project in four UK hospitals

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ABSTRACT

Background: Nonlinear analyses show promise for determining antibiotic use thresholds linked to antimicrobial resistance (AMR). An approach that allows aggregation of results from multiple models to capture context-specific AMR dynamics is needed to improve predictive accuracy and define realistic antibiotic use thresholds to reduce AMR.

Methods: We conducted TARGET-A, a retrospective multicentre ecological modeling study in four UK hospitals (2020–2024), applying a threshold-logistic ensemble consensus modeling approach to identify hospital-level antibiotic use thresholds and risk scores associated with increasing hospital-onset, healthcare-associated Clostridioides difficile infection (HOHA-CDI) incidence.

Results: Analysis set the cutoffs for critically high HOHA-CDI incidence at: Antrim Area Hospital (AAH), 75th percentile; Craigavon Area Hospital (CAH), 80th percentile; Pinderfields General Hospital (PGH), 82.5th percentile; St James's University Hospital (SJUH), 77.5th percentile. Antibiotic use thresholds (defined daily doses (DDD)/1000 occupied bed-days (OBD)) were identified: AAH- fluoroquinolones 62.3, macrolides 254.6; CAH- co-amoxiclav 75.8, carbapenems 16.1; PGH- co-amoxiclav 251.3, macrolides 129.2; SJUH- clindamycin 14.2, fluoroquinolones 128.3. Risk scores for exceeding high HOHA-CDI incidence were determined, supporting early warning alerts. A consensus approach was developed to establish attainable antibiotic use thresholds.

Conclusions: This approach provides a framework to define hospital-level quantitative antibiotic use targets to control HOHA-CDI incidence. Further validation is needed in prospective interventional studies.

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1. Introduction

Antimicrobial resistance (AMR) is a major global health threat, leading to increased morbidity, mortality, and healthcare costs [1–3]. It is largely driven by suboptimal antimicrobial usage [3–6]. Robust strategies are needed to optimize antibiotic prescribing practices, to both preserve the effectiveness of existing antibiotics and reduce the health and economic burden of AMR [1–3]. The relationship between antibiotic use and AMR is well established [7–16]. Antimicrobial stewardship (AMS) seeks to optimize prescribing of antibiotics to preserve their effectiveness [15]. Studies have demonstrated that the relationship between antibiotic use and the incidence of antibiotic-resistant pathogens in hospitals is non-linear, suggesting the existence of antibiotic use thresholds, beyond which AMR is likely to increase substantially [12–14,17–19]. Previously, we introduced a threshold-logistic modeling approach that combines nonlinear modeling with logistic regression to identify hospital-specific antibiotic use thresholds above which the probability of critically high incidence rates of antibiotic-resistant pathogens increases [20–24].

Although threshold-logistic models provide valuable insights into AMR dynamics, reliance on a single optimal model may limit the robustness and generalizability of the results [25]. When feasible, a single multivariable threshold-logistic model jointly estimates the effects of multiple

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antibiotic threshold predictors. However, when multicollinearity prevents all selected predictors from being retained within a single model, ensemble modeling increases robustness by integrating predictions from multiple optimal models, thereby preserving important antibiotic effects that might otherwise be excluded. Consensus modeling provides an additional level of robustness by evaluating whether the identified antibiotic use thresholds are supported across a range of candidate threshold values rather than depending solely on a single optimized threshold. Collectively, these complementary approaches improve confidence in the identified relationships and provide stronger evidence to support antimicrobial stewardship (AMS) interventions and public health policy [2,25–28]. We propose an integrated framework that combines threshold-logistic modeling with ensemble consensus modeling to identify realistic antibiotic use targets for AMS evaluation. Applied in four UK hospitals, this approach was used to identify antibiotic use levels associated with HOHA-CDI incidence, providing evidence to inform AMS strategies and policy.

2. Methods

2.1. Study design and population

The Targeted Antibiotic Reduction and Guidance for Enhanced antimicrobial stewardship and Timely interventions Approach (TARGET-A) study was a multi-center ecological modeling study using monthly retrospective data on antibiotic use and hospital-onset, healthcare-associated (HOHA) CDI across four UK hospitals. The participating hospitals were Antrim Area Hospital (AAH) and Craigavon Area Hospital (CAH) in Northern Ireland, and Pinderfields General Hospital (PGH) and St James's University Hospital (SJUH) in England. The characteristics of each hospital are shown in Table S1. The study included adult inpatients from January 2020 to December 2024 (to June 2024 for AAH) to ensure availability of sufficient and consistent observations to conduct robust modeling. The study used threshold-logistic modeling to examine whether HOHA-CDI incidence was linked to use of specific antibiotics/antibiotic groups, i.e. amoxicillin-clavulanic acid (co-amoxiclav), carbapenems, second- and third-generation cephalosporins, clindamycin, fluoroquinolones, macrolides and piperacillin-tazobactam. These were identified *a priori* based on published evidence highlighting their role as risk factors for increasing CDI incidence [11,29].

The study was approved by the University of Huddersfield Research Integrity and Ethics Committee (SAS-SRIEC-09.08.24-1). As this was a retrospective ecological study based on existing data, informed consent was not required.

2.2. Microbiology and pharmacy data

Only CDI cases that were HOHA were included in this study. HOHA-CDI was defined as any adult patient with confirmed CDI, where the specimen date is the same or more than 3 days after the current admission date (where day of admission is day 1); duplicate positive tests were excluded. Data detailing the HOHA-CDI definition and testing and infection prevention practices during this study for each hospital site are presented in Table S1. Data were obtained from the microbiology information management systems at each hospital. The monthly quantities of each antibiotic delivered for patient care at each hospital were obtained from the hospital pharmacy information system. Antibiotic consumption data were then converted to defined daily doses (DDD) according to the WHO Anatomical Therapeutic Chemical (ATC) classification for antimicrobials for systemic use (J01) and expressed as DDD per 1,000 occupied bed-days (OBD). Monthly OBD data were collected to adjust for hospital activity and to calculate antibiotic use rates (DDD per 1,000 OBD) and HOHA-CDI incidence (cases per 1,000 OBD).

2.3. Statistical analysis

We employed a multi-stage ensemble modeling framework to identify antibiotic use thresholds associated with increased risk of HOHA-CDI incidence. The approach integrates time series correlation screening, threshold-logistic regression, statistical filtering, and ensemble consensus modeling to establish data-driven, empirically grounded and policy-relevant antibiotic usage guidelines.

2.3.1. Screening for lagged associations

Cross-correlation functions (CCFs) were used as an exploratory screening step to identify positive time-lagged associations between antibiotic use and HOHA-CDI incidence. Antibiotic-lag combinations meeting the prespecified screening criterion ($p < 0.30$) were retained as candidates for threshold-logistic modeling. Because this deliberately liberal criterion was used for candidate screening rather than confirmatory inference, retained lags were subsequently required to demonstrate statistical significance and acceptable performance within the threshold-logistic models.

2.3.2. Threshold identification

Prior to identifying antibiotic-use thresholds, a hospital-specific cutoff defining critically high HOHA-CDI incidence was established. Candidate incidence cutoffs corresponding to alternative percentiles of the historical HOHA-CDI incidence distribution were evaluated. For each hospital, the cutoff yielding the strongest threshold-logistic classification performance, based on measures such as discrimination and predictive accuracy, was selected. Consequently, the final cutoffs differed across hospitals (75th, 80th, 82.5th, and 77.5th percentiles) because they were empirically optimized from each hospital's historical data rather than derived from a universal clinical cutoff.

For each selected antibiotic, threshold ranges defined as the usage levels (DDD/1000 OBD) above which the incidence of CDI increased were identified. These thresholds served as candidate breakpoints in the subsequent threshold-logistic modeling process. The optimized threshold was selected from the set of candidate thresholds evaluated during the one-at-a-time (OAT) threshold optimization procedure. The reported lower and upper interval limits represent the empirical range of acceptable candidate thresholds surrounding the optimized threshold, rather than conventional sampling-based confidence limits. This aligns with the antibiotic stewardship

focus on positive, left-truncated relationships, where pathogen risk increases above normal risk after a certain level of antibiotic exposure is exceeded.

2.3.3. Threshold-logistic modeling and statistical filtering

A brute-force search algorithm using threshold-logistic regression was used to evaluate whether lagged antibiotic use at varied lags predicted that HOHA-CDI incidence surpassed a critically high level; threshold-logistic analysis is described elsewhere [20–22]. Candidate thresholds of antibiotic use were considered in conjunction with other candidate antibiotics and their respective use thresholds in univariate and multivariate threshold models.

Candidate antibiotic-lag combinations identified during the cross-correlation screening stage were first evaluated individually in univariate threshold-logistic models. Where multiple statistically significant lags were identified for the same antibiotic, these were treated as alternative candidate lag structures. During multivariable model development, only one lag per antibiotic was permitted within any individual model to avoid redundancy and instability arising from highly correlated lagged versions of the same antibiotic use series. Alternative lag structures were evaluated through the brute-force search procedure, and the lag retained in the final model was the one associated with statistically significant coefficients and superior model performance. Models were retained only when all coefficients were statistically significant ($p < 0.05$), yielding a set of possible parsimonious models that identified single or combined effects of antibiotic use on HOHA-CDI incidence. To account for autocorrelation or serial correlation, lagged pathogen incidence rate was considered in the threshold-logistic models. The statistically viable models identified in this stage define a set of feasible models that individually may highlight a single antibiotic usage or combinations of antibiotic usage as key predictors of elevated CDI risk.

2.3.4. Ensemble modeling and consensus modeling

Feasible threshold-logistic models were used to construct an optimal ensemble for prediction while model-averaged probabilities were calculated from all feasible models for comparison. When the selected antibiotic threshold effects could be jointly represented within a single multivariable threshold-logistic regression model, predictions were obtained directly from that model ($m = 1$). When a single joint model was not feasible, an optimal ensemble was constructed by selecting, for each antibiotic effect in focus, the strongest feasible threshold-logistic model containing that effect. The predicted probabilities from the selected models were then averaged, with 'm' denoting the number of models included in the optimal ensemble. For comparison, a separate model-averaged probability was calculated by averaging the predicted probabilities from all feasible threshold-logistic models involving the antibiotics in focus, irrespective of whether they were selected for the optimal ensemble.

As part of a consensus-seeking framework, two complementary analytic approaches were applied: a count-based approach and a distribution-based approach. In both cases, antibiotic use was lagged as identified in Stage 1, and data were split into two groups based on whether the lagged antibiotic usage value exceeded specified candidate percentile thresholds (40th–85th). In essence, this provides a generalized sensitivity analysis to the model-identified antibiotic threshold. The count-based approach evaluates the frequency and relative likelihood of high values of the incidence of HOAHA-CDI cases. For each candidate antibiotic threshold, the dataset was split into an above-threshold group (A) and a below-threshold group (B). Within each group, we counted the number of observations where the incidence of HOHA-CDI exceeded six benchmark values derived from the overall distribution of the incidence of HOHA-CDI (the mean, and the 50th, 65th, 75th, 80th, and 85th percentiles). These counts were converted into proportions by dividing by the group sample size. To assess whether high outcomes were more common in group A than in group B, we applied one-sided Fisher's exact test for each benchmark. This method emphasizes differences in the prevalence of unusually high outcomes across threshold-defined groups.

The distribution-based approach compared the location and selected quantiles of the HOHA-CDI incidence distribution between months in which lagged antibiotic use was above versus below each candidate threshold. For descriptive purposes, the mean, median, and 75th, 80th, and 85th percentiles were calculated for the full sample and for each threshold-defined group, and between-group differences were reported. The Wilcoxon rank-sum test was used to assess an overall shift in the distributions. Quantile regression with bootstrap standard errors was used to test between-group differences at the 50th, 75th, 80th, and 85th quantiles. Together, the count-based and distribution-based approaches provide complementary perspectives: the former assesses whether high-incidence months occur more frequently above candidate antibiotic use thresholds, whereas the latter examines whether the distribution of HOHA-CDI incidence differs above and below those thresholds.

2.3.5. Predictive ability

Threshold-logistic regression models were used to estimate the probability that monthly HOHA-CDI incidence would exceed the predefined critical threshold. Where a single multivariable threshold-logistic model was not feasible because of multicollinearity, predictions were obtained from the optimal ensemble described above. Aggregated risk scores were subsequently converted into categorical alerts (Low, Medium, and High) using optimized cutoffs derived from a linear programming approach; this methodology is described elsewhere [20–22].

Predictive performance was evaluated using one-step-ahead forecasts for January-June 2024. For each hospital, monthly predictions were generated using the selected threshold-logistic model and, where applicable, the ensemble model. For each forecast month, model estimation was restricted to data available before that month, including only lagged antibiotic-use information available at the forecast origin. Consequently, each prediction was generated without access to future information, providing a rolling-origin temporal validation of model performance rather than predictions from a model fitted using the complete study period.

Table 1. Threshold-logistic regression and ensemble models for identifying antibiotic use thresholds associated with critically high hospital-onset, healthcare-associated *Clostridioides difficile* infection (HOHA-CDI) incidence in the four participating hospitals.

	Cutoff for critically high HOHA-CDI incidence		Monthly antibiotic use									
Hospital	Rate[a]	Percentile[b]	Identified antibiotic or antibiotic group	Lag[c]	Mean[d] (SD)	Median[d] (IQR)	Threshold[d] (95% candidate interval)[d]	Relation to threshold[e]	*p*-value	ROC AUC[f]	Odds Ratio for critically high HOHA-CDI incidence (95% CI)	Model type
Antrim Area Hospital	0.19	75th	Fluoroquinolones	4	65.0 (13.8)	64.6 (56.0–73.4)	62.3 (58.3–63.2)	Above	0.038	0.78	1.093 (1.005–1.188)	Threshold-logistic regression model
			Macrolides	3	248.0 (56.3)	235.9 (208.4–272.6)	254.6 (254.6–278.2)	Above	0.016		1.022 (1.004–1.041)	
Craigavon Area Hospital	0.43	80th	Co-amoxiclav	4	111.6 (37.4)	110.4 (85.1–131.0)	75.8 (75.8–89.1)	Above	0.015	0.77	1.044 (1.009–1.081)	Ensemble model
			Carbapenems	4	17.2 (4.3)	17.1 (14.8–19.0)	16.1 (14.1–16.8)	Above	0.035	0.75	1.241 (1.015–1.517)	
Pinderfields General Hospital	0.26	82.5th	Co-amoxiclav	3	255.1 (36.1)	250.6 (233.6–273.5)	251.3 (245.9–251.3)	Above	0.017	0.72	1.042 (1.008–1.078)	Ensemble model
			Macrolides	3	114.8 (25.0)	109.2 (95.8–129.4)	129.2 (121.8–129.2)	Above	0.026	0.62	1.088 (1.010–1.172)	
St James's University Hospital	0.36	77.5th	Clindamycin	2	18.8 (4.3)	18.6 (15.8–20.9)	14.2 (14.2–17.3)	Above	0.029	0.69	1.182 (1.017–1.374)	Ensemble model
			Fluoroquinolones	2	110.2 (24.2)	110.6 (96.7–121.5)	128.3 (116.0–128.3)	Above	0.031	0.66	1.084 (1.007–1.167)	

[a]Cases per 1,000 occupied bed-days (OBD);
[b]Cutoff point to define a critically high HOHA-CDI incidence on a certain month;
[c]Delay to observe the effect in months.
[d]Defined Daily Doses (DDD) per 1000 OBD. 95% empirical confidence limit around the optimized threshold value, which was derived using a one-at-a-time (OAT) approach.
[e]There is no direct statistical relationship between the mean or the median, and the identified threshold. 'Relation to threshold' refers to the spline function being left-truncated or right-truncated. A 'Relation to threshold' indicated as 'above' refers to a left-truncated spline in which the model coefficients are related to instances in which the spline function is above the threshold only.
[f]AUC, Area under the curve; CI, Confidence interval; IQR, Interquartile range; ROC, Receiver operating characteristic; SD, Standard deviation.

2.3.6. Final guideline integration and consensus review

Thresholds were stratified by HOHA-CDI incidence above or below antibiotic use thresholds. Risk classifications were automated through linear programming, and consensus thresholds evaluated using both count-based and distribution-based analyses. The results for CAH, which was presented as an example, were subsequently reviewed by the local antimicrobial stewardship (AMS) team to assess the operational feasibility and attainability of the model-derived thresholds. The count-based and distribution-based analyses were used to facilitate discussion regarding whether less restrictive thresholds retained sufficient statistical support while remaining achievable in routine practice. Final threshold recommendations reflected a balance between statistical evidence and practical implementation considerations. Preference was given to thresholds supported by both count-based and distribution-based analyses. Where statistical evidence differed between approaches, the AMS team may consider the overall pattern of evidence together with operational feasibility when selecting the final threshold.

The SCA Statistical System version 8.2 (Scientific Computing Associates Corp., River Forest, Illinois, U.S.A.) and R software version 4.5.0 (R Foundation for Statistical Computing, Vienna, Austria) were used to perform statistical analyses.

3. Results

The average monthly HOHA-CDI incidence (cases per 1,000 OBD) in the participating hospitals were: AAH, 0.132; CAH, 0.307; PGH, 0.172; and SJUH, 0.279. The 75th, 80th, 82.5th, and 77.5th percentiles of HOHA-CDI incidence were determined as the cutoff points to define a critically high level at AAH, CAH, PGH, and SJUH, respectively (Table 1). The empirical cumulative distribution function for HOHA-CDI incidence historical data for each hospital is shown in Figures S1, S2, S3 and S4.

3.1. Identified antibiotic use thresholds

Use of specific antibiotics/antibiotic groups (DDD/1000 OBD) above a defined threshold was associated with increasing HOHA-CDI incidence at AAH (fluoroquinolones, use threshold = 62.3; macrolides, use threshold = 254.6), CAH (co-amoxiclav, use threshold = 75.8; carbapenems, use threshold = 16.1), PGH (co-amoxiclav, use threshold = 251.3; macrolides, use threshold = 129.2) and SJUH (clindamycin, use threshold = 14.2; fluoroquinolones, use threshold = 128.3). Odds ratios for the association between antibiotic use and high HOHA-CDI incidence are presented in Table 1. For AAH, for example, threshold-logistic modeling showed that for every one unit DDD per 1000 OBD increase in fluoroquinolone use above 62.3 and in macrolide use above 254.6 DDD/1000 OBD, the average odds of the HOHA-CDI incidence (being >75th percentile of historical levels) increased by 9.3% and 2.2%, respectively. For each hospital and each antibiotic/antibiotic group, the area under the curve (AUC) for the receiver operating characteristic (ROC) is shown in Table 1.

3.2. HOHA-CDI incidence risk predictions

Table 2 presents the observed HOHA-CDI incidence together with hospital-specific historical benchmarks (the median, a percentile immediately below the critically high cutoff, and the cutoff itself), the estimated probability of exceeding the cutoff, and the corresponding categorical alert level.

3.3. Reaching practical and data-driven consensus antibiotic use thresholds

Tables 3, 4 and S2-S15 provide a structured basis for clinicians to consider antibiotic-use thresholds that are operationally attainable while retaining statistical evidence of lower HOHA-CDI incidence below the threshold. For CAH, the threshold-logistic model identified a carbapenem-use threshold of 16.1 DDD/1,000 OBD (40th percentile). This threshold would have been relatively restrictive because carbapenem use exceeded it in 60.7% of study months (Table 3). HOHA-CDI incidence exceeded the historical mean in 61.8% of months above this threshold compared with 22.7% of months below it ($p = 0.004$, Fisher exact test). Higher candidate thresholds could therefore be considered during consensus review. For example, thresholds of 19.0–19.9 DDD/1000 OBD (75th-80th percentiles) retained evidence of separation in the frequency of high-incidence months (Table 3). The distribution-based analysis also supported a difference in HOHA-CDI incidence between months above and below the 19.0 DDD/1000 OBD threshold (Wilcoxon rank-sum $p = 0.002$; Table 4). These findings support consideration of a less restrictive operationally feasible threshold. Figure 1 presents a consensus framework for selecting practical antibiotic use thresholds, illustrated through its application to carbapenem use at CAH.

3.4. Conceptual framework

Figure 2 presents a conceptual framework illustrating how hospital-specific antibiotic use thresholds can support national implementation of antibiotic use targets.

4. Discussion

The TARGET-A multicentre modeling study demonstrated the feasibility of applying a threshold-logistic ensemble consensus approach to identify candidate hospital-specific antibiotic use thresholds associated with HOHA-CDI incidence, generated estimated risk scores and provided a structured framework for operational review. These findings may inform AMS programs by providing quantitative antibiotic use targets for the purpose of controlling infection and AMR rates [13,14]. Whether implementation of these thresholds reduces HOHA-CDI or AMR rates requires evaluation in prospective interventional studies.

A threshold marks the point at which the exposure-response curve changes, not necessarily the point at which pathogen incidence is outside normal variation. However, as antibiotic use progressively rises above the threshold, the probability of pathogen incidence rates moving outside

Table 2. Risk predictions for hospital-onset, healthcare-associated *Clostridioides difficile* infection (HOHA-CDI) incidence for the four participating hospitals using the threshold-logistic regression and ensemble models, January-June 2024.

A. Antrim area hospital (cutoff point to define a critically high HOHA-CDI incidence on a certain month: 75th percentile, equivalent to 0.19 cases per 1,000 occupied bed-days)

		HOHA-CDI incidence is above the:			Probability risk score		
Month	HOHA-CDI incidence[a]	Median	70th percentile	75th percentile	Optimal multivariate threshold-logistic regression model ($m = 1$)[b]	Model-averaged probability (all feasible models) ($m = 10$)[b]	Alert score
January 2024	0.06	No	No	No	0.0910	0.1224	Low
February 2024	0.07	No	No	No	0.0910	0.1197	Low
March 2024	0.12	**YES**	No	No	0.0910	0.1232	**Medium**
April 2024	0.19	**YES**	**YES**	No	0.1685	0.1667	**High**
May 2024	0.19	**YES**	**YES**	No	0.0921	0.1347	**High**
June 2024	0.00	No	No	No	0.0910	0.1197	Low

B. Craigavon Area Hospital (cutoff point to define a critically high HOHA-CDI incidence on a certain month: 80th percentile, equivalent to 0.43 cases per 1,000 occupied bed-days)

		HOHA-CDI incidence is above the:			Probability risk score		
Month	HOHA-CDI incidence[a]	Median	75th percentile	80th percentile	Optimal ensemble model ($m = 2$)[b]	Model-averaged probability (all feasible models) ($m = 10$)[b]	Alert score
January 2024	0.43	**YES**	**YES**	**YES**	0.3473	0.5695	**High**
February 2024	0.67	**YES**	**YES**	**YES**	0.2018	0.2937	**Medium**
March 2024	0.21	No	No	No	0.2104	0.2805	**Medium**
April 2024	0.36	**YES**	No	No	0.1827	0.2267	Low
May 2024	0.43	**YES**	**YES**	**YES**	0.3257	0.3334	**High**
June 2024	0.59	**YES**	**YES**	**YES**	0.2855	0.3614	**High**

C. Pinderfields General Hospital (cutoff point to define a critically high HOHA-CDI incidence on a certain month: 82.5th percentile, equivalent to 0.26 cases per 1,000 occupied bed-days)

		HOHA-CDI incidence is above the:			Probability risk score		
Month	HOHA-CDI incidence[a]	Median	80th percentile	82.5th percentile	Optimal ensemble model ($m = 2$)[b]	Model-averaged probability (all feasible models) ($m = 8$)[b]	Alert score
January 2024	0.09	No	No	No	0.1403	0.1420	Low
February 2024	0.05	No	No	No	0.0940	0.1096	Low
March 2024	0.14	No	No	No	0.1582	0.1737	Low
April 2024	0.09	No	No	No	0.1101	0.1270	Low
May 2024	0.18	**YES**	No	No	0.0909	0.1099	Low
June 2024	0.14	No	No	No	0.0909	0.0945	Low

D. St James's University Hospital (cutoff point to define a critically high HOHA-CDI incidence on a certain month: 77.5th percentile, equivalent to 0.36 cases per 1,000 occupied bed-days)

		HOHA-CDI incidence is above the:			Probability risk score		
Month	HOHA-CDI incidence[a]	Median	70th percentile	77.5th percentile	Optimal ensemble model ($m = 2$)[b]	Model-averaged probability (all feasible models) ($m = 6$)[b]	Alert score
January 2024	0.14	No	No	No	0.6463	0.6156	Low
February 2024	0.27	**YES**	No	No	0.5917	0.5576	Low
March 2024	0.23	No	No	No	0.6583	0.6312	Low
April 2024	0.30	**YES**	No	No	0.6679	0.6428	**Medium**
May 2024	0.17	No	No	No	0.7214	0.6883	**Medium**
June 2024	0.18	No	No	No	0.7307	0.7128	**Medium**

[a]HOHA-CDI incidence, cases per 1,000 occupied bed-days.
[b]m, total number of included models.

Table 3. Consensus count-based analysis of associations to determine practical carbapenem use targets for managing hospital-onset, healthcare-associated *Clostridioides difficile* infection (HOHA-CDI) incidence, Craigavon Area Hospital, January 2020-December 2024.

Candidate carbapenem use threshold percentile	40th	50th	60th	70th	75th	80th	85th
Candidate carbapenem use threshold rate (DDD/1000 OBD)	16.1	17.1	17.9	18.6	19.0	19.9	20.6
No. of included months (sample)				56*			
No. of months when carbapenem use is above the candidate threshold	34	28	23	17	14	11	8
No. of months when carbapenem use does not exceed the candidate threshold	22	28	33	39	42	45	48
HOHA-CDI incidence benchmark	**No. of months with HOHA-CDI incidence above the benchmark when carbapenem use is above the candidate threshold**						
Mean	21	17	13	11	11	8	6
50th percentile (Median)	22	18	14	12	12	9	7
65th percentile	16	13	10	9	9	7	5
75th percentile	11	9	7	6	6	5	4
80th percentile	10	9	7	6	6	5	4
85th percentile	7	6	5	4	4	4	3
HOHA-CDI incidence benchmark	**No. of months with HOHA-CDI incidence above the benchmark when carbapenem use does not exceed the candidate threshold**						
Mean	5	9	13	15	15	18	20
50th percentile (Median)	6	10	14	16	16	19	21
65th percentile	4	7	10	11	11	13	15
75th percentile	3	5	7	8	8	9	10
80th percentile	1	2	4	5	5	6	7
85th percentile	1	2	3	4	4	4	5
HOHA-CDI incidence benchmark	**Proportion of months with HOHA-CDI incidence above the benchmark when carbapenem use is above the candidate threshold (A)**						
Mean	61.8	60.7	56.5	64.7	78.6	72.7	75.0
50th percentile (Median)	64.7	64.3	60.9	70.6	85.7	81.8	87.5
65th percentile	47.1	46.4	43.5	52.9	64.3	63.6	62.5
75th percentile	32.4	32.1	30.4	35.3	42.9	45.5	50.0
80th percentile	29.4	32.1	30.4	35.3	42.9	45.5	50.0
85th percentile	20.6	21.4	21.7	23.5	28.6	36.4	37.5
HOHA-CDI incidence benchmark	**Proportion of months with HOHA-CDI incidence above the benchmark when carbapenem use does not exceed the candidate threshold (B)**						
Mean	22.7	32.1	39.4	38.5	35.7	40.0	41.7
50th percentile (Median)	27.3	35.7	42.4	41.0	38.1	42.2	43.8
65th percentile	18.2	25.0	30.3	28.2	26.2	28.9	31.3
75th percentile	13.6	17.9	21.2	20.5	19.0	20.0	20.8
80th percentile	4.5	7.1	12.1	12.8	11.9	13.3	14.6
85th percentile	4.5	7.1	9.1	10.3	9.5	8.9	10.4
HOHA-CDI incidence statistical comparison	***p*-value (Fisher's exact test) for the difference in proportions, i.e. (A) vs. (B)**						
Mean	0.004	0.030	0.161	0.064	0.006	0.053	0.085
50th percentile (Median)	0.006	0.030	0.139	0.040	0.002	0.020	0.026
65th percentile	0.026	0.081	0.233	0.071	0.013	0.037	0.097
75th percentile	0.101	0.178	0.317	0.199	0.080	0.091	0.097
80th percentile	0.021	0.020	0.088	0.060	0.020	0.029	0.040
85th percentile	0.096	0.126	0.173	0.185	0.097	0.040	0.078

*Carbapenem use was lagged by four months. The analysis therefore included 56 lag-aligned monthly observations.
Abbreviations: DDD, defined daily doses; OBD, occupied bed-days.

normal variation increases [20–22]. Accordingly, we should define a pathogen high-incidence benchmark (cutoff point) and model the likelihood of reaching this benchmark once antibiotic use rises above the threshold. Within hospital settings, this pathogen high-incidence (critical) level may be informed by institutional targets, government guidance, or empirical evaluation of previous infection patterns [20–22]. In the present study, empirical analysis of historical HOHA-CDI incidence rates was used to determine the point at which HOHA-CDI incidence was considered critical. A pathogen high-incidence benchmark is not a single fixed number but rather a reference point that can be used to assess a pathogen's frequency of occurrence (incidence) in a specific context, e.g. a hospital or region, to understand its prevalence, guide control measures, and improve public health strategies. To address these issues and translate antibiotic use thresholds into action, we introduced the threshold-logistic modeling concept [20–24].

In this study, we used threshold-logistic models to define, from historical data, a cutoff point for critically high HOHA-CDI incidence and modeled the probability of exceeding this cutoff point. Using the threshold-logistic regression and ensemble models, we identified antibiotic use thresholds for key antibiotic/antibiotic groups, such that exceeding these thresholds was associated with increasing HOHA-CDI incidence and a higher estimated probability of reaching the cutoff point. Antibiotic exposure may drive CDI through disruption of the normal gut microbiota and, for some drug classes, through selection of epidemic *C. difficile* strains with reduced susceptibility or resistance [19,30]. In this context, antibiotic use thresholds may represent critical levels of population antibiotic pressure above which CDI risk is more likely to increase. Further work is needed to determine the relative contribution of these mechanisms. Fluoroquinolones are associated with CDI; however, the literature suggests potential differences in CDI-promoting capacity across different fluoroquinolone

Table 4. Consensus distribution-based analysis of associations to determine practical carbapenem use targets for managing hospital-onset, healthcare-associated *Clostridioides difficile* infection (HOHA-CDI) incidence, Craigavon Area Hospital, January 2020-December 2024.

Candidate carbapenem use threshold percentile	40th	50th	60th	70th	75th	80th	85th
Identified carbapenem use threshold rate (DDD/1000 OBD)	16.1	17.1	17.9	18.6	19.0	19.9	20.6
No. of included months (sample)				56*			
No. of months when carbapenem use is above the candidate threshold	34	28	23	17	14	11	8
No. of months when carbapenem use does not exceed the candidate threshold	22	28	33	39	42	45	48
HOHA-CDI incidence summary measure	**HOHA-CDI incidence (cases/1000 OBD) using the full sample**						
Mean				0.307			
50th percentile (Median)				0.300			
75th percentile				0.406			
80th percentile				0.427			
85th percentile				0.459			
HOHA-CDI incidence summary measure	**HOHA-CDI incidence (cases/1000 OBD) when carbapenem use is above the candidate threshold (A)**						
Mean	0.356	0.354	0.351	0.391	0.427	0.434	0.447
50th percentile (Median)	0.356	0.356	0.349	0.364	0.386	0.369	0.404
75th percentile	0.440	0.445	0.438	0.443	0.494	0.532	0.522
80th percentile	0.472	0.482	0.482	0.498	0.528	0.552	0.536
85th percentile	0.509	0.508	0.511	0.536	0.554	0.570	0.550
HOHA-CDI incidence summary measure	**HOHA-CDI incidence (cases/1000 OBD) when carbapenem use does not exceed the candidate threshold (B)**						
Mean	0.240	0.267	0.282	0.275	0.272	0.280	0.288
50th percentile (Median)	0.227	0.260	0.269	0.263	0.260	0.269	0.281
75th percentile	0.303	0.368	0.384	0.377	0.367	0.384	0.389
80th percentile	0.351	0.396	0.408	0.407	0.400	0.405	0.408
85th percentile	0.398	0.410	0.417	0.418	0.414	0.419	0.425
HOHA-CDI incidence summary measure	**Between groups difference, i.e. (A) - (B), in HOHA-CDI incidence (cases/1000 OBD)**						
Mean	0.116	0.087	0.069	0.116	0.155	0.154	0.159
50th percentile (Median)	0.129	0.097	0.080	0.101	0.126	0.099	0.122
75th percentile	0.138	0.077	0.054	0.066	0.127	0.148	0.133
80th percentile	0.121	0.085	0.074	0.091	0.128	0.147	0.128
85th percentile	0.111	0.098	0.094	0.118	0.139	0.151	0.125
HOHA-CDI incidence statistical comparison	***p*-value (Wilcoxon rank-sum test) for an overall between-group distributional difference, i.e. (A) – (B), in HOHA-CDI incidence (cases/1000 OBD)**						
Overall distribution	0.008	0.041	0.143	0.020	0.002	0.010	0.021
HOHA-CDI incidence statistical comparison	***p*-value (quantile regression) for the difference, i.e. (A) – (B), in HOHA-CDI incidence (cases/1000 OBD)**						
50th percentile (median)	0.005	0.050	0.108	0.054	0.039	0.172	0.438
75th percentile	0.070	0.330	0.402	0.434	0.117	0.087	0.371
80th percentile	0.052	0.136	0.151	0.166	0.070	0.197	0.269
85th percentile	0.221	0.184	0.309	0.215	0.216	0.155	0.400

*Carbapenem use was lagged by four months. The analysis therefore included 56 lag-aligned monthly observations.
Abbreviations: DDD, defined daily doses; OBD, occupied bed-days.

agents [30]. Our results are therefore best interpreted as class-level ecological associations.

During the modeling phase, we tested each antibiotic use series, both on its own and in combination with others. For AAH, all the significant antibiotic use series fit together into one threshold-logistic model, which outperformed all alternative models. Although we found other possible models that included some of the same significant antibiotic use series, none matched the performance of this single model. For the other three hospitals, the significant antibiotic use series could not all be captured within a single threshold-logistic model. Instead, we combined the best-performing models that included these series into an optimal ensemble model. Differences were observed among the four hospitals in the identified antibiotic classes and corresponding thresholds. Although national prescribing guidelines are in place, antibiotic prescribing practices may vary between hospitals because of differences in patient case-mix, local adaptations of national guidelines, variation in adherence to guidelines, and ongoing hospital outbreaks that may influence antibiotic choice. An earlier study from PGH [22], using a different study period, identified fluoroquinolones and piperacillin-tazobactam as significant predictors of elevated HOHA-CDI incidence and established corresponding antibiotic use thresholds. However, piperacillin-tazobactam did not emerge as a significant predictor in the final models developed in the present study. Of note, the two studies examined different observation periods and therefore reflect potentially different antimicrobial prescribing patterns, pathogen incidence, and healthcare environments. These findings highlight the dynamic nature of antibiotic-pathogen relationships and support the need for periodic recalibration of threshold-logistic models and stewardship targets using contemporary local data.

Table 2 presents monthly risk predictions for the four hospitals using threshold-logistic and, where applicable, ensemble models. The rolling-origin January-June 2024 evaluation is a strength because each prediction only used information available before the forecast month. Prospective evaluation in later implementation periods and in additional hospitals is still required. The alert score represents predicted risk that may inform proactive AMS strategies. Pei et al. discussed challenges in forecasting AMR and called for improved AMR

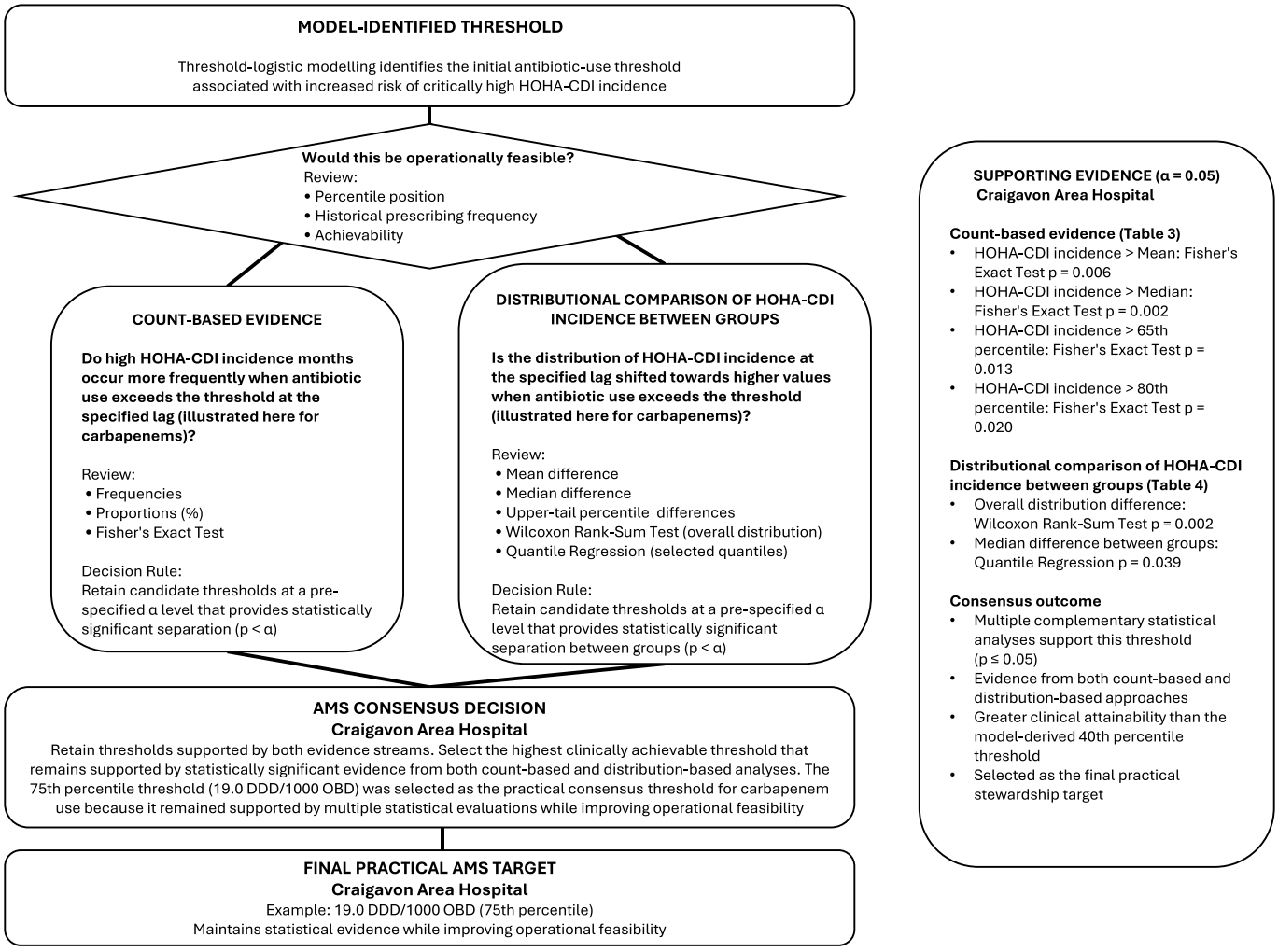

Figure 1. TARGET-A consensus framework for selecting practical antibiotic use thresholds, illustrated using carbapenem use at Craigavon Area Hospital (CAH).

*According to the UK national action plan, Confronting antimicrobial resistance 2024 to 2029 [36], the human health targets for 2029 are to reduce total antibiotic use in human populations by 5% from the 2019 baseline and for antibiotics from the Access category (new UK category) to account for 70% of total antibiotic use across the human healthcare system.

**'Contextual data' refers to factors that may influence antibiotic use or resistance, such as patient case mix, hospital activity, infection prevention and control measures, and other relevant contextual factors.

predictive intelligence [31]. At AAH, April and May 2024 generated high alert scores even though the observed incidence did not exceed the underlying 75th-percentile cutoff. At CAH, the observed incidence exceeded the 80th-percentile cutoff during several months in 2024. At SJUH, the observed incidence did not exceed its cutoff but generated medium alerts in later months, indicating model-estimated risk that warranted review rather than an observed threshold exceedance.

At PGH, the observed incidence remained in the low-alert category throughout the evaluation period. Nevertheless, the macrolide use model only demonstrated modest discrimination (AUC = 0.62), whereas the co-amoxiclav model showed acceptable discrimination (AUC = 0.72). Models with modest discriminatory ability may still have practical value as components of an early-warning surveillance framework, provided that medium- and high-risk alerts are used to prompt further review rather than serve as the sole basis for AMS interventions. In practice, such alerts should be interpreted alongside other surveillance information, including pathogen incidence trends, AMS activities, and IPC indicators. Model performance, including discrimination and calibration, should be monitored prospectively, with periodic recalibration and validation to ensure the models remain clinically useful and fit for purpose. Future work should focus on improving model performance by incorporating additional predictors, including routinely collected operational measures such as bed occupancy rates and environmental cleaning audit scores, other IPC or environmental indicators [32], and more refined measures of antibiotic use [33], to better account for variation in HOHA-CDI incidence.

From a guideline perspective, these findings highlight the utility of incorporating probabilistic modeling into hospital surveillance systems. By detecting elevated risk before threshold exceedance, ensemble-model alerts could support early interventions, including enhanced environmental cleaning, review of antimicrobial prescribing practices, and other IPC measures. For hospitals such as AAH and CAH, targeted efforts during high-alert periods could help prevent HOHA-CDI outbreaks. For hospitals like SJUH, where alert scores rise despite antibiotic use remaining below the identified threshold,

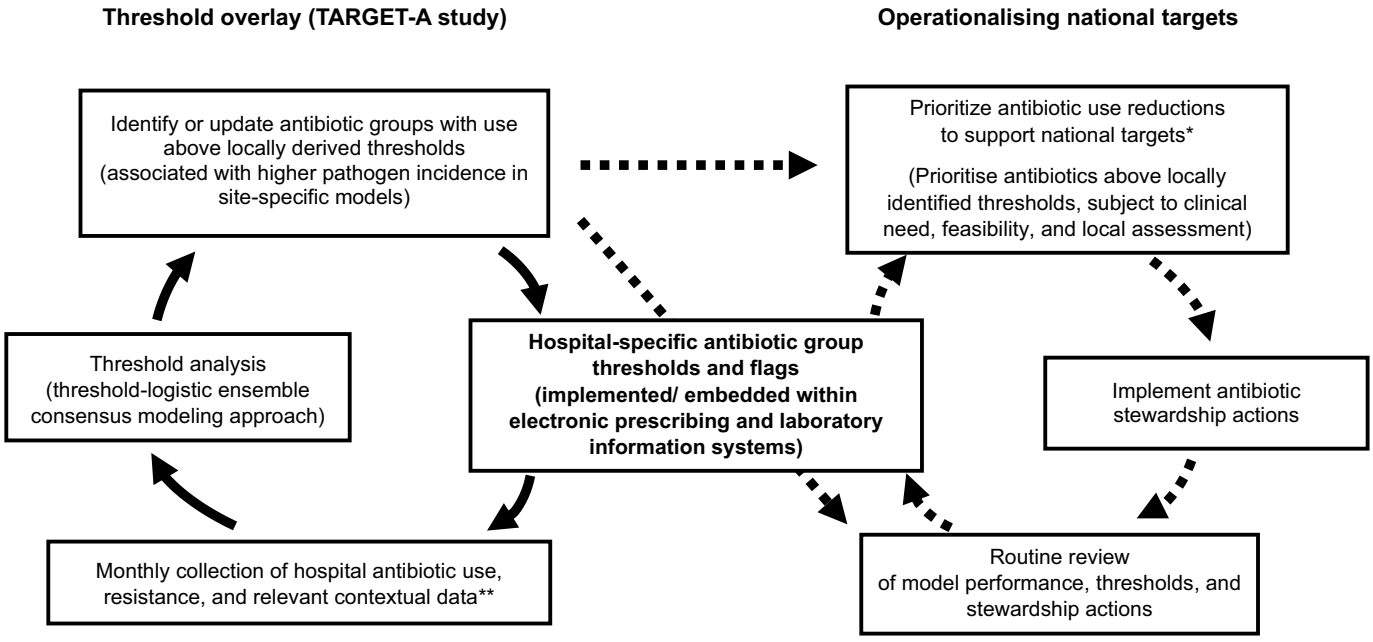

Figure 2. Conceptual framework illustrating how hospital-specific antibiotic use thresholds can support national implementation of antibiotic use targets.

*According to the UK national action plan, Confronting antimicrobial resistance 2024 to 2029 [36], the human health targets for 2029 are to reduce total antibiotic use in human populations by 5% from the 2019 baseline and for antibiotics from the Access category (new UK category) to account for 70% of total antibiotic use across the human healthcare system.

**'Contextual data' refers to factors that may influence antibiotic use or resistance, such as patient case mix, hospital activity, infection prevention and control measures, and other relevant contextual factors.

probabilistic alerts may provide an early warning signal, helping ensure that AMS interventions are timely, evidence-informed, and proportionate to the estimated level of risk.

A consensus approach may add value to guideline implementation by providing a structured way to consider statistical evidence alongside clinical feasibility. As demonstrated in the consensus analyses for CAH, purely model-identified antibiotic use thresholds, such as a low carbapenem use threshold, may be statistically optimal but impractical for everyday hospital operations. Consensus enables clinicians, epidemiologists, and policymakers to jointly interpret complementary evidence from count-based and distribution-based approaches, statistical comparisons, and ensemble risk predictions that are adjuncts to rigorous statistical modeling processes. Consensus also promotes the transdisciplinary model of care which transcends disciplinary boundaries, integrates knowledge from multiple disciplines, and requires a deeper level of collaboration to address complex clinical problems thereby leading to more holistic and innovative solutions. Consensus-based review may support shared ownership of AMS policies and improve the acceptability of proposed thresholds. Its effects on adherence, implementation and the timeliness of responses should be assessed prospectively. In the TARGET-A modeling study, count-based and distribution-based analyses were presented to the local AMS team, and candidate thresholds were discussed collectively to identify the highest clinically achievable threshold that remained supported by statistically significant evidence; this consensus process is illustrated using the CAH example.

Our approach has several strengths. It uses hospital-level antibiotic use and HOHA-CDI surveillance data that are routinely collected and can be updated monthly as new observations become available. The ensemble framework can integrate information from multiple feasible models when correlated antibiotic use predictors cannot be included together in a stable single model, thereby reducing dependence on one selected specification. The consensus component does not estimate variable importance; rather, it provides a structured way to compare model-derived thresholds with descriptive, count-based, distribution-based, and operational evidence. These features may improve robustness and help hospitals select thresholds that are evidence-informed and operationally achievable. Nevertheless, the identified thresholds are local reference points intended to guide the review of antibiotics associated with HOHA-CDI risk, rather than universal limits.

Several antibiotics with high AMR potential sit in the Watch group of the WHO Access/Watch/Reserve (AWaRe) classification, which is widely used to monitor antibiotic consumption, and support stewardship targets and benchmarking [34,35]. In 2024, at the United Nations General Assembly High-level Meeting on Antimicrobial Resistance, Member States endorsed a strengthened global antibiotic use target whereby, by 2030, at least 70% of global human antibiotic consumption should consist of WHO Access group antibiotics [35]. According to the UK national action plan, *Confronting Antimicrobial Resistance 2024 to 2029*, the human health targets for 2029 are to achieve 70% of total use of antibiotics from the Access category (new UK category) across the human healthcare system [36]. However, AWaRe is a category-based framework and does not, on its own, provide quantitative, hospital-specific action points for the antibiotics most strongly associated with resistance selection in a given setting. In the TARGET-A modeling

study, we identified a small set of antibiotic groups (co-amoxiclav, carbapenems, clindamycin, fluoroquinolones and macrolides) with statistically significant, hospital-specific use thresholds, expressed as DDD per 1000 occupied bed-days, associated with increased HOHA-CDI incidence (Table 1). Our approach could therefore complement existing AWaRe reporting, with outcome-linked, locally derived thresholds embedded as targets for specific antibiotics within each AWaRe category and supported by TARGET-A risk scoring and alert system. A conceptual framework is proposed in Figure 2. This would have practical importance because the AWaRe classification may have been adapted locally; for example, co-amoxiclav is classified as Access in the WHO AWaRe classification [34] but as Watch in the UK-adapted AWaRe list [37], which affects how hospitals interpret antibiotic consumption metrics and targets. Operationally, this approach could provide a mechanism for translating national targets into locally prioritized stewardship actions. Hospitals could consider initially reviewing antibiotics that exceed identified hospital-specific thresholds, particularly those within the AWaRe Watch group.

Importantly, the proposed framework is not intended to generate a single universal antibiotic use threshold applicable to all pathogens. Rather, it provides a standardized methodology for deriving pathogen-specific antibiotic use thresholds, risk scores, and stewardship targets. Different pathogens are expected to exhibit distinct threshold relationships, lag structures, and risk factors. Operationally, outputs from multiple pathogen-specific threshold-logistic models could be integrated into a unified antimicrobial stewardship dashboard or scorecard. Such a system would allow hospital AMS team to monitor pathogen-specific risks while identifying antibiotic groups that consistently emerge as important predictors or associated factors across multiple pathogens. Prioritizing interventions for antibiotics associated with elevated risk across several organisms may provide overall stewardship benefit and facilitate practical implementation within routine clinical practice. For example, if a specific antibiotic use at a hospital were associated with increased risk of more than one pathogen, separate threshold-logistic analyses may identify different pathogen-specific thresholds. Through the consensus process, hospital AMS team could evaluate whether a common operational target, such as the lowest clinically achievable threshold that remains supported by evidence across both pathogens, could be adopted. In this way, a single stewardship intervention may simultaneously reduce risk across multiple pathogens while simplifying implementation and monitoring, allowing stewardship teams to prioritize reductions in antibiotics that are repeatedly associated with elevated risk across several pathogens and AWaRe monitoring objectives. Ward- or department-level antibiotic consumption data were not available for the current study; however, future research using more granular prescribing and CDI surveillance data could explore these associations and may provide more clinically actionable insights.

As with all predictive model implementations, recalibration of the model is essential and should be performed periodically or when performance declines. Parameters can be re-estimated as new data are available, updating the model fit without changing the structure. However, if a parameter's statistical significance falls below the pre-specified level, the structural form may need revision. In practice, model estimation, evaluation, and forecast-accuracy monitoring can be automated. The recalibration frequency depends on the stability of the model's identified relationships and the extent of observed AMR trends.

4.1. Limitations

The study has the following limitations. Although HOHA-CDI definitions were broadly harmonized across sites, minor differences in diagnostic testing and duplicate-positive exclusion periods may have introduced some heterogeneity in case ascertainment. Nevertheless, all sites used established diagnostic methods, and because thresholds were developed separately for each hospital, they should be interpreted within the context of local diagnostic and clinical practice rather than universally transferable values. Additionally, the observed differences in HOHA-CDI incidence between hospitals are likely multifactorial and may reflect variation not only in antibiotic prescribing practices but also in IPC measures, environmental cleaning, patient case-mix, bed occupancy, local outbreaks, pre-admission antibiotic exposure, and other unmeasured factors not captured in the current study. The inclusion of these factors would likely improve the predictive performance of the models. Future work incorporating these additional explanatory variables may further enhance model performance and better capture the drivers of CDI incidence.

Furthermore, exposure to multiple antibiotic classes at the population level may be associated with higher pathogen incidence risk beyond that associated with individual antibiotic usage alone. The present framework evaluates antibiotic use at the population level and therefore should not be interpreted as a direct assessment of patient-level antibiotic combinations. Nevertheless, the threshold-logistic framework permits multiple antibiotic use variables to be incorporated simultaneously within multivariable models, thereby partially accounting for their combined ecological associations with HOHA-CDI incidence. Future threshold-logistic modeling studies could examine interaction effects between antibiotic classes using a similar methodology [23]. Such analyses may help identify antibiotic combinations associated with disproportionately high CDI or AMR outcomes and provide additional opportunities for targeted antimicrobial stewardship interventions.

5. Conclusion

In summary, this study showed that routinely collected hospital-level antibiotic use and HOHA-CDI surveillance data can be used to derive site-specific antibiotic use thresholds associated with elevated HOHA-CDI incidence and to generate alerts for periods of increased estimated risk. Antibiotic use thresholds are empirically derived provisional targets for local AMS, and

this study provided a structured framework for assessing their operational feasibility and local applicability. Prospective multicentre studies are now required to determine whether implementing AMS actions based on these thresholds changes antibiotic use and reduces HOHA-CDI incidence.

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Declaration of interest

W.J. Lattyak is affiliated with Scientific Computing Associates Corp but contributed statistical/methodological input in a personal capacity. Scientific Computing Associates Corp had no role in the study design, analysis, interpretation, manuscript preparation, or decision to submit. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

The authors declare the use of ChatGPT 5.2 for grammar corrections and copy-editing only. All AI-generated suggestions were carefully reviewed by the authors, who take full responsibility for the accuracy and final content of the manuscript. The authors confirm that all generative AI use complies with Taylor & Francis' policy on the responsible use of generative AI.

Ethics approval

The study was approved by the University of Huddersfield Research Integrity and Ethics Committee (SAS-SRIEC-09.08.24-1). As this was a retrospective ecological study based on existing data, the Ethics Committee determined informed consent was not required.

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M.A. Aldeyab and W.J. Lattyak conceived the study and developed its design. All authors contributed to the refinement of the methodological approach. S.E. Bond, D. Farren, M.G. Scott, G. Conlon-Bingham, K. Atack, A. Otu, A. Boulos, and J. Martin contributed to the collation of center-specific data. All authors contributed to the clinical and contextual interpretation of the findings. M.A. Aldeyab and W.J. Lattyak conducted the statistical analyses, with W.J. Lattyak serving as the principal analyst. M.A. Aldeyab, D.L. Monnet, and W.J. Lattyak prepared the initial draft of the manuscript. All authors discussed the results and contributed comments and revisions to the manuscript.

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Data availability statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request, subject to approval by the participating hospitals.

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