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Research Article

Antimicrobial Resistance Trends in Escherichia coli, Klebsiella pneumoniae, and Staphylococcus aureus: A Multinational WHO GLASS Analysis

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ABSTRACT

Background. Antimicrobial resistance (AMR) is a leading global health threat, and the WHO Global Antimicrobial Resistance and Use Surveillance System (GLASS) is the principal mechanism for multinational AMR surveillance. Countries participate voluntarily and report differing pathogen-antibiotic combinations in different years, so the reported data form an unbalanced panel whose composition changes over time. Objectives. To describe and quantify trends in reported resistance for Escherichia coli, Klebsiella pneumoniae and Staphylococcus aureus using GLASS country-reported data (2018–2023), and to determine how far those trends depend on which countries reported in each year. Methods. Retrospective ecological secondary analysis of WHO XMART country-reported GLASS AMR indicators for 2018–2023. The original extraction on 17 October 2026 was reproduced using a new retrieval on 31 October 2026. Eight clinically prioritised pathogen–antibiotic–specimen combinations were evaluated using binomial mixed-effects models with country-level and observation-level random intercepts. Balanced-panel, inclusion-threshold, country-exclusion and model-specification sensitivity analyses were undertaken, together with Holm adjustment across the eight primary temporal tests and exploratory overdispersion-aware regional analyses. Results. The eight sentinel combinations comprised 2,294 country–year strata from 65 reporting countries and 17,132,532 interpretable antimicrobial susceptibility test (AST) results; the broader descriptive subset contained 8,824 strata from 66 countries. Three combinations showed increasing reported resistance after accounting for extra-binomial heterogeneity and Holm adjustment: K. pneumoniae meropenem (annual OR 1.1453; 95% CI 1.1060–1.1861; adjusted $P = 2.34 \times 10^{-13}$), E. coli meropenem (OR 1.1860; 95% CI 1.1226–1.2529; adjusted $P = 8.14 \times 10^{-9}$), and K. pneumoniae ciprofloxacin (OR 1.0684; 95% CI 1.0430–1.0946; adjusted $P = 4.58 \times 10^{-7}$). All three retained direction and significance across seven alternative scenarios. The other five combinations had no statistically significant primary temporal association. Exploratory overdispersion-aware regional interaction tests were significant in three combinations. For E. coli ciprofloxacin resistance in blood, the all-reporter pooled change was −1.8 percentage points and the balanced-panel change was +7.4 percentage points, yielding a descriptive participation contrast of −9.2 percentage points. Conclusions. Among reporting countries, reported meropenem resistance in E. coli and K. pneumoniae and ciprofloxacin resistance in K. pneumoniae increased between 2018 and 2023. These associations were robust to sensitivity and multiplicity analyses, but they do not establish national population-level resistance trends or treatment outcomes. Changes in reporting-country composition materially affected crude comparisons, highlighting the need to report denominator, participation and model uncertainty when interpreting multinational surveillance data. **Keywords:** antimicrobial resistance; WHO GLASS; surveillance; multilevel models; overdispersion; reporting completeness; *Escherichia coli*; *Klebsiella pneumoniae*; *Staphylococcus aureus*.

INTRODUCTION

Antimicrobial resistance is among the most serious threats to modern medicine. The Global Research on Antimicrobial Resistance collaboration attributed an estimated 1.27 million deaths directly to bacterial AMR in 2019 (1), and subsequent projections anticipate a substantial further increase in attributable mortality by 2050 (2). Regional analyses have documented comparable or greater burdens in the WHO African and Eastern Mediterranean regions (3,4).

Three pathogens account for a large share of this burden and of the clinical difficulty of treatment. Escherichia coli is the most common cause of bloodstream and urinary tract infection worldwide, and the global dissemination of extended-spectrum beta-lactamase (ESBL) and, subsequently, carbapenemase determinants has progressively narrowed therapeutic options (5,6,7). Klebsiella pneumoniae is a major reservoir and vector of acquired resistance determinants, including carbapenemases, and carbapenem-resistant K. pneumoniae is classified as a critical-priority pathogen (8,9). Staphylococcus aureus remains a leading cause of bloodstream infection, and methicillin resistance continues to carry important consequences for empirical therapy (10,11).

The WHO Global Antimicrobial Resistance and Use Surveillance System (GLASS) was established to consolidate national AMR surveillance into a standardised multinational picture (12,13). GLASS publishes country-reported resistance proportions with the corresponding numerator and denominator for a defined set of pathogen-antibiotic combinations, by specimen type and reporting year, bringing more than 100 countries into a common reporting framework (14).

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Using GLASS data for comparative analysis nonetheless carries specific methodological hazards that are well documented in the surveillance literature. Participation is voluntary and unequal, so the set of reporting countries differs between years and between pathogen-antibiotic combinations (15,16,17,18,19). Denominators reflect national testing capacity as much as infection incidence, so a rising number of tested isolates may itself change the measured proportion (20,21). Pooling proportions across countries of very different sizes and surveillance maturity produces a denominator-weighted quantity that is not the average experience of any country (22,23). Aggregated counts from many laboratories are usually overdispersed relative to a binomial model, so unadjusted standard errors are anti-conservative (24,25). WHO's own 2025 report responds to several of these issues by publishing Bayesian model-based estimates adjusted for population structure and surveillance coverage, together with a national data-completeness scoring framework and missing-data diagnostics (14,26).

The present analysis examines the country-reported indicator values underlying multinational surveillance, with particular attention to how trend conclusions depend on participation and analytical specification. WHO already publishes adjusted global and regional trends for 2018–2023 and a national data-completeness framework (14). Published multi-country GLASS studies have examined cross-sectional associations (27) and forecasting or interrupted time-series approaches (28). Other work has used different data platforms (29) or structured European EARS-Net surveillance data (30,31). A critique of the 2025 WHO report has also documented country data gaps (32). The contribution of this study is therefore complementary: direct modelling of country-reported binomial counts, transparent comparison of pooled and country-level summaries, and quantification of the sensitivity of trend conclusions to the reporting panel.

This study therefore addresses three objectives:

- To describe reported resistance patterns for *E. coli*, *K. pneumoniae* and *S. aureus* across the 2018–2023 GLASS reporting panel, distinguishing pooled proportions from median country-level proportions.
- To estimate temporal associations using multilevel binomial models that account for country clustering and extra-binomial heterogeneity in aggregate resistance counts.
- To quantify how far each trend conclusion depends on which countries reported in which years, through balanced-panel, threshold, exclusion and influence sensitivity analyses.

The study is explicitly descriptive and associational. It reports what participating countries reported. It does not estimate national or global resistance prevalence, and it does not interpret a change in the reported proportion as a biological change in resistance.

MATERIALS AND METHODS

Study design and reporting

This retrospective ecological longitudinal study used secondary analysis of publicly available, country-level aggregate surveillance data for 2018–2023. The repeated analytical units were country–year–pathogen–antibiotic–specimen strata rather than individual patients. No primary data collection was undertaken and no patient-identifiable information was accessed. STROBE recommendations were used as a reporting framework to the extent applicable to published surveillance aggregates (33,34).

Data source and retrieval

Country-reported AMR indicator data were retrieved from the WHO XMART public API, table DATA_/RELAY_GLASS_AMR, at https://xmart-api-public.who.int/ (35). The GLASS dashboard and its published source code provide complementary documentation of the public reporting interface (36,37).

The complete analysis was rerun using a retrieval dated 31 October 2026 (397,037 indicator records); its SHA-256 digest, exact API parameters, variable dictionary and download timestamp are supplied with the reproducibility package (Supplementary Methods). The original 17 October raw CSV was not retained, so byte-for-byte equality cannot be proven. However, all eight primary odds ratios, their confidence intervals and the archived numerical outputs were reproduced.

Data structure and outcome definitions

The XMART relay table is a long indicator store in which each row is one value of one indicator for one geography-year, with generic `DIM_n` slots carrying the disaggregation. For AMR resistance records the slots are `DIM_1` = specimen type, `DIM_2` = pathogen and `DIM_3` = antibiotic target.

Two families of resistance indicator are present and were deliberately kept separate:

`RESISTANCE_ANTI_TIME_{PERCENTRESISTANT, RESISTANT, INTERPRETABLEAST, TOTALSPECIMENISOLATES}` carry **country-reported values on ISO3 geographies** and form the analysis dataset.

`RESISTANCE_ANTI_TIME_{MAX, MIN, Q1, Q3, MEDIAN, CTAS}` carry **WHO regional and global aggregates** on pseudo-geographies (`GLOBAL`, `AFR`, `AMR`, `EMR`, `EUR`, `SEAR`, `WPR`). These are WHO's own summaries, are stored in a separate object, and were never combined with country observations or treated as country data. A validation check asserts that no aggregate pseudo-geography survives into the country-level dataset.

The analysis unit is a **country-year-pathogen-antibiotic-specimen stratum**. For each stratum the primary outcome is the reported resistance proportion,

$$\hat{p} = \frac{\text{resistant isolates}}{\text{isolates with an interpretable AST result}} \times 100,$$

The proportion and corresponding percentage were computed from the integer numerator and denominator published by GLASS. The recomputed percentage matched the published GLASS percentage to floating-point precision for every stratum, with a maximum absolute difference of 4.996394×10^{-10} percentage points. This check supports the decoding of the indicator store and the numerator–denominator pairing. All 22 automated validation checks passed, including the assertion that no WHO aggregate pseudo-geography remained in the country-level dataset.

The 22 automated validation checks (all passed) test source indicators, country versus aggregate geographies, identifier uniqueness, numeric constraints, mappings and numerator–denominator consistency. The test code, check-level results and raw/processed data are supplied with the reproducibility package (Supplementary Tables S1 and S2).

A stratum was considered analysable if it had a positive denominator and a nonnegative resistant numerator no larger than that denominator. Available valid observations formed the unbalanced panel; the balanced-panel sensitivity analysis separately restricted inclusion to countries reporting in every study year. Figure 1 shows the transition from API indicator records to the three-pathogen descriptive dataset; the sentinel subset is a further selection from that dataset.

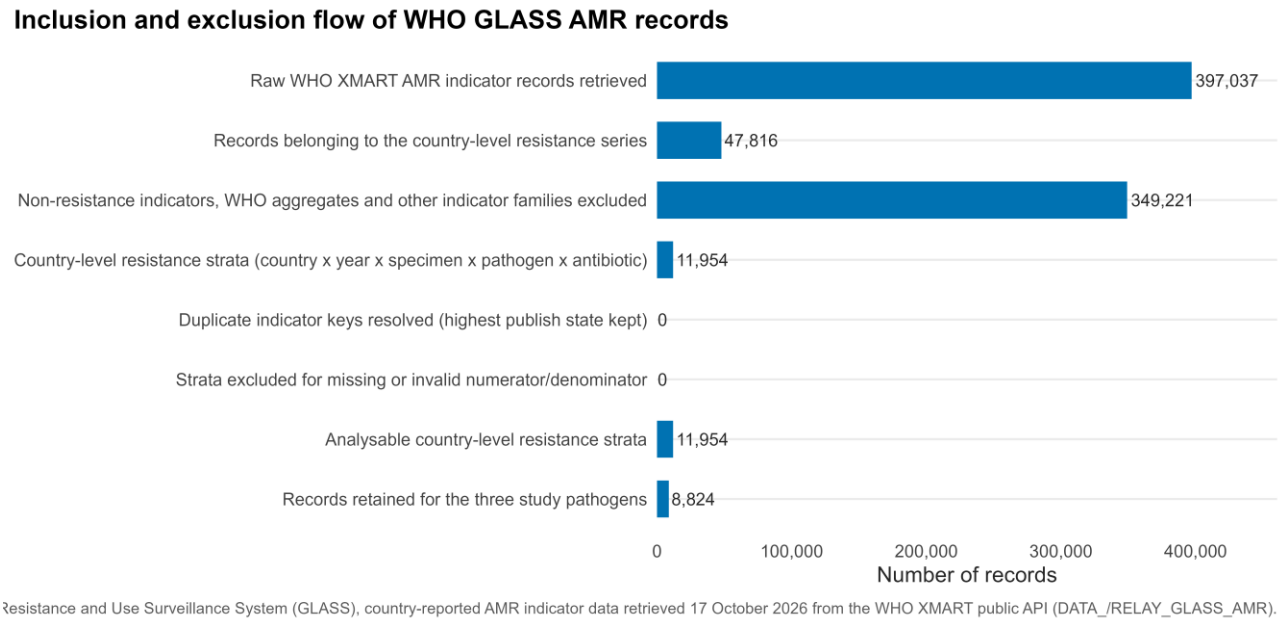


Figure 1. Inclusion and exclusion of WHO XMART AMR indicator records. The display changes units from individual indicator records to country–year–pathogen–antibiotic–specimen strata after pairing the four indicator values. The 8,824-stratum three-pathogen descriptive dataset contains the further 2,294-stratum sentinel subset. The original graphic carries the 17 October 2026 extraction label; the analysis was rerun on the 31 October snapshot.

Pathogens, antibiotics and specimen types

The analysis covers *Escherichia coli*, *Klebsiella pneumoniae* and *Staphylococcus aureus*. Antibiotic targets were analysed as reported, at the level of the individual agent. Where GLASS publishes a composite antibiotic-group indicator (for *E. coli*, "Third-generation cephalosporins"), it is retained as its own analytic unit and is flagged by `is_glass_antibiotic_group`; it was never pooled with the constituent single agents, because the same isolates contribute to both and pooling would double-count and artificially inflate precision.

Blood and urine specimen types were analysed separately because their testing populations and resistance distributions differ. Blood isolates provided the cross-pathogen comparison, and E. coli ciprofloxacin resistance in urine provided the urinary sentinel combination. Blood and urine identify specimen sources; these aggregate indicators do not independently establish patient-level clinical diagnoses of bloodstream or urinary tract infection.

Sentinel combinations and eligibility

Eight clinically prioritised pathogen–antibiotic–specimen combinations were defined in the analytical code. For E. coli these were the WHO third-generation cephalosporin composite in blood, meropenem in blood, and ciprofloxacin in blood and urine; for K. pneumoniae they were ceftazidime, meropenem and ciprofloxacin in blood; for S. aureus the endpoint was methicillin resistance in blood. The exact reported methicillin-resistance indicator was retained without combining it with other agents. Individual agents were not pooled with WHO composite indicators. Descriptive eligibility required at least five countries, four reporting years, 25 analysable strata and 1,000 interpretable AST results. All 46 eligible combinations, the eight sentinel definitions and their clinical rationale are listed in Supplementary Tables S4–S6 and S18. The analytical code defines the sentinel panel, but no independently dated prospective study protocol was available; the analysis is interpreted as an exploratory secondary surveillance study.

Statistical analysis

Descriptive summaries

Two different summaries are reported side by side throughout, because they answer different questions: the **pooled proportion**, the total number of resistant isolates divided by the total number of isolates with an interpretable AST result, with a Wilson score 95% confidence interval; the median country-level proportion, with its interquartile range, as a summary that does not weight countries by their AST denominators. The country grouping and reporting period determine the observations contributing to each descriptive summary. The two are never conflated. An unweighted mean of country percentages is reported for comparison only, to make the magnitude of the divergence explicit.

Multilevel binomial temporal model

For each observed country–year–combination stratum, the resistant count was modelled with a binomial likelihood and the number of interpretable AST results as the denominator. The log-odds of resistance was expressed as a linear function of reporting year with country- and observation-level random intercepts:

$$Y_i \sim Binomial(n_i, p_i); \quad logit(p_i) = \beta_0 + \beta_1(year_i - 2020.5) + u[country_i] + v_i.$$

Here Y_i is the reported resistant count, n_i is the number of interpretable AST results, p_i is the resistance probability for the reported stratum, $u[country_i]$ is a country random intercept, and v_i is an observation-level random effect. The year term was centred at 2020.5, the midpoint of 2018–2023. Models were fitted using lme4::glmer and the bobyqa optimiser, with a maximum of 200,000 evaluations (38).

Aggregated laboratory counts can exhibit extra-binomial variation, motivating an observation-level random effect (24,25). Pearson dispersion was calculated as the sum of squared Pearson residuals divided by residual degrees of freedom. Under the analytical rule, a value above 1.5 in the country-random-intercept model triggered use of the observation-level extension for primary inference. All eight sentinel combinations exceeded this threshold. The country-only model was retained as a comparator to show how allowing extra-binomial variation changed uncertainty and inference.

For each analysed stratum i in country c, $Y_i \sim$ Binomial(n_i,p_i), and logit(p_i) = $\beta_0 + \beta_1$(year$_i$ – 2020.5) + u_c + v_i, with u_c ~ N(0,σ^2_country) and $v_i \sim$ N(0,σ^2_observation). The observation-level random effect was implemented using one unique factor level per country–year–combination row, entered as (1 | obs). It captures residual extra-binomial heterogeneity but cannot identify, remove, or causally attribute time-varying surveillance biases. Pearson residual dispersion was assessed using residual degrees of freedom; a second definition accounting for variance parameters was also examined (Supplementary Table S7).

Six model specifications were examined for each combination: M1, a single-level binomial generalised linear model; M2, a country random-intercept model; M3, a model allowing country-specific slopes in time; M4, a region-adjusted model; M5, a year-by-region interaction model; and M6, M2 with an additional observation-level random intercept. M6 supplied the primary annual trend estimates. These are conditional temporal associations under the specified random-effects structure, rather than estimates of population prevalence or a causal effect of calendar time.

Convergence, singular fits, random-effect variances, goodness of fit, calibration and logit-normal versus beta-binomial/quasi-binomial comparisons were examined for all sentinel analyses. All eight primary models converged without singular fits. The overdispersion-aware primary model was retained because it accommodates country clustering and extra-binomial heterogeneity; alternative distributional assumptions and their resulting estimates are provided in Supplementary Tables S7–S11. Quasi-binomial estimates do not model country-level clustering and were therefore treated as a diagnostic comparator.

The year coefficient was exponentiated to give an annual odds ratio with a 95% Wald confidence interval. The associated absolute change over 2018–2023 was evaluated at each combination's pooled reference proportion. Numerators and denominators were taken directly from GLASS counts; sample sizes were not reconstructed from published percentages.

For annual odds ratio $\theta = \exp(\beta_1)$ and reference proportion p_0, the five-year reference-based absolute change was calculated as $100 \times \{\text{expit}[\text{logit}(p_0) + 5 \log(\theta)] - p_0\}$ percentage points. The reference p_0 was the pooled observed proportion for that sentinel combination across the study period. This is a reference-based transformation of the conditional annual odds ratio, not an observed 2018 baseline, an empirical endpoint difference, or a marginal prediction integrated over the random effects. Its interpretation and sensitivity to the reference choice are documented in Supplementary Table S13.

Region comparisons

Resistance was compared across WHO regions using pooled and median-country proportions, and the variance of country-level percentages was partitioned descriptively into between-region and within-region components by one-way analysis of variance on the percentage scale. Regional representation was quantified as each region's share of reporting countries and share of interpretable AST results, and the leverage of each region on the pooled estimate was computed as its share of the denominator. A likelihood-ratio test compared the region-adjusted and time-by-region interaction models where every region in the combination contributed at least three countries; regions that could not support a region-specific slope were excluded and named.

The eight sentinel annual trend tests were treated as one family for Holm multiple-comparison adjustment. Unadjusted and Holm-adjusted P values are distinguished throughout. Regional interactions, subgroup comparisons and descriptive contrasts were exploratory; their P values were not adjusted as confirmatory tests.

The year-by-region interaction was reevaluated with the observation-level random effect included in both nested models. Likelihood-ratio comparisons were restricted to regions with at least three countries and interpreted as exploratory because reporting was uneven. Region-specific country counts, exclusions and Wald intervals are reported in Supplementary Tables S14 and S15. Interaction tests describe heterogeneity among represented reporting countries, not all countries in a WHO region.

Sensitivity analyses

The primary analysis and seven alternative scenarios were evaluated. S0 used all analysable strata and the primary country-plus-observation random-intercept specification. Selection sensitivity analyses retained that primary specification while changing the observations included: S1, countries reporting in all six years; S2 and S3, stratum denominators of at least 100 and 500 interpretable AST results; S4, exclusion of countries contributing fewer than three years; and S5, exclusion of the two largest-denominator countries. Specification sensitivity analyses changed the model: S6 omitted random effects and fitted a single-level binomial GLM, and S7 allowed a country-specific slope in time. Thus, differences in S1–S5 concern data selection, whereas S6–S7 assess model specification. Targeted leave-one-country-out refits additionally examined the five largest-denominator countries and the five sparsest reporters in each combination.

Every scenario is reported irrespective of its result. No scenario was discarded because it disagreed with the primary analysis. The balanced panel for a combination contains countries with valid observations in each of the six study years

(2018–2023). The participation contrast is the 2018–2023 all-reporter pooled percentage-point change minus the change restricted to the balanced panel. This is a descriptive composition contrast, not a causal decomposition. Country membership and comparisons of complete versus incomplete reporters are given in Supplementary Tables S16 and S17.

Software and reproducibility

Analyses were conducted in R 4.6.1 (39). The reproducibility materials comprise the complete R project, package lockfile, API retrieval commands, saved model objects, source data, validation logs and figure-generation code. Software references include lme4 for mixed-effects modelling, tidyverse for data workflows and sf for spatial data handling (38,40,41). The project entry point is run_all.R. The archived 31 October 2026 snapshot provides the reference for reproducing this analysis; a new retrieval from the live WHO XMART service may differ as submissions are updated.

Ethics

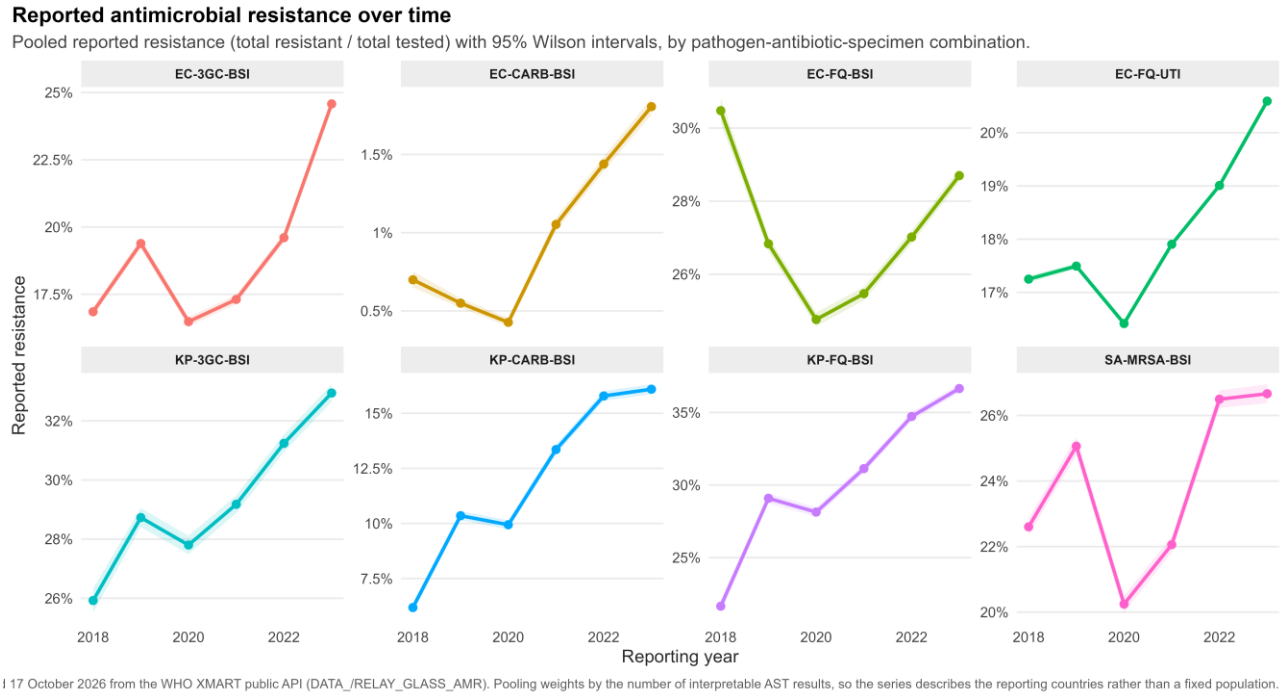
Only publicly available, country-level aggregate surveillance data released by WHO through an open API were analysed. No participants were recruited, no individual-level or patient-identifiable information was accessed, and no new clinical data were collected. Individual informed consent was not applicable to this secondary aggregate-data analysis. Data use remains subject to WHO's terms of use and citation requirements; retrieved files were retained unmodified with recorded provenance.

RESULTS

Data yield and coverage

The WHO XMART retrieval contained 397,037 indicator records. Across all country-level resistance indicators, 11,954 analysable strata were available; 8,824 strata from 66 countries represented the three study pathogens and their 46 eligible combinations. The 8,824-stratum descriptive subset comprised 85,654,485 AST results. The eight code-defined sentinel models contained 2,294 country–year strata from 65 countries, representing 17,132,532 interpretable AST results and 3,132,068 resistant AST results (Table 1; Figure 1). These are results of ASTs, not necessarily unique patients or isolates.

Across all study-pathogen indicators, annual reporting coverage was 59 countries in 2018, 65 in 2019, 66 in 2020 and 64 in each year from 2021 to 2023. Participation within individual sentinel combinations also changed over time (Figure 3). Europe contributed 26 countries (39.4% of the 66-country study-pathogen panel) and 54.9% of interpretable AST results; the Americas contributed two countries (3.0%) and 1.8%, respectively (Table 2). These percentages describe reporting representation and testing-volume distribution, not population coverage.



l 17 October 2026 from the WHO XMART public API (DATA_/RELAY_GLASS_AMR). Pooling weights by the number of interpretable AST results, so the series describes the reporting countries rather than a fixed population.

Figure 2. Pooled reported resistance by reporting year and sentinel pathogen–antibiotic–specimen combination. Error bars indicate 95% Wilson intervals. The reporting-country composition varies by year. In abbreviated plot labels, EC = E. coli, KP = K. pneumoniae, SA = S. aureus; CARB/Carbapenem denotes meropenem, FQ denotes ciprofloxacin, EC 3GC denotes the WHO third-generation cephalosporin composite, and KP 3GC denotes ceftazidime. BSI and UTI identify blood and urine specimen series, respectively, rather than confirmed patient-level diagnoses. Source graphics carry the original 17 October 2026 extraction label; the numerical re-extraction was performed on 31 October 2026.

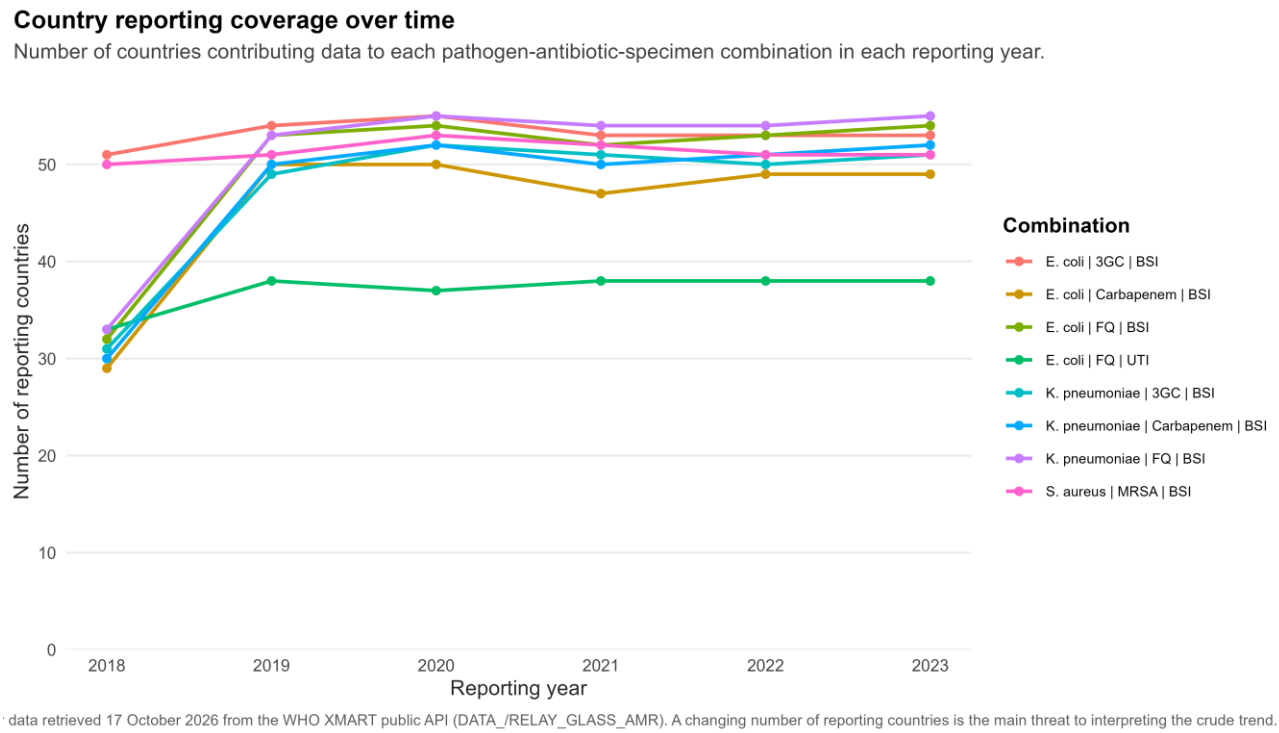


Figure 3. Number of reporting countries for each sentinel pathogen–antibiotic–specimen combination by year, demonstrating variation in surveillance coverage. Abbreviations and exact-agent mapping are defined in Figure 2.

Table 1. WHO GLASS dataset characteristics and sentinel analysis coverage.

Characteristic	Value
Source	WHO Global Antimicrobial Resistance and Use Surveillance System (GLASS)
Public API table	DATA_/RELAY_GLASS_AMR (WHO XMART)
Original extraction	17 October 2026 (re-extracted 31 October 2026)
API indicator records	397,037
Reporting years	2018–2023
WHO regions represented	6
Countries with study-pathogen reports	66
Countries in eight-combination sentinel subset	65
All country-level resistance strata	11,954
Sentinel analysable strata	2,294
AST results, all country-level resistance combinations	87,043,499
AST results, sentinel subset	17,132,532
Resistant AST results, all combinations	12,412,997
Resistant AST results, sentinel subset	3,132,068
Distinct study-pathogen combinations	46
Combinations meeting descriptive eligibility	46
Automated validation checks passed	22 of 22
Descriptive three-pathogen strata	8,824
AST results, descriptive three-pathogen subset	85,654,485

AST, antimicrobial susceptibility test. All country counts refer to reporting countries: the full study-pathogen panel includes 66 countries, the broader eligible-combination subset 66, and the eight sentinel combinations jointly 65. Total AST counts are not necessarily unique isolates or patients.

Table 2. Geographic representation in the full study-pathogen panel.

WHO region	Countries	Share of countries (%)	Share of AST results (%)
Europe	26	39.4	54.9
Eastern Mediterranean	15	22.7	5.8
Western Pacific	10	15.2	33.0
Africa	7	10.6	0.6
South-East Asia	6	9.1	3.9
Americas	2	3.0	1.8

Shares refer to the 66-country study-pathogen panel. Country participation and laboratory testing capacity differ between regions; these are not population-weighted estimates.

Reported resistance: pooled and median-country summaries diverge

Across the eight sentinel combinations the pooled proportion was generally lower than the median country-level proportion (Figure 4). The gap ranged from -25.7 to 0.6 percentage points (median -11.3). The largest divergences occurred where a small number of large reporting countries dominate the denominator: for K. pneumoniae ceftazidime resistance in bloodstream isolates, the pooled proportion was 29.7% against a median country proportion of 55.2%; for E. coli ciprofloxacin resistance in urinary isolates, 18.3% against 43.9%. The single largest country contributed 39.2% of the denominator for the most concentrated combination. The pooled proportion therefore describes a denominator-weighted mixture of national reports and is not the average experience of a participating country; both quantities are legitimate, but they are not interchangeable.

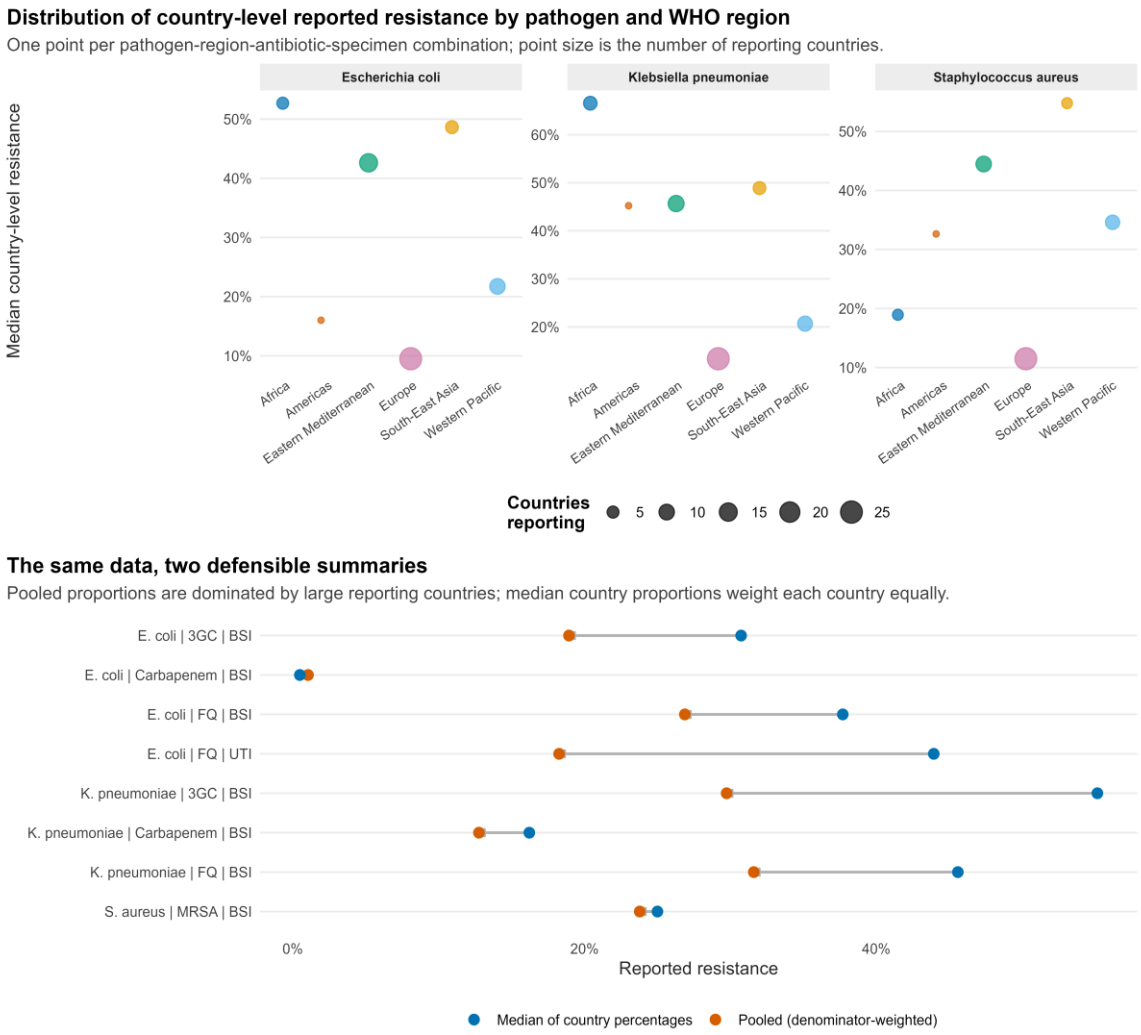


Figure 4. Reported resistance by pathogen and WHO region (upper panel), and pooled versus median country-level resistance proportions (lower panel). The two estimates apply different country weighting. Abbreviations and exact-agent mapping are defined in Figure 2.

Table 3. Selected pathogen–antibiotic–specimen resistance summaries.

Pathogen	Antibiotic	Specimen	Countries	AST results	Resistant results	Resistance (%)
E. coli	Cefepime	Blood	35	801,309	121,976	15.2
E. coli	Cefepime	Urine	29	4,587,758	639,104	13.9
E. coli	Cefotaxime	Blood	40	892,188	184,899	20.7
E. coli	Cefotaxime	Urine	33	6,283,458	1,003,312	16.0
E. coli	Ceftazidime	Blood	49	1,272,357	165,066	13.0
E. coli	Ceftazidime	Urine	36	7,511,497	804,995	10.7
E. coli	Ceftriaxone	Blood	40	709,179	145,914	20.6
E. coli	Ceftriaxone	Urine	30	4,312,800	881,925	20.4
E. coli	Ciprofloxacin	Blood	54	1,170,911	314,704	26.9
E. coli	Ciprofloxacin	Urine	39	11,469,625	2,094,064	18.3
E. coli	Co-trimoxazole	Blood	28	173,593	87,030	50.1
E. coli	Co-trimoxazole	Urine	33	5,461,244	1,406,317	25.8
E. coli	Colistin	Blood	19	97,756	929	1.0
E. coli	Colistin	Urine	13	262,882	3,146	1.2
E. coli	Ertapenem	Blood	36	490,897	9,639	2.0
E. coli	Ertapenem	Urine	21	4,344,322	46,528	1.1
E. coli	Imipenem	Blood	51	993,690	15,219	1.5
E. coli	Imipenem	Urine	34	4,160,520	72,879	1.8
E. coli	Levofloxacin	Blood	27	691,306	188,051	27.2
E. coli	Levofloxacin	Urine	22	4,506,795	1,175,426	26.1
E. coli	Meropenem	Blood	50	1,323,863	13,848	1.0
E. coli	Meropenem	Urine	31	8,087,702	58,112	0.7
E. coli	3rd-gen cephalosporins†	Blood	55	1,090,192	206,421	18.9
K. pneumoniae	Cefepime	Blood	36	373,879	108,494	29.0
K. pneumoniae	Cefepime	Urine	25	942,368	137,720	14.6
K. pneumoniae	Cefotaxime	Blood	40	340,942	103,645	30.4
K. pneumoniae	Cefotaxime	Urine	27	1,137,770	186,697	16.4
K. pneumoniae	Ceftazidime	Blood	52	489,298	145,525	29.7
K. pneumoniae	Ceftazidime	Urine	30	1,375,830	190,914	13.9
K. pneumoniae	Ceftriaxone	Blood	43	255,588	67,173	26.3
K. pneumoniae	Ceftriaxone	Urine	25	842,108	158,334	18.8
K. pneumoniae	Ciprofloxacin	Blood	55	468,843	148,174	31.6
K. pneumoniae	Ciprofloxacin	Urine	34	1,578,619	258,826	16.4
K. pneumoniae	Co-trimoxazole	Blood	28	148,818	79,511	53.4
K. pneumoniae	Co-trimoxazole	Urine	30	929,499	213,718	23.0
K. pneumoniae	Colistin	Blood	25	76,315	5,653	7.4
K. pneumoniae	Colistin	Urine	15	70,096	3,858	5.5
K. pneumoniae	Ertapenem	Blood	34	202,343	44,806	22.1
K. pneumoniae	Ertapenem	Urine	18	663,566	38,377	5.8
K. pneumoniae	Imipenem	Blood	48	424,946	62,940	14.8

Table 3 presents 40 of the 46 eligible descriptive combinations; the remaining six are listed in Supplementary Table S4. The eight primary sentinel models, including K. pneumoniae meropenem and S. aureus methicillin resistance, are reported together in Table 5. Full eligibility and composite-indicator handling are documented in Supplementary Tables S4–S6. Individual drug indicators were not combined with WHO composite indicators. † WHO composite indicator; AST, antimicrobial susceptibility test. Counts summed across antibiotic combinations are AST results and may include repeated testing of the same isolate.

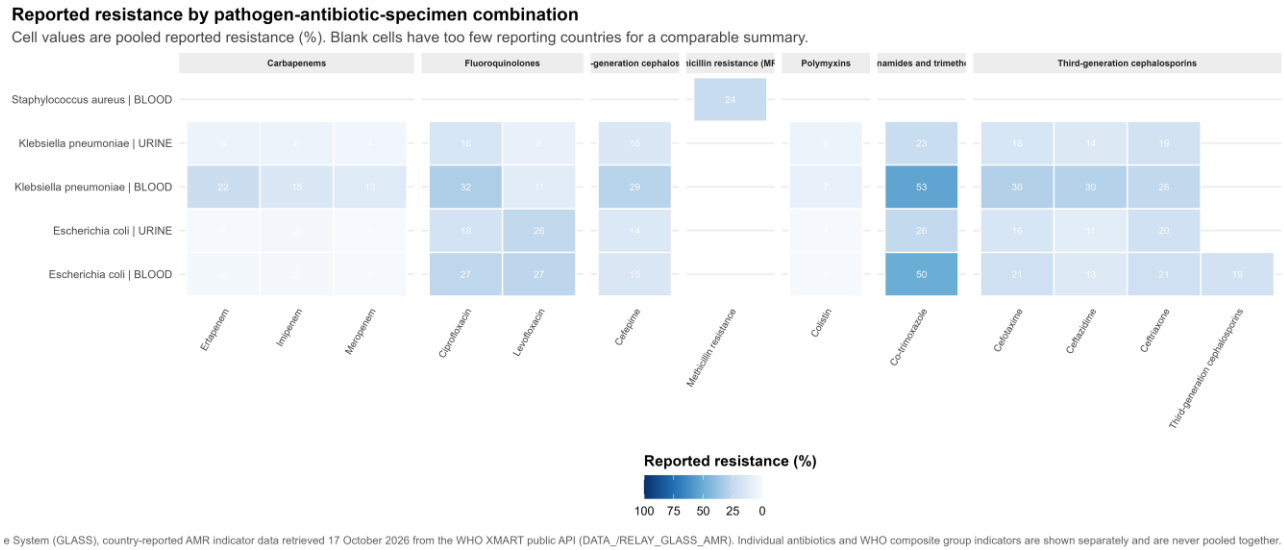


Figure 5. Pooled reported resistance for pathogen–antibiotic–specimen combinations meeting descriptive eligibility criteria. Blank cells indicate insufficient reporting for this display, not zero resistance. Composite antibiotic-group indicators and individual agents are distinct.

Descriptive change over the study period

Between 2018 and 2023, the pooled reported resistance proportion changed by between −1.8 and +15.0 percentage points across sentinel combinations (Figure 2). The largest increases were reported for K. pneumoniae ciprofloxacin resistance (+15.0 percentage points) and K. pneumoniae carbapenem resistance (+9.9 percentage points). E. coli ciprofloxacin resistance in bloodstream isolates declined by 1.8 percentage points in the crude pooled comparison. These comparisons are descriptive rather than model-adjusted. As the reporting-country panel changed over the same period (Figure 3), a portion of each crude difference may reflect which countries reported, rather than a within-country shift in resistance.

Sensitivity of crude change to reporting-country composition

Restricting comparisons to countries reporting in all six years altered the apparent trend in several combinations. The participation contrast, defined as the all-reporter 2018–2023 percentage-point difference minus its balanced-panel counterpart, ranged from −9.2 to +0.4 percentage points (median absolute difference 1.5 percentage points). It is a descriptive estimate of reporting-composition sensitivity, not the causal effect of participation (Supplementary Tables S16–S17). For E. coli ciprofloxacin resistance in bloodstream isolates, the crude pooled proportion declined by 1.8 percentage points, whereas among the 28 countries reporting in each year it increased by 7.4 percentage points; the resulting composition contrast was −9.2 percentage points. Country membership was determined separately for each sentinel combination. This discrepancy cannot distinguish selection into surveillance from changes in laboratory practice, testing indications or case mix. Country-specific trends were heterogeneous: for E. coli third-generation cephalosporin resistance, 27 countries had an increasing fitted slope and 28 a decreasing slope (median model-implied change −0.2 percentage points). Changes in the pooled series therefore should not be interpreted as uniform within-country biological changes.

Model diagnostics

The reported Pearson dispersion statistics ranged from 3.12 to 45.90 across the eight combinations, indicating extra-binomial variation under the diagnostic specification. Country-random-intercept intraclass correlation estimates ranged from 0.18 to 0.65. The diagnostic outputs cover convergence, variance-component tests, alternative residual degrees-of-freedom definitions, calibration and beta-binomial comparisons (Supplementary Tables S7–S11). The primary models added observation-level random effects to accommodate extra-binomial heterogeneity. The plain binomial country random-intercept model yielded excessively narrow intervals in several comparisons. Including the observation-level random effect altered the statistical conclusion in five of eight combinations (Table 4). The adjustment addresses unmodelled variance but not systematic temporal confounding.

Table 4. Effect of overdispersion adjustment on the temporal trend inference.

Combination	Country-only model trend	Country-only P	Country + observation model trend	Model P	Changed?
E. coli / 3GC composite / Blood	Decrease	0.004	Not significant	0.968	Yes
E. coli / meropenem / Blood	Increase	<0.001	Increase	<0.001	No
E. coli / ciprofloxacin / Blood	Decrease	<0.001	Not significant	0.190	Yes
E. coli / ciprofloxacin / Urine	Decrease	<0.001	Not significant	0.344	Yes
K. pneumoniae / ceftazidime / Blood	Increase	<0.001	Not significant	0.253	Yes
K. pneumoniae / meropenem / Blood	Increase	<0.001	Increase	<0.001	No
K. pneumoniae / ciprofloxacin / Blood	Increase	<0.001	Increase	<0.001	No
S. aureus / methicillin resistance / Blood	Decrease	<0.001	Not significant	0.685	Yes

The country-only comparator includes a country random intercept; the primary model includes country and observation-level random intercepts. Table P values are unadjusted. "Not significant" identifies a nonsignificant annual association, not proof of no change. Blood and urine denote specimen sources. E. coli 3GC is the WHO third-generation cephalosporin composite; the K. pneumoniae third-generation cephalosporin endpoint is ceftazidime.

Five of eight combinations changed from a statistically significant annual association in the country-only comparator to a nonsignificant association after the observation-level variance component was added. Statistical significance in the country-only models therefore depended materially on the variance specification. After accounting for overdispersion, three of eight code-defined combinations showed significant increases in reported resistance and none showed a significant decrease (Table 5; Figure 6). These same three increases remained significant after Holm correction across all eight tests (adjusted P = 2.34×10^{-13}, 8.14×10^{-9} and 4.58×10^{-7} for K. pneumoniae meropenem, E. coli meropenem and K. pneumoniae ciprofloxacin, respectively; Supplementary Table S19).

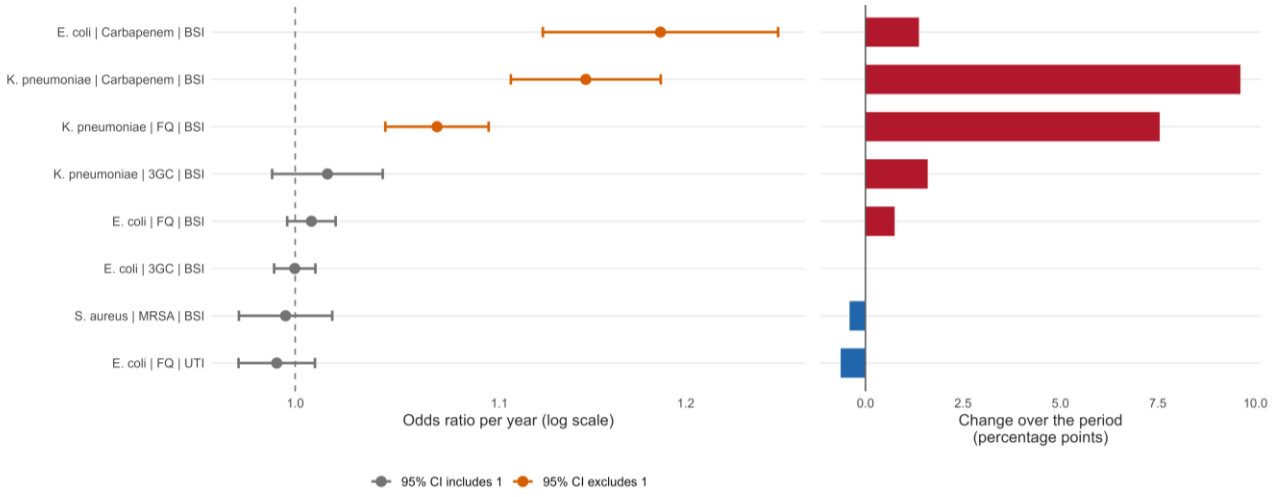


Figure 6. Estimated annual resistance trend from the overdispersion-adjusted multilevel binomial model: odds ratio per reporting year with 95% Wald confidence interval (left) and reference-based five-year percentage-point change (right). Abbreviations and exact-agent mapping are defined in Figure 2.

Table 5. Overdispersion-adjusted multilevel models for the eight sentinel combinations.

Combination	Strata	Country count	Diagnostic dispersion	OR/year (95% CI)	p	Δ (pp)
E. coli / meropenem / Blood	274	50	5.32	1.1860 (1.1226–1.2529)	<0.001	1.4
K. pneumoniae / meropenem / Blood	285	52	9.56	1.1453 (1.1060–1.1861)	<0.001	9.6
K. pneumoniae / ciprofloxacin / Blood	304	55	8.96	1.0684 (1.0430–1.0946)	<0.001	7.5
K. pneumoniae / ceftazidime / Blood	284	52	7.17	1.0152 (0.9893–1.0417)	0.253	1.6
E. coli / ciprofloxacin / Blood	298	54	5.89	1.0076 (0.9963–1.0191)	0.190	0.8
E. coli / 3GC composite / Blood	319	55	3.12	0.9998 (0.9902–1.0095)	0.968	0.0
S. aureus / methicillin resistance / Blood	308	53	5.03	0.9955 (0.9741–1.0174)	0.685	-0.4

Combination	Strata	Country count	Diagnostic dispersion	OR/year (95% CI)	p	Δ (pp)
E. coli / ciprofloxacin / Urine	222	39	45.90	0.9914 (0.9739–1.0093)	0.344	-0.6

OR, annual conditional odds ratio; CI, 95% confidence interval; Δ (pp), reference-based five-year absolute change calculated from the annual OR and the combination-specific pooled reference proportion. The dispersion column reproduces the reported Pearson diagnostic statistics; these are not effect estimates. Model-specific calculation details, variance components and fit diagnostics are provided in Supplementary Tables S7–S11. Table P values are unadjusted; Holm-adjusted values are reported in the text and Supplementary Table S19. Blood and urine indicate specimen types. The E. coli third-generation cephalosporin endpoint is a WHO composite; K. pneumoniae ceftazidime is an individual-agent endpoint. Increasing reported resistance was observed for K. pneumoniae meropenem (annual OR 1.1453; 95% CI 1.1060–1.1861; reference-based five-year change +9.6 percentage points), E. coli meropenem (OR 1.1860; 95% CI 1.1226–1.2529; +1.4 percentage points), and K. pneumoniae ciprofloxacin (OR 1.0684; 95% CI 1.0430–1.0946; +7.5 percentage points). These estimates refer to the specific agent and specimen combination, rather than all antibiotics in the corresponding class. No statistically significant annual association was detected for the E. coli third-generation cephalosporin composite (OR 0.9998; 95% CI 0.9902–1.0095), K. pneumoniae ceftazidime (1.0152; 0.9893–1.0417), E. coli ciprofloxacin in blood (1.0076; 0.9963–1.0191), E. coli ciprofloxacin in urine (0.9914; 0.9739–1.0093), or S. aureus methicillin resistance (0.9955; 0.9741–1.0174). Nonsignificance does not establish absence of change. An annual odds ratio describes relative change in the odds of reported resistance; a reference-based percentage-point change additionally depends on the selected starting proportion. E. coli meropenem resistance had an annual OR of 1.1860 but a reference-based five-year increase of 1.4 percentage points because its pooled reference proportion was approximately 1.0%. This transformed effect is distinct from the observed 2018–2023 pooled difference. Neither quantity measures treatment failure or population-level resistance prevalence.

Regional differences

With observation-level random effects included in both nested year-by-region models, exploratory likelihood-ratio tests were significant for three sentinel combinations: E. coli blood ciprofloxacin ($P = 5.41 \times 10^{-7}$), K. pneumoniae blood ciprofloxacin ($P = 3.13 \times 10^{-6}$), and S. aureus blood methicillin resistance ($P = 0.039$). The remaining five interactions were not statistically significant under this specification. The Americas was excluded from all interaction tests because of sparse participation; Africa was additionally excluded for E. coli meropenem. Region-specific estimates, country counts and exclusions are provided in Supplementary Tables S14–S15. These exploratory P values were not adjusted for multiple interaction tests. The median proportion of country-level percentage variance attributed to between-region differences was 29.3% across combinations. Thus, within-region variation accounted for the larger share on average across the combinations; this median summary does not establish that within-region variation exceeded between-region variation for every endpoint. Region-specific descriptive series are shown in Figure 7.

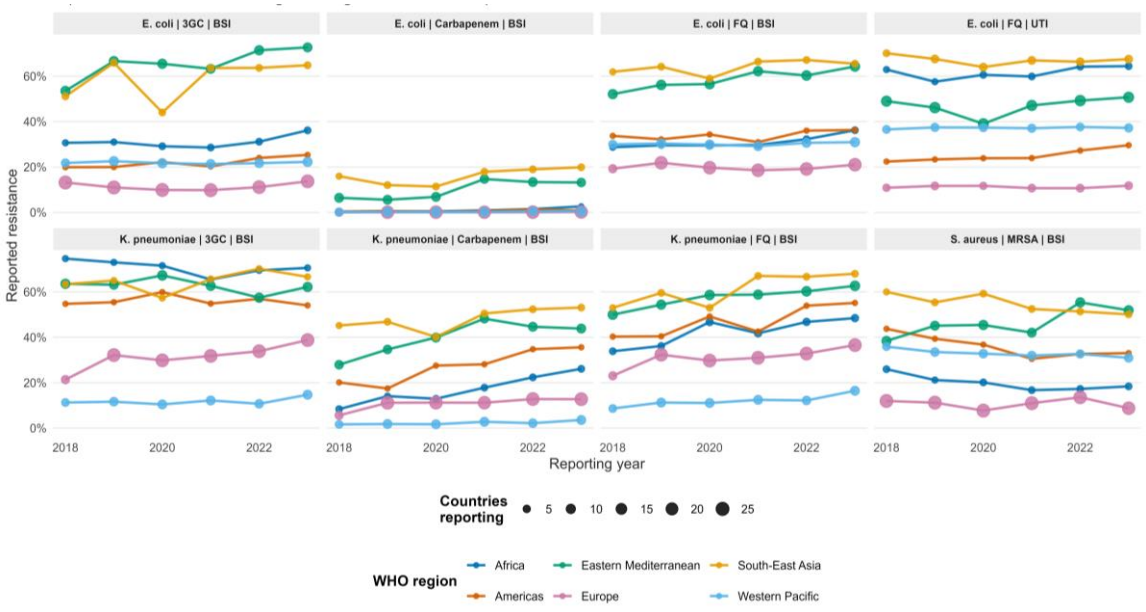


Figure 7. Pooled reported resistance by WHO region and year for the eight sentinel combinations. Point size denotes number of reporting countries; regional estimates are not necessarily representative. Abbreviations and exact-agent mapping are defined in Figure 2.

Sensitivity analyses

All three primary increasing associations retained their direction and statistical significance in the seven non-primary scenarios (S1–S7). The five nonsignificant primary comparisons were less stable: agreement with the primary inference category ranged from 4/7 (57.1%) to 6/7 (85.7%) scenarios (Tables 6–7; Supplementary Table S12). Agreement across these related analyses measures sensitivity to selection and specification; it is not independent replication or evidence that a nonsignificant trend is zero.

Table 6. Stability of the primary trend classification across alternative analyses.

Combination	Primary inference	Agreement	Agreement (%)	OR range
E. coli / meropenem / Blood	Increase	7/7	100.0	1.1636–1.3562
K. pneumoniae / meropenem / Blood	Increase	7/7	100.0	1.1243–1.1943
K. pneumoniae / ciprofloxacin / Blood	Increase	7/7	100.0	1.0544–1.1268
S. aureus / methicillin resistance / Blood	No trend detected	4/7	57.1	0.9516–1.0420
E. coli / ciprofloxacin / Blood	No trend detected	5/7	71.4	1.0020–1.0201
K. pneumoniae / ceftazidime / Blood	No trend detected	5/7	71.4	1.0113–1.0626
E. coli / 3GC composite / Blood	No trend detected	6/7	85.7	0.9970–1.0754
E. coli / ciprofloxacin / Urine	No trend detected	6/7	85.7	0.9898–1.0492

Agreement denotes agreement with the code-defined primary inference category in each of the seven non-primary scenarios. For nonsignificant primary findings, an alternative scenario can change statistical significance without reversing the point-estimate direction. The complete per-scenario ORs, 95% CIs, P values and fit diagnostics are in Supplementary Table S12.

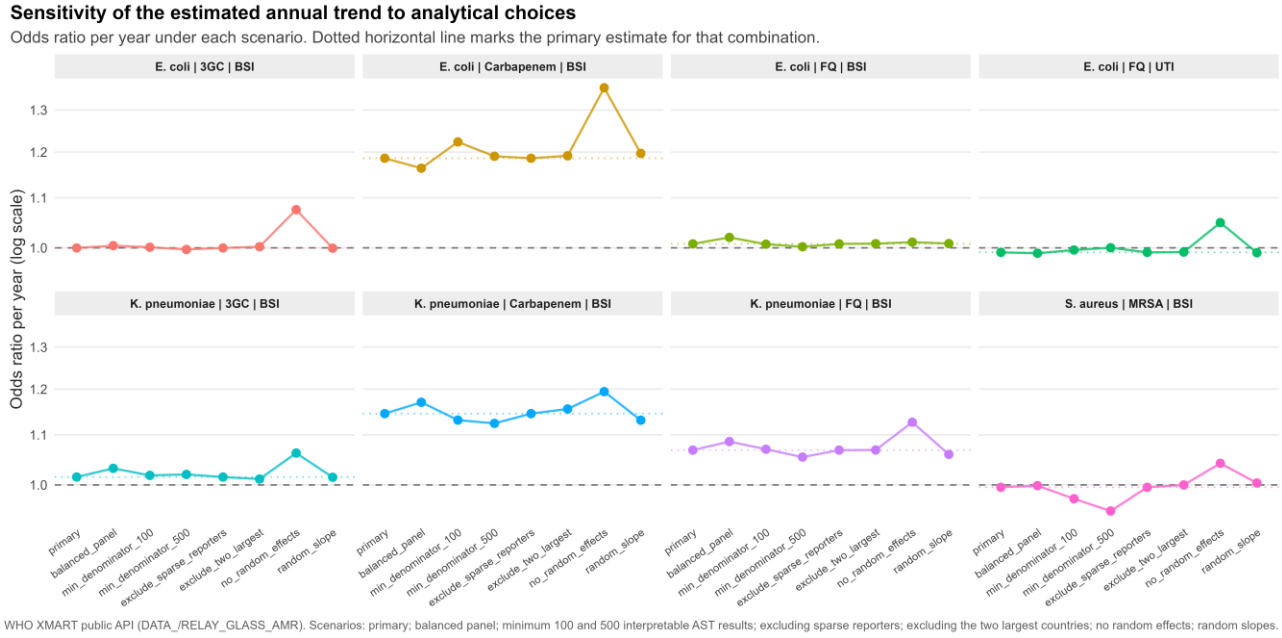


Figure 8. Sensitivity of estimated annual trends to alternative modelling and inclusion choices. Each panel displays annual odds ratios across scenarios; dotted coloured lines mark the primary estimates and the dashed horizontal reference at OR = 1 denotes no annual association. Abbreviations and exact-agent mapping are defined in Figure 2.

Omitting random effects changed the greatest number of inference categories (five of eight combinations). The ≥500-denominator sensitivity restriction altered two of eight. These differences reinforce that inference for the nonsignificant combinations is sensitive to the assumed variance structure; they are not independent confirmations of primary-model significance.

In the targeted leave-one-country-out refits, the largest absolute shift in an annual odds ratio was 0.0098. Excluding the two largest-denominator countries changed none of the primary inference categories. These checks did not identify a dominant influence among the countries examined; they did not evaluate removal of every reporting country.

Table 7. Sensitivity scenarios ranked by agreement with the primary model.

Scenario	Primary inference retained (%)	Combinations changed
S6: No random effects	37.5	5
S3: Minimum denominator 500	75.0	2
S1: Balanced panel	87.5	1
S2: Minimum denominator 100	87.5	1
S4: Exclude sparse reporters	100.0	0
S5: Exclude two largest countries	100.0	0
S7: Country random slope	100.0	0

"Changed" indicates that the alternative analysis produced a different inference category from the primary analysis. Agreement proportions are based on eight sentinel combinations; 3/8 = 37.5%, 6/8 = 75.0%, 7/8 = 87.5%, and 8/8 = 100%.

Geographical patterns and data gaps

Reported resistance at the end of the study period varied widely between countries (Figure 9), and reporting completeness was geographically patterned (Figure 10). For the E. coli third-generation cephalosporin composite in blood, 44 countries contributed data in all six years, within the 55-country combination panel reported in Table 5. Countries with no report are shown separately in grey on the maps and are not represented as having zero resistance.

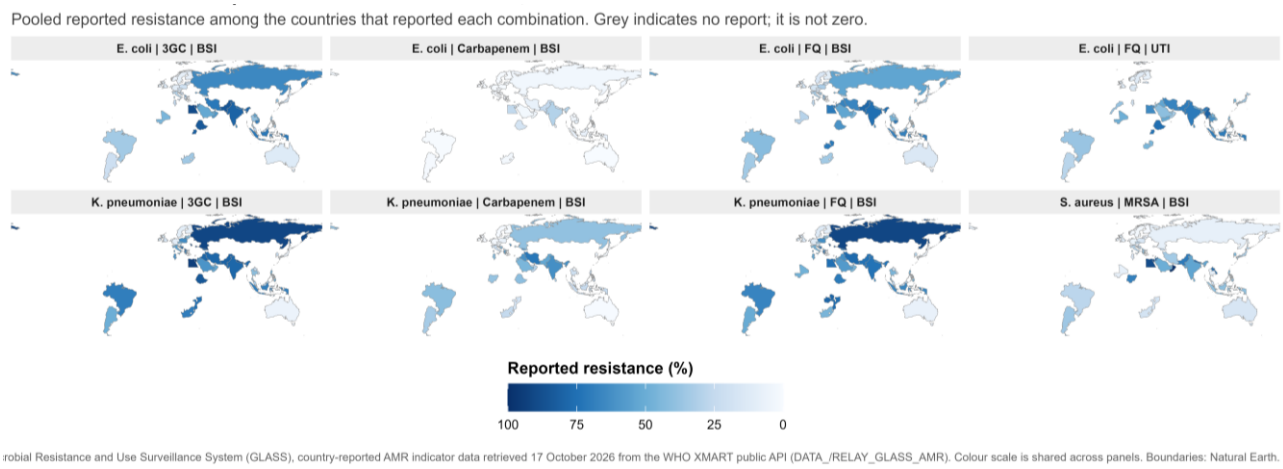


Figure 9. Geographic distribution of reported resistance at the end of the observation period. All panels share a colour scale; grey indicates no report rather than zero resistance. Boundaries: Natural Earth. Abbreviations and exact-agent mapping are defined in Figure 2.

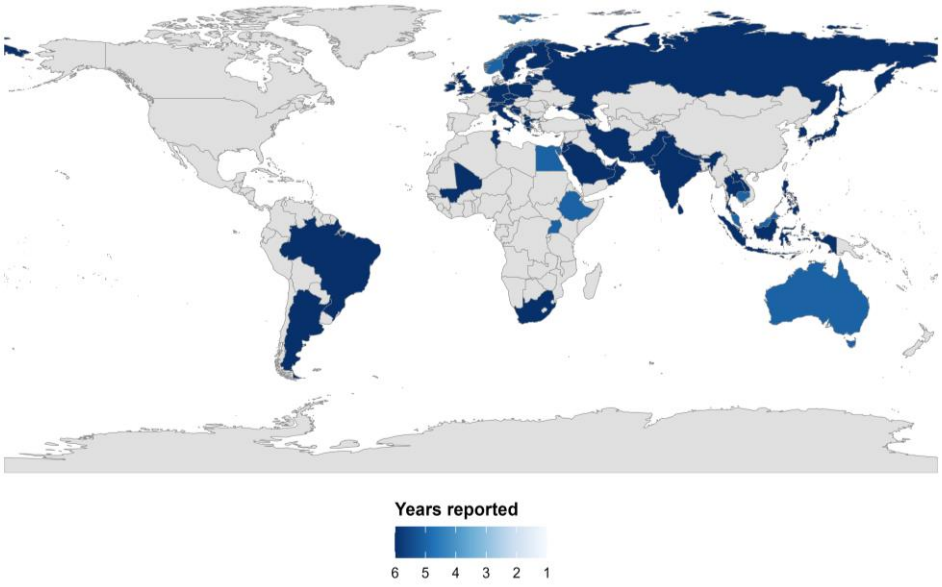


Figure 10. Reporting completeness for E. coli third-generation cephalosporin resistance in bloodstream isolates, shown as the number of years with data during 2018–2023. Grey denotes countries with no report.

DISCUSSION

Principal findings

This analysis used WHO GLASS country-reported AMR indicators for 2018–2023. The broader three-pathogen descriptive subset comprised 8,824 strata and 85,654,485 interpretable AST results from 66 countries; the primary sentinel subset comprised 2,294 strata and 17,132,532 interpretable AST results from 65 countries. These totals count AST results across combinations rather than unique patients or isolates. Three findings are central to interpretation.

First, reported meropenem resistance increased in K. pneumoniae (annual OR 1.1453) and E. coli (1.1860), and reported ciprofloxacin resistance increased in K. pneumoniae (1.0684). All three associations remained significant after Holm adjustment and across the seven alternative scenarios. Targeted country-exclusion analyses supported stability among the countries examined, while the scope of those analyses precludes a claim about the influence of every reporting country. Second, no statistically significant primary temporal association was detected for the E. coli third-generation cephalosporin composite, K. pneumoniae ceftazidime, E. coli ciprofloxacin in blood or urine, or S. aureus methicillin resistance. For the E. coli composite, the crude pooled increase was 7.7 percentage points, whereas the fitted primary association was close to the null. Country-specific fitted slopes were also heterogeneous: 27 increased and 28 decreased. The pooled comparison and multilevel association therefore describe different aspects of the reported data.

Third, crude resistance changes were sensitive to reporting-country composition. For E. coli ciprofloxacin in blood, the all-reporter pooled comparison declined by 1.8 percentage points, whereas the balanced panel increased by 7.4 percentage points, giving a contrast of −9.2 percentage points. This illustrates how participation restrictions can change the magnitude and direction of descriptive comparisons. It does not identify the causal contribution of surveillance participation or exclude concurrent changes in testing and case mix.

Interpretation of temporal patterns

The increases in carbapenem resistance are consistent with the trajectory described in the clinical literature, in which carbapenemase-producing Enterobacterales have progressively disseminated and carbapenem-resistant K. pneumoniae has become a critical-priority pathogen (6,8,9). The magnitude should nonetheless be read carefully. For E. coli, the reference prevalence was 1.0%, so a strong relative increase corresponds to an absolute change of +1.4 percentage points over the period. Both scales matter clinically: a small absolute increase at a very low baseline may still signal emerging carbapenem resistance in a pathogen for which carbapenems are a treatment option for susceptible infections (5,6).

For the E. coli third-generation cephalosporin composite, a nonsignificant primary annual association does not establish stable resistance. The multilevel model estimates a conditional association among reported country–year strata while allowing persistent country differences and extra-binomial variability. A country random intercept alone does not establish a purely within-country estimand or remove time-varying surveillance differences. The pooled series and fitted association use different weighting and modelling assumptions; their divergence is compatible with reporting-composition sensitivity but cannot be attributed exclusively to that mechanism (22,23).

The absence of a detectable trend in methicillin resistance is consistent with the plateau reported from several high-income surveillance systems following two decades of decline (42), but the present data cannot distinguish a genuine plateau from offsetting national trends, and S. aureus methicillin resistance was the combination with the lowest scenario agreement (57.1%).

Differences between pathogens

The three pathogens showed distinct patterns. Meropenem resistance increased in K. pneumoniae and E. coli, while ciprofloxacin resistance increased significantly in K. pneumoniae but not in E. coli under the primary specification. Among blood AST results, the pooled ciprofloxacin-resistant proportion was 31.6% for K. pneumoniae and 26.9% for E. coli. These comparisons concern the specific reported agent–specimen combinations. Direct clinical risk comparisons are unwarranted because countries, laboratory participation, tested populations and testing practices differed.

Geographical variation

Regional comparisons must be interpreted with explicit reference to the uneven composition of the panel. Europe contributed 26 countries and 54.9% of all interpretable AST results, while the least-represented region contributed 2

countries and 1.8% of interpretable AST results. Pooled regional values are correspondingly dominated by whichever countries test the most isolates; for most combinations a single region supplied more than 40% of the denominator. The median between-region share of country-level percentage variance was 29.3%, indicating that substantial heterogeneity remained within regions. Adding the observation-level variance component yielded significant exploratory year-by-region interactions in three of eight combinations. The S. aureus interaction, with P = 0.039, warrants particular caution because these interaction tests were not adjusted for multiplicity. Sparse representation, especially in the Americas, and unequal AST denominators preclude extrapolation to entire regional populations (Supplementary Tables S14–S15).

Comparison with published literature

The reported increases in carbapenem resistance are directionally consistent with model-based WHO estimates for the same period (14) and with earlier forecasts for invasive E. coli and K. pneumoniae isolates (29). They also align with multi-country prediction work that reported income-related gradients in third-generation cephalosporin and carbapenem resistance (28). Where this study differs from the closest prior multi-country GLASS analysis is in design: that analysis was cross-sectional and related resistance to antimicrobial consumption for two pathogens only (27). The present study is longitudinal, covers three pathogens, models the binomial count structure directly and quantifies participation sensitivity. The study does not supersede WHO's model-based adjusted estimates, which address a different and clinically important question using Bayesian methods that adjust for population structure and surveillance coverage (14,26). WHO has also published a national data-completeness scoring framework, so reporting completeness is an established concern in GLASS rather than a novel observation (14). The contribution here is complementary: a transparent analysis of the reported indicator values with an explicit, quantified account of how far conclusions depend on participant composition.

Clinical relevance and implications for antimicrobial stewardship

If the identified increases are confirmed in representative surveillance, they may inform local stewardship and infection-prevention priorities. This analysis alone does not demonstrate treatment failure, altered therapeutic effectiveness, or the benefit of any intervention; antibiotic selection must remain grounded in local susceptibility data, clinical guidelines and patient-level considerations.

The participation analysis supports presenting stable-panel comparisons alongside all-reporter pooled series. Differences between those summaries reveal sensitivity to reporting composition, although consistently reporting countries can themselves be selective. Neither comparison alone separates changes in participation from evolving laboratory practice or patient case mix. Stewardship communication should therefore state the contributing country panel and denominator, and avoid treating a change in the pooled percentage as an established biological change (14,21).

The nonsignificant methicillin-resistance association does not establish a plateau or demonstrate that GLASS cannot detect improvement. Its interpretation depends on the uncertainty of the fitted estimate, heterogeneous national trajectories, the six-year observation period and sensitivity to alternative specifications. A longer or more consistently reported series may improve interpretation, but this analysis did not evaluate the power of alternative surveillance designs.

Strengths and limitations

Strengths include use of published resistance numerators and interpretable-AST denominators rather than reconstruction from percentages; separation of country observations from WHO regional aggregates; a fixed sentinel panel defined in the analytical code; explicit modelling of country clustering and extra-binomial heterogeneity; reporting of every selection and specification scenario, including those that disagreed with the primary inference; and an archived computational workflow with 22 automated validation checks. The primary estimates were reproduced using the 31 October retrieval. These strengths improve analytical transparency without establishing prospective prespecification or national representativeness.

Voluntary, unbalanced participation. Countries differ in the pathogen–antibiotic combinations and years they report. The differences between all-reporter and balanced-panel comparisons show material sensitivity to these restrictions. A balanced panel holds country membership constant but does not hold AST-volume weights, laboratory participation or case mix constant. Countries reporting consistently may differ systematically from intermittent and nonreporting countries, so the panel restriction does not remove selection bias.

No national representativeness claim. GLASS does not establish that the reporting laboratories are nationally representative for every country, and neither do these data. Country values describe what was reported.

Denominators reflect testing capacity. The number of isolates with an interpretable AST result is a function of laboratory capacity and testing practice as well as of infection incidence. Trends in testing can therefore generate apparent trends in resistance, and this cannot be fully separated with aggregate data.

Residual temporal confounding and dependence. A country random intercept allows stable differences between countries, and a random-slope specification examined heterogeneous temporal slopes. Neither specification removes time-varying changes in testing policy, laboratory participation or patient composition. The primary model does not include an explicit residual serial-correlation structure. Consequently, the annual coefficient remains a model-dependent temporal association in the reported data rather than a causal or purely within-country effect.

Aggregate data. No age, sex, infection origin (community versus hospital) or outcome information is available, so no adjustment for case mix is possible and no patient-level inference is warranted. Ecological interpretation. Country-level proportions cannot be used to make statements about individual patients (23).

Specimen-specific combinations. Bloodstream and urinary isolates were analysed separately; results for one specimen type do not carry over to the other.

Composite antibiotic-group indicators. For *E. coli*, WHO publishes a composite third-generation cephalosporin group alongside the constituent agents. These were kept separate; the composite and the individual agents do not describe identical isolate sets.

Multiple comparisons. Holm adjustment was applied across the eight sentinel annual trend tests, and all three initially significant increases remained significant. Exploratory regional and descriptive contrasts were not confirmatory; the regional interaction P values were not multiplicity-adjusted. Stability across sensitivity scenarios does not substitute for multiple-testing control or independent replication.

Sensitivity analysis scope. Leave-one-out influence was restricted to the five largest-denominator countries and the five sparsest reporters per combination rather than all countries, for computational reasons; influence from mid-sized countries cannot be excluded.

Single age-standardisation strategy not possible. Age-standardised analyses, which WHO applies to testing rates, were not attempted here because the indicator table carries no age dimension.

Version dependence. The WHO XMART relay is a live source. The originally downloaded 17 October 2026 raw CSV is unavailable for byte-level verification; a fresh retrieval on 31 October 2026 reproduced all archived numerical estimates. The new raw data and SHA-256 checksum are preserved, but future retrievals may differ as WHO updates submissions.

Additional modelling limitations. Observation-level random intercepts accommodate extra-binomial variability without identifying its causes. Some nonsignificant combinations changed inference under alternative selection or variance specifications. Annual effects assume linear change on the log-odds scale across six years. The reference-based absolute changes are transformations evaluated at pooled proportions, not observed endpoint differences or population-standardised predictions. Exploratory region-specific interactions excluded sparsely represented regions and were not corrected for multiplicity. Model-based uncertainty therefore does not capture every source of surveillance selection and measurement bias.

Future research directions

Four research directions follow. First, suitable de-identified individual-level surveillance data, within the governance framework described in the revised GLASS manual, could support case-mix adjustment and specimen-level analyses beyond these aggregates (13). Second, linkage to national testing-volume, laboratory-participation and capacity data could help examine the denominator-dependent component of apparent change. Third, reporting-completeness indicators building on WHO's framework could accompany every temporal estimate (14). Fourth, joint modelling of resistance and reporting participation could examine their relationship under explicit assumptions, while recognising that informative missingness cannot generally be resolved from observed aggregate data alone.

CONCLUSION

In this analysis of WHO GLASS country-reported AMR data for 2018–2023, 8,824 eligible-combination descriptive strata were distinguished from the 2,294 strata in eight primary sentinel models. Reported meropenem resistance increased significantly in K. pneumoniae and E. coli, and reported ciprofloxacin resistance increased significantly in K. pneumoniae. These three findings were robust to seven sensitivity scenarios and Holm correction, but do not establish population-level resistance changes. The remaining five sentinel combinations had no statistically significant primary temporal association; these findings do not establish stable resistance. Crude pooled comparisons were sensitive to reporting-country composition, and exploratory regional heterogeneity was detected in three combinations under the overdispersion-aware specification. Transparent reporting of the country panel, testing denominators, exact antibiotic endpoints and model uncertainty is needed when interpreting multinational surveillance trends.

DECLARATIONS

Author Contributions:	**Concept: SK; Design: SZ, MB; Data Collection: GY, FT, SK; Analysis: SK, GY,FT**
Ethical Approval:	This secondary analysis used publicly available WHO country-level aggregate surveillance data. It involved no recruitment, intervention, individual-level records or patient-identifiable information. Individual informed consent was not applicable. Data use remains subject to WHO's terms of use.
Informed Consent:	Not Applicable
Conflict of Interest:	The authors declare no conflict of interest.
Funding:	No external funding was received for this study.
Data Availability:	WHO GLASS data were retrieved from the XMART public API (DATA_/RELAY_GLASS_AMR; https://xmart-api-public.who.int/). The 31 October 2026 snapshot, cleaned datasets, analysis scripts, package lockfile, SHA-256 provenance records, model outputs and 22 automated validation results are included in the accompanying reproducibility archive. The original 17 October 2026 raw CSV was not retained; numerical equivalence of the re-extraction was documented against the original archived analytical outputs. Code availability. The reproducibility materials comprise run_all.R, renv.lock, API retrieval and validation scripts, saved model outputs, diagnostic results, figure-generation code and the complete sensitivity export. The archived snapshot is the reference dataset for replication; rerunning a live retrieval can produce a different source version.
Acknowledgments:	None.
AI Declaration:	Generative AI tools were used solely for language and grammatical refinement. The authors verified the final manuscript and remain fully responsible for its accuracy, integrity, and scientific content.

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