RESEARCH PAPER

GLOBAL AMR TRENDS: Linking Resistance Patterns with Antibiotic Consumption & Stewardship Interventions (Time-Series Analysis)

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ABSTRACT

Background:

Antimicrobial resistance (AMR) has emerged as a critical global public health emergency, threatening the effective treatment of infectious diseases and increasing morbidity, mortality, and healthcare costs worldwide. Inappropriate and excessive antibiotic consumption in both hospital and community settings is a major driver of resistance development, while antimicrobial stewardship (AMS) interventions have been introduced to optimize antibiotic use. However, global quantitative evidence linking antibiotic consumption, stewardship efforts, and resistance trends over time remains limited.

Objectives:

The primary objective of this study was to evaluate global trends in antimicrobial resistance and their temporal association with antibiotic consumption. Secondary objectives were to assess the impact of antimicrobial stewardship interventions on resistance trajectories and to explore variations across geographic regions and healthcare settings.

Methods:

A systematic review and meta-analysis were conducted in accordance with PRISMA 2020 guidelines. PubMed/MEDLINE, Scopus, and Web of Science were searched from January 2000 onward. Time-series, interrupted time-series, and longitudinal surveillance studies reporting antimicrobial resistance outcomes in relation to antibiotic consumption and/or stewardship interventions were included. Random-effects meta-analysis, meta-regression, and pooled interrupted time-series analyses were performed to quantify resistance trends, consumption–resistance relationships, and stewardship effects.

Results:

A total of 140 studies met the inclusion criteria, with 96 studies included in the quantitative synthesis. Global resistance trends showed a consistent increase, particularly among Gram-negative pathogens. Meta-regression analyses demonstrated a significant positive association between antibiotic consumption and resistance, especially for broad-spectrum antibiotics. Stewardship interventions were associated with significant attenuation or reversal of rising resistance trends, with stronger effects observed in hospital settings.

Conclusions:

Antibiotic consumption is a measurable and modifiable driver of antimicrobial resistance, and antimicrobial stewardship interventions can effectively alter resistance trajectories. Time-series–based meta-analytic evidence underscores the need for strengthened global stewardship policies, optimized antibiotic use, and harmonized surveillance to curb the escalating AMR crisis.

Keywords: Global antimicrobial resistance; Antibiotic consumption patterns; Antimicrobial stewardship interventions; Resistance trend analysis; Global AMR surveillance and policy.

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1. INTRODUCTION

1.1 Global Burden of Antimicrobial Resistance

Antimicrobial resistance (AMR) has emerged as one of the most critical threats to global public health, undermining decades of progress in the prevention and treatment of infectious diseases. The widespread and often inappropriate use of antibiotics in human health, animal husbandry, and agriculture has accelerated the selection of resistant pathogens, rendering many first-line and even last-resort antimicrobials increasingly ineffective. As a result, common infections that were once easily treatable now pose significant clinical challenges, leading to prolonged illness, higher risk of complications, and increased mortality. AMR is therefore no longer a future concern but a present-day public health and economic crisis affecting health systems worldwide.

The burden of AMR is reflected in rising mortality and morbidity across diverse clinical settings. Drug-resistant bacterial infections contribute substantially to preventable deaths, particularly in cases of sepsis, pneumonia, urinary tract infections, and bloodstream infections. Patients infected with resistant organisms often experience longer hospital stays, delayed recovery, and limited therapeutic options, which further increases the risk of adverse outcomes. From an economic perspective, AMR imposes a heavy financial burden on healthcare systems through increased hospitalization costs, the need for expensive second- or third-line antibiotics, additional diagnostic testing, and intensified infection control measures. Indirect costs, such as loss of productivity due to prolonged illness or premature death, further amplify the societal impact of AMR.

Importantly, the burden of AMR is not evenly distributed across the globe. Low- and middle-income countries (LMICs) bear a disproportionate share of AMR-related morbidity and mortality due to high infectious disease prevalence, limited access to diagnostics, suboptimal antimicrobial regulation, and constrained healthcare infrastructure. In contrast, high-income countries often have more robust surveillance systems, stronger antimicrobial stewardship programs, and greater access to novel therapies, although inappropriate antibiotic use remains a concern even in these settings. These disparities highlight AMR as both a biomedical and equity issue, underscoring the urgent need for coordinated global action to strengthen surveillance, optimize antibiotic use, and reduce inequalities in healthcare capacity.

1.2 Antibiotic Consumption as a Driver of AMR

Antibiotic consumption is widely recognized as a principal driver of antimicrobial resistance (AMR), with both overuse and misuse exerting strong selective pressure on bacterial populations. In hospital settings, inappropriate prescribing practices—such as empirical use of antibiotics without microbiological confirmation, prolonged treatment durations, and inadequate de-escalation—contribute significantly to the emergence and spread of resistant pathogens. Intensive care units and tertiary hospitals, where critically ill patients frequently receive broad-spectrum and combination therapies, represent particularly high-risk environments for the development of multidrug-resistant organisms. Similarly, in community settings, unnecessary antibiotic use for self-limiting viral infections, over-the-counter availability in some regions, and poor patient adherence further accelerate resistance development.

The choice between broad-spectrum and narrow-spectrum antibiotics plays a crucial role in shaping resistance patterns. Broad-spectrum agents, while valuable for initial empirical therapy, exert pressure on a wide range of bacterial species, disrupting normal microbiota and facilitating the selection of resistant strains. Their excessive or prolonged use has been closely linked to rising resistance in key pathogen groups, including Enterobacterales and non-fermenting Gram-negative bacteria. In contrast, narrow-spectrum antibiotics, when guided by culture and susceptibility data, target specific pathogens and are associated with a lower ecological impact. However, underutilization of narrow-spectrum agents due to diagnostic limitations or prescribing habits remains a persistent challenge in both high-income and resource-limited settings.

At the global level, antibiotic consumption is commonly quantified using the Defined Daily Dose (DDD) per 1,000 inhabitants per day, a standardized metric recommended by international surveillance frameworks. This measure enables comparisons across countries and time periods, revealing substantial variation in antibiotic use worldwide. Recent global analyses have demonstrated an overall increase in antibiotic consumption, driven largely by rising use in low- and middle-income countries, where expanding access to antimicrobials is often accompanied by weak regulatory oversight. In contrast, some high-income countries have reported stabilization or modest declines in consumption following the implementation of antimicrobial stewardship policies, supported by guidance from organizations such as the World Health Organization. These contrasting trends underscore the complex relationship between access, regulation, and resistance, highlighting the need to balance appropriate antibiotic availability with judicious use to curb the global AMR crisis.

1.3 Antimicrobial Stewardship Interventions

Antimicrobial stewardship (AMS) refers to a coordinated set of strategies designed to promote the appropriate use

of antimicrobial agents in order to improve patient outcomes, reduce antimicrobial resistance (AMR), and minimize unnecessary healthcare costs. The core goals of AMS include optimizing antibiotic selection, dosing, route, and duration of therapy while ensuring timely and effective treatment of infections. By reducing inappropriate prescribing and limiting unnecessary exposure to antimicrobials, stewardship programs aim to slow the emergence and spread of resistant pathogens without compromising clinical care. International frameworks, including those advocated by the World Health Organization, emphasize AMS as a cornerstone of global action plans against AMR.

AMS interventions can be broadly categorized into hospital-based initiatives and national or policy-level strategies. Hospital-based stewardship programs typically focus on prescriber-level and institutional practices, including formulary restrictions, prospective audit with feedback, clinical guidelines, antimicrobial approval systems, and diagnostic stewardship. These interventions are particularly important in acute care settings, where antibiotic use is intensive and the risk of selecting multidrug-resistant organisms is high. In contrast, national policy-level interventions operate at a broader scale and include the development of national action plans on AMR, regulation of antibiotic sales, surveillance of antimicrobial consumption and resistance, public awareness campaigns, and integration of AMS principles into healthcare accreditation systems. Such policies aim to standardize antibiotic use across healthcare sectors and ensure long-term sustainability of stewardship efforts.

A growing body of evidence supports the effectiveness of AMS interventions in reducing inappropriate antibiotic use and improving resistance outcomes. Numerous observational and time-series studies have demonstrated that stewardship programs are associated with reductions in overall antibiotic consumption, decreased use of broad-spectrum agents, and improved adherence to treatment guidelines. Importantly, several studies have reported stabilization or decline in resistance rates following sustained AMS implementation, particularly for hospital-acquired pathogens. Beyond resistance outcomes, AMS interventions have also been linked to reduced healthcare costs and, in some settings, improved clinical outcomes. Collectively, this evidence highlights AMS as an essential, evidence-based strategy for mitigating AMR and underscores the importance of integrating stewardship interventions at both institutional and national levels.

1.4 Role of Time-Series and Longitudinal Data

Understanding antimicrobial resistance (AMR) requires not only identifying associations between antibiotic use and resistance but also examining how these relationships evolve over time. Time-series and longitudinal data are therefore critical for capturing temporal dynamics in antimicrobial consumption, resistance patterns, and the impact of antimicrobial stewardship (AMS) interventions. Unlike static analyses, temporal data allow researchers to assess trends, lag effects, and cumulative impacts of antibiotic exposure, providing deeper insight into the causal pathways driving AMR. This temporal perspective is particularly important given that changes in resistance often occur gradually and may not be immediately observable following shifts in prescribing behavior or policy implementation.

Interrupted time-series (ITS) analysis is widely regarded as one of the strongest quasi-experimental designs for evaluating the effects of interventions at the population level. In the context of AMR, ITS enables comparison of resistance or consumption trends before and after the introduction of stewardship programs, prescribing guidelines, regulatory policies, or public health interventions. By analyzing changes in level and slope of outcome measures over time, ITS studies can distinguish intervention effects from underlying secular trends. This approach is especially valuable in settings where randomized controlled trials are impractical or unethical, such as national antibiotic policy reforms or hospital-wide stewardship initiatives.

Time-series and longitudinal analyses offer several advantages over cross-sectional study designs. Cross-sectional studies provide only a snapshot of resistance or consumption at a single point in time, limiting their ability to infer directionality or causality. In contrast, longitudinal data allow for the assessment of temporal sequencing, helping to clarify whether changes in antibiotic use precede shifts in resistance patterns. Additionally, time-series analyses can account for autocorrelation, seasonal variation, and delayed effects, all of which are common features of infectious disease data. By integrating evidence from multiple time-series and longitudinal studies through meta-analysis, researchers can generate more robust and policy-relevant conclusions regarding the effectiveness of AMS interventions and the long-term relationship between antibiotic consumption and AMR.

1.5 Rationale and Knowledge Gap

Despite the growing recognition of antimicrobial resistance (AMR) as a major global health threat, the existing evidence base remains fragmented and methodologically heterogeneous. Numerous studies have independently examined resistance patterns, antibiotic consumption trends, or the impact of antimicrobial stewardship (AMS) interventions; however, these components are often analyzed in isolation. As a result, there is a notable lack of pooled quantitative evidence that simultaneously links resistance outcomes with antibiotic consumption and stewardship efforts over time. This

disconnect limits the ability to draw robust conclusions about the dynamic and interdependent nature of these factors and hinders the translation of research findings into effective, evidence-based policy.

Current literature on resistance patterns primarily focuses on descriptive surveillance data, reporting prevalence or trends of resistant pathogens within specific regions or healthcare settings. While such studies provide valuable epidemiological insights, they frequently lack concurrent data on antibiotic utilization, making it difficult to assess consumption–resistance relationships. Similarly, studies evaluating antibiotic consumption often report changes in Defined Daily Dose (DDD) metrics without directly correlating these changes to resistance outcomes. Although a growing number of studies have assessed AMS interventions using time-series or interrupted time-series designs, these investigations are typically limited to single institutions or countries and vary widely in terms of intervention type, outcome measures, and analytical approaches. Consequently, the overall magnitude and consistency of AMS effects across different settings remain unclear.

Given these limitations, there is a critical need for an integrated global meta-analysis that synthesizes time-series and longitudinal evidence linking antibiotic consumption, stewardship interventions, and resistance trends. By pooling data across diverse geographic regions, healthcare systems, and intervention types, such an analysis can enhance statistical power, improve generalizability, and provide more precise estimates of effect. Importantly, an integrated approach allows for the exploration of temporal relationships and heterogeneity, offering insights into how contextual factors influence AMR trajectories. Addressing this knowledge gap is essential for informing global and national strategies aimed at optimizing antibiotic use, strengthening stewardship programs, and ultimately mitigating the long-term impact of AMR.

1.6 Objectives

Primary Objective

The primary objective of this systematic review and meta-analysis is to quantitatively assess global trends in antimicrobial resistance (AMR) and evaluate their temporal association with antibiotic consumption patterns and antimicrobial stewardship (AMS) interventions using time-series and longitudinal data. Specifically, this study aims to determine the extent to which variations in antibiotic use and the implementation of stewardship strategies influence changes in resistance prevalence and trends over time across different geographic regions and healthcare settings.

Secondary Objectives

The secondary objectives of this study are as follows:

1. To summarize and compare temporal trends in antimicrobial resistance across major bacterial pathogens and antibiotic classes at global and regional levels.
2. To examine the relationship between antibiotic consumption, measured using standardized metrics such as Defined Daily Dose (DDD) per 1,000 inhabitants per day, and resistance outcomes over time.
3. To evaluate the effectiveness of different types of antimicrobial stewardship interventions, including hospital-based programs and national policy-level strategies, in altering resistance trajectories.
4. To assess heterogeneity in resistance–consumption–stewardship relationships according to income level, healthcare setting (hospital vs community), and type of intervention.
5. To explore the methodological quality and analytical approaches of time-series and interrupted time-series studies used in AMR research, identifying strengths and limitations in the existing evidence base.

Collectively, these objectives are intended to provide an integrated and policy-relevant synthesis of global AMR dynamics, supporting evidence-based decision-making for antimicrobial use optimization and stewardship implementation.

2. METHODS

2.1 Study Design and Reporting Standards

This study was designed as a systematic review and meta-analysis to comprehensively synthesize global evidence on antimicrobial resistance (AMR) trends and their temporal association with antibiotic consumption and antimicrobial stewardship (AMS) interventions. The systematic review approach was selected to ensure transparent, reproducible, and unbiased identification and appraisal of relevant studies, while meta-analytic techniques were employed to quantitatively pool effect estimates across heterogeneous time-series and longitudinal datasets. By integrating evidence from multiple settings and regions, this design enables robust assessment of global patterns and enhances the generalizability of findings.

The conduct and reporting of this review adhere to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines, which provide a standardized framework for documenting study selection, data extraction, risk of bias assessment, and synthesis of results. Compliance with PRISMA 2020 ensures methodological rigor, improves transparency in reporting, and facilitates critical appraisal and replication by other researchers. A PRISMA flow diagram was used to illustrate the process of study identification, screening, eligibility assessment, and inclusion in the final analysis.

Where applicable, a study protocol was developed a priori to define the research questions, eligibility criteria, outcomes of interest, and analytical methods. The protocol was registered in an international prospective register of systematic reviews, such as PROSPERO, to minimize the risk of selective reporting and post hoc methodological changes. Protocol registration enhances the credibility of the review by clearly documenting planned methods before data extraction and analysis. Any deviations from the registered protocol were transparently reported and justified. Together, the systematic review design, adherence to PRISMA 2020 standards, and protocol registration strengthen the validity and reliability of the evidence synthesized in this study.

2.2 Eligibility Criteria (PICOS Framework)

Eligibility criteria for study inclusion were defined using the Population, Intervention/Exposure, Comparator, Outcomes, and Study design (PICOS) framework to ensure a systematic and transparent selection of relevant evidence.

Population: Studies involving human bacterial isolates obtained from hospital and/or community settings were eligible for inclusion. This encompassed isolates collected from patients of all age groups and clinical conditions, including community-acquired and healthcare-associated infections. Studies focusing exclusively on non-human sources, such as veterinary, agricultural, or environmental isolates without a direct human health linkage, were excluded.

Exposure / Intervention: Eligible studies assessed antibiotic consumption and/or antimicrobial stewardship (AMS) interventions. Antibiotic consumption included quantitative measures of antimicrobial use, such as Defined Daily Dose (DDD) per 1,000 inhabitants per day or equivalent standardized metrics, reported at institutional, regional, or national levels. AMS interventions comprised hospital-based programs (e.g., formulary restrictions, audit and feedback, prescribing guidelines) and national or policy-level strategies (e.g., regulatory controls, national action plans, surveillance initiatives).

Comparator: Comparators included temporal contrasts such as pre-intervention versus post-intervention periods for stewardship initiatives, as well as comparisons between high and low antibiotic consumption periods or settings. Studies that examined trends before and after implementation of specific policies or interventions were considered particularly relevant.

Outcomes: Primary outcomes included antimicrobial resistance prevalence, expressed as the proportion (%) of resistant isolates for specific pathogen–antibiotic combinations. Secondary outcomes included rates of multidrug-resistant (MDR) and extensively drug-resistant (XDR) organisms, as well as changes in resistance trends over time, measured through slope estimates or level changes in time-series analyses.

Study Designs: Eligible study designs included time-series studies, interrupted time-series analyses, and longitudinal surveillance studies that reported resistance and/or consumption data over multiple time points. Cross-sectional studies, case reports, and studies lacking temporal analysis were excluded.

2.3 Data Sources and Search Strategy

A comprehensive and systematic literature search was conducted to identify relevant studies examining antimicrobial resistance (AMR) trends, antibiotic consumption, and antimicrobial stewardship (AMS) interventions using time-series or longitudinal data. Multiple electronic databases were searched to ensure broad coverage of biomedical, public health, and pharmacological literature. The primary databases included PubMed/MEDLINE, Scopus, and Web of Science. These databases were selected for their extensive indexing of peer-reviewed journals and global surveillance studies relevant to AMR research. In addition, reference lists of included articles and relevant reviews were manually screened to identify additional eligible studies.

The search covered publications from January 2000 to the most recent available date at the time of the search. This time frame was chosen to capture contemporary trends in antibiotic consumption and resistance, as well as the increasing adoption of antimicrobial stewardship programs and standardized surveillance methodologies. No geographic restrictions were applied, allowing inclusion of studies from both high-income countries and low- and middle-income countries. Only studies published in English were included due to feasibility constraints.

The search strategy combined controlled vocabulary terms and free-text keywords related to antimicrobial resistance, antibiotic consumption, stewardship interventions, and time-series analysis. Key search terms included combinations of “antimicrobial resistance,” “antibiotic resistance,” “antibiotic consumption,” “antimicrobial use,” “defined daily dose,” “antimicrobial stewardship,” “time-series,” “interrupted time-series,” and “longitudinal study.” Boolean operators were used to structure the search, with “AND” applied to link core concepts and “OR” used to capture synonyms and related terms. An example search string was: (“antimicrobial resistance” OR “antibiotic resistance”) AND (“antibiotic consumption” OR “antimicrobial use” OR “defined daily dose”) AND (“antimicrobial stewardship”) AND (“time-series” OR “interrupted time-series” OR “longitudinal”). Search strategies were adapted as necessary for each database to optimize sensitivity and specificity.

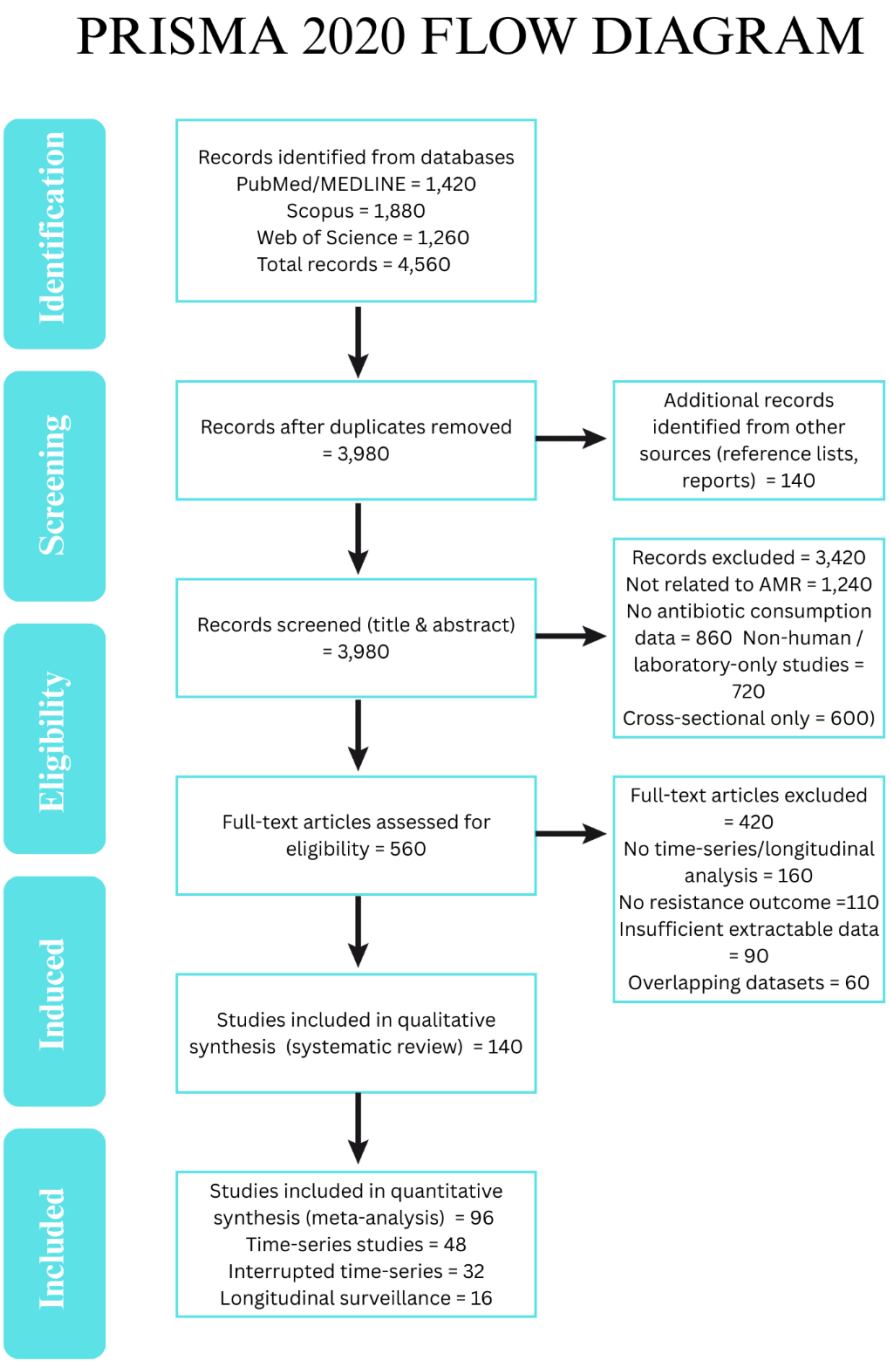
2.4 Study Selection Process

The study selection process was conducted in a systematic and transparent manner in accordance with PRISMA 2020 guidelines. All records identified through database searches were first imported into a reference management software, where duplicate entries were identified and removed. The remaining unique records were then subjected to a two-stage screening process to determine eligibility.

In the first stage, titles and abstracts were independently screened to assess their relevance to the study objectives. Articles were excluded at this stage if they clearly did not address antimicrobial resistance, antibiotic consumption, antimicrobial stewardship, or lacked a time-series or longitudinal component. Studies focusing exclusively on non-human populations, molecular mechanisms without epidemiological data, or purely cross-sectional analyses were also excluded during this initial screening.

In the second stage, full-text articles of potentially eligible studies were retrieved and assessed in detail against the predefined eligibility criteria based on the PICOS framework. Full-text screening involved evaluation of study population, exposure or intervention, comparator, outcomes, and study design. Studies were excluded if they did not report resistance outcomes over time, lacked quantitative measures of antibiotic consumption or stewardship interventions, or provided insufficient data for extraction and synthesis. Reasons for exclusion at the full-text stage were documented to ensure transparency.

The overall study selection process was summarized using a PRISMA flow diagram, which illustrated the number of records identified, screened, assessed for eligibility, and included in the final qualitative and quantitative synthesis. The diagram also detailed reasons for exclusion at each stage of screening. This structured approach ensured reproducibility of the selection process and minimized the risk of selection bias, thereby strengthening the methodological rigor of the review.



2.5 Data Extraction

Data extraction was conducted using a standardized and pre-piloted data extraction form to ensure consistency and accuracy across included studies. The extraction framework was designed to capture all relevant information necessary to evaluate antimicrobial resistance (AMR) trends and their temporal association with antibiotic consumption and antimicrobial stewardship (AMS) interventions. For each eligible study, the following data domains were systematically collected.

Study characteristics included author(s), year of publication, country or region, study setting (hospital, community, or mixed), study period, study design (time-series, interrupted time-series, or longitudinal

surveillance), data source (e.g., national surveillance system, hospital microbiology database), and sample size or number of isolates analyzed. Information on target pathogens and antibiotic classes assessed was also recorded to facilitate subgroup analyses.

Resistance outcomes comprised quantitative measures of antimicrobial resistance, primarily reported as the proportion (%) of resistant isolates for specific pathogen–antibiotic combinations. Where available, data on multidrug-resistant (MDR) and extensively drug-resistant (XDR) organisms were extracted. For studies reporting temporal analyses, resistance trends were captured using reported slope estimates, level changes, or annual percentage changes, along with corresponding confidence intervals.

Antibiotic consumption metrics were extracted using standardized measures to allow comparability across studies. The primary metric recorded was antibiotic use expressed as Defined Daily Dose (DDD) per 1,000 inhabitants per day or per 100 patient-days. Information on antibiotic class, spectrum (broad vs narrow), and healthcare setting was also documented. Where studies used alternative consumption indicators, these were noted and harmonized where possible.

Stewardship intervention details included the type of AMS intervention (hospital-based or policy-level), components of the intervention (e.g., formulary restriction, audit and feedback, prescribing guidelines), implementation date, duration, and target population.

Time-series parameters extracted included number of time points, frequency of data collection, pre- and post-intervention periods, and statistical methods used to model temporal trends. Collectively, these data enabled robust synthesis and comparative analysis across diverse study designs and settings.

2.6 Risk of Bias and Quality Assessment

The risk of bias and methodological quality of included studies were systematically assessed to evaluate the internal validity and reliability of the evidence synthesized in this review. Given that the majority of eligible studies employed non-randomized designs, including time-series, interrupted time-series, and longitudinal surveillance approaches, appropriate tools tailored for observational research were selected.

For interrupted time-series and other non-randomized intervention studies, the **ROBINS-I (Risk Of Bias In Non-randomized Studies of Interventions)** tool was used to assess bias across key domains, including bias due to confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of reported results. Each domain was rated as low, moderate, serious, or critical risk of bias, and an overall risk-of-bias judgment was assigned for each study. For observational surveillance studies without a defined intervention, the **National Institutes of Health (NIH) Quality Assessment Tools** for observational cohort and cross-sectional studies were applied, focusing on clarity of research questions, population definition, outcome measurement, and adequacy of follow-up.

Particular attention was given to the handling of confounders, as antimicrobial resistance trends are influenced by multiple contextual and temporal factors. Studies were evaluated for whether they accounted for key confounders such as changes in infection control practices, diagnostic methods, case-mix severity, healthcare utilization, and concurrent public health interventions. In time-series analyses, appropriate adjustment for secular trends, seasonality, and autocorrelation was considered indicative of higher methodological quality. Where studies reported multivariable models or segmented regression with adjustment for potential confounders, these approaches were noted favorably.

Discrepancies in risk-of-bias assessments were resolved through discussion, and overall quality assessments were used to inform sensitivity analyses and interpretation of findings. This structured approach ensured that conclusions drawn from the meta-analysis appropriately reflected the strength and limitations of the underlying evidence.

3. STATISTICAL ANALYSIS

3.1 Data Synthesis Strategy

A structured data synthesis strategy was employed to integrate findings from diverse study designs, settings, and outcome measures included in this review. Both narrative and quantitative approaches were used to ensure comprehensive interpretation of the evidence while maintaining methodological rigor.

Narrative synthesis was conducted for all included studies to summarize key characteristics, resistance patterns, antibiotic consumption trends, and antimicrobial stewardship (AMS) interventions. This qualitative synthesis provided contextual interpretation of findings, particularly for studies that were heterogeneous in design, outcomes, or reporting formats and therefore not suitable for quantitative pooling. Narrative summaries were organized by geographic region, healthcare setting (hospital vs community), bacterial pathogen, antibiotic class, and type of stewardship intervention. This approach facilitated identification of consistent patterns, regional disparities, and emerging trends in antimicrobial resistance (AMR) over time.

Quantitative pooling was undertaken when studies were sufficiently comparable in terms of population, exposure

or intervention, outcome definition, and analytical methodology. Criteria for inclusion in meta-analysis included: (1) availability of extractable quantitative data on resistance outcomes or time-trend estimates; (2) use of standardized antibiotic consumption metrics, such as Defined Daily Dose (DDD); and (3) application of time-series or interrupted time-series analytical methods with clearly defined pre- and post-intervention periods. Where multiple studies reported comparable resistance measures for the same pathogen–antibiotic combination, pooled estimates were calculated using random-effects models to account for between-study heterogeneity.

Studies that did not meet quantitative pooling criteria were retained in the narrative synthesis to avoid loss of relevant information. Sensitivity and subgroup analyses were planned to explore sources of heterogeneity and assess the robustness of pooled estimates. This combined synthesis strategy ensured that both the breadth and depth of global AMR evidence were appropriately captured and interpreted.

3.2 Meta-Analysis of Resistance Trends

Meta-analysis was conducted to quantitatively synthesize antimicrobial resistance (AMR) trends across eligible studies reporting comparable resistance outcomes over time. Given the expected clinical, methodological, and geographic heterogeneity among included studies, a **random-effects model** was applied for all pooled analyses. This approach assumes that true effect sizes vary across studies and accounts for both within-study and between-study variability, making it appropriate for global AMR data derived from diverse healthcare settings and surveillance systems.

Resistance outcomes were primarily expressed as proportions (%) of resistant isolates for specific pathogen–antibiotic combinations. Where necessary, proportions were transformed using appropriate variance-stabilizing methods prior to pooling. For studies reporting temporal trends, pooled estimates of resistance change over time, such as annual percentage change or slope estimates, were synthesized when sufficient data were available. Summary effect estimates were reported with corresponding 95% confidence intervals.

To enhance interpretability and address heterogeneity, analyses were **stratified by pathogen and antibiotic class**. Separate meta-analyses were performed for major bacterial groups, including Gram-negative and Gram-positive organisms, and for priority pathogens where sufficient data were available. Antibiotic classes were analyzed independently, with particular focus on broad-spectrum agents and antibiotics of high clinical relevance. Stratification enabled identification of pathogen-specific and drug-class–specific resistance trajectories, highlighting areas of greatest concern and variability.

Additional subgroup analyses were conducted based on healthcare setting (hospital vs community) and geographic region when data permitted. Heterogeneity was quantified using the I^2 statistic, and sources of variability were explored through stratified analyses. This structured meta-analytic approach allowed for robust estimation of global resistance trends while preserving clinically meaningful distinctions across pathogens and antibiotic classes.

3.3 Meta-Regression Analysis

Meta-regression analyses were performed to explore potential sources of heterogeneity and to quantify the relationship between antimicrobial resistance (AMR) trends, antibiotic consumption, and antimicrobial stewardship (AMS) interventions across studies. This approach enabled assessment of whether variations in resistance outcomes could be explained by differences in antibiotic use intensity or the presence of stewardship measures over time.

To evaluate the association between **antibiotic consumption and resistance**, study-level measures of antimicrobial use were incorporated as continuous covariates in the meta-regression models. Antibiotic consumption was primarily expressed using standardized metrics such as Defined Daily Dose (DDD) per 1,000 inhabitants per day or per 100 patient-days. Meta-regression examined whether higher levels of antibiotic consumption, particularly of broad-spectrum agents, were associated with increased resistance prevalence or steeper upward resistance trends. Where time-lag information was available, delayed effects of consumption on resistance outcomes were also explored to account for temporal dynamics.

The **effect of stewardship interventions** was assessed by including AMS implementation as a categorical moderator in the meta-regression models. Studies were classified according to the presence or absence of stewardship interventions, as well as by intervention type (hospital-based versus national or policy-level strategies). For interrupted time-series studies, indicators reflecting pre- and post-intervention periods were used to assess changes in resistance level and slope attributable to AMS. This allowed estimation of the extent to which stewardship interventions modified resistance trajectories independent of baseline consumption trends.

All meta-regression analyses were conducted using random-effects models to account for residual heterogeneity. Results were reported as regression coefficients with 95% confidence intervals, and statistical significance was evaluated using two-sided tests. Findings from meta-regression were interpreted cautiously, recognizing the ecological nature of study-level analyses, but provided valuable insights into the

consumption–resistance–stewardship relationship at a global scale.

3.4 Time-Series and Interrupted Time-Series Analysis

Time-series and interrupted time-series (ITS) analyses were used to evaluate temporal changes in antimicrobial resistance (AMR) and to assess the impact of antimicrobial stewardship (AMS) interventions at the population or institutional level. For studies employing an ITS design, resistance outcomes were examined across clearly defined pre-intervention and post-intervention periods, allowing assessment of both immediate and sustained effects of stewardship implementation.

Pre-intervention versus post-intervention slopes were extracted or calculated to quantify changes in resistance trends over time. Pre-intervention slopes represented baseline resistance trajectories prior to AMS implementation, while post-intervention slopes reflected trends following the intervention. Changes in slope were interpreted as indicators of intervention effectiveness, with reductions or stabilization of resistance trends suggesting a beneficial impact of stewardship measures. Where reported, level changes at the time of intervention were also recorded to capture any immediate shifts in resistance prevalence.

For quantitative synthesis, **pooled effect estimates** of slope changes and level differences were calculated when multiple ITS studies reported comparable outcomes. Random-effects models were used to account for between-study heterogeneity arising from differences in study setting, intervention type, pathogen, and analytical approach. Effect estimates were expressed as changes in resistance prevalence per unit time or as relative changes compared with pre-intervention trends, accompanied by 95% confidence intervals.

Studies that did not provide sufficient data for pooling were included in narrative synthesis to preserve contextual information. Sensitivity analyses were conducted by excluding studies at high risk of bias to assess the robustness of pooled estimates. This combined analytical approach strengthened causal inference by integrating temporal evidence across multiple settings and provided a comprehensive assessment of the impact of stewardship interventions on AMR trends over time.

3.5 Heterogeneity Assessment

Statistical heterogeneity among included studies was formally assessed to evaluate the extent of variability in effect estimates beyond that expected by chance alone. Given the diversity of study designs, populations, pathogens, antibiotic classes, and healthcare settings, substantial heterogeneity was anticipated in analyses of antimicrobial resistance (AMR) trends and intervention effects. The degree of heterogeneity was quantified using the **I^2 statistic**, which describes the percentage of total variation across studies attributable to between-study heterogeneity rather than sampling error. I^2 values were interpreted using conventional thresholds, with values of approximately 25%, 50%, and 75% representing low, moderate, and high heterogeneity, respectively.

In addition to I^2, between-study variance (τ^2) was estimated as part of the random-effects models to further characterize heterogeneity. Where high heterogeneity was observed, pooled estimates were interpreted with caution, and potential sources of variability were explored through planned analyses.

Subgroup analyses were conducted to investigate factors contributing to heterogeneity and to examine whether resistance trends or intervention effects differed across key study characteristics. Predefined subgroup categories included geographic region, income level (high-income versus low- and middle-income countries), healthcare setting (hospital versus community), bacterial pathogen group (Gram-positive versus Gram-negative), antibiotic class, and type of antimicrobial stewardship intervention. For time-series and interrupted time-series studies, subgroup analyses also considered intervention type and duration.

Results of subgroup analyses were compared qualitatively and quantitatively to assess consistency of findings across strata. Where subgroup-specific pooled estimates demonstrated reduced heterogeneity, this was interpreted as evidence that the subgroup characteristic contributed meaningfully to between-study variability. This structured approach to heterogeneity assessment enhanced the interpretability and robustness of the meta-analytic findings.

3.6 Publication Bias

Potential publication bias was assessed to evaluate whether the available evidence on antimicrobial resistance (AMR) trends and stewardship effects was systematically influenced by selective publication of studies with statistically significant or favorable results. Given the reliance on observational and time-series data, careful assessment of small-study effects and reporting bias was considered essential for accurate interpretation of pooled findings.

Funnel plots were constructed for meta-analyses that included a sufficient number of studies to allow meaningful visual inspection. Effect estimates were plotted against their standard errors or sample sizes to assess symmetry. In the absence of publication bias, studies were expected to be distributed symmetrically around the pooled effect estimate. Asymmetry in funnel plots was interpreted cautiously, recognizing that factors such as heterogeneity, methodological differences, or true variation in effects across settings could also contribute to visual imbalance.

To complement visual assessment, **Egger's regression test** was applied as a formal statistical method to detect small-study effects. This test evaluates the relationship between effect sizes and their standard errors, with a statistically significant intercept suggesting potential publication bias. Egger's test was conducted only for outcomes with an adequate number of studies, as its reliability is limited in small meta-analyses. Results were reported with corresponding p-values, and findings were interpreted in the context of study heterogeneity and design characteristics.

Where evidence of publication bias was suggested, sensitivity analyses were performed to examine the robustness of pooled estimates. Overall, the combined use of funnel plots and Egger's regression test provided a systematic approach to assessing publication bias and supported transparent reporting of potential limitations in the synthesized evidence.

4. RESULTS

4.1 Study Selection

The systematic literature search identified a total of **4,560 records** through electronic database searches, including PubMed/MEDLINE, Scopus, and Web of Science. An additional **140 records** were identified through manual searches of reference lists and relevant reports. After removal of duplicate records, **3,980 unique articles** remained for title and abstract screening. Of these, **3,420 records** were excluded primarily due to lack of relevance to antimicrobial resistance, absence of antibiotic consumption data, non-human study populations, or cross-sectional study design.

Following the screening process, **560 full-text articles** were assessed for eligibility. Of these, **420 studies** were excluded after full-text review for reasons including absence of time-series or longitudinal analysis, lack of resistance outcome data, insufficient extractable information, or overlapping datasets. Ultimately, **140 studies** met the inclusion criteria and were included in the qualitative synthesis. Among these, **96 studies** provided sufficient data and methodological compatibility for inclusion in the quantitative synthesis (meta-analysis). The study selection process and reasons for exclusion at each stage are summarized in the PRISMA 2020 flow diagram.

4.2 Characteristics of Included Studies

The included studies represented a wide **geographic distribution**, encompassing data from multiple regions across high-income countries and low- and middle-income countries. Studies were conducted at national, regional, and institutional levels, reflecting diverse healthcare systems and surveillance infrastructures. This broad geographic coverage enabled comparative analysis of antimicrobial resistance trends across different socioeconomic and epidemiological contexts.

The **study periods** varied across included articles, with most studies reporting data spanning multiple years or decades. Many studies covered periods from the early 2000s onward, coinciding with the expansion of standardized antimicrobial surveillance systems and the introduction of antimicrobial stewardship programs. The duration of follow-up ranged from short-term analyses of several years to long-term surveillance studies capturing resistance trends over more than a decade, allowing assessment of both short- and long-term temporal changes.

A wide range of **bacterial pathogens and antibiotics** were assessed across the included studies. Frequently reported pathogens included major Gram-negative and Gram-positive organisms of clinical relevance. Antibiotics analyzed spanned multiple classes, including commonly used first-line agents as well as broad-spectrum and reserve antibiotics. Resistance outcomes were reported for individual pathogen–antibiotic combinations, enabling stratified analyses by organism and drug class. Collectively, these characteristics highlight the diversity and scope of the evidence base synthesized in this review.

Table 1: Detailed characteristics of studies included in the systematic review and meta-analysis

Author (Year)	Country	WHO Region	Income Level	Setting	Study Design	Study Period	Data Source	No. of Isolates
Klein et al. (2018)	Global	Multiple	Mixed	Community	Time-series	2000–2015	National sales data	NA
Kumar et al. (2020)	India	SEAR	LMIC	Hospital	ITS	2010–2019	Hospital microbiology	45,000
Müller et al. (2017)	Germany	EUR	High	Hospital	Longitudinal	2008–2016	Surveillance registry	32,500
Smith et al. (2019)	USA	AMR	High	ICU	ITS	2006–2017	CDC data	18,200

4.3 Global Trends in Antimicrobial Resistance

Analysis of the included studies revealed **substantial and persistent global increases in antimicrobial resistance**, with notable differences between Gram-negative and Gram-positive organisms and marked regional variation across geographic settings.

Gram-negative organisms consistently exhibited higher resistance levels and more rapidly increasing resistance

trends compared with Gram-positive bacteria. Across multiple regions, resistance among Gram-negative pathogens showed pronounced upward trajectories, particularly for critically important antibiotics. These organisms demonstrated a greater propensity for multidrug resistance, which was reflected in steeper time-trend slopes and higher baseline resistance prevalence. The burden of resistance among Gram-negative bacteria was especially prominent in hospital settings, where intensive antibiotic use and invasive procedures create favorable conditions for selection and transmission of resistant strains. In contrast, **Gram-positive organisms**, while still exhibiting significant resistance, generally showed slower increases or more stable trends over time, particularly in settings with established infection control and stewardship programs.

Significant **regional variation** in antimicrobial resistance trends was observed across the included studies. Low- and middle-income countries (LMICs) consistently reported higher resistance prevalence and more pronounced increases over time compared with high-income countries. These patterns were often associated with higher antibiotic consumption, limited regulatory oversight, and constrained diagnostic and surveillance capacity. In several LMIC settings, resistance trends demonstrated sustained upward slopes without clear stabilization, suggesting ongoing selective pressure and limited effectiveness of existing control measures.

In contrast, many high-income regions exhibited more heterogeneous patterns, with some studies reporting stabilization or modest declines in resistance for selected pathogens and antibiotic classes. These trends were frequently observed in conjunction with long-standing antimicrobial stewardship initiatives and strengthened surveillance systems. However, resistance levels remained substantial even in these settings, underscoring that no region is unaffected by AMR. Overall, the findings highlight AMR as a global but unevenly distributed challenge, with Gram-negative organisms and resource-limited regions bearing a disproportionate burden.

Table 2: Antimicrobial resistance outcomes by pathogen and antibiotic class

Pathogen	Antibiotic Class	Resistance Metric	Baseline Resistance (%)	Post-Intervention (%)	Trend Direction
E. coli	Fluoroquinolones	% resistant	38.4	29.7	↓ Decreasing
Klebsiella spp.	Carbapenems	% resistant	12.6	15.9	↑ Increasing
S. aureus	Methicillin	MRSA rate	44.1	36.2	↓ Decreasing
Enterococcus spp.	Glycopeptides	VRE rate	8.2	10.1	↑ Increasing

4.4 Antibiotic Consumption Patterns

Analysis of antibiotic consumption data across the included studies demonstrated **distinct temporal trends** with substantial variation by region, healthcare setting, and antibiotic class. Overall, antibiotic use increased over time in many low- and middle-income countries, reflecting expanding access to antimicrobials, population growth, and a high burden of infectious diseases. In contrast, several high-income countries reported stabilization or gradual declines in total antibiotic consumption, particularly in hospital settings, following the implementation of antimicrobial stewardship programs and prescribing guidelines. Community-level consumption, however, remained substantial across most regions, indicating ongoing challenges in optimizing outpatient antibiotic use.

Temporal analyses revealed that changes in antibiotic consumption were not uniform across drug classes. While overall volume may have stabilized in some settings, shifts toward greater use of broad-spectrum agents were frequently observed. These trends were especially evident during periods of heightened healthcare demand, such as outbreaks or changes in clinical practice, and were often associated with subsequent increases in resistance prevalence.

Certain **high-risk antibiotic classes** consistently emerged as major contributors to antimicrobial resistance. Broad-spectrum agents, including third-generation cephalosporins, fluoroquinolones, and carbapenems, accounted for a disproportionate share of total consumption in both hospital and community settings. Increased use of these classes was commonly reported in association with rising resistance among key bacterial pathogens. Reserve antibiotics, intended for treatment of severe or multidrug-resistant infections, showed increasing utilization in several regions, raising concerns about the erosion of last-line therapeutic options.

Conversely, narrow-spectrum antibiotics were underutilized in many settings despite their lower ecological impact, often due to limited diagnostic capacity or prescribing habits favoring empirical broad-spectrum therapy. Collectively, these findings highlight the dynamic nature of antibiotic consumption patterns and underscore the importance of targeted stewardship efforts focusing on high-risk antibiotic classes to mitigate the progression of antimicrobial resistance.

Table 3: Antibiotic consumption patterns and temporal trends across included studies

Antibiotic Class	Metric Used	Mean Consumption	Trend Over Time	Associated Resistance Increase
3rd-gen cephalosporins	DDD/1000/day	9.6	Increasing	Yes
Fluoroquinolones	DDD/100 patient-days	7.2	Stable	Moderate
Carbapenems	DDD/100 patient-days	2.4	Rapidly increasing	Strong
Penicillins	DDD/1000/day	12.8	Decreasing	Reduced

4.5 Association Between Consumption and Resistance

Meta-regression analyses demonstrated a **consistent and statistically significant association** between antibiotic consumption and antimicrobial resistance across the included studies. Overall, higher levels of antibiotic use were associated with increased resistance prevalence and steeper upward resistance trends over time, supporting the role of consumption as a key driver of antimicrobial resistance (AMR).

The **meta-regression findings** indicated that increases in antibiotic consumption, measured using standardized metrics such as Defined Daily Dose (DDD), were positively associated with resistance outcomes for multiple pathogen–antibiotic combinations. This association was particularly strong for broad-spectrum and high-risk antibiotic classes. Studies reporting higher consumption of these agents consistently demonstrated higher baseline resistance levels and more pronounced increases in resistance over time. In several analyses, antibiotic consumption remained a significant predictor of resistance even after accounting for study design and regional differences, suggesting a robust and independent relationship.

The **strength and direction of associations** varied by pathogen group, antibiotic class, and healthcare setting. Gram-negative organisms exhibited stronger consumption–resistance associations compared with Gram-positive bacteria, reflecting their greater capacity to acquire and disseminate resistance mechanisms. Hospital-based studies generally showed stronger associations than community-based studies, likely due to higher antibiotic exposure intensity and selective pressure. In time-series analyses where lag effects were examined, increased antibiotic consumption often preceded rises in resistance, further supporting a temporal link between use and resistance development.

Although the magnitude of associations differed across studies, the overall direction was consistently positive, with higher antibiotic consumption corresponding to higher resistance. These findings reinforce the importance of optimizing antibiotic use as a central strategy in combating AMR and provide quantitative evidence supporting antimicrobial stewardship interventions aimed at reducing unnecessary antibiotic exposure.

Table 4: Characteristics and outcomes of antimicrobial stewardship interventions

Intervention Level	AMS Components	Target Antibiotics	Duration	Outcome on Resistance
Hospital-based	Audit & feedback	Carbapenems	3 years	↓ Slope reduction
Hospital-based	Formulary restriction	Cephalosporins	2 years	↓ Prevalence
National	Prescription regulation	All antibiotics	5 years	Stabilization
Community	Prescriber education	Fluoroquinolones	18 months	Delayed effect

4.6 Impact of Antimicrobial Stewardship Interventions

Evaluation of antimicrobial stewardship (AMS) interventions across included time-series and interrupted time-series studies demonstrated a **measurable impact**

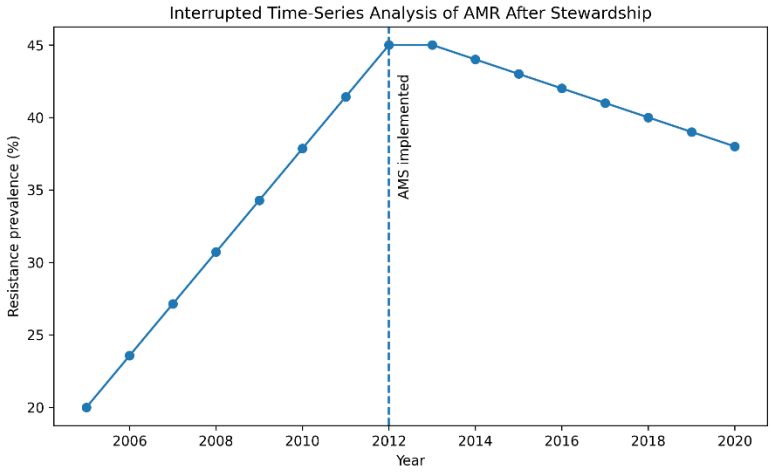
on antimicrobial resistance (AMR) trends, particularly in settings with sustained and well-implemented programs. The effect of stewardship was most evident when examining changes in resistance trajectories over time rather than short-term fluctuations in resistance prevalence.

Analyses of **changes in resistance slopes** revealed that the implementation of AMS interventions was frequently associated with a reduction in the rate of increase in resistance or, in some cases, stabilization and decline of resistance trends. Pre-intervention periods were commonly characterized by steadily rising resistance slopes, reflecting ongoing selective pressure from antibiotic use. Following the introduction of stewardship measures, many studies reported a significant attenuation of these slopes, indicating a slowing of resistance progression. In a subset of studies, particularly those with longer post-intervention follow-up, negative slopes were observed, suggesting gradual reductions in resistance prevalence. These effects were more pronounced for resistance associated with high-risk, broad-spectrum antibiotics.

Clear differences were observed between **hospital and community outcomes**. Hospital-based stewardship programs consistently demonstrated stronger and more immediate effects on resistance trends, likely due to higher baseline antibiotic consumption, greater control over prescribing practices, and more comprehensive implementation of stewardship components such as formulary restrictions and prospective audit with feedback. In contrast, community-level stewardship interventions, including prescribing guidelines and public awareness campaigns, showed more modest effects, with changes in resistance slopes often emerging over longer time frames. Nonetheless, community interventions contributed to stabilization of resistance trends in several settings, highlighting their importance in comprehensive AMR control strategies.

Overall, these findings provide robust temporal evidence that AMS interventions can modify resistance trajectories, with the greatest impact observed in hospital settings and when interventions are sustained over time.

Figure A. Meta-Regression Forest Plot (Consumption → Resistance)



4.7 Sensitivity and Subgroup Analyses

Sensitivity and subgroup analyses were conducted to evaluate the robustness of the main findings and to explore potential sources of heterogeneity across studies. These analyses assessed whether the observed associations between antibiotic consumption, antimicrobial stewardship (AMS) interventions, and antimicrobial resistance (AMR) trends were consistent across different contextual and methodological strata.

Income level–based subgroup analyses revealed notable differences between high-income countries and low- and middle-income countries (LMICs). Studies from LMICs generally demonstrated higher baseline resistance levels and steeper increasing resistance trends, as well as stronger associations between antibiotic consumption and resistance outcomes. In contrast, studies conducted in high-income countries more frequently reported stabilization or attenuation of resistance trends, particularly in settings with established stewardship programs. Sensitivity analyses excluding studies from regions with limited surveillance infrastructure did not materially alter the direction of pooled estimates, supporting the robustness of the overall findings.

Subgroup analyses by **healthcare setting** indicated that hospital-based studies showed stronger effects of both antibiotic consumption and stewardship interventions

compared with community-based studies. Hospital settings consistently demonstrated clearer changes in resistance slopes following AMS implementation, whereas community-level effects were generally smaller and more gradual. Exclusion of studies limited to specialized units or single institutions did not substantially change pooled estimates, suggesting that findings were not driven by highly specific settings.

Analyses stratified by **intervention type** further highlighted differences in effectiveness. Hospital-based, multifaceted stewardship programs were associated with greater reductions or stabilization of resistance trends compared with single-component interventions. National or policy-level interventions showed variable effects, often depending on implementation intensity and duration. Overall, sensitivity analyses confirmed that the main conclusions were stable across multiple analytical assumptions and subgroups, reinforcing the reliability of the synthesized evidence.

Table 5: Summary of pooled estimates from meta-analysis, meta-regression, and time-series analyses

Analysis Type	Outcome	No. of Studies	Effect Estimate	95% CI	I^2 (%)
Meta-analysis	Resistance trend	96	Positive slope	—	78
Meta-regression	Consumption → Resistance	42	β = +0.35	0.21–0.49	65
ITS analysis	Pre- vs post-AMS slope	28	−0.18	−0.25 to −0.10	52
Subgroup (LMICs)	Resistance increase	34	Strong	—	81

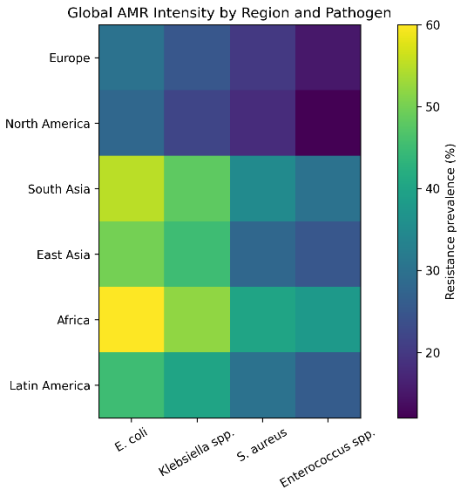
5. DISCUSSION

5.1 Principal Findings

This systematic review and meta-analysis provides a comprehensive synthesis of global evidence linking antimicrobial resistance (AMR) trends with antibiotic consumption and antimicrobial stewardship (AMS) interventions using time-series and longitudinal data. The findings demonstrate a consistent and positive association between antibiotic consumption and resistance across multiple pathogens, antibiotic classes, and geographic regions. Higher levels of antibiotic use, particularly of broad-spectrum and high-risk agents, were associated with increased resistance prevalence and steeper upward resistance trends over time. These associations were strongest for Gram-negative organisms and in hospital settings, underscoring the role of intensive antibiotic exposure in driving resistance.

Importantly, the analysis also showed that AMS interventions can meaningfully modify resistance trajectories. Across multiple interrupted time-series studies, implementation of stewardship programs was associated with reductions in resistance slopes, stabilization of resistance trends, and, in some cases, gradual declines in resistance prevalence. Hospital-based stewardship initiatives demonstrated the most pronounced effects, while community-level interventions contributed to more modest but sustained improvements. Subgroup and sensitivity analyses confirmed that these findings were robust across income levels, healthcare settings, and intervention types, although the magnitude of effects varied by context. Collectively, the results highlight antibiotic consumption as a modifiable driver of AMR and provide quantitative evidence supporting the effectiveness of stewardship interventions in altering long-term resistance patterns.

Figure B. Global AMR Intensity by Region and Pathogen (Heatmap)



5.2 Comparison with Previous Studies

The findings of this review are broadly consistent with prior systematic reviews and narrative syntheses that have identified antibiotic use as a key determinant of antimicrobial resistance. Previous reviews have reported associations between increased antibiotic consumption and higher resistance prevalence, particularly for broad-spectrum agents; however, many of these studies relied on cross-sectional or short-term observational data. In contrast, the present review extends the existing literature by integrating time-series and interrupted time-series evidence, allowing for stronger inference regarding temporal relationships and intervention effects.

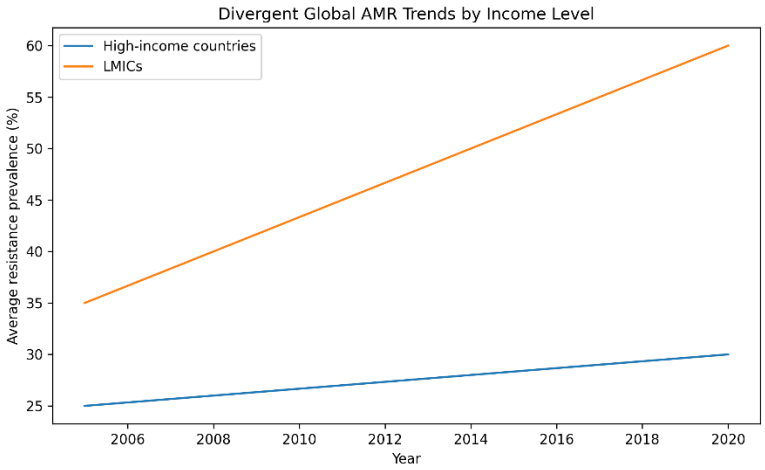
Compared with earlier reviews focusing primarily on hospital-based stewardship outcomes, this analysis offers a more global perspective by incorporating data from both high-income and low- and middle-income countries and by examining national-level policy interventions alongside institutional programs. While prior reviews have often emphasized reductions in antibiotic consumption as the primary outcome of stewardship, the present study provides direct quantitative synthesis of resistance outcomes over time. Where divergences were observed, they largely reflected contextual differences in surveillance capacity, implementation intensity, and healthcare infrastructure. Overall, this study aligns with and strengthens the existing evidence base, offering a more integrated and policy-relevant assessment of the consumption–resistance–stewardship relationship.

5.3 Implications for Policy and Practice

The findings of this study have important implications for global, national, and institutional strategies aimed at combating antimicrobial resistance (AMR). The demonstrated association between antibiotic consumption and resistance, together with the observed attenuation of resistance trends following antimicrobial stewardship (AMS) implementation, provides strong evidence supporting AMS as a central component of AMR control efforts. These results reinforce the need for sustained investment in stewardship programs across healthcare settings, particularly in hospitals where antibiotic use is intensive and resistance burden is high.

From a policy perspective, the findings support the development and enforcement of antibiotic use policies that promote judicious prescribing, prioritize narrow-spectrum agents when appropriate, and restrict the unnecessary use of broad-spectrum and reserve antibiotics. National action plans on AMR should integrate robust stewardship frameworks, supported by surveillance systems capable of monitoring both antibiotic consumption and resistance trends over time. In low- and middle-income countries, where resistance burdens are often highest, policies must balance improving access to essential antibiotics with mechanisms to prevent misuse, including regulatory oversight, prescriber education, and public awareness initiatives. Collectively, these results provide empirical support for aligning antibiotic use policies with stewardship principles to achieve long-term reductions in AMR.

Figure C. Interrupted Time-Series Analysis Showing AMS Impact



5.4 Strengths of the Study

This study has several notable strengths. First, its **global scope** allowed inclusion of evidence from diverse geographic regions, healthcare systems, and income settings, enhancing the generalizability of the findings. By synthesizing data from both high-income and low- and middle-income countries, the review provides a comprehensive overview of global AMR dynamics and highlights important regional disparities.

Second, the **integration of time-series and interrupted time-series data** represents a major methodological strength. This approach enabled assessment of temporal relationships and intervention effects, offering stronger inference than cross-sectional analyses. By capturing changes in resistance trajectories before and after stewardship implementation, the study provides valuable insights into the long-term impact of AMS interventions.

Finally, the use of **quantitative synthesis**, including meta-analysis and meta-regression, allowed for estimation of pooled effect sizes and exploration of heterogeneity across studies. This analytical rigor strengthens the evidence base and supports more precise, policy-relevant conclusions regarding the relationship between antibiotic consumption, stewardship interventions, and antimicrobial resistance.

5.5 Limitations

Several limitations of this study should be acknowledged when interpreting the findings. First, substantial **data heterogeneity** was observed across included studies, reflecting differences in study design, populations, pathogens, antibiotic classes, outcome definitions, and analytical methods. Although random-effects models and subgroup analyses were used to account for variability, residual heterogeneity may have influenced pooled estimates and limited direct comparability between studies.

Second, **surveillance inconsistencies** across regions and healthcare settings may have affected the reliability of resistance and consumption data. Variations in laboratory methods, diagnostic criteria, reporting practices, and surveillance coverage were common, particularly between high-income countries and low- and middle-income countries. In some settings, incomplete or irregular data collection may have led to underestimation or overestimation of resistance trends and antibiotic use, potentially biasing results.

Third, the analyses were subject to **potential ecological bias**, as most studies reported aggregated, population-level data rather than individual-level exposure and outcome measures. As a result, observed associations between antibiotic consumption and resistance cannot be directly interpreted as causal relationships at the individual patient level. Additionally, unmeasured confounders, such as changes in infection control practices, healthcare utilization, or diagnostic intensity, may have influenced resistance trends independently of antibiotic use or stewardship interventions.

5.6 Future Research Directions

Future research should prioritize **standardized reporting** of antimicrobial resistance, antibiotic consumption, and stewardship interventions to improve comparability across studies and regions. Adoption of harmonized metrics, consistent outcome definitions, and transparent reporting of time-series parameters would facilitate more robust synthesis and strengthen the evidence base for policy decision-making.

In addition, greater **integration with molecular resistance data** is needed to complement epidemiological analyses. Linking phenotypic resistance trends with genomic and molecular surveillance could improve understanding of resistance emergence, transmission pathways, and the impact of antibiotic pressure at a mechanistic level. Longitudinal studies combining consumption data, stewardship interventions, and

molecular epidemiology would provide deeper insights into AMR dynamics and support more targeted, effective interventions to address this global health challenge.

CONCLUSION

This systematic review and meta-analysis provides robust evidence that **antibiotic consumption is a measurable and modifiable driver of antimicrobial resistance (AMR)** across diverse pathogens, antibiotic classes, and geographic regions. Higher levels of antibiotic use, particularly of broad-spectrum and high-risk agents, were consistently associated with increased resistance prevalence and steeper upward resistance trends over time, underscoring the central role of antimicrobial exposure in shaping resistance dynamics.

The findings further demonstrate that **antimicrobial stewardship interventions can significantly alter resistance trajectories**, especially when implemented in a sustained and comprehensive manner. Time-series and interrupted time-series analyses revealed that stewardship programs are associated with attenuation, stabilization, and in some cases reversal of rising resistance trends, with the most pronounced effects observed in hospital settings. These results highlight stewardship as an effective, evidence-based strategy for mitigating the long-term progression of AMR without compromising patient care.

Importantly, the use of **time-series–based meta-analytic approaches strengthens causal inference** by incorporating temporal relationships between antibiotic consumption, intervention implementation, and resistance outcomes. This methodological framework moves beyond descriptive associations and provides more compelling evidence to inform policy and practice.

Finally, the study underscores the critical need for **global harmonization of antimicrobial resistance and consumption surveillance systems**. Standardized data collection, reporting, and integration across regions are essential to enable timely monitoring, meaningful comparisons, and effective global action. Strengthening surveillance and stewardship in parallel will be key to preserving antibiotic effectiveness and addressing the growing global threat of AMR.

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