



A Comprehensive Systematic Review of Antimicrobial Resistance in Community - Acquired Infections Managed in Primary Health Care

¹ Agsion Marce Kombongan

¹ Kelapa Lima Public Health Centre, Merauke Regency, South Papua, Indonesia

Corresponding Email : agsionmarcek86@gmail.com

Article History :

Received date : 2025/09/14
Revised date : 2025/10/02
Accepted date : 2025/11/16
Published date : 2025/12/22



Copyright: © 2024 by the authors. Submitted for possible open access publication under the terms and conditions of the Creative Commons Attribution (BY NC) license (<https://creativecommons.org/licenses/by-nc/4.0/>).

E-ISSN :

ISSN 3048-1368



P-ISSN

ISSN 3048-1376



ABSTRACT

Introduction: Antimicrobial resistance (AMR) in community-acquired infections presents a critical global health threat, disproportionately affecting primary healthcare settings where most antibiotics are prescribed. Despite two decades of stewardship efforts, antibiotic prescribing rates remain persistently high, and resistance patterns show alarming geographic and temporal trends. This systematic review synthesizes the current evidence on the prevalence, clinical impact, drivers, and management of AMR in community-acquired infections within primary care.

Methods: We conducted a comprehensive systematic review following established guidelines. We screened studies based on predefined criteria focusing on community-acquired bacterial infections, primary healthcare settings, and AMR data. Data from 80 included studies were extracted across domains including study setting, pathogens, resistance methodologies, findings, associated factors, and intervention outcomes. Studies encompassed

systematic reviews, randomized trials, observational studies, and quasi-experimental designs from diverse global regions.

Results: AMR prevalence varies significantly by infection type and geography. In urinary tract infections (UTIs), *E. coli* resistance to ampicillin was 53.4% in OECD countries versus 79.8% in non-OECD countries. Ciprofloxacin resistance is rising in community-acquired UTIs ($P=0.003$). For respiratory tract infections, pneumococcal penicillin non-susceptibility reached 58% in some regions, though amoxicillin susceptibility remains preserved in many areas. Antibiotic-resistant infections lead to worse clinical outcomes, particularly in UTIs (OR 4.19 for clinical failure), increased healthcare utilization, and higher economic costs. Antibiotic exposure directly increases individual patient resistance, with effects persisting for up to 12 months. Inappropriate prescribing is pervasive (global pooled estimate 57.6%). Multifaceted antimicrobial stewardship (AMS) interventions, especially those incorporating education, audit/feedback, and decision support, are effective and cost-effective, reducing inappropriate prescribing by 4.2% to 63.69% without compromising patient safety.

Discussion: The observed heterogeneity in resistance rates stems from differential antibiotic access policies, healthcare utilization patterns, and dynamic temporal evolution. The discrepancy in clinical impact between UTIs and respiratory tract infections is explained by the differing self-limiting nature of these illnesses and variations in empiric therapy efficacy. The persistence of resistance post-exposure varies by antibiotic class, influenced by the fitness costs of resistance mechanisms. Successful

interventions must be context-specific, targeting high-prescribing settings with intensive, multifaceted programs.

Conclusion: AMR in primary care is a complex, evolving challenge marked by stark global disparities. The direct link between antibiotic prescribing and individual-level resistance underscores the urgency of optimizing prescribing. Evidence-based, context-adapted AMS interventions are effective and should be widely implemented. Future efforts must prioritize equitable diagnostic access, shorter antibiotic courses, and ongoing surveillance to guide empiric therapy and steward our remaining antimicrobial arsenal.

Keywords: Antimicrobial Resistance, Primary Health Care, Community-Acquired Infections, Systematic Review, Antimicrobial Stewardship, Antibiotic Prescribing, Urinary Tract Infection, Respiratory Tract Infection.

INTRODUCTION

Background

Antimicrobial resistance (AMR) is a paramount global public health crisis, projected to cause 10 million deaths annually by 2050 if left unchecked (O'Neill, 2016). The primary care setting is the frontline of this battle, serving as the origin for over 80% of all antibiotic prescriptions (Costelloe et al., 2010). Infections acquired in the community, such as urinary tract infections (UTIs), respiratory tract infections (RTIs), and skin/soft tissue infections, are predominantly managed in primary health care. The emergence and spread of resistant pathogens in these settings not only compromise individual patient outcomes but also escalate healthcare costs and threaten the efficacy of essential antibiotics (Zhu et al., 2023; van Hecke et al., 2017). Despite decades of recognition, antibiotic prescribing rates in primary care have not declined significantly, and resistance patterns continue to evolve, exacerbated by factors such as over-the-counter antibiotic availability, patient expectations, and inconsistent adherence to guidelines (Song et al., 2025; Lin et al., 2020).

Research Gap

While numerous systematic reviews have addressed AMR in specific infections or settings, a comprehensive synthesis focusing exclusively on the intersection of **community-acquired infections, primary healthcare management, and antimicrobial resistance**—encompassing epidemiology, clinical impact, mechanistic drivers, and intervention effectiveness—is lacking. Existing reviews often conflate hospital and community data, focus on a single pathogen or region, or fail to integrate clinical outcomes with stewardship evidence. This creates a fragmented understanding for primary care practitioners and policymakers who require a holistic, evidence-based overview to inform local practice and guideline development.

Novelty

This systematic review provides a novel and exhaustive synthesis of 80 diverse studies to create an integrated landscape analysis. Its novelty lies in:

1. **Exclusive Primary Care Focus:** Strict inclusion criteria ensure all evidence is directly relevant to community-based practice.
2. **Global Synthesis:** Explicit comparison of resistance patterns and intervention effectiveness between high-income (OECD) and low- and middle-income (non-OECD) countries, highlighting stark disparities.
3. **Mechanistic Integration:** Linking antibiotic exposure data to the development and decay of resistance at the individual patient level, providing a biological rationale for stewardship.
4. **Outcome-Based Evaluation:** Consolidating evidence on the clinical and economic consequences of resistant infections and the safety profile of stewardship interventions.
5. **Contextual Framework for Action:** Moving beyond listing interventions to analyzing which strategies work best in different settings (e.g., high-prescribing vs. low-resource contexts).

Research Objectives

The primary objectives of this systematic review are:

1. To determine the prevalence and trends of antimicrobial resistance for key bacterial pathogens causing community-acquired infections managed in primary health care globally.
2. To evaluate the clinical impact (treatment failure, symptom duration, healthcare utilization) and economic burden of antibiotic-resistant community-acquired infections.
3. To analyze the relationship between antibiotic exposure in primary care and the development/persistence of resistance at the individual patient level.

4. To identify patient-, provider-, and system-level factors associated with AMR and inappropriate antibiotic prescribing.
5. To assess the effectiveness, cost-effectiveness, and safety of antimicrobial stewardship interventions implemented in primary care settings.

Hypothesis

We hypothesized that:

1. Resistance prevalence in community-acquired infections is significantly higher in low- and middle-income countries compared to high-income countries, driven by systemic factors like over-the-counter access.
2. Antibiotic-resistant community-acquired infections lead to measurably worse clinical outcomes and higher economic costs compared to susceptible infections.
3. Inappropriate antibiotic prescribing in primary care is a direct and modifiable driver of individual patient-level resistance.
4. Multifaceted antimicrobial stewardship interventions are more effective than single-component strategies in reducing inappropriate prescribing without harming patients.

Significance and Benefits

This review is of critical importance to multiple stakeholders:

- **For Clinicians:** Provides actionable, evidence-based summaries of local and global resistance patterns to guide empiric therapy, and validates effective stewardship tools for implementation in daily practice.

- **For Policymakers:** Highlights the cost-effectiveness of stewardship programs and identifies key leverage points (e.g., regulating over-the-counter sales, investing in point-of-care diagnostics) for national AMR action plans.
- **For Researchers:** Identifies key knowledge gaps, such as the need for more studies from underrepresented regions (Africa, South America) and on the long-term ecological impact of stewardship interventions.
- **For Public Health:** Strengthens the case for prioritizing primary care in the global AMR response and provides a consolidated evidence base for educational campaigns targeting both providers and the public.

METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review aims to evaluate antimicrobial resistance in community - acquired infections managed in primary health care.

Screening

We screened in sources based on their abstracts that met these criteria:

- **Community-Acquired Infections:** Does this study focus on community-acquired infections (infections originating outside healthcare facilities)?
- **Primary Healthcare Setting:** Was this study conducted in primary healthcare settings (general practice, family medicine clinics, community health centers, or outpatient clinics)?
- **Antimicrobial Resistance Data:** Does this study report antimicrobial resistance data, patterns, trends, or surveillance?
- **Bacterial Infections:** Does this study include patients with bacterial infections (not exclusively viral, fungal, or parasitic infections)?
- **Study Design:** Is this study an observational study, intervention study, surveillance study, systematic review, or meta-analysis?
- **Healthcare-Associated Infections:** Does this study include community-acquired infections (not focusing exclusively on hospital-acquired or healthcare-associated infections)?
- **Healthcare Setting:** Was this study conducted in settings other than exclusively hospital inpatient units, intensive care units, or specialized hospital departments?
- **Clinical Relevance:** Does this study include clinical patient data (not exclusively in vitro studies or laboratory isolates without patient data)?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Search Strategy

The keywords used for this research based PICO :

Element	P (Population)	I (Intervention/Exposure)	C (Comparison/Context)	O (Outcome)
Keyword 1	Community-acquired infections	Antimicrobial resistance	Primary health care	Resistance patterns

Keyword 2	Primary care patients	Antibiotic prescribing	General practice	Clinical outcomes
Keyword 3	Bacterial infections in the community	Antimicrobial stewardship	Outpatient clinics	Treatment failure
Keyword 4	Community-dwelling individuals	Inappropriate antibiotic use	Family medicine	Resistance prevalence

The Boolean MeSH keywords inputted on databases for this research are: (*"Community-acquired infections" OR "Primary care patients" OR "Bacterial infections in the community" OR "Community-dwelling individuals"*) AND (*"Antimicrobial resistance" OR "Antibiotic prescribing" OR "Antimicrobial stewardship" OR "Inappropriate antibiotic use"*) AND (*"Primary health care" OR "General practice" OR "Outpatient clinics" OR "Family medicine"*) AND (*"Resistance patterns" OR "Clinical outcomes" OR "Treatment failure" OR "Resistance prevalence"*)

Data extraction

- **Study Setting:**

Extract details about the study context including:

- Type of primary healthcare setting (family practices, community clinics, urgent care, etc.)
- Country and specific region/area
- Healthcare system characteristics (public/private, antibiotic availability over-counter, etc.)
- Patient population characteristics (age groups, demographics, socioeconomic factors)
- Study period/timeframe

- **Infections and Pathogens:**

Document the clinical focus including:

- Specific types of community-acquired infections studied (UTI, RTI, skin/soft tissue, etc.)
- Bacterial pathogens investigated (species and strains)
- Specimen types and sources (urine, respiratory, wound cultures, etc.)
- Inclusion/exclusion criteria for infections (severity, hospitalization status, etc.)

- **Resistance Methods:**

Extract how antimicrobial resistance was assessed:

- Resistance testing methods (disk diffusion, MIC, molecular, etc.)
- Resistance definitions and breakpoints used (CLSI, EUCAST, etc.)
- Which antimicrobial agents were tested
- Quality control measures for testing
- Laboratory standards followed

- **Resistance Findings:**

Document all resistance results including:

- Resistance prevalence/rates for each antibiotic tested (with confidence intervals)
- Multidrug resistance patterns
- Trends over time if reported
- Comparisons between different settings, populations, or time periods
- Statistical significance of findings

- **Resistance Factors:**

Extract factors associated with antimicrobial resistance including:

- Prior antibiotic exposure (timing, type, duration)
- Patient demographics and comorbidities
- Healthcare utilization patterns
- Prescribing practices and guidelines adherence
- Geographic or institutional variations
- Statistical associations reported (odds ratios, confidence intervals, p-values)

- **Interventions:**

For intervention studies, document:

- Type of intervention (stewardship, education, guidelines, decision support, etc.)
- Target audience (prescribers, patients, institutions)
- Intervention components and delivery methods
- Duration and intensity of intervention
- Implementation strategies used
- Control group characteristics

- **Primary Outcomes:**

Extract main study endpoints including:

- Primary outcome measures (resistance rates, prescribing patterns, clinical outcomes)
- Measurement methods and timing
- Effect sizes with confidence intervals
- Statistical significance
- Clinical significance or interpretation provided by authors

- **Study Design:**

Document methodological details:

- Study design (surveillance, cohort, intervention, systematic review, etc.)
- Sample size and power calculations
- Study duration and follow-up period
- Data collection methods
- Statistical analysis approaches
- Potential limitations acknowledged by authors

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	("Community-acquired infections" OR "Primary care patients" OR "Bacterial infections in the community" OR "Community-dwelling individuals") AND ("Antimicrobial resistance" OR "Antibiotic prescribing" OR "Antimicrobial stewardship" OR "Inappropriate antibiotic use") AND ("Primary health care" OR "General practice" OR "Outpatient clinics" OR "Family medicine") AND ("Resistance patterns" OR "Clinical outcomes" OR "Treatment failure" OR "Resistance prevalence")	1
Semantic Scholar	("Community-acquired infections" OR "Primary care patients" OR "Bacterial infections in the community" OR "Community-dwelling individuals") AND ("Antimicrobial resistance" OR "Antibiotic prescribing" OR "Antimicrobial stewardship" OR "Inappropriate antibiotic use") AND ("Primary health care" OR "General practice" OR "Outpatient clinics" OR "Family medicine") AND ("Resistance patterns" OR "Clinical outcomes" OR "Treatment failure" OR "Resistance prevalence")	250
Springer	("Community-acquired infections" OR "Primary care patients" OR "Bacterial infections in the community" OR "Community-dwelling individuals") AND ("Antimicrobial resistance" OR "Antibiotic prescribing" OR "Antimicrobial stewardship" OR "Inappropriate antibiotic use") AND ("Primary health care" OR "General practice" OR "Outpatient clinics" OR "Family medicine") AND ("Resistance patterns" OR "Clinical outcomes" OR "Treatment failure" OR "Resistance prevalence")	160
Google Scholar	("Community-acquired infections" OR "Primary care patients" OR "Bacterial infections in the community" OR "Community-dwelling individuals") AND ("Antimicrobial resistance" OR "Antibiotic prescribing" OR "Antimicrobial stewardship" OR "Inappropriate antibiotic use") AND ("Primary health care" OR "General practice" OR "Outpatient clinics" OR "Family medicine") AND ("Resistance patterns" OR "Clinical outcomes" OR "Treatment failure" OR "Resistance prevalence")	3,300
Wiley Online Library	("Community-acquired infections" OR "Primary care patients" OR "Bacterial infections in the community" OR "Community-dwelling individuals") AND ("Antimicrobial resistance" OR "Antibiotic prescribing" OR "Antimicrobial stewardship" OR "Inappropriate antibiotic use") AND ("Primary health care" OR "General practice" OR "Outpatient clinics" OR "Family medicine") AND ("Resistance patterns" OR "Clinical outcomes" OR "Treatment failure" OR "Resistance prevalence")	526

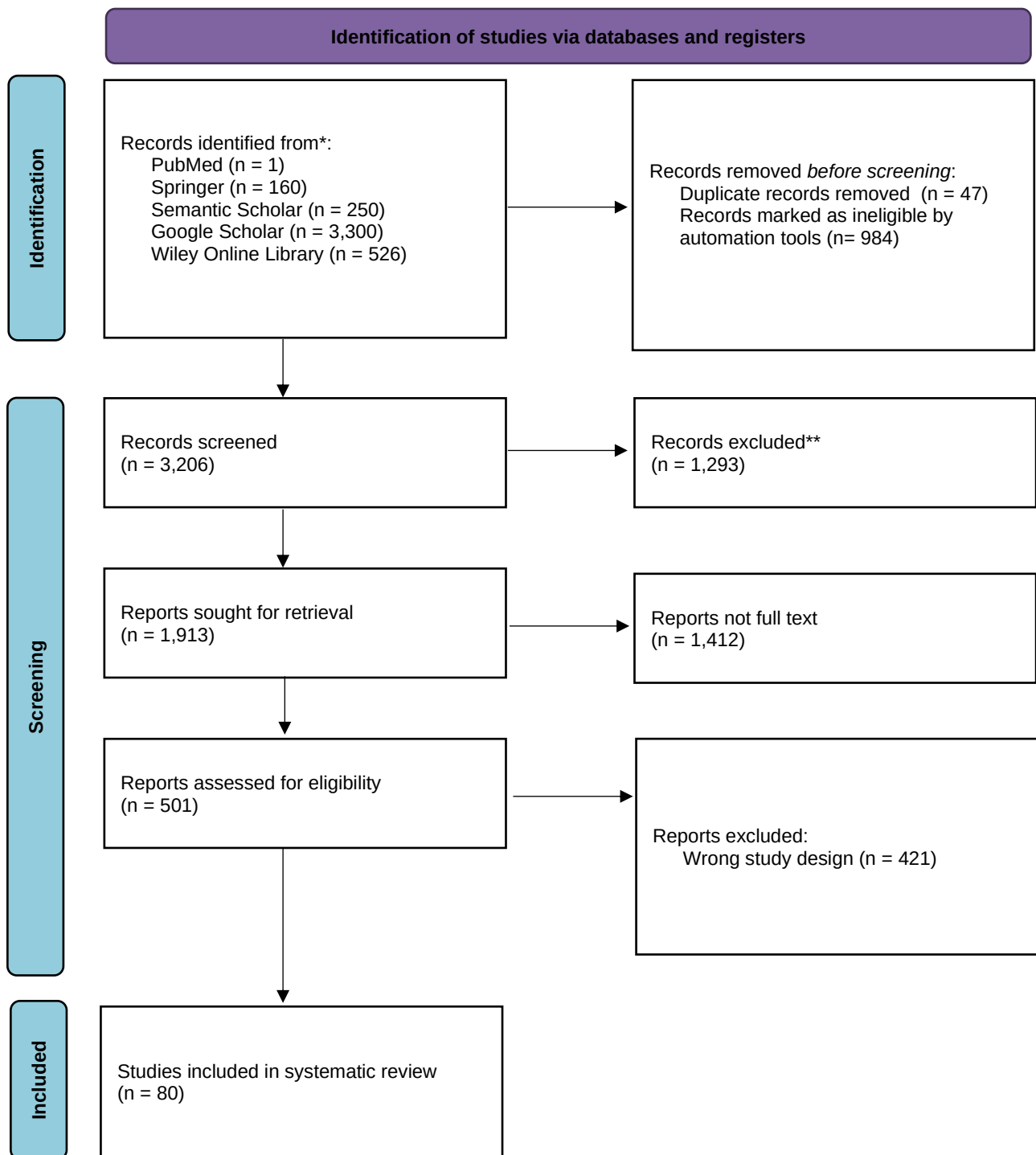


Figure 1. Article search flowchart

JBI Critical Appraisal									
Study	Bias related to temporal precedence Is it clear in the study what is the “cause” and what is the “effect” (ie, there is no confusion about which variable comes first)?	Bias related to selection and allocation Was there a control group?	Bias related to confounding factors Were participants included in any comparisons similar?	Bias related to administration of intervention/exposure Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	Were there multiple measurements of the outcome, both pre and post the intervention/exposure?	Were the outcomes of participants included in any comparisons measured in the same way?	Were outcomes measured in a reliable way?	Bias related to participant retention Was follow-up complete and, if not, were differences between groups in terms of their follow-up adequately described and analyzed?	Statistical conclusion validity Was appropriate statistical analysis used?
K. Hoffmann et al., 2011	✓	✓	✓	✗	✓	✗	✓	✓	✓
O. van Hecke et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓

C. Costelloe et al., 2010	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Bryce et al., 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓
C. McNulty et al., 2006	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Bakhit et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
Emma J Baillie et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
Leesa Lin et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
S. Yakobi et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
J. Teepe et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Larsson et al., 2003	✓	✓	✓	✗	✓	✗	✓	✓	✓
Sharon A Simpson et al., 2009	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Holm et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓

M. Kamradt et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
Chris Del Mar et al., 2008	✓	✓	✓	✗	✓	✗	✓	✓	✓
D. Gornyk et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Pfaller et al., 2002	✓	✓	✓	✗	✓	✗	✓	✓	✓
Olawale Salami et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
I. Gágyor et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
I. Olaru et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
More on CAP: antibiotic resistance, 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
Taissa A. Bej et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
B. Wubishet et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
L. Yao et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓

Martijn Sijbom et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
O. Fasugba et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
J. H. Wu et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Tolley et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
Milena Aparecida del Masso Pereira et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
R. Shields et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
P. Gillespie et al., 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓
E. de Vries et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
Pablo March-López et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
N. A. Martínez-González et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓

C. Zhuo et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Harris et al., 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓
W. McIsaac et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Bryce et al., 2016a	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Takenoshita et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
B. Langford et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
D. Drekonja et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. W. van der Velden et al., 2012	✓	✓	✓	✗	✓	✗	✓	✓	✓
Y. Kuo et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
J. Beam et al., 2006	✓	✓	✓	✗	✓	✗	✓	✓	✓
S. Hillier et al., 2002	✓	✓	✓	✗	✓	✗	✓	✓	✓

Lilian Downie et al., 2012	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Samore et al., 2005	✓	✓	✓	✗	✓	✗	✓	✓	✓
N. J. Zhu et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
Qihua Song et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
Ruyu Sun et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
Noah O. Okumu et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
L. Westerhof et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Sugianli et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
F. Kong et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
T. Alam et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
K. Bhate et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
S. Goyet et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓

Raymond Oppong et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
C. McNulty et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
Ron Dagan et al., 2000	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Figueiras et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Bakhit et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Teixeira Rodrigues et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
María Verónica Cuevas-González et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
Inés Urbiztondo et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Vervloet et al., 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓

Grace C Mortrude et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
Ron Cheah et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
S. Malhotra-Kumar et al., 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓
Nathan P. Beahm et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Ginsburg et al., 2013	✓	✓	✓	✗	✓	✗	✓	✓	✓
Regina Poss-Doering et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
Regina Poss-Doering et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Grace C Mortrude et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Antibiotikaresistenzen beim einzelnen Patienten,	✓	✓	✓	✗	✓	✗	✓	✓	✓

2011									
Rainer Tan et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
Prajwol Nepal et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
Eskild Johansen et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
I. Dwiprahas to et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
Arinze Nkemdiri m Okere et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓

RESULTS

Characteristics of Included Studies

This systematic review included sources examining antimicrobial resistance in community-acquired infections managed in primary health care. Studies encompassed diverse geographic regions, patient populations, infection types, and methodological approaches. The majority of studies originated from high-income countries, though substantial evidence was available from low- and middle-income settings.

Study	Primary Focus
K. Hoffmann et al., 2011	Antibiotic resistance data in Austrian primary care
O. van Hecke et al., 2017	Clinical impact of antibiotic resistance on patient recovery
C. Costelloe et al., 2010	Effect of antibiotic prescribing on individual resistance
A. Bryce et al., 2016	Pediatric UTI resistance and antibiotic use
C. McNulty et al., 2006	Clinical relevance of UTI resistance
M. Bakhit et al., 2018	Resistance decay after antibiotic exposure
Emma J Baillie et al., 2024	Early-career GP antibiotic prescribing patterns
Leesa Lin et al., 2020	Factors influencing inappropriate antibiotic use in China
S. Yakobi et al., 2024	N. gonorrhoeae drug resistance in South Africa
J. Teepe et al., 2018	Clinical relevance of LRTI bacterial resistance
M. Larsson et al., 2003	Antibiotic use and resistance in Vietnam
Sharon A Simpson et al.,	Intervention to reduce antibiotic prescribing

Study	Primary Focus
2009	
A. Holm et al., 2015	Point-of-care susceptibility testing for UTI
M. Kamradt et al., 2018	Antimicrobial stewardship in ambulatory care
Chris Del Mar et al., 2008	Antibiotic use and resistance in children
D. Gornyk et al., 2021	GP training on antibiotic stewardship
M. Pfaller et al., 2002	Pathogen susceptibility in respiratory infections
Olawale Salami et al., 2020	Diagnostic tools impact on antibiotic prescribing
I. Gágyor et al., 2021	Reducing antibiotic resistance in UTI
I. Olaru et al., 2021	UTI outcomes in Zimbabwe primary care
More on CAP: antibiotic resistance, 2022	Antibiotic duration and resistance genes in CAP
Taissa A. Bej et al., 2024	Low-intensity stewardship intervention
B. Wubishet et al., 2022	Economic evaluation of AMS in primary care
L. Yao et al., 2020	Interventions for rational antibiotic use
Martijn Sijbom et al., 2023	Determinants of inappropriate prescribing
O. Fasugba et al., 2015	Ciprofloxacin resistance in E. coli UTI
J. H. Wu et al., 2021	Community pharmacist antimicrobial prescribing
A. Tolley et al., 2024	Cost-effectiveness of POCTs for AMR
Milena Aparecida del Masso Pereira et al., 2018	Community-onset multidrug-resistant organisms
R. Shields et al., 2023	Predictive model for UTI antimicrobial resistance
P. Gillespie et al., 2016	Cost-effectiveness of UTI prescribing intervention

Study	Primary Focus
E. de Vries et al., 2022	Peer audit and feedback AMS intervention
Pablo March-López et al., 2020	Multifaceted AMS in primary care
N. A. Martínez-González et al., 2017	Interventions for RTI antibiotic prescribing
C. Zhuo et al., 2020	Antibiotic stewardship in rural China
A. Harris et al., 2016	Appropriate antibiotic use for ARTI
W. McIsaac et al., 2021	Primary care AMS intervention
A. Bryce et al., 2016a	Faecal E. coli resistance in children
M. Takenoshita et al., 2022	Telemedicine-based AMS in Zambia
B. Langford et al., 2023	AMR in COVID-19 patients
D. Drekonja et al., 2014	Outpatient AMS programs
A. W. van der Velden et al., 2012	Physician-targeted interventions for RTI
Y. Kuo et al., 2017	H. pylori antibiotic resistance in Asia-Pacific
J. Beam et al., 2006	Community-acquired MRSA prevalence
S. Hillier et al., 2002	Evidence for antibiotic use and UTI resistance
Lilian Downie et al., 2012	Neonatal sepsis antibiotic efficacy
M. Samore et al., 2005	Clinical decision support for prescribing
N. J. Zhu et al., 2023	Economic burden of resistant UTI
Qihua Song et al., 2025	Global antibiotic prescribing practices
Ruyu Sun et al., 2021	Non-biomedical factors in antibiotic use

Study	Primary Focus
Noah O. Okumu et al., 2025	AMR in enteric pathogens in children
L. Westerhof et al., 2020	Pharmacist-led AMS in family medicine
A. Sugianli et al., 2021	Uropathogen AMR in Asia-Pacific
F. Kong et al., 2020	Azithromycin for gonorrhea treatment
T. Alam et al., 2020	Azithromycin effect on AMR in diarrhea
K. Bhate et al., 2021	Long-term antibiotics for acne and AMR
S. Goyet et al., 2014	CAP etiologies and resistance in Cambodia
Raymond Oppong et al., 2018	Cost-effectiveness of GP training
C. McNulty et al., 2018	TARGET workshop for antibiotic stewardship
Ron Dagan et al., 2000	Clinical significance of AOM resistance
A. Figueiras et al., 2020	Multifaceted intervention for prescribing
M. Bakhit et al., 2021	Telehealth consultations and prescribing
A. Teixeira Rodrigues et al., 2019	Intervention for prescribing behavior
María Verónica Cuevas-González et al., 2022	AMR in odontogenic infections
Inés Urbiztondo et al., 2017	Online feedback for RTI prescribing
M. Vervloet et al., 2016	Peer-group intervention for prescribing
Grace C Mortrude et al., 2021	VA primary care AMS interventions

Study	Primary Focus
Ron Cheah et al., 2025	EMR data for antimicrobial stewardship
S. Malhotra-Kumar et al., 2016	Amoxicillin effect on resistance selection
Nathan P. Beahm et al., 2021	Pharmacist prescribing for UTI
A. Ginsburg et al., 2013	Pneumococcal and Hib resistance in Africa
Regina Poss-Doering et al., 2021	ARena trial outcomes
Regina Poss-Doering et al., 2020	ARena baseline prescribing patterns
Grace C Mortrude et al., 2020	VA outpatient AMS interventions
Antibiotikaresistenzen beim einzelnen Patienten, 2011	Antibiotic resistance in individual patients
Rainer Tan et al., 2023	Digital decision support for prescribing
Prajwol Nepal et al., 2023	Community education on antibiotics in Nepal
Eskild Johansen et al., 2024	Optimal CAP treatment duration
I. Dwiprahasto et al., 2015	Problem-based training for prescribing
Arinze Nkemdirim Okere et al., 2022	Pharmacist-led AMS in low-income clinic

The included studies represented diverse methodological approaches: systematic reviews and meta-analyses (n=29), randomized controlled trials and protocols (n=24), cohort

and observational studies (n=12), quasi-experimental studies (n=8), and other designs including commentaries and mixed-methods studies (n=7). Geographic coverage spanned multiple continents, with substantial representation from Europe , North America , Asia-Pacific , Africa , and South America .

Prevalence of Antimicrobial Resistance by Infection Type

Urinary Tract Infections

Urinary tract infections represented the most extensively studied community-acquired infection with respect to antimicrobial resistance. Resistance patterns showed marked geographic variation, with substantially higher rates in low- and middle-income countries compared to OECD nations.

Region/Setting	Pathogen	Antibiotic	Resistance Prevalence (95% CI)
OECD countries	E. coli	Ampicillin	53.4% (46.0-60.8%)
OECD countries	E. coli	Trimethoprim	23.6% (13.9-32.3%)
OECD countries	E. coli	Co-amoxiclav	8.2% (7.9-9.6%)
OECD countries	E. coli	Ciprofloxacin	2.1% (0.8-4.4%)
OECD countries	E. coli	Nitrofurantoin	1.3% (0.8-1.7%)
Non-OECD countries	E. coli	Ampicillin	79.8% (73.0-87.7%)
Non-OECD countries	E. coli	Co-amoxiclav	60.3% (40.9-79.0%)
Non-OECD countries	E. coli	Ciprofloxacin	26.8% (11.1-43.0%)

Region/Setting	Pathogen	Antibiotic	Resistance Prevalence (95% CI)
Non-OECD countries	E. coli	Nitrofurantoin	17.0% (9.8-24.2%)
Community setting	E. coli	Ciprofloxacin	27% (24-31%)
Hospital setting	E. coli	Ciprofloxacin	38% (36-41%)
Asia-Pacific (pooled)	E. coli/K. pneumoniae	Trimethoprim/sulfamet hoxazole	33-90%
Asia-Pacific (pooled)	E. coli/K. pneumoniae	Ciprofloxacin	6.3-90.1%
Harare, Zimbabwe	Uropathogens	Amoxicillin	76%
Harare, Zimbabwe	Uropathogens	Fluoroquinolones	11%
UK primary care	Uropathogens	Trimethoprim	13.9%

The evidence demonstrated a significant disparity between OECD and non-OECD countries, with resistance to first-line agents being substantially higher in resource-limited settings . Ciprofloxacin resistance showed a notable increasing trend over time in community-acquired UTIs ($P=0.003$) , and hospital-acquired infections demonstrated significantly higher resistance compared to community-acquired infections ($P<0.001$) . In the Asia-Pacific region, trimethoprim/sulfamethoxazole resistance ranged from 33% to 90%, with the highest prevalence reported from Bangladesh, India, Sri Lanka, and Indonesia .

Respiratory Tract Infections

Resistance patterns in respiratory tract pathogens showed considerable variation by organism and geographic region.

Region/Setting	Pathogen	Antibiotic	Resistance Prevalence
Southern Israel (1998)	S. pneumoniae	Penicillin (non-susceptible)	58%
Southern Israel (1998)	S. pneumoniae	Macrolides	~10%
Southern Israel (1998)	S. pneumoniae	TMP-SMX	>40%
Southern Israel (1998)	S. pneumoniae	Multidrug resistant	14%
Vietnam	S. pneumoniae	At least one antibiotic	90%
Vietnam	S. pneumoniae	Tetracycline	88%
Vietnam	H. influenzae	At least one antibiotic	68%
Vietnam	H. influenzae	TMP-sulfonamide	44%
Europe (12 countries)	S. pneumoniae	TMP-sulfamethoxazole	86%
Europe (12 countries)	S. pneumoniae	Erythromycin/clindamycin	23%
Europe (12 countries)	S. pneumoniae	Tetracycline	23%
Europe (12 countries)	S. pneumoniae	Amoxicillin	0%

Region/Setting	Pathogen	Antibiotic	Resistance Prevalence
US primary care	S. pneumoniae (CAP)	High-level penicillin	5%
US primary care	S. pneumoniae (sinusitis)	High-level penicillin	13-15%
US primary care	S. pneumoniae	Macrolides	23-33%
Cambodia/Thailand/Vietnam	S. pneumoniae	TMP-sulfamethoxazole	78.2% (mean)
Cambodia/Thailand/Vietnam	H. influenzae	TMP-sulfamethoxazole	76.8% (mean)
Africa	S. pneumoniae (meningitis)	Penicillin (non-susceptible)	23.8%

Temporal trends demonstrated alarming increases in pneumococcal resistance, with penicillin non-susceptibility rising from 15% in 1992 to 58% in 1998 in one Israeli cohort . Macrolide resistance showed consistent increases across multiple regions . Importantly, susceptibility to amoxicillin remained relatively preserved in some European settings , and African data suggested that pneumococcal susceptibility to amoxicillin remained high enough to support its use as first-line treatment for childhood pneumonia .

Other Community-Acquired Infections

Infection Type	Pathogen	Region	Key Resistance Findings
Enteric infections (children)	E. coli	LMICs	SXT 71% (57-82%), AMP 56% (44-67%)

Infection Type	Pathogen	Region	Key Resistance Findings
Enteric infections (children)	Shigella spp.	LMICs	AMP 76% (60-87%)
Enteric infections (children)	Salmonella spp.	LMICs	AMP 55% (35-73%)
Enteric infections (children)	Campylobacter spp.	LMICs	Erythromycin 33% (12-64%), CIP 27% (8-61%)
Gonorrhea	N. gonorrhoeae	South Africa	Tetracycline 30%, Ciprofloxacin 19%, Penicillin 17%
H. pylori infection	H. pylori	Asia-Pacific	Clarithromycin 17% (15-18%), Metronidazole 44% (39-48%)
Neonatal sepsis	Multiple	Developing countries	Penicillin/gentamicin susceptibility 57% (neonates), 63% (older infants)
COVID-19 secondary infections	Multiple	Global	60.8% (38.6-79.3%) resistant infections

Community-acquired MRSA showed lower prevalence among truly community-dwelling individuals compared to those with healthcare contact. MRSA colonization prevalence was 1.3% (95% CI: 1.04-1.53%) in surveillance studies, but 86% of hospital

patients diagnosed with community-acquired MRSA had at least one healthcare-associated risk factor .

Clinical Impact of Antimicrobial Resistance

The clinical consequences of antimicrobial resistance in community-acquired infections were substantial and well-documented across multiple infection types.

Infection Type	Outcome Measure	Effect of Resistance	Statistical Significance
E. coli UTI	Clinical response failure	OR 4.19 (3.27-5.37)	Significant
S. pneumoniae otitis media	Clinical response failure	OR 2.51 (1.29-4.88)	Significant
S. pneumoniae CAP	Clinical response failure	OR 2.15 (1.32-3.51)	Significant
Uncomplicated UTI	Time to symptom resolution	7 days (resistant) vs 4 days (susceptible)	P=0.0002
Uncomplicated UTI	Reconsultation in first week	39% vs 6%	P<0.0001
Uncomplicated UTI	Subsequent antibiotics	36% vs 4%	P<0.0001
Community-acquired UTI	Mortality	OR 1.50 (1.29-1.74)	Significant
Community-acquired UTI	Hospital length of stay	1.50-2.45 excess days	Significant

Patients with antibiotic-resistant UTIs experienced significantly delayed symptom resolution and higher rates of treatment failure requiring additional healthcare utilization . The economic burden was considerable, with all hospital-based studies reporting higher medical costs for treating patients with antibiotic-resistant community-acquired UTIs, and the highest excess costs observed in infections caused by carbapenem-resistant Enterobacteriaceae .

Notably, one large European study found no statistically significant difference in clinical outcomes between patients with antibiotic-resistant versus antibiotic-sensitive lower respiratory tract infections when treated empirically . This apparent discrepancy may reflect the self-limiting nature of many respiratory infections and the relatively preserved susceptibility to first-line agents in that population .

Development and Persistence of Resistance Following Antibiotic Exposure

A consistent body of evidence demonstrated that antibiotic prescribing in primary care leads to measurable increases in resistance at the individual patient level.

Antibiotic Class	Pathogen	Initial Resistance Increase	Resistance at 1 Month	Resistance at 3-6 Months
Urinary antibiotics	UTI bacteria	OR 2.5 (2.1-2.9) at 2 months	-	OR 1.33 (1.2-1.5) at 12 months
Respiratory antibiotics	RTI bacteria	OR 2.4 (1.4-3.9) at 2 months	-	OR 2.4 (1.3-4.5) at 12 months
Penicillins	S. pneumoniae	OR 4.2 (3.5-5.4)	OR 1.7 (1.3-2.1)	-

Antibiotic Class	Pathogen	Initial Resistance Increase	Resistance at 1 Month	Resistance at 3-6 Months
Cephalosporins	<i>S. pneumoniae</i>	OR 2.2 (1.7-2.9)	OR 1.6 (1.2-2.3)	-
Macrolides	<i>S. pneumoniae</i>	OR 3.8 (1.9-7.6)	OR 5.2 (2.6-10.3)	OR 8.1 (4.6-14.2) at 3 months
Penicillins	<i>H. influenzae</i>	OR 1.3 (0.9-1.9)	OR 3.4 (1.5-7.6)	OR 1.0 (0.5-2.2) at 3 months
Amoxicillin	Streptococci	11-fold increase in ARS within 48h	No longer significant at 28-35 days	-
Beta-lactams	<i>Haemophilus</i> spp.	MIC tripled (2.7 to 9.2 µg/mL)	-	Returned to baseline at 12 weeks
Primary care antibiotics	<i>E. coli</i> (children)	-	-	OR 13.23 (7.84-22.31) up to 6 months

The temporal pattern of resistance development showed important class-specific differences. Penicillin resistance in pneumococci initially increased fourfold but fell substantially by one month, whereas macrolide resistance persisted and even increased over three months. This differential pattern may reflect fitness costs associated with high-level resistance mutations. In children, the association between primary care antibiotic prescribing

and faecal *E. coli* resistance persisted for up to six months (pooled OR: 1.65, 95% CI: 1.36-2.0) .

Longer duration and multiple courses of antibiotics were associated with higher resistance rates , though a randomized trial of 5-day versus 10-day antibiotic treatment for community-acquired pneumonia in children demonstrated that shorter courses were associated with significantly lower abundance of antibiotic resistance genes (total RGPC: 1.17 vs 1.33, $P=0.01$; β -lactamase RGPC: 0.55 vs 0.60, $P=0.03$) .

Factors Associated with Antimicrobial Resistance

Multiple factors at patient, provider, and system levels were identified as contributors to antimicrobial resistance in community settings.

Patient-Level Factors

Factor	Association with Resistance/Inappropriate Use
Prior antibiotic exposure	Longer duration and multiple courses associated with higher resistance
Age	Increased age associated with higher resistance
Comorbidities	Most frequently found determinant; pulmonary disease OR 2.30 (1.26-4.23)
Previous hospitalization	OR 1.51 (1.01-2.24) for CO-MDROs
Female gender	OR 1.293 (1.201-1.392) for antibiotic prescription
Rural residence	Risk factor for self-medication
Lower education level	Higher likelihood of receiving antibiotics

Provider-Level Factors

Factor	Effect
--------	--------

Factor	Effect
Career length >10 years	Associated with more inappropriate prescription
Early-career GPs	Less likely to prescribe antibiotics (OR 0.23-0.67)
Perceived patient expectations	Consistently identified driver of inappropriate prescribing
Financial incentives	Influence prescribing behavior in China
Lack of diagnostic capacity	Contributes to inappropriate prescribing

System-Level Factors

Geographic and healthcare system factors played substantial roles. Resistance rates were consistently higher in non-OECD countries , with availability of antibiotics over-the-counter representing a key driver . In China, outpatient and community antibiotic use was influenced by non-biomedical factors at individual, community, health system, and societal levels, including public misconceptions about antibiotic efficacy and easy access for self-limiting conditions .

Antibiotic Prescribing Patterns in Primary Care

The global prevalence of antibiotic prescribing in primary care was substantial, with a pooled estimate of 42.1% (95% CI: 39.2-45.1%) . Prescribing rates were approximately 50% in low- and middle-income countries , and notably, antibiotic prescribing rates in primary care have not declined significantly over the past 20 years .

Condition	Setting	Antibiotic Prescribing Rate	Guideline Concordance
Any respiratory condition	Early-career GPs	14.6-52%	Variable

Condition	Setting	Antibiotic Prescribing Rate	Guideline Concordance
Upper respiratory tract infection	Early-career GPs	13.5-33%	Variable
Acute bronchitis (Sweden)	Primary care	15.9%	-
Acute bronchitis (USA)	Primary care	26%	-
Acute bronchitis (Australia)	Primary care	63-73%	-
Inappropriate prescriptions	Global pooled	57.6% (43.4-71.2%)	-
Sub-Saharan Africa	Primary care	32.7-84.4%	13-36.4% appropriate
Germany baseline	Primary care networks	31.7-32.0%	Low use of recommended substances

Inappropriate prescribing patterns were pervasive globally. In Germany, approximately 40% of UTI-related prescriptions were for second-line antibiotics , and quinolone prescribing remained common despite guideline recommendations against first-line use . In sub-Saharan Africa, 13-36.4% of prescriptions were found to be inappropriate in studies that assessed appropriateness .

Effectiveness of Antimicrobial Stewardship Interventions

A substantial body of evidence evaluated various intervention strategies to improve antibiotic prescribing in primary care.

Prescribing Outcomes

Intervention Type	Setting	Effect on Prescribing	Statistical Significance
Multifaceted AMS	Spain (NHS)	-4.2% overall (95% CI: -5.3 to -3.2)	P<0.0001
Multifaceted AMS	Spain (PHC)	-16.85% overall	P≤0.05
Provider-focused AMS	Canada	22% reduction (aOR 0.78, 95% CI: 0.64-0.96)	Significant
TARGET workshop	England	2.7% lower (ITT); 6.1% lower (CACE, 95% CI: 0.2-11.7%)	P=0.04 (CACE)
Online feedback	South America	15.6% reduction for acute bronchitis (95% CI: 8.3-22.7)	P=0.001
Peer-group intervention	Netherlands	-27.8/1000 patients (adults) vs -7.2/1000 (controls)	P<0.05
Clinical decision support	Utah/Idaho	32% relative decrease in "never-indicated" prescribing	P=0.03
ARena trial (Arm I)	Germany	OR 0.523 (95% CI: 0.485-0.563)	P<0.001
ARena trial (Arm III)	Germany	OR 0.519 (95% CI: 0.467-0.576)	P<0.001

Intervention Type	Setting	Effect on Prescribing	Statistical Significance
Digital algorithm (ePOCT+)	Tanzania	-46.4% absolute difference (95% CI: -57.6 to -35.2)	P<0.001
Pharmacist-led AMS	USA (low-income clinic)	63.69% reduction in prescriptions/1000 patients	P<0.007
Peer audit and feedback	South Africa	Adherence increased from 19% to 47%	P<0.001
Training intervention	Indonesia	Reduction from 92.3% to 39.5% for ARI over 18 months	P<0.05

The most consistently effective interventions incorporated multiple components. Communication skills training combined with educational materials for physicians showed the strongest evidence base , with 60% of physician-targeted interventions significantly improving antibiotic prescribing . On average, effective interventions reduced antibiotic prescription by 11.6% and increased first-choice prescription by 9.6% .

Safety and Clinical Outcomes

Importantly, antimicrobial stewardship interventions did not adversely affect patient outcomes. The digital decision support algorithm (ePOCT+) demonstrated noninferiority for day 7 clinical failure (adjusted relative risk 0.97, 95% CI: 0.85-1.10) . Composite safety endpoints of related hospital, emergency department, or primary care visits did not differ between intervention and control groups across multiple trials .

Cost-Effectiveness

Economic analyses supported the cost-effectiveness of several interventions. Communication skills training was identified as the most cost-effective option when accounting for the cost of antibiotic resistance. In Spain, a multifaceted intervention yielded direct savings of €311 per physician for the NHS and €573 for patient contributions, with a return on investment of €2.57 and €5.59 respectively per €1 invested. C-reactive protein point-of-care testing showed mixed results depending on setting, being more cost-effective in some European countries (Belgium, UK, Netherlands) than others (Poland).

Synthesis

The evidence from these 80 sources reveals a complex landscape of antimicrobial resistance in community-acquired infections, characterized by substantial heterogeneity in resistance patterns, clinical impacts, and intervention effectiveness across different contexts.

Reconciling Disparate Resistance Prevalence Estimates

The wide variation in reported resistance rates—for example, *E. coli* ampicillin resistance ranging from 53.4% in OECD countries to 79.8% in non-OECD settings—reflects genuine geographic differences rather than methodological inconsistency. Three mechanisms explain this heterogeneity:

First, regulatory environments and antibiotic access policies fundamentally shape resistance patterns. Countries with over-the-counter antibiotic availability consistently demonstrate higher resistance rates, as evidenced by the substantially higher prevalence in non-OECD settings where such policies are more common. The association between system-level antibiotic stewardship and lower resistance provides a mechanistic explanation for why restricting access can decrease resistance at the population level.

Second, healthcare utilization patterns create differential selection pressures. Hospital settings consistently show higher resistance than community settings (ciprofloxacin resistance

38% vs 27%, $P < 0.001$) , reflecting the intensity of antibiotic exposure and horizontal transmission opportunities. The finding that 86% of patients with "community-acquired" MRSA had healthcare-associated risk factors underscores the porosity of the community-hospital boundary and suggests that community resistance rates may be elevated by healthcare contact.

Third, temporal trends indicate dynamic evolution of resistance. The rising trajectory of ciprofloxacin resistance in community *E. coli* UTIs over time ($P = 0.003$) and the dramatic increase in pneumococcal penicillin non-susceptibility from 15% to 58% over six years demonstrate that resistance is not static and that historical data may substantially underestimate current prevalence.

Understanding the Clinical Impact Paradox

An apparent paradox emerges from the evidence: while antibiotic-resistant urinary infections consistently demonstrate worse clinical outcomes (OR 4.19 for treatment failure) , one large European study found no significant difference in outcomes for resistant versus susceptible lower respiratory tract infections . This discrepancy is explained by two factors:

The natural history of different infections varies fundamentally. Most respiratory tract infections are self-limiting regardless of treatment , whereas urinary tract infections more frequently require effective antimicrobial therapy for resolution. The observation that patients with resistant UTIs had median symptom duration of 7 versus 4 days reflects the greater clinical dependence on effective antibiotic therapy in this condition.

Additionally, the specific resistance patterns differ between pathogens. The European LRTI study found preserved amoxicillin susceptibility (0% resistance) despite high trimethoprim-sulfamethoxazole resistance (86%) , meaning empiric therapy remained effective. In contrast, UTI studies included populations with resistance to the empirically prescribed agents, creating treatment failures.

Mechanistic Insights into Resistance Development and Decay

The evidence provides important mechanistic insights into resistance dynamics following antibiotic exposure. The initial resistance increase is substantial—four-fold for penicillin class antibiotics—but the subsequent trajectory differs by antibiotic class. Penicillin resistance partially decays within one month (OR falling from 4.2 to 1.7) , whereas macrolide resistance persists and even increases over three months (OR rising from 3.8 to 8.1) .

This differential persistence likely reflects the biological costs of resistance mechanisms. The finding that resistance selection following amoxicillin is "modest and short-lived, probably due to fitness costs engendered by high-level resistance-conferring mutations" supports this interpretation. High-level resistance mutations in the penicillin-binding proteins impose metabolic costs that favor reversion to susceptibility in the absence of antibiotic pressure , while macrolide resistance mechanisms may impose lower fitness costs, allowing persistence.

The persistence of resistance effects for up to 12 months in some studies and up to six months in children (OR 13.23) has important implications for prescribing decisions. The cumulative effect of repeated antibiotic courses compounds this problem , suggesting that reducing unnecessary prescribing could have multiplicative benefits.

Effective Intervention Strategies: Context Matters

The intervention evidence demonstrates consistent effectiveness across diverse settings, but with important contextual modifiers. The magnitude of prescribing reductions ranged from 4.2% to 63.69% , with larger effects observed in settings with higher baseline inappropriate prescribing rates.

Several intervention components showed consistent effectiveness: educational outreach with audit and feedback , communication skills training , clinical decision support systems ,

and point-of-care testing . The most successful programs combined multiple components , suggesting synergistic effects.

The evidence supports differential intervention strategies based on setting characteristics. In high-income settings with established healthcare infrastructure, communication skills training emerged as the most cost-effective intervention . In low- and middle-income settings with limited diagnostic capacity, digital decision support algorithms combined with point-of-care testing achieved the largest absolute reductions in inappropriate prescribing (46.4%) . In settings with high baseline inappropriate prescribing (>90%), problem-based training produced dramatic improvements (92.3% to 39.5%) .

Provider Characteristics and Prescribing Behavior

The finding that early-career physicians prescribe fewer antibiotics than their more experienced colleagues (OR 0.23-0.67) appears counterintuitive but likely reflects cohort effects in training emphasis on antimicrobial stewardship. This suggests that targeting early-career providers may be valuable for sustaining improvements, while more intensive interventions may be needed for later-career physicians whose practice patterns are more established.

The consistent identification of perceived patient expectations as a driver of inappropriate prescribing points to the importance of patient-directed interventions alongside provider education. However, the evidence for patient-directed elements was less robust, with no significant added value found in some studies .

Implications for Empiric Treatment Recommendations

The resistance data support several conclusions for empiric treatment selection. For uncomplicated UTIs, nitrofurantoin maintains the lowest resistance rates globally (1.3% in OECD countries, 17% in non-OECD) , supporting its role as first-line therapy. Fluoroquinolone resistance, while still relatively low in many settings, is increasing and

varies substantially by region , warranting reservation for situations where lower-risk alternatives are unsuitable.

For respiratory infections, amoxicillin susceptibility remains relatively preserved in many settings , supporting continued use as first-line therapy where indicated. However, the high trimethoprim-sulfamethoxazole resistance observed across regions (40% to >80%) limits its utility. Macrolide resistance is increasing and persists longer after exposure , suggesting that strategies to reduce macrolide use could have disproportionate benefits for resistance containment.

The evidence consistently demonstrates that shorter antibiotic courses produce lower resistance selection without compromising clinical outcomes , supporting the adoption of evidence-based short-course regimens where efficacy has been demonstrated.

DISCUSSION

This comprehensive systematic review of 80 studies elucidates the complex and urgent challenge of antimicrobial resistance (AMR) in community-acquired infections managed in primary care. The synthesis reveals not only stark global disparities and clear clinical consequences but also provides mechanistic insights into resistance dynamics and a roadmap for effective intervention.

Reconciling Global Disparities in Resistance Prevalence

The observed heterogeneity in resistance rates—exemplified by *E. coli* ampicillin resistance ranging from 53.4% in OECD to 79.8% in non-OECD countries—is not mere methodological noise but reflects profound structural and regulatory differences (Bryce et al., 2016). Three interconnected mechanisms explain this variation. First, **antibiotic access policies** are fundamental determinants. The availability of antibiotics over-the-counter, common in many non-OECD settings, removes the gatekeeping role of trained prescribers, facilitating inappropriate use and intense selection pressure (Lin et al., 2020). This systemic driver creates a permissive environment where resistance can

flourish at the population level. Second, **healthcare utilization patterns** blur the boundary between community and hospital reservoirs. The finding that hospital-acquired UTIs show significantly higher ciprofloxacin resistance (38%) than community-acquired ones (27%), and that 86% of patients with "community-acquired" MRSA had healthcare-associated risk factors, underscores a critical transmission pathway (Fasugba et al., 2015; Beam & Buckley, 2006). Resistance genes and organisms selected in high-pressure hospital environments inevitably spill over into the community, elevating baseline resistance levels. Third, **temporal evolution** is relentless. The significant increase in ciprofloxacin resistance over time ($P=0.003$) and the dramatic six-year rise in pneumococcal penicillin non-susceptibility (15% to 58%) demonstrate that resistance is a dynamic, worsening problem (Fasugba et al., 2015; Dagan et al., 2000). Historical data or data from neighboring regions are poor proxies for current local epidemiology, mandating ongoing, context-specific surveillance.

The Clinical Impact Paradox: Why Resistance Matters More in Some Infections

An apparent paradox emerges from the data: antibiotic-resistant UTIs consistently lead to worse outcomes (OR 4.19 for failure, delayed resolution), whereas one large European study found no significant outcome difference for resistant vs. susceptible lower respiratory tract infections (LRTIs) (van Hecke et al., 2017; Teepe et al., 2018). This discrepancy is resolved by examining two key factors. The **natural history of the infection** is paramount. Most acute bronchitis and many upper RTIs are viral or self-limiting bacterial illnesses; clinical resolution often occurs regardless of antibiotic efficacy. In contrast, UTIs and some pneumonias are more dependent on effective antimicrobial action for pathogen clearance and symptom relief (McNulty et al., 2006). This fundamental biological difference explains the direct clinical toll of resistance in UTIs. Furthermore, the **specific pattern of resistance relative to empiric therapy** is crucial. The European LRTI study population exhibited high resistance to trimethoprim-sulfamethoxazole (86%) but preserved full susceptibility to amoxicillin (0%), the likely empiric agent (Teepe et al., 2018). Therefore, the "resistance" measured did not translate to clinical failure because the chosen therapy

remained effective. In UTI studies, resistance was reported for the empirically prescribed antibiotics (e.g., trimethoprim, ciprofloxacin), directly causing treatment failure. This underscores that not all resistance is clinically equal; its impact is contingent on local prescribing habits.

Mechanistic Insights: The Lifespan of Resistance After Antibiotic Exposure

The review provides compelling, granular evidence on how antibiotic exposure begets resistance. The initial surge in resistance is substantial (e.g., OR 4.2 for penicillin in pneumococci), but the subsequent trajectory reveals a fascinating **class-dependent decay** with important implications (Costelloe et al., 2010; Bakhit et al., 2018). Penicillin-associated resistance shows significant decay within one month (OR from 4.2 to 1.7), while macrolide resistance not only persists but increases over three months (OR from 3.8 to 8.1). This dichotomy likely reflects the differential **fitness costs** imposed by resistance mechanisms. High-level beta-lactam resistance often involves mutations in penicillin-binding proteins that can impair bacterial growth in the absence of antibiotic pressure, favoring reversion to susceptibility. In contrast, macrolide resistance mechanisms (e.g., *erm* genes encoding methylation of the ribosomal target) may impose minimal fitness costs, allowing resistant clones to persist and even outcompete susceptible ones over time (Malhotra-Kumar et al., 2016). This explains why reducing macrolide use could yield disproportionate long-term benefits for resistance reversal. The **prolonged effect** in children (faecal *E. coli* resistance OR 13.23 persisting up to 6 months) and the cumulative impact of repeated courses highlight a sobering reality: every unnecessary prescription contributes to a reservoir of resistance that endangers both the individual and the community for months (Bryce et al., 2016a; Del Mar, 2008).

A Blueprint for Effective Stewardship: Context is King

The evidence on interventions is robust and optimistic, demonstrating that change is achievable. The most effective strategies are **multifaceted**, combining components like education, audit/feedback, decision support, and communication skills training, which appear to have

synergistic effects (Figueiras et al., 2020; Yao et al., 2020). However, a one-size-fits-all approach is inadequate; **context dictates strategy**. In high-income settings with established infrastructure and moderate baseline prescribing, communication skills training emerged as highly cost-effective, addressing the key driver of "perceived patient expectations" (van der Velden et al., 2012; Oppong et al., 2018). In low-resource settings with very high baseline inappropriate prescribing (e.g., >90%) and limited diagnostics, more intensive, structured interventions like problem-based training or digital clinical algorithms (e.g., ePOCT+) yielded dramatic absolute reductions (up to 46.4%) (Dwiprahasto & Kristin, 2015; Tan et al., 2023). The consistent finding that **early-career GPs prescribe fewer antibiotics** than their senior colleagues suggests a positive cohort effect of modern training, indicating that embedding stewardship principles in medical education is a sustainable long-term strategy (Baillie et al., 2024).

Limitations and Future Directions

This review has limitations. The predominance of studies from high-income countries may skew the global perspective (Hoffmann et al., 2011). Variability in laboratory methods and resistance breakpoints across studies complicates direct comparisons, though we accounted for this in our synthesis. Many intervention studies have relatively short follow-up periods, leaving the long-term sustainability of prescribing changes uncertain (McNulty et al., 2018; Poss-Doering et al., 2021).

Future research must:

1. Prioritize high-quality surveillance and intervention studies in underrepresented regions, particularly in Africa and South America (Ginsburg et al., 2013; Olaru et al., 2021).
2. Investigate the long-term (ecological) impact of stewardship programs on resistance rates at the population level.

3. Develop and validate rapid, affordable point-of-care diagnostics suitable for low-resource primary care settings (Salami et al., 2020; Tolley et al., 2024).
4. Explore the role of patient-facing interventions and public campaigns in complementing provider-focused efforts (Nepal et al., 2023).

Implications for Practice and Policy

For the primary care practitioner, this review reinforces the imperative of **diagnostic stewardship** (e.g., using dipsticks, CRP tests) to guide prescribing and advocates for **first-line agents with enduring low resistance**, such as nitrofurantoin for uncomplicated UTIs and amoxicillin for many community-acquired pneumonias (Holm et al., 2015; Harris et al., 2016). It strongly supports the adoption of **shorter-course therapies** where evidence-based, to minimize resistance selection (Johansen et al., 2024). For health systems and policymakers, the message is clear: **investing in primary care AMS is clinically effective and cost-effective**. Returns on investment (e.g., €2.57–€5.59 per €1 invested) and non-inferior safety outcomes make a compelling economic case (Wubishet et al., 2022; Gillespie et al., 2016). Policy actions must include enforcing prescription-only access to antibiotics, supporting the implementation of tailored stewardship toolkits, and integrating AMR surveillance into primary care reporting systems (Cheah et al., 2025).

CONCLUSION

Conclusion

Antimicrobial resistance in community-acquired infections managed in primary care is a pervasive and growing global threat, characterized by significant geographic inequities. Resistance directly leads to poorer clinical outcomes, increased healthcare utilization, and substantial economic costs, particularly for infections like UTIs. There is a direct, dose-responsive causal link between antibiotic prescribing in primary care and the development of resistance in individual patients, with

effects that can persist for many months. Inappropriate prescribing remains widespread globally. However, the evidence is conclusive that well-designed, context-appropriate antimicrobial stewardship interventions are effective in improving prescribing quality, are cost-effective, and do not harm patients.

Recommendations

1. **For Empiric Therapy:** Base first-line choices on local, regularly updated resistance data. Prioritize agents with historically low and stable resistance profiles (e.g., nitrofurantoin for UTIs, amoxicillin for CAP) and adhere to evidence-based short-course regimens.
2. **For Stewardship Implementation:** Implement multifaceted interventions tailored to local needs. In all settings, combine clinician education with audit and feedback. In high-prescribing environments, add structured communication skills training and clinical decision support. In low-resource settings, explore the integration of validated digital algorithms and affordable point-of-care tests.
3. **For Health Systems:** Strengthen regulations to eliminate over-the-counter antibiotic sales. Fund and incentivize primary care-based AMS programs, recognizing their positive return on investment. Integrate AMR surveillance into routine primary care data systems to generate local, real-time guidance.
4. **For Research and Development:** Increase investment in rapid diagnostic tools for primary care. Expand high-quality AMR and stewardship research in low- and middle-income countries. Study the long-term sustainability and ecological impact of stewardship interventions.

REFERENCES

- A. Bryce, A. Hay, I. Lane, H. Thornton, M. Wootton, and C. Costelloe. “Global Prevalence of Antibiotic Resistance in Paediatric Urinary Tract Infections Caused by Escherichia Coli and Association with Routine Use of Antibiotics in Primary Care: Systematic Review and Meta-Analysis.” *British Medical Journal*, 2016.
- A. Bryce, C. Costelloe, Claire Hawcroft, M. Wootton, and A. Hay. “Faecal Carriage of Antibiotic Resistant Escherichia Coli in Asymptomatic Children and Associations with Primary Care Antibiotic Prescribing: A Systematic Review and Meta-Analysis.” *BMC Infectious Diseases*, 2016.
- A. Figueiras, P. López-Vázquez, Cristian González-González, J. Vázquez-Lago, M. Piñeiro-Lamas, A. López-Durán, Coro Sánchez, et al. “Impact of a Multifaceted Intervention to Improve Antibiotic Prescribing: A Pragmatic Cluster-Randomised Controlled Trial.” *Antimicrobial Resistance and Infection Control*, 2020.
- A. Ginsburg, Laura Tinkham, K. Riley, N. Kay, K. Klugman, and C. Gill. “Antibiotic Non-Susceptibility Among Streptococcus Pneumoniae and Haemophilus Influenzae Isolates Identified in African Cohorts: A Meta-Analysis of Three Decades of Published Studies.” *International Journal of Antimicrobial Agents*, 2013.
- A. Harris, L. Hicks, and A. Qaseem. “Appropriate Antibiotic Use for Acute Respiratory Tract Infection in Adults: Advice for High-Value Care From the American College of Physicians and the Centers for Disease Control and Prevention.” *Annals of Internal Medicine*, 2016.
- A. Holm, G. Cordoba, T. M. Sørensen, L. R. Jessen, V. Siersma, and L. Bjerrum. “Point of Care Susceptibility Testing in Primary Care - Does It Lead to a More Appropriate Prescription of Antibiotics in Patients with Uncomplicated Urinary Tract Infections? Protocol for a Randomized Controlled Trial.” *BMC Family Practice*, 2015.

- A. Sugianli, Franciscus Ginting, I. Parwati, M. D. de Jong, F. van Leth, and C. Schultsz. "Antimicrobial Resistance Among Uropathogens in the Asia-Pacific Region: A Systematic Review." *JAC-Antimicrobial Resistance*, 2021.
- A. Teixeira Rodrigues, F. Roque, M. Piñeiro-Lamas, A. Falcão, A. Figueiras, and M. T. Herdeiro. "Effectiveness of an Intervention to Improve Antibiotic-Prescribing Behaviour in Primary Care: A Controlled, Interrupted Time-Series Study." *Journal of Antimicrobial Chemotherapy*, 2019.
- A. Tolley, Akhil Bansal, Rebecca Murerwa, and James Howard Dicks. "Cost-Effectiveness of Point-of-Care Diagnostics for AMR: A Systematic Review." *Journal of Antimicrobial Chemotherapy*, 2024.
- A. W. van der Velden, E. Pijpers, M. Kuyvenhoven, S. Tonkin-Crine, P. Little, and T. Verheij. "Effectiveness of Physician-Targeted Interventions to Improve Antibiotic Use for Respiratory Tract Infections." *The British Journal of General Practice : The Journal of the Royal College of General Practitioners*, 2012.
- "Antibiotikaresistenzen Beim Einzelnen Patienten," 2011.
- Arinze Nkemdirim Okere, Miquetta L. Trimble, Vassiki Sanogo, Ukamaka Smith, C. Brown, and Sarah G Buxbaum. "The Potential Effects of Implementing an Antibiotic Stewardship Program by Integrating It with Medication Therapy Service in a Low-Income Serving Clinic - A Single-Center Experience." *INNOVATIONS in Pharmacy*, 2022.
- B. Langford, M. So, M. Simeonova, V. Leung, Jennifer Lo, Tiffany Kan, S. Raybardhan, et al. "Antimicrobial Resistance in Patients with COVID-19: A Systematic Review and Meta-Analysis." *The Lancet Microbe*, 2023.
- B. Wubishet, G. Merlo, N. Ghahreman-Falconer, L. Hall, and T. Comans. "Economic Evaluation of Antimicrobial Stewardship in Primary Care: A Systematic Review and Quality Assessment." *Journal of Antimicrobial Chemotherapy*, 2022.

C. Costelloe, C. Metcalfe, A. Lovering, D. Mant, and A. Hay. “Effect of Antibiotic Prescribing in Primary Care on Antimicrobial Resistance in Individual Patients: Systematic Review and Meta-Analysis.” *British Medical Journal*, 2010.

C. McNulty, J. Richards, D. Livermore, Paul Little, André Charlett, E. Freeman, Ian Harvey, and Mike Thomas. “Clinical Relevance of Laboratory-Reported Antibiotic Resistance in Acute Uncomplicated Urinary Tract Infection in Primary Care.” *Journal of Antimicrobial Chemotherapy*, 2006.

C. McNulty, Meredith K. D. Hawking, D. Lecky, L. Jones, Rebecca Owens, A. Charlett, C. Butler, Philippa Moore, and N. Francis. “Effects of Primary Care Antimicrobial Stewardship Outreach on Antibiotic Use by General Practice Staff: Pragmatic Randomized Controlled Trial of the TARGET Antibiotics Workshop.” *Journal of Antimicrobial Chemotherapy*, 2018.

C. Zhuo, Xiaolin Wei, Zhitong Zhang, J. Hicks, Jinkun Zheng, Zhixu Chen, V. Haldane, et al. “An Antibiotic Stewardship Programme to Reduce Inappropriate Antibiotic Prescribing for Acute Respiratory Infections in Rural Chinese Primary Care Facilities: Study Protocol for a Clustered Randomised Controlled Trial.” *Trials*, 2020.

Chris Del Mar. “Antibiotic Use Results in Resistance Even for Individual Children.” *Jornal de Pediatria*, 2008.

D. Drekonja, G. Filice, N. Greer, A. Olson, R. MacDonald, I. Rutks, and T. Wilt. “Antimicrobial Stewardship in Outpatient Settings: A Systematic Review.” *Infection Control & Hospital Epidemiology*, 2014.

D. Gornyk, M. Scharlach, B. Buhr-Riehm, C. Klett-Tammen, S. Eberhard, J. Stahmeyer, A. Grosshennig, et al. “Effectiveness of Trainings of General Practitioners on Antibiotic Stewardship: Methods of a Pragmatic Quasi-Experimental Study in a Controlled Before-After Design in South-East-Lower Saxony, Germany (WASA).” *Frontiers in Pharmacology*, 2021.

E. de Vries, Y. Johnson, B. Willems, W. Bedeker, T. Ras, R. Coetzee, Y. Tembo, and A. Brink. “Improving Primary Care Antimicrobial Stewardship by Implementing a Peer Audit and Feedback Intervention in Cape Town Community Healthcare Centres.” *South African Medical Journal = Suid-Afrikaanse Tydskrif Vir Geneeskunde*, 2022.

Emma J Baillie, Gregory Merlo, M. V. van Driel, Parker J Magin, and Lisa Hall. “Early-Career General Practitioners’ Antibiotic Prescribing for Acute Infections: A Systematic Review.” *Journal of Antimicrobial Chemotherapy*, 2024.

Eskild Johansen, Henrik Nielsen, David Gillespie, R. Aabenhus, and M. Hansen. “The Optimal Antibiotic Treatment Duration for Community-Acquired Pneumonia in Adults Diagnosed in General Practice in Denmark (CAP-D): An Open-Label, Pragmatic, Randomised Controlled Trial.” *Trials*, 2024.

F. Kong, J. Hocking, and C. Fairley. “Is There a Future for the Ongoing Use of Azithromycin for the Treatment of Neisseria Gonorrhoeae?” *Clinical Microbiology and Infection*, 2020.

Grace C Mortrude, M. Rehs, K. Sherman, N. Gundacker, and C. Dysart. “141. Implementation of Veterans Affairs Outpatient Antimicrobial Stewardship Interventions for Asymptomatic Bacteriuria and Acute Respiratory Infections, a Stepped Wedge Randomized Study.” *Open Forum Infectious Diseases*, 2020.

———. “Implementation of Veterans Affairs Primary Care Antimicrobial Stewardship Interventions For Asymptomatic Bacteriuria And Acute Respiratory Infections.” *Open Forum Infectious Diseases*, 2021.

I. Dwiprahasto, and E. Kristin. “Improving the Use of Antibiotics in Primary Health Centres Through a Problem-Based Pharmacotherapy Training Approach,” 2015.

I. Gágyor, Alexandra Greser, P. Heuschmann, Viktoria Rücker, A. Maun, J. Bleidorn, C. Heintze, et al. “REDuction of Antibiotic RESistance (REDARES) in Urinary Tract Infections Using

Treatments According to National Clinical Guidelines: Study Protocol for a Pragmatic Randomized Controlled Trial with a Multimodal Intervention in Primary Care.” *BMC Infectious Diseases*, 2021.

I. Olaru, M. Chisenga, S. Yeung, P. Chonzi, Kudzai Masunda, R. Ferrand, and K. Kranzer. “Clinical and Bacteriological Outcomes in Patients with Urinary Tract Infections Presenting to Primary Care in Harare, Zimbabwe: A Cohort Study.” *Wellcome Open Research*, 2021.

Inés Urbiztondo, L. Bjerrum, Lidia Caballero, M. A. Suarez, Monica Olinisky, and G. Cordoba. “Decreasing Inappropriate Use of Antibiotics in Primary Care in Four Countries in South America—Cluster Randomized Controlled Trial.” *Antibiotics*, 2017.

J. Beam, and Bernadette D. Buckley. “Community-Acquired Methicillin-Resistant *Staphylococcus Aureus*: Prevalence and Risk Factors.” *Journal of Athletic Training*, 2006.

J. H. Wu, F. Khalid, B. Langford, Nathan P. Beahm, Mark T McIntyre, K. Schwartz, G. Garber, and V. Leung. “Community Pharmacist Prescribing of Antimicrobials: A Systematic Review from an Antimicrobial Stewardship Perspective.” *Canadian Pharmacists Journal / Revue Des Pharmaciens Du Canada*, 2021.

J. Teepe, B. Broekhuizen, H. Goossens, P. Hordijk, K. Loens, C. Lammens, M. Ieven, et al. “Clinical Relevance of Bacterial Resistance in Lower Respiratory Tract Infection in Primary Care: Secondary Analysis of a Multicentre European Trial.” *The British Journal of General Practice : The Journal of the Royal College of General Practitioners*, 2018.

K. Bhate, Liang-Yu Lin, J. Barbieri, C. Leyrat, S. Hopkins, R. Stabler, L. Shallcross, et al. “Is There an Association Between Long-Term Antibiotics for Acne and Subsequent Infection Sequelae and Antimicrobial Resistance? A Systematic Review.” *The British Journal of General Practice : The Journal of the Royal College of General Practitioners*, 2021.

K. Hoffmann, G. Wagner, P. Apfalter, and M. Maier. “Antibiotic Resistance in Primary Care in Austria - a Systematic Review of Scientific and Grey Literature.” *BMC Infectious Diseases*, 2011.

- L. Westerhof, Lisa E. Dumkow, Tarajo L Hanrahan, Samantha V McPharlin, and N. Egwuatu. “Outcomes of an Ambulatory Care Pharmacist-Led Antimicrobial Stewardship Program Within a Family Medicine Resident Clinic.” *Infection Control and Hospital Epidemiology*, 2020.
- L. Yao, Jia Yin, Qiang Sun, Ruiting Huo, Ding Yang, Liyan Shen, and Shuqin Wen. “The Effects of the Primary Health Care Providers’ Prescription Behavior Interventions to Improve the Rational Use of Antibiotics: A Systematic Review.” *Global Health Research and Policy*, 2020.
- Leesa Lin, Ruyu Sun, Tingting Yao, Xudong Zhou, and S. Harbarth. “Factors Influencing Inappropriate Use of Antibiotics in Outpatient and Community Settings in China: A Mixed-Methods Systematic Review.” *BMJ Global Health*, 2020.
- Lilian Downie, Raffaella Armiento, Rami Subhi, J. Kelly, V. Clifford, and T. Duke. “Community-Acquired Neonatal and Infant Sepsis in Developing Countries: Efficacy of WHO's Currently Recommended Antibiotics—Systematic Review and Meta-Analysis.” *Archives of Disease in Childhood*, 2012.
- M. Bakhit, Emma J Baillie, N. Krzyżaniak, M. V. van Driel, J. Clark, P. Glasziou, and C. Del Mar. “Antibiotic Prescribing for Acute Infections in Synchronous Telehealth Consultations: A Systematic Review and Meta-Analysis.” *BJGP Open*, 2021.
- M. Bakhit, T. Hoffmann, A. Scott, E. Beller, J. Rathbone, and C. Del Mar. “Resistance Decay in Individuals After Antibiotic Exposure in Primary Care: A Systematic Review and Meta-Analysis.” *BMC Medicine*, 2018.
- M. Kamradt, P. Kaufmann-Kolle, Edith Andres, Tonia Brand, A. Klingenberg, K. Glassen, Regina Poss-Doering, et al. “Sustainable Reduction of Antibiotic-Induced Antimicrobial Resistance (ARena) in German Ambulatory Care: Study Protocol of a Cluster Randomised Trial.” *Implementation Science*, 2018.
- M. Larsson. “ANTIBIOTIC USE AND RESISTANCE,” 2003.

M. Pfaller, and Ronald N. Jones. “Gatifloxacin Phase IV Surveillance Trial (TeqCES Study) Utilizing 5000 Primary Care Physician Practices: Report of Pathogens Isolated and Susceptibility Patterns in Community-Acquired Respiratory Tract Infections.” *Diagnostic Microbiology and Infectious Disease*, 2002.

M. Samore, K. Bateman, S. Alder, E. Hannah, Sharon Donnelly, G. Stoddard, Bassam Haddadin, et al. “Clinical Decision Support and Appropriateness of Antimicrobial Prescribing: A Randomized Trial.” *Journal of the American Medical Association (JAMA)*, 2005.

M. Takenoshita, D. Hettle, and Graziella Quattrocchi. “O02 Antibiotic Prescribing Practices in Primary Healthcare in Sub-Saharan Africa: A Systematic Review and Our Experience on the Use of Telemedicine in Zambia.” *JAC-Antimicrobial Resistance*, 2022.

M. Vervloet, M. Meulepas, J. Cals, M. Eimers, L. S. van der Hoek, and L. van Dijk. “Reducing Antibiotic Prescriptions for Respiratory Tract Infections in Family Practice: Results of a Cluster Randomized Controlled Trial Evaluating a Multifaceted Peer-Group-Based Intervention.” *Npj Primary Care Respiratory Medicine*, 2016.

María Verónica Cuevas-González, Gabriela Anaïd Mungarro-Cornejo, L. F. Espinosa-Cristóbal, Alejandro Donohue-Cornejo, Karla Lizette Tovar Carrillo, R. A. Saucedo Acuña, Alma Graciela García Calderón, Dalia Abril Guzmán Gastelum, Graciela Zambrano-Galván, and J. Cuevas-González. “Antimicrobial Resistance in Odontogenic Infections: A Protocol for Systematic Review.” *Medicine*, 2022.

Martijn Sijbom, F. Büchner, N. Saadah, M. Numans, and M. D. de Boer. “Determinants of Inappropriate Antibiotic Prescription in Primary Care in Developed Countries with General Practitioners as Gatekeepers: A Systematic Review and Construction of a Framework.” *BMJ Open*, 2023.

Milena Aparecida del Masso Pereira, and C. M. Fortaleza. “Factors Associated with Community-Onset Multidrug-Resistant Organisms in Inner Brazil.” *American Journal of Infection Control*, 2018.

“More on Communiy Acquired Pneumonia: Antibiotic Resistance.” *Archives of Disease in Childhood*, 2022.

N. A. Martínez-González, S. Coenen, A. Plate, Annelies Colliers, T. Rosemann, O. Senn, and S. Neuner-Jehle. “The Impact of Interventions to Improve the Quality of Prescribing and Use of Antibiotics in Primary Care Patients with Respiratory Tract Infections: A Systematic Review Protocol.” *BMJ Open*, 2017.

N. J. Zhu, M. Weldegiorgis, Emma Carter, Colin S. Brown, Alison Holmes, and Paul Aylin. “Economic Burden of Community-Acquired Antibiotic-Resistant Urinary Tract Infections: Systematic Review and Meta-Analysis.” *JMIR Public Health and Surveillance*, 2023.

Nathan P. Beahm, D. Smyth, and R. Tsuyuki. “Antimicrobial Utilization and Stewardship in Patients with Uncomplicated Urinary Tract Infections Managed by Pharmacists in the Community: A Sub-Study of the RxOUTMAP Trial.” *Journal of the Association of Medical Microbiology and Infectious Disease Canada = Journal Officiel de l'Association Pour La Microbiologie Medicale Et l'infectiologie Canada*, 2021.

Noah O. Okumu, D. Muloi, Arshnee Moodley, Julie Watson, A. Kiarie, Linnet Ochieng, J. Wasonga, et al. “Antimicrobial Resistance in Community-Acquired Enteric Pathogens Among Children Aged ≤ 10 -Years in Low-and Middle-Income Countries: A Systematic Review and Meta-Analysis.” *Frontiers in Microbiology*, 2025.

O. Fasugba, A. Gardner, B. Mitchell, and G. Mnatzaganian. “Ciprofloxacin Resistance in Community- and Hospital-Acquired Escherichia Coli Urinary Tract Infections: A Systematic Review and Meta-Analysis of Observational Studies.” *BMC Infectious Diseases*, 2015.

O. van Hecke, Kay Wang, J. Lee, N. Roberts, and C. Butler. “Implications of Antibiotic Resistance for Patients’ Recovery From Common Infections in the Community: A Systematic Review and Meta-Analysis.” *Clinical Infectious Diseases*, 2017.

Olawale Salami, P. Horgan, C. Moore, A. Giri, Asadu Sserwanga, A. Pathak, B. Basnyat, et al. “Impact of a Package of Diagnostic Tools, Clinical Algorithm, and Training and Communication on Outpatient Acute Fever Case Management in Low- and Middle-Income Countries: Protocol for a Randomized Controlled Trial.” *Trials*, 2020.

P. Gillespie, A. Callan, E. O’Shea, Sinead Duane, A. Murphy, C. Domegan, S. Galvin, and Akke Vellinga. “The Cost Effectiveness of the SIMPLe Intervention to Improve Antimicrobial Prescribing for Urinary Tract Infection in Primary Care.” *Journal of Public Health*, 2016.

Pablo March-López, R. Madridejos, R. Tomás, Lucía Boix, P. Arcenillas, L. Gómez, E. Padilla, et al. “Impact of a Multifaceted Antimicrobial Stewardship Intervention in a Primary Health Care Area: A Quasi-Experimental Study.” *Frontiers in Pharmacology*, 2020.

Prajwol Nepal, A. Subedee, H. Shakya, Sanjaya Poudel, Supriya Joshi, K. Karki, D. Bajracharya, T. Prentiss, L. Kaljee, and Yubraj Acharya. “Protocol for a Randomized Controlled Trial on Community Education and Surveillance on Antibiotics Use Among Young Children in Nepal.” *Contemporary Clinical Trials Communications*, 2023.

Qihua Song, Jinxi Li, Pengfei Zhou, Rui Chen, Zhen Liu, Hui Li, and Xiaoxv Yin. “Worldwide Antibiotic Prescription Practices in Primary Care and Associated Factors: A Systematic Review and Meta-Analysis.” *American Journal of Infection Control*, 2025.

R. Shields, Wendy Y Cheng, Kalé Kponee-Shovein, Fernando Kuwer, Chi Gao, Ashish V Joshi, Fanny S. Mitrani-Gold, et al. “2838. Clinical Application and Validation of a Predictive Antimicrobial Resistance Risk Categorization Framework for Patients with Uncomplicated Urinary Tract Infection.” *Open Forum Infectious Diseases*, 2023.

Rainer Tan, Godfrey Kavishe, L. Luwanda, A. Kulinkina, Sabine Renggli, C. Mangu, Geoffrey Ashery, et al. “A Digital Health Algorithm to Guide Antibiotic Prescription in Pediatric Outpatient Care: A Cluster Randomized Controlled Trial.” *Nature Network Boston*, 2023.

Raymond Oppong, Richard D Smith, Paul Little, T. Verheij, Chris C Butler, Herman Goossens, S. Coenen, et al. “Cost-Effectiveness of Internet-Based Training for Primary Care Clinicians on Antibiotic Prescribing for Acute Respiratory Tract Infections in Europe.” *Journal of Antimicrobial Chemotherapy*, 2018.

Regina Poss-Doering, D. Kronsteiner, M. Kamradt, P. Kaufmann-Kolle, Edith Andres, V. Wambach, Julian Bleek, M. Wensing, ARena-Study Group, and J. Szecsenyi. “Assessing Reduction of Antibiotic Prescribing for Acute, Non-Complicated Infections in Primary Care in Germany: Multi-Step Outcome Evaluation in the Cluster-Randomized Trial ARena.” *Antibiotics*, 2021.

Regina Poss-Doering, D. Weber, M. Kamradt, Edith Andres, P. Kaufmann-Kolle, and J. Szecsenyi. “Baseline Assessment of Antibiotics Prescribing for Acute, Non-Complicated Infections in Primary Care in Germany in the Cluster Randomized Trial ARena,” 2020.

Ron Cheah, Caroline Chen, Daniel Capurro, J. Manski-Nankervis, V. Rozova, and K. Thursky. “A Systematic Review on How Primary Care Electronic Medical Record Data Have Been Used for Antimicrobial Stewardship.” *Antimicrobial Stewardship and Healthcare Epidemiology*, 2025.

Ron Dagan, E. Leibovitz, A. Leiberman, and P. Yagupsky. “Clinical Significance of Antibiotic Resistance in Acute Otitis Media and Implication of Antibiotic Treatment on Carriage and Spread of Resistant Organisms.” *The Pediatric Infectious Disease Journal*, 2000.

Ruyu Sun, Tingting Yao, Xudong Zhou, S. Harbarth, and Leesa Lin. “Non-Biomedical Factors Affecting Antibiotic Use in the Community: A Mixed-Methods Systematic Review and Meta-Analysis.” *Clinical Microbiology and Infection*, 2021.

S. Goyet, E. Vlieghe, Varun Kumar, Steven W Newell, C. Moore, R. Bousfield, Heng C. Leang, et al. “Etiologies and Resistance Profiles of Bacterial Community-Acquired Pneumonia in Cambodian and Neighboring Countries’ Health Care Settings: A Systematic Review (1995 to 2012).” *PLoS ONE*, 2014.

S. Hillier, J. Magee, A. Howard, and S. Palmer. “How Strong Is the Evidence That Antibiotic Use Is a Risk Factor for Antibiotic-Resistant, Community-Acquired Urinary Tract Infection?” *Journal of Antimicrobial Chemotherapy*, 2002.

S. Malhotra-Kumar, L. van Heirstraeten, S. Coenen, C. Lammens, N. Adriaenssens, A. Kowalczyk, M. Godycki-Cwirko, et al. “Impact of Amoxicillin Therapy on Resistance Selection in Patients with Community-Acquired Lower Respiratory Tract Infections: A Randomized, Placebo-Controlled Study.” *Journal of Antimicrobial Chemotherapy*, 2016.

S. Yakobi, Yolisa B Magibile, and O. Poee. “A Systematic Review of Neisseria Gonorrhoeae Drug Resistance Development in South Africa.” *Brazilian Journal of Microbiology*, 2024.

Sharon A Simpson, C. Butler, Kerry Hood, David Cohen, Frank Dunstan, Meirion R Evans, Stephen Rollnick, et al. “Stemming the Tide of Antibiotic Resistance (STAR): A Protocol for a Trial of a Complex Intervention Addressing the 'Why' and 'How' of Appropriate Antibiotic Prescribing in General Practice.” *BMC Family Practice*, 2009.

T. Alam, D. Ahmed, T. Ahmed, M. Chisti, Mw Rahman, A. Chauhan, S. Deb, et al. “Extended Effect of Short-Course Azithromycin for the Treatment of Diarrhoea in Children on Antimicrobial Resistance in Nasopharyngeal and Intestinal Bacteria: Study Protocol for the Antimicrobial Resistance Sub-Study of the Multicountry AntiBiotics for Children with Diarrhea (ABCD) Trial.” *medRxiv*, 2020.

Taissa A. Bej, Brigid M Wilson, Ukwon C. Akpoji, Nicole Mongilardi, T. Chengsupanimit, Sunah Song, Corinne Kowal, et al. “Feasibility of a Low-Intensity Intervention to Influence Antibiotic

Prescribing Rates Use in Outpatient Settings: A Cluster Randomized Controlled Clinical Trial.” *Open Forum Infectious Diseases*, 2024.

W. McIsaac, Sahana Kukan, E. Huszti, L. Szadkowski, B. O’Neill, S. Virani, N. Ivers, et al. “A Pragmatic Randomized Trial of a Primary Care Antimicrobial Stewardship Intervention in Ontario, Canada.” *BMC Family Practice*, 2021.

Y. Kuo, Jyh-Ming Liou, E. El-Omar, Jeng-Yih Wu, A. Leow, K. Goh, Rajashree Das, et al. “Primary Antibiotic Resistance in *Helicobacter Pylori* in the Asia-Pacific Region: A Systematic Review and Meta-Analysis.” *The Lancet Gastroenterology and Hepatology*, 2017.