

Original Article

Institutional spillover effects of antimicrobial use on antimicrobial resistance and *Clostridioides difficile*: a systematic review

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Abstract

Objective: To synthesize evidence on institutional spillover effects of antimicrobial use (AMU) on antimicrobial resistance (AMR) and *Clostridioides difficile* infections on individuals without direct antimicrobial exposure.

Design: Systematic review.

Methods: Three databases were searched through August 2024 for studies evaluating spillover effects of AMU on unexposed individuals in institutional settings. Study characteristics, AMU, and outcomes were extracted. Study quality was assessed based on underlying methodology to detect spillover effect. A hybrid synthesis, including effect direction and meta-analysis of studies reporting continuous AMU and non-aggregate outcomes was utilized. Reporting followed PRISMA guidelines.

Results: Of 5916 screened studies, five observational studies met inclusion criteria. Three were conducted across 68 hospital wards (ward-level exposure), and two across 693 nursing homes (facility-level exposure). Three studies evaluated all antimicrobial classes; two focused on penicillins, fluoroquinolones, and carbapenems. Two studies examined *C. difficile*, one MRSA, one carbapenem-resistant *Enterobacteriales*, and one reported combined AMR and *C. difficile* outcomes. Low to moderate quality evidence indicated a positive spillover effect direction with increasing facility AMU. Meta-analysis of three studies yielded a pooled IRR of 1.54 (95% CI 0.85–2.80) per 100 days of therapy per 1,000 patient-days, with significant heterogeneity ($I^2 = 97.6\%$).

Conclusions: This review identified five studies suggesting a positive association between institutional AMU and collateral risks of AMR and *C. difficile* among unexposed individuals. Findings were limited by methodological heterogeneity and potential publication bias. Standardizing terminology, specifying spillover mechanisms, and adopting robust observational designs can enhance future research on spillover effects.

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Introduction

Antimicrobial resistance (AMR) poses a public health challenge with significant attributable global mortality in humans.¹ AMR is primarily driven by antimicrobial use (AMU); however, the use-resistance relationship is complex, poorly understood, and modified by factors such as transmission of resistant bacteria and antimicrobial effects beyond the target pathogen. Direct effects of AMU on selecting for AMR on recipients themselves are well understood. However, the total impact extends to those indirectly exposed, especially in settings with close contact with recipients such as patients, residents, or staff within healthcare facilities.²

Direct antimicrobial exposure increases the risk of AMR and collateral risks, such as *Clostridioides difficile* infection, because

broad-spectrum antimicrobials affect not only targeted pathogens but also commensal bacteria (pathogenic and non-pathogenic) that comprise the human microbiome.³ This selective pressure disrupts microbial balance while also enriching resistant strains and facilitating horizontal transfer of resistance mechanisms among non-target bystander bacteria.⁴ The “bystander effect” has implications at the population-level as transmission of resistance organisms can occur even among individuals not receiving antimicrobials.⁵

In the context of AMU, spillover is an indirect risk where people near the recipient of an antimicrobial are affected even if they do not receive the antimicrobial themselves.⁶ One example where spillover effects have been observed is mass azithromycin drug administration campaigns for infant child morbidity and mortality, where a secondary analysis showed a small spillover effect of resistance determinants among unexposed children in targeted communities.⁷

However, in the broader context of routine AMU the unintended population spillover consequences have had limited

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characterization. Institutional settings such as hospitals, rehabilitation facilities, complex continuing care centers, and nursing homes have high-intensity AMU and prevalence of antimicrobial-resistant organisms, with calls for antimicrobial stewardship initiatives to optimize AMU and reduce AMR and collateral risks.^{8,9}

Understanding spillover is important for quantifying the combined effects of AMU. This knowledge is valuable for communicating the benefits and risks of AMU and informing the interpretation of stewardship interventions.^{6,10} Given these considerations, we conducted a systematic review to synthesize and characterize the existing evidence regarding the direction, consistency, and magnitude of the association between institutional AMU and the collateral outcomes of AMR and *C. difficile* among individuals without antimicrobial exposure.

Methods

Search criteria and eligibility

We conducted a literature search in August 2024 using OVID Medline, Healthstar, and EMBASE databases. The search included no language or date restrictions. In consultation with a research librarian we developed four search concepts: spillover (including terms such as “indirect effects” and “secondary effects”), institution (including “long term care,” “NH,” and “hospital”), AMU (including “antibiotic prescribing” and “antibiotic utilization”), and AMR (including “antibiotic resistance” and “*C. difficile*”). These concepts were operationalized using keywords and controlled vocabulary subject headings (see Appendix A). The term “spillover” is used infrequently in AMR research, where similar concepts are more commonly referred to as “indirect effects”.¹¹ To increase sensitivity of the search, we incorporated proximity search strategies which involved using adjacent terms within a specified number of words to capture the relevant search concept. These were informed by a previously published systematic review on spillover effects.¹¹ The search concepts were linked using a boolean “and” operator and refined using test citations. From identified sources, we supplemented our primary search by citation searches using forward and backward approaches of study reference lists.

We included studies looking at antimicrobial spillover effects on adults or children based on human AMU in institutional settings. Studies of selective digestive decontamination (SDD) in intensive care settings were excluded, as our focus was on describing spillover effects based on routine AMU. All studies reporting institutional level AMU were included, with no restriction on utilization metric. We considered all study reported resistant organisms, demonstrated phenotypically or through genotypic markers corresponding with antimicrobial susceptibility phenotypes. For *C. difficile*, studies reporting stool toxin using toxigenic culture, nucleic acid amplification tests, or enzyme immunoassay assay, were considered.

Both observational and randomized study designs were considered. A spillover effect was defined *a priori* as an association between institutional AMU and antimicrobial-resistant infection or *C. difficile* among individuals without direct antimicrobial exposure during a defined non-exposure window, with outcomes reported or extractable at the institutional level. The systematic review protocol was registered on PROSPERO¹² and reporting was conducted using the PRISMA guidelines.¹³

Screening

Duplicate entries were identified using a citation manager (Zotero) and removed prior to importation to a systematic review software. All records were managed using Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia). Double screening of title and abstracts was completed independently by two authors (SR, BJL, RF) for eligibility and inclusion. Identified abstracts underwent full text screening independently by two authors (SR, BJL, RF) for eligibility and inclusion. Any discrepancies were adjudicated through discussion and consensus.

Data extraction

Data extraction was conducted using a standardized electronic form. Single author data (SR) abstraction was conducted with verification by a second author (BJL, RF) for included studies. Relevant information not readily available in the manuscript or *supplemental* material was requested from the corresponding author(s) or extracted from figures using digitized plotting techniques.¹⁴

Study characteristics

Data items extracted included study design (cohort with multilevel modeling, case-control with multilevel modeling, cluster-randomized controlled trial); country; time period of study; study setting; and any study-defined control for variables that might impact AMR/*C. difficile* transmission.

Antimicrobial measures

Data items extracted included measure of institutional AMU (eg days of therapy), the antimicrobial class evaluated (eg carbapenems), and the study-defined non-exposure window used to classify individuals as unexposed to antimicrobials. The type of antimicrobial exposure comparison was also categorized as either an incremental comparison per standard unit of AMU (eg per 10% relative increase in DOT/1,000 patient-days), categorical comparison per study defined metric (eg tertile-based groupings), or absolute comparisons by cumulative AMU (eg DOT). These distinctions were important for understanding how each study operationalized the exposure and how comparability across studies might be affected.

Outcome measures

The primary outcome was the rate of antimicrobial resistant or *C. difficile* infection/colonization among non-exposed individuals, quantified per institutional unit population over the study period. When available, overall effects of institutional AMU, irrespective of individual exposure, were also extracted.

Study quality

Study quality was assessed using a previously published modified GRADE approach that incorporates spillover assessment considerations based on underlying study methodology.¹¹ A quality score of 3 was given for cluster-randomized design estimating cluster-level spillover effects among unexposed individuals, observational studies estimating cluster-level spillovers received a score of 2, and purely ecological studies received a score of 1. Validity of spillover effects depends strongly on the chosen analytic approaches, including the ability to adequately control for confounding, address interference (individual's outcome is affected by exposures of others), and isolate indirect transmission pathways.^{15,16} Scores

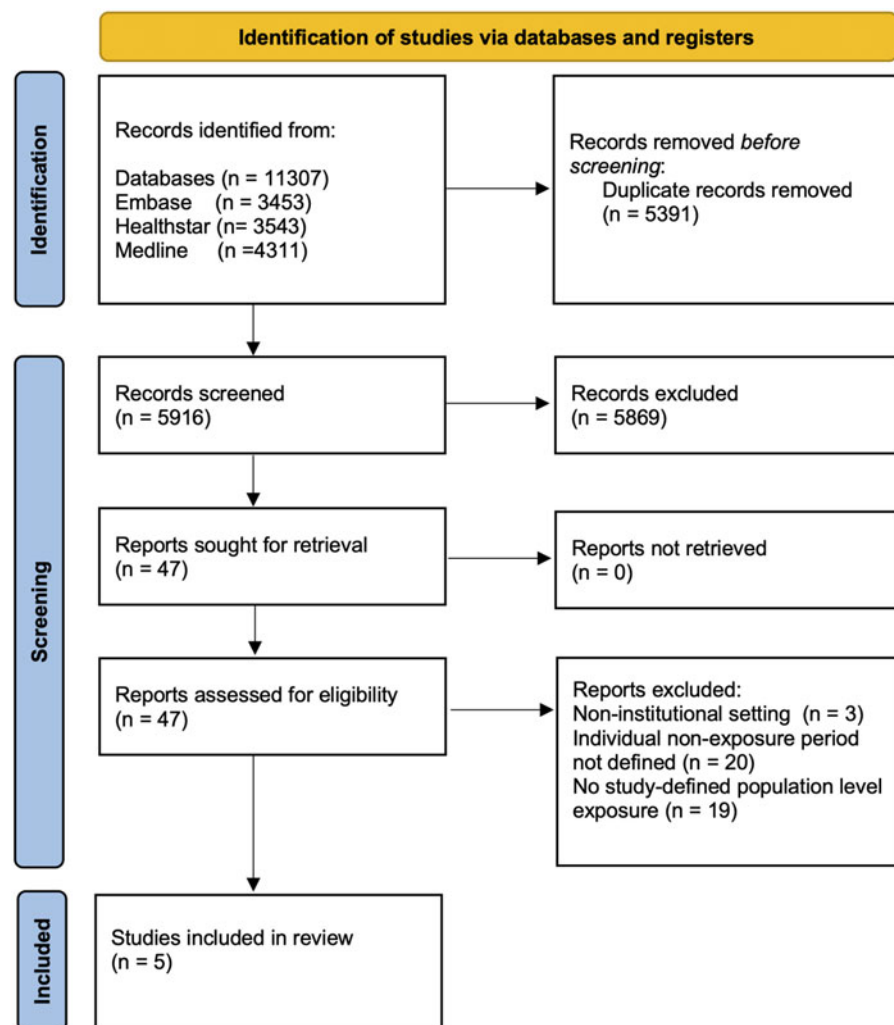


Figure 1. PRISMA flowchart of study selection for the systematic review.

were upgraded by 1 point if studies demonstrated control for confounding at both facility and patient levels, provided evidence of dose-response relationship between institutional AMU and the outcome regardless of the direction of association, or prespecified a spillover mechanism to reduce selective reporting.¹¹ Scores were reduced by 1 point if spillover effects were not explicitly stated in the manuscript, if evidence for spillover was indirect, or limitations in study design that would suggest a likelihood of bias. Because no cluster-randomized trials were identified, maximum observed scores ranged from 2 to 4, with scores of 4 being moderate-quality evidence, whereas scores 2–3 were classified as low-quality evidence.

Synthesis methods

A meta-analysis using a random-effects model was planned for studies reporting standardized continuous antimicrobial exposure metrics and non-aggregate outcomes to enable interpretability and assessment of the direction of effect. A 95% prediction interval was calculated for the range of effects expected if similar studies were to be conducted in different institutional settings.¹⁷

Given the small number of eligible studies and the heterogeneity in outcome definitions and exposure metrics, we adopted a hybrid synthesis approach. A narrative synthesis was structured according to the Synthesis Without Meta-analysis reporting guideline.¹⁸ For the narrative synthesis, studies were grouped by

primary outcome (e.g. AMR vs *C difficile*), study setting, and antimicrobial class, prioritizing study-reported effect measures and using effect direction as a standardized summary metric.¹⁸ An effect direction plot enabled visual comparison of the direction and consistency of spillover effects across studies, despite differences in exposure comparison and outcome reporting.¹⁹

Where a summary measure was not reported, we used digitized plot data extraction techniques to calculate the rate ratio with approximated person-time at risk, equally allocated between exposure groups.²⁰ Estimated number of events were calculated by multiplying incidence rates by group-specific person-time and standard errors were derived accordingly. When the IRR was not reported, it was calculated based on the event rate and assuming equal study follow-up time,²¹ or by refitting a log-linear model from digitized ecological data points.²² Where multiple analyses were presented within a study (eg ecological vs cohort),²² we extracted both estimates and prioritized those adjusted for individual or institutional confounding for pooled estimates. The complete extracted data and transformations can be found on an open data repository.²³

Results

Of the 5,916 studies screened, 47 studies were retrieved for full-text review, with 5 studies meeting inclusion criteria (see Figure 1).

Table 1. Characteristics of included studies assessing spillover effects of antimicrobial use

Study characteristic	Brown et al 2015 ²⁴	Brown et al 2016 ²⁵	Daneman et al ²¹	Muller et al ²⁰	Oliveira et al ²²
Publication year, country	2015 Canada	2016 USA	2015 Canada	2006 France	2022 Brazil
Study design	Cohort	Nested case-control	Cohort	Cohort	Cohort-Ecological
Study population (N)	34,298	169,453	110,656	18,596	579
Setting	Hospital	Nursing home	Nursing home	Hospital	Hospital
Cluster (N)	Ward (16)	Facility (86)	Facility (607)	Ward (50)	Ward (2)
Study period	2010–2014	2006–2012	2010–2011	2001	2013–2018
Facility AMU class	All	All	All	Penicillin Fluoroquinolone	Carbapenem
Facility AMU exposure	DOT/100	DOT/1,000	DOT/1,000	DDD/1,000	DOT/1,000
Facility AMU comparison	Per 10% increase	Per doubling	Highest vs lowest tertile facility use	Above vs below median ward use	Per unit increase
Outcome [†]	<i>C. difficile</i>	<i>C. difficile</i>	Composite	MRSA	CR-GNB
Spillover effect (95% CI), measure	1.34 (1.16–1.57) IRR	2.81 (2.2–3.58) IRR	1.13 (1.02–1.25) IRR	2.95 (1.62–5.36) 1.33 (0.79–2.24) IRR	1.003 (1.001–1.005) IRR
Overall effect (95% CI), measure	1.34 (1.16–1.57) IRR	1.36 (1.15–1.60) IRR	1.24 (1.07–1.42) OR	2.52 (1.15–5.51) 0.85 (0.37–1.96) OR	NR
Modeling strategy	Multilevel Poisson model	Multilevel Poisson model	GEE model with facility clustering	Multilevel time-logistic model	Single-level Poisson model / linear regression
Non-exposure window (days)	10	28	NR	NR	5
Confounder control	Yes	Yes	Yes	Yes	Yes (patient-only)*

Note. AMU, antimicrobial use; DOT, days of therapy; DDD, defined daily dose; MRSA, methicillin-resistant *Staphylococcus aureus*; CR-GNB, carbapenem resistant gram negative bacilli GEE, generalized estimating equation; NR, Not reported.

[†]Composite outcome = Antimicrobial resistant organisms including methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus*, extended-spectrum β -lactamase producing *Enterobacteriales*; *C. difficile*; and adverse drug event.

*No facility-level confounder control reported.

All studies were observational, with three studies using a cohort design, one study using a mixed ecological-cohort design, and one study using a nested case-control design (see Table 1). Three of the studies were conducted across 68 hospital wards, measuring antimicrobial exposure at the ward-level, and two were conducted across 693 NH facilities, measuring exposure at the facility-level.

Four studies measured antimicrobial utilization using days of therapy (DOT) and one study reported the exposure in defined daily doses. Exposure classifications varied between studies, with three studies reporting an incremental comparison (eg per DOT or DDD/ 1,000 patient-days) and two studies reporting a categorical comparison (eg highest vs lowest tertile use).

One study²² presented two measures of antimicrobial utilization: a cohort-level cumulative DOTs during each patient's time at risk and an ecological measure standardized as DOT per 1,000 resident-days. For study characteristics (see Table 1), we included the ecological measure (DOT per 1,000 resident-days) to facilitate comparability with other studies and used the adjusted cumulative measure for pooled estimates. Three of the studies looked at overall antimicrobial utilization, while two studies reported class-specific antimicrobial utilization. The median non-exposure window reported for three studies was 10 days (IQR 5–28), with four studies reporting facility and patient-level confounder control,

and one study reporting patient-level confounder control among unexposed individuals. Study reported outcomes included *C. difficile*,^{24,25} methicillin-resistant *S. aureus*,²⁰ carbapenem-resistant *Enterobacteriales*,²² and aggregate of adverse drug events, AMR, and *C. difficile*.²¹

Study quality

Two studies were of moderate quality and three studies were of low quality (see Table 2). Studies with higher quality ratings used multilevel models that accounted for clustering and reported both facility and patient-level confounding control. One study used a mixed ecological-cohort design, because the primary AMU exposure was an aggregated DOT/1,000 patient-day metric, the study was assigned the ecological baseline score (1 point) and was upgraded because a consistent dose-response gradient was demonstrated in both the ecological time-series and the patient-level cohort studies.

Risk of bias was driven by limited reporting of confounder adjustment for unexposed individuals and the non-exposure window. Precision was influenced by the rarity of the outcome and the varying facility-level exposure comparisons. Consistency of effect was supported as all studies reported a positive association between facility-level exposure and the outcome

Study	Setting	Cluster	Antimicrobial Class	Spillover Effect		
				AMR	CDI	AMR/CDI
Brown 2015	Hospital	Ward	All		▲	
Brown 2016	Nursing Home	Facility	All		▲	
Daneman 2015	Nursing Home	Facility	All			▲
Muller 2006	Hospital	Ward	Penicillin	▲		
Muller 2006	Hospital	Ward	Fluoroquinolone	▲		
Oliveira 2022	Hospital	Ward	Carbapenem	▲		

Spillover effect size (IRR): Large arrow ≥ 2.00 ; Medium arrow 1.10 - 1.99; Small arrow <1.10
Exposure comparisons: Grey arrow = incremental; Black arrow = categorical; White arrow = cumulative
Study quality: Row colour light grey = Moderate; Row colour dark grey = Low

Figure 2. Effect-direction plot of spillover effects of institutional AMU among unexposed individuals. AMR, antimicrobial resistance; CDI, *Clostridioides difficile*; IRR, incidence rate ratio.

among unexposed individuals. Of the four studies that also reported the overall effect of facility-level exposure (irrespective of individual-level exposure) the magnitude of the spillover estimate was similar or slightly attenuated compared to the overall effect. With only five studies identified, a formal meta-bias assessment was not completed.²⁶

Evidence synthesis

Five studies met inclusion criteria and were included in the narrative synthesis. The five studies reported IRRs greater than 1.0 (range 1.003 to 2.95), demonstrating a consistent positive direction of association between higher institutional AMU and increased AMR or *C. difficile* among unexposed individuals (see Figure 2), with the strength of the association driven primarily by moderate-quality observational evidence (see Table 2). For *C. difficile*, in nursing-home settings a doubling in DOT/1,000 resident-days corresponded to an IRR 2.81 (95% CI 2.20–3.58), whereas in hospital settings a 10% relative increase in DOT/100 patient-days yielded an IRR 1.34 (95% CI 1.16–1.57). Among AMR studies, effect size varied by drug–pathogen pair: penicillin use and MRSA yielded the largest increase (IRR 2.95 [1.62–5.36]), fluoroquinolone use and MRSA showed a smaller, statistically non-significant rise (IRR 1.33 [0.79–2.24], and carbapenem use and carbapenem-resistant *Enterobacterales* exhibited a modest elevation (IRR 1.003 [1.001–1.005]). Despite heterogeneity in exposure metrics, all estimates favored a positive direction of association with higher facility use and AMR or *C. difficile* among the unexposed.

Meta-analysis

Three studies reported continuous measures of institutional AMU and non-aggregate outcomes. We standardized the outcome to a common unit, specifically the estimated incidence rate ratio per 100 DOT increase in antimicrobial utilization per 1,000 patient-days. This increment was selected for interpretability and to minimize transformations required for standardization across studies (see Appendix B).

The meta-analysis, utilizing a random effects model, revealed a pooled incidence rate ratio of 1.54 (95% CI: 0.85–2.80, *p*-value .15), which did not reach statistical significance (see Figure 3). The corresponding prediction interval ranged from 0.12 to 20.51, indicating a true effect in similar settings could plausibly range from an 88% reduction to a twenty-fold increase. Significant heterogeneity was observed across the included studies, with an *I*² of 97.6% (*p* value < .001).

Discussion

To our knowledge this is the first systematic review to examine the effects of institutional AMU among unexposed individuals. Despite a comprehensive search strategy including adjacent terms for spillover and indirect effects, we identified only five studies. Inconsistent terminology, evolving definitions, and inadequate indexing of spillover concepts within routine AMU literature impeded identification. Citation searches of identified studies did not yield any additional studies and relevant studies may have been missed. While a meta-bias assessment could not be undertaken, accurate spillover estimation depends on prespecifying

Table 2. Quality assessment of included studies evaluating spillover effects

Study	Quality assessment	Rationale
Brown 2015 ²⁴	Moderate	Observational study estimating cluster-level spillover Plausible confounding for spillover effect controlled Dose-response gradient for spillover effect
Brown 2016 ²⁵	Moderate	Observational study estimating cluster-level spillover Plausible confounding for spillover effect controlled Dose-response gradient for spillover effect
Daneman 2015 ²¹	Low	Observational study estimating cluster-level spillover Plausible confounding for spillover effect controlled Indirect evidence (composite end point)
Oliveira 2022 ²²	Low	Mixed ecological-cohort observational study Prespecified spillover mechanism Dose-response gradient for spillover effect (ecological analysis) Limited confounding for spillover effect controlled (patient-level only) Imprecision of results (exposure metric not standardized)
Muller 2006 ²⁰	Low	Observational study estimating cluster-level spillover Prespecified spillover mechanism Plausible confounding for spillover effect controlled Spillover effect not explicitly reported in published manuscript

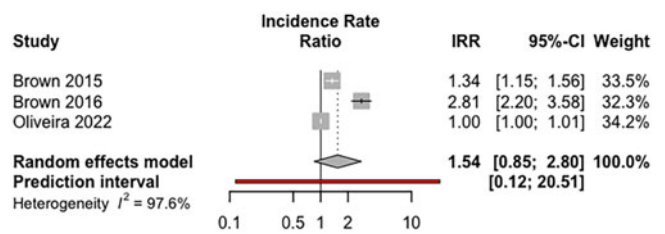


Figure 3. Forest plot of meta-analysis of spillover effects per 100 DOT increase in institutional AMU (per 1,000 patient-days). DOT, days of therapy.

hypothesized mechanisms, yet only two studies explicitly did so. This lack of prespecification can lead to missed spillover measurement or under-reporting of spillover findings. Beyond publication bias, spillover estimates may be affected by selection bias within studies due to exposure misclassification or differential outcome detection correlated with institutional AMU, potentially attenuating or inflating associations.^{12,15} Although several studies adjusted for individual- and institutional-level confounders, such adjustment may not fully address selection processes, contributing to variability in spillover estimates across studies. Recently, a checklist for reporting of spillover effects in health interventions has been advocated¹¹; however, this tool postdated all included studies and none reported use of an equivalent structured reporting framework. Adoption of standardized reporting tools can enhance methodological rigor and comparability of spillover effects with routine AMU.

Our review suggests that higher facility-level AMU is associated with increased AMR or *C difficile* among individuals not recently exposed to antimicrobials. A subset meta-analysis of three studies reporting continuous institutional AMU supported a positive direction of effect (IRR 1.54). However, the wide 95% prediction interval (0.12–20.51) reflects significant heterogeneity ($I^2 = 97.6\%$) and a small number of studies; therefore findings should be interpreted as hypothesis-generating rather than definitive evidence of spillover effects.

Accurate spillover effects estimation is crucial for understanding how institutional AMU impacts unexposed individuals, yet

methodological challenges persist. Observational studies employing cluster-level designs can address these challenges by accounting for facility- and patient-level confounding through multilevel analytic strategies or cluster-level propensity scores.^{15,16,27–29} These methods enhance validity by explicitly considering how cluster-level antimicrobial exposure (eg wards, facilities) influences outcomes among unexposed individuals. While four of five studies in this review used multilevel techniques, one lacked explicit reporting of confounder control for spillover. Future studies should explicitly report adjustment strategies, including exploring propensity-score methods to handle interference, where one individual’s exposure impacts another individual’s outcome.

Population-level spillover effects of AMU have been reported in mass-drug-administration trials, household studies, and community settings. However, comparable evidence for routine institutional use is limited. The ecological impact of SDD in institutional intensive care unit settings has been assessed in a prospective cluster randomized trial, however did not specifically look at unexposed individuals and did not have enough power to detect changes in AMR given the low prevalence AMR in the study settings.^{30,31} We did not include SDD studies in our systematic review as these interventions did not constitute routine AMU in institutional settings.

Peterson et al reported a 3.4 % (95 % CI –4.1 to 10.8) increase in macrolide-resistance genes among unexposed children in a secondary analysis of the cluster-randomized trial of azithromycin mass administration across 30 communities in Niger.⁷ At the household level, Gottesman et al. found maternal fluoroquinolone use was associated with a 50 % increase in odds of resistant gram-negative bacteriuria among unexposed children.³² In a population-based study, Low et al. showed women living in neighborhoods with the highest quintile of fluoroquinolone use had 1.47-fold (95 % CI 1.33–1.65) higher odds of resistant *E. coli* urinary isolates despite no personal antibiotic exposure.³³ Together, these data confirm that antimicrobial pressure can extend beyond treated individuals; however, none of these studies quantify indirect effects within healthcare institutions—a setting characterized by concentrated antibiotic use and high transmission potential.

Several important limitations affect the interpretation of our systematic review, including considerable heterogeneity in study design, exposure definitions, and confounder adjustment, as well as challenges in identifying relevant studies and the potential for publication bias limit the certainty of these findings. These issues likely obscure mechanistic reasons for differences seen in the magnitude of the spillover effect between antimicrobial pathogen pairs that could be driven by differential impact of bystander selection,⁴ cross-class AMR,^{34,35} and environmental persistence.^{36,37} Improved standardization of terminology, explicit prespecification of spillover mechanisms, and adoption of robust observational designs can advance research of spillover effects with routine AMU.

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Appendix A. Search strategy

(spillover* adj5 effect*) or (spill over adj5 effect*) or (externalit* adj5 effect*) or (contamination adj5 effect*) or (indirect adj5 effect*) or (indirect adj5 \$receipt*) or (indirect adj5 risk*) or (herd adj5 effect*) or (seconda* adj5 effect*) or (unexpected adj5 effect*) or (diffusion adj5 effect*) or (ecolog* adj5 effect*) or (independent adj5 effect*) or (independent adj5 risk*) or (independent adj5 association*) or (without adj5 exposure*) or nonreceipt or (prior adj3 use*) or (prior adj3 antibiotic*) or (previous adj3 use*) or (previous adj3 antibiotic*) or multilevel* or multi-level* or cluster*).tw,kf.

Beds/ or Hospitalization/ or Intensive Care Units/ or Hospitals/ Inpatients/ or Homes for the Aged/ or Nursing Homes/ or Residential Facilities/

Skilled Nursing Facilities/

exp Health Facilities/

(bed* or hospitali?ation or intensive care unit or ICU or hospital* or inpatient*).tw,kf.

(homes for the aged or senior home* or old folks home* or retirement home or nursing home* or residential facilities or complex continuing care or rehabilitation facil*).tw,kf.

or/2-7 [Institutional]

Anti-Bacterial Agents/ or Practice Patterns, Physicians'/ or Drug Prescriptions/ or exp Beta-lactamase inhibitors/ or Quinolones/ or exp Fluoroquinolones/ or exp beta-Lactams/ or azithromycin/ or clarithromycin/ or erythromycin/ or trimethoprim/ or exp trimethoprim, sulfamethoxazole drug combination/ or nitrofurantoin/ or anti-infective agents, urinary/

(antibiotic or antibiotic utili?ation or antibiotic usage or antibiotic prescrib* or antibacterial* or anti-bacterial* or quinolone* or fluoroquinolone* or beta-lactam* or azithromycin or clarithromycin or erythromycin or trimethoprim or sulfamethoxazole or trimethoprim-sulfamethoxazole or urinary tract anti-infective*).tw,kf.

or/9-10 [antibiotic usage]

Cross Infection/ or Community-Acquired Infections/ or *Clostridioides difficile*/ or *Clostridium* Infections/ or exp Drug

Resistance, bacterial/ or exp beta-lactam resistance/ or vancomycin-resistant enterococci/ or carbapenem-resistant enterobacteriaceae/

(cross infection* or community acquired infection or drug resistan* or *C difficile* or *Clostridioides difficile* or colonization or bacterial resistance* or antibacterial resistance* or Extended Spectrum Beta-Lactamase* or ESBL).tw,kf.

or/12-13 [Antibacterial resistance]

1 and 8 and 11 and 14

Appendix B. Outcome standardization

For studies reporting a one DOT increase in exposure (Oliviera 2022) we assumed a log-linear model. The beta coefficient was back-calculated from the reported IRR using the study reported median duration of exposure and scaled for the corresponding 100 DOT/1000 patient-days. Brown (2016) originally reported IRR per doubling, which corresponds approximately to a 100 DOT increase. Thus, the reported IRR (2.81; 95% CI, 2.20–3.58) was directly used without transformation to reflect an increase per 100 DOT per 1000 patient-days. For studies reporting an IRR for a 10% relative increase DOT/100 patient-days (Brown 2015) we used the study-reported IRR, as the proportional change is equivalent to 100 DOT/1000 patient-days.

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1. Log-linear Poisson Model equation:

$$\ln(E[Y_i]) = \beta_0 + \beta_1 X_{i1}$$

Solving for β_1 (per DOT exposure)

$$1.009 = e^{\beta_1}$$

$$\beta_1 = 0.00896$$

2. Convert to DOT/Patient-day based on study reported median time at risk (5 days)

$$\beta'_1 = 0.00896 \times 5 = 0.0448$$

3. Calculate standardized IRR for 100 DOT per 1000 patient-days

$$100 \text{ DOT per } 1000 \text{ patient-days} = 0.1 \text{ DOT per patient-day}$$

$$\text{IRR} = e^{0.0448 \times 0.1} = 1.004 \text{ (95\% CI 1.000, 1.009)}$$