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# Hidden antibiotic exposures: A scoping review of residues detected in humans without recent, intentional use

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# Abstract

## Background

Antibiotic residues are commonly reported in food, water, and soil. Despite concerns that chronic, low-dose exposures could perturb the human gut microbiome and select for antimicrobial resistance, it remains unclear how prevalent these exposures are in the general population. The goal of this scoping review was to compile and summarize existing evidence for the detection of antibiotic residues in human samples (e.g., blood, breast milk, urine, stool) from individuals without known, recent antibiotic use.

## Methods

We systematically searched PubMed, Embase, and Scopus (1990 through October 2025) for studies reporting antibiotic detection in humans with no recent antibiotic use, hereafter termed “inadvertent antibiotic exposure” (IAE). All methods for ascertaining recent antibiotic use (e.g. medical record review, self-report) were eligible. No minimum antibiotic abstention period was required for inclusion. Any age, sex, country, or human specimen type was eligible. Literature reviews, case-series, and case control study designs were excluded. Abstract screening, full-text screening, and data extraction were performed in duplicate.

## Results

Thirty-two studies including 11,499 participants from 10 predominantly low- and middle-income countries met inclusion criteria. Most assessed antibiotic activity in urine (n = 24), though stool, breast milk, blood, and fat were also analyzed (< 5 studies each). The average minimum antibiotic abstention time was 3.1 months. At the person level, half of tested participants (standard deviation (SD): 30%) were positive for at least one antibiotic residue or metabolite. Norfloxacin, ofloxacin, and ciprofloxacin were each identified in one fifth of participants. Reported maximum urinary concentrations of ciprofloxacin were comparable to therapeutic levels. We noted substantial gaps that limit the generalizability of current evidence, including no published studies from Europe and North America, reliance on self-report for ascertaining recent antibiotic exposure, and heterogeneity in analytical methods and outcome reporting.

## Discussion

Overall, this review finds evidence of a broad range of antibiotic residues - including agents classified as critically important for human health - in up to 50% of individuals with no recent, self-reported antibiotic exposure. Our results indicate that IAE is common in many low and middle-income countries, although it remains poorly characterized in other settings. Our findings underscore the relevance of investigating the sources and consequences of IAE, including its potential effects on the microbiome and global antimicrobial resistance.

# Introduction

Infections with antimicrobial-resistant organisms are a major public health threat, causing an estimated 1 million deaths worldwide each year.[1] Human antibiotic use is considered a key driver of antimicrobial resistance (AMR), [2–4] and reducing unnecessary human antibiotic use has been a primary focus of ongoing prevention efforts.[5] However, mounting evidence indicates that human antibiotic use is not the only driver of AMR burden in many community settings across the globe, both in low- and middle-income countries[6–12] and in Western settings.[13] Identifying ongoing selection pressures other than human antibiotic use that may be contributing to the continued global rise in AMR is critical for informing targeted mitigation efforts.

Environmental exposure to antibiotic residues could be one mechanism by which AMR is chronically selected for in the community.[14] Antibiotic residues – persisting active ingredients or metabolites of antibiotic drugs – are pervasive in the environment. An estimated 130,000 tons of antibiotics are consumed annually by humans and food animals across the globe,[15,16] with up to 90% excreted unchanged in urine or feces.[17] Because conventional wastewater treatment processes do not efficiently eliminate antibiotic residues, residues and their transformation products are routinely discharged into the environment (Fig. 1).[18] This has led to widespread environmental contamination, with ubiquitous detection of antibiotic residues in waterways worldwide.[15] While human and animal excretion is likely the largest contributor to environmental contamination, other sources include direct disposal of unused antibiotics[19], aquaculture production run-off, and pharmaceutical manufacturing byproducts (Fig. 1),[20,21] with some of the highest concentrations in waterways observed downstream of manufacturing sites.[20]

Once in the environment, antibiotic residues can “recirculate” to humans through multiple pathways (Fig. 1). Laboratory studies suggest that these chronic, low-dose exposures could select for antimicrobial-resistant organisms, increase antibiotic resistance gene abundance, and promote horizontal gene transfer in the gut.[14,22] Drinking water may be a source of inadvertent antibiotic exposure (IAE), as many treatment processes do not fully eliminate residues that have leached into groundwater or contaminated surface waters.[23] For example, some bottled water contains antibiotic residues at concentrations higher than 100 ng/L.[24] Animal products like meat, eggs, and milk may also contain trace residues from antibiotics administered to food animals for treatment, growth promotion, or prophylaxis; [25–31] residue levels are likely much higher in settings where antibiotic withdrawal periods are not respected before animals or their products are harvested. Produce may also be a source of residues by concentrating residues from contaminated soil or irrigation water[32] or antibiotics that were directly applied.[33] Of note, IAE via contaminated water or consumption of foods containing trace residues may be especially common in settings where antibiotic use in humans and animals is poorly regulated, and where inadequate sanitation infrastructure results in antibiotic-rich waste streams being discharged directly into the environment or used for food production.

Prior studies have examined the presence and levels of antibiotic residues in food and water to gain insight into their possible impacts on human health. However, comparatively fewer studies have measured antibiotic residues in humans with no reported antibiotic use, indicating IAE. Thus, while compelling laboratory evidence suggests that environmental exposures to antibiotic residues could select for AMR,[14,22] it remains unclear whether IAE is prevalent enough to merit consideration as a potential driver of global AMR. Scoping reviews aim to provide an overview or map of existing evidence, while also identifying gaps in knowledge. The specific objective of this scoping review was to compile and summarize existing evidence for the detection of antibiotic residues in human samples (e.g., blood, breast milk, urine, stool) from individuals with no known, recent antibiotic use.

## Methods

# Search strategy and selection criteria

The search strategy, database selection, and search terms/string were developed in consultation with experts and an Emory University information specialist. The search strategy used a combination of controlled vocabulary and free-text keywords related to the following concepts: antibiotics, exposure, biological monitoring, and mass spectrometry. The search results were further limited by language (English, Spanish, or French), species (human), and publication type (primary journal articles). The full search strategy is reported in **Supplementary Table 1**. PubMed, Embase, and Scopus were searched from 1990 through October 2025. References were collected and deduplicated using Endnote X9 prior to export to Covidence for screening and management.[34]

We included peer-reviewed articles that reported antibiotic detection in humans with no recent antibiotic use. All methods for ascertaining recent antibiotic use (e.g. medical record review, self-report) were eligible. No minimum antibiotic abstention period was required for inclusion. As the objective was to obtain population-level estimates of IAE, case-series or case-control study designs were excluded. Literature reviews were also not included. Any age, sex, country, or human specimen type was eligible. Studies that reported the presence of antibiotic activity in human specimens were eligible even if the specific antibiotic was not identified (*e.g.*, via bioassay). Studies that reported antibiotic detection but not concentration were eligible. We excluded studies where participants had recently used antibiotics, or where recent antibiotic use was unclear or not reported. We excluded studies where we were unable to extract antibiotic detection results solely for participants with no recent antibiotic use. Finally, we excluded studies that were suspected to have been derived from the same cohorts (as we risked duplicating data); in these situations, only the study with the largest sample size was included.

As a supplementary search strategy, a backward snowball search of papers referenced by the included studies was performed to identify additional studies that were missed by our original search string but could potentially qualify for inclusion. All potentially relevant primary studies that were cited by included studies were imported into Covidence, de-duplicated, and considered for inclusion using the same criteria described above.

## Study Selection, Data Extraction, and Synthesis

All screening steps were performed independently by two members of the study team. Titles and abstracts were screened in Covidence using the predefined inclusion/exclusion criteria before proceeding to full-text review. Differences were resolved by group consensus during weekly team meetings. A customized extraction form was created in Microsoft Excel by the study team to capture the following information: study design characteristics, study setting and population characteristics, antibiotic-free period before sample collection, human specimen tested and analytical approach, and antibiotics tested and their prevalence and concentrations. All team members piloted the extraction form to ensure it captured all relevant data. Following refinement and initial training, two team members independently extracted each study, and any discrepancies were resolved during weekly group meetings.

We classified antibiotic residues into antibiotic classes for the purposes of data visualization; initial classifications were completed by Claude AI (Sonnet 4.6) and independently reviewed by an infectious disease physician (Dr. Lorraine Vitek) (**Supplementary Table 2**). Extracted data were summarized in tables and figures using RStudio versions 2026.01.0 + 392 (for data tables) and R 4.5.1 (for visualizations). As a sensitivity analysis, we summarized extracted data after excluding studies that reported a minimum antibiotic abstention time of less than two weeks. This review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for reporting scoping reviews (**Supplementary Material**).

## Results

Our initial search strategies yielded 1672 articles that potentially met eligibility criteria; 1001 articles remained after eliminating duplicate records (Fig. 2). Following title and abstract review, 89 abstracts met eligibility criteria and proceeded to full-text review. Of full-text articles that were excluded (n = 57), most were excluded because participants reported intentional antibiotic use or participants' antibiotic use was unclear (50/57). Additionally, some manuscripts were derived from the same cohorts; only one from each cohort was retained. Overall, 32 studies comprising 11,499 unique participants were identified for this review (**Supplementary Table 3**).

## Study characteristics

Of the 32 studies included, all but two were conducted in low- or middle-income countries (Table 1). Most were conducted in East and South Asian countries (n = 22), predominantly China (n = 18). African countries including Ghana (n = 4), Tanzania (n = 1), and Malawi (n = 1) were also represented. There were no studies from Europe or North America. Nearly all studies were cross-sectional (n = 30) and included samples collected in the community (n = 18) and from participants living in urban or mixed (n = 21) locales. Urine was most frequently tested (n = 24), followed by stool (n = 4), breast milk (n = 2), blood (n = 2), and fat (n = 1). Most studies quantified antibiotic residues using liquid chromatography mass spectrometry (LC-MS) (n = 9) alone or along with tandem mass spectrometry (LC-MS/MS) (n = 17), which

involves additional fragmentation steps that allow compounds to be identified with greater sensitivity and selectivity. Five studies used a form of bioassay, e.g., an agar diffusion bioassay, to detect antibiotic activity without identifying the specific compounds exerting these effects.

Table 1
Characteristics of 32 included studies investigating inadvertent antibiotic exposures, published from 1990–2025.

| | **N = 32 (%)** |
|---|---|
| **Country** | |
| Argentina | 1 (3.1) |
| Bangladesh | 1 (3.1) |
| China | 19 (59.4) |
| Ghana | 4 (12.5) |
| Korea | 2 (6.3) |
| Laos | 1 (3.1) |
| Lebanon | 1 (3.1) |
| Malawi | 1 (3.1) |
| Tanzania | 1 (3.1) |
| Turkey | 1 (3.1) |
| Study Design | |
| Cross-sectional | 30 (93.8) |
| Longitudinal | 2 (6.3) |
| Urbanicity | |
| Urban | 17 (53.1) |
| Rural | 3 (9.4) |
| Both rural and urban settings included | 4 (12.5) |
| Other or not reported | 8 (25) |
| Setting | |
| Hospital (both in- and outpatient) | 3 (9.4) |
| Hospital (inpatients only) | 3 (9.4) |
| Hospital (outpatients only) | 3 (9.4) |
| Community | 18 (56.3) |
| Not reported | 6 (18.8) |
| Special population included | |

| | N = 32 (%) |
|---|---|
| **Country** | |
| Children | 8 (25.0) |
| Elderly | 2 (6.3) |
| Postpartum women | 2 (6.3) |
| Pregnant women | 4 (12.5) |
| None | 17 (53.1) |
| Human specimen analyzed[a] | |
| Urine | 24 (71.9) |
| Stool | 4 (9.4) |
| Blood | 2 (6.3) |
| Breast milk | 2 (6.3) |
| Fat | 1 (3.1) |
| Time without intentional antibiotic use prior to sampling (in months)[b] | |
| < 1 | 8 (25.0) |
| 1 to < 2 | 9 (28.1) |
| 2 to < 6 | 4 (12.4) |
| 6 or more | 7 (21.8) |
| Not reported[c] | 5 (12.5) |
| Method of antibiotic assessment [b] | |
| Self-report or caregiver report | 17 (53.1) |
| Medical record | 1 (3.1) |
| Medical record and self-report | 2 (6.2) |
| Not specifed | 13 (37.5) |
| Analytical method[a] | |
| Bioassay | 5 (15.6) |
| LC-MS | 9 (28.1) |
| LC-MS/MS | 17 (53.1) |

| | N = 32 (%) |
|---|---|
| **Country** | |
| Other | 2 (6.3) |
| Analytical approach[c] | |
| Targeted | 28 (84.4) |
| Untargeted | 5 (12.5) |
| Limit of detection (LOD) reported for analytes | |
| Yes | 22 (78.6) |
| No | 6 (21.4) |
| Missing (bioassay only) | 4 (12.5) |
| Limit of quantification (LOQ) reported for analytes | |
| Yes | 14 (50.0) |
| No | 14 (50.0) |
| Missing (bioassay only) | 4 (12.5) |
| Number of antibiotics measured, mean (SD)[d] | 19.61 (16.89) |
| Percent of samples with at least one antibiotic residue detected, mean (SD)[e] | 49.4 (35.6) |
| [a]Percentages sum to > 100% because Alexandrova et al. (2019) assessed more than one human specimen and used more than one analytical approach. | |
| [b]Numbers do not sum to 32 because we extracted data from two distinct populations from Khennavong et al. (2011); the prospective cohort had a reported minimum antibiotic abstention time of 48 hours (assessed by self-report), healthy volunteers had no abstention time reported. | |
| [c]Study reported that participants were not taking antibiotics at the time of sample collection, but no additional information was reported. | |
| [d]All studies classified as using an “untargeted” approach used bioassays to assess antimicrobial activity. | |
| [d]Not reported for 4/32 studies. | |
| [e]Weighted mean and standard deviation among the 21 studies that reported this per-study metric. | |

More than half of studies assessed participants’ recent antibiotic use through self-report or caregiver report (n = 17). One study relied exclusively on medical record review to ascertain women’s antibiotic use during pregnancy,[35] two used medical record review in combination with self-report, and 13 did not

clearly specify a method for assessing recent antibiotic use. While all studies reported that participants were not taking antibiotics at the time of sampling, the minimum length of time that participants were required to have abstained from antibiotics prior to sampling ranged from 48 hours to one year with an average of 3.1 months.[18,19] Four studies (12.5%) did not specify length of antibiotic-free intervals prior to sampling.

Notably, only three studies considered the effects of residues on gut bacteria[36–38] and only one on AMR genes harbored by gut bacteria.[36] Instead, studies examined associations between antibiotic residues in human samples and other outcomes like infant growth trajectories,[39,40] overweight/obesity,[41] and depression,[42,43] among others.

## Prevalence of antibiotic residue detection in human specimens

Twenty-eight studies quantified antibiotic residues in samples from 10,126 unique participants. A total of 108 distinct antibiotic residues or metabolites comprising 17 classes were assessed. On average, studies tested 19.61 (SD = 16.89) residues each (Table 1). The most commonly tested residues included ciprofloxacin and tetracycline (each tested in n = 19 studies), trimethoprim (n = 17), and enrofloxacin, sulfadimidine, and sulfamethoxazole (each n = 14) (**Supplementary Figure S1**).

Forty-nine percent of tested participants (SD 35.6%) were positive for at least one antibiotic residue or residue metabolite (weighted average among the 21 studies that reported this per-study metric) (Table 1). Norfloxacin, ofloxacin, and ciprofloxacin were the most commonly detected antibiotics overall, identified in 22.9% of 5,995, 22.4% of 4,858, and 19.9% of 9,037 tested participants, respectively (Fig. 3). After fluoroquinolones, sulfonamides, tetracyclines, and trimethoprims were the next most frequently detected antibiotic classes (**Supplementary Figure S2**); residues belonging to each class were typically identified in > 10% of tested participants. Antibiotics that were frequently tested (3 or more studies) but rarely detected (< 1%) included: difloxacin (0.8% of 1419 participants), cloxacillin (0.3% of 1821), ceftriaxone (0.1% of 1890), and penicillin G (0.1% of 1865) (**Supplementary Figure S1**).

Antibiotic residues were sometimes reported in vulnerable populations for whom the detected antibiotics are contraindicated. Studies in China (n = 4) detected antibiotics that are contraindicated for use during pregnancy in the urine and blood of pregnant women,[44] including tetracyclines, fluoroquinolones, chloramphenicols, and sulfonamides/trimethoprim. This included one study that used medical records to confirm women's absention from prescribed antibiotics during pregnancy.[35] Studies of children's urine and blood in China (n = 5) and Tanzania (n = 1) detected chloramphenicol, azithromycin, and/or tetracycline, which are not recommended for use in children.[45] Only two studies considered human breast milk[46,47] and both detected residues, including beta lactams (84% of 34 women in Dinleyici et al.), quinolones (24% of 34 women in Dinleyici et al.), and oxytetracycline (3% of 120 women in Smadi et al; fluoroquinolones and tetracyclines are contraindicated in women who are breastfeeding.

In a sensitivity analysis that excluded studies with unclear antibiotic abstention times or minimum abstention times of less than two weeks (n = 6 removed from Laos,[48] Malawi,[49] Bangladesh,[50] Ghana[51] and China[37,52]), norfloxacin, ofloxacin, and ciprofloxacin continued to be the most commonly detected antibiotics, identified in 22.5% of 5,893, 21.0% of 4,756, and 19.2% of 8,910 tested participants, respectively (**Supplementary Figure S3**). Similar to the primary analysis, 51% of participants (SD 36.0%) were positive for at least one antibiotic residue or residue metabolite (weighted average among the 16 studies that reported this per-study metric).

# Residue concentrations in human specimens

Among the 28 studies that quantified residues, maximum concentration was the most commonly reported metric. Maximum concentrations detected in urine are reported in Table 2 and depicted in Fig. 4. Maximum concentrations detected in all other specimen types are reported in **Supplementary Table 4**.

Table 2

Maximum urinary antibiotic concentrations among participants without recent, intentional antibiotic use.

| Antibiotic | Studies with maximum urinary concentrations reported | Maximum concentrations (ng/mL)[a] | Urinary concentrations following therapeutic doses (ng/mL)[b] |
|---|---|---|---|
| Amoxicillin | Sun H. et al., Bekoe et al. 2022, Bekoe et al. 2020, Huang et al. | 70851 (14891.07, 711000) | 122800-1300000[53,79] |
| Cefuroxime | Bekoe et al. 2020 | 122000 | 1000000-7000000[53] |
| Chlortetracycline | Zhang et al. 2022, Sun H. et al., Lin et al., Liu Y. et al., Chu et al. | 6 (0.88, 120) | 64000-128000[80] |
| Ciprofloxacin | Zhang et al. 2022, Lin et al., Huang et al., Sun H. et al., Chu et al., Bekoe et al. 2022, Zhong, Bekoe et al. 2020 | 1171 (7.54, 846950) | 300-892000[53–55] |
| Clarithromycin | Sun H. et al., Lin et al., Liu Y. et al., Chu et al., Huang et al. | 32 (0.05, 10200) | 2840-450000[81,82] |
| Erythromycin | Liu Y. et al., Sun H. et al., Huang et al., Bekoe et al. 2020 | 792 (2.81, 335000) | 5300-50000[83,84] |
| Flumequine | Zhang et al. 2022 | 1.49 | 3000-114000[85] |
| Levofloxacin | Lin et al. | 44.58 | 300-498000[53–55] |
| Lomefloxacin | Zhang et al. 2022, Sun H. et al. | 0.1, 0.65 | 35000-700000[86] |
| Metronidazole | Lin et al., Bekoe et al. 2022, Zhong et al., Bekoe et al. 2020 | 8791 (25.24, 325000) | 76400-115000[87] |
| Norfloxacin | Sun H. et al., Zhang et al. 2022, Lin et al., Huang et al., Chu et al., Zhong et al. | 416 (3.15, 54200) | 300-300000[56] |
| Ofloxacin | Sun H. et al., Jin et al., Liu Y. et al., Zhang et al. 2022, Chu et al., Huang et al., Zhong et al. | 1686 (3.03, 3517000) | 141000-330000[88,89] |
| Sulfadiazine | Zhang et al. 2022, Liu Y. et al., Chu et al., Huang et al., Lin et al., Zhong et al. | 41 (0.64, 425000) | 65000-623000[90] |

[a]Geometric means and ranges are reported for studies included in this review that reported this metric (column 2). If less than 3 studies reported a given antibiotic, then concentrations from those studies are individually reported.

[b]Among studies in the literature reporting urinary concentrations in therapeutic dosing.

| Antibiotic | Studies with maximum urinary concentrations reported | Maximum concentrations (ng/mL)[a] | Urinary concentrations following therapeutic doses (ng/mL)[b] |
|---|---|---|---|
| Sulfamethoxazole | Zhang et al. 2022, Sun H. et al., Liu Y. et al., Lin et al., Bekoe et al. 2022, Chu et al. | 30 (0.5, 78000) | 38900-2000000[53,91] |
| Tetracycline | Zhang et al. 2022, Sun H. et al., Lin et al., Bekoe et al. 2022, Liu Y. et al., Chu et al., Bekoe et al. 2020, Huang et al. | 955 (0.49, 408000) | Up to 300000[92] |
| Trimethoprim | Liu Y. et al., Bekoe et al. 2022, Lin et al., Sun H. et al., Chu et al., Bekoe et al. 2020 | 174 (2.54, 666990) | 24200-100000[53,90] |

[a]Geometric means and ranges are reported for studies included in this review that reported this metric (column 2). If less than 3 studies reported a given antibiotic, then concentrations from those studies are individually reported.

[b]Among studies in the literature reporting urinary concentrations in therapeutic dosing.

For studies reporting maximum antibiotic concentrations in urine, we compared observed levels to concentrations in persons taking therapeutic doses, as reported in the literature. This comparison was restricted to studies reporting residue concentrations in urine as this was the most commonly tested human specimen in our review and because pharmacokinetic studies were commonly performed with urine. For ciprofloxacin, 75% of studies (6/8) reported maximum urinary concentrations that were comparable to what would be expected following therapeutic use (Fig. 4). For norfloxacin (3/6), erythromycin (2/4), metronidazole (2/4) and amoxicillin (2/4), half of studies reported maximum urinary concentrations at therapeutic or even supratherapeutic levels. For all other antibiotics, studies largely reported concentrations that were several orders of magnitude lower than what would be expected following therapeutic use.

As a sensitivity analysis, we repeated this comparison after excluding studies with unclear antibiotic abstention times or minimum abstention times less than two weeks (n = 6). The proportion of studies reporting maximum urinary concentrations at therapeutic levels increased for some antibiotics (*e.g.*, ciprofloxacin to 86% from 75%, norfloxacin to 60% from 50%) and remained similar for all others (**Supplementary Figure S4**).

# Discussion

This review finds evidence suggesting high rates of antibiotic residues in the blood, urine, stool, and breast milk of individuals with no known recent antibiotic use across ten countries in three continents. Concerningly, several studies reported urinary ciprofloxacin concentrations that are comparable to levels expected following therapeutic use,[53–56] even though participants reported no recent, intentional

antibiotic use.[57,58] Antibiotics preferred for use in veterinary medicine (e.g., enrofloxacin, florfenicol, chlortetracycline)[16,59,60] and human medicine (e.g., ciprofloxacin, clarithromycin)[41,57] were both commonly detected. Every study included in this scoping review that looked for evidence of IAE detected it, and half of participants had at least one detectable antibiotic residue (among the 21 studies that reported this per-study metric). Our findings suggest that IAE is common in several low and middle-income countries, though it remains poorly characterized elsewhere and estimates may be imprecise due to frequent reliance on self-reported absence of antibiotic use. We identified several research gaps that we suggest should be addressed to more accurately assess IAE prevalence and whether it may be impacting global AMR trends.

Many studies included here identified IAE at subtherapeutic concentrations that could plausibly select for AMR in the human gut. Ciprofloxacin, trimethoprim/sulfamethoxazole, and doxycycline – highly or critically important antibiotics[61] used to treat common infections (e.g., urinary tract infections, skin and soft tissue infections, pneumonia) - were detected in nearly a fifth of participants included in this review. Just one to two courses of ciprofloxacin can irreversibly alter gut microbiome composition[62] and select for mutations conferring high-level fluoroquinolone resistance among human gut bacteria.[63] Concentrations of ciprofloxacin reported among studies here (e.g., 86.1-645.1 µg/kg among positive stool samples in Zhang *et al*.[64]) have been demonstrated to support the establishment of antimicrobial-resistant Enterobacterales species in the human gut.[22] Specifically, a recent experimental study by Martak *et al*. found that 50 µg/L ciprofloxacin spiked in a pooled fecal slurry enriched *E. coli* encoding extended spectrum-beta-lactamase and carbapenemase-producing genes by up to 21-fold. This same study found that low-dose mixtures of 15 preferred veterinary antibiotics, each of which were detected among studies included here, induced similar effects.[22] Despite common detection of IAE, only 3 of the 32 studies in this review explored effects on AMR selection or the gut microbiome, highlighting a clear research gap.

A small subset of studies reported IAE at concentrations that exceed therapeutic levels. Studies that reported maximum antibiotic concentrations above therapeutic levels had reported antibiotic abstention periods ranging from 2 weeks to 3 months, and like many other studies in this review, relied on self-report from participants or their caregivers to assess recent antibiotic use, potentially introducing bias due to recall error, undisclosed unintentional use, or misunderstanding of what constitutes an antibiotic (even when prescribed). One study by Bekoe et al.[65] reported supratherapeutic concentrations of erythromycin, metronidazole, and trimethoprim in the urine of healthy volunteers in Ghana, none of whom had knowingly consumed or had been prescribed antibiotics in the past two weeks. Given that participants did not report any antibiotic use, the study authors hypothesized that participants consumed herbal medicines that were adulterated with antibiotics, as use of herbal medicines was common. Other studies that reported supratherapeutic antibiotic concentrations in urine hypothesized that environmental exposures through antibiotic-contaminated food and drinking water were likely sources.[57,58] If these results are truly a result of environmental exposures, and not recall error or

undisclosed or unknown use, these findings would suggest that some individuals may be inadvertently exposed to antibiotic doses that may cause substantial gut dysbiosis.

Fluoroquinolones, sulfonamides, and tetracyclines were among the most commonly detected antibiotics in included studies, potentially reflecting their environmental persistence. River and sediment batch studies indicate that sulfonamides have half lives in the environment up to 26 days,[66] indicating they could travel up to 400 km downstream on a typical river with only half the concentration lost. Other antibiotic classes like fluoroquinolones strongly adsorb to sediment and can be detected months to years after initial application to soil.[67] Up to 70% of tetracyclines administered to humans and animals are excreted in their active form, and they can accumulate in organic manure that is subsequently applied to plants and crops. Chlortetracycline, which was detected in urine[41,43,52,68,69] and feces[36,70] among studies included in this review has a reported half-life of ~ 1 month in soil, while oxytetracycline, which was detected in urine,[41,43,57,68,69,71] feces,[36,64,70] and breast milk[47] among studies included in this review, has no observed degradation in marine sediment.[23] In contrast, beta lactams, which are highly susceptible to phytodegradation, comprised most of the least commonly detected residues (< 1% of tested participants), suggesting environmental persistence could be a key determinant of IAE.

All but two studies included in this review were cross-sectional, limiting causal inference for specific risk factors. One study that collected paired samples from participants before and after an imposed vegetarian diet demonstrated that animal product consumption impacts antibiotic levels in urine.[72] Specifically, Ji et al. found that among 25 participants participating in a “temple stay” in Korea, levels of creatinine-adjusted trimethoprim and ciprofloxacin significantly decreased following a five-day vegetarian diet that excluded animal products previously consumed by all participants (primarily beef, pork, and dairy products). While changes in drinking water source may also have contributed to these differences, the authors noted that antibiotic residue levels in drinking water in Korea tend to be very low. Several studies included in our review attempted to link dietary exposures to IAE, but given diverse community exposure pathways to IAE (Fig. 1), study designs that support causal inference would be more helpful to elucidate risk factors for IAE in different settings and among different sub-populations.

This scoping review revealed several gaps that limit the generalizability of existing evidence for IAE and interpretations of its public health significance. First, we identified no studies conducted in Western settings, despite high rates of antibiotic use in humans and animals in the global North[16,59] and widespread ineffectiveness of wastewater treatment plants in removing these compounds.[18] Nearly 60% of studies were conducted in China, and most other countries only had one representative study. Though regional variations in IAE could theoretically contribute to regional differences in AMR prevalence or other health outcomes, this is not possible to investigate with currently published evidence. Second, studies did not measure or report antibiotic residue concentrations in a standard way, making cross-study comparisons challenging. A variety of methodologies were noted (e.g., LC/MS versus LC/MS-MS), and while some studies reported concentrations adjusted for creatine[35,73] or protein,[74] others did not. More standardized measurement and reporting may facilitate future meta-analyses on the health effects

of IAE. Third, although quantifying IAE concentrations in human specimens is important for interpreting their potential health effects, most studies only reported maximum concentrations, which could be influenced by outliers and hampers interpretation of the public health significance of IAE. Reporting median antibiotic concentrations in future studies of IAE woud help facilitate future meta-analyses.

We noted other gaps related to antibiotic assessment in human specimens. First, nearly all studies used a targeted approach to measure pre-specified antibiotics of interest. Antibiotic co-occurrence was often reported among studies that tested for multiple antibiotics,[36,50,57,64,65,75,76] suggesting that using an untargeted analytical approach – which casts a wider net – could be beneficial for discovery-driven studies seeking to assess the single and combined effects of IAE on health outcomes. Future work could consider using untargeted high-resolution mass spectrometry to assess antimicrobial compounds in human samples. Second, several studies used urine bioassays to assess antibiotic activity, but these are susceptible to yielding "false positives" as non-antibiotic compounds that exert antibiotic activity may be excreted in urine.[48] Nevertheless, bioassays remain an important and attractive option for screening large cohorts, particularly in LMICs, given that they are 80-160x cheaper than LC/MS.[50]

This review has several notable strengths. We conducted a comprehensive and systematic literature search in collaboration with a librarian (S.P.), with search terms developed iteratively in consultation with experts in infectious diseases (A.S.), global AMR surveillance (A.S., M.L.N.), and One Health (M.L.N.). To reduce subjectivity and enhance methodological rigor, study screening and data extraction were performed independently by two reviewers. The review included 32 studies, comprising an analytical dataset of 11,499 participants. To our knowledge, this represents the first comprehensive synthesis of global evidence on IAE.

A key limitation of this review is that many studies relied on self-reported antibiotic use, which could bias IAE prevalence estimates due to recall error, undisclosed use, or failure to recognize medications as antibiotics (even if prescribed). Although medical or prescription records can provide more objective measures of recent antibiotic use in high-income country settings, these assessment methods have lower sensitivity in LMIC settings where antibiotics are commonly obtained without a prescription. We retained studies using self-report because excluding them would have removed most LMIC studies, limiting our ability to compile evidence of IAE in settings where it may be most common.

Two lines of evidence indicate that our IAE prevalence estimates were not driven by pharmacokinetic persistence following recent, intentional use. First, the top 10 most commonly detected residues in this review have half-lives of < 24 hours, indicating they would be eliminated within one week of a therapeutic dose (< 1% remaining). Studies have demonstrated that time frames of one month or shorter are reasonably accurate for correctly recalling antibiotic use,[77,78] meaning that recall error should not substantially bias prevalence estimates for these residues. Second, excluding studies with unclear or < 2 week minimum abstention times did not meaningfully alter IAE prevalence estimates, suggesting residual antibiotics from intentional use were not the primary cause of detection. Importantly, we note that while self-report is imperfect, it has long been used by major global health surveys to assess

antibiotic use patterns in LMICs, e.g., USAID Demographic and Health Surveys and UNICEF Multiple Indicator Cluster Surveys, largely because more objective measures are not feasible. Nevertheless, this remains a limitation of this review.

# Conclusions

This scoping review, which included studies predominantly from LMICs, found a broad range of antibiotic residues - including agents classified as critically important for human health - in 49% of individuals with no known recent antibiotic exposure. Notably, antibiotic concentrations in some participants reached therapeutic levels. Overall, our findings underscore the relevancy of investigating the sources, frequency, and consequences of IAE, including its potential effects on the microbiome and global AMR trends.

# Declarations


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### Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

### Disclosure

Claude AI (Sonnet 4.6) was used for grouping antibiotics into classes; final categorizations were reviewed and approved by an external expert. Figure 1 was developed using ChatGPT to visually synthesize pathways proposed by the authors; authors reviewed and confirmed that the outputs were accurate.

### Conflict of Interest

None to declare


### Funding

None to declare


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# Figures

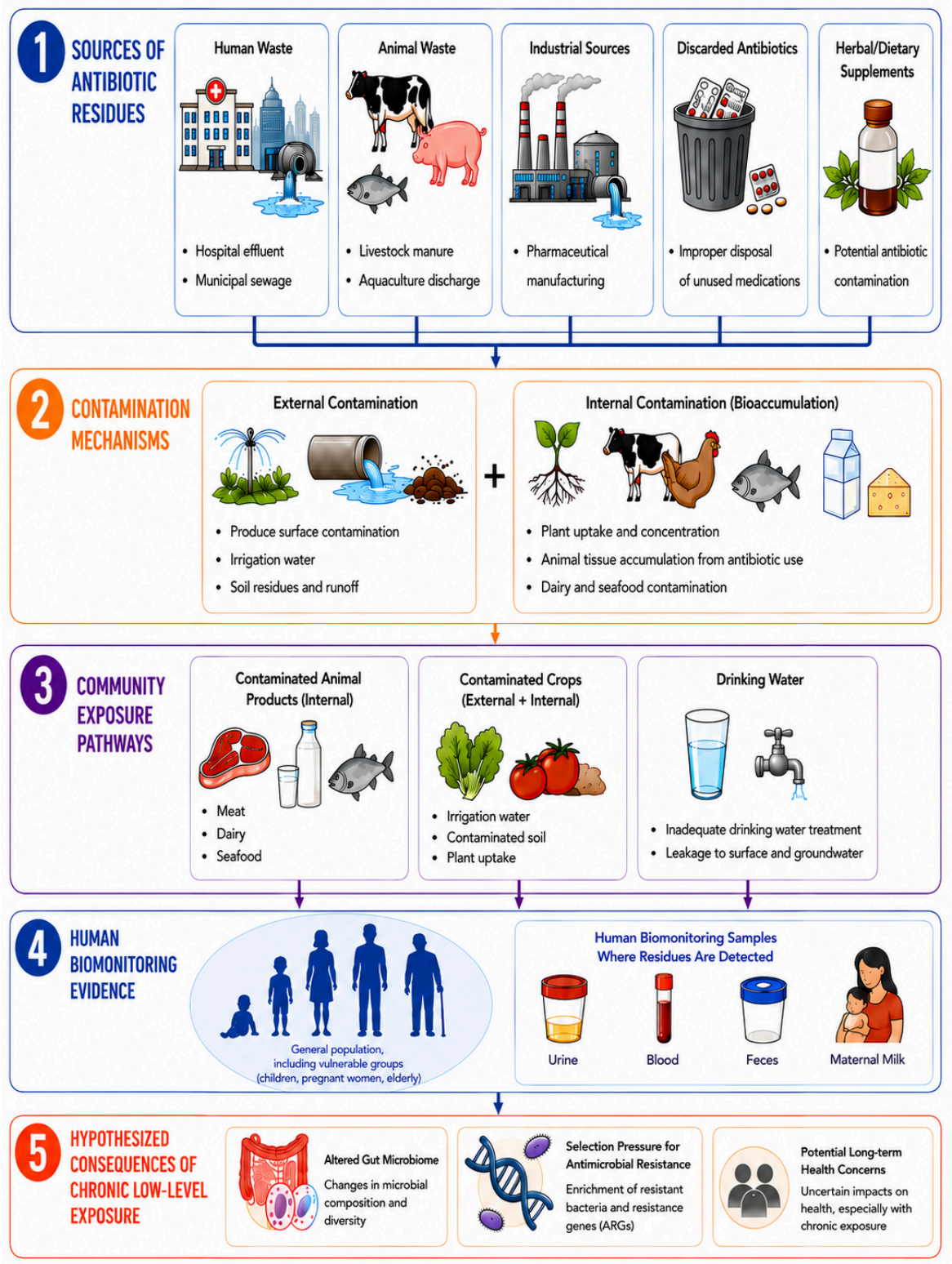



**Figure 1**

Conceptual diagram of environmental antibiotic residue exposure pathways and uptake by humans.

Diagram generated using ChatGPT

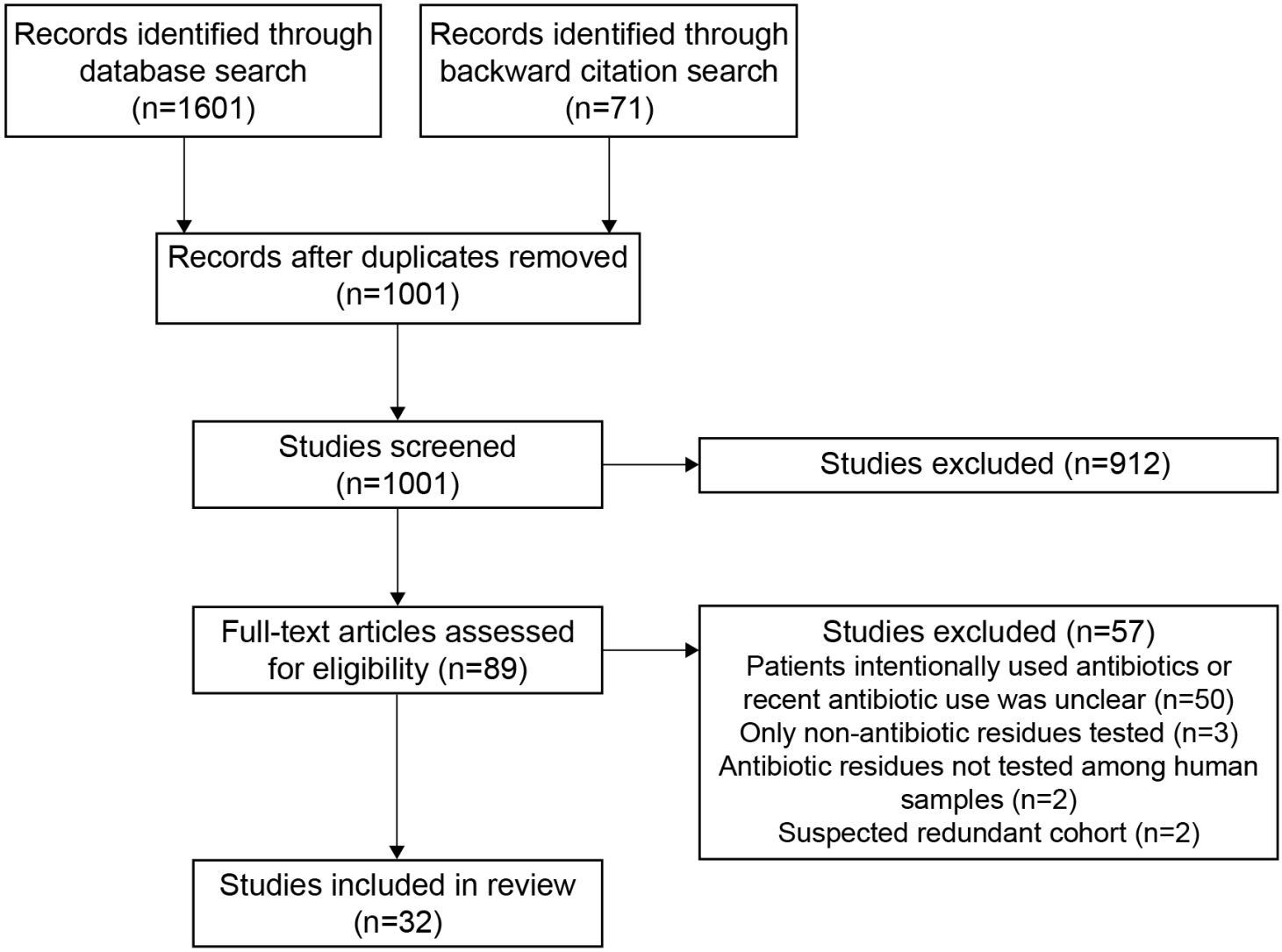
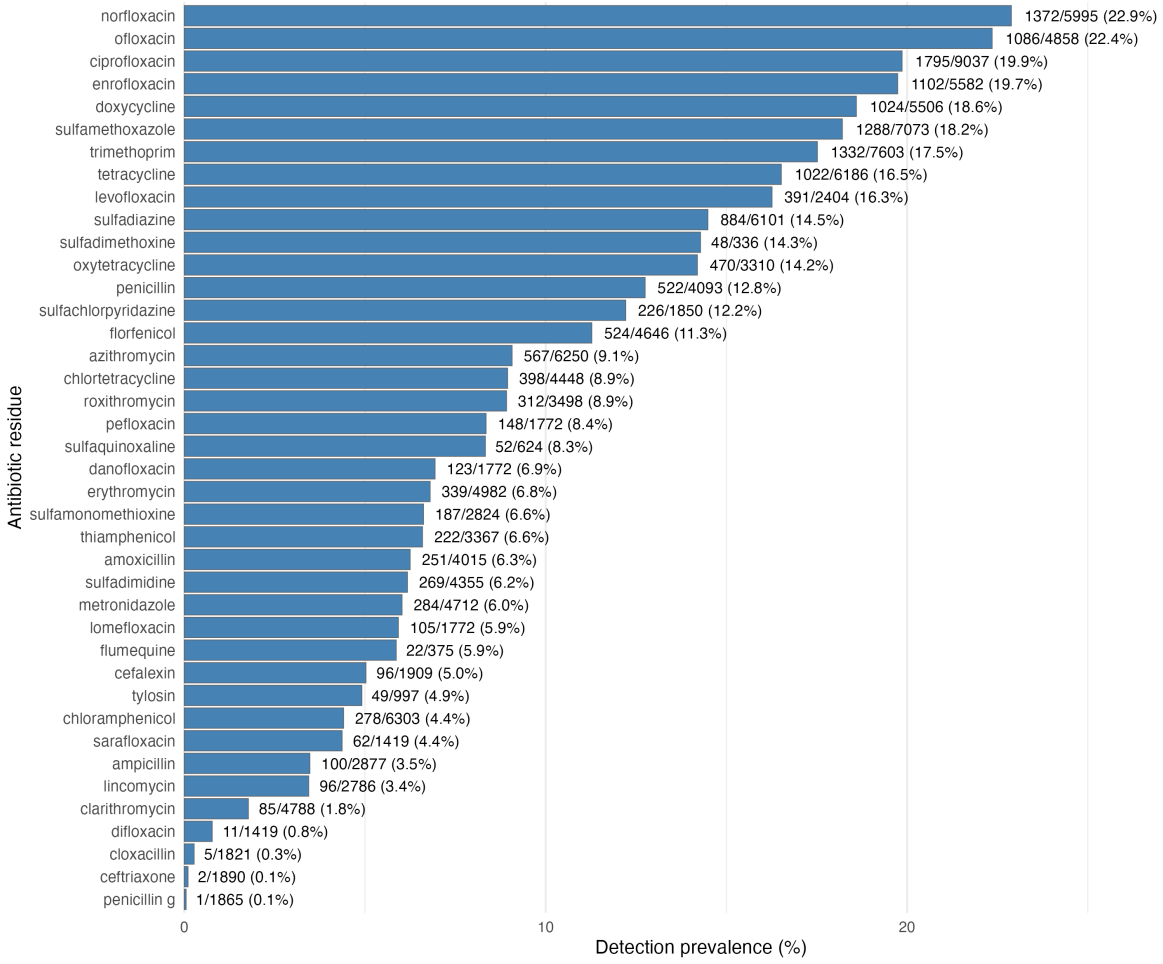



**Figure 2**

Study inclusion schema for current scoping review of evidence for inadvertent antibiotic exposures in humans, 1990-2025.




## Figure 3

Frequency of detection of 40 antibiotic residues examined in the blood, urine, stool, breast milk, or fat of up to 10,126 unique persons with no recent, intentional antibiotic use. Residues assessed in fewer than 3 studies are not depicted.

*Note*: To avoid double-counting data from the same participants, only urine results were retained from Alexandrova *et al*. 2019 and only results from the 42-day timepoint were retained for Fan *et al*. 2023.

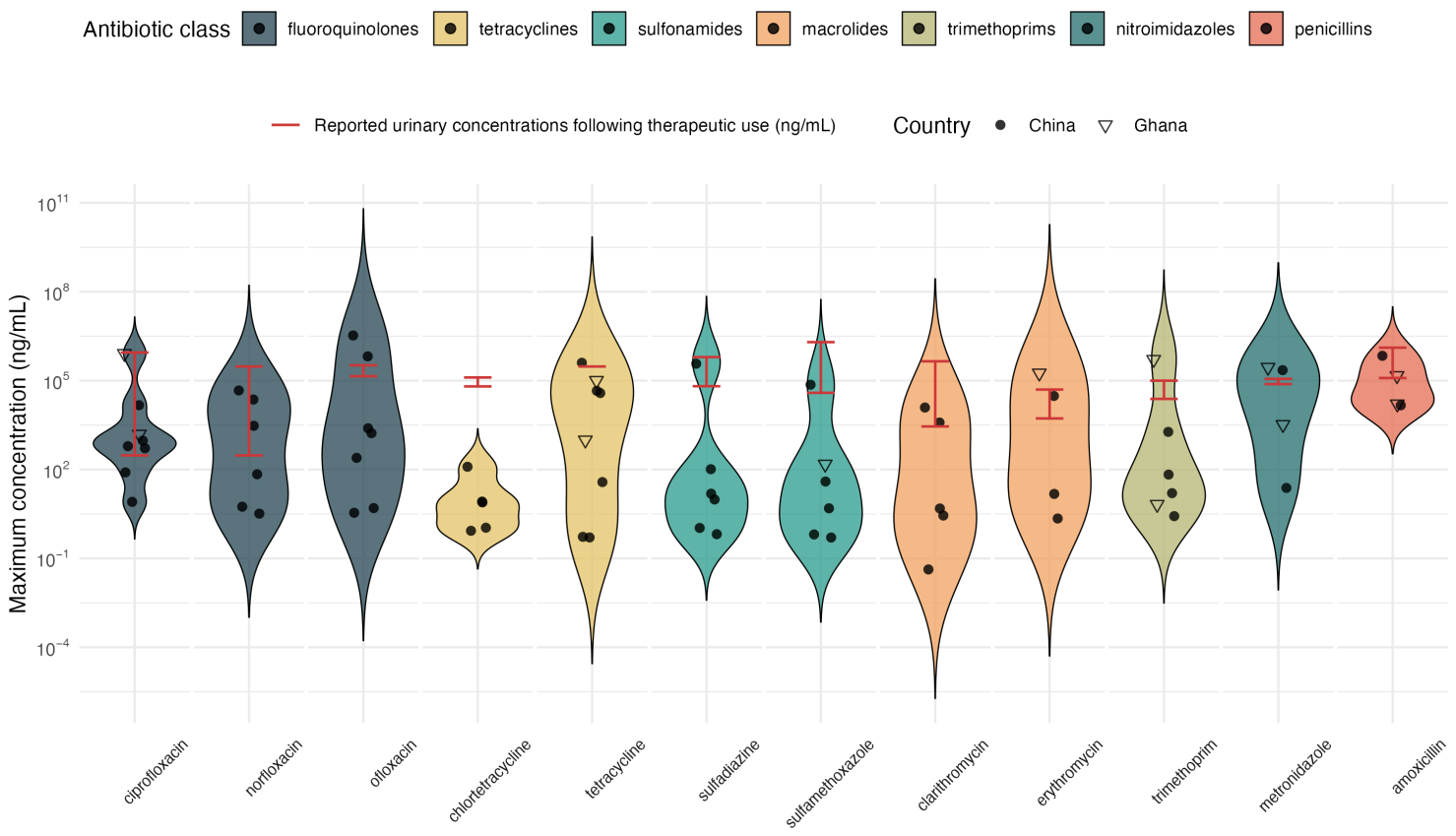



**Figure 4**

Maximum urinary antibiotic concentrations among participants with no recent antibiotic use reported, relative to concentrations expected following therapeutic use.

Only antibiotics for which at least 3 studies reported maximum antibiotic concentrations are depicted. Each point represents results from a unique study. References are provided in Table 2.

# Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- 25SeptresiduesSUPPMATERIAL.docx