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Eco-Pharmacovigilance in Emerging Economies: Advanced Analytical Methodologies for Detecting Pharmaceutical Residues and Mitigating AMR Risks in Aquatic Ecosystems

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ABSTRACT

Background. Pharmaceutical residues are increasingly recognized as emerging environmental pollutants, particularly in developing economies where rapid urbanization, increased medicine consumption, insufficient wastewater treatment, and limited surveillance capacity may amplify ecological risks and antimicrobial resistance (AMR).

Purpose. This study aimed to develop an integrated eco-pharmacovigilance framework for identifying priority pharmaceutical contaminants and assessing the relationship between antibiotic exposure and AMR indicators across aquatic ecosystems.

Method. A multicountry longitudinal design was applied by combining seasonal sampling of wastewater, surface water, sediments, and biofilms with solid-phase extraction, targeted UHPLC–MS/MS, high-resolution suspect screening, passive sampling, antimicrobial susceptibility testing, quantitative PCR, and metagenomic analysis. Environmental, chemical, and microbiological datasets were integrated to evaluate contamination patterns and resistance-related outcomes.

Results. Simulated findings indicated that pharmaceutical manufacturing sites and hospital effluents represented major contamination sources, with persistent residues detected in downstream environments. Integrated chemical screening improved compound identification beyond targeted analysis, while antibiotic concentrations showed positive associations with resistance genes, class 1 integrons, and multidrug-resistant isolates after controlling for environmental factors. Source-control interventions substantially reduced ciprofloxacin levels at a manufacturing hotspot, although microbial recovery was not confirmed during the observation period.

Conclusion. The proposed framework demonstrates the potential of combined chemical and microbiological surveillance for identifying pharmaceutical pollution hotspots and supporting One Health AMR governance. Further longitudinal validation is required to establish causal relationships and inform regulatory implementation.

KEYWORDS

Antimicrobial resistance, Aquatic ecosystems, Eco-pharmacovigilance.

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INTRODUCTION

Pharmaceutical contamination has emerged as a significant dimension of global environmental change because medicinal compounds are continuously released into natural ecosystems through human and veterinary use.

Antibiotics, analgesics, hormones, antidepressants, antidiabetic agents, and other biologically active substances may enter aquatic environments through unicipal wastewater, hospital effluent, pharmaceutical manufacturing, agricultural runoff, aquaculture, and improper disposal. Many compounds are only partially removed by conventional wastewater-treatment systems and can therefore persist in rivers, lakes, groundwater, sediments, and aquatic organisms (Abd-AlGhafar dkk., 2024; Ala dkk., 2026; Castaño-Trias dkk., 2023). The opening paragraph should establish pharmaceutical residues as contaminants of emerging concern whose ecological relevance arises from their biological activity, continuous release, environmental persistence, and potential effects at concentrations below conventional toxicological thresholds.

Emerging economies require particular attention because rapid urbanization, population growth, expanding pharmaceutical consumption, and intensified food production often develop more quickly than wastewater infrastructure and environmental regulation (Çalık dkk., 2026; Giri dkk., 2026; Yıldız Özenç dkk., 2025). Limited sewerage coverage, poorly controlled industrial discharge, informal medicine disposal, and the widespread use of antimicrobials in healthcare, livestock production, and aquaculture can create multiple pathways through which pharmaceutical residues reach aquatic systems. Monitoring capacity may remain concentrated in a small number of laboratories, while routine environmental surveillance is constrained by limited funding, analytical equipment, reference standards, and trained personnel. This paragraph should frame pharmaceutical pollution as both an environmental problem and a structural development challenge shaped by unequal technical, institutional, and financial capacity.

Eco-pharmacovigilance provides a framework for monitoring, evaluating, preventing, and communicating the environmental risks of pharmaceutical products throughout their life cycles. Its scope extends from drug development and manufacturing to prescription, consumption, excretion, waste management, environmental occurrence, and ecological effects. The concept also connects environmental chemistry with public health because antimicrobial residues may impose selective pressure on microbial communities and contribute to the persistence or spread of antimicrobial resistance (Elshenawy dkk., 2026; Gad dkk., 2026; Zhou dkk., 2026). This paragraph should introduce aquatic ecosystems as critical interfaces where pharmaceutical exposure, microbial adaptation, ecological disturbance, and human contact may converge, while avoiding the unsupported assumption that every detected antibiotic concentration necessarily produces a measurable antimicrobial-resistance outcome.

Reliable detection of pharmaceutical residues remains analytically difficult because aquatic matrices contain complex mixtures of target compounds, metabolites, transformation products, natural organic matter, suspended particles, and other contaminants. Residue concentrations frequently occur at trace or ultra-trace levels, while compounds differ substantially in polarity, ionization, solubility, stability, and affinity for sediments or biological tissues. Sampling location, season, hydrological conditions, wastewater flow, and storage procedures can further influence measured concentrations (Mavuluru dkk., 2026; Rozaini dkk., 2025; Subaihi dkk., 2026). This paragraph should define the first research problem as the need for sensitive, selective, reproducible, and matrix-appropriate methodologies capable of identifying chemically diverse pharmaceutical contaminants across water, sediment, biofilm, and biotic samples.

Conventional analytical approaches may fail to characterize the full extent of pharmaceutical contamination when monitoring programs rely on narrow target lists, infrequent grab sampling, or instruments with insufficient sensitivity (Arunagiri dkk., 2026; Elbanna dkk., 2025; Planinšek Parfant & Roškar, 2025). Targeted liquid chromatography–tandem mass spectrometry provides strong quantitative performance for known compounds but may overlook unexpected contaminants

and transformation products. High-resolution mass spectrometry, suspect screening, non-target analysis, passive sampling, effect-based assays, and biosensor technologies offer broader analytical possibilities, yet their costs, data-processing requirements, validation needs, and technical complexity can restrict their adoption in resource-constrained settings. This paragraph should formulate the methodological problem as a mismatch between the sophistication needed to characterize complex pharmaceutical mixtures and the practical capacity available in many emerging economies.

Antimicrobial resistance introduces an additional layer of uncertainty because the relationship between chemical exposure and resistance development is neither simple nor linear. Antibiotic residues may select for resistant bacteria at sub-inhibitory concentrations, but resistance patterns are also affected by microbial ecology, co-selective chemicals, sanitation conditions, mobile genetic elements, antibiotic consumption, and the movement of organisms between environmental, animal, and human compartments (Golla dkk., 2025; Mahgoub dkk., 2023; Waqar dkk., 2026). Detection of a pharmaceutical residue alone cannot demonstrate that it caused a specific resistance phenotype or gene distribution. This paragraph should define the central problem as the absence of integrated surveillance frameworks that combine chemical measurements, microbiological indicators, resistance genes, ecological context, and exposure pathways to produce defensible assessments of antimicrobial-resistance risks.

The primary objective of the proposed study is to develop and evaluate an integrated eco-pharmacovigilance framework for detecting pharmaceutical residues in aquatic ecosystems within emerging economies (Grangeia dkk., 2026; Kanagaddi dkk., 2025; Wahba dkk., 2026). This framework should combine optimized sampling strategies with advanced analytical methodologies, including solid-phase extraction, liquid chromatography coupled with tandem or high-resolution mass spectrometry, suspect and non-target screening, passive sampling, and selected effect-based techniques. The objective should emphasize the accurate identification and quantification of priority pharmaceuticals, metabolites, and transformation products across wastewater effluent, receiving waters, sediments, and relevant biological matrices. Analytical performance should be evaluated through sensitivity, selectivity, accuracy, precision, recovery, matrix effects, detection limits, and interlaboratory reproducibility.

A second objective is to examine the relationship between environmental antimicrobial residues and indicators of antimicrobial resistance in aquatic microbial communities. The proposed research should measure antibiotic concentrations alongside resistant bacterial isolates, antimicrobial-resistance genes, mobile genetic elements, and microbial-community characteristics (Beykaya, 2026; Burini dkk., 2026; Trout dkk., 2026). Culture-based susceptibility testing, quantitative polymerase chain reaction, metagenomic sequencing, and bioinformatic analysis may be integrated to distinguish chemical occurrence from biologically meaningful selection patterns. This paragraph should clarify that the study aims to identify associations, spatial concordance, and plausible risk pathways rather than automatically infer direct causation from cross-sectional co-occurrence.

A third objective is to translate analytical and microbiological evidence into context-sensitive mitigation strategies for emerging economies. The research should identify pollution sources, contamination hotspots, priority compounds, vulnerable ecosystems, and intervention points across the pharmaceutical life cycle. Expected outputs may include a risk-based monitoring protocol, an analytical decision framework, proposed discharge priorities, recommendations for wastewater treatment, and mechanisms for communication among regulators, healthcare providers, manufacturers, farmers, laboratories, and local communities. This paragraph should present the

intended achievement as a scalable surveillance and mitigation model that balances scientific rigor with affordability, institutional feasibility, and local environmental conditions.

Existing environmental studies have documented numerous pharmaceutical compounds in wastewater and surface waters, yet the geographical distribution of evidence remains uneven. Research is often concentrated in high-income countries with established monitoring networks, advanced laboratories, and relatively consistent wastewater infrastructure. Evidence from emerging economies is frequently based on isolated locations, short sampling periods, small compound panels, or inconsistent analytical protocols. Such fragmentation limits comparisons among regions and may conceal seasonal variation, rural exposure pathways, informal discharge, and contamination associated with pharmaceutical production or intensive aquaculture. This paragraph should identify the lack of harmonized, longitudinal, and geographically representative data as a major empirical gap.

Current analytical literature also reveals a separation between methodological sophistication and implementation feasibility. Advanced high-resolution techniques can discover previously unrecognized substances, but many published workflows depend on expensive instruments, proprietary databases, specialist expertise, and computational resources that are not widely accessible. Lower-cost methods may be more deployable but can sacrifice compound coverage, confirmation confidence, or quantitative sensitivity. Limited attention has been paid to tiered monitoring systems in which affordable screening identifies priority samples and advanced confirmatory analysis is used selectively. This paragraph should highlight the need for validated methodological combinations that preserve analytical credibility while responding to the resource limitations of laboratories in emerging economies.

Research on pharmaceutical contamination and antimicrobial resistance often proceeds in parallel rather than through genuinely integrated investigation. Chemical studies may quantify antibiotic residues without characterizing resistant organisms or genes, while microbiological studies may report resistance markers without measuring the selective agents present in the same samples. Environmental concentrations are also frequently compared with clinical susceptibility thresholds that were not designed to assess ecological selection. This paragraph should identify the absence of coordinated chemical, genomic, microbiological, and ecological evidence as a conceptual gap that weakens causal interpretation, risk prioritization, and the design of targeted interventions.

The proposed research is novel because it integrates advanced chemical analytics with antimicrobial-resistance surveillance within a single eco-pharmacovigilance architecture. Targeted quantification would provide reliable concentration data for priority pharmaceuticals, while suspect and non-target screening would expand detection beyond predetermined compound lists. Passive samplers could capture time-weighted exposure, and effect-based assays could reveal biological activity that chemical measurements alone may not adequately represent. Parallel analysis of resistant bacteria, resistance genes, mobile genetic elements, and microbial-community structure would connect contaminant occurrence with biologically relevant responses. This paragraph should position the integrated design as an advance over studies that examine chemical residues or resistance indicators in isolation.

A second element of novelty lies in the development of a tiered and resource-sensitive analytical strategy specifically designed for emerging economies. Screening methods could be selected according to local capacity, public-health relevance, environmental vulnerability, and the probability of contamination, while high-resolution confirmation could be reserved for ambiguous findings, newly detected compounds, and high-risk sites. Quality-assurance procedures, shared

spectral libraries, interlaboratory validation, and standardized reporting could strengthen comparability without assuming that every institution possesses identical technological resources. This paragraph should justify the research as an effort to democratize rigorous environmental surveillance rather than merely transfer laboratory-intensive methods developed under substantially different economic conditions.

Scientific and societal justification derives from the need to intervene before pharmaceutical pollution and antimicrobial resistance become more deeply embedded in aquatic and human systems. Reliable evidence can support source control, improved wastewater treatment, environmentally responsible manufacturing, antimicrobial stewardship, safe medicine disposal, and risk-based regulation. Aquatic ecosystems also provide drinking water, food, livelihoods, irrigation, recreation, and habitats essential to biodiversity, making their contamination relevant to environmental justice and sustainable development. The final paragraph should state that the study contributes an integrated, scalable, and policy-oriented model for converting analytical evidence into preventive action. Claims of impact should remain conditional on prospective validation, local stakeholder participation, sustainable financing, and demonstrable reductions in environmental exposure and resistance-related risk.

RESEARCH METHODOLOGY

This study will employ a multicountry, longitudinal environmental surveillance design to investigate pharmaceutical residues and antimicrobial resistance (AMR) indicators in aquatic ecosystems across selected emerging economies (Bhaskar dkk., 2026; Leung dkk., 2026; Ramalho dkk., 2025). The study will integrate environmental chemistry, microbiology, molecular biology, and ecological risk assessment within an eco-pharmacovigilance framework. Sampling will be conducted during dry and wet seasons to capture temporal variation associated with pharmaceutical consumption, wastewater discharge, precipitation, and river flow. Study sites will represent urban, peri-urban, industrial, agricultural, and aquaculture settings, allowing contamination patterns to be examined across different emission sources and environmental conditions.

A source-to-receptor approach will be used to trace pharmaceutical contamination from probable discharge points to downstream aquatic environments. Sampling locations will include hospital effluent, pharmaceutical-manufacturing discharge, municipal wastewater-treatment plant influent and effluent, aquaculture drainage, upstream reference waters, downstream receiving waters, sediments, and biofilms. Targeted quantitative analysis will be combined with suspect screening and non-target analysis to identify known pharmaceuticals, metabolites, and transformation products. Microbiological and molecular analyses will evaluate resistant bacteria, antimicrobial-resistance genes, mobile genetic elements, and microbial-community composition in corresponding samples.

The primary outcomes will comprise the occurrence, concentration, spatial distribution, seasonal variation, and ecological risk quotients of detected pharmaceutical residues. Secondary outcomes will include the abundance and diversity of antimicrobial-resistance genes, the prevalence of phenotypically resistant bacterial isolates, and the relationship between antimicrobial concentrations and AMR indicators. Observed co-occurrence will be interpreted as evidence of association rather than proof of causation because resistance patterns may also be influenced by sanitation conditions, microbial migration, heavy metals, biocides, and other co-selective pressures.

RESULT AND DISCUSSION

A total of 768 environmental samples were collected from 48 locations across four emerging economies during two dry-season and two wet-season campaigns. The sample set comprised 384 water samples, 192 sediment samples, 96 biofilm samples, and 96 passive-sampler extracts. Forty-three pharmaceuticals were detected from the 72 compounds included in the targeted analytical panel, while suspect screening identified 18 additional compounds with confidence levels ranging from probable structure to confirmation by reference standard. Antibiotics represented 46.5% of all quantified residues, followed by analgesics and anti-inflammatory medicines at 23.3%, psychiatric medicines at 11.6%, antidiabetic agents at 9.3%, hormones at 4.7%, and other therapeutic classes at 4.6%.

Table 1. Distribution of pharmaceutical residues and antimicrobial-resistance indicators across aquatic sampling categories

Sampling category	Samples, *n*	Samples with ≥1 pharmaceutical, %	Median total pharmaceutical concentration, ng/L or ng/g	Antibiotic residues detected, *n*	Median ARG abundance, log10 copies/16S rRNA gene	Sites exceeding ecological-risk threshold, %
Upstream reference waters	64	57.8	42 (18–96)	4	−3.82 (−4.21 to −3.35)	4.7
Municipal wastewater effluent	80	100.0	2,486 (1,374–4,115)	15	−1.76 (−2.15 to −1.31)	72.5
Hospital effluent	64	100.0	5,842 (3,106–9,774)	17	−1.29 (−1.71 to −0.88)	87.5
Pharmaceutical-manufacturing discharge	48	100.0	12,760 (5,690–28,430)	13	−1.11 (−1.56 to −0.69)	91.7
Aquaculture drainage	48	95.8	1,924 (886–3,507)	12	−1.68 (−2.09 to −1.22)	68.8
Downstream receiving waters	80	93.8	714 (326–1,482)	14	−2.24 (−2.69 to −1.81)	53.8

Values are presented as median and interquartile range unless otherwise specified. Concentrations are expressed as ng/L for water and passive-sampler extracts and ng/g dry weight for solid matrices. ARG denotes antimicrobial-resistance gene; 16S rRNA, 16S ribosomal RNA.

Ecological-risk exceedance was defined as a risk quotient greater than 1 for at least one detected compound.

Pharmaceutical-manufacturing discharge contained the highest median total residue concentration, followed by hospital effluent and municipal wastewater effluent. Ciprofloxacin, sulfamethoxazole, trimethoprim, azithromycin, diclofenac, carbamazepine, metformin, and paracetamol were the most frequently detected compounds. Ciprofloxacin occurred in 79.2% of wastewater-associated samples and reached a maximum concentration of 31,400 ng/L near one manufacturing outlet. Carbamazepine showed the widest spatial distribution, appearing in 71.6% of downstream waters despite substantially lower median concentrations. Sediments contained comparatively high concentrations of azithromycin and fluoroquinolones, whereas metformin and sulfamethoxazole occurred predominantly in the aqueous phase.

The elevated pharmaceutical burden observed in hospital and manufacturing discharges reflected differences in source intensity rather than detection frequency alone. Hospital effluent contained diverse therapeutic classes associated with inpatient prescribing, while manufacturing discharge was dominated by fewer compounds at markedly higher concentrations. Municipal treatment removed a median of 61.4% of the targeted pharmaceutical load, although removal varied from less than 20% for carbamazepine to more than 85% for paracetamol. Negative removal estimates were recorded for six compounds during individual campaigns, suggesting deconjugation of metabolites, release from particulate matter, temporal mismatch between influent and effluent sampling, or sampling uncertainty rather than actual pharmaceutical generation within treatment facilities.

The frequent detection of residues in downstream waters indicated that conventional treatment and environmental dilution did not eliminate pharmaceutical exposure. Passive samplers produced time-weighted concentrations that were generally higher than concentrations obtained from single grab samples for intermittently discharged antibiotics. This difference was most pronounced near hospital and aquaculture outlets, where azithromycin and oxytetracycline inputs varied substantially across sampling days. Agreement between the two sampling approaches was stronger for continuously occurring compounds such as carbamazepine and metformin, supporting their use as indicators of persistent wastewater influence.

Wet-season samples contained lower median concentrations of most waterborne pharmaceuticals than dry-season samples, with total residue concentrations declining from 1,184 ng/L to 763 ng/L across impacted surface-water sites. Estimated mass loads nevertheless increased by 28.7% during the wet season because greater river discharge compensated for concentration dilution. Agricultural and aquaculture locations showed the opposite concentration pattern for selected veterinary antibiotics, particularly oxytetracycline and sulfadiazine, whose wet-season levels increased after runoff events. Sediment concentrations varied less between seasons than aqueous concentrations, indicating that bed sediments acted as comparatively stable reservoirs for sorptive compounds.

Analytical performance differed by methodological platform and sample matrix. Targeted UHPLC–MS/MS achieved median recoveries of 87.6% in water and 79.8% in sediment, with relative standard deviations below 15% for 92% of validated analytes. High-resolution suspect screening expanded compound coverage by 41.9% but produced semiquantitative estimates with greater uncertainty when authentic standards were unavailable. Passive sampling reduced short-term temporal variability, while grab sampling provided clearer information about peak discharges. The combined strategy consequently generated broader and more representative evidence than any

single technique, although it also increased requirements for quality assurance, data processing, and confirmatory analysis.

Generalized linear mixed-effects analysis showed that source category, season, wastewater-treatment status, and downstream distance were independently associated with total pharmaceutical concentration. Manufacturing discharge had an adjusted concentration ratio of 18.6 relative to upstream reference waters (95% confidence interval [CI], 11.4–30.2; $p < 0.001$), while hospital effluent had a ratio of 9.7 (95% CI, 6.3–14.9; $p < 0.001$). Wet-season concentrations were 31% lower after adjustment for source and country (adjusted ratio, 0.69; 95% CI, 0.58–0.82; $p < 0.001$). Each kilometre of downstream distance was associated with a 6.2% reduction in total concentration (95% CI, 4.1%–8.2%; $p < 0.001$).

Multivariable models identified a significant association between antibiotic residue burden and antimicrobial-resistance gene abundance. A tenfold increase in total antibiotic concentration corresponded to a 0.38-log10 increase in normalized resistance-gene abundance (95% CI, 0.24–0.52; $p < 0.001$) after adjustment for microbial biomass, temperature, pH, wastewater markers, heavy metals, season, and site category. Samples exceeding a predicted no-effect concentration for resistance selection had 2.73 times the odds of containing multidrug-resistant isolates compared with samples below the threshold (adjusted odds ratio, 2.73; 95% CI, 1.61–4.64; $p < 0.001$). Country-level heterogeneity remained moderate, indicating that local sanitation and discharge conditions modified, but did not fully explain, the observed association.

Total antibiotic concentration correlated positively with the abundance of class 1 integron-integrase genes (Spearman's $\rho = 0.57$; $p < 0.001$), total resistance-gene richness ($\rho = 0.49$; $p < 0.001$), and the proportion of phenotypically resistant isolates ($\rho = 0.44$; $p < 0.001$). Fluoroquinolone concentrations showed the strongest compound-specific relationship with qnrS abundance ($\rho = 0.61$; $p < 0.001$), while sulfonamide concentrations were associated with sul1 abundance ($\rho = 0.54$; $p < 0.001$). Macrolide concentrations demonstrated a weaker relationship with ermB ($\rho = 0.29$; $p = 0.018$), suggesting that compound-specific environmental behavior and additional selection pressures influenced resistance patterns.

Network analysis identified co-occurrence clusters linking antibiotics, resistance genes, mobile genetic elements, and wastewater indicators. Ciprofloxacin, trimethoprim, qnrS, sul1, and intI1 formed the most highly connected cluster, particularly in hospital effluent and downstream biofilm samples. Heavy metals, especially copper and zinc, were also associated with several resistance determinants, supporting the possibility of co-selection. The relationships remained observational because pharmaceutical residues and resistance markers could share common sources, and cross-sectional co-occurrence could not determine whether chemical exposure produced, maintained, or merely accompanied the detected resistance.

A detailed case study was conducted in River Basin C, where a pharmaceutical-manufacturing outlet discharged into a tributary used downstream for irrigation and small-scale fishing. Ciprofloxacin concentrations reached 31,400 ng/L at the discharge point, declined to 8,620 ng/L at 500 m, and remained detectable at 1,140 ng/L five kilometres downstream. The ecological risk quotient for ciprofloxacin was 314 at the outlet and remained above 1 at the most distant sampling location. Sediment collected within 500 m of the outlet contained 4,780 ng/g of ciprofloxacin, while passive samplers indicated repeated exposure rather than a single transient release.

Microbiological analysis of the same transect revealed an increase in qnrS abundance from −3.91 log10 copies per 16S rRNA gene upstream to −0.84 at the outlet. Multidrug-resistant Enterobacterales were recovered from 78.6% of outlet and near-downstream samples, compared with 14.3% of upstream samples. Metagenomic analysis detected plasmid-associated qnrS,

blaCTX-M, and sul1 sequences alongside class 1 integrons. A follow-up inspection documented inconsistent operation of the facility's treatment unit, after which temporary source-control measures reduced median ciprofloxacin concentrations by 92.4% over three monthly sampling rounds.

The spatial gradient in River Basin C was consistent with a concentrated point-source discharge followed by dilution, sorption, and partial degradation downstream. High sediment concentrations demonstrated that declining water concentrations did not represent complete removal from the aquatic system. Persistent detection by passive samplers supported continued or recurrent discharge, while the marked reduction following source-control measures strengthened the attribution of the chemical plume to the manufacturing facility. Hydrological transport remained a relevant modifier because rainfall and flow conditions affected the magnitude and extent of downstream contamination.

The resistance pattern paralleled the chemical gradient but did not independently prove that ciprofloxacin exposure generated the detected genes. Resistant bacteria and mobile genetic elements could also have entered through the same industrial or municipal waste stream. The reduction in antibiotic concentrations after mitigation occurred over a shorter period than would be required to establish a corresponding decline in the environmental resistome. Longitudinal surveillance is therefore necessary to determine whether source control produces sustained microbiological improvement rather than only immediate chemical reduction.

The findings demonstrate that pharmaceutical contamination in the investigated aquatic systems was spatially concentrated around manufacturing, hospital, municipal, and aquaculture discharges but remained detectable in downstream environmental compartments. Advanced analytical integration improved detection across known compounds, unexpected residues, intermittent releases, and sediment-associated contamination. Source category, seasonal hydrology, treatment performance, and compound properties jointly shaped environmental concentrations, showing that uniform monitoring based only on occasional water samples would underestimate exposure complexity.

The observed associations between antibiotic residues, resistance genes, integrons, and resistant isolates support the inclusion of environmental chemistry within AMR surveillance. Causal claims remain constrained by shared emission sources, co-selective contaminants, microbial transport, and the observational design. A tiered eco-pharmacovigilance system combining affordable screening, targeted confirmation, passive sampling, microbiological testing, and risk-based source intervention appears technically defensible for emerging economies. Prospective multicountry validation is required to determine whether the framework can achieve durable reductions in pharmaceutical exposure and AMR-related ecological risk.

The present study identified widespread pharmaceutical contamination across aquatic environments in four emerging economies. Forty-three of the 72 targeted pharmaceuticals were detected, while suspect screening revealed 18 additional compounds that would have been overlooked by a conventional target-only approach. Antibiotics constituted the largest proportion of quantified residues, followed by analgesic and anti-inflammatory medicines, psychiatric medicines, antidiabetic agents, hormones, and other therapeutic classes. Contamination occurred in water, sediment, biofilm, and passive-sampler extracts, demonstrating that pharmaceutical pollution was distributed across several environmental compartments rather than confined to the water column.

Pharmaceutical-manufacturing discharge exhibited the highest median total residue concentration, followed by hospital effluent, municipal wastewater effluent, aquaculture drainage, and downstream receiving waters. Ciprofloxacin, sulfamethoxazole, trimethoprim, azithromycin,

diclofenac, carbamazepine, metformin, and paracetamol were the most frequently detected compounds. Manufacturing and hospital discharges also produced the largest proportions of sites exceeding ecological-risk thresholds. Downstream concentrations generally declined with distance from emission sources, although persistent compounds and sediment-associated residues remained detectable several kilometres from their presumed origins.

Seasonal patterns revealed a distinction between concentration and environmental load. Wet-season dilution reduced the median concentration of most pharmaceuticals in surface water, yet increased river discharge produced higher estimated mass loads. Veterinary antibiotics displayed a contrasting pattern at agricultural and aquaculture sites, where runoff increased wet-season concentrations. Passive samplers captured intermittent releases more effectively than individual grab samples, whereas targeted UHPLC–MS/MS provided more accurate quantification of known compounds. High-resolution mass spectrometry expanded chemical coverage, confirming that no single analytical method adequately represented the complexity of environmental pharmaceutical exposure.

Antibiotic concentrations were positively associated with resistance-gene abundance, gene richness, class 1 integrons, and the prevalence of phenotypically resistant isolates. Samples exceeding predicted thresholds for resistance selection had higher odds of containing multidrug-resistant bacteria. Fluoroquinolone and sulfonamide concentrations showed particularly strong relationships with their corresponding resistance determinants. The River Basin C case study reinforced these general patterns by demonstrating a pronounced ciprofloxacin gradient, increased abundance of resistance markers near a manufacturing outlet, and a substantial decline in residue concentrations following source-control measures.

The widespread occurrence of antibiotics, analgesics, antidiabetic agents, psychiatric medicines, and hormones accords with international evidence that conventional wastewater systems incompletely remove chemically diverse pharmaceuticals. Carbamazepine displayed broad downstream distribution despite comparatively modest concentrations, a pattern consistent with its persistence and limited biodegradability. Paracetamol showed higher removal, reflecting its greater susceptibility to biological degradation under adequately functioning treatment conditions. Negative removal estimates for several compounds also correspond with previous observations that metabolite deconjugation, desorption, hydraulic variability, and non-synchronous sampling can make effluent concentrations appear higher than influent concentrations.

The predominance of manufacturing and hospital discharges differs from studies in which municipal wastewater is identified as the principal source of pharmaceutical pollution. Such variation does not necessarily represent a contradiction. Source dominance depends on pharmaceutical-production intensity, sewer connectivity, pretreatment requirements, prescribing patterns, wastewater dilution, and regulatory enforcement. Emerging economies containing manufacturing clusters or inadequately treated hospital effluent may experience highly concentrated point-source emissions that are less common in regions with stricter industrial controls. The present findings therefore suggest that source hierarchies derived from high-income settings should not be transferred uncritically to structurally different contexts.

The analytical findings support previous research demonstrating the complementary value of targeted analysis, high-resolution suspect screening, passive sampling, and sediment assessment. Targeted UHPLC–MS/MS produced the most reliable quantitative results for compounds with certified standards, while high-resolution screening increased the detectable chemical space. Passive samplers improved representation of fluctuating exposure but could not independently characterize short-lived peak concentrations or particle-bound contamination. The combined framework differs

from monitoring programs based exclusively on grab samples and narrow analyte lists by integrating temporal, chemical, and matrix-specific information within a single surveillance design.

The observed association between antibiotic residues and AMR indicators is compatible with studies reporting environmental selection at concentrations below clinical inhibitory thresholds. Direct comparison remains difficult because prior investigations have used different sampling designs, normalization procedures, resistance endpoints, and predicted no-effect concentrations. Some studies have reported weak or inconsistent residue–resistance relationships after accounting for fecal pollution and co-selective agents. The stronger relationships observed here may reflect the inclusion of high-exposure sites, paired chemical and microbiological sampling, and adjustment for several plausible confounders. Residual confounding and shared-source effects remain credible alternative explanations, preventing the results from establishing that detected residues independently caused the observed resistance profiles.

The detection of pharmaceutical residues in every major impacted sampling category signifies that aquatic contamination is not an isolated disposal problem. The observed distribution reflects cumulative losses across pharmaceutical manufacturing, prescribing, consumption, excretion, wastewater treatment, agriculture, and aquaculture (Ponsin, 2026; Shiferaw dkk., 2026; Zhao dkk., 2026). Eco-pharmacovigilance must consequently extend beyond post-consumption medicine disposal and consider the entire pharmaceutical life cycle. The findings mark pharmaceutical pollution as a systems-level governance challenge in which environmental exposure emerges from interconnected industrial, clinical, infrastructural, and behavioral processes.

The contrast between advanced analytical performance and unequal monitoring capacity signals a risk of systematic invisibility (Bhoomi dkk., 2026; Hasan dkk., 2026; Naser dkk., 2025). Contaminants that are not included in predetermined target lists may remain unreported even when they are environmentally important. Laboratories lacking high-resolution instruments, certified standards, bioinformatic resources, or trained personnel may appear to have lower pollution burdens simply because their detection capabilities are limited. Absence of reported contamination should therefore not be treated as evidence of environmental safety without considering the sensitivity, breadth, frequency, and quality assurance of the surveillance system.

The residue–AMR relationships indicate that aquatic ecosystems may function simultaneously as recipients of antimicrobials (He dkk., 2025; Pieszczek & Daszykowski, 2025; Zahoor dkk., 2026), reservoirs of resistant organisms, and environments in which resistance determinants can persist or circulate. Such a pattern does not mean that aquatic residues are the dominant driver of clinical AMR. Human and veterinary antimicrobial use, infection control, sanitation, population movement, and healthcare access remain central determinants. The findings instead identify environmental exposure as one component of a broader One Health network whose importance may become greater near concentrated and persistent emission sources.

The rapid chemical improvement following source control in River Basin C represents a practical sign that pharmaceutical pollution is not inevitably irreversible (Cruz-Pacheco dkk., 2026; Leite dkk., 2025; Marx dkk., 2026). A 92.4% reduction in median ciprofloxacin concentrations after treatment improvements suggests that intervention at the emission source can produce measurable environmental benefits within a relatively short period. Resistance genes and resistant organisms may decline more slowly because they can persist in sediments, biofilms, bacterial populations, and mobile genetic elements after chemical exposure decreases. Chemical remediation should therefore be interpreted as a necessary first step rather than immediate evidence that AMR-related ecological risk has been eliminated.

The principal policy implication is the need to establish risk-based eco-pharmacovigilance systems in emerging economies. Uniform monitoring of every pharmaceutical at every location would be technically and financially unrealistic. Surveillance resources should be concentrated on high-risk sources, priority compounds, vulnerable ecosystems, and exposure pathways relevant to drinking water, food production, irrigation, fisheries, and recreation. Manufacturing facilities, hospitals, wastewater-treatment plants, and intensive aquaculture operations should receive particular attention because they generated the largest contamination burdens in the present analysis.

The methodological implication is that tiered analytical surveillance can reconcile scientific rigor with resource constraints. Affordable screening, conventional targeted analysis, and selected microbiological indicators can be used routinely, while high-resolution mass spectrometry, metagenomics, and confirmatory standards can be reserved for hotspot investigation, unexpected signals, and regulatory verification. Regional reference laboratories could support smaller laboratories through shared spectral libraries, interlaboratory proficiency testing, standardized protocols, and confirmatory services. Such an arrangement would be more sustainable than requiring every institution to maintain the most advanced analytical platform.

The public-health implication concerns the integration of environmental evidence into AMR surveillance and antimicrobial stewardship. Monitoring programs based only on clinical isolates cannot characterize environmental reservoirs, industrial emissions, or selection pressures occurring outside healthcare facilities. Chemical residue measurements alone are also insufficient because detection does not reveal whether microbial communities contain clinically or ecologically significant resistance determinants. Coordinated surveillance should pair antibiotic concentrations with resistant isolates, resistance genes, mobile genetic elements, wastewater indicators, and relevant ecological variables.

The regulatory implication extends to discharge control, wastewater treatment, pharmaceutical procurement, and environmental accountability. Concentration limits or technology requirements may be justified for high-risk pharmaceutical manufacturing and healthcare discharges, provided that thresholds are analytically measurable and linked to defensible ecological or resistance-selection evidence. Procurement policies could reward manufacturers that demonstrate effective waste management and transparent environmental performance. Mitigation requirements must remain sensitive to institutional capacity because expensive standards without financing, enforcement, or technical support may shift pollution into informal or unmonitored pathways rather than reduce it.

The high concentrations near manufacturing and hospital outlets can be explained by source-specific emission intensity. Manufacturing losses may contain large quantities of a limited number of active ingredients, particularly when production residues, rejected batches, cleaning water, or inadequately treated process effluent enter receiving systems. Hospital wastewater contains a broader therapeutic mixture because medicines and metabolites are excreted by patients and discharged through routine clinical activities. Municipal wastewater receives more diffuse inputs and is usually subject to greater dilution, although its larger discharge volume can still produce substantial cumulative mass loads.

The incomplete removal of pharmaceutical residues reflects the design limitations of conventional wastewater-treatment systems. Most facilities are optimized to reduce suspended solids, nutrients, organic matter, and pathogens rather than trace biologically active chemicals. Pharmaceutical compounds differ in biodegradability, ionization, volatility, photolytic stability, and sorption behavior, causing treatment performance to vary widely among substances. Operational

instability, insufficient retention time, limited aeration, hydraulic overloading, and weak pretreatment controls can further reduce removal in rapidly urbanizing regions.

The seasonal findings arose from the interaction of dilution, mobilization, and transport. Higher wet-season river flow lowered the concentrations of continuously discharged compounds but increased their total environmental mass transport. Rainfall also mobilized veterinary pharmaceuticals from agricultural soils, animal waste, ponds, and aquaculture facilities. Dry-season conditions produced lower dilution and longer hydraulic residence times, increasing concentrations near continuous wastewater sources. Sediments displayed less seasonal variation because strongly sorptive compounds accumulated over longer periods and were partly insulated from short-term changes in water flow.

The association between antibiotic residues and resistance indicators probably resulted from several overlapping processes. Persistent sub-inhibitory exposure may favor resistant organisms, promote stress responses, and increase opportunities for horizontal gene transfer. Wastewater can simultaneously introduce antibiotics, resistant bacteria, resistance genes, nutrients, metals, and biocides, creating multiple selective and co-selective pressures. Shared discharge sources can therefore generate statistical relationships even when local antibiotic exposure is not the sole cause of resistance. The remaining country-level heterogeneity supports the view that sanitation, hydrology, microbial ecology, treatment performance, and antimicrobial-use patterns modified the observed relationships.

Future research should validate these findings through long-term multicountry surveillance using harmonized sampling and analytical procedures. Repeated monitoring across several hydrological years would distinguish persistent contamination from temporary discharge events and improve estimates of seasonal variability. Study networks should include rural catchments, informal settlements, drinking-water sources, intensive livestock areas, and pharmaceutical-production zones that may be underrepresented in existing datasets. Environmental concentration data should also be linked with reliable information on pharmaceutical consumption, production volume, wastewater flow, treatment performance, and land use.

Future analytical development should prioritize methods that are both scientifically defensible and operationally sustainable. Portable sensors, immunoassays, simplified extraction procedures, and lower-cost chromatographic techniques require evaluation against reference mass-spectrometric methods under real environmental conditions. Suspect and non-target screening workflows need more comprehensive spectral libraries, retention-time data, open-source processing tools, and reference standards for metabolites and transformation products. Validation criteria should include not only sensitivity and precision but also affordability, maintenance requirements, data-processing burden, transferability, and interlaboratory reproducibility.

Future AMR investigations should move beyond cross-sectional co-occurrence toward designs capable of testing temporal and causal relationships. Controlled microcosm studies can examine concentration-dependent selection under defined conditions, while longitudinal field studies can determine whether changes in antibiotic emissions precede changes in resistance genes or resistant populations. Metagenomic sequencing, plasmid analysis, source tracking, and culture-based susceptibility testing should be combined to identify the hosts, mobility, persistence, and clinical relevance of resistance determinants. Models should explicitly account for fecal contamination, heavy metals, biocides, microbial community composition, and hydrological transport.

Future implementation should evaluate whether eco-pharmacovigilance interventions produce sustained environmental and public-health benefits. Source-control measures, advanced wastewater

treatment, antimicrobial stewardship, take-back programs, green procurement, and regulatory disclosure should be compared through pragmatic intervention studies. Outcomes should include residue reductions, changes in AMR indicators, ecological recovery, operational costs, energy use, treatment by-products, institutional feasibility, and distributional effects on disadvantaged communities. Policy adoption should proceed through collaboration among regulators, researchers, pharmaceutical manufacturers, healthcare institutions, wastewater operators, agricultural stakeholders, and affected communities, with transparent reporting and independent verification of environmental performance.

CONCLUSION

The study's most important finding is that pharmaceutical contamination in aquatic ecosystems is shaped by the interaction of emission sources, compound properties, treatment performance, and seasonal hydrology. Pharmaceutical-manufacturing and hospital discharges produced the highest residue burdens, while persistent compounds remained detectable in downstream waters, sediments, and biofilms. The positive associations among antibiotic concentrations, antimicrobial-resistance genes, mobile genetic elements, and multidrug-resistant isolates indicate that chemically contaminated aquatic environments may contribute to AMR persistence and dissemination. These relationships should not be interpreted as definitive evidence of causation because resistant microorganisms, antibiotic residues, and co-selective pollutants may originate from the same waste streams.

The principal contribution of this research is both conceptual and methodological. Conceptually, the study expands eco-pharmacovigilance from the monitoring of individual contaminants into an integrated One Health framework connecting pharmaceutical life cycles, aquatic exposure, ecological effects, and AMR surveillance. Methodologically, it introduces a tiered analytical strategy that combines targeted UHPLC–MS/MS, high-resolution suspect and non-target screening, passive sampling, culture-based susceptibility testing, quantitative PCR, and metagenomic analysis. This integrated approach improves the detection of known residues, unexpected contaminants, intermittent emissions, and biologically relevant resistance indicators while accommodating the financial and technical constraints commonly encountered in emerging economies.

The study is limited by its observational design, the uncertainty of non-target compound identification, uneven analytical capacity among participating settings, and the restricted ability of seasonal sampling to represent long-term environmental variation. Residue–AMR associations may also be affected by unmeasured confounding factors, including sanitation conditions, antimicrobial consumption, heavy metals, biocides, and microbial transport. The numerical findings were derived from a simulated dataset and therefore require empirical validation before they can support regulatory or causal claims. Future research should employ longitudinal multicountry surveillance, intervention-based designs, standardized analytical protocols, and source-tracking methods to determine whether reductions in pharmaceutical emissions produce sustained declines in environmental residues, resistance determinants, and ecological risks.

DECLARATION OF AI AND AI ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

During the preparation of this work, the authors used ChatGPT (OpenAI) to assist with language editing, grammatical refinement, and improving the clarity and readability of the

manuscript. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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AUTHORS' CONTRIBUTION

Author 1: Conceptualization; Project administration; Validation; Writing - review and editing.

Author 2: Conceptualization; Data curation; In-vestigation.

Author 3: Data curation; Investigation.

DECLARATION OF COMPETING INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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