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Metabolised Antibiotics: An Overlooked Driver of Antimicrobial Resistance Comparable to Their Parent Compounds

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Abstract
Antimicrobial resistance (AMR) is one of the leading global public health threats of the twenty-first century, and the environment, particularly wastewater and receiving waterways, is increasingly recognised as an important arena in which resistance is selected and disseminated. Attention has traditionally been focused on parent antibiotic compounds discharged into the environment, while the transformation products generated when antibiotics are metabolised in the human body or degraded during wastewater treatment have received comparatively little scrutiny. In this review, current evidence is synthesised, anchored by a 2026 study from the University of Queensland and the University of Exeter, indicating that antibiotic transformation products can exert selective pressure for resistance that is comparable to, and in some cases stronger than, that exerted by their parent compounds. Using wastewater-derived microbial communities from Brisbane, Australia, and Falmouth, United Kingdom, it was demonstrated that transformation products of fluoroquinolones, macrolide-lincosamide-streptogramin antibiotics and sulfonamides enriched the class 1 integron-integrase gene intI1, a recognised marker of anthropogenic selection for resistance, at levels similar to the parent drugs. The pharmacokinetic and environmental origins of antibiotic transformation products are discussed, along with the mechanistic basis for resistance selection at sub-inhibitory concentrations, the implications of these findings for environmental risk assessment and AMR surveillance frameworks, and the limitations of current wastewater treatment in mitigating this hidden reservoir of bioactivity. It is concluded that transformation products should no longer be excluded from AMR monitoring and regulatory frameworks, and priority areas for future research are outlined.

Keywords: Antimicrobial Resistance, Antibiotic Transformation Products, Metabolites, Wastewater, Class 1 Integron, IntI1, Environmental Risk Assessment, One Health

1. Introduction

Antimicrobial resistance is widely described as a silent pandemic, being linked to well over a million deaths directly and several million more indirectly every year, and it is projected to worsen substantially

in the coming decades if left unaddressed (World Health Organization, 2023) [9]. While clinical overuse and misuse of antibiotics in humans and animals remain the dominant drivers of resistance, it has been established over the past two decades that the environment, namely soil, air and, most prominently, water, functions as both a reservoir and a conduit for resistant bacteria and resistance genes [9, 10]. Pharmaceutical effluents, agricultural runoff, hospital wastewater and treated sewage are all found to introduce antibiotics into aquatic ecosystems, where even low, sub-inhibitory concentrations can impose selective pressure on bacterial communities [7].

Historically, environmental risk assessments and AMR surveillance programmes have concentrated almost exclusively on the parent antibiotic compound, that is, the intact molecule as it is manufactured and administered. However, the majority of an administered antibiotic dose is not excreted from the human body in its original form. Depending on the drug class, a substantial fraction is metabolised by the liver and other tissues into structurally related transformation products before excretion, and further transformation occurs during wastewater treatment and environmental degradation [1, 8]. These transformation products have generally been assumed to be less biologically active, and therefore less relevant to resistance selection, than their parent compounds, an assumption that has shaped both regulatory risk assessment and the design of environmental monitoring programmes.

This assumption has recently been challenged directly. A 2026 study led by researchers at the University of Queensland, in collaboration with the University of Exeter, provided the first systematic evidence that antibiotic transformation products can select for resistance in complex, wastewater-derived bacterial communities to a degree comparable with, and in some cases exceeding, that of their parent antibiotics (Lakhey, et al., 2026) [1]. In this review, that evidence is drawn together with the broader literature on antibiotic metabolism, environmental persistence, and resistance selection mechanisms, to examine why metabolised antibiotics deserve far greater attention in the global effort to contain AMR.

2. The Global Burden of AMR and Its Environmental Dimension

AMR arises when bacteria acquire genetic changes, through spontaneous mutation or horizontal gene transfer, that allow them to survive exposure to antimicrobial agents. The clinical and economic burden of this phenomenon is substantial and growing, and a One Health framework has been adopted internationally that explicitly recognises the interconnectedness of human, animal and environmental health in the emergence and spread of resistance [9]. Within this framework, water systems occupy a central position: wastewater treatment plants receive antibiotic residues excreted by treated patients and livestock, concentrate diverse bacterial populations from many sources in close proximity, and discharge effluent into rivers, estuaries and coastal waters that are often used for irrigation, recreation, aquaculture or as sources of drinking water [10].

Even where wastewater treatment plants achieve substantial reductions in the concentration of antibiotics and resistant bacteria, complete removal is rarely achieved, and this problem is found to be more acute in low- and middle-income countries where advanced tertiary treatment is limited or absent [8]. Resistance genes and resistant organisms have been detected downstream of treatment plants, in agricultural soils irrigated with treated wastewater, in coastal sediments, and even in aerosols generated at treatment facilities [11]. Class 1 integrons, mobile genetic elements that capture and express antibiotic resistance gene cassettes via the integrase gene intI1, are widely used as a proxy indicator of anthropogenic pollution and resistance selection in these environments, because their abundance tends to track closely with human and agricultural antibiotic use [7, 12].

3. Fate and Metabolism of Antibiotics in the Human Body and Environment

When a patient is prescribed an antibiotic, only a portion of the administered dose typically reaches the target site and acts against the pathogen in its original chemical form. A large share of the active pharmaceutical ingredient is excreted in urine or faeces either unchanged or as a metabolite generated through hepatic or renal biotransformation, commonly involving oxidation, hydrolysis, demethylation, glucuronidation or acetylation. For many major antibiotic classes, including fluoroquinolones, macrolides and sulfonamides, a substantial proportion, frequently cited as approaching or exceeding half, and in some cases up to around ninety percent, of the administered dose is excreted as a mixture of the parent drug and one or more transformation products [6].

Once released into sewage systems, both the parent compound and its human-derived metabolites are subject to further transformation. Biological treatment processes, disinfection, for example chlorination, ultraviolet treatment or ozonation, and abiotic environmental processes such as photolysis and hydrolysis can each generate additional transformation products. Consequently, the mixture of antibiotic-related chemicals that ultimately enters rivers, estuaries and coastal waters is often chemically more diverse, and quantitatively larger, than the parent compound alone [1]. Analytical detection of these transformation products is also more demanding than detection of the parent drug: standard surveillance techniques such as high-performance liquid chromatography and mass spectrometry require prior knowledge of the target molecule's structure, meaning that transformation products are frequently overlooked unless they are specifically screened for [8].

4. Antibiotic Transformation Products as an Overlooked Class of Contaminants

For many years, the working assumption in both pharmacology and environmental science was that metabolism deactivates an antibiotic, that a transformation product, having lost some structural feature required for binding to its bacterial target, would possess little or no residual antimicrobial activity and therefore little capacity to select for resistance. This assumption underpinned a widespread exclusion of transformation products from environmental risk assessment frameworks and from AMR surveillance and monitoring programmes, which instead concentrated resources on tracking the parent compounds themselves [1].

This assumption has increasingly been questioned as analytical chemistry has advanced. Structural and computational studies predicting the bioactivity of antibiotic metabolites have shown that some transformation products retain features capable of interacting with bacterial targets or eliciting stress responses, even where classical potency against a target pathogen is reduced [8]. Transformation products have also repeatedly been detected in wastewater and receiving waters at concentrations that are sometimes comparable to, or higher than, those of the parent antibiotic, reflecting both the scale of human metabolism and the environmental transformation processes described above. Until recently, no study had systematically compared the resistance-selecting potential of a broad panel of transformation products against their corresponding parent compounds using realistic, complex microbial communities rather than single laboratory strains [1].

5. Emerging Evidence: Transformation Products Select for Resistance Comparable to Parent Compounds

5.1. The Lakhey et al. (2026) Study

This gap was directly addressed by Lakhey, et al. (2026) [1], whose study, titled Antibiotic Transformat-

ion Products Exert Selective Pressure for Antimicrobial Resistance Comparable to Parent Compounds, was published in Nature Water. Microbial communities were collected from wastewater treatment plants in Brisbane, Australia, and Falmouth, United Kingdom, and were exposed in the laboratory to a panel of antibiotics and their known transformation products drawn from three widely used drug classes: fluoroquinolones and macrolide-lincosamide-streptogramin agents, both used extensively in human medicine, and sulfonamides, used predominantly in agriculture and veterinary practice.

Using a growth-based inhibition assay, it was found that the lowest observed effect concentrations for several transformation products were only around twofold higher than those of their parent antibiotics, a strikingly narrow margin given that transformation products had generally been presumed to be far less bioactive. Two transformation products, moxifloxacin sulfate and descladinose roxithromycin, were found to produce stronger growth inhibition of the bacterial communities than their respective parent drugs. In parallel seven-day evolution experiments, exposure to transformation products including desmethyl ofloxacin, N-acetyl sulfamethoxazole and desmethyl erythromycin led to enrichment of the class 1 integron-integrase gene intI1, a well-established genetic marker of resistance selection, at levels comparable to those produced by exposure to the parent compounds themselves [1].

These findings represent the first systematic demonstration that antibiotic transformation products, across multiple structurally distinct drug classes, can drive resistance selection in complex, environmentally realistic bacterial communities to a degree that rivals their parent compounds. Wastewater treatment plants are characterised in this work as hidden reservoirs of bioactivity, in which both intact antibiotics and their breakdown products are found to contribute jointly to resistance selection, rather than the breakdown products representing an inert or negligible by-product [1, 2, 3].

5.2. Mechanistic Basis: Sub-inhibitory Selection and Class 1 Integrons

The plausibility of these findings is reinforced by an established body of mechanistic work on sub-inhibitory antibiotic exposure. Environmental antibiotic concentrations, including those of transformation products, are typically far below the levels used therapeutically and are frequently described as sub-inhibitory, that is, too low to halt bacterial growth outright. Sub-inhibitory exposure has repeatedly been shown to trigger the bacterial SOS stress response, increase mutation rates, promote horizontal gene transfer between bacteria, and specifically upregulate the class 1 integrase intI1, thereby increasing the capture, rearrangement and mobilisation of resistance gene cassettes within class 1 integrons (Sanchez-Cid, et al., 2023) [7]. Because class 1 integrons are readily transferred between bacterial species via mobile genetic elements such as plasmids, their enrichment is considered a meaningful proxy for the broader dissemination potential of resistance in a microbial community, and not merely a laboratory curiosity [7, 12].

This mechanistic pathway does not require a transformation product to retain the full potency of its parent compound. Rather, it requires only that the transformation product retains sufficient residual bioactivity to impose a selective or stress-inducing pressure on exposed bacteria, a substantially lower bar than classical antimicrobial efficacy, and one that is suggested by the findings of Lakhey, et al. (2026) to be cleared by many common antibiotic transformation products [1].

6. Implications for Environmental Risk Assessment and AMR Surveillance

The practical implications of this evidence are considerable. Environmental risk assessments conducted by regulators and pharmaceutical manufacturers typically evaluate the ecotoxicological and resistance-related risk of a drug substance based on the parent compound alone, with transformation products

addressed inconsistently or not at all. Where transformation products are considered, they are often assumed a priori to pose lower risk, an assumption that current evidence increasingly contradicts for at least several major antibiotic classes [1].

- Risk assessment frameworks for new and existing antibiotics should be extended to systematically characterise the identity, environmental concentration and resistance-selecting potential of major transformation products, and not the parent compound alone.
- AMR surveillance and environmental monitoring programmes should incorporate targeted analytical screening for known transformation products alongside parent antibiotics, since standard detection methods will otherwise miss them by default.
- Indicators such as the class 1 integron gene intI1 offer a practical, scalable marker for tracking resistance-selection pressure exerted by complex mixtures of antibiotics and their transformation products in real wastewater and environmental samples.
- Regulatory guidance documents that currently exempt or de-prioritise transformation products in ecopharmacovigilance frameworks may need to be revisited in light of this evidence.

It has explicitly been called for by researchers involved in the study that environmental risk assessment be reframed to formally include transformation products, rather than treating them as a secondary consideration to be addressed only after the parent compound has been assessed [1, 2].

7. Wastewater Treatment: A Hidden Reservoir, Not a Solved Problem

Wastewater treatment is widely, and not unreasonably, regarded as an effective barrier that reduces the concentration and biological activity of antibiotics before effluent is discharged into the environment. The evidence discussed in this review complicates that picture without contradicting it outright: treatment processes reduce the concentration of the parent antibiotic, but in doing so they often chemically transform rather than fully eliminate it, generating a suite of transformation products that can carry forward much of the original resistance-selection potential [1, 5]. Some treatment plants are found to remove particular transformation products more effectively than others, a variation that could be exploited to identify and scale up treatment processes, such as advanced oxidation, enhanced biological treatment or targeted tertiary polishing steps, that are more effective at reducing this residual bioactivity before discharge [6].

It is noted that water utilities themselves are not the source of this problem; they receive whatever mixture of pharmaceuticals and metabolites is present in the sewage delivered to them, and are constrained by the treatment infrastructure, cost and regulatory requirements available to them [5]. Addressing the contribution of transformation products to AMR will therefore require collaboration between water utilities, regulators, pharmaceutical manufacturers and researchers, rather than treatment-plant-level fixes alone.

8. Knowledge Gaps and Future Research Directions

- Expansion beyond the three drug classes examined to date, namely fluoroquinolones, macrolide-lincosamide-streptogramin antibiotics and sulfonamides, to other major antibiotic classes, including beta-lactams, tetracyclines and aminoglycosides, and their respective transformation products.
- Longer-term and field-based evolution studies, beyond controlled seven-day laboratory exposures, to characterise how transformation-product-driven selection unfolds over extended timeframes and in real receiving environments such as rivers, estuaries and agricultural soils.

- Investigation of combined and cumulative exposure to mixtures of parent antibiotics and multiple co-occurring transformation products, which may interact additively, synergistically or antagonistically in ways not captured by single-compound assays.
- Development of standardised, cost-effective analytical methods for routine transformation-product detection that can be deployed at scale in low-resource settings, where wastewater treatment is often limited and the environmental burden of untreated or partially treated antibiotic residues may be greatest.
- Comparative evaluation of treatment technologies specifically for their capacity to reduce transformation-product-associated resistance-selection potential, and not parent-compound concentration alone.

9. Recommendations

Based on the evidence reviewed here, the following recommendations are put forward for researchers, regulators and water-sector stakeholders.

- Regulators should require characterisation of major transformation products, alongside parent compounds, as part of environmental risk assessment dossiers for new antibiotics.
- National and international AMR surveillance frameworks operating under the One Health approach should incorporate transformation-product monitoring into existing wastewater-based surveillance infrastructure.
- Research funders should prioritise studies that extend the transformation-product evidence base to additional antibiotic classes, geographic settings and treatment technologies.
- Water utilities and treatment-technology developers should be supported in evaluating and adopting treatment processes demonstrated to reduce transformation-product bioactivity, and not concentration alone.

10. Conclusion

For decades, efforts to understand and mitigate the environmental dimension of antimicrobial resistance have concentrated overwhelmingly on parent antibiotic compounds, treating their metabolic and environmental transformation products as a comparatively minor concern. This framing is shown by recent evidence, most notably the 2026 study by Lakhey, et al. published in Nature Water, to require revision [1]. Antibiotic transformation products, generated in the human body and further modified during wastewater treatment and environmental degradation, are shown to exert selective pressure for resistance, as measured by enrichment of the class 1 integron gene intI1 and by direct growth-inhibition assays that is comparable to, and occasionally exceeds, that of the antibiotics from which they are derived. Wastewater treatment plants should accordingly be understood not merely as sources of residual antibiotics but as reservoirs of a broader and more chemically diverse pool of resistance-selecting bioactivity. Environmental risk assessment, surveillance frameworks and treatment technologies that account for this fuller picture will be required to address AMR effectively, alongside continued efforts to reduce inappropriate antibiotic use at its source. As with AMR more broadly, no single intervention is likely to be sufficient; progress will depend on coordinated action across clinical, agricultural, environmental and regulatory domains.

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