Advancing ecopharmacovigilance in South Africa: a call to action for pharmaceutical stakeholders

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Abstract

Ecopharmacovigilance (EPV) represents an essential evolution of pharmacovigilance (PV), expanding the monitoring of pharmaceutical safety to environmental contexts. As pharmaceuticals enter ecosystems through anthropogenic activity, they persist as active pharmaco-environmental compounds (APECs), posing significant ecological and public health risks. Their contribution to the development and spread of antimicrobial resistance (AMR) is a growing global health threat. This article explores the connection between EPV and AMR, using the One Health approach to frame the interdependence of human, animal, and environmental health. It examines how insights derived from expanded monitoring of the pharmaceutical lifecycle can enhance strategies to mitigate contamination risks effectively. Healthcare facilities, community practices, and agriculture are key sources of antimicrobial waste. As antimicrobial waste continues to persist in wastewater, soil, and aquatic ecosystems, it exerts selective pressure on microbial populations, accelerating the spread of resistance traits through horizontal gene transfer. This environmental dimension of AMR reinforces the need for stewardship models that integrate healthcare policy, environmental science, and regulatory interventions. Pharmacists link antimicrobial stewardship (AMS) with EPV by guiding responsible medicine use and disposal. Integrating EPV into national and global AMR strategies is essential for reducing pharmaceutical pollution, strengthening environmental surveillance, and fostering more sustainable healthcare systems.

Keywords: ecopharmacovigilance, pharmaceutical safety, environmental contexts

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Introduction

The emergence of ecopharmacovigilance (EPV) as a scientific discipline highlights an urgent need to monitor, assess, and mitigate the environmental risks associated with pharmaceuticals.[1] EPV is defined as *"the science and activities concerned with the detection, assessment, understanding, and prevention of adverse effects or other problems caused by pharmaceuticals in the environment that affect people and other animal species"*.[2] As biologically active residues of medicines increasingly infiltrate ecosystems, EPV provides a critical bridge between environmental and public health.[3] In South Africa, the scale of pharmaceutical pollution is becoming more apparent and is driven by excessive use, poor disposal practices, and inadequate wastewater treatment.[4,5] The environmental accumulation of antimicrobials threatens biodiversity and contributes to antimicrobial resistance (AMR), one of the most pressing global public health challenges.[6,7] As a narrative review, this article connects EPV to AMR, framing their interdependence through the life cycle of pharmaceuticals, mechanisms of resistance, and the implications of policy and stewardship interventions. It argues that embedding EPV practices into national and global health strategies is essential to addressing AMR, requiring multi-stakeholder engagement to mitigate both human health risks and environmental consequences. This article aims to highlight the role of EPV in mitigating AMR in South Africa, emphasising pharmacist-led interventions and the One Health approach.

The One Health approach and interconnectedness

The One Health framework offers a valuable perspective for integrating EPV into healthcare strategies, emphasising the interconnectedness of human, animal, and environmental health.[8] It responds to the complexities introduced by globalisation and emphasises integrated approaches to public health. While medicines improve health outcomes, they also pose risks to ecosystems and non-target organisms.[9–11] This interconnectedness necessitates an expansion of vigilance beyond human safety to include environmental endpoints.

Medicines: Life-saving tools with environmental consequences

Since the discovery of active pharmaceutical ingredients (APIs), medicines have transformed global health. These compounds, whether synthesised or derived from nature, are essential in human, veterinary, and agricultural health.[12] However, APIs follow a complex lifecycle beyond their intended therapeutic use. Unmetabolised APIs and their respective biologically active metabolites frequently continue their journey in an unintended environment.[11] Understanding this extension of the life cycle is critical for refining EPV interventions, ensuring that pharmaceutical governance aligns with both public health and ecological protection measures.

From ADME to EDD: A framework for environmental risk

The traditional pharmacological framework of Absorption, Distribution, Metabolism, and Excretion (ADME) explains API processing within the body. Yet, once excreted, APIs no longer serving their intended purpose, subsequently referred to as active pharmaco-environmental compounds (APECs), possess the potential to interact with the environment.[13,14] APECs follow a second trajectory governed by Exposure, Dispersion, and Degradation (EDD).[15] This environmental pathway determines how they interact with ecosystems, with the potential for bioaccumulation. Factors like solubility, polarity, and chemical stability influence degradation rates.[6] While some compounds biodegrade into inactive residues, others persist and accumulate, disrupting microbial populations, aquatic life, and plant physiology.[13] Laboratory models help predict these dynamics, and insights from these experiments are crucial for identifying pharmaceuticals that resist degradation. However, real-world degradation is often incomplete due to limitations in current wastewater treatment plants (WWTPs).[16,17]

Ecopharmacovigilance: Surveillance beyond the patient

EPV mirrors pharmacovigilance (PV) but expands its focus to include environmental safety.[2] While PV addresses adverse drug effects in humans, EPV extends vigilance to what happens after APIs leave the human or animal body, where APIs become APECs with the potential to contaminate water, soil, and air, and induce unintended ecological effects.[2,18] Through environmental sampling, modelling, and risk assessment, EPV supports the development of greener pharmaceuticals and informs regulatory policies.[19] A shift away from the production of "forever" chemicals and advancements in efficient WWTP technologies hold great promise for overcoming the environmental challenge of APEC removal.[20] As with PV, EPV requires a collaborative approach, which requires engaging regulatory authorities, pharmacists, researchers, healthcare professionals, and the public. When paired with One Health and AMR strategies, EPV offers a holistic pathway to mitigate pharmaceutical pollution and promote sustainable health systems.[14]

Antimicrobial resistance: The environmental dimension

The occurrence of emerging pharmaceutical contaminants originates from extensive pharmaceutical use in human and veterinary medicine, agriculture, and aquaculture. A recent study revealed the presence of APIs in rivers across over 100 countries, highlighting the global nature of this issue and the harmful concentrations frequently observed in ecosystems.[21] Pharmaceuticals, particularly antimicrobials, potentiate significant selective pressures in the environment.[9,22,23] When antimicrobial APECs accumulate in aquatic or terrestrial systems, they expose microbial populations to sub-lethal concentrations, fostering the development of resistance genes.[24,25] These genes spread rapidly through horizontal gene transfer, affecting bacteria that were once susceptible.[26] The result is an alarming rise in AMR, where pathogens evade standard treatments, forcing reliance on last-resort antibiotics. Environmental reservoirs, including rivers, soil, and WWTP effluents, now harbour resistant bacteria, making AMR not only a clinical challenge but an ecological one as well. For instance, ammonia-oxidising bacteria, which play a vital role in global nitrogen recycling and wastewater nitrogen removal, are susceptible to disruption by APECs.[27]

Sources of antimicrobial waste

Pharmaceutical waste, contributing to AMR, originates from a variety of sectors.[28]

Collectively, these sources of antimicrobial waste increase the environmental presence of APECs and contribute to the amplification of AMR. Without coordinated interventions across sectors, the problem is likely to intensify, affecting both ecological integrity and human health.

Table I: Sources of antimicrobial waste and the environmental impact on AMR

Source of Antimicrobial Waste	Description	Environmental Impact
Pharmaceutical Manufacturers	Release effluent containing APIs during production, treated by inefficient WWTPs.	High concentrations of antimicrobials in production effluent contribute to concentrated environmental contamination and create hotspots for AMR.
Healthcare Facilities [29,30]	Hospitals, clinics, and other medical establishments lacking effective systems for treating pharmaceutical effluent and sewage.	APECs and resistant microbes enter natural ecosystems due to inadequate wastewater treatment.
Communities[31–33]	Economic vulnerability and geographic barriers often leading to antimicrobial procurement and access through unregulated sources. Antimicrobial use resulting in physiological elimination of APECs, improper disposal of unused or expired medicines, such as flushing or discarding with household waste.	Pharmaceuticals accumulate in landfills, soil, and water bodies, enabling APECs to persist in the environment and contribute to microbial resistance.
Agriculture and Veterinary Use [34–36]	Antimicrobials used in livestock and poultry for disease prevention and growth promotion, often without sufficient regulation. E.g. non-prescription procurement of antibiotics registered under stock feeds.	High usage of antibiotics by farmers in South Africa due to low restriction leads to uncontrolled release via animal waste and agricultural runoff. This introduces antimicrobials into the environment, exacerbating AMR.

Table II: Legislative contributions to pharmaceutical waste mitigation

Legislation	Key Provisions	Impact on Waste Mitigation
National Health Act (Act 61 of 2003)	Establishes norms and standards for health service delivery, including safe handling of medicines.	Enables integration of pharmaceutical waste into broader health system governance. Supports facility-level accountability for safe disposal practices.
Pharmacy Act (Act 53 of 1974)	Defines good pharmacy practice, including safe storage and stock rotation, disposal and destruction of medicines.	Mandates disposal via authorised waste treatment facilities only. Prohibits disposal into municipal sewerage systems unless explicitly permitted by SAHPRA.
Medicines and Related Substances Act (Act 101 of 1965)	Regulates medicines, including post-market surveillance and disposal.	Aligns disposal protocols with SAHPRA's guidelines. Requires denaturing and destruction to restrict availability, access and prevent re-entry into supply chains.

Table III: Pharmacist-led interventions targeting specific pharmaceutical waste sources

Source of pharmaceutical waste	Pharmacist-led interventions
Expired stock in facilities	Rational pharmaceutical procurement, inventory audits, disposal protocols, EPV training.
Patient non-adherence	Rational dispensing, counselling, dose optimisation, return-to-pharmacy schemes.
Improper disposal (e.g. flushing)	Public education, take-back programmes, awareness campaigns.
Manufacturing residues	Advocacy for green chemistry, regulatory feedback, adherence to waste management protocols
Wastewater contamination	Surveillance partnerships, policy input on effluent standards and contamination alerts.

Global and South African policy landscape

Globally, organisations such as the United Nations and the WHO are calling for integrated responses to AMR, emphasising environmental dimensions.[37] Many countries have begun incorporating EPV into National Action Plans for AMR, though progress is uneven.[21] South Africa has made strides through legislation (Table I), with oversight by regulatory bodies such as the South African Health Products Regulatory Authority (SAHPRA). While EPV is not yet explicitly stated in policy, existing legislative frameworks offer a foundation for its operationalisation.

Nevertheless, gaps remain, especially in integrating EPV into monitoring frameworks and addressing the environmental persistence of APECs. The absence of EPV indicators in facility level health service standards and licensing criteria in the National Health Act creates a barrier for existing oversight mechanisms to promote environmental stewardship in medicine handling and disposal. Good Pharmacy Practice standards do not include EPV-specific waste segregation and reporting protocols which align pharmacy waste management operations which facilitate environmental risk mitigation. The absence of EPV as an explicit subdomain of PV creates a gap for reporting triggers highlighting environmental contamination events.

Waste Water Treatment Plants: The convergence points for potential AMR

Recent research highlights the widespread detection of antimicrobial residues in South African water bodies traced from WWTP effluent. WWTPs serve as a convergence point for antimicrobials and resistant microorganisms from various sources, creating an environment that favours the selection and spread of AMR.[38] At coastal sites in the Western Cape, the environmental accumulation of APECs such as azithromycin, clarithromycin and erythromycin, was indirectly affected by WWTP discharges.[9] In the Gauteng Province, flumequine, an unregistered fluoroquinolone in South Africa, was detected in a stream carrying WWTP effluents in concentrations of environmental concern.[39] High concentrations of pharmaceuticals (e.g. sulfamethoxazole, efavirenz) have been found in WWTP effluent and sludge in Eastern Cape.[40] Removal efficiencies were as low as 2–12%, highlighting infrastructure dysfunction and environmental risk. The poor state of WTTP infrastructure is corroborated by the Green Drop Report, 2022, which highlighted infrastructure overload and poor effluent quality as key concerns. 39% of wastewater systems were in a critical state and only 5% of rural municipalities scored above 50% compliance.[41] Surveillance of rivers and WWTP effluent reveals high levels of resistant bacteria, such as *Acinetobacter baumannii* and *Campylobacter spp*., raising urgent concerns for public and ecological health.[35,42–44] These isolates exhibit resistance to multiple classes of antibiotics, including beta-lactams, aminoglycosides, and tetracyclines.[30,45] Treatment of infections caused by such resistant microbes often requires antibiotics classified under the WHO's AWaRe framework "Reserve" category, such as colistin or tigecycline, which are last-resort options reserved for severe, multidrug-resistant infections.[46]

Addressing the gaps: Pharmacist-led interventions

Pharmacists, as stewards of medicine use, are uniquely positioned to play a central role in mitigating the environmental and public health impacts of antimicrobial waste.[47]

One of their key responsibilities is implementing antimicrobial stewardship (AMS) by promoting the rational prescribing and dispensing of antimicrobials.[48] This helps reduce the economic and social drivers behind inappropriate antimicrobial use, such as limited access to health care, and reduces the amount of APECs entering the environment. Additionally, by leading initiatives that integrate infection prevention and control (IPC) with water, sanitation, and hygiene (WASH) efforts, pharmacists can address AMR more comprehensively.[49,50]

In addition to their clinical role, pharmacists are instrumental in public education, raising awareness about the environmental consequences of improper medicine disposal and the risks of self-medication to influence behaviour at the community level.[51] Education campaigns and outreach can encourage the return of unused medications and promote safer disposal practices.[1,7]

Effective inventory management is another vital area where pharmacists can contribute. Practices such as First-Expire-First-Out (FEFO) and First-In-First-Out (FIFO) ensure that older stock is used before expiration, reducing the volume of expired medicines and minimising pharmaceutical waste.[52]

Pharmacists are also well-placed to engage with policy processes. Their contribution to the development of guidelines and regulations on pharmaceutical disposal, can influence national and local waste management strategies and support the integration of EPV principles into AMR mitigation frameworks.[53] These interventions can reduce the burden of infections and the subsequent need for antimicrobial use, thereby decreasing the environmental presence of APECs.[49]

Advancing EPV in South Africa

South Africa stands at a pivotal moment to embed EPV within its national AMR strategies. Integrating EPV into national frameworks will require a diversified approach, which will include prioritising environmental surveillance of APECs to better understand the extent of pharmaceutical contamination and alert its ecological impacts.[37] EPV should be embedded within existing PV, Pharmacy Act, and health service delivery frameworks to enhance surveillance capacity and ensure that environmental risks are treated with the same urgency and accountability as clinical ones.

Incorporating EPV into health education curricula can build capacity among future health professionals, ensuring a long-term commitment to pharmaceutical safety beyond patient care.[1] Developing greener pharmaceuticals, establishing national pharmaceutical take-back schemes, and investing in environmentally sustainable disposal infrastructure are also critical for reducing the environmental burden of unused and expired medicines.[54]

Pharmacists are well-positioned to champion AMS programmes, combining their expertise with advocacy for environmentally sustainable practices. These programmes can facilitate rational antimicrobial use, reduce consumption and improve disposal habits, ensuring that multiple stakeholders adopt sustainable practices, fostering a culture of environmental responsibility.[28] Furthermore, improving intersectoral data sharing, particularly between health, environment, and water sectors, will enhance early warning systems and enable coordinated responses to pharmaceutical pollution.[49]

Conclusion

Pharmaceuticals are indispensable to modern medicine, but their benefits must be balanced with environmental responsibility. The rise of AMR, driven in part by environmental exposure to APECs, underscores the need for EPV as a central pillar of public health policy. Embedding EPV into AMR strategies ensures a proactive, systems-level approach to safeguarding ecosystems and human health. Through multidisciplinary collaboration, effective governance, and pharmacist leadership, we can build a more sustainable future for medicines and the planet.

Conflict of interest

The authors declare they have no conflicts of interest that are directly or indirectly related to the research.

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