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Review

Insight into on-site sewage facilities as an overlooked contributor to antimicrobial resistance: Environmental impacts and existing mitigation strategies

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ABSTRACT

Antimicrobial chemicals and resistance genes (ARG) drive antimicrobial resistance (AMR) proliferation. Decentralized, on-site sewage facilities (OSSF), usually with small serving capacities, are commonly exempted from secondary treatment requirements. To date, dissemination of AMR contaminants from OSSF to the environment remains underexplored. This review aims to critically examine the environmental impacts of OSSF on AMR and the effectiveness of existing mitigation strategies, with a comprehensive synthesis of literature on the fate and mitigation of AMR contaminants in OSSF. The typical design of septic tank followed by soil infiltration often poorly remove AMR contaminants, especially in winter, with high leaching potential into groundwater and occasionally posing AMR selection and ecological risks. Additional treatments (e.g., constructed wetlands, aerobic systems) can overall provide better mitigation. We further perform a meta-analysis of AMR selection risk, ecological risk, and environmental hazards to result in a list of priority AMR chemicals in OSSF-impacted waters, with erythromycin-H_2O, ciprofloxacin, triclocarban of top concerns. Despite limited literature on ARG, those of clinical relevance are highly abundant in OSSF systems. AMR dissemination could be influenced by different factors. Particularly, chemical diversities tend to increase with OSSF serving capacities and sampling methods can influence their detection. Our review highlights the overlooked role of OSSF in environmental AMR dissemination, and the limited research suggests a poor understanding of this issue, that needs future studies, especially on ARG and broader geographical context including low-/middle-income countries. This review also urges for improving existing mitigation strategies at OSSF to better manage and control AMR dissemination globally.

1. Introduction

Antimicrobial resistance (AMR) is a major burden on global health, responsible for almost five million deaths worldwide in 2019 alone (Murray et al., 2022). By 2030, the impact of AMR is projected to lower the global gross domestic product by 1–3.2 % depending on different scenarios (Jonas et al., 2017). AMR development is driven by the presence of antimicrobial chemicals, acting a selective pressure on the endemic microbial communities. Thereby, AMR proliferation is triggered, and further enhanced, by horizontal gene transfer, with the sharing and acquisition among bacteria of mobile genetic elements (MGE), such as integrons or plasmids carrying antimicrobial resistance genes (ARG). Hence, both antimicrobial chemicals and AMR-related genetic components (i.e., ARG, MGE) are important AMR contaminants when investigating the spread and further development of AMR, for instance, from consumption of antimicrobial chemicals to their discharge into the environment.

To effectively combat AMR, it is crucial to interconnect the human, animal, and environment compartments according to the One Health concept (UNEP, 2023). Effluent wastewater is a key emission source of

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AMR contaminants that can further promote AMR in the receiving waters (Sambaza and Naicker, 2023). In this light, centralized, municipal wastewater treatment plants (WWTP) are well-known for the occurrence and dissemination of AMR contaminants in effluent discharge (Hu et al., 2018; Göbel et al., 2007; Cai et al., 2021; Kahle et al., 2008; Monapathi et al., 2021; Östman et al., 2018; Cacace et al., 2019). In contrast, attention towards decentralized, on-site sewage facilities (OSSF) is relatively limited. These are typically employed by households (domestics) located in rural and sub-urban areas for wastewater sanitization (Schaider et al., 2017; Gao et al., 2019; Tan et al., 2021). Similar to conventional WWTP, OSSF are designed for the removal of nutrients (e.g., nitrate, phosphate) to prevent eutrophication in the receiving waters. OSSF typically consists of a septic tank followed by infiltration fields, together offering sedimentation, adsorption, and (bio)degradation treatment processes. Due to their connection to a small number of inhabitants (i.e., serving capacity), OSSF are often exempted from legal requirements to implement secondary and more advanced treatments. This can be seen in Europe, through the European Union (EU) Urban Waste Water Treatment Directive (91/271/EEC) and in the latest recast (EU 2024/3019) (European Commission, 2024; European Commission, 2014b). Hence, unlike WWTP, OSSF usually only have primary treatment and lack secondary and tertiary treatment steps (e.g., activated sludge, membrane bioreactors), which can further enhance (bio)degradation of antimicrobial contaminants (Langbehn et al., 2021; McConnell et al., 2018; Quach-Cu et al., 2018). Knowledge gaps on chemical fate in OSSF was previously emphasized (Meyer et al., 2019). To date, the literature still lacks an overview of OSSF regarding their potential of disseminating AMR contaminants, being a silent, neglected contributor to AMR in the environment.

In the recast EU directive (EU 2024/3019), OSSF are referred to as "individual systems", and they have recently came to be considered as one of the main actions with implementation plans, in which EU member states would be required to establish regular inspections for OSSF and EU standards for these facilities would be developed by January 2028 (European Commission, 2024). Similarly, wastewater monitoring for AMR, that was not previously included in the EU directive, would be applied to systems exceeding 100000 population equivalence (PE) in the future. For EU member states, wastewater collection and treatment have been required for a catchment serving more than 2000 PE (91/271/EEC) (European Commission, 2014b), but this has been narrowed down to 1000 PE in the recast directive (EU 2024/3019) (European Commission, 2024). This revision highlight the growing need for better management of environmental challenges posed by OSSF, emphasizing improved treatments even serving smaller numbers of inhabitants, and addressing the pressing concern of AMR. Other nations also have similar regulations on wastewater collection and implementation of secondary treatment. For example, in Canada, the minimum threshold for treatment is set at 100 m^3/day of wastewater (Government of Canada, 2012), while in the US states, all publicly-owned treatment should provide secondary treatment (US EPA, 2024b) and "small communities" (where decentralized treatment is implemented) is defined for areas below 10000 inhabitants and average wastewater daily flow below one million gallons (~four million liters) (US EPA, 2025).

In this review article, we provide a comprehensive data synthesis of AMR contaminants (both chemical and microbial) occurring in OSSF and their associated receiving waters, with aims to critically examine the environmental impacts of OSSF on AMR and the effectiveness of existing mitigation strategies. Our originality also lies in the meta-analysis of AMR selection risk, ecological risk and environmental hazards to result in a list of prioritized antimicrobial chemicals from high to low concern, that can facilitate future policy direction, e.g., the EU directives. We further discuss the potential factors influencing the dissemination of AMR contaminants in these environmental systems, and pinpoint the knowledge gaps and challenges in this topic, along with suggestions for future research.

2. Methods

2.1. Literature search and data compilation

We established relevant English keywords and search strings (Table S1) to search for scientific articles in Scopus and Web of Science Core Collection databases, available by August 16, 2023. To ensure that there were no additional studies that were either from countries not represented in the search results, or using different terminologies to define OSSF, we validated the search strings a) to result within a specific nation using the country's name (e.g., Sweden) as an additional keyword, and b) with additional synonyms of the OSSF terminology found in the search results (i.e., "individual sewage disposal system", "decentralized wastewater treatment system", "small community wastewater treatment system", "sewage disposal unit") (Table S1). The validation search did not provide any additional results, confirming that adequate keywords were used in the search string. We obtained a total of 497 articles (241 from Scopus and 256 from Web of Science, Fig. S1). After the removal of 179 duplicate articles, abstract screening was performed on 318 articles using Rayyan (Ouzzani et al., 2016). This left 66 relevant articles for a manual review, supplemented by three additional articles obtained through cross-referencing. A total of 33 peer-reviewed research articles were selected for further data analysis and interpretation (Fig. S1, Table S2). These articles focus on decentralized systems treating household (domestic) wastewater (i.e., blackwater, greywater, or a mixture of both) and/or aquatic environments influenced by such systems (receiving waters), as well as providing occurrence data on antimicrobial pollutants, i.e., concentrations of antimicrobial chemicals and/or abundances of ARG.

From the selected research articles, data were extracted and compiled as following: (i) contaminant types (antimicrobial chemicals or AMR-related genetic contaminants), (ii) measured concentrations or abundances in raw wastewater, effluent wastewater, and/or receiving waters, (iii) serving capacity and treatment-trains of the studied OSSF, (iv) sampling methods and time periods, and (v) country. Quantifiable frequency (QF, %) of each antimicrobial chemical (Table 1 and S3) in wastewaters and receiving waters was calculated based on the total number of data entries retrieved from the literature and the number of data points above quantification limits (quantifiable data points) (Equation (1)) (Figs. S2 and S3).

$$QF(\%) = \frac{\sum_{i=1}^{n} \textit{numbers of quantifiable data points}}{\sum_{i=1}^{n} \textit{total numbers of data entries}} * 100\% \tag{1}$$

2.2. Removal efficiency

When chemical concentrations in both raw and effluent wastewaters were provided for the same OSSF, the removal efficiency (RE, %) was calculated (Equation (2)).

$$RE(\%) = \left[\frac{(Conc_{raw} - Conc_{effluent})}{Conc_{raw}}\right] * 100\% \tag{2}$$

Because antimicrobial chemical detection and concentration data were sparsely distributed across studies and treatment types, statistical analysis comparing removal efficiencies between OSSF systems (e.g., ANOVA) could not be meaningfully performed.

2.3. Assessment of AMR selection and ecological risks

To evaluate the risk of antimicrobial chemicals for AMR selection and non-target aquatic organisms, a risk quotient (RQ) was calculated by comparing the antimicrobial concentrations against the respective predicted-no-effect-concentrations (PNEC). Calculations of RQ for AMR selection (RQ_{AMR}) (Equation (3)) used $PNEC_{AMR}$ proposed by Bengtsson-

Table 1
Quantifiable frequency (QF, %) and maximum measured concentrations (ng/L) of antimicrobial chemicals in OSSF raw and effluent wastewater and receiving waters across the literature.

Antimicrobial group	Compound name	Raw wastewater		Effluent wastewater		Receiving waters		References[a]
		QF (%)	ng/L	QF (%)	ng/L	QF (%)	ng/L	
Antivirals	Acyclovir	–	–	–	–	14	284	Fisher et al. (2016)
	Nevirapine	–	–	–	–	14	25.2	Fisher et al. (2016)
	Oseltamivir	–	–	–	–	14	3.65	Fisher et al. (2016)
Antifungals	Climbazole	100	1.8	100	9.3	50	2.6	Gao et al. (2019)
	Fluconazole	33	250	50	19	100	640	Gao et al. (2019), Phillips et al. (2015)
β-lactams	Amoxicillin	0	nd	0	nd	33	74	Hayward et al. (2019)
	Cefaclor	100	90	0	nd	100	166	Hayward et al. (2019)
	Cefdinir	0	nd	0	nd	100	120	Hayward et al. (2019)
	Cefprozil	0	nd	0	nd	100	322	Hayward et al. (2019)
Fluoroquinolones	Ciprofloxacin	100	180	25	540	100	699	Hayward et al. (2019), Clyde et al. (2021)
	Levofloxacin	0	nd	0	nd	100	144	Hayward et al. (2019)
Macrolides	Azithromycin	100	181	60	57	25	8	Hayward et al. (2019), Ferrell and Grimes (2014)
	Clarithromycin	50	140	60	104	50	89	Hayward et al. (2019)
	Erythromycin	67	140	71	137	19	5.4	Gao et al. (2019), Du et al. (2014), Conn et al. (2006)
	Erythromycin-H_2O	–	–	100	18000	33	750	Godfrey et al. (2007), Verstraeten et al. (2005)
	Roxithromycin	0	nd	25	0.1	0	nd	Gao et al. (2019)
	Tylosin	–	–	0	nd	25	25	Ferrell and Grimes (2014)
Sulfonamides	Sulfachloropyridazine	–	–	0	nd	33	0.7	Schaider et al. (2016)
	Sulfamethazine	50	45	25	36	17	21	Kang et al. (2019)
	Sulfamethizole	–	–	–	–	11	1	Schaider et al. (2014)
	Sulfamethoxazole	100	11200	75	37700	89	1300	Phillips et al. (2015), Subedi et al. (2015), Teerlink et al. (2012)
	Sulfathiazole	–	–	0	nd	25	0.2	Schaider et al. (2016)
Tetracyclines	Doxycycline	100	3160	33	1850	0	nd	Osińska et al. (2020)
	Tetracycline	100	100	75	20000	25	3.9	Gao et al. (2019), Conn et al. (2006)
Others	Clindamycin	100	137	100	138	100	191	Hayward et al. (2019)
	Metronidazole	100	6.9	100	33.8	50	0.1	Gao et al. (2019)
	Monensin	–	–	–	–	50	0.8	Schaider et al. (2016)
	Trimethoprim	100	5690	64	2900	48	580	Teerlink et al. (2012) Clyde et al. (2021) Verstraeten et al. (2005)
Antimicrobial PCPs	Triclocarban	100	14800	67	457	100	124	Hayward et al. (2019) Teerlink et al. (2012) Yang et al. (2017)
	Triclosan	100	230000	75	57000	33	54.8	Conn et al. (2010a) Li et al. (2013)
Number of detected compounds		*16*		*17*		*28*		

[a] Reference for the maximum measured concentration; -) not sampled; nd) not detected.

Palme and Larsson in 2016 (Table S4) while ecological RQ (RQ_{eco}) (Equation (4)) used $PNEC_{eco}$ (Table S5). Where available, $PNEC_{eco}$ were taken from curated expert sources, such as the Swedish FASS pharmaceuticals database (FASS, 2024), the European Chemicals Agency (ECHA, 2024b), the Pesticides Properties Database (PPDB, 2024), and scientific literature (Lützhøft et al., 1999; Isidori et al., 2005; Brain et al., 2004; Ando et al., 2007; Chen et al., 2014; Yang et al., 2008; Białk--Bielińska et al., 2011; Park and Choi, 2008; González-Pleiter et al., 2013; US EPA, 1992). For chemicals lacking previously established $PNEC_{eco}$, these were calculated according to published methods in European guidelines for chemical risk assessment (ECHA, 2024a). Ecotoxicity data were obtained from the US EPA ECOTOX database (US EPA, 2024a). For each chemical, a single datum was used from the most sensitive species, or the geometric mean was used if more than one value was reported. Chronic data from standard test species for algae, daphnids, and fish were used by preference, although acute data and data for non-standard species were also used in cases with poor data availability. For data-gap chemicals, where no empirical data were available, quantitative structure activity relationship (QSAR) data were obtained using TRIDENT (Gustavsson et al., 2024). The appropriate assessment factor (AF) was then applied (ECHA, 2024a). For QSAR data, an AF of 1000 was used. Further details and data sources used for the derivation of $PNEC_{eco}$ are provided in the Supplementary Information (Table S5).

$$RQ_{AMR} = \frac{measured\ concentration}{PNEC_{AMR}} \tag{3}$$

$$RQ_{eco} = \frac{measured\ concentration}{PNEC_{eco}} \tag{4}$$

For both RQ_{AMR} and RQ_{eco}, obtained values below 0.1 represent low risk, between 0.1 and 1 medium risk, and above 1 high risk.

2.4. Environmental hazard prediction

Persistence, mobility, and bioaccumulation were determined to understand the potential environmental hazards of antimicrobial chemicals The VEGA software was used to predict chemicals' half-life in water, soil, and sediment (quantitative IRFMN model v.1.0.0), water solubility (IRFMN model v.1.0.0), sorption coefficient (K_{oc}; OPERA model v.1.0.0), and bio-concentration factor (BCF; Meylan model v.1.0.3), as previously applied (Löffler et al., 2023). The VEGA software also provided an analysis of the prediction reliability (good, moderate, or low) (Manganaro et al., 2016; Benfenati et al., 2019; Pizzo et al., 2016).

2.5. Scoring and prioritization

A binary score (0 or 1) was assigned to each environmental risk and hazard parameters, according to the following criteria. For $RQ_{AMR} > 1$ and $RQ_{eco} > 1$ in receiving waters, $Score_{AMR}$ and $Score_{eco}$ of 1 was given, respectively; otherwise, a score of 0. Based on the REACH guidelines (Löffler et al., 2023; European Commission, 2014a), chemicals were considered persistent in water with a half-life >40 days, mobile with water solubility >0.15 mg/L and $K_{oc} \leq 4.5$, and bioaccumulative with log BCF >3.3. A score of 1 was assigned to each of these parameters when the REACH criteria were met. The environmental hazard score, $Score_{EH}$ (Equation (5)), was an average of the scores for persistence, mobility, and bioaccumulation. A final score for each antimicrobial chemical was obtained as a sum of $Score_{AMR}$, $Score_{eco}$, and $Score_{EH}$. By ranking the final scores from high to low, a list of antimicrobial chemicals of concern was prioritized, with a maximum final score of 3 (highest concern) and a minimum score of 0 (lowest concern). Such scoring and prioritization meta-analysis has been applied in previous studies (Löffler et al., 2023).

$$Score_{EH} = \frac{Score_{persistence} + Score_{mobility} + Score_{BCF}}{3} \tag{5}$$

2.6. Groundwater ubiquity score (GUS)

First proposed by Gustafson in 1989 and recently considered as potential indicator of chemical mobility for drinking water resource protection (Gustafson, 1989; Pawlowski et al., 2023), GUS (Equation (6)) enables an assessment of the leachability of antimicrobial chemicals from soil in infiltration fields to groundwater. This is calculated based on their half-life in soil and sorption coefficient (K_{oc}) predicted from the VEGA software. The leachability is considered either extremely low (GUS<0), low (0<GUS<1.8), moderate (1.8<GUS<2.8), or high (GUS>2.8) (Gustafson, 1989; Pawlowski et al., 2023).

$$GUS = \log_{10} halflife_{soil} * (4 - \log_{10} K_{oc}) \tag{6}$$

3. Result overview of the literature's analysis

Overview of the research trends. Over the last 18 years, the literature (Fig. 1) shows the overall study interests in OSSF expanding from initially mainly inorganic substances (metals) to later including organic compounds and nutrients, followed by, more recently, AMR-related microbial contaminants. As AMR was not a primary focus early-on, the literature often covers only a limited number of representative antimicrobial chemicals, mostly sulfamethoxazole and trimethoprim, among many other families of organic compounds (e.g., flame retardants, stimulants, etc.). Recently, the literature has shown an emerging interest in AMR, particularly regarding the occurrence of microbial contaminants such as ARG, resistant bacteria, and pathogens in OSSF (Fig. 1). This aligns with the increased promotion and awareness of the One Health concept (UNEP, 2023), and also the advancements in (bio)analytical instrumentation, which have enhanced the capability and sensitivity for measuring AMR contaminants in waters. Most studies solely focus on either chemical or microbial contaminants in such settings. Only one study has simultaneously monitored both antimicrobial chemicals and ARG within the same treatment system (Hayward et al., 2019).

Geographical distribution. There is no specific pattern observed for the publishing years, with a median of two publications per year. Geographically, the distribution of the selected articles shows a predominance of studies from the United States (n = 18), followed by Sweden (n = 4), Canada (n = 3), China (n = 2), Korea (n = 1), Kenya (n = 1), and Poland (n = 1). Peer-reviewed articles from other countries are scarce, possibly due to a lack of studies or their publication being primarily in grey literature, which is hampered by language barriers, and thus its inclusion in this review is unfeasible. The limited geographical coverage of the available literature provides only a small snapshot of OSSF worldwide, potentially leading to an underestimation of the global risk of AMR dissemination from these systems.

OSSF-related terminology. During our review, we observed that the literature uses a wide variety of terminologies to refer to decentralized wastewater treatment systems. This includes, "on-site wastewater treatment", "fecal sewage treatment facility", "on-site treatment facility", "domestic wastewater", "residential wastewater", "on-site wastewater", "on-site wastewater infiltration system", "septic systems", "on-site sewage treatment plant", "septic drainfield", "on-site treatment system", "onsite wastewater disposal system", "rural wastewater treatment", "decentralized wastewater catchment", "septic tank drainfield", "onsite wastewater system", or "onsite wastewater treatment system". No pattern was identified for these terminologies; for instance, various terminologies were used even within a country (e.g., in the USA: "septic system", "onsite wastewater disposal system", "on-site wastewater treatment system", "decentralized wastewater catchment", "residential wastewater") (Carrara et al., 2008; Schaider et al., 2016; Phillips et al., 2015; Fisher et al., 2016; Subedi et al., 2015; Ferrell and Grimes, 2014; Du et al., 2014; Teerlink et al., 2012; Park et al., 2016). Additionally, the articles obtained from cross-referencing used different terminologies compared to the search string, being "private wastewater treatment facility", "informal settlement", and "small-scale wastewater treatment plant". Overall, this suggests that there is an evident need for

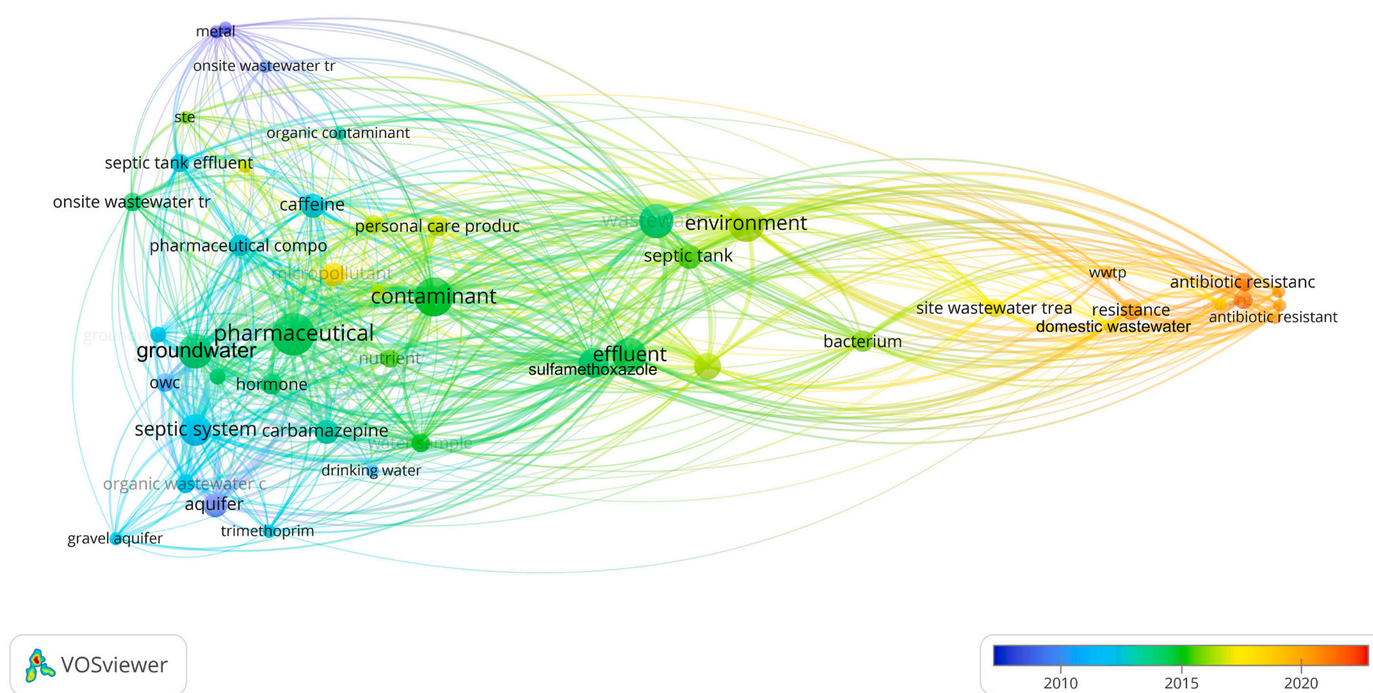

Fig. 1. Visualization of distribution and connectivity of terms in abstract and title of the selected articles (realized with VosViewer Map). The size of the circle means how many times a term has been used. Abbreviations: owc, organic wastewater contaminants; ste, septic tank effluent; wwtp, wastewater treatment plant; args, antimicrobial resistance genes.

establishing a more standardized terminology to characterize these decentralized systems. While the keywords used in this review were thoroughly validated to account for numerous synonyms of OSSF (see section 2, Table S1), there could still be missing publications if other additional terminologies outside of our domains were used.

4. Antimicrobial chemicals in OSSF settings

A total of 74 different antimicrobial chemicals (Fig. S3) have been targeted in the OSSF literature, belonging to the groups of antibacterial, antifungal, and antiviral for human administration (systemic use), as well as antimicrobial personal care products (PCPs, i.e., triclocarban and triclosan) (topical use) (Lipsky et al., 2008). Within the antibacterial group, various families are covered, including beta-lactams, fluoroquinolones, macrolides, sulfonamides, and tetracyclines, in addition to other types of antibacterial (clindamycin, metronidazole, monensin, chloramphenicol, lincomycin, trimethoprim, and ormetoprim). Among the 74 chemicals, 30 were measured at least once above quantification limits in the matrices of raw wastewater, effluent wastewater, or receiving water (Table 1). There were 13 antimicrobial chemicals showing a quantifiable frequency above 30 % and with at least three quantifiable data points across all the water matrices (Fig. 2, Fig. S3, Table S3), including (in decreasing order of quantifiable data points): sulfamethoxazole, trimethoprim, triclosan, triclocarban, fluconazole, clarithromycin, azithromycin, erythromycin, climbazole, metronidazole, tetracycline, clindamycin, and ciprofloxacin.

4.1. Chemical fate and their existing mitigation strategies

All articles included in this review studied OSSF that treated wastewater from households only (i.e., human origin). A similar number of compounds occurred in raw (16) and effluent (17) wastewater (Table 1), with maximum measured concentrations (in decreasing order) observed for triclosan, triclocarban, sulfamethoxazole, trimethoprim, fluconazole in raw wastewater, and for triclosan, sulfamethoxazole, trimethoprim, ciprofloxacin, triclocarban in effluent wastewater.

The antimicrobial PCPs, triclosan (4650–230000 ng/L) and triclocarban (198–14800 ng/L), were highly quantified in OSSF raw wastewater (QF 100 %) (Hayward et al., 2019; Teerlink et al., 2012; Conn et al., 2010a; Li et al., 2013). Both were still commonly found in OSSF effluent wastewater (QF 75 %, 20–57000 ng/L; QF 67 %, 37–457 ng/L, respectively) although at reduced concentrations (Carrara et al., 2008; Subedi et al., 2015; Conn et al., 2010a, 2010b; Li et al., 2013; Yang et al., 2016, 2017; Blum et al., 2017). The presence of these antimicrobial PCPs is in line with their wide usage as biocides and preservatives in cosmetics, toothpaste, disinfectants, and detergents, as well as toys and furniture in some cases (FDA, 2024; Milanović et al., 2023). Being an endocrine disruptor, triclosan has been banned in US cosmetics since 2017 and is restricted in the EU (e.g., 0.3 % limit in adult toothpaste) (FDA, 2024; European Commission, 2022). During OSSF treatment, triclosan was efficiently removed – 90 % in a system with septic tank and soil beds (Blum et al., 2017), and 95–99 % in a system with bar screen, aerated lagoons and a sand tank (Li et al., 2013). In the latter OSSF, triclocarban removal was lower (70–88 %) (Li et al., 2013).

Sulfamethoxazole was frequently found in OSSF raw wastewater (QF 100 %, 0.28–11200 ng/L) (Gao et al., 2019; Du et al., 2014; Teerlink et al., 2012; Li et al., 2013), and was still highly common in OSSF effluent wastewater (QF 75 %, 2.8–37700 ng/L) (Gao et al., 2019; Subedi et al., 2015; Li et al., 2013; Yang et al., 2016, 2017; Katz et al., 2010; Clyde et al., 2021). Trimethoprim was found in a comparable frequency to sulfamethoxazole in both OSSF raw (QF 100 %, 1.5–5690 ng/L) and effluent (QF 64 %, 1.1–2900 ng/L) wastewaters (Gao et al., 2019; Subedi et al., 2015; Du et al., 2014; Teerlink et al., 2012; Li et al., 2013; Clyde et al., 2021). These two antibacterials, which inhibit folic acid synthesis, are bacteriostatic alone but bactericidal in combination, and are commonly used for urinary tract infections and bronchitis (Kemnic and Coleman, 2022). Their combined use – typically with higher sulfamethoxazole concentration – explains their co-occurrence and corresponding concentrations in wastewater (Karimi et al., 2023). In OSSF, septic tanks showed low removal of both (7–11 % for sulfamethoxazole, 12–20 % for trimethoprim) (Du et al., 2014). Trimethoprim removal improved with a constructed wetland (93–100 %) or an aerobic treatment system (46–86 %), though sulfamethoxazole remained poorly removed (<50 %) (Du et al., 2014). Nitrogen-removing

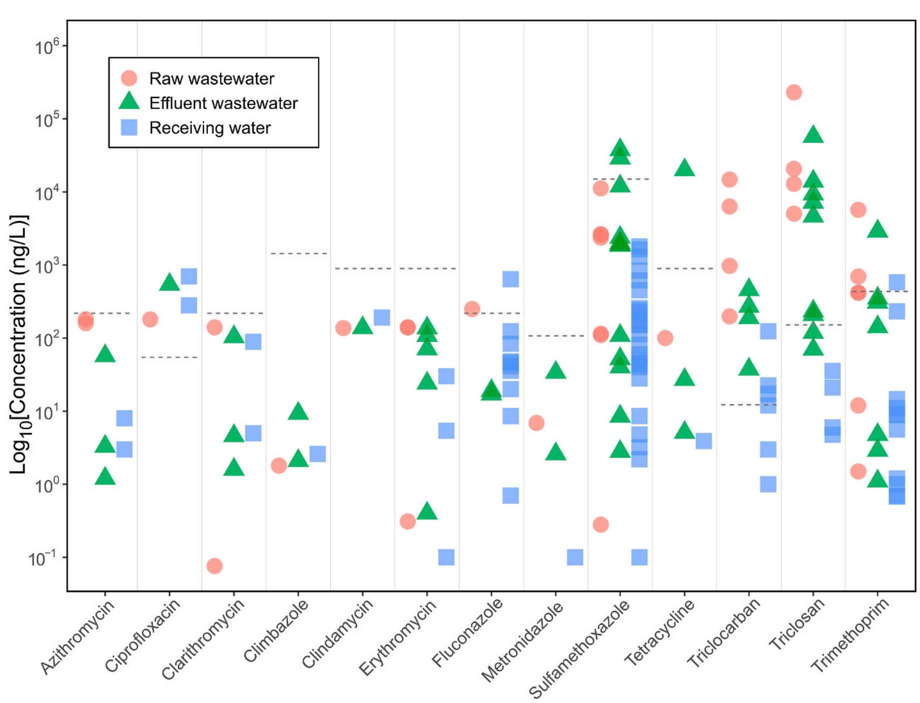

Fig. 2. Maximum measured concentration (ng/L, logarithmic scale) of the antimicrobial chemicals most frequently detected (QF>30 %, quantifiable data points >3) in raw and effluent wastewater and receiving waters. Dotted grey lines represent the available $PNEC_{AMR}$ (see Table S4).

biofilters achieved high removal for both (88–99 % for sulfamethoxazole and 92–96 % for trimethoprim) (Clyde et al., 2021), and trimethoprim was also well removed (97 %) with a bar screen, aerated lagoon and a sand tank treatment (Li et al., 2013).

Compared to the above-mentioned antimicrobial chemicals, fluconazole was less frequently quantifiable in OSSF raw (QF 33 %, 250 ng/L) and effluent (QF 50 %, 17–19 ng/L) wastewaters, although still at considerable concentrations (Gao et al., 2019). This antifungal is widely prescribed in the primary care sector, usually for urinary tract infections or vaginal candidiasis treatment (Govindarajan et al., 2024). The median concentrations measured in raw (19 ng/L) and effluent (14 ng/L) wastewaters of a OSSF with both a septic tank and infiltration field showed a low removal efficiency (26 %) (Gao et al., 2019).

Ciprofloxacin, a fluoroquinolone antibacterial, was rarely targeted in the OSSF raw wastewater analysis (only 1 data point; Fig. S3) (QF 100 %, 180 ng/L) (Hayward et al., 2019), and was also often not quantifiable in effluent wastewater (QF 25 %, 540 ng/L) (Clyde et al., 2021). Fluoroquinolones are classified as essential medicines by the World Health Organization and belong to the Watch group of the AWaRe classification, meaning that they are prescribed only when treatment with first-line antibacterials (e.g., penicillins) fails (World Health Organization, 2021). Given their sporadic use, primarily in hospital settings, it is reasonable to expect low and infrequent detections of these antibacterials in household-serving OSSF. Treatment of nitrogen-removing biofilters showed appropriate removal (48–76 %) of ciprofloxacin (Clyde et al., 2021).

Three macrolide antibacterials were quantified in both OSSF raw and effluent wastewater, including azithromycin (raw: QF 100 %, 160–180 ng/L; effluent: QF 60 %, 1.2–57 ng/L), clarithromycin (QF 50 %, 0.08–140 ng/L; QF 60 %, 1.6–104 ng/L), and erythromycin (QF 67 %, 0.3–140 ng/L; QF 71 %, 0.4–24 ng/L) (Gao et al., 2019; Hayward et al., 2019; Du et al., 2014). Another macrolide, roxithromycin, was detected only in effluent wastewater (QF 25 %, 0.1 ng/L) (Gao et al., 2019), as well as the dehydrated metabolite of erythromycin (erythromycin-H_2O) (QF 100 %, 18000 ng/L) (Godfrey et al., 2007). Similar to ciprofloxacin, the low occurrences of these macrolides in OSSF reflects the low consumption in primary care sectors, since they are alternatives to first-line antibacterials. Treatment in septic tanks barely removed any of these macrolides (Gao et al., 2019; Hayward et al., 2019; Du et al., 2014). For erythromycin, constructed wetlands and aerobic treatment systems improved its removal efficiency (up to 70 %), and occasionally the constructed wetland gave an even higher removal efficiency (90 %) (Du et al., 2014). Sand-filter treatment can highly remove azithromycin (100 %), but not at all clarithromycin (~4 %) (Hayward et al., 2019).

A few antimicrobials were seldom (data point 1–4) targeted in OSSF wastewater, even though they were frequently quantifiable (QF 75–100 %). These included climbazole (raw: 1.8 ng/L; effluent: 2.1–9.3 ng/L), metronidazole (6.9 ng/L; 2.6–34 ng/L), tetracycline (100 ng/L; 5.1–20000 ng/L), and clindamycin (137 ng/L; 138 ng/L) (Gao et al., 2019; Hayward et al., 2019). The minor focus throughout the literature on metronidazole, tetracycline, and clindamycin contrasts to the usual prescription practices, as they are commonly used as first-line antibiotics and listed as "Access" compounds according to the AWaRe classification (World Health Organization, 2021). Septic tanks showed appropriate removal for tetracycline (~70 %) and metronidazole (~60 %), but not at all for climbazole and clindamycin (Gao et al., 2019; Hayward et al., 2019). The latter was not removed even with additional sand-filter treatment (Hayward et al., 2019).

In comparison to the conventional treatments at municipal WWTP, the reviewed OSSF systems performed equally well for the removal of triclosan and triclocarban (Yun et al., 2020), which is in line with the hydrophobicity of these compounds. On the other hand, sulfamethoxazole, trimethoprim, fluconazole, and macrolide antibacterials were recalcitrant to treatments in the primary treatment (sedimentation) of both OSSF and WWTP (Hu et al., 2018; Göbel et al., 2007; Cai et al., 2021; Kahle et al., 2008; Monapathi et al., 2021; Östman et al., 2018; Zuccato et al., 2010; Pan and Yau, 2021; Abbasi and Ahmadi, 2021). Sulfamethoxazole and fluconazole persisted even after secondary (biological) treatment (i.e., wetlands in OSSF and activated sludge in WWTP) (Göbel et al., 2007; Du et al., 2014; Sochacki et al., 2021), while removal of trimethoprim and macrolides improved (Du et al., 2014; Abbasi and Ahmadi, 2021). The low removal of ciprofloxacin observed in OSSF contrasts with WWTP, where it is usually highly biodegraded (>90 %) during activated sludge treatment (Östman et al., 2018; Hazra and Durso, 2022). This underlines the benefit of upgrading OSSF with additional secondary treatments to improve the removal of certain antimicrobial chemicals (e.g., trimethoprim, macrolides), which are recalcitrant in the current common setting, predominantly with septic tanks.

4.2. Impact of insufficient mitigation on receiving waters

Infiltration fields are often employed as the final, natural barrier before OSSF effluent reaches the aquatic environment. Of the two types of receiving waters (downstream of OSSF), groundwater was studied more than surface water (Fig. 4). Among the 28 measured antimicrobial chemicals, sulfamethoxazole, ciprofloxacin, fluconazole, cefprozil, and acyclovir were found in the top 5 highest concentrations (in decreasing order) (Table 1).

Sulfamethoxazole was frequently found in OSSF receiving waters (QF 89 %, 0.1–1300 ng/L) (Gao et al., 2019; Schaider et al., 2014, 2016; Phillips et al., 2015; Subedi et al., 2015; Li et al., 2013; Yang et al., 2016, 2017; Katz et al., 2010; Gago-Ferrero et al., 2017; Elliott et al., 2018). The highest concentration was measured in groundwater underneath a leach-bed (silty sand in shallow surficial aquifers) (Phillips et al., 2015). Since septic tanks and additional treatment are not efficient in removing sulfamethoxazole (see section 4.1 above), infiltration fields become crucial in preventing its transport to groundwater. Its removal in infiltration fields depends on soil properties – clay-rich, organic, or acidic soils improve adsorption (Archundia et al., 2019), but sandy-loam is typically used to avoid wastewater stagnation (Gerba et al., 2023). As a result, sulfamethoxazole often reaches groundwater when present in raw wastewater. Even with US regulations requiring 60–120 cm of unsaturated soil between the infiltration system and groundwater, sulfamethoxazole was still detected in pore water at those depths (7000 ng/L at 60 cm and 1800 ng/L at 120 cm) (Conn et al., 2010b), indicating poor removal in typical OSSF. In contrast, trimethoprim was detected less often and at lower concentrations (QF 48 %, 0.7–11 ng/L) in receiving waters, likely due to smaller proportion in combined prescriptions (Karimi et al., 2023).

Ciprofloxacin could be subjected to a similar fate in infiltration fields, as its degree of adsorption onto soil is suggested to be more based on ion-exchange interactions than hydrophobic interactions, and pH and organic matter contents in soil, as well as ciprofloxacin speciation (ionic forms varying with pKa), are crucial (Chen et al., 2023; Girardi et al., 2011; Kümmerer, 2009; Harrower et al., 2021). Sandy soil often lacks organic particles or clay minerals for adsorption, and accordingly, sand-filters showed inefficient removal for ciprofloxacin (Hayward et al., 2019).

Another antimicrobial chemical ubiquitously found in receiving waters was fluconazole (QF 100 %, 0.7–640 ng/L), with the highest concentration in groundwater underneath a leach-bed and the lowest in groundwater downstream of an open pond infiltration site (Gao et al., 2019; Hayward et al., 2019). Fluconazole also commonly occurs in other settings (Kahle et al., 2008; Chen and Ying, 2015; Assress et al., 2020). Its selective pressure on opportunistic pathogenic yeasts (e.g., *Candida albicans*) in the aquatic environment is of human health concern, especially when related to drinking water sources (Monapathi et al., 2021; Cupozak-Pinheiro et al., 2022; Steffen et al., 2023; Novak Babič et al., 2017).

Four macrolides, azithromycin (QF 25 %, 3–8 ng/L), clarithromycin (QF 50 %, 5–89 ng/L), erythromycin (QF 19 %, 0.1–5.4 ng/L), and tylosin (QF 25 %, 25 ng/L) were measured in surface water, sand-filter effluent, and groundwater (Gao et al., 2019; Hayward et al., 2019; Ferrell and Grimes, 2014). These macrolides are also monitored at the EU level as they are commonly found in receiving waters, and they are considered recalcitrant compounds in the aquatic environment (Gao et al., 2019; Harrower et al., 2021; Li et al., 2022; Baranauskaite-Fedorova and Dvarioniene, 2023). The metabolite erythromycin-H_2O was measured in downstream groundwater (QF 33 %, 750 ng/L) (Verstraeten et al., 2005).

Tetracycline (QF 25 %) was measured in downstream groundwater after soil infiltration (3.9 ng/L), at a much lower concentration compared to raw wastewater (100 ng/L) and septic tank effluent (27 ng/L) (Gao et al., 2019). Tetracycline is known to strongly interact with redox active minerals, which could increase adsorption during the soil infiltration (Chen et al., 2023).

Despite the high maximum concentrations measured in raw wastewater for the two antimicrobial PCPs, triclosan (QF 33 %, 4.76–54.8 ng/L) and triclocarban (QF 100 %, 1–124 ng/L) concentrations in receiving waters were reduced by two orders of magnitude (Hayward et al., 2019; Subedi et al., 2015; Li et al., 2013; Yang et al., 2016, 2017). In spite of these reduced concentrations, both compounds can potentially accumulate in soil, sediment, and aquatic organisms, and they are considered to be among the most common pollutants in the aquatic environment (Halden, 2014; von der Ohe et al., 2012).

Three antivirals, acyclovir (284 ng/L), nevirapine (25.2 ng/L), and oseltamivir (3.65 ng/L) were rarely detected in downstream groundwater (QF 14 %, for all compounds) (Fisher et al., 2016). Acyclovir concentrations may be overestimated due to matrix enhancement in the used analytical methodology (Fisher et al., 2016). Acyclovir in the downstream groundwater was detected only after OSSF overflowing due to a hurricane.

5. Risk and hazard evaluations of antimicrobial chemicals

5.1. Risk assessment of AMR selection

Risk assessment for AMR selection was performed for 17 (out of 30) measured antimicrobial chemicals (Table 1), for which $PNEC_{AMR}$ were available (Table S4). In OSSF raw and effluent wastewaters, the risk of AMR selection was found between moderate ($0.1 < RQ_{AMR} < 1$) and high ($RQ_{AMR} > 1$) for most of the antimicrobial chemicals, while in receiving waters, the risk was mainly low ($RQ_{AMR} < 0.1$) and moderate (Fig. S4, Table S6). High risk of AMR selection was observed for ciprofloxacin and trimethoprim in both wastewaters, for doxycycline and fluconazole in raw wastewater, and for sulfamethoxazole and tetracycline in effluent wastewater (Gao et al., 2019; Hayward et al., 2019; Subedi et al., 2015; Teerlink et al., 2012; Li et al., 2013; Clyde et al., 2021; Godfrey et al., 2007; Osińska et al., 2020; Conn et al., 2006). In a study where OSSF effluent was discharged into lake water that also served as a drinking water source for nearby households, sulfamethoxazole in the septic tank effluent occasionally posed a high risk of AMR selection (Subedi et al., 2015). Even after OSSF treatments, ciprofloxacin, fluconazole, and trimethoprim still posed a high risk of AMR selection in some receiving waters (Hayward et al., 2019; Phillips et al., 2015; Clyde et al., 2021; Verstraeten et al., 2005). Ciprofloxacin was found in treated effluent after additional treatments of the septic tank effluent with sand-filters and nitrogen removing biofilters at two experimental (pilot) facilities (Hayward et al., 2019; Clyde et al., 2021). Fluconazole was reported in groundwater underneath a leach-bed of an OSSF treating wastewater sourced from an elderly care facility (Phillips et al., 2015). Trimethoprim was found in a sand-point well in groundwater downstream of an OSSF (Verstraeten et al., 2005). Overall, antimicrobial chemical concentrations were found to be reduced in receiving waters compared to the OSSF raw wastewater which is attributed to either their removal in OSSF treatment, dilution, or environmental degradation. For instance, at the same sites, sulfamethoxazole exhibited a high risk for AMR selection in effluent wastewater but a low risk in receiving waters (Subedi et al., 2015; Godfrey et al., 2007). Nonetheless, although the presence of antimicrobial chemicals in receiving waters posing a high risk for AMR selection is infrequent, it should not be underestimated.

5.2. Ecological risk assessment

The ecological risk assessment for the 30 measured antimicrobial chemicals (Table 1) was comparable to the risk for AMR selection, with moderate to high risks in raw and effluent wastewater, and low to moderate in receiving waters (Fig. S5, Table S7). Azithromycin, ciprofloxacin, clarithromycin, clindamycin, doxycycline, sulfamethoxazole, triclocarban, and triclosan showed high risks in both raw and effluent wastewater, and erythromycin-H_2O and tetracycline in effluent wastewater (Table S7). For the anhydrous form of erythromycin, the QSAR-derived (Gustavsson et al., 2024) $PNEC_{eco}$ was four times lower than the parent compound, suggesting a higher toxicity of this transformation product, although experimental data are needed to confirm this increased toxicity. After OSSF treatments, some antimicrobial chemicals still showed high ecological risk, including additional treatments with sand-filtration (i.e., amoxicillin, ciprofloxacin, clarithromycin, clindamycin, and triclocarban) (Hayward et al., 2019), nitrogen removing biofilters (i.e., ciprofloxacin, sulfamethoxazole) (Clyde et al., 2021), and constructed wetland (i.e., sulfamethoxazole) (Du et al., 2014), as well as in receiving waters (i.e., clarithromycin, erythromycin-H_2O, sulfamethoxazole, triclocarban, triclosan) (Gao et al., 2019; Phillips et al., 2015; Subedi et al., 2015; Li et al., 2013; Blum et al., 2017; Yang et al., 2017; Verstraeten et al., 2005). Within the groups of sulfonamides (e.g., sulfamethoxazole), macrolides (e.g., clarithromycin), lincosamides (e.g., clindamycin), and β-lactams (e.g., amoxicillin), their transformation products were previously identified with human health and environmental concern (Löffler et al., 2023). Similar to the risk of AMR selection, a decreased ecological risk, from high in effluent wastewater to low or moderate in the connected receiving waters, is observed for some antimicrobial chemicals (i.e., sulfamethoxazole and triclosan) (Subedi et al., 2015; Godfrey et al., 2007), likely due to dilution or environmental degradation. However, these processes are not always sufficient in reducing the ecological risk (with $RQ_{eco} < 1$) in the receiving waters (i.e., triclocarban, triclosan and clarithromycin) (Gao et al., 2019; Subedi et al., 2015; Li et al., 2013; Yang et al., 2017).

5.3. Environmental hazard prediction

Among the 30 compiled antimicrobial chemicals (Table 1), nine were predicted to be persistent in water, including azithromycin, clarithromycin, clindamycin, erythromycin, erythromycin-H_2O, monensin, oseltamivir, roxithromycin, and tylosin (Tables S8 and S9). Most of the antimicrobial chemicals were predicted mobile, except for five (i.e., monensin, triclosan, azithromycin, clarithromycin, and erythromycin), whereas none of them could be considered bioaccumulative (Tables S8 and S9). As the models, particularly those predicting persistence and bioaccumulation factor, showed moderate and high reliability for only some chemicals (Table S8), caution is advised when interpreting predictions for these chemicals due to the potential uncertainties in the model outputs. Low reliability is estimated for most chemicals because they were dissimilar (see section 2.4) from the chemicals used for the model's training and test. The higher sorption capacity of triclosan ($K_{oc} = 4.56$) in comparison to triclocarban ($K_{oc} = 3.61$) could suggest a better removal of triclosan in OSSF (section 4.1), specifically during sedimentation in the septic tank, although both are predicted to persist in water for ∼20 days. It is worth noting that nine compounds were estimated to be persistent in sediment (i.e., fluconazole, climbazole, clindamycin, triclocarban, ciprofloxacin, cefaclor, nevirapine, erythromycin-H_2O, triclosan) and two in soil (i.e., climbazole, triclosan) with a half-life exceeding 120 days (Table S8) (European Commission, 2014a). This information could be useful, for example, to understand the selective pressure of these chemicals on microbial communities within the soil of infiltration fields or receiving water sediments, where, additionally, the potential re-suspension of chemicals from sediment to the water phase via sediment erosion or bio-turbation (Banta and Andersen, 2003; Maghsodian et al., 2022), could cause a delayed selection pressure on the aquatic microbial communities.

5.4. Scoring and prioritization of antimicrobial chemicals in receiving waters

With available $PNEC_{AMR}$, five compounds (ciprofloxacin, fluconazole and trimethoprim) were assigned a $Score_{AMR}$ of 1 (Table S9). As for 12 compounds $PNEC_{AMR}$ was not available, a $Score_{AMR}$ of 1 was given as conservative risk assessment (Table S9), which may be revised in the future when a $PNEC_{AMR}$ is provided. A $Score_{eco}$ of 1 was assigned to ciprofloxacin, triclocarban, triclosan, erythromycin-H_2O, clindamycin, amoxicillin, clarithromycin, and sulfamethoxazole. The highest $Score_{EH}$ (0.67) was determined for clindamycin, erythromycin-H_2O, oseltamivir, roxithromycin and tylosin, being persistent and mobile but not bioaccumulative, while triclosan was the only compound, according to the REACH guidelines, that was not persistent (half-$life_{water}$ < 40 days), not mobile (Koc >4.5 and water solubility <0.15 mg/L) and not bioaccumulative (log BCF <3.3), resulting in a $Score_{EH}$ of 0 (Table S9).

By ranking the final scores, a list of prioritized antimicrobial chemicals from high to low concern for OSSF settings was obtained (Fig. 3, Table S9). Six of them had a final score >1.5 (half of maximum score). Erythromycin-H_2O (2.67), ciprofloxacin (2.33), and triclocarban (2.33) are the top three priority antimicrobial chemicals. Triclosan (2.00), despite being predicted with minimal environmental hazards, was the fourth ranked, followed by clindamycin (1.67) and oseltamivir (1.67). There were 10 chemicals (final scores of <0.67) ranked at very low concern, with scores mainly coming from environmental hazards but not AMR and ecological risks. These included roxithromycin, tylosin, azithromycin, cefaclor, cefdinir, doxycycline, erythromycin, levofloxacin, metronidazole, and tetracycline. In contrast to its transformation product (erythromycin-H_2O), erythromycin (0.33) showed a low final score with much lower risks and environmental hazards concern. This finding aligns with the importance of studying antimicrobial transformation products as recently reviewed in the global surface water environments (Löffler et al., 2023). Several antimicrobial chemicals of concern on our list have been previously identified in global aquatic environments (e.g., ciprofloxacin, triclosan, sulfamethoxazole, trimethoprim, clarithromycin, amoxicillin) (Yang et al., 2022).

5.5. Groundwater ubiquity score (GUS)

Among the 30 compiled antimicrobial chemicals (Table 1), almost all (GUS 3–10) showed high leachability potential (Fig. S6, Table S10). With high persistence and likelihood of adsorption in soil, the highest GUS was observed for climbazole, triclosan, cefaclor, triclocarban, and clindamycin. Sulfamethoxazole, cefprozil, and amoxicillin were found with moderate leachability (GUS 2.6 each), as they were the least persistent and had less adsorption tendency in soil (Fig. S6, Table S10). All six prioritized compounds (see section 5.4), erythromycin-H2O, ciprofloxacin, triclocarban, triclosan, clindamycin, and oseltamivir, showed high leachability (GUS>2.8) from soil to groundwater, potentially posing a threat to this water resource.

6. AMR-related genetic contaminants: fate and existing mitigation

Occurrence in OSSF wastewater. Only six articles investigated OSSF regarding the occurrence of ARG and MGE (Tan et al., 2021; Hayward et al., 2019, 2021; Park et al., 2016; Osińska et al., 2020; Ma et al., 2023). The most abundant ARG in raw and effluent wastewater were *ermB*, *qnrS*, *sul1* and *tetO*, as well as other genes encoding for multidrug,

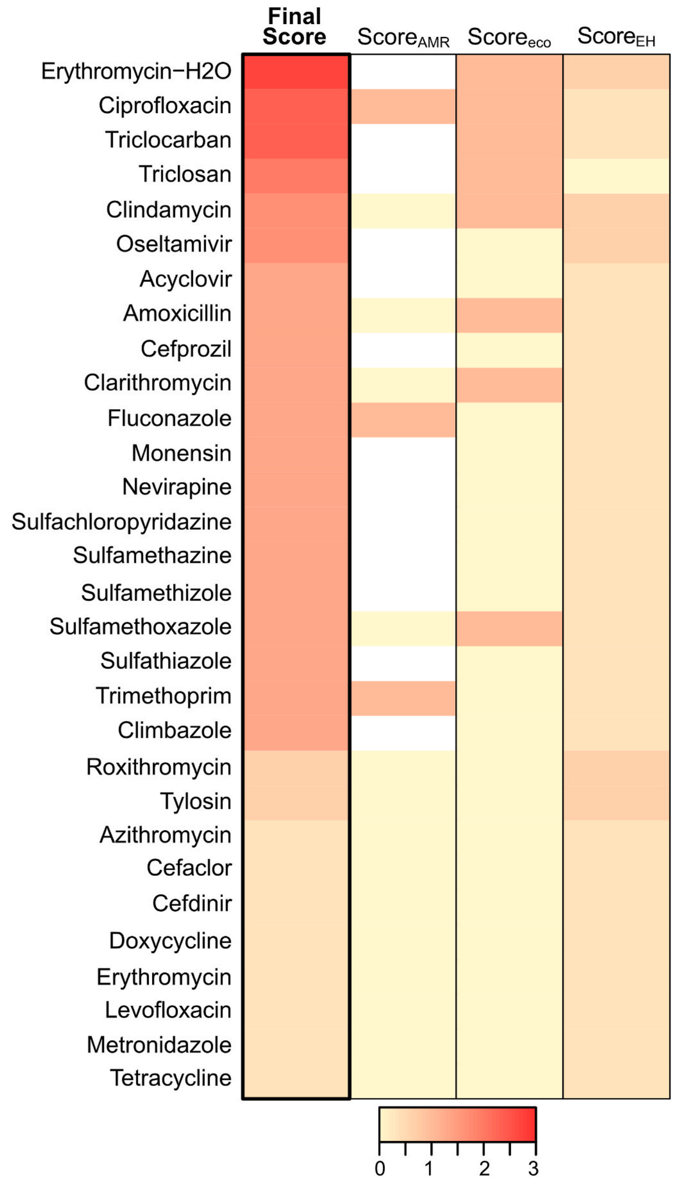

Fig. 3. Prioritization of antimicrobial chemicals in receiving waters based on the AMR selection risk ($Score_{AMR}$), ecological risk ($Score_{eco}$), and environmental hazard (persistence, mobility and bioaccumulation; $Score_{EH}$). White cells for $Score_{AMR}$ indicates that the $PNEC_{AMR}$ was not available, yet a $Score_{AMR}$ of 1 was given as conservative approach.

sulfonamides, beta-lactams (e.g., *bla_{TEM-1}*), aminoglycosides, macrolide-lincosamide-streptograminB (MLSB), chloramphenicol and bacitracin resistance (Hayward et al., 2019; Ma et al., 2023). Generally, the primary wastewater treatment in septic tanks did not reduce the loads of ARG (Tan et al., 2021; Hayward et al., 2019; Ma et al., 2023). Through metagenomic sequencing, enrichment of total ARG was observed in septic tanks' effluent water (Tan et al., 2021; Ma et al., 2023). Similarly, increased diversity and abundance of β-lactams resistance genes were also observed, suggesting that conditions in septic tanks are suitable for proliferation of these genes (Tan et al., 2021). However, this may not apply to all other ARG; for instance, no significant enrichment of *tetQ* was observed in a similar treatment setting (Park et al., 2016). The presence of *ermB*, *tetQ*, *tetO*, *sul1*, *bla_{TEM-1}* and *qnrS* in the effluent wastewater is concerning as they are classified in the highest risk category for AMR related to human health (Zhang et al., 2022), and some are linked to the usage of first-line antibiotics (e.g., β-lactams) (Tan et al., 2021; Jovetic et al., 2010). Similar occurrences of these ARG

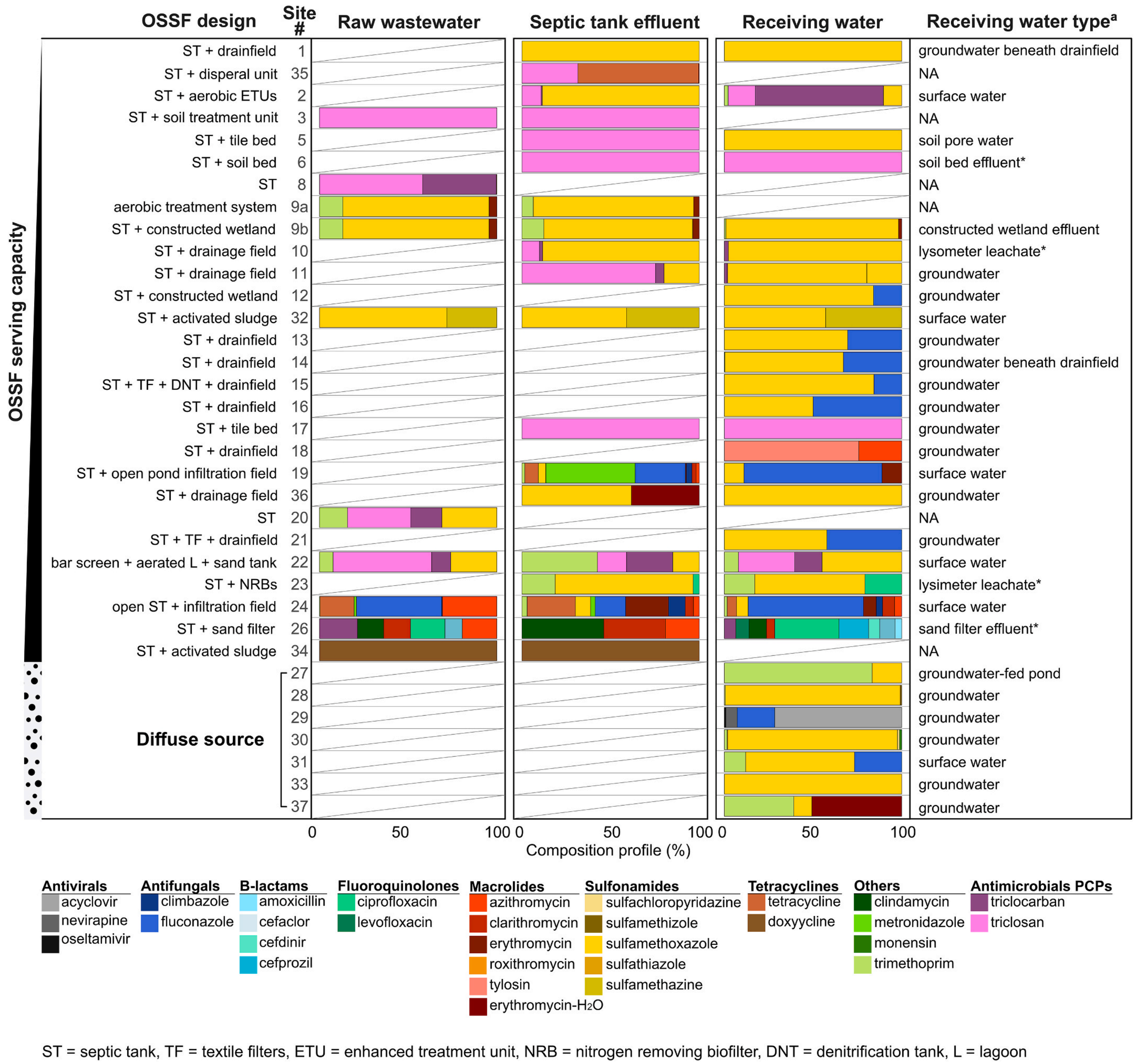

Fig. 4. Composition profiles of measured antimicrobial chemicals in raw wastewater, septic tank effluent and receiving waters. See Table S7 for details. [a] Downstream of OSSF. * For experimental facilities, effluent water was reported instead. NA, receiving waters were not sampled. "Site #" is referred to the site number listed in Table S11.

groups and their persistence over treatments are reported in centralized WWTP (Raza et al., 2022; Yoo and Lee, 2021; Pazda et al., 2020). This highlights that the potential of OSSF in contributing to AMR proliferation is equally important. For ARG-carrier MGE, *IntI1* was partially removed in septic tanks, and most multidrug-resistance-gene-carrier MGE were found in *Gammaproteobacteria* (Tan et al., 2021).

Occurrence in alternative OSSF wastewater treatments and the receiving environment. Additional wastewater treatment steps were used to improve the removal of the genetic contaminants. For *tetQ*, removal using peat bio-filtration was found efficient, but not with chlorination (Park et al., 2016). In combined treatments of anaerobic tank, biological aerated treatment and constructed wetland, about half of the total ARG abundance was eliminated (Ma et al., 2023). Sand filtration can also be a promising solution to ARG removals, with degradation and size-exclusion as the main mechanisms instead of adsorption (Hayward et al., 2019, 2021). Regardless of sand-particle sizes, ARG were generally retained in the upper layer of sand filters, although potential enrichment of resistant bacteria was observed in the lower layer of the filters (Hayward et al., 2021). In the downstream receiving waters, ARG conferring resistance to multidrug, MLSB, and bacitracin were generally found, though in lower abundances than those in the OSSF effluent wastewater, with the exception of multidrug-resistant genes exhibiting levels similar to those in the OSSF effluent wastewater (Ma et al., 2023).

Microbial community and AMR-related genetic contaminants. A previous study has observed no shift in microbial community composition during septic tank treatment (Tan et al., 2021). In addition, the bacterial class *Gammaproteobacteria* (gram-negative bacteria), including the families *Enterobacteriaceae* and *Pseudomonadaceae*, and the phylum *Firmicutes* (gram-positive bacteria) were found to be potential hosts for

ARG in OSSF systems (Tan et al., 2021; Ma et al., 2023). Some human pathogens belong to these classes and phyla, such as *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, which were the top six pathogens responsible for AMR associated deaths in 2019 (Murray et al., 2022). This suggests that OSSF systems could serve as reservoirs and vectors of these pathogens, with a potential of contributing to the development of AMR in such pathogens, posing risks to human health.

7. Potential influencing factors on AMR dissemination

OSSF serving capacity and treatment. Within the existing literature, the number of people connected to OSSF varied substantially, ranging from just a few to thousands of individuals (Fig. 4, Table S11). There seems to be a pattern showing that the diversity of antimicrobial chemicals occurring in OSSF systems and their associated receiving waters is in relation to the OSSF serving capacity (Fig. 4), where the greater the number of people connected to the system, the greater the diversity of chemicals. For example, less than 3 chemicals (e.g., triclosan, triclocarban, and sulfamethoxazole) occur in small OSSF (serving <20 individuals) in contrast with ~9 chemicals in large OSSF (serving >500 individuals) compiled herein (Fig. 4). Moreover, macrolides, fluoroquinolones, and beta-lactams are found in large OSSF systems, but not in small ones (Fig. 4). However, the correlation remains weak and the only significance ($p < 0.05$) is observed for the receiving water environment (Fig. S7). Similarly, serving capacity does not appear to be a factor influencing the concentrations of these chemicals in the OSSF settings, nor does it affect their potential risk for AMR selection or ecological risk in any of the (waste)water matrices, as no relevant correlations were found (Figs. S8–S10). Besides serving capacities, demographic variability can also be a factor contributing to the diversity of antimicrobial chemicals found in OSSF setting. For example, previous studies reported higher chemical diversity in OSSF serving non-residential areas (e.g., restaurants, hotels, schools) compared to OSSF serving residential areas (Fisher et al., 2016; Conn et al., 2006).

In most studies, OSSF were primarily used for the treatment of domestic wastewater (i.e., a mixture of blackwater and greywater) (Table S11), and in one case for blackwater treatment only (Tan et al., 2021). Commonly, OSSF consist of septic tank followed by infiltration fields. Primary treatment in septic tanks has limited removal efficiency, thus a large proportion of contaminant removal relies on the natural soil sorption capacities, mechanical filtration, and the biodegradation processes by the indigenous soil microbial communities (Gao et al., 2019). Hence, contaminant dissemination is linked to their degree of removal which is driven by the properties of both soil (e.g., texture, pH, cation exchange capacity) and contaminants (e.g., speciation, hydrophobicity) (Harrower et al., 2021). Alternative OSSF designs, which help reduce their disseminations, include the employment of additional, secondary treatment trains that use aerobic enhanced treatment units, package plants with trickling filters, or activated sludge with phosphorous removal, advanced aerobic treatment system, constructed wetland, textile filters, denitrification tank, aerated lagoons, nitrogen removing biofilters, and sand filters (Hayward et al., 2019; Subedi et al., 2015; Du et al., 2014; Li et al., 2013; Elliott et al., 2018; Vidal et al., 2023). Dissemination of antimicrobial contaminants could also depend on aquifer types, where shallow and unconfined aquifers are susceptible to their percolation from infiltration fields (Schaider et al., 2017).

Regardless of the serving capacities or applied treatments, the composition profiles (Fig. 4) of OSSF wastewater, both raw and effluent, are generally dominated by sulfamethoxazole, trimethoprim, triclosan, and triclocarban, while in the OSSF-impacted aquatic environment, sulfamethoxazole and fluconazole often constitute the larger proportions. Information on OSSF serving capacities and applied treatments are not always provided in the literature, especially in studies focusing only on their impacted receiving waters, in which OSSF are considered as diffuse sources (Fig. 4) (Schaider et al., 2014, 2016; Fisher et al., 2016; Gago-Ferrero et al., 2017; Standley et al., 2008). Here, sulfamethoxazole is again the predominant antimicrobial chemical, which was also previously identified as a micropollutant of global concern (Yang et al., 2022).

Seasonal effects. Enhanced dissemination of antimicrobial chemicals (e.g., triclocarban, sulfamethoxazole, trimethoprim) would likely occur during the winter season, as the overall removal efficiency of OSSF systems declines (Du et al., 2014; Li et al., 2013). This can be seen, for example, with trimethoprim, where limited and negative removal (−162 %) leads to its presence in downstream surface water in winter (Li et al., 2013). In contrast to antimicrobial chemicals, variations in the dissemination of AMR-related genetic contaminants appear to be less influenced by seasonal changes, as they are consistently present in OSSF with similar removal efficiency year-round (Hayward et al., 2021).

Other water parameters. Certain environmental water parameters can be associated with the dissemination of AMR contaminants, as reflected by their correlations (Kümmerer, 2009; Harrower et al., 2021; Ma et al., 2023; Felis et al., 2022). In the OSSF-impacted receiving waters, *vanR* was positively correlated with heavy metals but negatively correlated with pH and total organic carbon, while other highly abundant ARG (e.g., *sul1*, *sul2*, *ereA*, *tetC*, *aadA*, *qacEdelta1*) were positively correlated to total organic carbon (Ma et al., 2023). Similarly, total organic carbon, pH, temperature and light, can also influence the dissemination of antimicrobial chemicals (e.g., oxytetracycline, tetracycline and norfloxacin) in such receiving waters (Kümmerer, 2009; Harrower et al., 2021; Felis et al., 2022). These together suggest that water parameters are among the most important factors to consider when assessing the occurrence of AMR-related contaminants and their dissemination to receiving waters in OSSF settings.

Sampling methods. Although sampling is not a direct factor in the occurrence of antimicrobial chemicals in OSSF and receiving waters, it could influence the possibility of their detection and therefore, lead to artefact results. In most of the studies targeting antimicrobial chemicals, wastewater samples were collected in different seasons as grab samples, with a few exceptions where time- or flow-integrated sampling were used (Table S11). Grab sampling was always used for collecting recipient water samples. As usage of antimicrobial chemicals can be rather sporadic, grab sampling may not provide representative samples compared to flow-integrated sampling or high frequency time-integrated sampling. This is particularly important when sampling wastewater in small catchments (small numbers of households) (Ort and Gujer, 2006; Ort et al., 2010a, 2010b, 2014). This could possibly support the rather low detection rate observed with less than half (30) of the overall compiled antimicrobial chemicals (74) measured above their respective quantification limits or, in some cases, none of the targeted antimicrobial chemicals were detected (Carrara et al., 2008; Vidal et al., 2023). To reliably study the occurrence of antimicrobial chemicals in the future, seasonal variations, hydraulic retention time within sewer systems, and sampling methods are important factors to consider when developing sampling plans for OSSF settings. On the other hand, as AMR-related genetic contaminants are less fluctuating in abundances (Hayward et al., 2021), the reliability of studying their dissemination is less sensitive to the use of different sampling methods.

8. Identified knowledge gaps and remarks for future research

This review identified several aspects and knowledge gaps that are noteworthy for future research on OSSF.

OSSF terminology standardization. Throughout our literature review process, the wide variety of terminologies used to describe OSSF was a challenge in adequately retrieving articles from scientific databases and gaining information on design, performance, or OSSF guidelines worldwide. There is an urgent need for terminology standardization, as these difficulties could also prevent us from finding and replicating successful models. The use of terms such as *"on-site sewage facilities (OSSF)"* or *"on-site wastewater treatment (OSWT)"* (in line with the US EPA) is a potential suggestion, as they can comprehend a wide range of treatment designs. These terms are also clearly defined, allowing for differentiation from centralized (*off-site*) wastewater systems and facilitating their identification in systematic searches. Furthermore, the type of information on OSSF settings, as well as the degree and detail of reporting, greatly varies across the literature, especially on the serving capacity (households or population equivalences). This data is useful in understanding the trends of occurrence and fate of AMR contaminants in such settings, enabling inter-study comparisons, and ultimately supporting OSSF regulation.

More studies from different geographical locations. While OSSF are widely used in many countries (Schaider et al., 2017; Gao et al., 2019; Tan et al., 2021), there is a substantial knowledge gap in studying their impacts as a diffuse source of emission with AMR contaminants to the environment. In this review, the literature is from only seven countries and almost no studies or data from low- and middle-income countries, except two from China and one from Kenya (Table S2). In these countries, consumption of antimicrobial chemicals is often high and unregulated (Sharma et al., 2022; Otaigbe and Elikwu, 2023). We recognize the challenge of performing these studies consistently as we have a high disparity in sanitation services around the world (SDG sanitation ladder) (UNICEF, 2024). However, more studies on OSSF from other countries, beyond those found in this review, are needed to better understand their environmental impacts as a diffuse source of AMR contaminants.

Better sampling strategies. Given the sporadic occurrence of AMR chemicals in OSSF treating only household wastewater, there is a need to increase sample representativeness and extend the detection window. Where possible, future research should prioritize the use of time-integrated sampling in high frequency or flow-integrated sampling while accounting for seasonal variation (recurring sampling campaigns). Additionally, sampling wastewater at both inlet and outlet of the OSSF would provide a better understanding of OSSF's overall performance in removing AMR contaminants, as most studies lack raw wastewater sampling (Fig. 4).

Increasing knowledge on AMR-related genetic contaminants. Apart from antimicrobial chemicals, in order to study AMR in a holistic approach, in accordance with the One Health concept, it would be better to consider microbial contamination as well. There is a substantial knowledge gap in studying occurrences and removals of AMR-related genetic contaminants (i.e., ARG, MGE, integrons) in OSSF, with only six studies, out of 33, investigating this. Among these studies, ARG results are reported in different measuring units, including relative abundances expressed as copy/cell or ppm, and absolute abundances as gene copies/mL. This, became a challenge for this review in performing inter-study comparison of ARG abundances. For future studies, with quantitative PCR, ARG results as absolute abundances in the unit of gene copies/mL will be highly useful, for example, enabling human risk assessment for ARG uptake via drinking water (Gros et al., 2023; Gao et al., 2020). Because of the interdisciplinary nature of AMR, studies targeting both antimicrobial chemicals and AMR-related genetic contaminants are encouraged where feasible to improve the overall understanding of AMR.

Further investigation of the potential for water reuse. There is an interest, although this is still very limited, in the potential of reusing the OSSF effluent water for irrigation (Park et al., 2016; Ma et al., 2023). However, the water quality (Park et al., 2016; Ma et al., 2023) did not meet the requirements for reuse, due to the presence of pathogens and ARG. The reuse potential of OSSF effluent remains challenging as the existing designs with either septic tanks, peat biofiltration, or batch chlorination (Park et al., 2016; Ma et al., 2023) cannot ensure an efficient removal of harmful contaminants and pathogens. Further investigation is needed in this context, as water reuse may be particularly relevant in areas that are subjected to droughts.

9. Conclusions

Neglecting OSSF as source of AMR contaminants could lead to major human health consequences, thus understanding their role in environmental spreading of AMR is highly relevant. Available data indicates that antimicrobial chemicals (e.g., sulfamethoxazole, fluconazole) and AMR-related genetic components still occur in effluent wastewater and receiving waters, despite OSSF treatment. While concentrations are reduced compared to untreated wastewater, they remain high enough to pose ecological risks and contribute to resistance selection in aquatic microorganisms. This highlights the inefficiency of current OSSF designs in sufficiently removing AMR contaminants and implies a negative impact of OSSFs on the receiving waters. Additionally, there is both a low number of studies and spatial coverage emphasizing that OSSF are a neglected source of AMR. We encourage more research to further understand AMR contaminants' occurrences and removal in OSSF, which will be crucial for informing future wastewater treatment policies and improving regulation and design of these systems.

CRediT authorship contribution statement

Valentina Ugolini: Writing – original draft, Visualization, Investigation, Formal analysis, Data curation, Conceptualization. **Uzair Akbar Khan:** Writing – review & editing, Validation, Supervision, Methodology, Conceptualization. **Paul Löffler:** Writing – review & editing, Methodology. **Francis Spilsbury:** Writing – review & editing, Methodology, Data curation. **Foon Yin Lai:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization.

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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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jenvman.2025.126528.

Data availability

Data will be made available on request.

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