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Review

Household Disposal of Pharmaceuticals in Low-Income Settings: Practices, Health Hazards, and Research Needs

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Abstract: Pharmaceuticals are widely used in Africa due to the high burden of human and animal diseases. However, a review of the current practices and pollution risks arising from the disposal of pharmaceuticals in low-income settings in Africa is still lacking. Therefore, the present review examined the literature to address the following questions: (1) what are the key factors driving the accumulation of unused and expired pharmaceuticals?, (2) what are the current disposal practices for unused and expired pharmaceuticals, and wastewater (feces and urine) containing excreted pharmaceuticals?, (3) what are the potential environmental and human health hazards posed by current disposal practices?, and (4) what are the key research needs on the disposal of pharmaceuticals in low-income settings? Evidence shows that, in low-income settings, wastewater comprising predominantly of feces and urine containing excreted pharmaceuticals often end up in on-site sanitation systems such as pit latrines, septic tanks, and the environment in the case of open defecation. Unused and expired pharmaceuticals are disposed of in pit latrines, household solid waste, and/or burned. The pollution risks of current disposal practices are poorly understood, but pharmaceutical pollution of groundwater sources, including those used for drinking water supply, may occur via strong hydrological connectivity between pit latrines and groundwater systems. Potential high-risk pollution and human exposure hotspots are discussed. However, compared to other environmental compartments, the occurrence, dissemination, fate, and human health risks of pharmaceuticals in the pit latrine-groundwater continuum are still understudied. Future research directions are discussed to address these gaps using the Source-Pathway-Receptor-Impact-Mitigation (SPRIM) continuum as an organizing framework.

Keywords: unused pharmaceuticals; expired pharmaceuticals; disposal practices; pharmaceutical pollution; pit latrines; hydrological connectivity; low-income countries; environmental hazards; human health hazards

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1. Introduction

A wide range of pharmaceuticals is widely used in animal and human health care in both high- and low-income countries. For example, predictions show that in 2020 alone, approximately 4.5 trillion doses of pharmaceuticals were used globally [1]. Efforts to improve animal and human health have witnessed an increase in the consumption of pharmaceuticals in low and middle-income countries. Moreover, following the global spread of COVID-19 in 2020, a rapid increase in the consumption of pharmaceuticals has been witnessed [2,3]. However, the increased use of pharmaceuticals has potential unintended impacts, including (1) the accumulation of unused and expired pharmaceuticals and (2) the

increased release of pharmaceutical wastes into the environment and their associated ecological and human health risks [2]. However, studies on the latter tend to dominate in the literature compared to those investigating unused and expired pharmaceuticals.

The accumulation of unused and expired pharmaceuticals has attracted significant global research and policy attention, with early studies being conducted in the context of developed countries [4–6]. Several reviews focusing on developed regions or specific high-income countries in Europe and North America also exist [7–9], while other studies provide a global overview [10,11].

Research interest in unused or expired pharmaceuticals has been recently increasing in low and middle-income countries. For example, a number of studies have investigated the occurrence and disposal of unused and expired pharmaceuticals in low- and middle-income countries located in (1) Africa [12–18], (2) Asia [19–24], (3) South/Latin America [25,26], (4) Caribbean and Pacific regions [27,28], and Eastern Europe (e.g., Bulgaria, [29]; Romania, [30,31]. These studies show the increasing research and public interest in the subject.

The USA and various European countries adopted the disposal of unused or expired pharmaceuticals through take-back locations, which are available in retail, hospital, clinical pharmacies, or law enforcement facilities [32,33]. Periodically, additional temporary take-back sites are established for annual events such as National Drug Prescription Day [33]. Moreover, if the take-back option is not readily available, the FDA has published a list of pharmaceuticals (encompassing 15 active ingredients) that can be flushed down in the sink or toilet. The medicines on this list include those that can result in death from one dose if inappropriately taken and sough-after their misuse/and/or abuse potential [34]. As assessed, pharmaceutical ingredients on the FDA's "flush list" present negligible risk through the ingestion of water and fish [34,35]. Methods of final disposal of pharmaceuticals can differ depending on the type and form of medicines. World Health Organization provides the guideline on these methods that encompass high (>1200 °C) or medium ($\geq$850 °C) temperature incineration, immobilization by waste encapsulation or inertization, landfill disposal through highly engineered sanitary landfill, fast-flowing watercourse, and chemical decomposition [35]. Disposal of pharmaceuticals through a sewer, open non-engineered dump, or burning in open containers is considered the last resort method for some medicines [35]. However, compared to high-income regions such as Western Europe and North America, limited information exists on the disposal of pharmaceuticals in low-and middle-income countries.

Therefore, the present paper investigates the present disposal practices of unused and expired pharmaceuticals and their potential health risks focusing on low-income settings. For the purpose of this review, these settings also include those in middle-income countries. This is because, unlike in developed or high-income countries, even in middle-income countries such as South Africa and Brazil, many households have socio-economic status and lifestyles typical of those in low-income settings [36]. Such low-income settings often lack: (1) proper solid waste and wastewater management systems, (2) access to clean drinking water, (3) comprehensive environmental surveillance, and (4) knowledge of global best practices in the use and disposal of hazardous wastes such as systematic take-back programs for unused and expired pharmaceuticals.

The present review focusing on the household seeks to address the following questions; (1) what are the key factors driving the accumulation of unused and expired pharmaceuticals?, (2) what are the current disposal practices for unused and expired pharmaceuticals, and those used and finally excreted?, and (3) what are the potential environmental and human health hazards posed by current disposal practices? Finally, future research directions are discussed to address these gaps using the Source-Pathway-Receptor-Impact-Mitigation (SPRIM) continuum as an organizing framework. The SPRIM continuum framework has been proposed as a powerful conceptual tool for identifying well-studied aspects of emerging contaminants relative to under-studied ones [37]. In this regard, the available evidence was examined to track pharmaceuticals along the SPRIM continuum in order to identify aspects that are poorly studied. Figure 1 presents a summary of the focus of the present

paper, including; (1) factors driving the accumulation of unused and expired pharmaceuticals, (2) disposal practices, (3) environmental and human health hazards, (4) mitigation and control measures, and (5) future research directions.

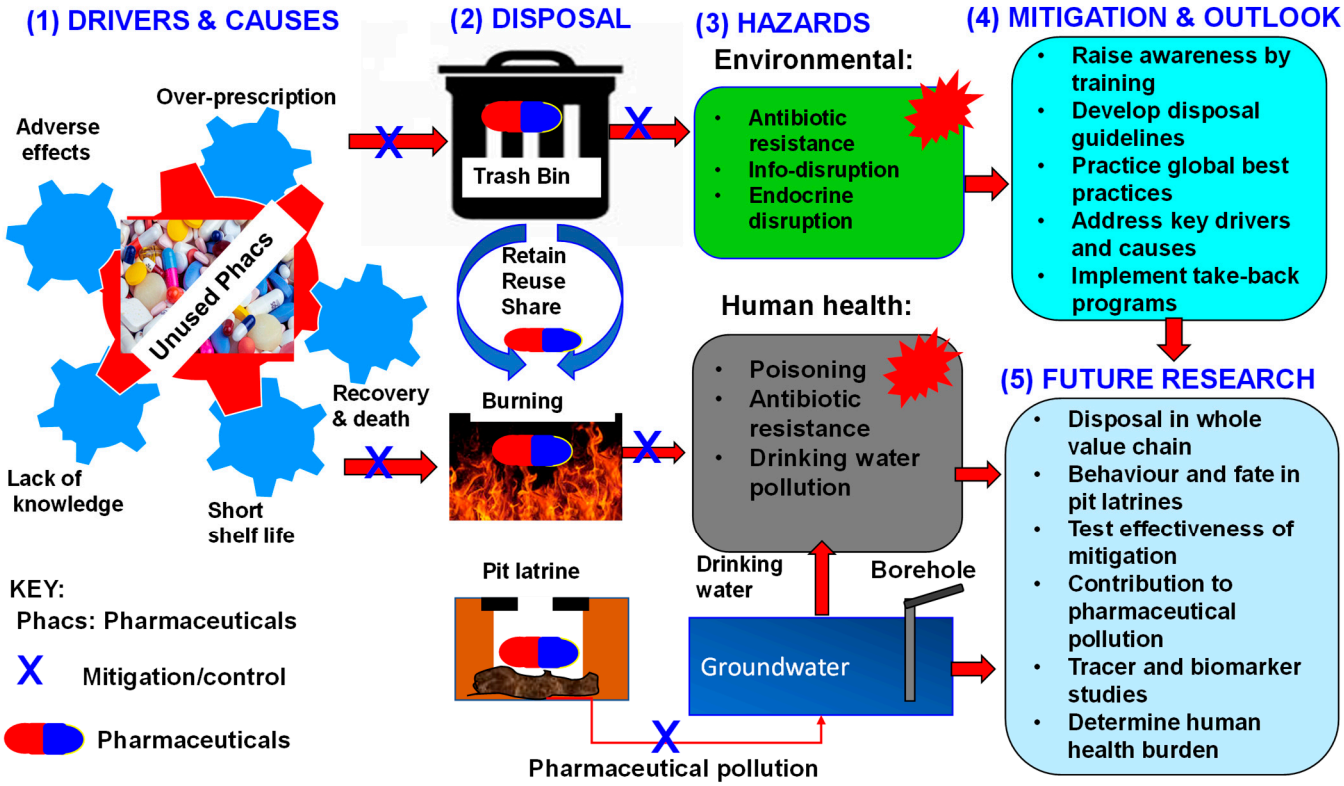

Figure 1. Summary depiction of the key findings highlighting: (1) factors driving the accumulation of unused and expired pharmaceuticals, (2) disposal practices, (3) environmental and human health hazards, (4) mitigation and control measures, and (5) future research directions.

2. Materials and Methods

The present review applied a semi-quantitative approach combining: (1) Boolean searches and retrieval of articles from scholarly databases (Google Scholar, Web of Science, Scopus, ScienceDirect) and (2) subsequent qualitative screening and analysis of the evidence. The Boolean searches were conducted at two levels: (1) the retrieval of literature pertaining to disposal practices of unused and/or expired pharmaceuticals and (2) putative evidence on the occurrence of pharmaceuticals in on-site sanitation systems and their impacted aquatic environments. The search process covered the period 2000 to date (2022), but the first empirical studies were published from 2006 onwards. Since the search was limited to English scholarly databases, the study may have excluded studies published in non-English Languages.

2.1. Disposal of Unused and Expired Pharmaceuticals

The databases were searched using search strings combining pharmaceuticals AND/OR disposal AND/OR and unused/expired AND/OR low-income countries and their variants. The specific search terms used were as follows:

(i) Pharmaceuticals: 'pharmaceutical(s)' 'antibiotics', 'medicine(s)', 'medication(s)', 'pharmaceutical products', 'drug(s)',
(ii) Disposal: 'disposal', 'dispose', disposing' 'discarding'
(iii) Unused/expired: 'unused, expire(d), 'unwanted', 'excess', 'left(-)over', 'outdated', 'out-of-date', 'stale', 'obsolete'

(iv) Low-income settings: low-income countries/regions, southeast (Asia), South/Latin America, Africa/sub-Saharan Africa, Caribbean(s), Pacific region(s), and specific countries in the various low-income regions.

2.2. Linking Pharmaceutical Pollution of Aquatic Environments to On-Site Sanitation Systems

A second literature search was conducted to putatively link pharmaceutical pollution of aquatic systems to on-site sanitation systems, and to infer environmental and human health risks. To achieve this, the following search terms were combined with those for pharmaceuticals to account for on-site sanitation systems AND/OR aquatic pollution:

(i) On-site sanitation: "on-site sanitation", "pit latrine(s)" "flying toilet(s)", "bucket toilet", "septic tank(s)", "cesspool". Due to limited studies documenting pharmaceuticals in on-site sanitation systems in low-income settings, the articles were supplemented with those detecting pharmaceuticals and their metabolites in putative on-site sanitation media, including "feces", "fecal", "fecal sludge", "fecal effluent", and "urine".
(ii) Aquatic systems: "aquatic", "water", "surface water", "groundwater", "aquifer", "river(s)".

Note that the present paper is not meant to be a fully quantitative review based on bibliometric or meta-analytic methodology. Instead, the Boolean search technique was meant to extract the bulk of the evidence to address the study objectives. Thus, in both search stages, the individual articles were qualitatively screened and verified to determine their relevance to the study objectives, and irrelevant ones, including reviews, were discarded. The remaining original articles were reviewed, and the key findings were tabulated (Tables 1 and 2).

Table 1. Summary of household disposal practices for pharmaceuticals reported in Africa.

Country	Methodology	*n*	Main Findings and Remarks on Disposal Practices	Reference
South Africa, Johannesburg area	Online survey based on self-administered questionnaires	371	- 77% claimed that they have some knowledge about the disposal of household pharmaceutical wastes. - 11% flushed their unused medicines in toilet drains and kitchen sinks.	[38]
Tanzania	The cross-sectional interview study of household members.	359	- 70% had medications kept in their houses at the time of data collection. - 4% households had kept medications at their houses because they were still continuing with treatment, while 96% kept unused medications that were supposed to be discarded. - The major discarding practices for medications were disposing of domestic trashes (76%) and pit latrines (16%). - Majority of respondents (76%) were aware that improper disposal of expired medications is generally harmful to human health and the environment	[39]
Nairobi City—the capital of Kenya.	A cross-sectional study of household residents involving quantitative and qualitative methods	164	- Knowledge of disposal practices of unused medicines was relatively weak and attributed to a lack of public outreach and awareness campaigns. - Participants had different perceptions on what they consider as safe disposal practices of unused medicines: throw in garbage bins (28%), flush in the toilet (25%), special garbage bins (17%), burry (14%), burn (9%), take-back programs (4%),	[40]
South Africa	A descriptive study of healthcare professionals (HCPs) at 16 primary healthcare clinics	165	- 24% of HCPs stated they participated in the destruction of medicines within their facilities. - 58% reported they always counsel patients regarding the safe storage of their medicines in their homes. - 28% indicated they counsel patients on the safe disposal of their medicines during consultations. - 65% reported that patients never asked about the disposal of medicines. - Disposal methods regarded by HCPs as appropriate were incineration (32%), flushing down the toilet (21%), and flushing down the sink (10%).	[18]
South Africa	A descriptive and quantitative study with patients among 16 primary healthcare clinics	171	- 75% of patients reported having unused medicines at home, and 35% wanted these medicines disposed of. However, 65% did not know how to dispose of them, while 95% reported never being informed by healthcare professionals in this regard. - Results showed that currently, patients flushed medicines down the sewer (32%) or disposed of them in municipal bins (24%)	[18]
Southern Ghana	A cross-sectional questionnaire survey of household members	600	- 80% and 89% of respondents discarded unwanted medicines and sharps in household refuse bins, respectively - 23% and 35% of respondents discarded these items without a container.	[41]

Table 1. *Cont.*

Country	Methodology	*n*	Main Findings and Remarks on Disposal Practices	Reference
Maiduguri metropolis, north-eastern Nigeria.	A cross-sectional, population-based survey employing a pre-validated questionnaire	1010	- 35% of the participants kept unused/unwanted medicines at home for future use/until expiration. - 60% of the study population got rid of expired medicine through household garbage. - 1% buried unwanted/unused medicines in the ground as a way of disposal.	[42]
KwaZulu Natal, South Africa	A descriptive, cross-sectional, quantitative study of HIV-positive patients and their caregivers employing a self-administered questionnaire	484	- 87% of the participants knew that improper disposal of medicines was harmful to the environment, with only 28% aware there were laws governing how medicines should be disposed of. - The most common route of medicine disposal for ARVs was throwing these medicines into the bin (56%). - Only 24% of participants were informed by healthcare professionals about the proper method of medicine disposal.	[17]
Lusaka, Zambia	A cross-sectional study of students interviewed face-to-face	385	- Throwing unused and expired medicine in household garbage bins was the most frequently used disposal practice (60%), followed by flushing them in the toilet/sink (33%). - Only 4% reported returning unused and expired medicines to the nearest pharmacy.	[43]
Anambra State, southeast Nigeria	A questionnaire survey of pharmacies	77	- Disposal methods were: through a national medical agency (32%), drug distributors (24%), and rubbish bins (9%); this was mainly for solid dosage forms. - 7% reported that they used the sink to dispose of their liquid dosage forms - Only 23% complied fully with the national guideline on the disposal of expired drugs	[44]
Kisumu, Kenya	A random cross-sectional sample of households	447	- 32% disposed of the remainder of the antibiotics in pit latrines and compost pits (10%), while 4% disposed of through burning.	[45]
Ashanti Region of Ghana	Residents were surveyed by anonymous questionnaires using a random sampling technique	500	- Over 98% declared they had never received any information about proper medication disposal. - Almost all respondents (98%) reported having medications in the home they wished to dispose of. - The most common method of disposal of unused, unwanted, or expired medications was to throw them in the waste bin (29%), dig a hole in the ground and bury the medication (38%), flush the medication down the toilet or sink (4%).	[46]
Thekwini area, South Africa	Questionnaire survey of randomly selected residents	200	- Medicines were mainly disposed of by throwing them away (63%).	[47]

Table 1. *Cont.*

Country	Methodology	*n*	Main Findings and Remarks on Disposal Practices	Reference
Lagos State, Nigeria	A descriptive cross-sectional questionnaire-based study of residents	534	- 78% of participants have not received advice on pharmaceutical waste from health professionals. - 73% of participants admitted to throwing unused medicines away in household garbage.	[15]
South C area, Nairobi City County, Kenya	Quantitative data collection methods, through semi-structured interviews of household residents	164	- 85% of the respondents still opted to keep unused medicines at home. - The study found that 96% of the respondents did not receive adequate information from healthcare providers related to the safe disposal of unused medicines and did not read or follow unused medicines disposal instructions.	[40]
Dodoma City, Tanzania	A descriptive, cross-sectional survey using face-to-face interviews of household residents	100	- 83% of the respondents reported not receiving any information on safe disposal practices. - The study also found that throwing into garbage bins was the most preferred disposal method.	[48]
Mizan-Aman, Southwest Ethiopia	A descriptive cross-sectional study of residents	374	- 98% of respondents had never heard about the drug-take-back system, and 96% had never received any information about how to dispose of unused and expired medication. - The most preferred disposal practice of expired medications was to throw them with garbage (80%).	[49]
Sunyani Municipality, Ghana	A descriptive cross-sectional of residents	400	- Household respondents disposed of unused and expired medications mainly by dumping them in garbage cans (71%), incineration (12%), and flushing down the sink (9%).	[14]
Nakuru Town, Kenya	A social survey of household residents	384	- 78% of the respondents did not know pharmaceutical waste handling and management. - 80% have never received any information on how to dispose of unwanted pharmaceuticals.	[50]
Adigrat City, Northern Ethiopia	A cross-sectional study	359	- 50% had good knowledge concerning the disposal of unused and expired pharmaceuticals. - 82% of the respondents have a positive attitude toward the disposal of unused and expired pharmaceuticals.	[51]

Table 2. Summary of household disposal practices for pharmaceuticals in Southeast Asia, Latin America, the Caribbeans, and the Pacific region.

Country	Methodology	*n*	Main Findings and Remarks on Disposal Practices	Reference
A: Southeast Asia				
Quetta city, Pakistan	A cross-sectional questionnaire-based survey of residents	830	- 87% of the respondents kept unused medicines at home, and 50% kept them for reuse- - The proper procedure to dispose of nearly - Expired or expired medicines were unknown to 88% of the respondents. - Medicines were disposed of either in household trash or flushed in the toilet or sink. - Medicines were kept at home even after being expired by 27% of the respondents.	[52]
Malaysia	Interviews with patients	28	- 57% disposal method was throwing unused medication into the trash. - 55% of the participants were not aware of the bad effect of unused medication.	[53]
Malaysia	Questionnaire survey of students	885	- 87% of the participants knew about drug waste, but only 2% of them followed the drug take-back system. - 83% of the participants disposed of unwanted medicines in the landfill.	[54]
Malaysia (Rawang)	Questionnaire survey of parents of school-aged children	384	- 70% of the respondents were not aware of medication waste. - Majority of them (74%) turf out medication waste into the trash bin	[55]
Malaysia (Selangro)	Questionnaire survey of household residents	103	- 83% of participants stated that information on the proper disposal of pharmaceuticals is insufficient - 50% of the participants disposed of pharmaceuticals in trash bins, & flushed them in the sink or toilet, and 25% returned them through the take-back program	[56]
Malaysia	Questionnaire survey of residents	354	- Most participants (94%) knew that improper drug disposal harms the environment. However, their knowledge was low (11%) regarding the disposal of pressurized metered-dose inhalers in the garbage.	[57]
Pakistan (Karachi)	Questionnaire survey of students	1022	- The predominant method of disposal of expired medications was through a dustbin (82.8%); 82% of the respondents do not know what should be done with the unused medications, so until they expire, they store them.	[58]
South India	Questionnaires survey and face-to-face semi-structured interviews with medical doctors & nurses	480	- 83% of respondents were not aware of the consequence of drug disposal in the environment. - 46% disposed of unused medicines in the dustbin.	[59]

Table 2. *Cont.*

Country	Methodology	*n*	Main Findings and Remarks on Disposal Practices	Reference
A: Southeast Asia				
India	Interviews with patients	56	- Unused medications were thrown in the trash (57%). - 55% of the participants admitted not knowing the harmful effect of unused medication.	[60]
North India	Questionnaire survey of dental students	236	- 46% of participants acknowledged that they were not aware of drug environment interaction - The primary mode of drug (unused or expired) disposal was trashing (94%)	[61]
South India	Interviews with patients	158	- 65% of patients were unaware of the risk of inappropriate disposal of pharmaceuticals. - 64% disposed of pharmaceuticals in the dustbin/trash (64%).	[62]
North India	Questionnaire survey of pharmacists	84	- 90% of the participants had some medication stored at home. - Regardless of the dosage form, the most common method was disposing of via dustbin	[63]
South India	Face-to-face interviews with pharmacists	127	- 64% of the participant were not aware of the environmental hazards of disposal of unwanted medicines by throwing them in the trash (35%)	[64]
India	An observational, cross-sectional, questionnaire-based study of medicine consumers	956	- Most consumers (87%) stored medicines at home. Almost all of them (93%) threw away expired medicines after storing them for a few days. Consumers discarded expired medicines mainly in household trash (73%).	[20]
Thailand (Khon Kaen city	Interviews with villagers	331	- Most participants (73%) supported that the drug take-back program could be used to manage leftover drug issues. However, most of them (89%) mentioned that they were not being taught about safe drug disposal.	[65]
Nepal (Pokhara)	Semi-structured questionnaires; Interview; Observation checklist to 54 pharmacy supervisor	54	- 52% of the participants disposed of their medication waste in the municipal dump; they were lack of awareness about the impact of disposing of medicinal waste	[66]

Table 2. *Cont.*

Country	Methodology	*n*	Main Findings and Remarks on Disposal Practices	Reference
A: Southeast Asia				
Nepal (Butwal)	Multi-stage random sampling technique was done, and an interventional study was conducted on undergraduate paramedical students through a self-administered questionnaire	150	- Among the disposal practice of unused medicines, 33% gave them to friends or relatives, 28% kept unused till expiry. - 33% disposed of the expired medicines through flush, 32% threw away in household garbage.	[67]
Bandung, Indonesia	A descriptive cross-sectional survey conducted among 497 respondents	497	- The most common disposal method of unwanted medicines was throwing away in household garbage (82%). - Approximately 95% of the respondents had unused medicines stored in their homes, with nonsteroidal anti-inflammatory drugs, vitamins/nutritional supplements, and antibiotics being the most common types of medicines left unused.	[68]
B: South/Latin America				
Peru	The hypothetical-deductive quantitative approach based on a questionnaire survey of 385 households	385	- 48% of the respondents had an average level of knowledge of how to dispose of medicines. Only 3% of the respondents have a positive attitude towards the disposal of medicines, and there is a relationship between the level of knowledge and attitude towards the disposal of medicines.	[25]
Ecuador	A cross-sectional study of students	498	- Data show that up to 30% of students had flushed their medicines down the toilet at least once, while 7% acknowledged that they had removed the medicines from their packaging to deposit them in a household garbage disposal.	[69]
Brazil	An online survey of residents from different country areas	540	- 66% of respondents disposed of the disused or expired medicines in the garbage. - 72% of respondents never received any information about the appropriate disposal of medicines.	[70]

Table 2. *Cont.*

Country	Methodology	*n*	Main Findings and Remarks on Disposal Practices	Reference
B: South/Latin America				
Brazil (southern region)	A descriptive and quantitative study of residents	309	- 70% of participants had expired pharmaceuticals at home. - 70% discarded pharmaceuticals in domestic waste, 11% flushed them in the toilet or sink, 7% returned them to healthcare clinics, and 4% to pharmacies. - Only <15% of the participants adequately disposed of their medication waste.	[71]
Itapetininga City, São Paulo State, Brazil	A cross-sectional study of patients	182	- Only 3% appropriately disposed of medications, 62% kept them for further use, 10% gave them away to neighbors, friends, and relatives	[72]
C: Caribbean & Pacific regions				
Solomon Islands	A questionnaire survey of healthcare facilities	22	- Expired drugs were stocked in surveyed facilities - 55% had stocks of expired oral rehydration solutions, 15%—albendazole, 5%—vitamin A	[28]
Trinidad Islands	A questionnaire survey of patients	547	- Disposal of unused/expired medication via household trash was the most commonly encountered practice (86%).	[73]

3. Results

3.1. What Drives the Accumulation of Pharmaceuticals at the Household Level?

The disposal of pharmaceuticals occurs along the whole value chain from production, logistics, and healthcare facilities up to households. The present paper focuses on disposal practices at the household level. This is because limited knowledge of global best practices in low-income settings, coupled with local attitudes and practices, promotes poor and unsafe disposal of pharmaceuticals. Thus, the household level could be considered a hotspot compared to other points along the pharmaceutical value chain. Households are more widely distributed than other points in the value chain, such as manufacturing plants, warehouses, health facilities, and pharmacies. Thus poor and unsafe disposal is likely to result in broader dissemination of active pharmaceutical ingredients to the environment.

The factors driving the accumulation of pharmaceuticals at the household level in low-income settings are still poorly understood. A few studies conducted in the context of developed countries have investigated the factors driving the accumulation of unused or expired pharmaceuticals at the household level [4–6]. The key potential driving factors highlighted in these investigations include; (1) imprudent prescribing or over-prescription, where patients are given more pharmaceuticals than required, and (2) discontinued medications following the recovery or death of a patient. Prescriptions uncompleted due to various reasons, including poor compliance by patients, non-effectiveness, and/or adverse reactions, may also contribute to the accumulation of pharmaceuticals. In some cases, pharmaceuticals approaching their expiry date, hence with a short shelf life, are distributed to healthcare centers and pharmacies and ultimately sold or dispensed to individuals. Such pharmaceuticals are likely to expire before the patient completes the prescription. Further work is required to understand and rank the key driving factors in low-income settings, including the role of knowledge, attitudes, and practices.

In the present review paper, there is a distinction between excess, unwanted, or residual but valid pharmaceuticals, hereafter collectively referred to as "unused", and those that are out-of-date or expired. This is because disposal practices may differ between unused and expired pharmaceuticals. For example, in the literature, in some cases, the former is sometimes retained for future use or shared or returned to the drugstore [74–76], while the latter is disposed of right away [45,77]. For completeness, the disposal of used pharmaceuticals, which are finally excreted in feces, urine, and sweat as parent compounds or metabolites, is discussed.

3.2. Unused Pharmaceuticals

As discussed earlier, unused but unexpired pharmaceuticals may accumulate for several reasons, including the change or discontinuation of medications due to adverse reactions or recovery of the patient or holder. In the literature drawn from the African region, various disposal practices are used for unused pharmaceuticals (Table 1). Similar practices have been reported in the literature from Southeast Asia, Latin/South America, the Caribbeans, and the Pacific region (Table 2). Because such unused pharmaceuticals will still be valid, they are often retained and kept at the household level for future administration. This practice has been reported in a number of studies conducted in low-income countries [75,78]. For example, in a survey conducted in Iraq, approximately 65% of the respondents indicated that they retained unused pharmaceuticals for future use [78]. In other studies, unused pharmaceuticals were shared with family members, acquaintances, and friends [76], while others donated them to the poor who cannot afford them e.g., in India [79]. However, the bulk of the studies investigating the disposal of pharmaceuticals does not separate between unused but valid pharmaceuticals and those that have expired but rather lump the two together as unused or unwanted without indicating whether they are expired (Table 1). Consequently, some other disposal practices are reported for unused pharmaceuticals, but it is unclear whether they were expired (Table 1).

3.3. Expired Pharmaceuticals

Expired pharmaceuticals accumulate due to several reasons, including dispensing of medicines close to their expiry and with short shelf-lives or due to over-prescription. A number of disposal practices for expired pharmaceuticals are reported in the literature from Africa (Table 1), Southeast Asia, Latin/South America, the Caribbean, and the Pacific region (Table 2). In addition, many studies from low-income settings, including from Africa, report the disposal of expired pharmaceuticals in pit latrines [38,45,80]. A study conducted in South Africa showed that this practice is common in rural healthcare facilities such as clinics [81]. In other studies, the use of pit, including those used to make compost, have been reported as a disposal practice for expired pharmaceuticals [45], while in other studies burning has been reported [11,82]. The disposal of expired pharmaceuticals with household solid waste has also been reported [21]. For example, in Kabul, Afghanistan, a study based on a survey indicated that 77% of the respondents discarded expired pharmaceuticals wastes in household trash or rubbish [21]. For liquid pharmaceuticals, flushing in toilets has been reported in a number of countries, including Pakistan [52,58], Ethiopia [51], and Ghana [14]. Flushing in the sewer system is not limited to low-income countries, as it has also been reported in developed countries such as the USA [35] and Europe [83,84]. For example, the US FDA developed a list of pharmaceuticals that can be flushed for immediate disposal (if a take-back program is not readily available due to logistical constraints) that encompass selected drugs that are harmful and even fatal with just one dose if not used as prescribed [34,35]. Table 1 presents other disposal practices for expired pharmaceuticals reported in low-income settings.

3.4. Household Wastewater Containing Pharmaceuticals

A large proportion of the used pharmaceuticals are excreted in feces, urine, and sweat as parent compounds and/or their metabolites [2,85]. Barreto [86], discuss the absorption, distribution, metabolism, and excretion (ADME) process of pharmaceutical drugs following intake. Here, it suffices to state that, in low-income settings, pharmaceutical parent compounds and their metabolites excreted in feces and urine into wastewater often end up in the sanitation system. In low-income settings lacking access to centralized wastewater systems, this includes on-site sanitation systems (pit latrines, septic tanks, cesspools), bucket toilets, and even the environment in the case of flying toilets and open defecation. However, globally, the pit latrine is the most common on-site sanitation system in low-income countries. For example, estimates show that approximately 1.8 billion people use pit latrines for basic sanitation, the bulk of them in low-income regions of Africa, Asia, Latin/South America, the Caribbean, and Pacific regions [87,88]. Daily, approximately 600 million kg of feces and 2.1 billion kg of urine are deposited in pit latrines. Therefore, on a global scale, given its function as a receptacle for unused, expired, and used pharmaceuticals, the pit latrine represents a major pharmaceutical reservoir. Yet as discussed later in Section 4.3, in low-income settings, pit latrines are often connected to groundwater systems serving as drinking water sources through the exchange of water and the associated contaminants, including pharmaceuticals.

4. Health Hazards

4.1. Environmental and Ecological Hazards

Pharmaceuticals pose severe environmental and ecological hazards, and these have been the subject of some original studies and reviews [89,90]. The environmental and ecological hazards posed by pharmaceuticals depend on several factors, including their inherent chemical features, concentration, exposure dose, environmental parameters (e.g., pH, temperature, microbial communities), and the receptor organisms and their characteristics [91,92]. For example, the occurrence of antibiotics in the environment contributes to the emergence of antibiotic resistance in previously susceptible bacteria [91]. In fact, a few studies suggest that the poor and unsafe disposal of unused and expired pharmaceuticals, such as antimicrobials/antibiotics, drives antimicrobial/antibiotic resistance [93,94].

Numerous papers, including reviews, show that exposure to pharmaceuticals also causes acute and chronic toxicity in terrestrial and aquatic organisms [91,92,95]. For example, some pharmaceuticals are endocrine-disrupting compounds [96,97]. In addition, pharmaceuticals act as info-disrupting compounds, which interfere with or disrupt the flow of natural chemical information that controls the interactions of species in aquatic and terrestrial ecosystems [91,98]. There is also evidence that mental health medications (e.g., anti-depressants and anti-anxiety drugs) may induce behavioral changes in non-target organisms, e.g., compulsive feeding, aggression, and boldness in fish [99]. However, evidence directly linking poor and unsafe disposal of unused and expired pharmaceuticals to specific environmental and ecological health outcomes is still lacking.

The health hazards of pharmaceuticals may occur at various scales of biological organization, spanning molecular level to ecosystem structure, function, goods, services, and benefits [91]. However, as pointed out in earlier studies, the ecological risks of pharmaceuticals at higher levels of biological organization, including ecosystem goods, services, benefits, and biodiversity loss, are still poorly understood [91]. In fact, addressing this gap is one of the next research frontiers on pharmaceuticals' environmental and ecological health risks [100].

4.2. Human Health Hazards

Poor and unsafe disposal of pharmaceuticals poses direct and indirect human health hazards. Here, direct human health hazards are associated with the inappropriate use, misuse, abuse, and overuse of the original pharmaceuticals, while indirect hazards occur via human exposure to contaminated media such as drinking water. For example, evidence shows that unused pharmaceuticals are sometimes shared with family members, acquaintances, and friends [76]. This practice may appear attractive because it reduces wastage and the disposal and release of pharmaceuticals into the environment, but it has a number of drawbacks, including human health hazards. For example, this practice may increase the risk of wrong prescriptions and other inappropriate uses such as drug abuse and overdose. This is particularly true for opioids medications such as analgesics used for pain treatment [101], which have high addictive potential and are prone to abuse and overdose as recreation drugs, which may lead to adverse human health effects, including morbidity and even mortality [102,103].

In the case of antibiotics/antimicrobials, inappropriate use may contribute to the emergence of antimicrobial/antibiotic resistance in previously susceptible human pathogens [51,93,104]. The availability of unused or expired drugs at household levels also increases the risks of unintentional or accidental use and abuse by children, leading to poisoning [105,106]. The human health risks of using expired drugs are documented in the literature [20,107]. These risks include: (1) loss of therapeutic efficacy, (2) compromised human safety due to changes in chemical composition and microbial contamination during prolonged storage, (3) formation of toxic products or metabolites, and (4) emergence of antimicrobial/antibiotic resistance [20,107,108].

Indirect human health hazards associated with exposure to parent pharmaceuticals and their metabolites may occur via ingestion of contaminated food and water, inhalation of airborne pharmaceuticals, and to a lesser extent, via dermal or skin intake [108]. In low-income settings, human exposure via ingestion of contaminated drinking water could be one of the dominant intake routes due to the lack of clean drinking water [108]. This aspect is discussed in detail in Section 4.3. However, an increasing number of studies show that active pharmaceutical ingredients originating from different groups of medicines (e.g., cardiovascular, anti-inflammatory, psychiatric, analgesic, contraceptives, and antimicrobial drugs) can chronically present in drinking water at ng/L levels (which cannot induce severe effects but can still contribute to unwanted human exposure) also in high-income countries due to insufficiency of conventional treatment methods to remove the pharmaceuticals from wastewater and raw water completely [92,109].

Yet besides inferential evidence, direct evidence linking pharmaceutical pollution by on-site sanitation systems to adverse human health outcomes is still missing. However, in

mass media, human exposure to pharmaceuticals such as endocrine-disrupting compounds is often touted as contributing to the decline in fertility [104]. For example, mass media articles insinuating the role of pharmaceuticals in the decline in human fertility have been published in many countries [104]. The examples include (1) the UK, "Warning on drugs in river water" (The Guardian Newspaper, UK, 3 July 2003 and "Why are sperm counts falling?" (The Guardian Newspaper, UK, 8 January 2004), (2) Canada, "Tests find drug taint in water" (The Globe and Mail, Canada, 12 January 2004), and the USA, "Drug found in area fish stirs concern" (The Star Telegram, (TX, USA) 17 October 2003). In 2012, World Health Organization concluded that due to the occurrence of pharmaceutical residues in drinking water much below the lowest therapeutic doses, adverse effects on human health are very unlikely [110]. However, it was also highlighted that due to the co-occurrence of various pharmaceuticals in water, the potential additive or synergistic effects of such mixtures cannot be excluded and requires further attention [110]. Although potential human health hazards exist, further work, besides studies documenting poisoning and fatalities due to inappropriate use and overdose, is required to link pharmaceutical pollution to adverse human health outcomes.

4.3. Risk of Pharmaceutical Pollution of Drinking Water Sources

4.3.1. The Pit Latrine Paradox: A Disposal Facility and Source of Pharmaceutical Pollution?

In low-income settings, pit latrines serve multiple functions as (1) a common disposal receptacle for unused and expired pharmaceuticals [39], (2) a sanitation facility that collects pharmaceuticals excreted via human feces and urine [111], and (3) a hygiene facility for bathing, laundering, and washing, which are considered as secondary sources of pharmaceuticals [5]. Thus, pit latrines and other on-site sanitation systems used in low-income settings can be considered hotspot reservoirs for pharmaceuticals. This is because on-site sanitation facilities receive and harbor pharmaceuticals from multiple sources in a catchment area and disseminate them to other environmental receptors. For example, once in pit latrines and other on-site sanitation systems, pharmaceuticals and their metabolites may disseminate and migrate into aquatic systems such as surface water and groundwater systems serving as drinking water sources. Although studies directly tracking pharmaceuticals' migration from pit latrines to aquatic systems, such as groundwater systems, are still lacking, the connectivity between pit latrines and groundwater systems has been established [112]. For example, a phenomenon of connectivity between pit latrines and groundwater systems has been documented in the case of legacy contaminants such as fecal bacteria, pathogens, and nutrients (nitrates, phosphates [88,113]).

4.3.2. Pharmaceuticals in the Pit Latrine-Water Continuum

Early evidence exists on the occurrence of pharmaceuticals in the pit latrine-water continuum. For example, a few studies have documented active pharmaceutical ingredients accumulation in the pit latrines and their presence in the associated media, including feces, urine, fecal sludge, and fecal effluent [114–117]. A few other studies conducted in low-income countries have detected pharmaceuticals in aquatic systems, including groundwater sources impacted by on-site sanitation systems, particularly pit latrines [111,118–121]. Overall, these studies point to the connectivity of on-site sanitation systems to groundwater sources, which often serve as potable water sources in low-income settings. In fact, pharmaceuticals have the potential to be used as tracers of wastewater or fecal pollution of aquatic systems [85].

4.3.3. High-Risk Biophysical Settings

The risk of pharmaceutical pollution of aquatic systems serving as potable water sources is particularly higher under socio-economic and biophysical conditions common in low-income settings. These settings, which are similar to pollution caused by other sewage-derived contaminants, have been discussed in several earlier studies focusing on low-income settings, including those investigating COVID-19 caused by SARS-CoV-2 [122–124]. Over-crowded informal urban and peri-urban settlements such as slums and refugee camps are potential

high-risk settings in this regard [122–124]. This is because, in such settlements; (1) the shared on-site sanitation systems are often overloaded and overflowing, thereby increasing risks of migration of pharmaceuticals and other contaminants, and (2) communities lack access to centralized drinking water systems, hence, rely on raw drinking water abstracted from unsafe sources prone to anthropogenic pollution. In addition, the landholding is often too small to meet the separation distance between on-site sanitation facilities and drinking water sources recommended by the World Health Organization. Hydrogeological conditions promoting strong hydrological connectivity between the on-site sanitation systems and groundwater sources include [122–126]: (1) highly porous geological systems with high saturated hydraulic conductivity or transmissivity (e.g., sandy, gravelly, karst aquifers), coupled with (2) shallow groundwater systems in low-lying areas such as wetlands or close to river systems. Collectively, such hydrological conditions are characterized by short travel distances and rapid travel times of contaminants. Therefore, such settings provide ideal sites for investigating the occurrence of pharmaceuticals in drinking water sources and the link to human exposure and health risks. Yet to date, studies investigating the detection and human health risks of pharmaceutical pollution in such high risks settings are still lacking. This calls for case-control epidemiological studies encompassing various ages, including infants, pregnant women, and the elderly. Such studies, which should include the sampling and analysis of human media (e.g., feces, urine, blood), may also be linked to the development and application of tracers and biomarkers of pharmaceutical pollution.

5. Future Research Directions and Perspectives

The present review highlighted that poor and unsafe disposal of unused or expired pharmaceuticals at the household level is prevalent in low-come settings. The pit latrines, a typical sanitation facility in low-income settings, act as 'catch-all' receptacles for used and excreted unused and expired pharmaceuticals. Understanding the disposal of pharmaceuticals and the associated health risks and mitigation is an emerging research topic in low-income settings. Hence, further work is required to address the following knowledge gaps:

(1) Educational campaigns to raise awareness

Knowledge of the proper disposal of pharmaceuticals and the awareness of health risks of poor and safe disposal appears limited in most low-income settings. Therefore, there is a need to raise awareness and provide knowledge on global best practices for the disposal of pharmaceuticals, including using take-back programs to change attitudes and practices in the whole pharmaceutical value chain.

(2) Establishing national guidelines on the disposal of pharmaceuticals

In some countries, guidelines for the disposal of pharmaceuticals are still lacking or are not widely disseminated to key stakeholders in the pharmaceutical value chain, including the users. In such cases, there is a need to establish guidelines based on global best practices provided by leading global health agencies such as the World Health Organization [36]. The guidelines should be simplified and translated into vernacular languages so that community environmental and health workers can explain them to individuals or households. Innovative methods such as the barcoding of pharmaceutical information as a way to facilitate the recycling of pharmaceuticals [127] may also be pilot-tested and adapted to low-income settings, and their effectiveness validated.

(3) Understanding disposal practices along the whole pharmaceutical value chain

The present review focused on disposal practices at the household level, but information on the disposal of pharmaceuticals along the whole value chain from manufacturing, logistics, and health facilities or dispensaries is still lacking. In some countries, the selling of expired pharmaceuticals has been reported (e.g., Bangladesh, [128], Zimbabwe [129]. In addition, given that most low-income countries lack disposal facilities such as incinerators, the fate of pharmaceuticals returned to pharmacies through take-back programs remains unknown. Thus, further studies focusing on the whole value chain are required in low-income countries.

(4) *Behavior and fate of pharmaceuticals in pit latrines*

In remote low-income settings, where the implementation of take-back programs should present logistical challenges, pit latrines are likely to remain a common receptacle for pharmaceuticals. However, unlike conventional and advanced wastewater treatment systems, the behavior and fate of pharmaceuticals in on-site sanitation systems used in low-income settings such as pit latrines remain unknown. This calls for research to understand pharmaceuticals' inherent nature, occurrence, behavior, and fate in on-site sanitation systems in low-income settings.

(5) *Developing and testing mitigation methods*

As reported for legacy contaminants such as nutrients and fecal bacteria, the risk of hydrological connectivity and contamination of groundwater systems by pit latrines could be very high in some settings, such as crowded informal settlements. In such settings, isolating drinking water sources by adhering to the recommended distance between on-site sanitation and drinking water sources may not be feasible due to small land holdings and overcrowding. Hence, there is a need to develop and validate mitigation measures to reduce the risk of drinking water pollution. Such mitigation measures may include using hydraulic barriers and in-situ (bio)degradation of pharmaceuticals. One should note that in low-income settings, it is essential to mitigate and prevent pharmaceutical pollution at its very source because the methods of pharmaceutical removal from the environment, e.g., such as advanced oxidation processes, activated carbon absorption, or application of organic polymers, are high-cost processes due to the use of costly chemicals and increased energy consumption [130–133].

(6) *Contaminant tracer studies to understand the pit latrine-groundwater connectivity*

Research focusing on contaminant hydrology of the pit latrine-groundwater continuum to understand the transport phenomena, behavior, and fate of contaminants, including pharmaceuticals, is still limited. Thus, there is a need to conduct natural and anthropogenic artificial tracer studies to understand these aspects to devise mitigation measures. Examples of anthropogenic tracers include artificial sweeteners and caffeine [126]. Research on tracer studies can also be linked to modelling of the transport, behavior, and fate of the various contaminants in the pit latrine-groundwater continuum. Such models should be based on the source-pathway-receptor-impact-mitigation (SPRIM) continuum concept [124]. Yet, in the case of emerging contaminants, such models are still lacking, hence, need to be developed, validated, and then applied [134]. This aspect is discussed in detail in an Editorial Perspective to the present Special Issue by the first author [134].

(7) *Development and application of pharmaceutical biomarkers*

Limited studies exist on developing biomarkers for pharmaceutical pollution in low-income settings. Thus, developing, validating, and applying appropriate biomarkers for pharmaceutical pollution of aquatic systems by pit latrines is a potential topic for further investigation. Such biomarkers can be used to track and understand ecological and human health risks associated with the occurrence of pharmaceuticals in aquatic systems impacted by on-site sanitation systems used as receptacles for unused and expired pharmaceuticals.

(8) *Relative contribution of various sources to pharmaceutical pollution*

In low-income settings, pharmaceutical pollution may occur through poor and safe disposal of unused and expired medicines and the excretion of used drugs via feces and urine. However, the relative contribution of the various sources to pharmaceutical pollution remains unknown, highlighting the need for source tracking and partitioning studies.

(9) *Development of novel models for behavioral change*

Knowledge and attitudes influence human behaviors that drive the accumulation of unused and expired pharmaceuticals. Yet limited studies have investigated these aspects and how they can be manipulated to change human behavior with respect to the disposal of pharmaceuticals. This calls for further research, including developing and testing

appropriate models for take-back programs for low-income settings (e.g., voluntary versus the use of incentives).

(10) The human health burden of poor and unsafe disposal of pharmaceuticals

The potential ecological and human health hazards associated with poor and unsafe disposal of pharmaceuticals, including driving the emergence of antibiotic resistance, were discussed. However, there is limited empirical data on the ecological and human health burden of such disposal practices.

6. Conclusions

The poor and unsafe disposal of pharmaceuticals poses public and environmental health risks, but reviews of the evidence in Africa have been lacking. Therefore, the current review examined the evidence on the current practices and potential health risks of the disposal of used, unused, and expired pharmaceuticals in Africa. Several factors account for the accumulation of unused and expired pharmaceuticals at the household level, including discontinued use following recovery from diseases or death of a patient. Sharing excess pharmaceuticals among sick family members, acquaintances, and friends is common in Africa. Unused and expired pharmaceuticals are often retained, reused, or disposed of in on-site sanitation systems such as pit latrines, domestic solid waste, and/or burned. Lacking access to centralized sewer systems, used pharmaceuticals excreted via feces and urine often end up in on-site sanitation, such as pit latrines and septic tanks, and the environment in the case of open defecation and bucket toilets. The pollution risks of current disposal practices are poorly understood, but pharmaceutical pollution of groundwater sources, including those used for drinking water supply, may occur via close hydrological connectivity between pit latrines and groundwater systems. Current evidence of pharmaceutical pollution of groundwater sources via pit latrines was discussed. The potential pharmaceutical pollution and human exposure hotspots were discussed. These include crowded informal settlements, where on-site sanitation systems are closed and juxtaposed with drinking water supply systems based on shallow groundwater consumed without treatment. Compared to other environmental compartments, the occurrence, dissemination, fate, and human health risks of pharmaceuticals in the pit latrine-groundwater continuum are still understudied. Therefore, future research directions are discussed to address these gaps using the Source-Pathway-Receptor-Impact-Mitigation (SPRIM) continuum as an organizing framework. In addition, novel methodologies, including tracers such as artificial sweeteners and biomarkers, were proposed to understand better the hydrological connectivity between pit latrines and groundwater systems used as drinking water sources.

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