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Occurrence and toxicological assessment of selected active pharmaceutical ingredients in effluents of pharmaceutical manufacturing plants and wastewater treatment plants in Kampala, Uganda

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ABSTRACT

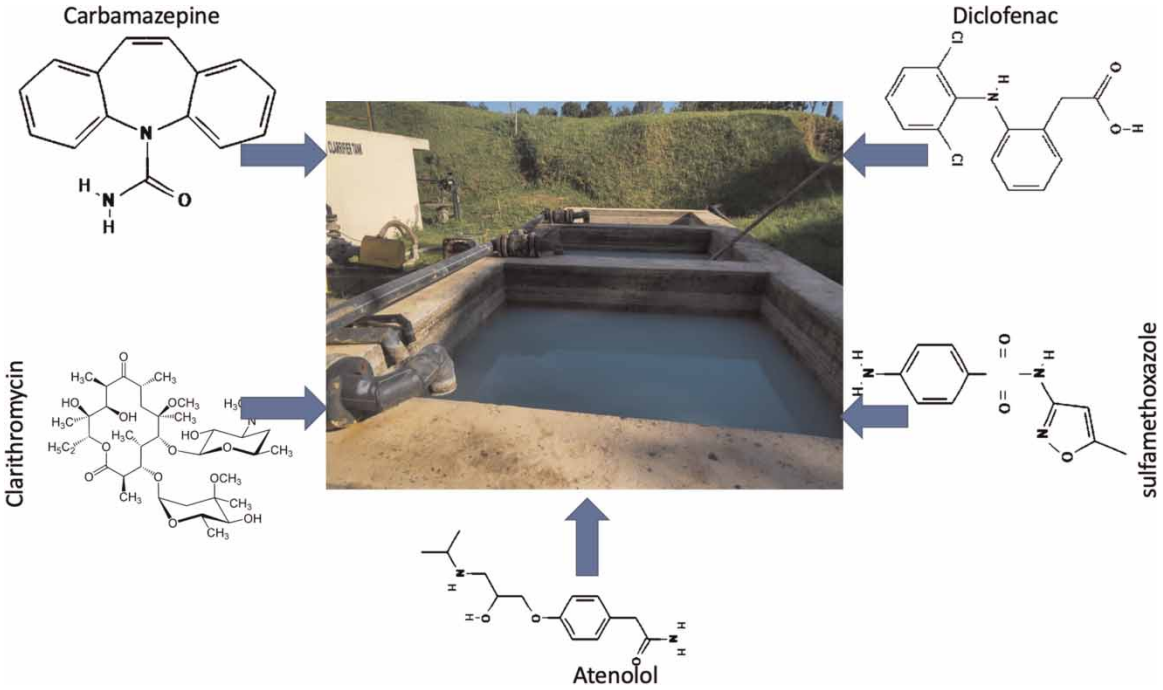
There is an increasing eco-toxicological risk associated with pharmaceuticals globally. The prevalence of six active pharmaceutical ingredients (APIs) was studied in effluents of three pharmaceutical manufacturing plants (PMPs) and two wastewater treatment plants (WWTPs) in Kampala, Uganda to ascertain the removal potentials for APIs. The APIs include atenolol, losartan, carbamazepine, sulfamethoxazole, clarithromycin, and diclofenac. The APIs were extracted using solid-phase extraction cartridges and concentrations were analyzed using a liquid chromatography-mass spectrometer system. The concentration ranges of the APIs were <limit of detection (LOD), <LOD – 4.75, <LOD – 1.37, <LOD – 1.17, and 0.28–19.55 mgL^{-1} for losartan, diclofenac, sulfamethoxazole, carbamazepine, and clarithromycin respectively in effluents of WWTPs, whereas in treated wastewater from PMPs concentrations were 0.00, 0.00–0.23, 5.30–7.4, 0.00–0.14, and 0.12–4.53 mgL^{-1} for losartan, diclofenac, sulfamethoxazole, carbamazepine, and clarithromycin respectively. The API removal efficiency of PMPs was higher than WWTPs with some APIs removed to concentrations of <LOD. The range of hazard quotients (HQs) for APIs was 0.018–0.9775000 with most of the APIs posing remarkably high environmental risks at HQs way greater than 1. Only sulfamethoxazole from the effluents of Lubigi WWTP, Bugolobi WWTP, and PMP C posed low risks with HQs of <1 at 0.018, 0.305, and 0.018 respectively. The high HQs for most APIs imply that immediate recipients are at very high toxicological risks, yet most studies have focused on the final destinations of APIs in environments where toxicological risks are often minimal due to dilution effects.

Key words: active pharmaceutical ingredients, pharmaceutical manufacturing plants, prevalence, risk assessment, wastewater treatment plants

HIGHLIGHTS

- Pharmaceuticals assessed in Kampala Pharmaceutical manufacturing plants' effluents.
- Pharmaceuticals assessed in Kampala wastewater treatment plants' effluents.
- High inefficiency in the removal of pharmaceuticals from wastewater in Kampala.
- High eco-toxicological risk posed by pharmaceutical ingredients in the effluents.

GRAPHICAL ABSTRACT



1. INTRODUCTION

Pharmaceutical-based environmental pollution has become an international issue that requires considerable attention and change in policies and regulations (WHO 2011, 2012; Aswal *et al.* 2016; European Commission 2020). There are approximately 9,700 active pharmaceutical ingredients (APIs) resulting from molecular entities of pharmaceuticals that are approved worldwide with 8,969 holding the potential for entering the environment worldwide (Caban & Stepnowski 2021). These compounds and their bioactive metabolites are continuously routed into the aquatic systems at ngL^{-1} or μgL^{-1} levels by several channels including residues from production sites, through human and animal excreta, and unregulated disposal of drugs in households and health centers. Unfortunately, some of the APIs are resistant to biological degradation processes, escaping almost intact from conventional wastewater treatments (Kanama *et al.* 2018; Frascaroli *et al.* 2021).

Despite some removal efficiencies of 20 to >90% reported by some conventional wastewater treatment methods such as conventional activated sludge (Hatoum *et al.* 2019; Peng *et al.* 2019), several parameters require close monitoring to achieve commendable success in this regard globally. Some of the parameters include sludge age, activated sludge tank temperature, and hydraulic retention time (WHO 2012). These wastewater treatment plants (WWTPs) have been categorized as 'hotspots' for APIs (Guillossou *et al.* 2019). Of even more concern is the case where detected APIs are present in higher mean concentrations in effluents than in influents of WWTPs (Dalahmeh *et al.* 2020). In Uganda, most factories do not have effluent treatment plants, even where they exist, most industrial WWTPs are poorly designed and constructed (LVEMP 2002; Angiro *et al.* 2020). This negates their APIs removal potential. The water quality monitoring frameworks in most African countries are poor and only capable of monitoring a few parameters like pH, turbidity, and alkalinity (Wang *et al.* 2014). This implies that APIs are left to join mainstream water sources unnoticed. Besides, there are no API compliance limits in many countries for direct discharge of liquid waste streams to surface waters, Uganda inclusive (NEMA 2020). The more pressing issue is that most drinking water and other local beverage processing companies rely on treated wastewater in several processes. For example, the Namanve industrial park with several beverage processing factories in Uganda relies on water from Lake Victoria (Angiro *et al.* 2020), yet it has a remarkable prevalence of APIs (Nantaba *et al.* 2020). The consequence is that some of these residual pharmaceuticals are consumed hence posing a high health risk. Besides their prevalence in drinking water, they are also highly likely to enter the aquatic food web, for example fish that is consumed by humans (Pereira *et al.* 2020). Such unregulated drug intake has been reported to cause drug resistance for some pathogenic infections. For

example, the globally exacerbated antibiotic resistance has been attributed to the prevalence of antibiotics in aquatic systems even at trace levels (Sandegren 2019).

Most of the studies conducted on micropollutant prevalence in Uganda and the greater east Africa are focused on the receiving end for both treated and untreated wastewater. For example, most recently APIs occurrence and ecotoxicological risk in water from Lake Victoria were assessed by Nantaba *et al.* (2020). Another study assessed the pharmaceutical pollution of water resources in the Nakivubo wetlands and Lake Victoria (Dalahmeh *et al.* 2020). The pollution effects of these emerging micropollutants are less controllable at such points. It is therefore pertinent to assess the prevalence of these pharmaceuticals at the source and devise possible mitigation measures implementable at these source points. Several studies have estimated the predicted environmental concentration (PEC) of pharmaceuticals in receiving water systems based on pharmaceutical consumption, excretion rate, and the efficiency of WWTPs (Alves *et al.* 2018; He *et al.* 2020). More so, pharmaceutical prevalence levels have correlated well with consumption data in several studies (ter Laak *et al.* 2010; He *et al.* 2020). Arguably, this assumes that active pharmaceutical ingredients in receiving water systems are from human and animal excretion and a percentage is curbed by WWTPs. A very important source of such pollutants could be the effluents of drug manufacturing plants (Fick *et al.* 2009). Despite the large research body on the occurrence of APIs in the environment in the past decade, very few studies have explicitly focused on the potency of drug production facilities as API sources to the environment (Larsson 2008). The concessional but rather notional view that the direct contribution from pharmaceutical production facilities is relatively unimportant had blanketed such a crucial environmental issue (Larsson 2008). Recently, direct emission from drug manufacturing has been identified as a source of much higher environmental discharges, with the toxic threshold exceeded in some cases (Larsson 2014; Caban & Stepnowski 2021). It is pertinent therefore to ascertain the residual escape of such micropollutants at their source to measure the related environmental and human risks and aid other bioassays.

This study aimed at elucidating the efficacy of three pharmaceutical-manufacturing plants (PMPs) in Kampala, Uganda in treating their wastewater prior to disposal into the environment based on data on selected APIs' concentration in their wastewater. It also presents selected API concentration findings from the two wastewater treatment plants in Kampala to paint a comparative picture of the API-curbing capabilities of the two plants that deploy biological stabilization ponds. It also aimed at assessing the potential toxicological risks posed by APIs in effluents of PMPs and WWTPs to the immediate recipient ecosystems.

2. MATERIALS AND METHODS

2.1. Description of the sampling sites

Samples were collected from the two sewage treatment plants operated by the National Water and Sewerage Corporation (NWSC), a government-managed public utility company in Uganda, and three PMPs in Kampala. The Lubigi sewage treatment plant has the capacity to treat 5,400 m^3 wastewater/day and lies on the outskirts of Kampala. Lubigi treats piped wastewater as well as fecal sludge brought in from private cesspools, especially pit latrines and septic tanks using stabilization ponds. More detail on the processes at Lubigi WWTP is reported by (Lindberg & Rost 2018). For the Lubigi WWTP, the immediate recipient ecosystem for the effluent is the Lubigi swamp. Bugolobi is a newer plant that supplements the ponds with aerobic treatment in high-rate trickling filters and secondary clarifiers. It has a 45,000 m^3/day design capacity, although the current flow is 13,000 m^3/day. It handles both domestic wastewater (from septic tanks in homes and other premises, transported to the treatment plant via trucks) and the Nakivubo channel surface flow. The wastewater is mostly piped sewage from the business district of Kampala. The effluent from the Bugolobi WWTP is channeled directly to Nakivubo channel, which then links to Lake Victoria. The treatment processes for the WWTPs are shown in Figure 1.

Three PMPs (A, B, and C) in Kampala consented to this study. B and C dispose of their treated effluents into surrounding swamps whereas A routes the effluent into Nakivubo channel. All the PMPs deploy powdered activated carbon preceded by screening and neutralization for their onsite wastewater treatment as shown in Figure 2.

2.2. Sample collection and pretreatment

Wastewater samples were collected from three (3) PMPs and the two WWTPs in Kampala between 27 March 2021 and 13 April 2021. Two grab samples were picked from each sampling point in a space of 1 week from the time of the first sampling. At the 3 PMPs, samples were picked from the untreated wastewater flowing from their production chambers and from the points en route to the treated wastewater collection tanks. For

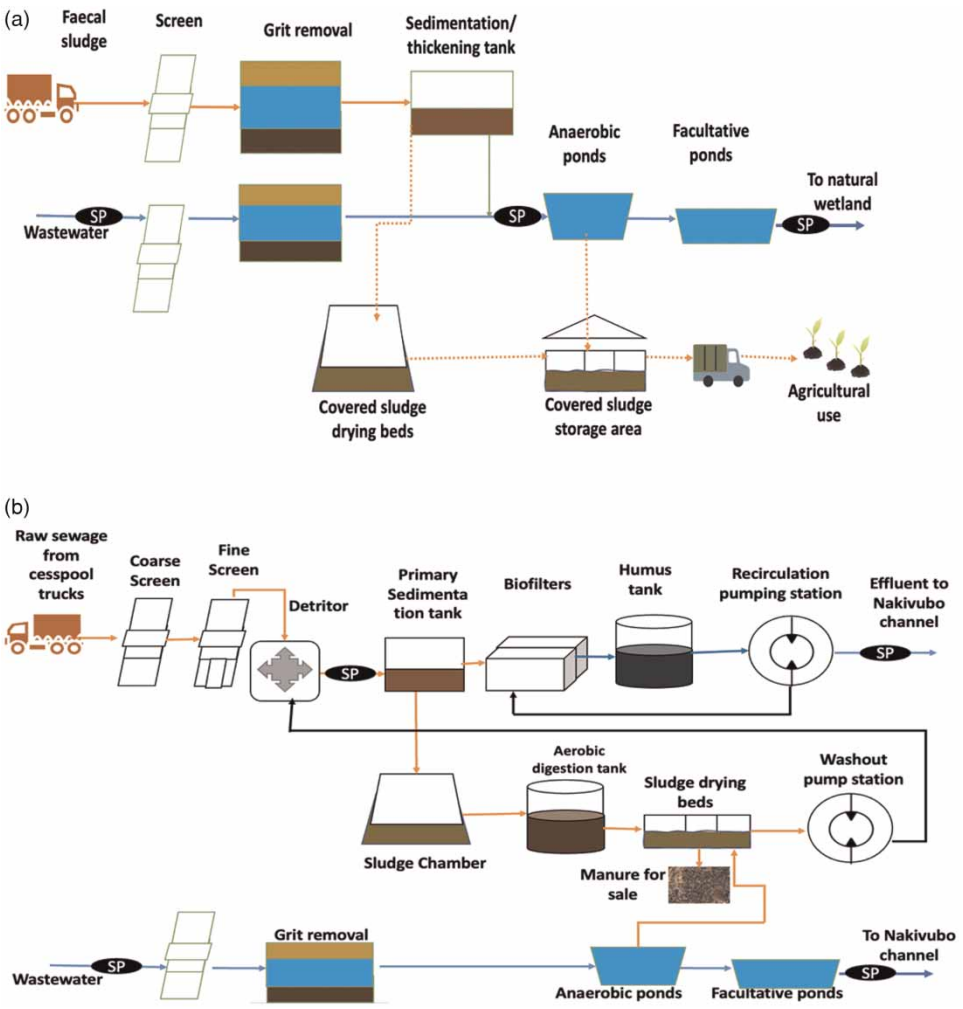


Figure 1 | Wastewater treatment process flows at (a) Lubigi and (b) Bugolobi WWTPs. SP=sampling point.

anonymity, the selected plants were identified as A, B, and C in this study. For Bugolobi WWTP, samples were picked from four points: the cesspool wastewater, the raw incoming wastewater from Nakivubo channel, the treated cesspool effluent, and the final pond for the treated Nakivubo channel wastewater ready for discharge. For Lubigi, samples were picked from the incoming domestic wastewater, the pond where wastewater from the sludge treatment line joins the domestic wastewater, and at the final effluent ready for discharge. The effluent samples were collected 3–4 h later than the influent samples at Bugolobi WWTP to account for its hydraulic retention time of <3 h. At the PMPs, the treated wastewater samples were collected 10–11 h later than the raw wastewater to cater for the 8 h production shifts and 1–2 h wastewater treatment system retention times. At each sampling point, two to four 1.5-liter grab samples were collected at a maximum of 30 cm depth using buckets to avoid debris contamination. In total 26 samples were collected.

These samples were pretreated with 2 mL of 0.01 M sulfuric acid for preservation and then kept in amber glass bottles. Each bottle was labeled with the source, date, and time of collection. These were then frozen at −20 °C prior to the analyses. The wastewater physiochemical analyses, API extraction, and analyses were conducted at the Directorate of Government Analytical Laboratories Wandegeya, Kampala.

2.3. Determination of water quality parameters in the wastewater samples

The quality of the wastewater was determined based on; pH, total suspended solids (TSS), biochemical oxygen demand (BOD), chemical oxygen demand (COD), total nitrogen (TN), phosphorous as phosphate (PO_4-P), and total organic carbon (TOC). These were determined to assess any association with the API concentrations. The procedure described by Fuhrimann *et al.* (2015) was followed for all the parameters

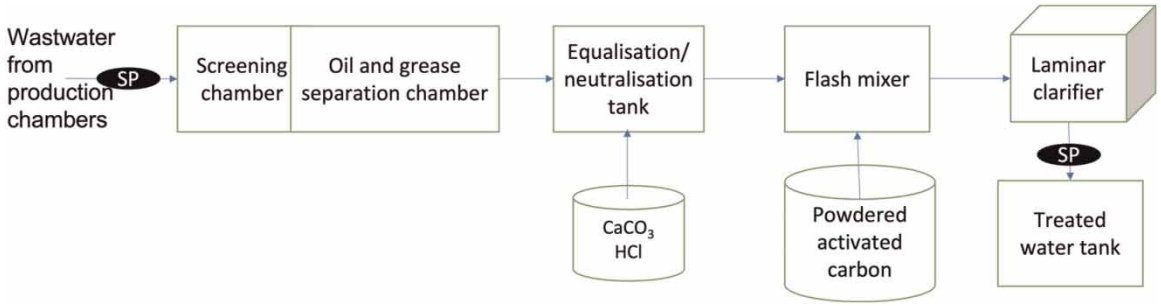


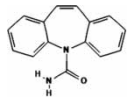
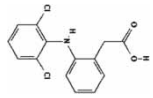
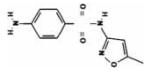
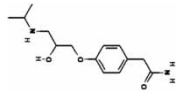
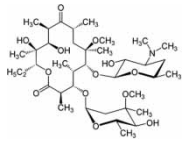
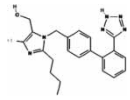
Figure 2 | PMPs wastewater treatment processes. SP=sampling point.

2.4. Analyses of pharmaceuticals in wastewater

2.4.1. Selected APIs

Six active pharmaceutical ingredients (carbamazepine, diclofenac, sulfamethoxazole, atenolol, clarithromycin, and losartan) were selected for this analysis. These were reported as most prevalent in water systems in Uganda as per earlier studies (Dalahmeh *et al.* 2020; Nantaba *et al.* 2020). Their concentrations in water systems were sulfamethoxazole (1–5,600 ngL^{-1}), diclofenac (2–160 ngL^{-1}), clarithromycin (22–305 ngL^{-1}) carbamazepine (5–240 ngL^{-1}), atenolol (270–1,300 ngL^{-1}), and losartan (60–190 ngL^{-1}). These water bodies are recipients of treated wastewater from WWTPs and PMPs; hence the need to investigate the occurrence of APIs at the probable sources. Moreover, these were crosscutting as per the product catalogs of the three drug-manufacturing companies selected for this study. The API properties including the distribution coefficient (Log K_D), octanol/water partition coefficient of water (Log K_{OW}), and the acid dissociation constants (P^{Ka}) are shown in Table 1.

Table 1 | Selected physical and chemical properties of studied APIs

API	Therapeutic classification	Log K_D/ Log K_{ow}	Water solubility at 20–25 °C (mgL^{-1})	p^{Ka}	Predicted CEC (μgL^{-1})
Carbamazepine 	Antieleptic	−/2.45	Practically insoluble	13.9	346.496
Diclofenac 	Analgesic	1.2/4.51	2.37	4.01–4.15	4.560
Sulfamethoxazole 	Antibiotic	2.4/0.89	Practically insoluble	1.69–5.57	9.8×10^4
Atenolol 	β-blocker	3.2/0.16	13,300	8.0–9.6	792.332
Clarithromycin 	Antibiotic	−/3.2	0.33	8.99	7.267
Losartan 	Antihypertensive	−/4.01	8.22	5.5	1.824

$LogK_D$, $LogK_{ow}$, p^{Ka}, and predicted critical environmental concentration (CEC) values are as per (Patel *et al.* 2019) and (Baresel *et al.* 2015).

2.4.2. Extraction of APIs from wastewater samples

The samples were filtered using a vacuum filter funnel (porosity 25–50 μm, Aldrich). To each 500 mL of filtered samples, a 2 mL solution containing Na_2EDTA (5.00 g L^{-1}, used as a metal chelating agent) and ascorbic acid (25.0 mg L^{-1}, used to remove any chlorine residues that could have been present in the samples) was added before extraction. Analytes in the samples were extracted one day after collection using Oasis MCX cartridges (mixed mode, 150 mg from Waters, Milford, MA, USA). All SPE cartridges were conditioned with ACN (6 mL) followed by reagent water (6 mL) before extraction. The extraction followed the procedure described by (Batt *et al.* 2008). The prepared samples as described above were passed through reconditioned cartridges at a rate of 3–5 mL min^{-1} with the help of a vacuum pump. Each cartridge was then rinsed with a 2 mL solution of formic acid (2%) and dried under a vacuum.

Acidic and neutral analytes in each sample were first eluted with ACN (2×4 mL) into a small glass tube with the aid of a vacuum manifold (20 positions from Waters, Milford, MA, USA). Basic analytes retained on the cartridge material were then eluted by ACN solution (2×4 mL) containing ammonium hydroxide (5%) into a separate glass tube. Then 8 mL of each eluate was then concentrated to dryness with the help of a TurboVap LV Concentration Evaporator Workstation (Caliper Life Sciences, Runcorn, UK) at 40 °C under a stream of N_2. The first tube contents were reconstituted with ACN in water (0.50 mL, 20:80), whereas those within the other tube were reconstituted with methanol in water (0.50 mL, 20:80). The first and second tube constituents were code-named as 'acidics & neutrals,' and 'basics' respectively. Reconstituted samples were transferred to glass vials and analyzed by liquid chromatography-mass spectrometer (LC-MS).

2.4.3. Instrumental analysis

The API detection was performed using a LC-MS system following an identical procedure by (Batt *et al.* 2008). To quantify the molecular ion masses and the retention times of the analytes, a 10 μL solution of each analyte (1,000.0 μg mL^{-1}) was injected into the LC-MS system (Agilent 1290 UHPLC and 6460 MS/MS series with Jet Steam ESI source) using a mobile phase flow rate of 0.5 mL min^{-1}. Then, a product ion scan employing the multiple reaction-monitoring mode (MRM) was performed to collect data for suitable product ions. For all analytes, the MRM transitions selection was based on the two most intense transitions. Optimization of the MRM transitions was effected using different collision energies. The MS settings used are listed in Table 2. Finally,

Table 2 | Common MS settings utilized in the instrumental analysis

Instrumentation		
LC:	1,200 LC	
Column:	ZORBAX Extend-C-18, RRHT, 2.1 mm×100 mm, 1.8 μm	
Column temperature:	40 °C	
Mobile phases:	A: 0.1% formic acid in water, add NH4OH buffer to pH 5.5 B: Acetonitrile (ACN)	
Flow rate:	0.3 mL/min	
Gradient:	**Time**	**%B**
	0	0
	15	100
	20	100
	21.5	0
Injection volume:	1.0 μL	
MS:	G6420A QQQ	
Ionization:	ESI–(+)	
Mass range:	125 to 800 amu	
Scan time:	300 ms	
Capillary voltage:	3,500 V	
Nebulizer P:	35 psi	
Drying gas:	9 L/min	
Gas temperature:	350 °C	

calibration internal standard solutions and treated samples solutions were injected into the LC-MS system. For quantification of the analytes, a 4-point calibration curve for each analyte was constructed at concentrations of 0.000, 100.00, 500.00, and 1,000.0 μg mL^{-1}. For detection of the analytes both the retention time and product ion ratios were used. Analytes were positively identified if both product ions are present in abundance more than the limit of detection (LOD) and the ratio of the ions is within 30% of the anticipated ratio.

2.5. Quality control

All glass and plastic ware used was soaked overnight in 10% nitric acid, rinsed with distilled water, and finally rinsed with reagent water before use. Glassware used for the preparation and storage of drug solutions was rinsed with toluene and several times of methanol washing before use. The LOD for each analyte was determined using 5–7 replicate injections of a reagent blank and was calculated as the average concentration measured for the blank multiplied by 3 times its standard deviation. The API detection method was validated for each analyte in terms of LOD as shown in Table 3. The recoveries for all APIs in the wastewater samples were investigated by spiking the samples with a known concentration of the target APIs. The recovery for all analytes was determined through a comparison of the resultant concentrations from the solid phase extraction procedure with the spiking concentrations.

Table 3 | LOD validation data

Analyte	LOD, μg/L	R^2 (linear fit)	Equation of line
Losartan	2.65	0.9975	Y=236.57X−121.07
Diclofenac	0.54	0.9998	Y=701.68X−115.68
Atenolol	0.91	0.9852	Y=780.18X−233.66
Sulfamethoxazole	0.18	0.9992	Y=12.47X+15.05
Carbamazepine	0.05	0.9971	Y=186.19X+4.69
Clarithromycin	1.52	0.9986	Y=463.79X+216.96

2.6. Eco-toxicological risk assessment

The risk assessment was based on the hazard quotients calculated as ratios of the maximum measured concentrations (MMC) in the effluents to the predicted no-effect concentrations (PNEC) (Hazard quotient (HQ)=MMC/PNEC) as per the EMA guideline on the environmental risk assessment of medicinal products for human use (EMA 2006). For the risk assessment, LOD values were considered as the MMC for the APIs that were undetected in effluents. For the Lubigi WWTP, the immediate destination for the effluent is a swamp whereas the effluent from the Bugolobi WWTP is channeled directly to a constructed water channel, which then links to Lake Victoria. Two of the PMPs, B and C, dispose of their treated effluents into swamps whereas A channels the effluent into a constructed water channel. Therefore, the PNECs for the effluents disposed of in swamps were based on algae whereas those routed to the water channel into Lake Victoria were based on fish and invertebrates.

3. RESULTS AND DISCUSSION

3.1. Overall detection of APIs

The limits of detection for all the APIs are shown in Table 4 and give validation of the API detection as detailed in Table 3. Clarithromycin was the most detected API at 100% followed by sulfamethoxazole and diclofenac at 38.5% detection frequency (DF) for both. These have been reported as some of the most detected pharmaceuticals in water systems globally (Zuccato *et al.* 2006; Aus Der Beek *et al.* 2016). Besides the unregulated consumption of these pharmaceuticals, they are prescribed as a part of several medications and are easily accessible over the counter making them ubiquitous in the environment (Michael *et al.* 2013; Ocan *et al.* 2017). Their usage in treating both humans and animals within and around Kampala could have contributed to the high detection frequencies (Nayiga *et al.* 2020). Moreover, clarithromycin is the most hydrophilic and is hence expected to thrive in wastewater. The other APIs were at appreciable DFs of 30.8% and 15.4% for carbamazepine and losartan respectively. Atenolol, a *β*-blocker, was below detection levels in all the samples, yet it was detected in

Table 4 | Overall ranges and frequencies of the APIs at the sampled sites (n=26)

API	Limit of detection (μgL^{-1})	Detection frequency (%)	Concentration (mgL^{-1})		
			Minimum	Maximum	Median
Carbamazepine	0.05	30.8	<LOD	1.17	0.14
Diclofenac	0.54	38.5	<LOD	4.75	0.00
Sulfamethoxazole	0.18	38.5	1.37	57.96	7.44
Atenolol	0.91	0.00	<LOD	<LOD	<LOD
Clarithromycin	1.52	100.0	0.12	240.83	2.27
Losartan	2.65	15.4	<LOD	6.82	<LOD

WWTPs in South Africa with a total mean concentration of 4.4 μgL^{-1} (Kanama *et al.* 2018). This is probably because that is prescribed in low dosages and for rare illnesses that are uncommon in Uganda. However, carbamazepine had a relatively higher DF since antileptics have a higher persistence than antihypertensives in water (Mompelat *et al.* 2009).

3.1.1. Specific API prevalence in WWTPs

At the influent of WWTPs, only clarithromycin and diclofenac were detected at concentrations of 0.28–22.8 mgL^{-1} and 0.18 mgL^{-1} respectively. The rest of the APIs were not detected in this study. K'oreje *et al.* (2018) detected carbamazepine, sulfamethoxazole, and diclofenac in wastewater stabilization ponds in Kenya at 90–2,210 ngL^{-1}, >10 $ngL^{-1,}$ and 5,520–98,850 ngL^{-1} respectively. In 2019 Dalahmeh *et al.* (2020) detected APIs in Bugolobi WWTP in concentrations of 660–800, 100–160, 200–1,300, and 550–2,000 ngL^{-1} for sulfamethoxazole, losartan, carbamazepine, and atenolol respectively. The failure to detect APIs in the same medium at the same facilities has been partly attributed to high LODs for some equipment (Madikizela *et al.* 2017). This could have been the case with losartan, which had a LOD of 2,650 ngL^{-1} in this study. The rest of the APIs LODs as per Table 4 were within the concentration ranges of APIs reported by (Dalahmeh *et al.* 2020) and hence they should have been detected. Possibly, the seasonal variations like storm rains that lead to dilutions to undetectable concentration levels, and the difference in sampling times could be the reasons for the undetected APIs in WWTP influents.

Different classes of pharmaceuticals degraded differently in different weather conditions (Aus Der Beek *et al.* 2016). For example, Kot-Wasik *et al.* (2016) reported the maximum concentration of carbamazepine in spring at 0.84 μgL^{-1} whereas triclosan and ibuprofen had their highest concentrations detected in summer at 0.155 and 0.735 μgL^{-1} respectively in a drinking water treatment plant in Turkey. K'oreje *et al.* (2018) reported the highest overall concentration of pharmaceuticals in the river Nzoia basin in Kenya in the dry season and the lowest in the rainy season whereas, in Brazil, Reis *et al.* (2019) reported the highest total concentrations and the maximum concentration values for the most frequently detected pharmaceuticals in winter. Moreover, in some studies, variations in concentrations of APIs have been reported to occur over hours of sampling time difference in the same day (Amdany *et al.* 2014). Of all target APIs in this study, clarithromycin was detected with the highest concentration because of its recalcitrance to all biological processes that happen along the surface flow to the WWTPs. Diclofenac was only detected in the Nakivubo channel influent of Bugolobi WWTP at 0.18 ± 0.06 mgL^{-1} whereas clarithromycin was detected in both WWTP influents in the range of 0.52 ± 0.04 to 20.38 ± 0.40 mgL^{-1}. The relatively higher concentration of clarithromycin is probably due to its high consumption in and around Kampala (Nayiga *et al.* 2020). Besides, clarithromycin is practically insoluble in water, and this partially explains its relatively higher persistence in the influent samples. At the effluent of Bugolobi WWTP, diclofenac concentration was way higher than its concentration in the influent from Nakivubo channel at 4.75 ± 0.27 mgL^{-1}. This ambiguity was also reported by Dalahmeh *et al.* (2020) on APIs including atenolol, carbamazepine, trimethoprim, and others. A probable explanation was that it was due to the overloading and ineffective functioning of the plant during the sampling period. However, for our study, the plant was fully functional. The increase in the concentration of diclofenac in the effluent could possibly have been due to the accumulation of the treated wastewater outside the fence of the plant (where the sample was taken), at which point reversal of APIs to their parent form and possibly desorption from sediments

and other particulate matter could have occurred. The same explanation accounts for the detected sulfamethoxazole and carbamazepine in the treated cesspool water at Bugolobi WWTP at 1.37 and 1.17 mgL^{-1} respectively, yet both were below the LODs in the raw cesspool water. These phenomena of deconjugation of active metabolites, reverse transformation products from hydrolysis, and desorption from sludge during wastewater treatment have been reported elsewhere (Kosma *et al.* 2014; Lindholm-Lehto *et al.* 2015; Yang *et al.* 2017). Kot-Wasik *et al.* (2016) also reported higher concentrations of carbamazepine in effluents than influents of a wastewater treatment plant in Turkey. This was attributed to the cleavage of glucuronide conjugates of the drug during the enzymatic processes in the WWTP. The percentage removal of APIs in both WWTPs is shown in Figure 3.

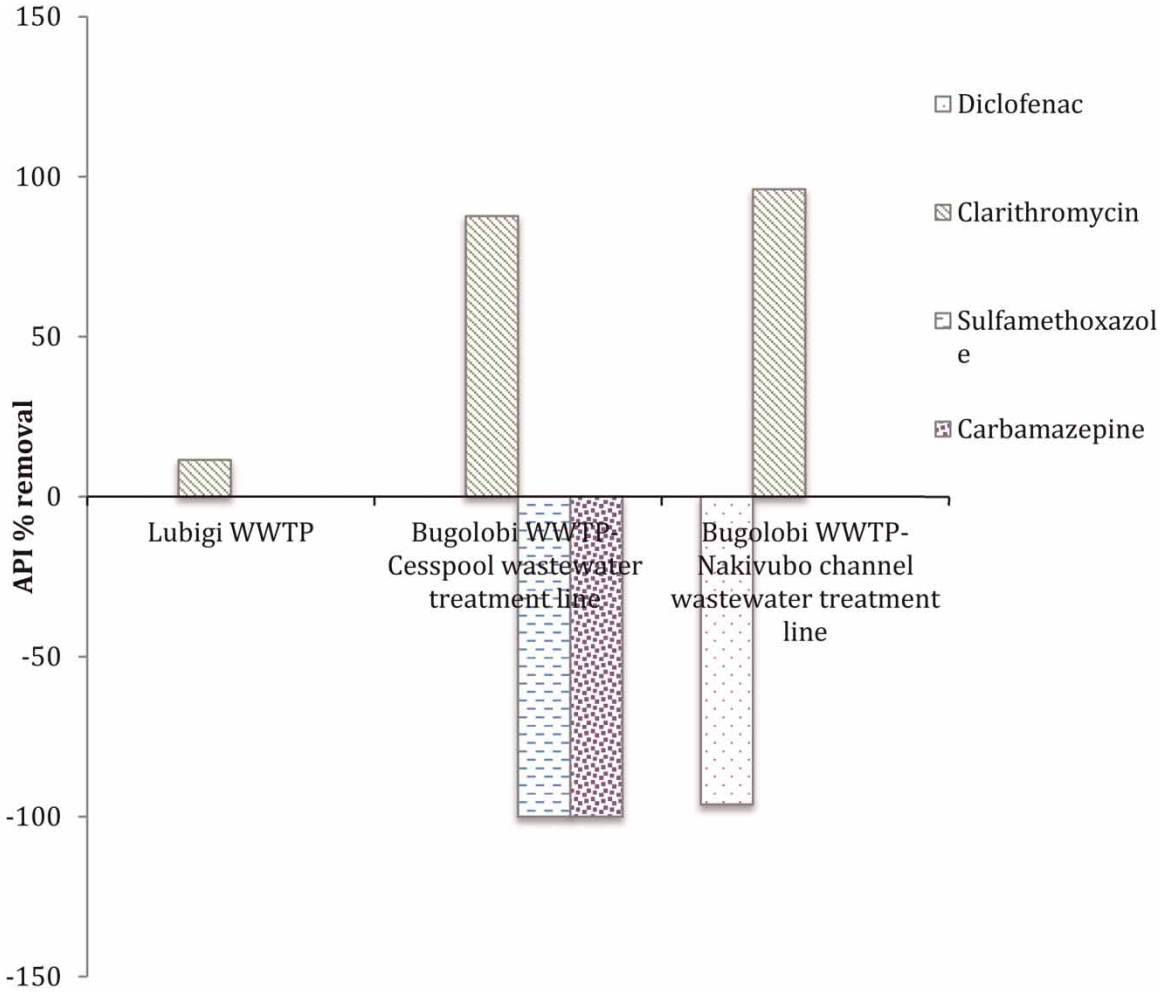


Figure 3 | WWTPs' removal efficiencies for APIs. Note: Diclofenac, sulfamethoxazole, and carbamazepine were below the LODs in the raw wastewater at Lubigi WWTP and cesspool wastewater at Bugolobi WWTP, whereas atenolol and losartan were below the LODs in all the samples.

For Lubigi WWTP, only clarithromycin was detected in the raw wastewater channeled to the plant from areas of Mulago, Katanga, Kamwokya, and Lubigi surroundings at an average concentration of 0.52 ± 0.04 mgL^{-1}. The concentration is way higher at the sampling point where the cesspool truck-delivered wastewater mixes with the channeled water from Kamwokya, Mulago, Katanga, and Lubigi surroundings at 22.08 ± 0.23 mgL^{-1}. This implies that the cesspool wastewater contributes largely to this concentration. This is attributable to the uncontrolled drug usage in the slum areas of Katanga and Kamwokya (Nayiga *et al.* 2020). The cesspool from Mulago national referral hospital could also be a major source of such high clarithromycin content. Clarithromycin exhibited the highest degree of recalcitrance at the Lubigi WWTP. The percentage reduction in its concentration was 11.46%. This low removal efficiency could partially be due to the ineffective biodegradation processes in the

stabilization ponds at the plant. This recalcitrance is also attributable to the antimicrobial activity of antibiotics that render the biological removal less effective (Aydin 2016). The other possible cause could be the tendency of reverse transformation of clarithromycin to its original form at the accumulation ponds of the treated wastewater from the plant. Atenolol was below LODs in all the samples from WWTPs. This is attributable to its low affinity for sorption to sediment (Dalahmeh *et al.* 2020). Moreover, atenolol's metabolite atenolol acid is positively charged, yet pharmaceuticals with a positive charge are more likely to be found in suspended particles, sediment, and soils rather than in surface waters (Brooks & Huggett 2012). Another possible reason for atenolol's absence in all WWTP samples could be its hydrophilic nature. The octanol-water partition coefficient ($LogK_{ow}$) is the lowest. According to Lee *et al.* 2011, compounds with greater hydrophilicity could be more efficiently removed than hydrophobic compounds. Thus, it could have been sequestrated to concentrations lower than the LOD along the channels to the WWTPs and the septic tanks for the cesspool wastewater.

The differences in performance of the two WWTPs on API removal despite the same processes in the establishment are most likely due to natural diurnal environmental variations (Norvill *et al.* 2016). The stabilization ponds at Lubigi WWTP have a naturally occurring thin layer of algae, unlike those of Bugolobi. Algae are known to release a large amount of dissolved oxygen during day while raising the pH due to the high consumption of CO_2 (Molazadeh *et al.* 2019; Mohsenpour *et al.* 2021). Moreover, the pH of the wastewater in Lubigi WWTP is higher than that of the wastewater from Bugolobi WWTP as shown in Table 5. This partly explains why hydrophobic APIs such as clarithromycin were at higher concentrations in effluents of Lubigi relative to Bugolobi. More so, the high-rate trickling filters supplement the stabilization ponds at Bugolobi WWTP aerobically.

3.1.2. Specific API occurrence in PMP wastewater

In PMP raw wastewater, the concentrations of APIs (in mgL^{-1}) were at 0.72–6.80, <LOD – 0.93, 32.30–57.96, <LOD – 0.14, and 0.19–240.83 for losartan, diclofenac, sulfamethoxazole, carbamazepine, and clarithromycin respectively. Given that the wastewater is almost entirely from these production lines, these concentrations are due to the wastes in form of wash-overs, spillovers, and uncontrolled disposal of defective drugs. These concentrations are relatively higher than those reported in other similar studies (Larsson 2008; Ashfaq *et al.* 2017; Pérez *et al.* 2017). This is due to the difference in the targeted sample sites. In other studies APIs in effluents from PMPs have been detected along channel flows and secondary collection points possibly involving other environmental contaminations such as stormwater and other industrial effluents. For example, Larsson (2008) and Fick *et al.* (2009) examined the concentration of APIs from a major production site of generic drugs for the world market in India, but the samples were taken from the wastewater treatment plant serving most of the drug manufacturers in the area. In Nigeria, the concentrations of metronidazole in wastewater from a drug manufacturing plant and in the final recipient river were 8.04 ± 0.56 and 2.24 ± 0.57 μgL^{-1} respectively due to the dilution factor (Lan *et al.* 2019). Similar scenarios have been reported in other studies (Larsson 2014; Luo *et al.* 2019). In this study, the effluent samples were collected on PMP premises, implying limited contamination and dilution. In all the PMPs atenolol was below LODs, whereas losartan was undetected in raw wastewater of A. Diclofenac was also undetected in raw wastewater of both B and C, whereas carbamazepine was undetected in C only. This could have been due to well-managed processes during the production shifts for these pharmaceuticals that could probably have allowed minimal spills and better handling of defective drugs. The highest concentration of APIs in untreated wastewater was observed in A with $\sum$APIs of 274.2 mgL^{-1}, and the least was in C with $\sum$APIs of 0.19 mgL^{-1}. The differences are attributable to the handling practices at the production lines with C predictably having the least spillovers and uncontrolled disposal of defective drugs.

The concentrations of APIs in the treated wastewater were 0.23, 5.37–7.44, 0.14, and 0.12–4.53 mgL^{-1} for diclofenac, sulfamethoxazole, carbamazepine, and clarithromycin respectively. The rest of the APIs were not detected in the treated wastewater. With reference to the API concentrations (those detected in the raw wastewater) in the treated wastewater of the PMPs, their wastewater treatment facilities are to an extent efficient regarding the removal of some of the APIs. This is partly because of less organic matter as shown in Table 5 in the raw wastewater from the PMPs implying less competition for the adsorbent in the treatment systems (K'oreje *et al.* 2018). The percentages of APIs are shown in Figure 4.

However, the recalcitrance of carbamazepine and clarithromycin for PMP A and C respectively was observed. This discrepancy in comparison with 99.91% and 98.12% of diclofenac and losartan for C and clarithromycin for A could be due to the adsorption medium and or mechanism applied in the treatment facilities of both PMPs.

Table 5 | Average physical-chemical property values of wastewater from WWTPs and PMPs (all concentrations are in mgL^{-1})

		Wastewater treatment plants							Pharmaceutical manufacturing plants					
		Lubigi			Bugolobi				A		B		C	
Paramete	Maximum permissible limits	Channeled wastewater from katanga, Mulago, Kamwokya (12)	Cesspool wastewater & channeled wastewater (5)	Effluent (9)	Cesspool raw wastewater (8)	Treated cesspool wastewater (1)	Nakivubo channel raw wastewater (11)	Treated Nakivubo channel wastewater (10)	Raw (4)	Treated (2)	Raw (3)	Treated (13)	Raw (7)	Treated (6)
PO_4-P	10	10.19 ± 0.10	23.14 ± 0.76	13.12 ± 1.44	13.69 ± 1.63	10.63 ± 0.01	9.06 ± 0.45	6.15 ± 0.42	2.31 ± 0.42	1.53 ± 0.16	2.62 ± 0.24	2.51 ± 0.06	3.22 ± 0.47	2.36 ± 0.30
TN	20	61 ± 3	65 ± 3	52 ± 6	56 ± 3	50 ± 4	54 ± 3	45 ± 0	0.13 ± 0.03	0.04 ± 0.00	0.11 ± 0.04	0.03 ± 0.01	0.05 ± 0.01	0.07 ± 0.01
COD	100	800 ± 57	920 ± 28	320 ± 28	760 ± 21	980 ± 14	780 ± 7	240 ± 14	36 ± 6	140 ± 21	160 ± 14	180 ± 0	180 ± 7	132 ± 3
BOD_5	50	250 ± 14	310 ± 14	188 ± 4	245 ± 7	320 ± 14	280 ± 0	185 ± 7	8 ± 3	80 ± 7	66 ± 1	88 ± 3	80 ± 14	76 ± 0
TOC	50	3,680 ± 28	3,890 ± 14	3,460 ± 85	3,770 ± 57	3,310 ± 85	3,820 ± 28	3,280 ± 57	17 ± 1	22 ± 3	42 ± 6	57 ± 7	47 ± 3	45 ± 4
TSS	100	265 ± 7	272 ± 3	205 ± 21	220 ± 14	242 ± 11	250 ± 7	268 ± 4	110 ± 14	86 ± 3	98 ± 1	72 ± 3	86 ± 3	74 ± 3
pH	6.0–8.0	7.34 ± 0.04	6.89 ± 0.01	6.94 ± 0.20	6.12 ± 0.01	6.22 ± 0.14	5.99 ± 0.62	6.29 ± 0.27	3.82 ± 0.38	5.36 ± 0.20	5.50 ± 0.01	6.19 ± 0.01	5.23 ± 0.07	6.7 ± 0.08

Maximum permissible limits are as per NEMA (NEMA 2020). The bracketed numbers 1,2,.....12,13 are the site allocations for the API probability distribution represented in Figure 5.

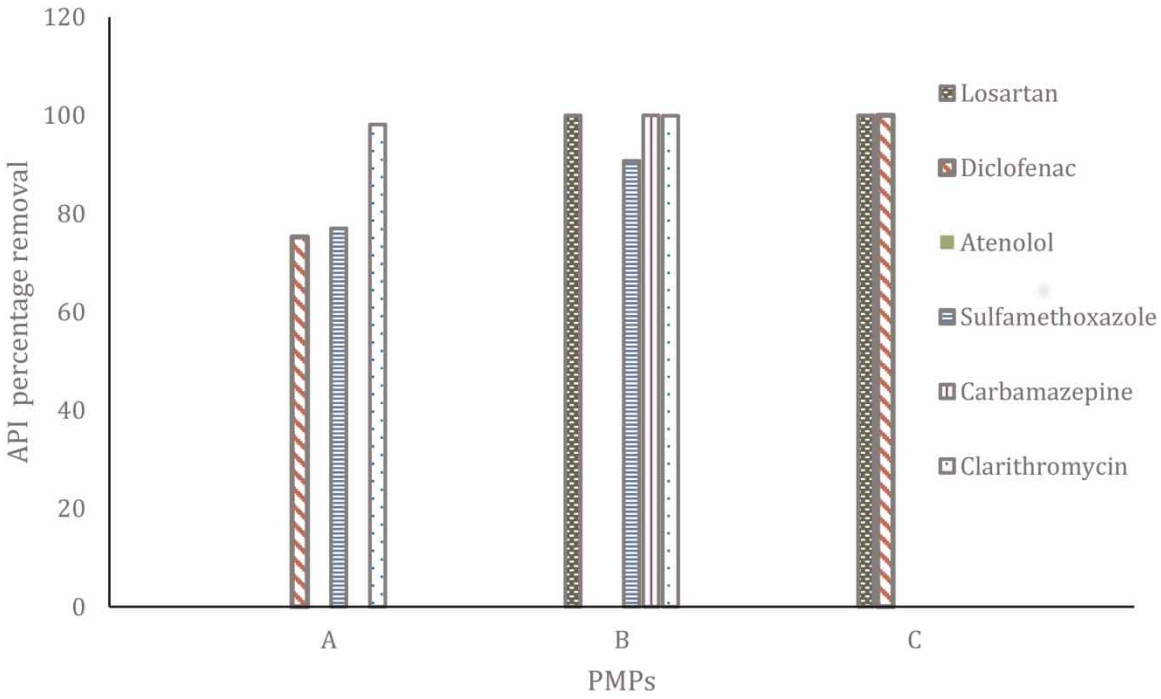


Figure 4 | PMPs' wastewater treatment facilities' removal efficiencies for APIs. Note: Losartan, diclofenac, and sulfamethoxazole, and carbamazepine were not detected in the raw waste of PMP A, B, and C respectively. Losartan as well was below detection limits in all PMP raw and treated wastewater.

Another factor could be the difference in the contact times of the powdered activated carbon with the wastewater. The longer the contact times the higher the absorptivity (Reza *et al.* 2014).

3.1.3. Organic matter and its effects on API prevalence and removal

Generally, organics including COD, TN, and BOD_5 were lower in effluents of PMPs than in WWTPs effluents as shown in Table 5. This is because milli-q water is used in the production process for PMPs. The low organic content could have come from the contamination en route from the production lines during cleaning which is increased at the collection points. This partly accounts for better API removal at PMPs relative to WWTPs. The presence of background organic matter creates adsorption competition with the intended APIs and may also block the adsorbent pores (Delgado *et al.* 2012). This explains why in PMPs effluents and in treated wastewater from WWTPs there is a zero probability of detecting some APIs (as shown in Figure 5) as treatment media have less organic matter to work on and hence sequestrate most APIs. Figure 5 presents the probability of detecting an API at a particular sampling point. Generally, the treated wastewater at the PMPs has lower COD, TN, and BOD_5 values compared with the raw water. The COD and BOD_5 for A and B were higher in the treated than in the raw wastewater.

This could have been due to the relatively longer retention time that the wastewater takes in the treatment processes prior to disposal in the nearby wetland. During sampling, we had to wait for over 5 h for A and B between picking the untreated wastewater and the treated wastewater which was longer than the 1 to 2 h taken for C. This could have enabled the accumulation of more organic matter due to the rotting tendency onset. The TSS in the influent of Lubigi and Bugolobi WWTPs were 265–272 and 220–250 mgL^{-1} respectively. For Bugolobi, the TSS in the effluent were higher than those in the influent at 265, whereas the Lubigi effluent had lower TSS in the effluent at 205. This could be due to the much higher retention time at Lubigi >3 days compared to <3 hours at Bugolobi. For all the PMPs, the TSS were appreciably lower than the WWTPs both in the raw and treated wastewater. This is expected since the wastewater from these plants has less foreign solids contamination like dust due to the indoor production lines that are the source. The pH of the raw wastewater at the PMPs was relatively lower (3.82–5.50) compared to that of the influent at the WWTPs (5.89–7.34). Partly, this could have contributed to higher API removal potentials. In other studies, removal potentials have been reported to reduce with an increase in pH (Sekulic *et al.* 2019). This is due to the reduced H^+ ions, which reduce the interaction of the adsorbent (the electron donor).

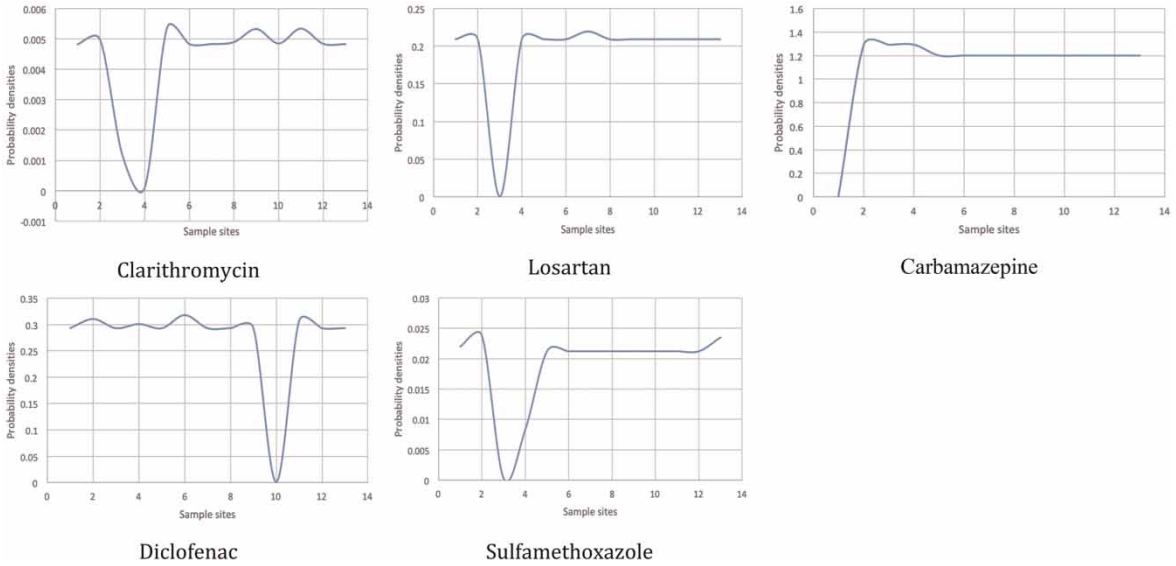


Figure 5 | Distribution curves for concentrations of APIs across the sampling sites. Sampling sites 1,2,3…….12,13 are named in Table 5.

3.2. General efficacy of WWTPs and PMPs in API removal

The Lubigi WWTP had the lowest API efficiency for clarithromycin at 11.46%. The concentration of clarithromycin in the final effluent was 19.55 mgL^{-1}. This implies that other APIs with properties close to those of clarithromycin could escape almost intact. This poses a serious challenge since the treated wastewater from the plant is channeled to the Lubigi swamp, where surrounding communities grow food crops (Fuhrimann *et al.* 2015). The average percentage reductions in clarithromycin concentrations in the Bugolobi WWTP effluents were remarkable at 96.10% and 87.67% for Nakivubo channel-sourced wastewater and Kampala community cesspool-sourced wastewater respectively (Figure 3). However, regarding the ecotoxicological effect of the clarithromycin in Bugolobi WWTP effluent, its concentration of 0.28 ± 0.08–20.38 ± 0.4 mgL^{-1} and that in the Lubigi WWTP effluent are remarkably above its lowest observed effect concentration (LOEC) of 40 ngL^{-1} (Baresel *et al.* 2015). This, therefore, has a critical environmental effect and needs to be checked. The accumulation of diclofenac in the treated Nakivubo channel wastewater at 4.75 ± 0.27 mgL^{-1} also poses a key risk. This concentration is above the diclofenac LOEC and the critical environmental concentration (CEC) of 4,560 ngL^{-1} (Fick *et al.* 2010). These concentrations still pose high ecotoxicological risks despite the relatively high efficiencies of the WWTPs.

The PMPs exhibited higher removal efficiencies with **B** and **C** hitting 99.96% for some APIs as shown in Figure 4. However, carbamazepine showed 100% recalcitrance in **A** despite its relatively low concentration of 0.14 mgL^{-1}. This could be due to the high competition for adsorbents with other pharmaceuticals and notably the highest concentration of clarithromycin in the raw wastewater at 240.83 ± 3.01 mgL^{-1}. Nevertheless, the carbamazepine concentration of 0.14 mgL^{-1} may not be of major concern, in this case, it being below the ecotoxicological LOEC of 0.346 mgL^{-1} (Fick *et al.* 2010). Operationally, it should be monitored due to the possibility of higher concentrations (above LOEC) escaping during other production periods. The other APIs in the PMP treated wastewater were in ranges 0.23–0.57, 5.37–7.44, and 0.19–4.53 mgL^{-1} for diclofenac, sulfamethoxazole, and clarithromycin. These are all above the CECs of the three APIs at 4,560, 10,000, and 40 ngL^{-1} respectively (Baresel *et al.* 2015). It is therefore pertinent to improve and regulate these treatment systems to lower the disposed wastewater API concentrations below CECs and LOECs. One possible improvement could be supplementing the current activated sludge process with anaerobic treatment methods. These have been found effective in API removal due to the high organic strength nature and low operating costs (Ji *et al.* 2013; Shi *et al.* 2017). Aerobic treatment methods are more effective than anaerobic processes and could also be opted if the techno-economic evaluation allows (Komolafe *et al.* 2021). This is because they are more energy-intensive, implying more operating costs. The more advanced methods including Fenton oxidation and conductive-diamond electro-oxidation (Pérez *et al.* 2017) could also be explored notwithstanding the relatively higher costs still. Besides the high operating costs, proper control of the oxidation by-products is required if oxidation processes are opted for (Liu *et al.* 2018).

3.3. Eco-toxicological risk assessment of APIs in the immediate effluent recipient environments

The hazard quotients for the APIs detected in effluents were in the range 0.018–9775,000 (Table 6) with the highest risk being posed by clarithromycin from Lubigi WWTP effluent and the lowest by sulfamethoxazole from PMP C effluent and Lubigi WWTP effluent. Only sulfamethoxazole from the effluents of Lubigi WWTP, Bugolobi WWTP, and PMP C posed low risks with hazard quotients of <1 at 0.018,0.305, and 0.018 respectively. The rest of the API hazard quotients are >1 and higher than those reported in other related studies (Ashfaq *et al.* 2017; K'oreje *et al.* 2018; Nantaba *et al.* 2020). This is due to the dilution effect in those studies. For example, the risk assessment done by (Nantaba *et al.* 2020) was based on samples from Lake Victoria, implying that a high dilution factor accounts for the relatively lower hazard quotients. In this study, the risk assessment shows that the immediate recipients of the effluents directly from the PMPs and the WWTPs are at very high risk. For example, the communities along Nakivubo channel utilize the wastewater for both domestic and agricultural irrigation. Besides, the swamps are also being encroached on for agriculture. Uptake of such APIs by crops leads to high phytotoxicity (Yakubu 2017). This has been reported to potentially cause health distortions such as drug resistance due to the consumption of such crops (Al-Farsi *et al.* 2017; Yakubu 2017).

Table 6 | Predicted no-effect concentrations, maximum measured concentrations, and hazard quotients of the studied APIs in the immediate effluent recipient environments

API	Effluent source	PNEC ($\times 10^{-3}$ mgL^{-1})	MMC (mgL^{-1})	Hazard quotient
Carbamazepine	Lubigi	0.01[a]	0.00005	5
	Bugolobi	2.500[b]	1.17	468
	A	2.500[b]	0.14	56
	B	0.01[a]	0.00005	5
	C	0.01[a]	0.00005	5
Diclofenac	Lubigi	0.200[c]	0.00054	2.7
	Bugolobi	0.050[c]	4.75	95000
	A	0.050[c]	0.23	4600
	B	0.200[c]	0.00054	2.7
	C	0.200[c]	0.57	2850
Sulfamethoxazole	Lubigi	10.000[a]	0.00018	0.018
	Bugolobi	0.590[b]	0.00018	0.305
	A	0.590[b]	7.44	12611
	B	10.000[a]	5.37	537
	C	10.000[a]	0.00018	0.018
Clarithromycin	Lubigi	0.002[c]	19.55	9775000
	Bugolobi	8.160[c]	1.08	132
	A	8.160[c]	4.53	555
	B	0.002[c]	0.12	60000
	C	0.002[c]	0.19	9500
Losartan	Lubigi	0.078[d]	0.00265	33.97
	Bugolobi	0.078[d]	0.00265	33.97
	A	0.0637[d]	0.00265	41.60
	B	0.0637[d]	0.00265	41.60
	C	0.0637[d]	0.00265	41.60

[a]Baresel *et al.* (2015).
[b]Nantaba *et al.* (2020).
[c]Pereira *et al.* (2020).
[d]Godoy *et al.* (2015).

3.4. Limitations of the study

- The wastewater samples were collected within 3 weeks with no consideration of the seasonal variations that could have influenced the wastewater physicochemical composition and the target APIs.
- The LC-MS equipment used in this study had relatively high LODs for the studied APIs. This could have rendered some APIs with trace concentrations in nanograms undetectable in some wastewater samples.

4. CONCLUSION

- The concentration ranges of the APIs were <LOD, <LOD – 4.75, <LOD – 1.37, <LOD – 1.17 and 0.28–19.55 mgL^{-1} for losartan, diclofenac, sulfamethoxazole, carbamazepine, and clarithromycin respectively in effluents of WWTPs, whereas in treated wastewater from PMPs concentrations were 0.00, 0.00–0.23, 5.30–7.4, 0.00–0.14, and 0.12–4.53 mgL^{-1} for losartan, diclofenac, sulfamethoxazole, carbamazepine, and clarithromycin respectively.
- The API removal efficiencies of PMPs are relatively higher than WWTPs at >99% removal efficiencies for some APIs. However, for some APIs, the effluent concentrations are way higher than the LOECs and hence pose a high ecotoxicological risk. The wastewater treatment systems should be checked and regulated by NEMA based on LOECs of all the pharmaceuticals that they produce rather than the efficiencies.
- The presence of APIs in the effluents of PMPs could inherently have a fatal or growth-deterring effect on the microorganisms that are core in the biological wastewater treatment. This may have consequences on treatment costs due to longer hydraulic retention times. It is therefore pertinent to carry out a study on this.
- With the removal inefficacy revealed for the APIs in this study, this opens a larger need to study other classes of APIs with possibly LOD experimentation that is at least lower than the LOECs of the studied APIs. The HQs from the eco-toxicological assessment further reveal an important issue of the APIs to the immediate recipient ecosystems, which urgently requires prior curbing mechanisms
- The HQs of most of the APIs in effluents were greater than 1 and pose a very high ecotoxicological risk.

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DATA AVAILABILITY STATEMENT

All relevant data are included in the paper or its Supplementary Information.

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