Pharmaceuticals in Wastewater Treatment Plants: A Systematic Review on the Substances of Greatest Concern Responsible for the Development of Antimicrobial Resistance

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***Table S1**. Pre-set list of exclusion and inclusion criteria for the title and abstract screening phases.*

Key elements	**Inclusion and exclusion criteria during the phase of the title screening**	**Explanations of the inclusion and exclusion criteria**
Pharmaceuticals	**Inclusion of studies dealing with**: - PRs, Antibiotics, Antimicrobials, Contaminants, Drugs, Residues **Exclusion of studies dealing exclusively with**: - Heavy Metals, Plastics, Nutrients, Phosphates, Nitrates - PRs Non-relevant to AMR, Veterinary products	It is unlikely that authors of extensive studies list in the title all the PRs they have analysed. However, it is more probable that, in researches focused on a limited number of compounds, the names of these are reported in the title. Therefore, the studies dealing with veterinary products or PRs non-relevant to AMR (see below) were excluded from this review. Moreover, the exclusion criteria also covered the literature concerning the presence of non-PRs compounds.
Wastewater	**Inclusion of studies dealing with**: - WW **Exclusion of studies dealing exclusively with**: - Drinking water - Water from Water Basins (Rivers, Lakes, Seas) - Soil, Sewage, Other forms of non-specific and non-representative WW (Dairy, Swine, Poultry, Slaughterhouse Synthetic WW)	During the title screening phase of the review, it was necessary to focus only on WW relevant to the question in order to reduce the heterogeneity of the primary search. Therefore, wastes deriving from solid or semi-solid matrices (soil, sewage, manure) or deriving from animal or industrial activities were not considered in this review.
Topic	**Inclusion of studies dealing with**: - Occurrence of PRs in WW - Resistant-Bacteria/Fungi/Genes or Removal Treatments, in addition to the study of PRs occurrence **Exclusion of studies dealing exclusively with**: - Resistant-Bacteria/Fungi or Resistant-Genes - Removal or Abatement Treatments (Biological, Physical or Chemical) - Reviews *et similia*	In some cases, the title of a study represents a clear indication of its general topic. This review did not cover the specific literature on treatment systems, resistant-bacteria or fungi, or analyses of PRs in water basins or potable water. However, chimeric studies dealing with both the occurrence and removal of PRs from WW passed the eligibility selection.
Language	**Inclusion of studies:** - in English, Italian or Spanish **Exclusion of studies:** - in other Languages different from the three above	In this phase, language bias and publication bias (Song *et al.*, 2010; Dickersin, 2006) may occur.
Key elements	**Inclusion and exclusion criteria during the phase of the abstract screening**	**Reasons for the inclusion and exclusion**
PRs	**Inclusion of studies dealing with**: - Antibiotics, Antifungals or Personal-care products relevant to AMR **Exclusion of studies dealing exclusively with**:	Typically, in the abstracts of their studies, authors are prone to make explicit the objects of their research. Only researches dealing with antibiotics (WHO, 2019), antifungals

	- Heavy Metals, Nutrients, Plastics - PRs Non-relevant to AMR, Veterinary products - Only one PR	(CDC, 2019 and 2020; NHS, 2020) and personal-care products (Yadav *et al.*, 2019) that are at relatively high risk of selection of bacterial resistance moved to the critical appraisal phase. Moreover, great importance was given to studies that analysed more than one PRs in WW. A list of the relevant PRs is provided in the supplementary material (Data_extraction.xlsx, Sheet PRs List).
WW	**Inclusion of studies dealing with**: - WW **Exclusion of studies dealing exclusively with**: - Drinking water, Water Basins (Rivers, Lakes, Seas), Soil, Sewage, Other forms of non-specific and not representative WW (Dairy, Swine, Saline, Synthetic WW)	Thorough research was carried on through the screening of the abstract when the type of WW was not completely clear after the title screening.
Wastewater Treatment Plants	**Inclusion of studies dealing with**: - Urban or Hospital WWTPs **Exclusion of studies dealing exclusively with**: - Other forms of specific and not relevant WWTPs (Animal, Industrial)	During the abstract screening, it was essential to select only the studies dealing with WW of urban and hospital sewage. Thus the literature about animal or industrial wastes, in which is unlikely to find PRs prescribed for humans, was rejected from this work.
Topic	**Inclusion of studies dealing with**: - Occurrence of PRs in WW **Exclusion of studies dealing exclusively with**: - Resistant-Bacteria/Fungi or Resistant-Genes - Analysis of Water from Water Basins (Rivers, Lakes, Seas) - Removal Treatments (Biological, Physical or Chemical Degradation) - A Specific Phase of the Treatment - Reviews *et similia*	A further screening at the level of the abstract was necessary to identify the topic of the studies. During this phase, the majority of studies was excluded due to lack of relevance with the review question. In detail, studies dealing specifically with removal treatments or with the research of resistant genes, bacteria or fungi were rejected from this review.

***Table S2**. Pre-set list of characteristics and results that were coded and extracted from each study.*

Bibliographic information
Title
Authors
Date of publication
Number of citations[a] (average citations per month)
Journal - impact factor of the journal (year, source)
Country or countries of the study

Sponsorship		
DOI		
Information relating to the study		
Methodologies and Research techniques	WWTPs number	
	WWTPs name - site	
	Population served by the WWTPs	
	Treatments	
	Characteristics (HRT, SRT, DWF)[b]	
	Tertiary Treatment (Y/N – specifications)	
	Sampling campaigns: Daily, Weekly, Monthly, Annual (characteristics)	
	Composite sampling (Y/N)	
	Season of sampling	
	Locations of sampling in the WWTPs	
	Number of samples for each point of sampling	
	Sample gathered size Same size for all the samples (Y/N)	
	PRs extraction technique - Solid Phase (Y/N) Extraction within 24h from the sampling (Y/N, if not specify the maximum time) Volume of WW analysed Cartridge type Flow Same extraction technique for all the replicas (Y/N)	
	PRs detection technique Gas or Liquid chromatography coupled to Mass Spectrophotometry (Y/N) Column Volume injected Ionisation mode Same technique for all the replicas (Y/N)	
	PRs relevant to the question[c] discovered in WW	
	PRs concentrations influent (standard deviation), if applicable	
	PRs concentrations effluent (standard deviation)	
	Removal efficiency (standard deviation), if applicable	
	Risk assessment, if applicable	
Other information		
Practical and historical significance of the study according to authors		
Perspectives identified by authors in which to focus future attention		

[a] Google Scholar. [b] HDR: Hydraulic retention time; SRT: sludge retention time; DWF: daily water flow. [c] Look at the supplementary material (Data_extraction.xlsx, Sheet PRs List) for the list of all the 218 relevant PRs.

Table S3*. Strings designed for each database.*

Database	Search Strings
Web of Science	ALL=(occurrence OR presence OR level* OR distribution OR determination) AND ALL=(pharmaceutical* OR antibiotic* OR antimicrobial*) AND ALL=(wastewater OR "waste water*" OR effluent* OR influent* OR sewage*) AND ALL=("a

	nti* resistance") AND ALL=("wastewater treatment plant*" OR WWTP*) NOT TI=(review) NOT TI=(gene*) NOT TI=(resistant) NOT TI=(dairy OR swine)
PubMed/Medline	(occurrence OR presence OR level* OR distribution OR determination) AND (pharmaceutical* OR antibiotic* OR antimicrobial*) AND (wastewater OR "waste water*" OR effluent* OR influent* OR sewage*) AND ("anti* resistance") AND ("wastewater treatment plant*" OR WWTP*) NOT (gene*[Title]) NOT (resistant[Title]) NOT (dairy[Title] OR swine[Title])
ProQuest 1st search string	((occurrence OR presence OR level* OR distribution OR determination) AND (pharmaceutical* OR antibiotic* OR antimicrobial*) AND (wastewater OR WW OR ("waste water" OR "waste waters") OR effluent* OR influent* OR sewage*) AND ("antibiotic resistance" OR "antimicrobial resistance") AND ("wastewater treatment plant*" OR WWTP*)) NOT ti(review) NOT ti(gene*) NOT ti(resistant) NOT ti(dairy OR swine)
ProQuest 2nd search string	noft((occurrence OR presence OR level* OR distribution OR determination) AND (pharmaceutical* OR antibiotic* OR antimicrobial*) AND (wastewater OR WW OR ("waste water" OR "waste waters") OR effluent* OR influent* OR sewage*) AND ("antibiotic resistance" OR "antimicrobial resistance") AND ("wastewater treatment plant*" OR WWTP*)) NOT ti(review) NOT ti(gene*) NOT ti(resistant) NOT ti(dairy OR swine)
BASE	(occurrence OR presence OR level* OR distribution OR determination) AND (pharmaceutical* OR antibiotic* OR antimicrobial*) AND (wastewater OR WW OR ("waste water" OR "waste waters") OR effluent* OR influent* OR sewage*) AND ("antibiotic resistance" OR "antimicrobial resistance") AND ("wastewater treatment plant*" OR WWTP*) (NOT tit:review) (NOT tit:gene*) (NOT tit:resistant) (NOT tit:dairy) (NOT tit:swine) year:[2015 TO *]

PR	Total				Autumn				Summer				Spring				Winter			
	Std.	Medi	Maxi	Mini	Std.	Medi	Maxi	Mini	Std.	Medi	Maxi	Mini	Std.	Medi	Maxi	Mini	Std.	Medi	Maxi	Mini
Azithromycin	3207	125.4	1154	10.00	48.22	53.95	102.1	10.00	148.1	114.0	328.0	13.10	.	148.7	148.7	148.7	4285	3471	1154	63.20
Ciprofloxacin	2678	207.0	8801	1.00	2705	6161	8801	3534	129.1	163.0	345.0	1.00	.	207.0	207.0	207.0	1126.	139.0	3000.	15.80
Clarithromycin	1582.	130.0	6917.	20.20	1220.	642.8	2822.	72.70	254.3	51.60	619.4	20.20	61.65	122.5	260.0	86.30	2671.	1413.	6917.	65.00
Clindamycin	14.69	14.15	41.10	8.40	14.69	14.15	41.10	8.40												
Erythromycin	378.4	266.0	1193.	5.50	22.77	31.75	58.60	5.50					346.4	390.0	1193.	266.0				
Metronidazole	7766.	102.8	2065	2.10	1030	66.85	2065	13.60					191.2	140.0	380.0	2.10				
Norfloxacin	651.1	272.0	2800.	5.06	44.03	62.70	143.4	45.30	299.8	447.0	778.0	5.06					909.0	612.0	2800.	38.60
Ofloxacin	1170.	638.5	5741.	22.00	1969.	1947.	5741.	1578.	409.1	678.0	942.0	22.00	240.9	419.0	868.0	138.0	303.3	636.5	870.0	166.0
Oxytetracycline	379.6	121.6	1531.	1.75					176.6	187.0	448.0	1.75	.	92.60	92.60	92.60	628.0	121.6	1531.	104.0
Roxithromycin	5155.	106.0	1913	16.70	579.4	268.7	1275.	23.80	26.92	27.55	75.10	16.70	7.000	101.0	106.0	96.10	7513.	3422.	1913	155.6
Sulfadiazine	210.0	67.70	574.0	1.72					241.6	177.0	574.0	1.72	91.92	255.0	320.0	190.0	28.94	18.75	67.70	2.24
Sulfamethoxazole	1363	237.0	4930	2.95	1703.	1426.	4569.	845.3	94.31	120.8	237.0	2.95	1150.	164.6	3790.	40.00	2110	1491.	4930	52.20
Tetracycline	130.8	26.20	374.0	.48					144.9	124.0	374.0	.48					23.27	17.00	55.60	5.04
Trimethoprim	2220.	400.0	8430.	6.84	712.3	995.4	1926.	400.0	19.63	10.01	48.10	6.84	4100.	335.0	8430.	31.40	2093.	900.0	5600.	34.60

Table S4. *Statistics for the 14 most occurring PRs in INFLUENTS by Seasons [4-10, 14, 16, 18, 19, 22-24].*

***Table S5**. One-way ANOVA with Bonferroni correction for the 14 most occurring PRs in INFLUENTS by Seasons[4-10, 14, 16, 18, 19, 22-24].*

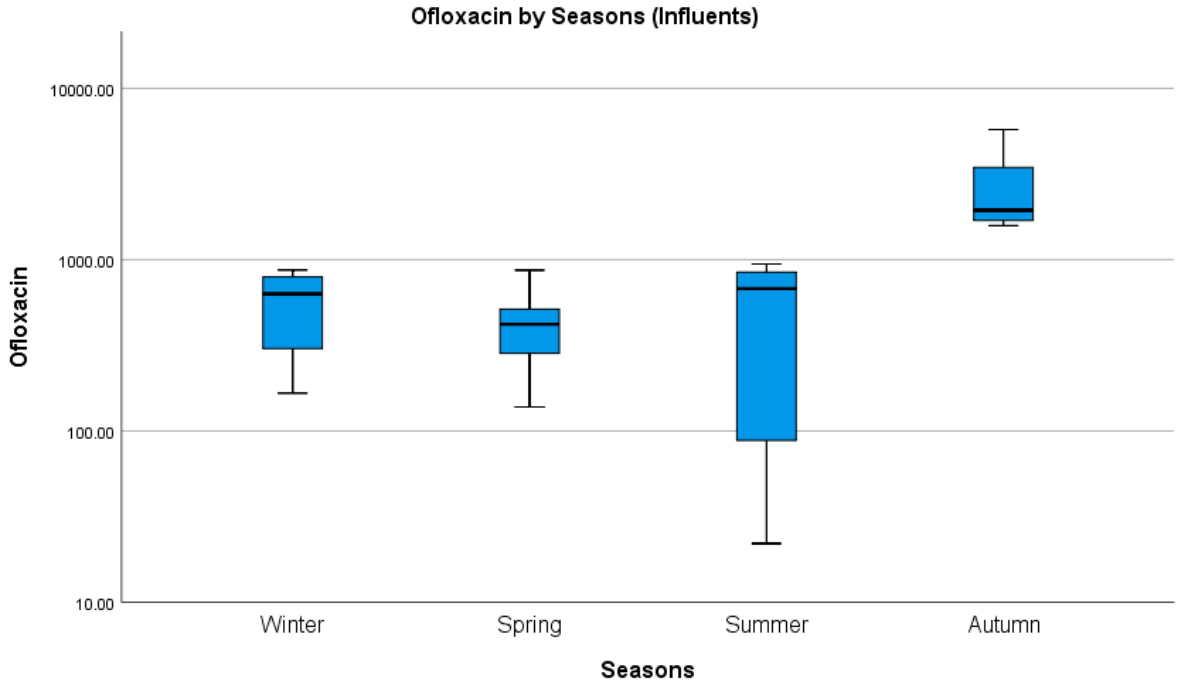
Bonferroni

Dependent Variable	(I) Seasons	(J) Seasons	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval Lower Bound	95% Confidence Interval Upper Bound
Clarithromycin	Winter	Spring	2193.38333	848.14641	.115	-337.5209	4724.2876
		Summer	2136.54333	848.14641	.132	-394.3609	4667.4476
		Autumn	1286.30000	939.59646	1.000	-1517.4950	4090.0950
	Spring	Winter	-2193.38333	848.14641	.115	-4724.2876	337.5209
		Summer	-56.84000	808.67587	1.000	-2469.9625	2356.2825
		Autumn	-907.08333	904.12711	1.000	-3605.0363	1790.8696
	Summer	Winter	-2136.54333	848.14641	.132	-4667.4476	394.3609
		Spring	56.84000	808.67587	1.000	-2356.2825	2469.9625
		Autumn	-850.24333	904.12711	1.000	-3548.1963	1847.7096
	Autumn	Winter	-1286.30000	939.59646	1.000	-4090.0950	1517.4950
		Spring	907.08333	904.12711	1.000	-1790.8696	3605.0363
		Summer	850.24333	904.12711	1.000	-1847.7096	3548.1963
Ofloxacin	Winter	Spring	143.82143	516.77567	1.000	-1368.8425	1656.4854
		Summer	87.35000	495.45608	1.000	-1362.9090	1537.6090
		Autumn	-2226.77500*	583.00159	.006	-3933.2901	-520.2599
	Spring	Winter	-143.82143	516.77567	1.000	-1656.4854	1368.8425
		Summer	-56.47143	415.50327	1.000	-1272.6990	1159.7561
		Autumn	-2370.59643*	516.77567	.001	-3883.2604	-857.9325
	Summer	Winter	-87.35000	495.45608	1.000	-1537.6090	1362.9090
		Spring	56.47143	415.50327	1.000	-1159.7561	1272.6990
		Autumn	-2314.12500*	495.45608	.001	-3764.3840	-863.8660
	Autumn	Winter	**2226.77500***	583.00159	**.006**	520.2599	3933.2901
		Spring	**2370.59643***	516.77567	**.001**	857.9325	3883.2604
		Summer	**2314.12500***	495.45608	**.001**	863.8660	3764.3840
Roxithromycin	Winter	Spring	6709.27000	3799.18207	.631	-5478.9709	18897.5109
		Summer	6773.59500	3046.12236	.288	-2998.7382	16545.9282
		Autumn	6351.12000	3046.12236	.367	-3421.2132	16123.4532
	Spring	Winter	-6709.27000	3799.18207	.631	-18897.5109	5478.9709
		Summer	64.32500	3932.52705	1.000	-12551.7029	12680.3529
		Autumn	-358.15000	3932.52705	1.000	-12974.1779	12257.8779
	Summer	Winter	-6773.59500	3046.12236	.288	-16545.9282	2998.7382
		Spring	-64.32500	3932.52705	1.000	-12680.3529	12551.7029
		Autumn	-422.47500	3210.89489	1.000	-10723.4186	9878.4686
	Autumn	Winter	-6351.12000	3046.12236	.367	-16123.4532	3421.2132
		Spring	358.15000	3932.52705	1.000	-12257.8779	12974.1779
		Summer	422.47500	3210.89489	1.000	-9878.4686	10723.4186

Sulfamethoxazole	Winter	Spring	**16294.78000***	5501.20919	**.040**	534.4406	32055.1194
		Summer	16703.72500	6310.31972	.083	-1374.6241	34782.0741
		Autumn	14764.45000	7194.87147	.305	-5848.0394	35376.9394
	Spring	Winter	-16294.78000*	5501.20919	.040	-32055.1194	-534.4406
		Summer	408.94500	6182.82537	1.000	-17304.1473	18122.0373
		Autumn	-1530.33000	7083.31632	1.000	-21823.2265	18762.5665
	Summer	Winter	-16703.72500	6310.31972	.083	-34782.0741	1374.6241
		Spring	-408.94500	6182.82537	1.000	-18122.0373	17304.1473
		Autumn	-1939.27500	7728.53171	1.000	-24080.6404	20202.0904
	Autumn	Winter	-14764.45000	7194.87147	.305	-35376.9394	5848.0394
		Spring	1530.33000	7083.31632	1.000	-18762.5665	21823.2265
		Summer	1939.27500	7728.53171	1.000	-20202.0904	24080.6404
Trimethoprim	Winter	Spring	-653.78333	1359.57529	1.000	-4710.8126	3403.2460
		Summer	1610.32417	1359.57529	1.000	-2446.7051	5667.3535
		Autumn	549.64167	1359.57529	1.000	-3507.3876	4606.6710
	Spring	Winter	653.78333	1359.57529	1.000	-3403.2460	4710.8126
		Summer	2264.10750	1599.80790	1.000	-2509.7859	7038.0009
		Autumn	1203.42500	1599.80790	1.000	-3570.4684	5977.3184
	Summer	Winter	-1610.32417	1359.57529	1.000	-5667.3535	2446.7051
		Spring	-2264.10750	1599.80790	1.000	-7038.0009	2509.7859
		Autumn	-1060.68250	1599.80790	1.000	-5834.5759	3713.2109
	Autumn	Winter	-549.64167	1359.57529	1.000	-4606.6710	3507.3876
		Spring	-1203.42500	1599.80790	1.000	-5977.3184	3570.4684
		Summer	1060.68250	1599.80790	1.000	-3713.2109	5834.5759

*. The mean difference is significant at the 0.05 level.

***Table S6**. Box Plot and multiple comparison test for Ofloxacin detected in INFLUENTS by seasons [4-10, 14, 16, 18, 19, 22-24].*



Multiple Comparisons

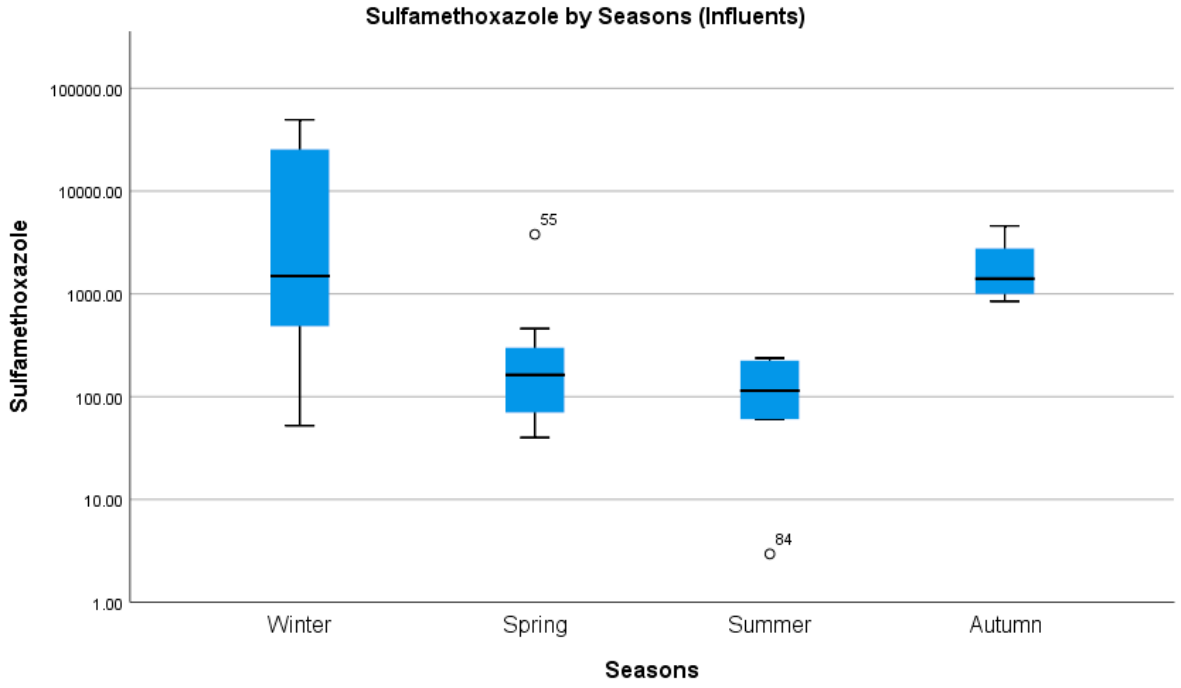
Dependent Variable: Ofloxacin

Bonferroni

(I) Seasons	(J) Seasons	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval Lower Bound	95% Confidence Interval Upper Bound
Winter	Spring	143.82143	516.77567	1.000	-1368.8425	1656.4854
	Summer	87.35000	495.45608	1.000	-1362.9090	1537.6090
	Autumn	-2226.77500*	583.00159	.006	-3933.2901	-520.2599
Spring	Winter	-143.82143	516.77567	1.000	-1656.4854	1368.8425
	Summer	-56.47143	415.50327	1.000	-1272.6990	1159.7561
	Autumn	-2370.59643*	516.77567	.001	-3883.2604	-857.9325
Summer	Winter	-87.35000	495.45608	1.000	-1537.6090	1362.9090
	Spring	56.47143	415.50327	1.000	-1159.7561	1272.6990
	Autumn	-2314.12500*	495.45608	.001	-3764.3840	-863.8660
Autumn	**Winter**	**2226.77500***	583.00159	**.006**	520.2599	3933.2901
	Spring	**2370.59643***	516.77567	**.001**	857.9325	3883.2604
	Summer	**2314.12500***	495.45608	**.001**	863.8660	3764.3840

*. The mean difference is significant at the 0.05 level.

***Table S7**. Box Plot and multiple comparison test for Sulfamethoxazole detected in INFLUENTS by seasons [4-10, 14, 16, 18, 19, 22-24].*



Multiple Comparisons

Dependent Variable: Sulfamethoxazole

Bonferroni

(I) Seasons	(J) Seasons	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval Lower Bound	95% Confidence Interval Upper Bound
Winter	**Spring**	**16294.78000***	5501.20919	**.040**	534.4406	32055.1194
	Summer	16703.72500	6310.31972	.083	-1374.6241	34782.0741
	Autumn	14764.45000	7194.87147	.305	-5848.0394	35376.9394
Spring	Winter	-16294.78000*	5501.20919	.040	-32055.1194	-534.4406
	Summer	408.94500	6182.82537	1.000	-17304.1473	18122.0373
	Autumn	-1530.33000	7083.31632	1.000	-21823.2265	18762.5665
Summer	Winter	-16703.72500	6310.31972	.083	-34782.0741	1374.6241
	Spring	-408.94500	6182.82537	1.000	-18122.0373	17304.1473
	Autumn	-1939.27500	7728.53171	1.000	-24080.6404	20202.0904
Autumn	Winter	-14764.45000	7194.87147	.305	-35376.9394	5848.0394
	Spring	1530.33000	7083.31632	1.000	-18762.5665	21823.2265
	Summer	1939.27500	7728.53171	1.000	-20202.0904	24080.6404

*. The mean difference is significant at the 0.05 level.

Table 58. *Statistics for the 14 most occurring PRs in EFFLUENTS by Seasons [1-10, 14, 16, 18-20, 22-24].*

PR	Total				Autumn				Summer				Spring				Winter			
	Med	Std.	N	Mean	Med	Std.	N	Mean	Med	Std.	N	Mean	Med	Std.	N	Mean	Med	Std.	N	Mean
Azithromycin	11.3	1210	23	3931.41	.400	.424	2	.4000	8.60	13.0	14	12.1300	207.	271.	2	207.700	1152	2217	5	17967.3
Ciprofloxacin	73.2	4172	33	1069.13	237.	278.	4	310.750	45.1	34.4	19	48.8821	2100	1270	3	9333.33	300.	1042	7	729.952
Clarithromycin	102.	2597	33	661.822	8.00	17.0	4	13.4750	90.0	174.	18	138.473	195.	6057	6	2637.61	373.	697.	5	693.600
Clindamycin	8.10	9.23	13	8.7769	1.00	3.64	4	2.6500	8.40	3.63	8	8.4375	36.0	.	1	36.0000				
Erythromycin	81.1	450.	23	363.556	2.55	8.37	4	5.8500	48.6	226.	10	133.640	1083	421.	9	778.000				
Metronidazole	15.5	811.	14	357.178	10.0	7.27	4	9.7750	4.85	3.02	4	6.1250	680.	1179	5	977.200	50.9	.	1	50.9000
Norfloxacin	40.2	574.	27	256.858	.800	.300	3	.8000	46.6	117.	16	112.788					285.	975.	8	641.021
Ofloxacin	162.	3198	39	5430.21	29.4	26.1	4	33.4500	85.0	654.	21	319.107	450.	6308	10	20447.7	115.	57.0	4	116.625
Oxytetracycline	39.5	109.	13	66.0777					54.1	35.1	8	43.0400					27.4	175.	5	102.938
Roxithromycin	81.3	2000	10	1199.34					4.69	11.1	4	9.9275	114.	.	1	114.300	1457	2364	5	2367.88
Sulfadiazine	7.90	107.	24	68.5333					5.22	122.	17	73.0900	130.	45.8	3	120.000	7.43	10.4	4	10.5675
Sulfamethoxazole	158.	5006	32	2017.80	181.	129.	4	194.250	49.6	26.7	6	46.0917	184.	2418	13	1094.70	578.	8302	9	5476.11
Tetracycline	13.5	32.7	11	30.5436					56.8	28.7	6	52.7033					.790	5.56	5	3.9520
Trimethoprim	130.	5520	22	1479.27	11.0	75.6	4	48.3500	11.7	6.14	3	8.6633	285.	1044	6	4846.21	300.	309.	9	360.811

***Table S9**. One-way ANOVA with Bonferroni correction for the 14 most occurring PRs in EFFLUENTS by Seasons [1-10, 14, 16, 18-20, 22-24].*

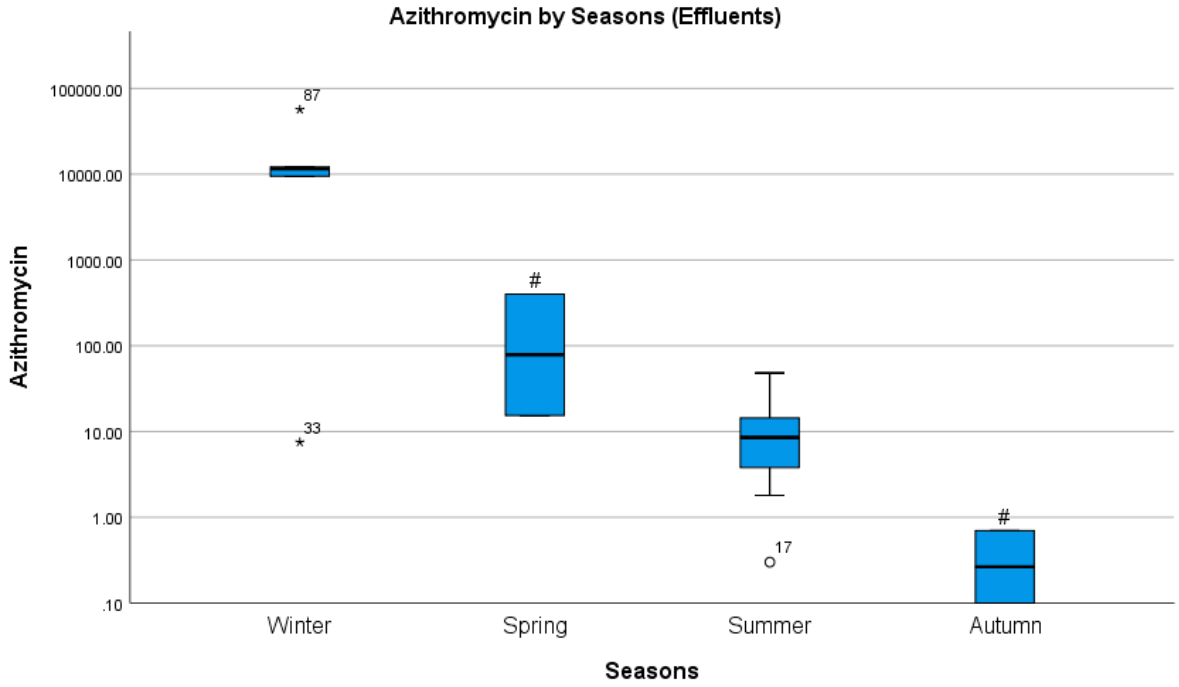
Bonferroni

Dependent Variable	(I) Seasons	(J) Seasons	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
Azithromycin	Winter	Spring	17759.60000	8513.68465	.304	-7303.7950	42822.9950
		Summer	**17955.17000***	5301.47015	**.019**	2348.1977	33562.1423
		Autumn	17966.90000	8513.68465	.290	-7096.4950	43030.2950
	Spring	Winter	-17759.60000	8513.68465	.304	-42822.9950	7303.7950
		Summer	195.57000	7692.18136	1.000	-22449.4054	22840.5454
		Autumn	207.30000	10175.79946	1.000	-29749.1867	30163.7867
	Summer	Winter	-17955.17000*	5301.47015	.019	-33562.1423	-2348.1977
		Spring	-195.57000	7692.18136	1.000	-22840.5454	22449.4054
		Autumn	11.73000	7692.18136	1.000	-22633.2454	22656.7054
	Autumn	Winter	-17966.90000	8513.68465	.290	-43030.2950	7096.4950
		Spring	-207.30000	10175.79946	1.000	-30163.7867	29749.1867
		Summer	-11.73000	7692.18136	1.000	-22656.7054	22633.2454
Ciprofloxacin	Winter	Spring	-8603.38048*	2325.90964	.005	-15189.3162	-2017.4448
		Summer	681.07075	1490.26444	1.000	-3538.6915	4900.8330
		Autumn	419.20286	2112.61234	1.000	-5562.7703	6401.1760
	Spring	Winter	**8603.38048***	2325.90964	**.005**	2017.4448	15189.3162
		Summer	**9284.45123***	2093.99866	**.001**	3355.1837	15213.7188
		Autumn	**9022.58333***	2574.31023	**.009**	1733.2883	16311.8784
	Summer	Winter	-681.07075	1490.26444	1.000	-4900.8330	3538.6915
		Spring	-9284.45123*	2093.99866	.001	-15213.7188	-3355.1837
		Autumn	-261.86789	1854.21294	1.000	-5512.1695	4988.4337
	Autumn	Winter	-419.20286	2112.61234	1.000	-6401.1760	5562.7703
		Spring	-9022.58333*	2574.31023	.009	-16311.8784	-1733.2883
		Summer	261.86789	1854.21294	1.000	-4988.4337	5512.1695
Clarithromycin	Winter	Spring	-1944.01667	1533.26925	1.000	-6285.5493	2397.5160
		Summer	555.12611	1280.04540	1.000	-3069.3899	4179.6421
		Autumn	680.12500	1698.59158	1.000	-4129.5265	5489.7765
	Spring	Winter	1944.01667	1533.26925	1.000	-2397.5160	6285.5493
		Summer	2499.14278	1193.64849	.271	-880.7358	5879.0214
		Autumn	2624.14167	1634.47051	.715	-2003.9477	7252.2310
	Summer	Winter	-555.12611	1280.04540	1.000	-4179.6421	3069.3899
		Spring	-2499.14278	1193.64849	.271	-5879.0214	880.7358
		Autumn	124.99889	1399.67692	1.000	-3838.2601	4088.2578
	Autumn	Winter	-680.12500	1698.59158	1.000	-5489.7765	4129.5265
		Spring	-2624.14167	1634.47051	.715	-7252.2310	2003.9477
		Summer	-124.99889	1399.67692	1.000	-4088.2578	3838.2601

Ofloxacin	Winter	Spring	-20331.07500	18929.05981	1.000	-73268.1724	32606.0224
		Summer	-202.48214	17455.22224	1.000	-49017.8384	48612.8742
		Autumn	83.17500	22624.55383	1.000	-63188.7583	63355.1083
	Spring	Winter	20331.07500	18929.05981	1.000	-32606.0224	73268.1724
		Summer	20128.59286	12293.23605	.663	-14250.7287	54507.9144
		Autumn	20414.25000	18929.05981	1.000	-32522.8474	73351.3474
	Summer	Winter	202.48214	17455.22224	1.000	-48612.8742	49017.8384
		Spring	-20128.59286	12293.23605	.663	-54507.9144	14250.7287
		Autumn	285.65714	17455.22224	1.000	-48529.6992	49101.0134
	Autumn	Winter	-83.17500	22624.55383	1.000	-63355.1083	63188.7583
		Spring	-20414.25000	18929.05981	1.000	-73351.3474	32522.8474
		Summer	-285.65714	17455.22224	1.000	-49101.0134	48529.6992
Sulfamethoxazole	Winter	Spring	4381.41111	2043.23110	.245	-1419.1846	10182.0068
		Summer	5430.01944	2483.40660	.224	-1620.2049	12480.2437
		Autumn	5281.86111	2831.51917	.436	-2756.6314	13320.3536
	Spring	Winter	-4381.41111	2043.23110	.245	-10182.0068	1419.1846
		Summer	1048.60833	2325.56552	1.000	-5553.5158	7650.7324
		Autumn	900.45000	2694.15061	1.000	-6748.0624	8548.9624
	Summer	Winter	-5430.01944	2483.40660	.224	-12480.2437	1620.2049
		Spring	-1048.60833	2325.56552	1.000	-7650.7324	5553.5158
		Autumn	-148.15833	3041.53949	1.000	-8782.8844	8486.5677
	Autumn	Winter	-5281.86111	2831.51917	.436	-13320.3536	2756.6314
		Spring	-900.45000	2694.15061	1.000	-8548.9624	6748.0624
		Summer	148.15833	3041.53949	1.000	-8486.5677	8782.8844
Trimethoprim	Winter	Spring	-4485.40556	2903.09169	.838	-13086.4955	4115.6844
		Summer	352.14778	3672.15280	1.000	-10527.4661	11231.7616
		Autumn	312.46111	3310.03381	1.000	-9494.2903	10119.2125
	Spring	Winter	4485.40556	2903.09169	.838	-4115.6844	13086.4955
		Summer	4837.55333	3894.90622	1.000	-6702.0197	16377.1264
		Autumn	4797.86667	3555.54666	1.000	-5736.2741	15332.0075
	Summer	Winter	-352.14778	3672.15280	1.000	-11231.7616	10527.4661
		Spring	-4837.55333	3894.90622	1.000	-16377.1264	6702.0197
		Autumn	-39.68667	4206.97955	1.000	-12503.8502	12424.4768
	Autumn	Winter	-312.46111	3310.03381	1.000	-10119.2125	9494.2903
		Spring	-4797.86667	3555.54666	1.000	-15332.0075	5736.2741
		Summer	39.68667	4206.97955	1.000	-12424.4768	12503.8502

*. The mean difference is significant at the 0.05 level.

***Table S10**. Box Plot and multiple comparison test for azithromycin detected in EFFLUENTS by seasons. Comparisons were not performed for azithromycin in spring and autumn because the two groups had fewer than two cases (WWTPs) [1-10, 14, 16, 18-20, 22-24].*



Multiple Comparisons

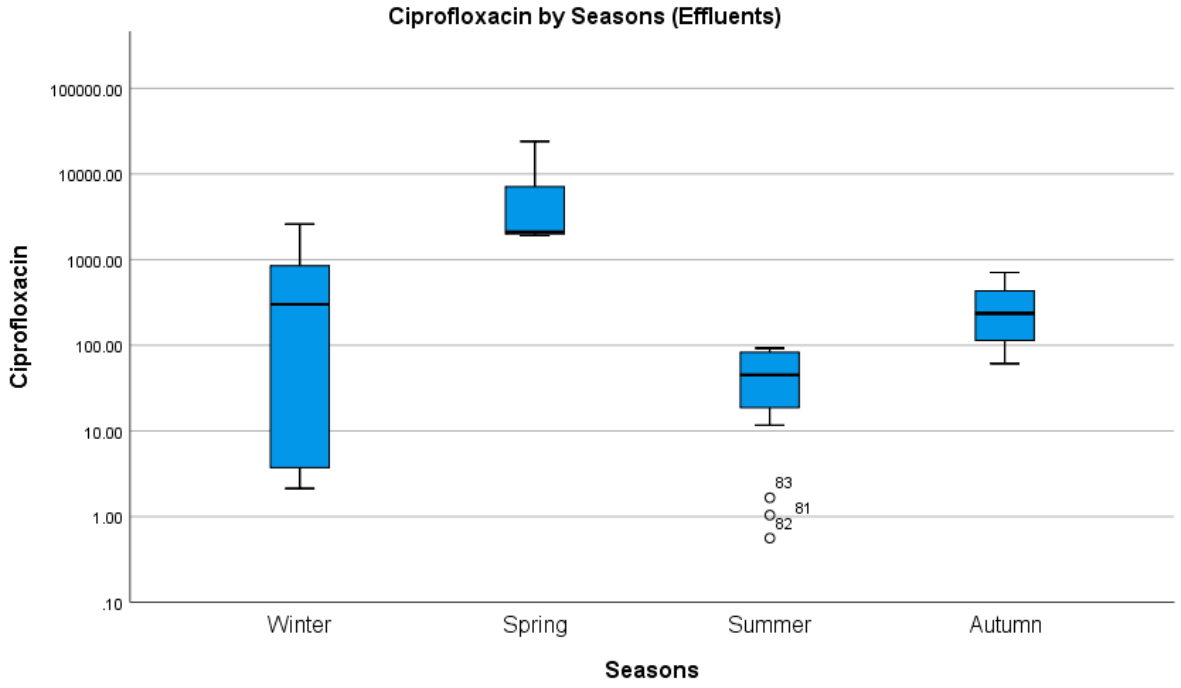
Dependent Variable: Azithromycin

Bonferroni

(I) Seasons	(J) Seasons	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval Lower Bound	95% Confidence Interval Upper Bound
Winter	Spring	17759.60000	8513.68465	.304	-7303.7950	42822.9950
	Summer	**17955.17000***	5301.47015	**.019**	2348.1977	33562.1423
	Autumn	17966.90000	8513.68465	.290	-7096.4950	43030.2950
Spring	Winter	-17759.60000	8513.68465	.304	-42822.9950	7303.7950
	Summer	195.57000	7692.18136	1.000	-22449.4054	22840.5454
	Autumn	207.30000	10175.79946	1.000	-29749.1867	30163.7867
Summer	Winter	-17955.17000*	5301.47015	.019	-33562.1423	-2348.1977
	Spring	-195.57000	7692.18136	1.000	-22840.5454	22449.4054
	Autumn	11.73000	7692.18136	1.000	-22633.2454	22656.7054
Autumn	Winter	-17966.90000	8513.68465	.290	-43030.2950	7096.4950
	Spring	-207.30000	10175.79946	1.000	-30163.7867	29749.1867
	Summer	-11.73000	7692.18136	1.000	-22656.7054	22633.2454

*. The mean difference is significant at the 0.05 level.

***Table S11**. Statistics, Box Plot and Independent Samples Test for Ciprofloxacin detected in EFFLUENTS by seasons [1-10, 14, 16, 18-20, 22-24].*



Multiple Comparisons

Dependent Variable: Ciprofloxacin

Bonferroni

(I) Seasons	(J) Seasons	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval Lower Bound	95% Confidence Interval Upper Bound
Winter	Spring	-8603.38048*	2325.90964	.005	-15189.3162	-2017.4448
	Summer	681.07075	1490.26444	1.000	-3538.6915	4900.8330
	Autumn	419.20286	2112.61234	1.000	-5562.7703	6401.1760
Spring	**Winter**	**8603.38048***	2325.90964	**.005**	2017.4448	15189.3162
	Summer	**9284.45123***	2093.99866	**.001**	3355.1837	15213.7188
	Autumn	**9022.58333***	2574.31023	**.009**	1733.2883	16311.8784
Summer	Winter	-681.07075	1490.26444	1.000	-4900.8330	3538.6915
	Spring	-9284.45123*	2093.99866	.001	-15213.7188	-3355.1837
	Autumn	-261.86789	1854.21294	1.000	-5512.1695	4988.4337
Autumn	Winter	-419.20286	2112.61234	1.000	-6401.1760	5562.7703
	Spring	-9022.58333*	2574.31023	.009	-16311.8784	-1733.2883
	Summer	261.86789	1854.21294	1.000	-4988.4337	5512.1695

*. The mean difference is significant at the 0.05 level.

***Table S12**. Statistics for the 14 most occurring PRs in INFLUENTS of Municipal and Hospital WWTPs [1-10, 14, 16, 18-20, 22-24].*

Group Statistics

	WWTP	N	Mean	Std. Deviation	Std. Error Mean
Azithromycin	Municipal WWTP	17	12855.5353	29537.81516	7163.97246
	Hospital WWTP	0[a]	.	.	.
Ciprofloxacin	Municipal WWTP	25	10640.1700	24684.57261	4936.91452
	Hospital WWTP	6	647.3333	1010.40995	412.49813
Clarithromycin	Municipal WWTP	25	760.9908	1462.38281	292.47656
	Hospital WWTP	1	6.0000	.	.
Clindamycin	Municipal WWTP	6	52.9667	53.88976	22.00040
	Hospital WWTP	0[a]	.	.	.
Erythromycin	Municipal WWTP	18	306.3339	377.58327	88.99723
	Hospital WWTP	1	83.0000	.	.
Metronidazole	Municipal WWTP	15	2135.0333	5452.44027	1407.81403
	Hospital WWTP	1	4.0000	.	.
Norfloxacin	Municipal WWTP	20	442.0935	693.67078	155.10950
	Hospital WWTP	6	494.1667	256.63314	104.77004
Ofloxacin	Municipal WWTP	29	769.9197	1156.79874	214.81213
	Hospital WWTP	6	733.6667	249.55854	101.88185
Oxytetracycline	Municipal WWTP	12	209.3100	426.15298	123.01977
	Hospital WWTP	5	317.8000	105.49265	47.17775
Roxithromycin	Municipal WWTP	18	2044.6056	4756.63088	1121.14865
	Hospital WWTP	0[a]	.	.	.
Sulfadiazine	Municipal WWTP	13	96.6331	133.33539	36.98058
	Hospital WWTP	6	356.8333	215.31132	87.90048
Sulfamethoxazole	Municipal WWTP	38	4541.2534	12061.39947	1956.61736
	Hospital WWTP	1	367.0000	.	.
Tetracycline	Municipal WWTP	11	56.1391	78.58991	23.69575
	Hospital WWTP	5	244.2000	98.51497	44.05724
Trimethoprim	Municipal WWTP	30	1012.4267	1919.24580	350.40474
	Hospital WWTP	1	59.0000	.	.

a. t cannot be computed because at least one of the groups is empty.

***Table S13**. Independent t-test based on Levene's Test for equality of variances for the 14 most occurring PRs in INFLUENTS of Municipal and Hospital WWTPs [1-10, 14, 16, 18-20, 22-24].*

Independent Samples Test

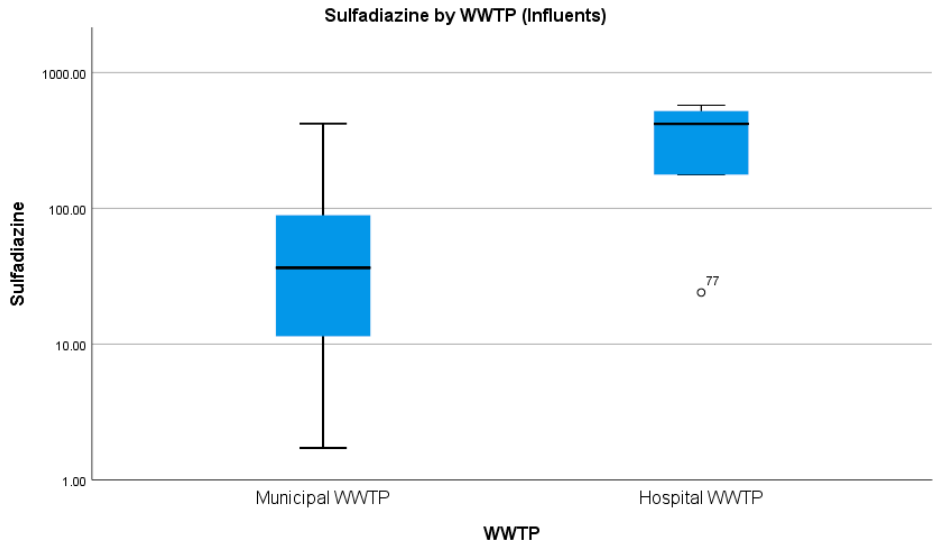
		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
Ciprofloxacin	Equal variances assumed	4.307	.047	.979	29	.336	9992.83667	10210.41128	-10889.79915	30875.47248
	Equal variances not assumed			2.017	24.331	.055	9992.83667	4954.11745	-224.61255	20210.28588
Clarithromycin	Equal variances assumed	.	.	.506	24	.617	754.99080	1491.34370	-2322.99132	3832.97292
	Equal variances not assumed			.	.	.	754.99080	.	.	.
Erythromycin	Equal variances assumed	.	.	.576	17	.572	223.33389	387.92994	-595.12673	1041.79451
	Equal variances not assumed			.	.	.	223.33389	.	.	.
Metronidazole	Equal variances assumed	.	.	.378	14	.711	2131.03333	5631.25610	-9946.80979	14208.87645
	Equal variances not assumed			.	.	.	2131.03333	.	.	.
Norfloxacin	Equal variances assumed	2.710	.113	-.178	24	.860	-52.07317	292.41830	-655.59488	551.44854
	Equal variances not assumed			-.278	22.497	.783	-52.07317	187.17831	-439.76055	335.61422
Ofloxacin	Equal variances assumed	2.278	.141	.076	33	.940	36.25299	479.88420	-940.07876	1012.58474
	Equal variances not assumed			.152	32.737	.880	36.25299	237.74811	-447.59670	520.10268
Oxytetracycline	Equal variances assumed	.946	.346	-.552	15	.589	-108.49000	196.40418	-527.11560	310.13560
	Equal variances not assumed			-.823	13.661	.424	-108.49000	131.75585	-391.73770	174.75770

Sulfadiazine*	Equal variances assumed	2.540	.129	-3.258	17	.005	-260.20026	79.86395	-428.69846	-91.70205
	Equal variances not assumed			-2.729	6.837	**.030***	-260.20026	95.36277	-486.78933	-33.61118
Sulfamethoxazole	Equal variances assumed	.	.	.342	37	.735	4174.25342	12219.07152	-20583.93719	28932.44403
	Equal variances not assumed			.	.	.	4174.25342	.	.	.
Tetracycline*	Equal variances assumed	.321	.580	-4.114	14	.001	-188.06091	45.71726	-286.11469	-90.00713
	Equal variances not assumed			-3.759	6.434	**.008***	-188.06091	50.02528	-308.49633	-67.62548
Trimethoprim	Equal variances assumed	.	.	.489	29	.629	953.42667	1950.97102	-3036.75709	4943.61042
	Equal variances not assumed			.	.	.	953.42667	.	.	.

Table S14. *Statistics, Box Plot and Independent Samples Test for Sulfadiazine detected in PRs in INFLUENTS of Municipal and Hospital WWTPs [1-10, 14, 16, 18-20, 22-24].*

Group Statistics

	WWTP	N	Mean	Std. Deviation	Std. Error Mean
Sulfadiazine	Municipal WWTP	13	96.6331	133.33539	36.98058
	Hospital WWTP	6	356.8333	215.31132	87.90048



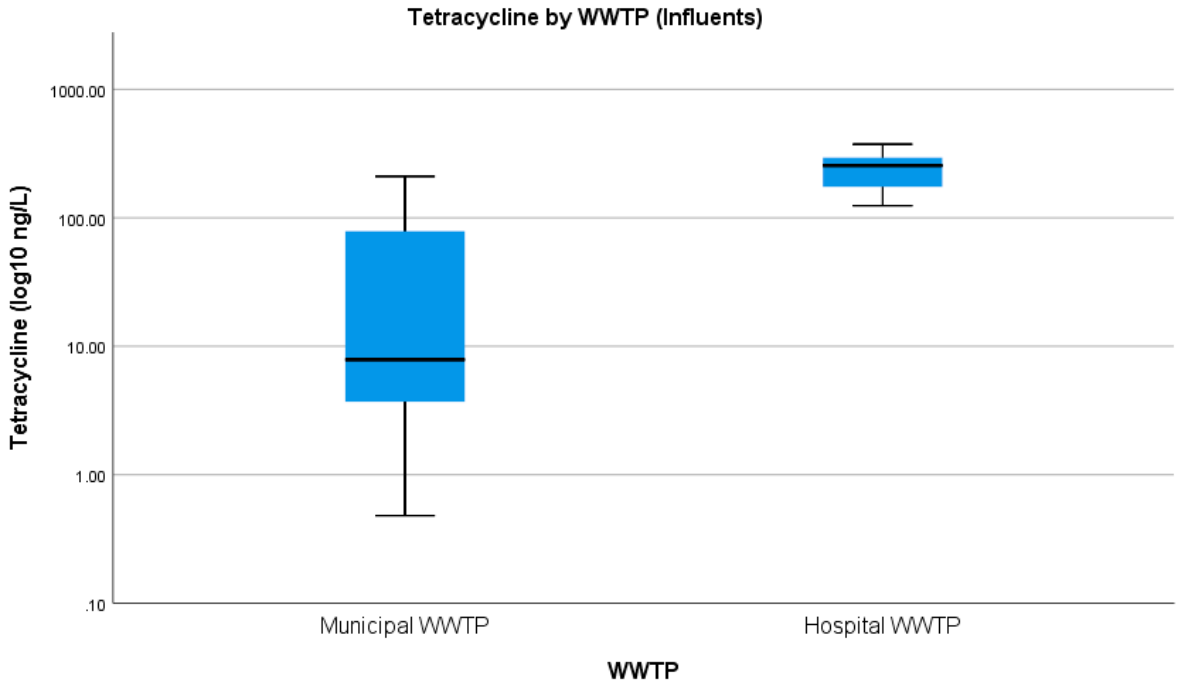
Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
Sulfadiazine	Equal variances assumed	2.540	.129	-3.258	17	.005	-260.20026	79.86395	-428.69846	-91.70205
	Equal variances not assumed			-2.729	6.837	.030	-260.20026	95.36277	-486.78933	-33.61118

***Table S15**. Statistics, Box Plot and Independent Samples Test for Tetracycline detected in PRs in INFLUENTS of Municipal and Hospital WWTPs [1-10, 14, 16, 18-20, 22-24].*

Group Statistics

	WWTP	N	Mean	Std. Deviation	Std. Error Mean
Tetracycline	Municipal WWTP	11	56.1391	78.58991	23.69575
	Hospital WWTP	5	244.2000	98.51497	44.05724



Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
Tetracycline	Equal variances assumed	.321	.580	-4.114	14	.001	-188.06091	45.71726	-286.11469	-90.00713
	Equal variances not assumed			-3.759	6.434	.008	-188.06091	50.02528	-308.49633	-67.62548

***Table S16**. Statistics for the 14 most occurring PRs in EFFLUENTS of Municipal and Hospital WWTPs [1-10, 14, 16, 18-20, 22-24].*

Group Statistics

	WWTP	N	Mean	Std. Deviation	Std. Error Mean
Azithromycin	Municipal WWTP	39	2413.9544	9397.13716	1504.74622
	Hospital WWTP	2	204.5000	276.47875	195.50000
Ciprofloxacin	Municipal WWTP	53	213.5155	432.01967	59.34247
	Hospital WWTP	13	2287.9308	6560.77320	1819.63109
Clarithromycin	Municipal WWTP	47	173.8745	301.14743	43.92687
	Hospital WWTP	3	5137.6667	8542.23661	4931.86261
Clindamycin	Municipal WWTP	26	49.5692	66.90383	13.12092
	Hospital WWTP	1	36.0000	.	.
Erythromycin	Municipal WWTP	29	315.1528	415.12190	77.08620
	Hospital WWTP	0[a]	.	.	.
Metronidazole	Municipal WWTP	25	81.0840	178.41305	35.68261
	Hospital WWTP	3	1229.0000	1570.21113	906.56182
Norfloxacin	Municipal WWTP	26	230.2369	589.93737	115.69624
	Hospital WWTP	5	253.6000	74.62774	33.37454
Ofloxacin	Municipal WWTP	49	208.4661	450.19670	64.31381
	Hospital WWTP	8	25467.5000	70522.79208	24933.57225
Oxytetracycline	Municipal WWTP	10	62.5600	127.91192	40.44930
	Hospital WWTP	5	67.1400	14.87575	6.65264
Roxithromycin	Municipal WWTP	13	936.5977	1803.50919	500.20345
	Hospital WWTP	0[a]	.	.	.
Sulfadiazine	Municipal WWTP	22	27.0523	46.67452	9.95104

	Hospital WWTP	7	195.6714	120.41078	45.51100
Sulfamethoxazole	Municipal WWTP	49	1220.6094	3991.52529	570.21790
	Hospital WWTP	6	1628.5000	3376.30056	1378.36893
Tetracycline	Municipal WWTP	20	69.2890	76.43242	17.09081
	Hospital WWTP	5	62.9600	15.59721	6.97528
Trimethoprim	Municipal WWTP	40	808.7740	4105.95590	649.20863
	Hospital WWTP	2	1190.0000	1428.35570	1010.00000

a. t cannot be computed because at least one of the groups is empty.

Table S17*. Independent t-test based on Levene's Test for equality of variances for the 14 most occurring PRs in EFFLUENTS of Municipal and Hospital WWTPs [1-10, 14, 16, 18-20, 22-24].*

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means					
								95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
Azithromycin	Equal variances assumed	.422	.520	.329	39	.744	2209.45436	6725.19117	-11393.52875	15812.43747
	Equal variances not assumed			1.456	38.873	.153	2209.45436	1517.39298	-860.08376	5278.99248
Ciprofloxacin	Equal variances assumed	17.213	.000	-2.337	64	.023	-2074.41530	887.48349	-3847.36739	-301.46321
	Equal variances not assumed			-1.139	12.026	.277	-2074.41530	1820.59848	-6040.22460	1891.39401
Clarithromycin	Equal variances assumed	290.611	.000	-4.714	48	.000	-4963.79220	1053.08053	-7081.15251	-2846.43189
	Equal variances not assumed			-1.006	2.000	.420	-4963.79220	4932.05823	-26181.50021	16253.91582

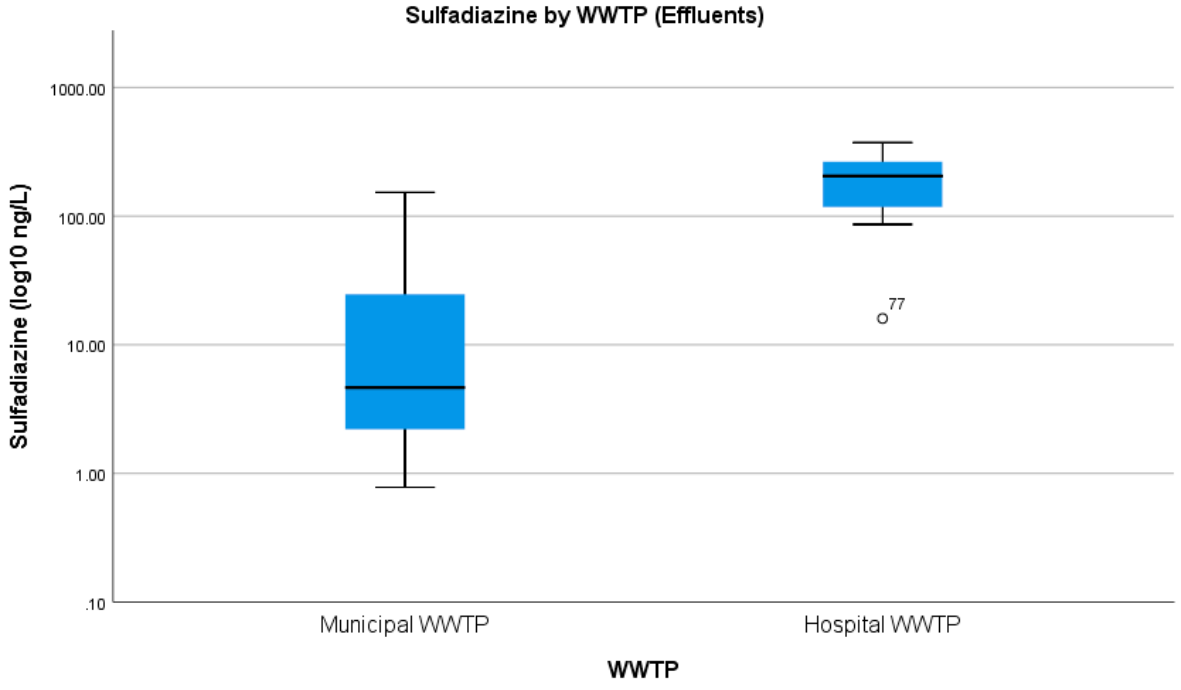
Clindamycin	Equal variances assumed	.	.	.199	25	.844	13.56923	68.17831	-126.84662	153.98508
	Equal variances not assumed			.	.	.	13.56923	.	.	.
Metronidazole	Equal variances assumed	62.434	.000	-4.014	26	.000	-1147.91600	285.96405	-1735.72353	-560.10847
	Equal variances not assumed			-1.265	2.006	.333	-1147.91600	907.26379	-5040.01654	2744.18454
Norfloxacin	Equal variances assumed	1.381	.249	-.087	29	.931	-23.36308	267.81898	-571.11440	524.38825
	Equal variances not assumed			-.194	28.117	.848	-23.36308	120.41378	-269.97332	223.24717
Ofloxacin	Equal variances assumed	36.397	.000	-2.632	55	.011	-25259.03388	9595.16040	-44488.16502	-6029.90274
	Equal variances not assumed			-1.013	7.000	.345	-25259.03388	24933.65520	-84217.60061	33699.53285
Oxytetracycline	Equal variances assumed	2.351	.149	-.078	13	.939	-4.58000	58.46859	-130.89371	121.73371
	Equal variances not assumed			-.112	9.478	.913	-4.58000	40.99273	-96.60413	87.44413
Sulfadiazine*	Equal variances assumed	10.562	.003	-5.542	27	.000	-168.61916	30.42704	-231.05029	-106.18802
	Equal variances not assumed			-3.620	6.583	**.009***	-168.61916	46.58620	-280.20807	-57.03024

Sulfamethoxazole	Equal variances assumed	.083	.775	-.239	53	.812	-407.89061	1703.09390	-3823.86438	3008.08316
	Equal variances not assumed			-.273	6.837	.793	-407.89061	1491.65994	-3952.22658	3136.44536
Tetracycline	Equal variances assumed	8.774	.007	.181	23	.858	6.32900	34.88638	-65.83898	78.49698
	Equal variances not assumed			.343	22.846	.735	6.32900	18.45943	-31.87148	44.52948
Trimethoprim	Equal variances assumed	.008	.928	-.130	40	.898	-381.22600	2942.17839	-6327.59034	5565.13834
	Equal variances not assumed			-.318	1.988	.781	-381.22600	1200.65476	-5576.37042	4813.91842

***Table S18**. Statistics, Box Plot and Independent Samples Test for Tetracycline detected in PRs in EFFLUENTS of Municipal and Hospital WWTPs [1-10, 14, 16, 18-20, 22-24].*

Group Statistics

	WWTP	N	Mean	Std. Deviation	Std. Error Mean
Sulfadiazine	Municipal WWTP	22	27.0523	46.67452	9.95104
	Hospital WWTP	7	195.6714	120.41078	45.51100



Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
Sulfadiazine	Equal variances assumed	10.562	.003	-5.542	27	.000	-168.61916	30.42704	-231.05029	-106.18802
	Equal variances not assumed			-3.620	6.583	.009	-168.61916	46.58620	-280.20807	-57.03024

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References of the studies included after the Critical Appraisal. To avoid confusion, the reference number is the same as before the Critical Appraisal. Studies were placed in order of reviewing. In square brackets, the reference number corresponding to the article system of reference.

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