**Pharmaceuticals in Wastewater Treatment Plants: A Systematic Review on the substances of greatest concern responsible for the development of Antimicrobial Resistance.**

**Gabriele Frascaroli 1,\*, Deborah Reid 2, Colin Hunter 3, Joanne Roberts 4, Karin Helwig 5, Janice Spencer 6 and Ania Escudero 7**

1 Glasgow Caledonian University, Department of Civil Engineering and Environmental Management, School of Computing, Engineering and Built Environment, Cowcaddens Road, Glasgow, G4 0BA, Scotland, UK; [Gabriele.Frascaroli@gcu.ac.uk](mailto:Gabriele.Frascaroli@gcu.ac.uk)

2 Glasgow Caledonian University, Department of Civil Engineering and Environmental Management, School of Computing, Engineering and Built Environment; [Deborah.Reid@gcu.ac.uk](mailto:Deborah.Reid@gcu.ac.uk)

3 Glasgow Caledonian University, Department of Civil Engineering and Environmental Management, School of Computing, Engineering and Built Environment; [Colin.Hunter@gcu.ac.uk](mailto:Colin.Hunter@gcu.ac.uk)

4 Glasgow Caledonian University, Department of Applied Science, School of Computing, Engineering and Built Environment; [Joanne.Roberts@gcu.ac.uk](mailto:Joanne.Roberts@gcu.ac.uk)

5 Glasgow Caledonian University, Department of Civil Engineering and Environmental Management, School of Computing, Engineering and Built Environment; [Karin.Helwig@gcu.ac.uk](mailto:Karin.Helwig@gcu.ac.uk)

6 Glasgow Caledonian University, Department of Biological and Biomedical Sciences, School of Health and Life Sciences; [Janice.Spencer@gcu.ac.uk](mailto:Janice.Spencer@gcu.ac.uk)

7 Glasgow Caledonian University, Department of Civil Engineering and Environmental Management, School of Computing, Engineering and Built Environment; [Ania.Escudero@gcu.ac.uk](mailto:Ania.Escudero@gcu.ac.uk)

\* Correspondence: [Gabriele.Frascaroli@gcu.ac.uk](mailto:Gabriele.Frascaroli@gcu.ac.uk); 0141 331 8790; Glasgow, Scotland, G2 3LG

***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**:   * Heavy Metals, Nutrients, Plastics * PRs Non-relevant to AMR, Veterinary products * Only one PR | 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 (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 citationsa (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 questionc 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=("anti\*  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 \*] |

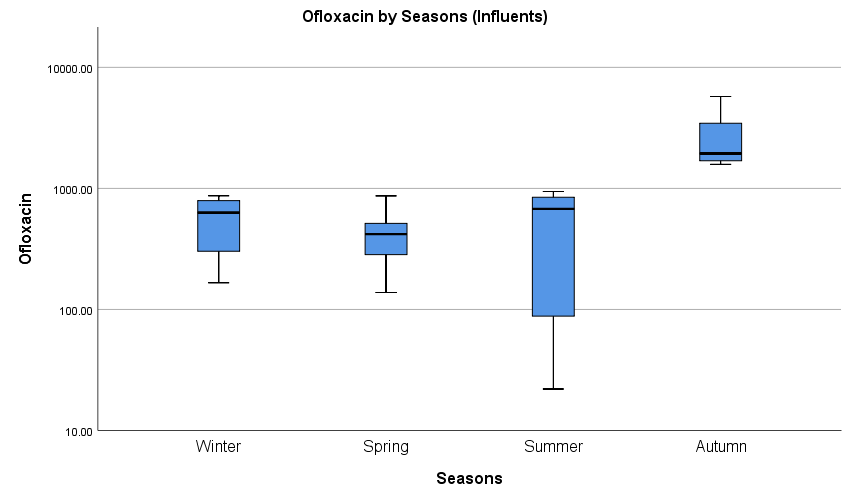
**Table S4**. Statistics for the 14 most occurring PRs in INFLUENTS by Seasons.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Winter | Minimum | | 63.20 | | 15.80 | | 65.00 | |  | |  | |  | | 38.60 | | 166.00 | | 104.00 | | 155.60 | | 2.24 | | 52.20 | | 5.04 | | 34.60 |
| Maximum | | 115413.00 | | 3000.00 | | 6917.00 | |  | |  | |  | | 2800.00 | | 870.00 | | 1531.00 | | 19135.00 | | 67.70 | | 49300.00 | | 55.60 | | 5600.00 |
| Median | | 34719.0000 | | 139.0000 | | 1413.0000 | |  | |  | |  | | 612.0000 | | 636.5000 | | 121.6000 | | 3422.0000 | | 18.7500 | | 1491.0000 | | 17.0050 | | 900.0000 |
| Std. Deviation | | 42850.45993 | | 1126.07620 | | 2671.03328 | |  | |  | |  | | 909.02842 | | 303.38685 | | 628.01007 | | 7513.43798 | | 28.94615 | | 21104.37047 | | 23.27045 | | 2093.09724 |
| Spring | Minimum | | 148.70 | | 207.00 | | 86.30 | |  | | 266.00 | | 2.10 | |  | | 138.00 | | 92.60 | | 96.10 | | 190.00 | | 40.00 | |  | | 31.40 |
| Maximum | | 148.70 | | 207.00 | | 260.00 | |  | | 1193.00 | | 380.00 | |  | | 868.00 | | 92.60 | | 106.00 | | 320.00 | | 3790.00 | |  | | 8430.00 |
| Median | | 148.7000 | | 207.0000 | | 122.5000 | |  | | 390.0000 | | 140.0000 | |  | | 419.0000 | | 92.6000 | | 101.0500 | | 255.0000 | | 164.6000 | |  | | 335.0000 |
| Std. Deviation | | . | | . | | 61.65324 | |  | | 346.41243 | | 191.23494 | |  | | 240.99921 | | . | | 7.00036 | | 91.92388 | | 1150.26193 | |  | | 4100.69789 |
| Summer | Minimum | | 13.10 | | 1.00 | | 20.20 | |  | |  | |  | | 5.06 | | 22.00 | | 1.75 | | 16.70 | | 1.72 | | 2.95 | | .48 | | 6.84 |
| Maximum | | 328.00 | | 345.00 | | 619.48 | |  | |  | |  | | 778.00 | | 942.00 | | 448.00 | | 75.10 | | 574.00 | | 237.00 | | 374.00 | | 48.10 |
| Median | | 114.0500 | | 163.0000 | | 51.6000 | |  | |  | |  | | 447.0000 | | 678.0000 | | 187.0000 | | 27.5500 | | 177.0000 | | 120.8800 | | 124.0000 | | 10.0150 |
| Std. Deviation | | 148.18801 | | 129.18937 | | 254.34894 | |  | |  | |  | | 299.86581 | | 409.18555 | | 176.68711 | | 26.92488 | | 241.64849 | | 94.31212 | | 144.97468 | | 19.63462 |
| Autumn | Minimum | | 10.00 | | 35341.10 | | 72.70 | | 8.40 | | 5.50 | | 13.60 | | 45.30 | | 1578.50 | |  | | 23.80 | |  | | 845.30 | |  | | 400.00 |
| Maximum | | 102.10 | | 88011.80 | | 2822.80 | | 41.10 | | 58.60 | | 20656.10 | | 143.40 | | 5741.70 | |  | | 1275.60 | |  | | 4569.30 | |  | | 1926.90 |
| Median | | 53.9500 | | 61617.4500 | | 642.8500 | | 14.1500 | | 31.7500 | | 66.8500 | | 62.7000 | | 1947.9500 | |  | | 268.7000 | |  | | 1426.6000 | |  | | 995.4000 |
| Std. Deviation | | 48.22247 | | 27057.41510 | | 1220.87977 | | 14.69841 | | 22.77499 | | 10303.57239 | | 44.03009 | | 1969.05705 | |  | | 579.47900 | |  | | 1703.34246 | |  | | 712.34979 |
| Total | Minimum | | 10.00 | | 1.00 | | 20.20 | | 8.40 | | 5.50 | | 2.10 | | 5.06 | | 22.00 | | 1.75 | | 16.70 | | 1.72 | | 2.95 | | .48 | | 6.84 |
| Maximum | | 115413.00 | | 88011.80 | | 6917.00 | | 41.10 | | 1193.00 | | 20656.10 | | 2800.00 | | 5741.70 | | 1531.00 | | 19135.00 | | 574.00 | | 49300.00 | | 374.00 | | 8430.00 |
| Median | | 125.4000 | | 207.0000 | | 130.0000 | | 14.1500 | | 266.0000 | | 102.8000 | | 272.0000 | | 638.5000 | | 121.6000 | | 106.0000 | | 67.7000 | | 237.0000 | | 26.2000 | | 400.0000 |
| Std. Deviation | | 32074.58750 | | 26781.88762 | | 1582.61750 | | 14.69841 | | 378.44877 | | 7766.18786 | | 651.10333 | | 1170.92266 | | 379.67580 | | 5155.05926 | | 210.06892 | | 13633.83267 | | 130.81060 | | 2220.15073 |
| PR | | Azithromycin | | Ciprofloxacin | | Clarithromycin | | Clindamycin | | Erythromycin | | Metronidazole | | Norfloxacin | | Ofloxacin | | Oxytetracycline | | Roxithromycin | | Sulfadiazine | | Sulfamethoxazole | | Tetracycline | | Trimethoprim | |

**Table S5**. One-way ANOVA with Bonferroni correction for the 14 most occurring PRs in INFLUENTS by Seasons.

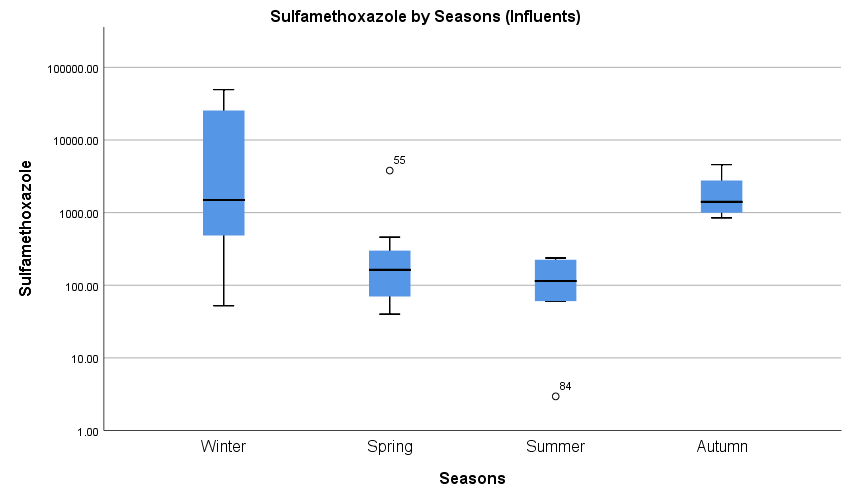
|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Bonferroni | | | | | | | |
| Dependent Variable | (I) Seasons | (J) Seasons | Mean Difference (I-J) | Std. Error | Sig. | 95% Confidence Interval | |
| Lower Bound | Upper Bound |
| Clarithromycin | Winter | Spring | 2193.38333 | 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.



|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Multiple Comparisons** | | | | | | |
| Dependent Variable: Ofloxacin | | | | | | |
| Bonferroni | | | | | | |
| (I) Seasons | (J) Seasons | Mean Difference (I-J) | Std. Error | Sig. | 95% Confidence Interval | |
| Lower Bound | 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.



|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Multiple Comparisons** | | | | | | |
| Dependent Variable: Sulfamethoxazole | | | | | | |
| Bonferroni | | | | | | |
| (I) Seasons | (J) Seasons | Mean Difference (I-J) | Std. Error | Sig. | 95% Confidence Interval | |
| Lower Bound | 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. | | | | | | |

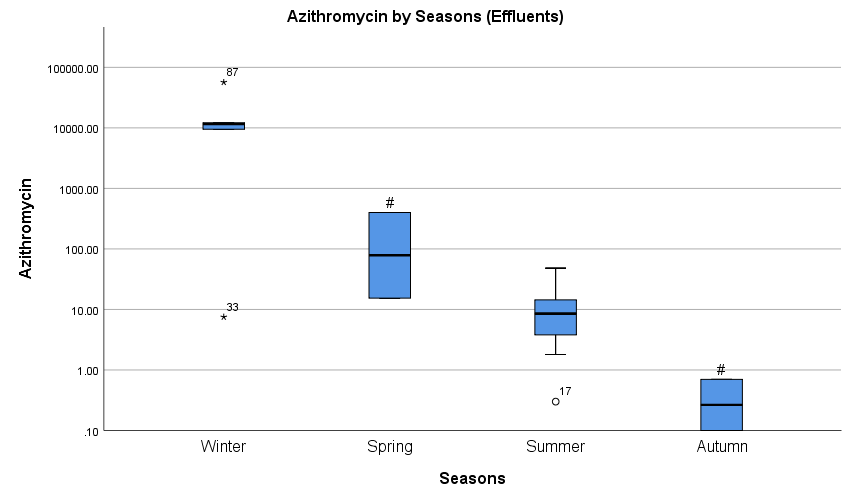
**Table S8.** Statistics for the 14 most occurring PRs in EFFLUENTS by Seasons.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Winter | Mean | 17967.3000 | 729.9529 | 693.6000 |  |  | 50.9000 | 641.0213 | 116.6250 | 102.9380 | 2367.8800 | 10.5675 | 5476.1111 | 3.9520 | 360.8111 |
| N | 5 | 7 | 5 |  |  | 1 | 8 | 4 | 5 | 5 | 4 | 9 | 5 | 9 |
| Std. Deviation | 22177.21152 | 1042.45027 | 697.63264 |  |  | . | 975.35710 | 57.09807 | 175.30677 | 2364.24391 | 10.40470 | 8302.46710 | 5.56680 | 309.88141 |
| Median | 11523.0000 | 300.0000 | 373.0000 |  |  | 50.9000 | 285.7500 | 115.8500 | 27.4000 | 1457.0000 | 7.4300 | 578.0000 | .7900 | 300.0000 |
| Spring | Mean | 207.7000 | 9333.3333 | 2637.6167 | 36.0000 | 778.0000 | 977.2000 |  | 20447.7000 |  | 114.3000 | 120.0000 | 1094.7000 |  | 4846.2167 |
| N | 2 | 3 | 6 | 1 | 9 | 5 |  | 10 |  | 1 | 3 | 13 |  | 6 |
| Std. Deviation | 271.95327 | 12702.09956 | 6057.54660 | . | 421.65389 | 1179.34694 |  | 63089.30976 |  | . | 45.82576 | 2418.03866 |  | 10443.61192 |
| Median | 207.7000 | 2100.0000 | 195.0000 | 36.0000 | 1083.0000 | 680.0000 |  | 450.5000 |  | 114.3000 | 130.0000 | 184.0000 |  | 285.0000 |
| Summer | Mean | 12.1300 | 48.8821 | 138.4739 | 8.4375 | 133.6400 | 6.1250 | 112.7881 | 319.1071 | 43.0400 | 9.9275 | 73.0900 | 46.0917 | 52.7033 | 8.6633 |
| N | 14 | 19 | 18 | 8 | 10 | 4 | 16 | 21 | 8 | 4 | 17 | 6 | 6 | 3 |
| Std. Deviation | 13.00346 | 34.49095 | 174.72241 | 3.63237 | 226.83448 | 3.02145 | 117.20859 | 654.58581 | 35.13519 | 11.19690 | 122.12855 | 26.70473 | 28.73697 | 6.14606 |
| Median | 8.6000 | 45.1000 | 90.0500 | 8.4000 | 48.6000 | 4.8500 | 46.6000 | 85.0000 | 54.1500 | 4.6900 | 5.2200 | 49.6400 | 56.8000 | 11.7000 |
| Autumn | Mean | .4000 | 310.7500 | 13.4750 | 2.6500 | 5.8500 | 9.7750 | .8000 | 33.4500 |  |  |  | 194.2500 |  | 48.3500 |
| N | 2 | 4 | 4 | 4 | 4 | 4 | 3 | 4 |  |  |  | 4 |  | 4 |
| Std. Deviation | .42426 | 278.03733 | 17.09881 | 3.64097 | 8.37636 | 7.27708 | .30000 | 26.10013 |  |  |  | 129.74677 |  | 75.64155 |
| Median | .4000 | 237.1000 | 8.0000 | 1.0000 | 2.5500 | 10.0000 | .8000 | 29.4500 |  |  |  | 181.9000 |  | 11.0000 |
| Total | Mean | 3931.4139 | 1069.1342 | 661.8221 | 8.7769 | 363.5565 | 357.1786 | 256.8585 | 5430.2192 | 66.0777 | 1199.3410 | 68.5333 | 2017.8016 | 30.5436 | 1479.2723 |
| N | 23 | 33 | 33 | 13 | 23 | 14 | 27 | 39 | 13 | 10 | 24 | 32 | 11 | 22 |
| Std. Deviation | 12109.55733 | 4172.95773 | 2597.92647 | 9.23897 | 450.85444 | 811.23239 | 574.28098 | 31980.34274 | 109.01472 | 2000.62551 | 107.32123 | 5006.47497 | 32.76418 | 5520.89241 |
| Median | 11.3000 | 73.2000 | 102.6000 | 8.1000 | 81.1000 | 15.5000 | 40.2000 | 162.4000 | 39.5900 | 81.3500 | 7.9000 | 158.0500 | 13.5000 | 130.9000 |
| PR | | Azithromycin | Ciprofloxacin | Clarithromycin | Clindamycin | Erythromycin | Metronidazole | Norfloxacin | Ofloxacin | Oxytetracycline | Roxithromycin | Sulfadiazine | Sulfamethoxazole | Tetracycline | Trimethoprim |

**Table S9**. One-way ANOVA with Bonferroni correction for the 14 most occurring PRs in EFFLUENTS by Seasons.

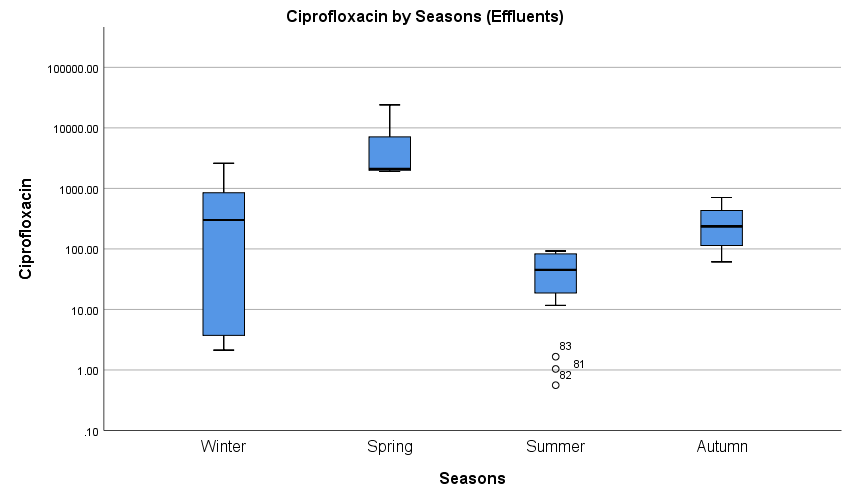
|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Bonferroni | | | | | | | |
| Dependent Variable | (I) Seasons | (J) Seasons | Mean Difference (I-J) | Std. Error | Sig. | 95% Confidence Interval | |
| Lower Bound | Upper Bound |
| **Azithromycin** | Winter | Spring | 17759.60000 | 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).



|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Multiple Comparisons** | | | | | | |
| Dependent Variable: Azithromycin | | | | | | |
| Bonferroni | | | | | | |
| (I) Seasons | (J) Seasons | Mean Difference (I-J) | Std. Error | Sig. | 95% Confidence Interval | |
| Lower Bound | 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.



|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Multiple Comparisons** | | | | | | |
| Dependent Variable: Ciprofloxacin | | | | | | |
| Bonferroni | | | | | | |
| (I) Seasons | (J) Seasons | Mean Difference (I-J) | Std. Error | Sig. | 95% Confidence Interval | |
| Lower Bound | 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.

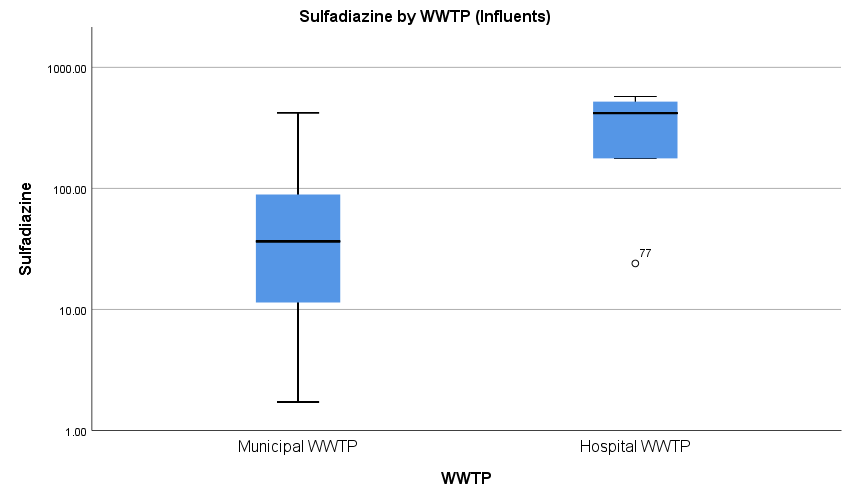
|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Group Statistics** | | | | | |
|  | WWTP | N | Mean | Std. Deviation | Std. Error Mean |
| Azithromycin | Municipal WWTP | 17 | 12855.5353 | 29537.81516 | 7163.97246 |
| Hospital WWTP | 0a | . | . | . |
| Ciprofloxacin | Municipal WWTP | 25 | 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 | 0a | . | . | . |
| 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 | 0a | . | . | . |
| 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.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Independent Samples Test** | | | | | | | | | | |
|  | | Levene's Test for Equality of Variances | | t-test for Equality of Means | | | | | | |
| F | Sig. | t | df | Sig. (2-tailed) | Mean Difference | Std. Error Difference | 95% Confidence Interval of the 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.

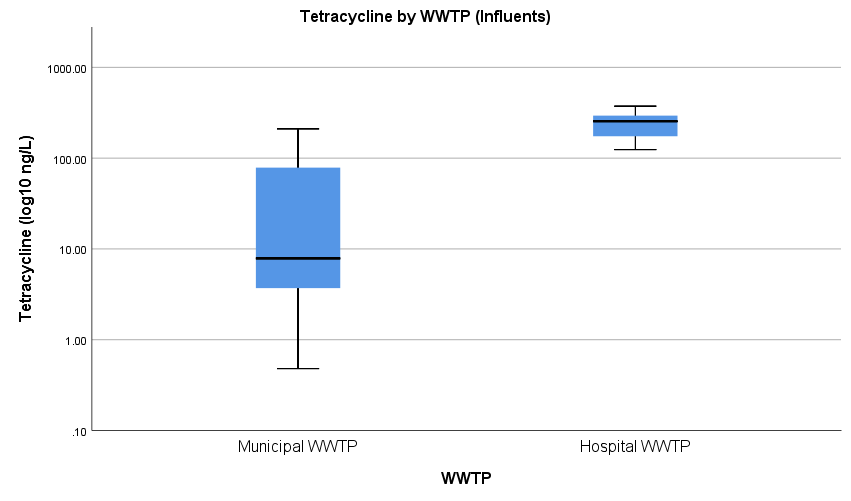
|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Group Statistics** | | | | | |
|  | WWTP | N | Mean | Std. Deviation | Std. Error Mean |
| Sulfadiazine | Municipal WWTP | 13 | 96.6331 | 133.33539 | 36.98058 |
| Hospital WWTP | 6 | 356.8333 | 215.31132 | 87.90048 |



|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Independent Samples Test** | | | | | | | | | | |
|  | | Levene's Test for Equality of Variances | | t-test for Equality of Means | | | | | | |
| F | Sig. | t | df | Sig. (2-tailed) | Mean Difference | Std. Error Difference | 95% Confidence Interval of the 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.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **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 | | | | | | |
| F | Sig. | t | df | Sig. (2-tailed) | Mean Difference | Std. Error Difference | 95% Confidence Interval of the 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.

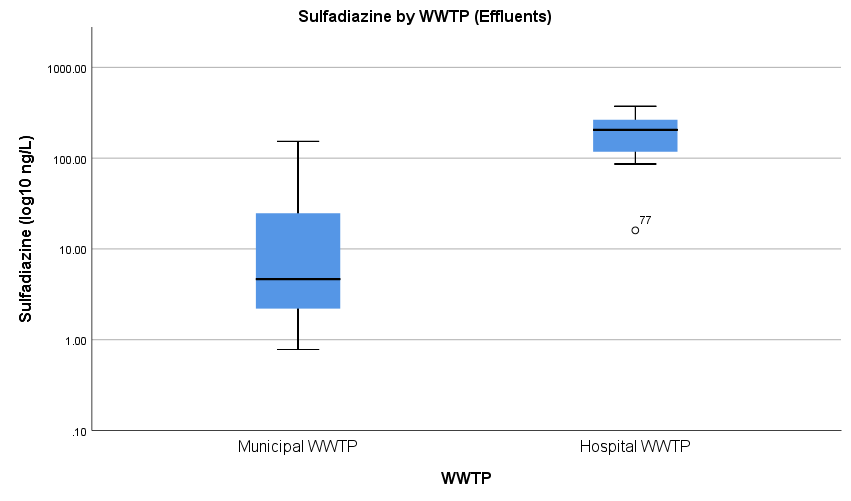
|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Group Statistics** | | | | | |
|  | WWTP | N | Mean | Std. Deviation | Std. Error Mean |
| Azithromycin | Municipal WWTP | 39 | 2413.9544 | 9397.13716 | 1504.74622 |
| Hospital WWTP | 2 | 204.5000 | 276.47875 | 195.50000 |
| Ciprofloxacin | 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 | 0a | . | . | . |
| 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 | 0a | . | . | . |
| 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.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Independent Samples Test** | | | | | | | | | | |
|  | | Levene's Test for Equality of Variances | | t-test for Equality of Means | | | | | | |
| F | Sig. | t | df | Sig. (2-tailed) | Mean Difference | Std. Error Difference | 95% Confidence Interval of the 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.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **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 | | | | | | |
| F | Sig. | t | df | Sig. (2-tailed) | Mean Difference | Std. Error Difference | 95% Confidence Interval of the 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 |