Discharge of Sewage Rich in Pharmaceuticals Responsible for the Development of Antimicrobial Resistance – A Systematic Review.

An analysis of the literature on the effluents of 88 wastewater treatment plants discharging 45 pharmaceuticals correlated to the spread of drug-resistant microorganisms.

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1. Background

Recalcitrant pharmaceuticals reach wastewater treatment plants, in which treatment solutions are not designed to eliminate them.

A consistent flow of pharmaceuticals enters the aquatic environment, where resistant microorganisms may spread.

Antimicrobial resistance causes 33,000 mortalities and costs EUR 1.1 billion per year to the health care systems in the European Union.

In 2015, the European Commission developed the Watch List listing some pharmaceuticals suspected to pose a significant threat to aquatic organisms, mammals and human health.

2. Objective and Method

A Systematic Review was conducted to examine the relevant literature on pharmaceuticals detected in wastewater in order to propose a classification of the compounds of greatest concern and provide an updated source for the management of antimicrobial resistance.

- 4 Databases;
- 546 Records screened;
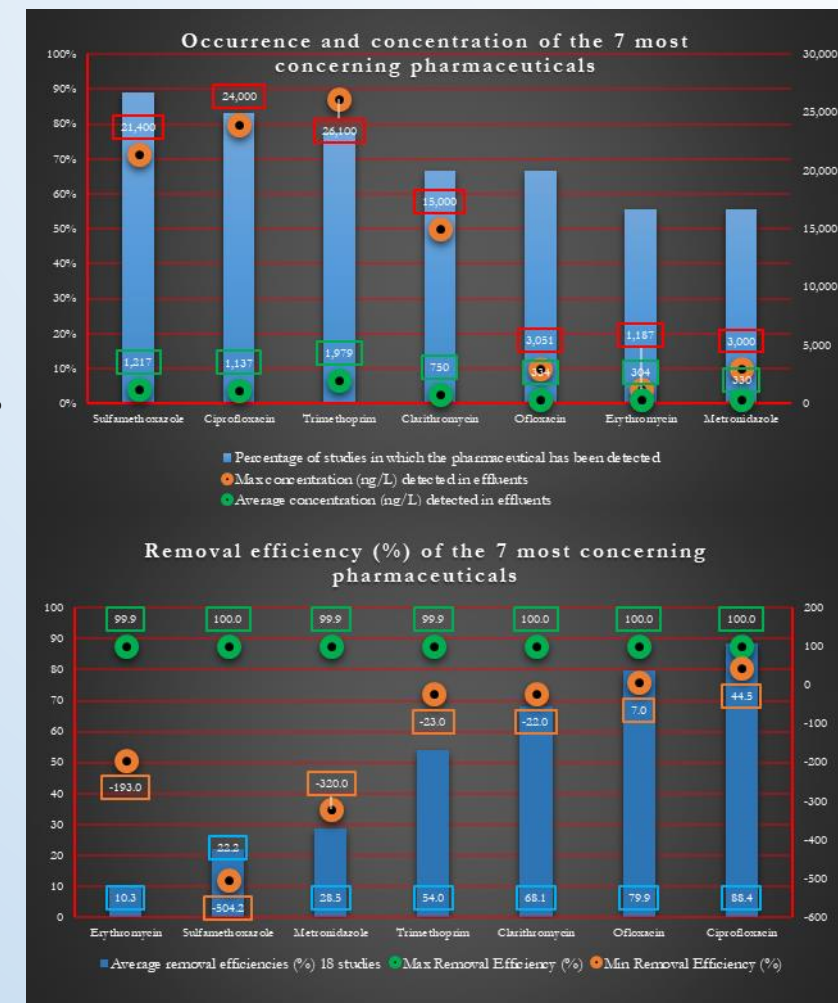- 18 Studies included in the Narrative Synthesis.

3. Results

Details of the studies:

- 45 Pharmaceuticals responsible for antimicrobial resistance belonging to 16 different classes of antibiotics, antifungals, antiprotozoals and antimalarials detected;
- 88 Wastewater treatment plants (75 municipal and 13 hospital) and effluents investigated;
- 25 Countries in Europe, Africa, Asia covered by the review.

Details of the pharmaceuticals:

- Sulfamethoxazole, ofloxacin and erythromycin detected in more than 61% of studies (eleven) as the substances with the highest concentrations among the other pharmaceuticals;
- Sulfadiazine concentrations in hospital wastewater statistically higher than in municipal wastewater;
- Azithromycin, ciprofloxacin, clarithromycin, sulfamethoxazole and ofloxacin reported as the pharmaceuticals with the highest risk quotients.

4. Conclusions and Recommendations

- Include ofloxacin, trimethoprim, metronidazole and sulfamethoxazole in the Watch List;
- More studies assessing the environmental risk of receiving water basins to better assess the impact of wastewater treatment plants on the environment are required;
- Year-long or multi-seasonal screenings to capture pharmaceutical variations are desirable;
- Studies correlating the removal efficiency of wastewater treatment plants with treatments used are needed.

Occurrence and concentration of the 7 most concerning pharmaceuticals

- Percentage of studies in which the pharmaceutical has been detected
- Max concentration (ng/L) detected in effluents
- Average concentration (ng/L) detected in effluents

Removal efficiency (%) of the 7 most concerning pharmaceuticals

- Average removal efficiencies (%) 18 studies
- Max Removal Efficiency (%)
- Min Removal Efficiency (%)

Classification of the pharmaceuticals of greatest concern sorted according to the percentage of studies in which the reported concentrations in effluents exceeded the PNECs for resistance selection (adapted from Bengtsson-Palme and Larsson, 2016)

Pharmaceutical	No. of Different Species with Reported MIC	Size-Adjusted Lowest MIC [a] (ng/L)	PNEC [b] Resistance Selection (ng/L)	% > MIC [c] (No. of Studies)	% > PNEC [d] (No. of Studies)
Ciprofloxacin	70	1,000	64	11.11 (2)	50.00 (9)
Clarithromycin	15	2,000	250	5.56 (1)	27.78 (5)
Ofloxacin	26	4,000	500	5.56 (1)	27.78 (5)
Trimethoprim	22	8,000	500	5.56 (1)	22.22 (4)
Metronidazole	6	2,000	125	5.56 (1)	11.11 (2)
Erythromycin	39	8,000	1,000	0 (0)	11.11 (2)
Sulfamethoxazole	8	125,000		0 (0)	5.56 (1)
		Bengtsson-Palme and Larsson study			This study

[a] MIC: minimum inhibitory concentration, corresponding to the estimated minimum selective concentration. [b] PNEC: predicted no effect concentration for resistance selection.

[c] Percentage of studies in which the pharmaceutical concentration exceeded the size-adjusted lowest MIC. [d] Percentage of studies in which the pharmaceutical concentration exceeded the PNEC resistance selection.

Bengtsson-Palme, J.; Larsson, D.G.J. Concentrations of antibiotics predicted to select for resistant bacteria: Proposed limits for environmental regulation. *Environ. Int.* **2016**, *86*, 140–149.

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