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Antibiotics: even low levels found in the environment might drive resistance

3rd March 2021
Issue 557

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Source:
Chow, L.K., Ghaly, T.M. and Gillings, M.R. (2021) A survey of sub-inhibitory concentrations of antibiotics in the environment. *Journal of Environmental Sciences*, 99: 21–27.

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Researchers behind a new literature survey of antibiotic levels in the environment call for regulators to recognise antimicrobials as pollutants and to regulate them similarly to other hazardous substances — for which environmental limits, reference standards and treatment protocols have been set. Recognising that low-level contamination from antibiotics in waste and waste-water streams, agricultural run-off[1], and pharmaceutical effluent[2] may be important risk factors linked to antibiotic resistance, they suggest setting maximum acceptable levels that are below those selecting for antimicrobial resistance. They suggest that it is vital to view antibiotics as a contaminant and to monitor levels in soil and water[3].

Antibiotic resistance is a serious threat to human health in the 21st century[4]. It is estimated that antibiotic resistant infections might account for 10 million deaths annually by 2050[4]. An increasing problem, resistance to antimicrobial medicines is strengthened by low-level exposure to antibiotics that stimulate genetic changes in bacteria. Resistant strains then multiply. Researchers behind this new survey of data on antibiotics in the environment posit that regulation is urgently needed to address this issue, as the levels detected in the environment are often high enough to drive resistance. Up to 90% of antibiotics used by humans and in animals may be excreted and are not removed by standard waste-management and waste-water treatment processes before they are released into the environment.

The researchers reviewed 40 studies published between 1999 and 2018, drawing together 887 records of antibiotic concentrations from analysis of aquatic and sediment samples in Europe, Asia and North America[5]. Using methods such as high-performance liquid chromatography (HPLC) (a technique used to separate, identify, and quantify each component in a mixture), these studies detected 39 different antibiotics, belonging to nine different antibiotic classes.

By comparing levels reported with minimum inhibitory and minimum selective concentrations, as described below, they suggest that antibiotic levels in the environment may be high enough to

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"Science for Environment Policy": European Commission DG Environment News Alert Service, edited by SCU, The University of the West of England, Bristol..

potentially drive genetic changes that cause resistant strains to develop. Minimum inhibitory concentrations (MICs) represent the lowest concentration of a certain antibiotic at which the visual growth of bacteria is inhibited. Levels above the MICs of an antimicrobial can result in the selection of antimicrobial resistant bacteria. But concentrations below the MIC (sub-inhibitory concentrations) can be selective and underline the potential for very low levels of antimicrobials to act as drivers of resistance evolution in natural settings. The minimum selective concentration is the minimum concentration of an antibiotic that provides resistant strains with a growth advantage over susceptible strains.

The researchers compared their collated data on environmental antibiotic concentrations to the MIC distributions for wild type bacteria from the European Committee on Antimicrobial Susceptibility Testing (EUCAST)[6], available for 24 antibiotics[7]. Approximately 2% of these concentrations were in the MIC ranges observed in the EUCAST database for a wide range of microorganisms[8].

Most concentrations recorded were well below the MICs for several antibiotics and thus predicted to have no effect on the growth of sensitive bacteria. However, a significant proportion of samples contained sub-inhibitory antibiotic levels below the MIC, but still high enough to encourage the development of resistant strains. The researchers note that some antibiotics are likely to cause selective pressure at levels lower than it is possible to detect using common methods. For example, it is only possible to detect ciprofloxacin and amoxicillin at levels over 0.005 milligrams per litre (mg/L) using HPLC, but they can cause effects on bacteria even at 0.002 mg/L.

It is important to study the rate at which antibiotics degrade, the researchers stress; if they are released faster than they decompose, they could accumulate in the environment. They also posit that degradation products of some antibiotics maintain antimicrobial action.

The researchers point out that there are no global guidelines for antibiotic reference standards and treatment of sewage effluent, therefore countries differ in how they monitor and address antibiotic loads. For example, only a few countries treat hospital effluent, which is high in antibiotics, separately from domestic sewage.

Globally, agricultural antibiotic use likely exceeds human consumption[9], though the amounts used vary significantly by country. For example, in 2018, the sales of antimicrobials for veterinary use in Sweden amounted to 12.5 milligrams of antibiotics per Population Correction Unit (PCU; a measure of the average animal biomass produced, which is used to normalise the antimicrobial sales data for the animal population in each country) compared to 244 mg/PCU for Italy; according to the most recent report from the European Medicines Agency[10].

European Commission

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Antibiotics: even low levels found in the environment might drive resistance (continued)

For the EU, the latest European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) report shows a decline in sales (mg/PCU) in most European countries with an overall reduction of 34.6% (for the 25 countries which provided sales data for all years between 2011 and 2018) [11]. The EU's Farm to Fork strategy includes a target of halving the use and risk of chemical and more hazardous pesticides by 2030. While the study states that global use of last-resort antibiotics, such as carbapenems and colistin, has increased, this is not necessarily the case in the EU — and certainly not for animal use.

The researchers posit that, to conserve their efficacy, antibiotics vital for human health should not be used in agriculture.

By January 2022, the EU is set to designate a list of antimicrobials that should be reserved for use only in humans and to collect and report relevant and comparable data on antimicrobial medicinal products used in animals by the different Member States, as part of the measures to fight antimicrobial resistance outlined in the Veterinary Medicines Regulation (Regulation (EU) 2019/6) [12].

Once antibiotics in the environment have been given regulated status, it will be easier to enforce waste and waste-water treatment to remove them, propose the researchers. They also stress that, to find solutions to the problem of resistance, the true extent of antibiotic use must be known. Targeted control measures to mitigate the risk to public health will rely on increasing knowledge of the threat posed, for example through extending systematic data collection on antimicrobial consumption in animals.

1. In 2019, the EU adopted two regulations to ensure a more prudent use of antimicrobials in animals: Regulation (EU) 2019/6 and Regulation (EU) 2019/4.

2. The EU's Water Framework Directive Watch List which includes several antimicrobials that Member States could monitor (Commission Implementing Decision (EU) 2020/1161).

3.The study takes a global view of antibiotics in the environment and some of its recommendations are already being addressed in the EU.

4. Review on Antimicrobial Resistance (2014) *Antimicrobial Resistance:* Tackling a Crisis for the Health and Wealth of Nations.

5. It is important to note that multiple observations from the same study were included in this study, which can lead to bias, and data may not reflect current levels in the environment.

6. EUCAST's database contains MIC distributions for many different antimicrobials for many different bacteria. The EUCAST epidemiological cut-off values (ECOFFS) "distinguish microorganisms without (wild type) and with phenotypically detectable acquired resistance mechanisms (non-wild type) to the agent in question https://mic.eucast.org/).. A microorganism is defined as wild type for a species by the absence of phenotypically detectable acquired resistance mechanisms to the agent in question. The MIC or zone diameter distribution for a collection of organisms devoid of phenotypically detectable acquired resistance is described as a wild type MIC or zone diameter distribution. The EUCAST MIC and zone diameter distribution website includes aggregated distributions for each species-agent combination." (https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/General_documents/Splitting_WT_and_resistant_populations_20160626.pdf)

7. For more information see: European Committee on Antimicrobial Susceptibility Testing (EUCAST).

8. The values they found overlap with those observed for a wide range of microorganisms: https://mic.eucast.org/search/?search%5Bmethod%5D=mic&search%5Bantibiotic%5D=1&search%5Bspecies%5D=-1&search%5Bdisk_content%5D=-1&search%5Blimit%5D=50

9. Van Boeckel T.P., Brower C., Gilbert M., Grenfell B.T., Leven S.A., Robinson T.P., Teillant A., Laxminarayan R. (2015) Global trends in antimicrobial use in food animals. *PNAS* 112: 5649–5654.

10. European Medicines Agency 2020, European Surveillance of Veterinary Antimicrobial Consumption (ESVAC). Sales of veterinary antimicrobial agents in 31 European countries in 2018. (EMA/24309/2020)

11. The ESVAC project's latest report presents standardised sales data on veterinary antimicrobial agents by class from 31 European countries during 2018. An overall decline in sales (mg/PCU) of 34.6% has been observed among those 25 countries which provided sales data between 2011 and 2018, including a decreasing trend in the veterinary sales of antibiotics considered critically important in human medicine.

12. For more information see: Implementation of the new veterinary medicines regulation (European Medicines Agency).