Emerging threats of antibiotics in the environment: what about the pharmaceutical industry?

Véronique Mondain, Florence Lieutier-Colas

Véronique Mondain
Infectious Diseases Department, University Hospital of Nice, France

Florence Lieutier-Colas
AntibioEst Infectiology Regional Network, University Hospital of Nancy, France

"Antibiotic resistance is no longer a prediction for the future."
The World Health Organization (WHO) 2014 report on Global Surveillance of Antimicrobial Resistance (AMR) revealed that: "It is happening right now, across the world, and it is putting at risk the ability to treat common infections in the community and hospitals"[1]. WHO and other eminent global health experts warn that we are at the dawn of a "post-antibiotic era". The UK Independent Review on AMR projects a worldwide death toll of 10 million people per annum by 2050, if resistance is left unchecked, with a cost of up to $100 trillion.

Several interconnected human, animal and environmental habitats can contribute to the emergence, evolution and spread of AMR. Better managing this problem includes taking steps to preserve the continued effectiveness of existing antimicrobials such as trying to eliminate their inappropriate use in both human and veterinary medicine. Despite publication of WHO guidelines recommending the discontinuation of the prescription of antibiotics as growth factors, many countries do not comply and even plan to increase the use of those antibiotics in intensive industrial farming[2]. Pollution from inadequate treatment of industrial, residential and farm waste increases the spread of resistant bacteria in the environment. Numerous countries and several international agencies have now included a "One Health Approach" within their action plans to fight AMR. "One Health" is defined as a concept and approach to "designing and implementing programmes, policies, legislation and research, in which multiple sectors communicate and work together to achieve better public health outcomes". This term is now globally recognised, having been widely used in the EU and in the 2016 United Nations Political Declaration on AMR[3].

The natural environment presents a transmission route and a reservoir for resistant microorganisms. It is well known that such bacteria and antibiotic resistance genes (ARG) are ubiquitous in nature: they can indeed be found in high concentrations in clinical, industrial and urban wastewater, as well as in animal husbandry. Moreover, the environments frequently contain very high levels of antibiotics and pharmaceuticals[4,5,6,7]. One of the very first to take an interest, Larsson *et al* analysed pharmaceuticals in the effluent from a wastewater treatment plant serving approximately 90 bulk drug manufacturers in Patancheru, near Hyderabad, India which is a major production site of generic drugs for the world market[8]. The samples contained by far the highest levels of pharmaceuticals reported in any effluent. The high levels of several broad-spectrum antibiotics raise concerns about resistance development. The concentration of the most abundant drug, ciprofloxacin (up to 31,000 µg/l), exceeds levels toxic to some bacteria by over 1000-fold. In 2017, Lübbert *et al* sampled different sites and wastewaters in an urban Indian territory where a major production area is also settled for the global bulk drug market: they found that all environmental sampling sites were contaminated with very high concentrations of antimicrobials, in particular moxifloxacin, voriconazole and fluconazole; and that microbiological analyses revealed an extensive presence of Extended Spectrum Beta Lactamase (ESBL), Carbapenemase Producing Enterobacteriaceae (CPE) and non-fermenters in more than 95% of the samples[7]. The relative abundance of total ARG was 30-fold higher in river sediments within the city, compared to upstream sites.

"Information about the origin of Active Pharmaceutical Ingredients and the finished products that end up on our pharmacy shelves is kept confidential by drug firms."

Despite those studies, few actions have been taken to improve the situation. It was not until 2011 that a European action plan against AMR mentioned the problem of pollution from production sites. In 2013, a directive required member states to develop a strategic approach against water pollution by pharmaceutical substances within two years. One of the measures envisaged plans to include environmental criteria in the guides to "Good Manufacturing Practice". However, the opacity is such that to date it is almost impossible to obtain manufacturing traceability and therefore it is actually difficult for a pharmaceutical firms to follow compliance with environmental standards. Information about the origin of Active Pharmaceutical Ingredients (APIs) and the finished products that end up on our pharmacy shelves is kept confidential by drug firms, which are unwilling to open up their supplier relationships to public scrutiny. Regulators, who could easily demand greater transparency from the pharmaceutical industry, have so far shied away from taking action[9].

Practical proposals could be made: hospitals could revise supply policies to integrate environmental clauses into their specifications for antimicrobial purchases. They could blacklist polluting companies and more legal means should allow agencies to sue companies for ecocide. Under these conditions, the question of the relocation of production factories must be asked by pharmacists and prescribers, who do not have an ethical vocation to be at the origin of the worldwide dissemination of AMR. The COVID-19 crisis, which also results in drug shortages, could be a trigger for this movement towards greater security of medicine supply.

However, these concerns no longer apply only to low- to middle– income countries (LMICs) where hygiene and sanitation may be lower. Czekalski *et al* showed increased levels of multi drug resistant (MDR) bacteria and ARGs after wastewater treatment and dissemination into Lake Geneva, in Switzerland[4]. Finally, it must be remembered that healthcare settings themselves may act as a potential reservoir for environmental pollution with MDR or even hospital-acquired outbreaks with MDR pathogens[10, 11, 12].

To conclude, we have to act on different scales in human medicine, in farms and in our environment, by limiting antibiotic consumptions and effluents, and improving surveillance and research in these areas. In 2018, WHO issued a public document whose target is to improve awareness and to educate any kind of healthcare worker to fight AMR[13]. And we can also get involved as a prescriber and a citizen, by asking for transparency on our antimicrobial market, and on the management of pharmaceutical industry effluents.
We should start acting rapidly to protect our whole world from the threat of AMR in every setting of our life.

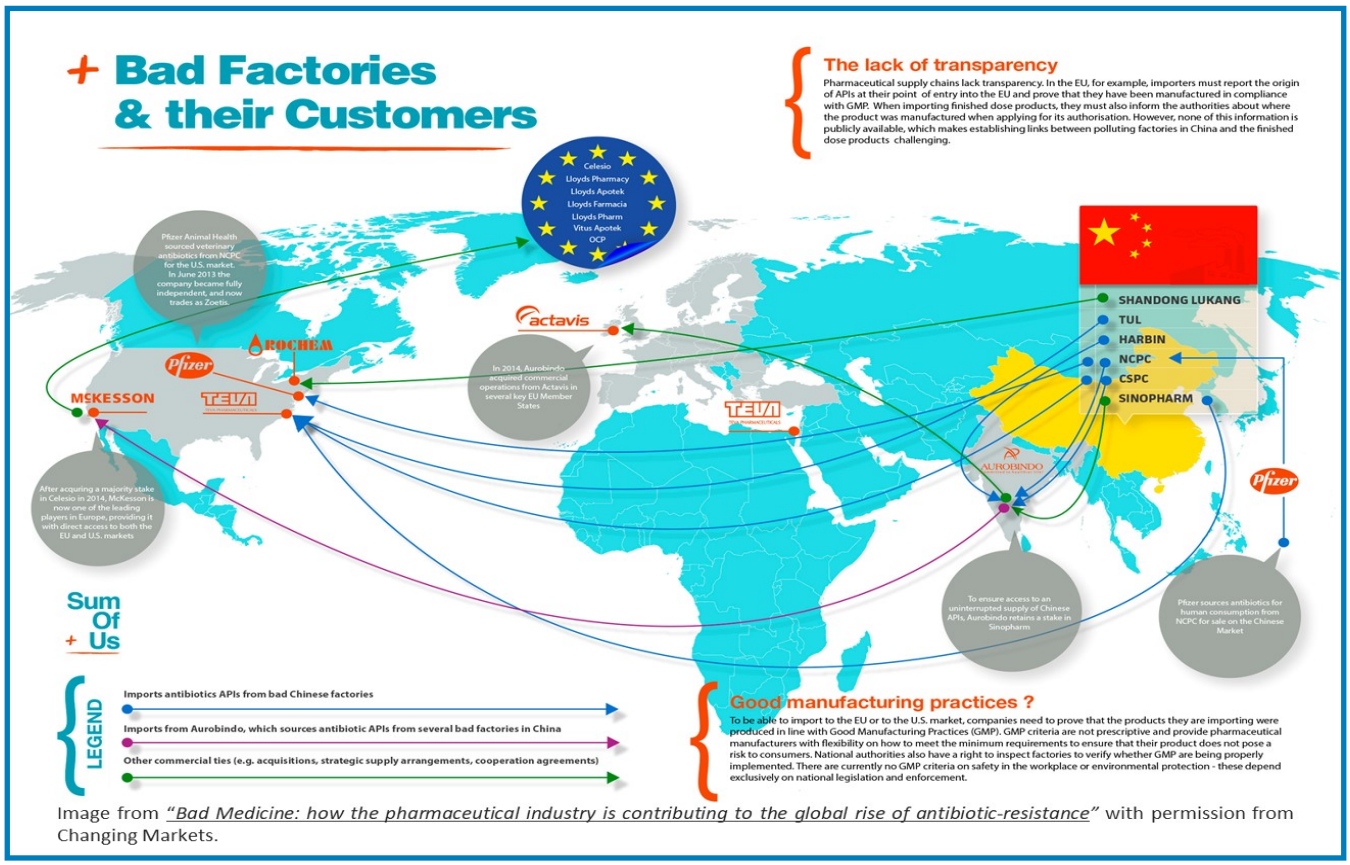
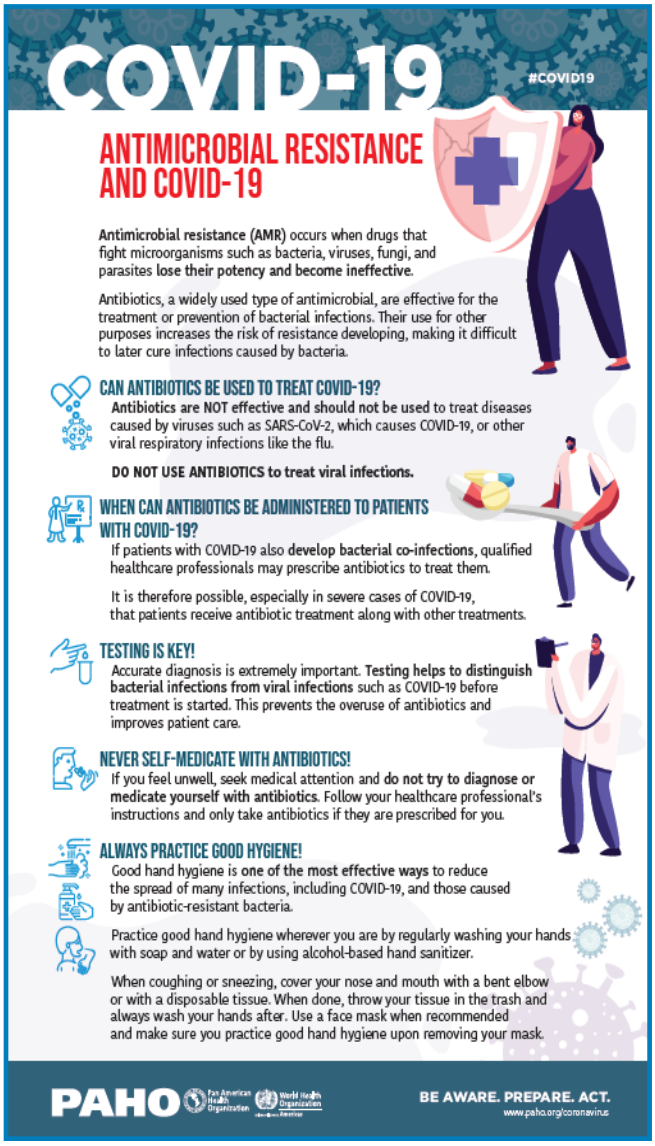


Image from *"Bad Medicine: how the pharmaceutical industry is contributing to the global rise of antibiotic-resistance"* with permission from Changing Markets.

References

1. World Health Organization. Antimicrobial resistance: global report on Surveillance. April 2014
2. Aidara-Kane A *et al*. World Health Organization (WHO) guidelines on use of medically important antimicrobials in food-producing animals. *Antimicrob Resist Infecti Control.* 2018;7:7
3. European Commission. A European One Health Action Plan against Antimicrobial Resistance (AMR). 2017
4. Czekalski N *et al.* Increased Levels of Multiresistant Bacteria and Resistance Genes after Wastewater Treatment and Their Dissemination into Lake Geneva, Switzerland. *Front Microbiol*. 2012;3:106
5. Larsson DGJ. Pollution from drug manufacturing: review and perspectives. *Philos Trans R Soc B Biol Sci*. 2014;369:20130571
6. Waseem H *et al*. Antimicrobial Resistance in the Environment. *Water Environ Res* 2017;89:921–941
7. Lübbert C *et al*. Environmental pollution with antimicrobial agents from bulk drug manufacturing industries in Hyderabad, South India, is associated with dissemination of extended-spectrum beta-lactamase and carbapenemase-producing pathogens. *Infection* 2017;45:479–491
8. Larsson DGJ *et al*. Effluent from drug manufactures contains extremely high levels of pharmaceuticals. *J Hazard Mater*. 2007;148:751–755
9. Changing markets and Ecostorm. Impacts of pharmaceutical pollution on communities and environment in India. February 2016
10. Ory J *et al.* Ciprofloxacin residue and antibiotic-resistant biofilm bacteria in hospital effluent. *Environ Pollut*. 2016;214:635-645
12. Carling PC. Wastewater drains: epidemiology and interventions in 23 carbapenem- resistant organism outbreaks. *Infect Control Hosp Epidemiol* 2018;39:972–979
11. Marathe NP *et al*. Sewage effluent from an Indian hospital harbors novel carbapenemases and integron- borne antibiotic resistance genes. *Microbiome*. 2019;7:97
13. World Health Organization. WHO competency framework for health workers' education and training on antimicrobial resistance. 2018



Events

GARDP | Developing antibiotics for children
Medical need and regulatory challenges
28 October 2020 | Webinar

World Antimicrobial Awareness Week 2020
18—24 November 2020

National OPAT Conference 2020
2 December 2020 | Virtual Event
A global overview of drug development and effective use through diagnostics, stewardship and shared learning.

BSAC Spring Conference 2021
1 March 2021
50 years of BSAC. Details to follow

Association of Medical Microbiology & Infectious Diseases Canada Annual Conference
25—30 April 2021 | Virtual Event

18th Asia Pacific Congress of Clinical Microbiology & Infection
11—13 November 2021 | Singapore

19th International Symposium on Staphylococci and Staphylococcal Infections
28—31 August 2022 | Perth, Australia
ISSSI 2022 will cover many interdisciplinary subjects regarding staphylococci and staphylococcal infections.