



**HAL**  
open science

# Reducing the Consumption of Antibiotics: Would That Be Enough to Slow Down the Dissemination of Resistances in the Downstream Environment?

Christophe Merlin

► **To cite this version:**

Christophe Merlin. Reducing the Consumption of Antibiotics: Would That Be Enough to Slow Down the Dissemination of Resistances in the Downstream Environment?. *Frontiers in Microbiology*, 2020, 11, 10.3389/fmicb.2020.00033 . hal-02477836

**HAL Id: hal-02477836**

**<https://hal.univ-lorraine.fr/hal-02477836>**

Submitted on 13 Feb 2020

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution 4.0 International License



# Reducing the Consumption of Antibiotics: Would That Be Enough to Slow Down the Dissemination of Resistances in the Downstream Environment?

Christophe Merlin\*

Université de Lorraine, CNRS, LCPME, Nancy, France

**Keywords:** antibiotic resistance dissemination, antibiotic consumption, collateral antibiotic effect, resistance gene transfer, downstream environment

## CONTROLLING THE CONSUMPTION OF ANTIBIOTICS

### OPEN ACCESS

#### Edited by:

Luciene Andrade Da Rocha Minarini,  
Federal University of São Paulo, Brazil

#### Reviewed by:

Diamantis Plachouras,  
European Centre for Disease  
Prevention and Control  
(ECDC), Sweden  
Martina Barchitta,  
University of Catania, Italy

#### \*Correspondence:

Christophe Merlin  
christophe.merlin@univ-lorraine.fr

#### Specialty section:

This article was submitted to  
Antimicrobials, Resistance and  
Chemotherapy,  
a section of the journal  
Frontiers in Microbiology

**Received:** 17 October 2019

**Accepted:** 09 January 2020

**Published:** 28 January 2020

#### Citation:

Merlin C (2020) Reducing the  
Consumption of Antibiotics: Would  
That Be Enough to Slow Down the  
Dissemination of Resistances in the  
Downstream Environment?  
*Front. Microbiol.* 11:33.  
doi: 10.3389/fmicb.2020.00033

The emergence and dissemination of antibiotic resistance is now understood as an unavoidable aspect of bacterial evolution following the consumption of antibiotics (Courvalin, 2005). This dramatic phenomenon is well illustrated by the relationship existing between the occurrence of resistances and the consumption of antibiotics (Furuya and Lowy, 2006; Davies, 2007; Davies and Davies, 2010). Mechanistically speaking, the increasing occurrence of antibiotic resistant bacteria (ARB) has been widely attributed to the selection of resistant variants that pre-exist in susceptible communities (Andersson and Hughes, 2014). Such resistant bacteria are supposedly outcompeting the rest of the microbial communities in a context where antibiotics are administrated at relatively high levels, which means that local concentrations are well-over the Minimum Inhibitory Concentrations (MICs). Despite the fact that the increasing occurrence of antibiotic resistances among bacteria has been recognized decades ago as resulting from antimicrobial drug consumption, only recently has the seriousness of the situation been considered by international, national and local health organizations/agencies. This awareness led to series of reports and recommendations intending to educate and improve practices of health professionals and consumers, in order to preserve the effectiveness of our therapeutic potential (MSS, 2011; World Health Organization, 2015; O'Neil Report, 2016; EUR-Lex, 2018). Considering the correlation between antibiotic consumption and occurrence of resistances in bacteria (Davies, 2007), most recommendations proposed to take action in the public health and veterinary/farming domains by limiting the inappropriate exposure of bacteria to antibiotics in order to slow down a natural evolution toward resistance and its spread in the downstream environment in a One Health context (World Health Organization, 2015, 2017). Limiting the inappropriate exposure of bacteria to antibiotics implicitly means (i) reducing the need for antibiotics, which can be achieved with infection control measures that would limit the epidemic spread of resistant bacteria, and (ii) a better usage of antibiotics so as to reduce our overall antibiotic consumption when unnecessary.

Even if there is a great disparity between countries regarding the consumption of antibiotics (European Centre for Disease Prevention and Control (ECDC), 2017), change in practice remains difficult to implement when public health is concerned. In any case, taking action to reduce antibiotic resistance requires a coordinated and multi-sectorial approach combining political commitment, resources, specific governance mechanisms, and practical managements, as recently reported by World Health Organization (2018). In its 2018 reports, the ECDC indicated that the overall consumption of antibiotics in the EU did not significantly change in the community

and the hospital sectors, while a few decreasing and increasing trends were observed for some countries over the 2013–2017 period. Changes in consumption were probably more visible in veterinary medicine. In a report covering the 2011–2016 period on veterinary antibiotics sale, the European Surveillance of Veterinary Antimicrobial Consumption related an overall decrease of 20% aggregated for 25 countries (European Surveillance of Veterinary Antimicrobial Consumption (ESVAC), 2018). This was tentatively explained by the implementation of policies and measures aiming at reducing the misuse of antibiotics. Even if the studied period is too short yet to draw robust conclusion, the first effects of such responsible-use campaigns start to be visible. In France for instance, an unprecedented national plan to reduce the antibiotic consumption in the animal sector has been initiated (Ecoantibio, 2017). This led to a drastic 39% reduction of antibiotic prescription in veterinary medicine in 6 years, all animals considered. The reduction was even stronger for critical antibiotics such as fluoroquinolones (81% reduction) and last generation cephalosporin (75% reduction). According to the French surveillance network of antimicrobial resistance in pathogenic bacteria of animal origin, these measures were followed by a net diminution of pathogenic ARBs (RESAPATH, 2016). As reported by the French National Public Health Agency (Santé Publique France, 2018), using data also presented by the European Food Safety Agency, the proportion of resistant *E. coli* for C3G went down from 16% to <2% in poultry between 2010 and 2017, which was dramatically increasing before 2010 (Bourély et al., 2018; European Food Safety Agency (EFSA), 2018; Santé Publique France, 2018). Although more results are necessary to comfort these results, they tend to demonstrate that a better use leading to a reduced consumption of antibiotics can rapidly result in a sensible decrease of the relative occurrence of ARBs. If several other reports are rather encouraging to pursue in that direction (Seppala et al., 1997; Aarestrup et al., 2001; Dutil et al., 2010), the relationship between occurrence of resistance and antibiotic consumption does not always follow this trend. Indeed, even if it is not the vast majority of the reported cases, stopping or increasing the consumption of a given antibiotic does not always result in the concomitant decrease or increase of the corresponding resistances, and this may vary according to the studied environment, the public/animal concerned, and the antibiotic and bacteria considered. For instance, Lai et al. (2011) reported a negative correlation between a decreasing consumption of cefotaxime and the rate of cefotaxime resistant-*Escherichia coli* pathogens isolated in a Taiwanese university hospital. Similar trends were reported for the consumption of ceftriaxone and ceftriaxone-resistant *E. coli* and *Klebsiella* spp. in a Turkish hospital setting (Altunsoy et al., 2011). Negative correlations between antibiotic consumptions and development of resistances can also work the other way around, and may depend on the bacterial species considered. In a Korean study covering six university hospitals, Kim et al. (2018) observed contrasted results following an increased consumption of fluoroquinolones, where the resistance rate for ciprofloxacin in *E. coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*, either increased,

remained stable or decreased, respectively over an 8-years period. Surprisingly, the same authors also found negative correlation between decreasing consumptions of aminoglycosides and the resistance rate for third generation cephalosporins and ciprofloxacin, thus disconnecting a given drug consumption from its effect on the corresponding antibiotic resistance, at least for a few documented cases. To go further, it is worth noting that carbapenem-resistant *P. aeruginosa* could be isolated from animals that have not been previously treated with carbapenems. In this case, the resistance to carbapenem was attributed to an efflux pump dysregulation (rather than a carbapenemase) resulting from mutations possibly selected by disinfectants and other antibiotics in veterinary practices (Haenni et al., 2017), thus showing that resistant phenotypes can emerge independently from the presence of the corresponding antibiotics. On the other hand, the identification of antibiotic resistance genes in metagenomes from 30,000-years old sediments reminds us that resistance phenotypes and their corresponding genes probably existed before the so-called antibiotic era (D'Costa et al., 2011). Taken together, these observations clearly indicate that the emergence and the dissemination of antibiotic resistances in bacteria cannot solely be explained by a simple selective process occurring during antibiotics therapy, even if the latter is an important driving parameter in many instances.

## THE ANTIBIOTIC COLLATERAL EFFECTS

Tackling the spread of antibiotic resistance will surely require a better usage of antibiotics in order to slow down the emergence of resistant variants associated to antibiotic therapies. But, considering the indispensability of antibiotics in modern medicine, antibiotic resistances will continue to be released in anthropogenically-impacted environments where ARBs can persist, accumulate, transfer their resistant genes (ARGs) to indigenous microbes, and finally re-enter the food chain and contaminate human and animal guts for a new round of selection (Davies and Davies, 2010). It should be noted here that the environment has been described as a reservoir of ARGs in several occasions (Berendonk et al., 2015). Considering that the dissemination of antibiotic resistances lies on the acquisition of resistance but also implies a transmission, and therefore a contact, between people, or with wastewater, or manure, or animals, tackling the dissemination of ARB and ARGs will surely require controlling both the usage of antibiotics but also the route of transmission, especially at the environmental level. With that respect, Collignon et al. (2018) recently proposed that the transmission of ARB and ARGs was probably the dominant contributor to consider for controlling antibiotic resistance, which implies to act at other levels than the antibiotic consumption as well.

The global reduction of consumption is not the sole important measure implemented by national and international organizations for better usage antibiotics. The classification of antimicrobial agents as critically important molecules for human health (WHO classification list), the restriction of their availability/delivery, and the confinement of particular

antibiotic usages to human medicine are important measures aiming at preventing the emergence of particular resistances in the animal husbandry sector and their dissemination in the human health sector (EUR-Lex, 2018; OIE: World Organisation for Animal Health, 2018; World Health Organization, 2019). Nevertheless, confining the usage of a given antibiotic is likely to be of limited impact if collateral effects were to be observed between antibiotics of different nature on the emergence and the dissemination of unrelated ARGs. Lately, Scornec et al. (2017) demonstrated that *Tn916*, a mobile genetic element involved in the dissemination of an ARG for tetracycline, could exhibit a 1,000-fold increase of its transfer frequency when exposed to sub-inhibitory concentrations of tetracyclines, but also macrolides, lincosamides, and streptogramins. This means that not only sub-inhibitory concentrations of an antibiotic could stimulate the dissemination of its corresponding resistant gene, but that collateral stimulation by other antibiotics is also possible. This tends to rule out the effectiveness, at least partially, of any measure that would be based on confining the usage of cross-reacting antibiotics. On another ground, the use of trace metal elements such as zinc oxide or copper sulfate, is frequently used as an antibiotic alternative to promote growth of livestock and poultry. Consequently to such practices, several authors reported a concomitant increase of ARB and ARGs that are likely to result from co-selective processes, as ARGs and metal resistance genes can collocate on the same genetic entities (mobile genetic elements) (Hasman et al., 2006; Yin et al., 2017; van Alen et al., 2018).

## CONCLUSION

Collateral effects of antibiotics at sub-inhibitory concentrations and trace metal elements clearly highlight the fact that the

## REFERENCES

- Aarestrup, F. M., Seyfarth, A. M., Emborg, H.-D., Pedersen, K., Hendriksen, R. S., and Bager, F. (2001). Effect of abolishment of the use of antimicrobial agents for growth promotion on occurrence of antimicrobial resistance in fecal enterococci from food animals in Denmark. *Antimicrob. Agents Chemother.* 45, 2054–2059. doi: 10.1128/AAC.45.7.2054-2059.2001
- Altunsoy, A., Aypak, C., Azap, A., Ergönül, Ö., and Balik I. (2011). The impact of a nationwide antibiotic restriction program on antibiotic usage and resistance against nosocomial pathogens in Turkey. *Int. J. Med. Sci.* 8, 339–44. doi: 10.7150/ijms.8.339
- Andersson, D. I., and Hughes, D. (2014). Microbiological effects of sublethal levels of antibiotics. *Nat. Rev. Microbiol.* 12, 465–478. doi: 10.1038/nrmicro3270
- Berendonk, T. U., Manaia, C. M., Merlin, C., Fatta-Kassinos, D., Cytryn, E., Walsh, F., et al. (2015). Tackling antibiotic resistance: the environmental framework. *Nat. Rev. Microbiol.* 13, 310–317. doi: 10.1038/nrmicro3439
- Bourély, C., Chauvin, C., Jouy, É., Cazeau, G., Jarrige, N., Leblond, A., et al. (2018). Comparative epidemiology of *E. coli* resistance to third-generation cephalosporins in diseased food-producing animals. *Vet. Microbiol.* 223, 72–78. doi: 10.1016/j.vetmic.2018.07.025
- Collignon, P., Beggs, J. J., Walsh, T. R., Gandra, S., and Laxminarayan, R. (2018). Anthropological and socioeconomic factors contributing to global antimicrobial resistance: a univariate and multivariable analysis. *Lancet Planetary Health* 2, e398–e405. doi: 10.1016/S2542-5196(18)30186-4

antibiotic resistance risk should not be associated with the sole antibiotic therapy practices, and should rather be considered as a multifactorial problem where co-selection and stimulation of horizontal gene transfer also fully applies. Further in depth epidemiological studies should allow determining the extent of such collateral effects outside the context of a Petri dish, and may explain why some antibiotic resistances escape any reduction of occurrence while reducing the corresponding antibiotic consumption. On the other hand determining exhaustively which antibiotic molecules exhibit collateral effects, and at which concentrations, would be an additional step toward antibiotic risk assessment, whether for therapeutic practices or for the effect of antibiotics once diluted in the downstream environments.

## AUTHOR CONTRIBUTIONS

CM wrote this opinion paper.

## FUNDING

The author wishes to thank the French National Agency for Research (ANR) (Project ReguloMobile, No. ANR-13-ADAP-0009) and the French Agency for Food, Environmental and Occupational Health & Safety (Project AquaResist, PNREST Anses, 2018/1/052) for research funding.

## ACKNOWLEDGMENTS

This article was based upon work carried out in the framework of the COST Action ES1403: New and emerging challenges and opportunities in wastewater reuse (NEREUS), supported by COST (European Cooperation in Science and Technology). The author also wishes to thank Sandrine Baron for fruitful discussion during the preparation of the manuscript.

- Courvalin, P. (2005). Antimicrobial drug resistance: “prediction is very difficult, especially about the future”. *Emerg. Infect. Dis.* 11, 1503–1506. doi: 10.3201/eid1110.051014
- Davies, J. (2007). Microbes have the last word. A drastic re-evaluation of antimicrobial treatment is needed to overcome the threat of antibiotic-resistant bacteria. *EMBO Rep.* 8, 616–621. doi: 10.1038/sj.embor.7401022
- Davies, J., and Davies, D. (2010). Origins and evolution of antibiotic resistance. *Microbiol. Mol. Biol. Rev.* 74, 417–433. doi: 10.1128/MMBR.00016-10
- D’Costa, V. M., King, C. E., Kalan, L., Morar, M., Sung, W. W., Schwarz, C., et al. (2011). Antibiotic resistance is ancient. *Nature.* 477, 457–461. doi: 10.1038/nature10388
- Dutil, L., Irwin, R., Finley, R., Ng, L. K., Avery, B., Boerlin, P., et al. (2010). Ceftiofur resistance in *Salmonella enterica* serovar Heidelberg from chicken meat and humans, Canada. *Emerg. Infect. Dis.* 16, 48–54. doi: 10.3201/eid1601.090729
- Ecoantibio (2017). *Écoantibio 2: The French National Plan for the Reduction of the Risks of Antimicrobial Resistance in Veterinary Medicine*. Available online at: <https://agriculture.gouv.fr/le-plan-ecoantibio-2-2017-2021> (accessed October 15, 2019).
- EUR-Lex (2018). *European Parliament Legislative Resolution of 25 October 2018 on the Proposal for a Regulation of the European Parliament and of the Council on Veterinary Medicinal Products (Document P8\_TA(2018)0421)*. Available online at: [https://eur-lex.europa.eu/legal-content/FR/TXT/?uri=EP%3AP8\\_TA%282018%290421](https://eur-lex.europa.eu/legal-content/FR/TXT/?uri=EP%3AP8_TA%282018%290421) (accessed October 14, 2019).

- European Centre for Disease Prevention and Control (ECDC) (2017). *Antimicrobial consumption - Annual Epidemiological Report for 2017*. Available online at: <https://www.ecdc.europa.eu/en/publications-data/antimicrobial-consumption-annual-epidemiological-report-2017> (accessed October 15, 2019).
- European Food Safety Agency (EFSA) (2018). *The European Union Summary Report on Antimicrobial Resistance in Zoonotic and Indicator Bacteria from Humans, Animals and Food in 2016*. Available online at: <https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2018.5182> (accessed October 15, 2019).
- European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) (2018). *Sales of Veterinary Antimicrobial Agents in 30 European Countries in 2016*. Available online at: [https://www.ema.europa.eu/en/documents/report/sales-veterinary-antimicrobial-agents-30-european-countries-2016-trends-2010-2016-eighth-esvac\\_en.pdf](https://www.ema.europa.eu/en/documents/report/sales-veterinary-antimicrobial-agents-30-european-countries-2016-trends-2010-2016-eighth-esvac_en.pdf) (accessed October 15, 2019).
- Furuya, E. Y., and Lowy, F. D. (2006). Antimicrobial-resistant bacteria in the community setting. *Nat. Rev. Microbiol.* 4, 36–45. doi: 10.1038/nrmicro1325
- Haenni, M., Bour, M., Châtre, P., Madec, J.-Y., Plésiat, P., and Jeannot, K. (2017). Resistance of animal strains of *Pseudomonas aeruginosa* to carbapenems. *Front. Microbiol.* 8:1847. doi: 10.3389/fmicb.2017.01847
- Hasman, H., Kempf, I., Chidaïne, B., Cariolet, R., Ersbøll, A. K., Houe, H., et al. (2006). Copper resistance in *Enterococcus faecium*, mediated by the *tcrB* gene, is selected by supplementation of pig feed with copper sulfate. *Appl. Environ. Microbiol.* 72, 5784–5789. doi: 10.1128/AEM.02979-05
- Kim, B., Kim, Y., Hwang, H., Kim, J., Kim, S. W., Bae, I. G., et al. (2018). Trends and correlation between antibiotic usage and resistance pattern among hospitalized patients at university hospitals in Korea, 2004 to 2012: a nationwide multicenter study. *Medicine* 97:e13719. doi: 10.1097/MD.00000000000013719
- Lai, C.-C., Wang, C.-Y., Chu, C.-C., Tan, C.-K., Lu, C.-L., Lee, Y.-C., et al. (2011). Correlation between antibiotic consumption and resistance of Gram-negative bacteria causing healthcare-associated infections at a university hospital in Taiwan from 2000 to 2009. *J. Antimicrob. Chemother.* 66, 1374–1382. doi: 10.1093/jac/dkr103
- MSS, Ministère des Solidarités et de la Santé/French Ministry of Health (2011). *Plan national d'alerte sur les antibiotiques 2011-2016/National Antibiotic Alert Plan 2011-2016*. Available online at: [https://solidarites-sante.gouv.fr/IMG/pdf/Plan\\_antibiotiques\\_2011-2016\\_.pdf](https://solidarites-sante.gouv.fr/IMG/pdf/Plan_antibiotiques_2011-2016_.pdf) (accessed October 14, 2019).
- OIE: World Organisation for Animal Health (2018). *OIE List of Antimicrobial Agents of Veterinary Importance*. Available online at: [https://www.oie.int/fileadmin/Home/eng/Our\\_scientific\\_expertise/docs/pdf/AMR/A\\_OIE\\_List\\_antimicrobials\\_May2018.pdf](https://www.oie.int/fileadmin/Home/eng/Our_scientific_expertise/docs/pdf/AMR/A_OIE_List_antimicrobials_May2018.pdf) (accessed October 15, 2019).
- O'Neil Report (2016). *Tackling Drug-Resistant Infections Globally: Final Report and Recommendations*. Available online at: [https://amr-review.org/sites/default/files/160518\\_Final%20paper\\_with%20cover.pdf](https://amr-review.org/sites/default/files/160518_Final%20paper_with%20cover.pdf) (accessed October 14, 2019).
- RESAPATH (2016). RESAPATH: French surveillance network for antimicrobial resistance in pathogenic bacteria of animal origin (2016). *2016 Annual Report*. Available online at: <https://www.anses.fr/en/system/files/LABO-Ra-Resapath2016EN.pdf> (accessed October 15, 2019).
- Santé Publique France (2018) *Consommation d'antibiotiques et résistance aux antibiotiques en France : une infection évitée, c'est un antibiotique préservé!* Available online at: <https://www.santepubliquefrance.fr/maladies-et-traumatismes/infections-associees-aux-soins-et-resistance-aux-antibiotiques/resistance-aux-antibiotiques/documents/rapport-synthese/consommation-d-antibiotiques-et-resistance-aux-antibiotiques-en-france-une-infection-evitee-c-est-un-antibiotique-preserve> (accessed October 15, 2019).
- Scornec, H., Bellanger, X., Guilloteau, H., Groshenry, G. and Merlin, C. (2017). Inducibility of Tn916 conjugative transfer in *Enterococcus faecalis* by subinhibitory concentrations of ribosome-targeting antibiotics. *J. Antimicrob. Chemother.* 72, 2722–2728. doi: 10.1093/jac/dkx202
- Seppala, H., Klaukka, T., Vuopio-varkila, J., Muotiala, A., Helenius, H., Lager, K., et al. (1997). The effect of changes in the consumption of macrolide antibiotics on erythromycin resistance in group A streptococci in Finland. *N. Engl. J. Med.* 337, 441–446. doi: 10.1056/NEJM199708143370701
- van Alen, S., Kaspar, U., Idelevich, E. A., Köck, R., and Becker, K. (2018). Increase of zinc resistance in German human derived livestock-associated MRSA between 2000 and 2014. *Vet. Microbiol.* 214, 7–12. doi: 10.1016/j.vetmic.2017.11.032
- World Health Organization (2015). *Global Action Plan on Antimicrobial Resistance*. Available online at: <http://www.emro.who.int/health-topics/drug-resistance/global-action-plan.html> (accessed October 14, 2019).
- World Health Organization (2017). *Global Framework for Development & Stewardship to Combat Antimicrobial Resistance*. Available online at: [http://www.who.int/antimicrobial-resistance/global-action-plan/UpdatedRoadmap-Global-Framework-for-Development-Stewardship-to-combatAMR\\_2017\\_11\\_03.pdf?ua=1](http://www.who.int/antimicrobial-resistance/global-action-plan/UpdatedRoadmap-Global-Framework-for-Development-Stewardship-to-combatAMR_2017_11_03.pdf?ua=1) (accessed October 14, 2019).
- World Health Organization (2018). *Tackling Antimicrobial Resistance Together. Working paper 1.0: Multisectoral coordination*. Available online at: <https://www.who.int/antimicrobial-resistance/publications/workingpaper1multisectoralcoordinationAMR/en/> (accessed October 15, 2019).
- World Health Organization (2019). *WHO Model List of Essential Medicines, 21st List*. Available online at: <https://www.who.int/medicines/publications/essentialmedicines/en/> (accessed October 15, 2019).
- Yin, Y., Gu, J., Wang, X., Song, W., Zhang, K., Sun, W., et al. (2017). Effects of copper addition on copper resistance, antibiotic resistance genes, and *intI1* during swine manure composting. *Front. Microbiol.* 8:344. doi: 10.3389/fmicb.2017.00344

**Conflict of Interest:** The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2020 Merlin. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.