SOIL ECOLOGY LETTERS

SEL

PERSPECTIVE

Volume 6 / Issue 4 / 240244 / 2024

https://doi.org/10.1007/s42832-024-0244-4

Metals are overlooked in the evolution of antibiotic resistance

Yi Zhao[1,2,*], Rui Xu[1,2], Siobhan F. Cox[3], Min Qiao[4], Huaming Guo[1,2]

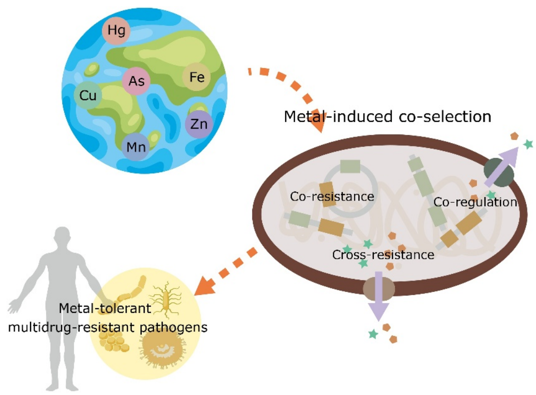
1 State Key Laboratory of Biogeology and Environmental Geology, China University of Geosciences (Beijing), Beijing 100083, China
2 Key Laboratory of Groundwater Conservation of MWR & School of Water Resources and Environment, China University of Geosciences (Beijing), Beijing 100083, China
3 School of Natural and Built Environment, Queen's University of Belfast, David Keir Building, Stranmillis Road, Belfast BT9 6AX, United Kingdom
4 Research Center for Eco-Environmental Sciences, Chinese Academy of Sciences, Beijing 100085, China
* Corresponding author. E-mail: y.zhao@cugb.edu.cn (Y. Zhao)

Received February 1, 2024; Revised March 1, 2024; Accepted March 10, 2024

ABSTRACT

• Metals are increasingly important risk factors for the evolution of antibiotic resistance in environments.

The rapid development of antibiotic resistance is occurring at a global scale. We therefore stride into the post-antibiotic era and have to battle antibiotic resistance in the Anthropocene. Metals are widely used and their pollution is widespread worldwide. More importantly, metal-induced co-selection greatly expands the environmental resistomes and increases the health risk of antibiotic resistance in environments. Here, we reviewed the metal-induced co-selection and their increasingly important roles in the development of antibiotic resistance. In particular, we highlight the metal-rich environments that maintain reservoirs for high-risk antibiotic resistance genes with horizontally transferable potentials. We also call for considerations and further investigations of other co-selective agents and the efficacy of metal-based interventions to better manage and combat the global antibiotic resistance crisis within the One Health framework.



Keywords antibiotic resistance, metals, co-selection, mobile genetic elements, One Health

1 Introduction

The rapid development of antibiotic resistance is occurring at a global scale and has become a global health crisis (Larsson and Flach, 2022). About 1.27 million people died globally as a result of antibiotic resistance in 2019, and this is expected to increase to 10 million people annually by 2050 (Kwon and Powderly, 2021). It is evident that overuse and misuse of antibiotics have been the main drivers in the emergence and development of antibiotic resistance genes (ARGs) via their selection pressure on bacterial communities (van Boeckel et al., 2014). As we enter the Anthropocene, we also are entering a post-antibiotic era, during which we will have to respond to antibiotic resistance (Kwon and Powderly, 2021). However, metals and their co-selection remain one of the biggest challenges to combat antibiotic resistance.

Cite this: Soil Ecol. Lett., 2024, 6(4): 240244

2 Metals are widespread

Metals are widely used to support animal and human health and well-being as feed additives, antimicrobials, and active pharmaceutical ingredients. Pharmaceutical products for humans such as thimerosal, thiazide diuretics, and antacids often contain mercury (Hg) or aluminum (Al) (WHO, 2015), while many regular commodities including deodorants, cosmetics, and household cleaning products also usually frequently contain metals such as Al, lead (Pb), selenium (Se), arsenic (As), or copper (Cu). Added to this, recent bans on the use of antibiotics as in-feed growth promoters in many countries have meant that metals such as Cu and zinc (Zn) have acquired growing attention as alternative feed supplements and are therefore being used in increasing concentrations in livestock farming (Poole, 2017). Metal contaminations are widespread in environments and affect millions of people worldwide (Nriagu, 1996). Millions of contaminated sites were identified across the world with over 35% of these presented with metal pollution. Metals are common environmental stressors that drive microbial community reassembly and evolution (Lemire et al., 2013). With extensive anthropogenic activities such as farming, mining, and wastewater discharges, the exposure of environmental microbiomes to metals at toxic levels has been accelerating over recent decades.

Excessive metal accumulation in environments can lead to cell toxication or death from enzyme inactivation, protein disruption or formation of chelates or precipitates from metabolites (Lemire et al., 2013). Microbes have rapidly adapted to high metal burdens via a variety of chromosomal and mobile genetic element (MGE) mediated metal resistance mechanisms (Hao et al., 2021). Metal resistance mechanisms mainly include (1) efflux pump, which can exclude the metals out of the cell, (2) reducing uptake, which can reduce the concentration of metals uptake by cell with a permeability barrier, (3) enzymatic detoxification/biotransformation, which can alter metal redox states to less toxic forms, (4) intracellular sequestration, which can protect metal-sensitive targets by protein binning, and (5) extracellular sequestration, which can trap or precipitate metals in extracellular environments. Moreover, microbes can switch to a slow growth strategy, form biofilms, or acquire metal resistance via mutation or horizontal gene transfer to develop a tolerance for toxic metals. Horizontal gene transfer via mobile genetic elements (MGEs) serves as a critical tache for the evolution and succession of microbial communities and therefore contributes to community stability and the self-coordination ability of the ecosystem. However, widespread metal contamination and its persistent selection pressure create hotspots for the development of metal resistance and drive the evolution of microbiomes.

3 Metal-induced co-selection

Co-selection is one of the biggest challenges in combating antibiotic resistance, as it is very difficult to reverse antibiotic resistance once it is established in the environmental microbiome. One antibiotic class can co-select for resistance conferring to another antibiotic class. More importantly, widespread metals can provide selection pressure and persistently co-select for antibiotic resistance, causing an accumulation of mutations that incidentally also confer decreased antibiotic susceptibility without antibiotic exposure (Knöppel et al., 2017). Therefore stopping antibiotic use might not reverse antibiotic resistance in environments where there is a growing co-selection of metals.

Metal-induced co-selection mainly occurs via mechanisms including (1) co-resistance, in which resistance genes of metals and antibiotics are physically located together on the same MGE or in the same cell, (2) cross-resistance, in which resistance genes can confer resistance to both antibiotics and metals via one single mechanism, and (3) co-regulation, in which one regulatory gene can regulate expression of different resistance genes for antibiotics and metals (Fig. 1) (Baker-Austin et al., 2006). There are numerous studies have reported the potential co-selection of resistance between metals and antibiotics via different co-selection mechanisms (Li et al., 2017; Roberto et al., 2019).

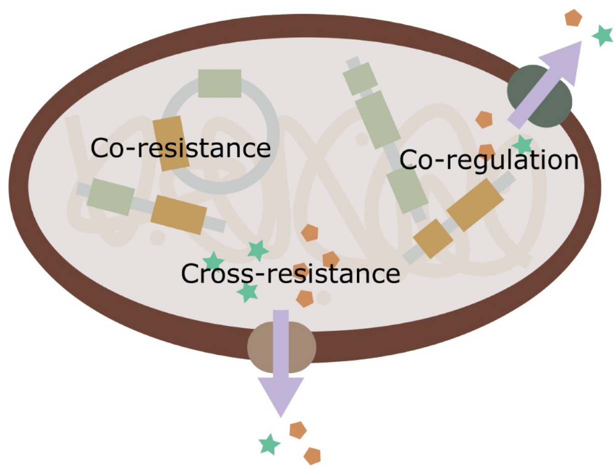


Fig. 1 Molecular mechanisms of metal-induced co-selection.

Close location and co-occurrence of metal resistance and antibiotic resistance genes have been frequently detected, suggesting the importance of co-resistance mechanisms in metal-induced co-selection (Pal et al., 2015; Li et al., 2017). Moreover, the co-occurrence was found to be stronger and more frequent in human pathogens than in bacteria that are associated less frequently with humans, highlighting the potential risk to humans associated with co-selection via co-resistance of both environmental and clinical relevance (Li et al., 2017).

Co-resistance potential and their corresponding co-occurrence structures varied among different scenarios, related to the type, speciation, toxicity, bioavailability, and concentration of metal(loid)s (Cantón and Ruiz-Garbajosa, 2011). Co-resistance was also greatly influenced by gene transfer potentials, MGE profiles, microbial community and their interspecific interactions (Li et al., 2015). Cross-resistance, associated with microbial efflux systems, also emerges as an essential role in metal-induced co-selection. Efflux pumps are widespread and “cost-effective” for microbes as they are often non-specific and can confer resistance to various metals and antibiotics, which eventually leads to the development of resistance to one antimicrobial agent accompanied to another agent (Du et al., 2018). The continuous stimulation of widespread metals thus can facilitate the activation of membrane-bound efflux systems and promote the multidrug phenotype.

Mobile genetic elements (such as integrons, transposons, or plasmids) play important roles in metal-induced co-selection (Frost et al., 2005). MGEs carrying both ARGs and metal resistance genes (MRGs) are enriched via metal-induced co-selection with co-resistance as the mechanism, thus increasing the horizontal gene transfer of ARGs and providing a higher possibility for the spread of high-risk ARGs (Frost et al., 2005; Zhang et al., 2022). Detection of MGEs therefore not only implies the potential of ARG horizontal transfer, but also the potential for co-resistance. For instance, integrons are essential elements for microbial evolution as they act like toolboxes, with a variety of captured active genes such as MRGs and ARGs assembled inside to help microorganisms to cope with environmental stress (Gillings, 2014). Thus integrons are often considered as ARG and MRG capture platforms. Although integrons themselves are not mobile, they are easily disseminated in environments with the aid of transposons or plasmids and are therefore proposed as a proxy for anthropogenic pollution (Gillings et al., 2015).

Transposons, also known as the “jumping genes”, can mobilize DNA sequences and genes within the chromosome, between chromosomes and plasmids, and between different bacterial genomes (Babakhani and Oloomi, 2018). Therefore they often co-occur with ARGs and MRGs on plasmids or integrons. Plasmids are important MGEs in co-selection as they can carry both metal and antibiotic resistances and therefore provide advantages to their host bacteria under co-selection pressures.

4 Metals are overlooked in the evolution of antibiotic resistance

Metal-contaminated environments are hotspots for ARGs, where they persist via co-selection. Unlike other selective agents, metals do not degrade and can easily accumulate in environments, and therefore provide a persistent selection pressure on microbiomes. Metals are widespread in environments from both geogenic and anthropogenic sources, however due to the alarming increase of anthropogenic metal pollution in the environment, co-selection has been frequently reported in environments affected by agriculture, livestock farming, aquaculture, and urbanization (Table 1) (Seiler and Berendonk, 2012; Zhao et al., 2018, 2019, 2021; Mazhar et al., 2021). Environments represent potential sources of contamination by metals of moderate to high toxicity including Hg, Cd, Cu, and Zn, which warrant consideration as important co-selective agents (Seiler and Berendonk, 2012). Moreover, as antibiotics have been banned in many countries as in-feed growth promoters, Cu and Zn are emerging as alternative feed additives for animal growth promotion, which will require continuous attention to ensure an integrated consideration of impacts on humans, animals, and the environment under the One Health framework.

Apart from anthropogenic inputs, environments with high geogenic levels of metal burdens are also overlooked as reservoirs for co-selecting antibiotic resistance (Table 1) (Knapp et al., 2011; Wang et al., 2022). Given the ubiquitousness of trace elements including metals and metalloids in Earth’s lithosphere, hydrosphere, biosphere, and atmosphere, these natural background geogenic sources of metals also play an important role in the maintenance of antibiotic resistance in environments.

Metal-induced co-selection can greatly increase health risks from antibiotic resistance due to its greater availability in clinical settings, animal and human pathogenicity, human accessibility, and mobility. Human and animal microbiomes tend to harbor a higher proportion of microbiota with co-selection potential compared to other environments, due to the widespread use of disinfectants, antiseptics, and other metal-based antimicrobial products in health care and animal farming (Li et al., 2017). There is also an increasing risk of infectious diseases from metal exposure in these settings as metals are considered alternative antimicrobials

Table 1 Selected previous studies that provide potential evidence of metal-induced co-selection for antibiotic resistance in soils, water, and animal microbiomes.

Metals	Scenarios	References
Cu, Hg, Zn, Cd	Agricultural soils	Berg et al., 2005; Seiler and Berendonk, 2012; Song et al., 2017; Kang et al., 2018; Mahbub et al., 2020; Zhao et al., 2021
Cu, Hg, Zn, Cd	Agricultural surface water	Seiler and Berendonk, 2012
As, Cd, Cu, Pb, Zn	Animal farm soils	Zhu et al., 2013; Zhou et al., 2016; Mazhar et al., 2021
Al, As, Cd, Co, Cr, Cu, Hg, Mn, Ni, Pb, Zn	Urban soils, residential soils	Knapp et al., 2011, 2017; Zhao et al., 2019; Ding et al., 2021
Se	Wetland, forest soils	Shi et al., 2021; Wang et al., 2022
Cd	Freshwater, Brackish water	Stepanauskas et al., 2006; Pu et al., 2021
Cd, Co, Cr, Cu, Ni, Pb, Zn	Urban surface water	Roberto et al., 2019; Gupta et al., 2022
As, Co, Cr, Ni, Pb	Terrestrial subsurface soils	Wang et al., 2021
As, Cd, Cu, Pb, Zn	Animal microbiome	Zhu et al., 2013; Yazdankhah et al., 2014; Zhou et al., 2016; Zhao et al., 2018; Mazhar et al., 2021

for combating clinical antibiotic-resistant infections (Frei et al., 2023).

The presence of ARGs on MGEs is particularly frequent in clinically important bacteria, therefore enhancing the potential of co-selection and horizontal gene transfer in clinical settings (Pal et al., 2015; Li et al., 2017). There is growing evidence of metal-induced co-selection on ARGs and MGEs (Pal et al., 2015; Zhao et al., 2019), which presents a high-risk scenario for MGE-facilitated mobile ARGs horizontally transferring to human pathogens. If infections are caused by human pathogenic bacteria with resistance to multiple metals and antibiotics, there is a significantly higher risk for human health as access to potentially successful antimicrobial treatments such as antibiotics or metals can be significantly restricted. Therefore metal-rich environments maintain reservoirs of high-risk ARGs with horizontally transferable potentials.

In the battle against antibiotic resistance, global efforts have committed to a Global Action Plan under the One Health framework with the improved management of antibiotic use in humans and animals to attain better public health outcomes. However, we still lack management and legislation considering co-selective agents, especially metals, to control antibiotic resistance. Under such scenarios, metals become increasingly important health risks in the evolution of ARGs and expansion of the environmental resistome. Future studies that evaluate the relationship between the concentration/toxicity/bioavailability of different metals and the co-selection/persistence of antibiotic resistance in various media and scenarios are needed to enhance current knowledge. We also call for consideration and further investigation of other co-selective agents, and the efficacy of metal-based interventions to better manage and combat the global antibiotic resistance crisis, within the One Health framework.

Acknowledgments

We thank Yong-Guan Zhu and Kristian K. Brandt for their feedback and advice on this work. This study was supported by the National Natural Science Foundation of China (Grant Nos. 41825017, 42377392, and 42107407) and the Fundamental Research Funds for the Central Universities (Grant No. 265QZ2022006).

Competing interests

The authors declare no competing interests.

References

Babakhani, S., Oloomi, M., 2018. Transposons: the agents of antibiotic resistance in bacteria. Journal of Basic Microbiology 58, 905–917.

Baker-Austin, C., Wright, M.S., Stepanauskas, R., McArthur, J.V., 2006. Co-selection of antibiotic and metal resistance. Trends in Microbiology 14, 176–182.

Berg, J., Tom-Petersen, A., Nybroe, O., 2005. Copper amendment of agricultural soil selects for bacterial antibiotic resistance in the field. Letters in Applied Microbiology 40, 146–151.

Cantón, R., Ruiz-Garbajosa, P., 2011. Co-resistance: an opportunity for the bacteria and resistance genes. Current Opinion in Pharmacology 11, 477–485.

Ding, J., Zhu, D., Wang, Y., Wang, H.T., Liang, A.P., Sun, H.W., Chen, Q.L., Lassen, S.B., Lv, M., Chen, Q.L., 2021. Exposure to heavy metal and antibiotic enriches antibiotic resistant genes on the tire particles in soil. Science of the Total Environment 792, 148417.

Du, D.J., Wang-Kan, X., Neuberger, A., van Veen, H.W., Pos, K.M., Piddock, L.J.V., Luisi, B.F., 2018. Multidrug efflux pumps: structure, function and regulation. Nature Reviews Microbiology 16, 523–539.

Frei, A., Verderosa, A.D., Elliott, A.G., Zuegg, J., Blaskovich, M.A.T., 2023. Metals to combat antimicrobial resistance. Nature Reviews Chemistry 7, 202–224.

Frost, L.S., Leplae, R., Summers, A.O., Toussaint, A., 2005. Mobile genetic elements: the agents of open source evolution. Nature Reviews Microbiology 3, 722–732.

Gillings, M.R., 2014. Integrons: past, present, and future. Microbiology and Molecular Biology Reviews 78, 257–277.

Gillings, M.R., Gaze, W.H., Pruden, A., Smalla, K., Tiedje, J.M., Zhu, Y.G., 2015. Using the class 1 integron-integrase gene as a proxy for anthropogenic pollution. The ISME Journal 9, 1269–1279.

Gupta, S., Graham, D.W., Sreekrishnan, T.R., Ahammad, S.Z., 2022. Effects of heavy metals pollution on the co-selection of metal and antibiotic resistance in urban rivers in UK and India. Environmental Pollution 306, 119326.

Hao, X.L., Zhu, J.J., Rensing, C., Liu, Y., Gao, S.H., Chen, W.L., Huang, Q.Y.; Liu, Y.R., 2021. Recent advances in exploring the heavy metal(loid) resistant microbiome. Computational and Structural Biotechnology Journal 19, 94–109.

Kang, W., Zhang, Y.J., Shi, X., He, J.Z., Hu, H.W., 2018. Short-term copper exposure as a selection pressure for antibiotic resistance and metal resistance in an agricultural soil. Environmental Science and Pollution Research 25, 29314–29324.

Knapp, C.W., Callan, A.C., Aitken, B., Shearn, R., Koenders, A., Hinwood, A., 2017. Relationship between antibiotic resistance genes and metals in residential soil samples from Western Australia. Environmental Science and Pollution Research 24, 2484–2494.

Knapp, C.W., McCluskey, S.M., Singh, B.K., Campbell, C.D., Hudson, G., Graham, D.W., 2011. Antibiotic resistance gene abundances correlate with metal and geochemical conditions in archived Scottish soils. PLoS One 6, e27300.

Knöppel, A., Näsvall, J., Andersson, D.I., 2017. Evolution of antibiotic resistance without antibiotic exposure. Antimicrobial Agents and Chemotherapy 61, e01495–17.

Kwon, J.H., Powderly, W.G., 2021. The post-antibiotic era is here. Science 373, 471–471.

Larsson, D.G.J., Flach, C.F., 2022. Antibiotic resistance in the environment. Nature Reviews Microbiology 20, 257–269.

Lemire, J.A., Harrison, J.J., Turner, R.J., 2013. Antimicrobial activity of metals: mechanisms, molecular targets and applications. Nature Reviews Microbiology 11, 371–384.

Li, B., Yang, Y., Ma, L.P., Ju, F., Guo, F., Tiedje, J.M., Zhang, T., 2015. Metagenomic and network analysis reveal wide distribution and co-occurrence of environmental antibiotic resistance genes. The ISME Journal 9, 2490–2502.

Li, L.G., Xia, Y., Zhang, T., 2017. Co-occurrence of antibiotic and metal resistance genes revealed in complete genome collection. The ISME Journal 11, 651–662.

Mahbub, K.R., King, W.L., Siboni, N., Nguyen, V.K., Rahman, M.M., Megharaj, M., Seymour, J.R., Franks, A.E., Labbate, M., 2020. Long-lasting effect of mercury contamination on the soil microbiota and its co-selection of antibiotic resistance. Environmental Pollution 265, 115057.

Mazhar, S.H., Li, X.J., Rashid, A., Su, J.M., Xu, J.Q., Brejnrod, A.D., Su, J.Q., Wu, Y.J., Zhu, Y.G., Zhou, S.G., Feng, R.W., Rensing, C., 2021. Co-selection of antibiotic resistance genes, and mobile genetic elements in the presence of heavy metals in poultry farm environments. Science of the Total Environment 755, 142702.

Nriagu, J.O., 1996. A history of global metal pollution. Science 272, 223–223.

Pal, C., Bengtsson-Palme, J., Kristiansson, E., Larsson, D.G.J., 2015. Co-occurrence of resistance genes to antibiotics, biocides and metals reveals novel insights into their co-selection potential. BMC Genomics 16, 964.

Poole, K., 2017. At the nexus of antibiotics and metals: the impact of Cu and Zn on antibiotic activity and resistance. Trends in Microbiology 25, 820–832.

Pu, Q., Fan, X.T., Sun, A.Q., Pan, T., Li, H., Bo Lassen, S., An, X.L., Su, J.Q., 2021. Co-effect of cadmium and iron oxide nanoparticles on plasmid-mediated conjugative transfer of antibiotic resistance genes. Environment International 152, 106453.

Roberto, A.A., Van Gray, J.B., Engohang-Ndong, J., Leff, L.G., 2019. Distribution and co-occurrence of antibiotic and metal resistance genes in biofilms of an anthropogenically impacted stream. Science of the Total Environment 688, 437–449.

Seiler, C., Berendonk, T.U., 2012. Heavy metal driven co-selection of antibiotic resistance in soil and water bodies impacted by agriculture and aquaculture. Frontiers in Microbiology 3, 399.

Shi, L.D., Xu, Q.J., Liu, J.Y., Han, Z.X., Zhu, Y.G., Zhao, H.P., 2021. Will a non-antibiotic metalloid enhance the spread of antibiotic resistance genes: the selenate story. Environmental Science & Technology 55, 1004–1014.

Song, J.X., Rensing, C., Holm, P.E., Virta, M., Brandt, K.K., 2017. Comparison of metals and tetracycline as selective agents for development of tetracycline resistant bacterial communities in agricultural soil. Environmental Science & Technology 51, 3040–3047.

Stepanauskas, R., Glenn, T.C., Jagoe, C.H., Tuckfield, R.C., Lindell, A.H., King, C.J., McArthur, J.V., 2006. Coselection for microbial resistance to metals and antibiotics in freshwater microcosms. Environmental Microbiology 8, 1510–1514.

van Boeckel, T.P., Gandra, S., Ashok, A., Caudron, Q., Grenfell, B. T., Levin, S.A., Laxminarayan, R., 2014. Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data. The Lancet Infectious Diseases 14, 742–750.

Wang, F.F., Liu, G.P., Zhang, F., Li, Z.M., Yang, X.L., Yang, C.D., Shen, J.L., He, J.Z., Li, B.L., Zeng, J.G., 2022. Natural selenium stress influences the changes of antibiotic resistome in seleniferous forest soils. Environmental Microbiome 17, 26.

Wang, X.M., Lan, B.R., Fei, H.X., Wang, S.Y., Zhu, G.B., 2021. Heavy metal could drive co-selection of antibiotic resistance in terrestrial subsurface soils. Journal of Hazardous Materials 411, 124848.

WHO, 2015. WHO Model Lists of Essential Medicines [Online]. available at the WHO website.

Yazdankhah, S., Rudi, K., Bernhoft, A., 2014. Zinc and copper in animal feed - development of resistance and co-resistance to antimicrobial agents in bacteria of animal origin. Microbial Ecology in Health and Disease 25.

Zhang, Z.Y., Zhang, Q., Wang, T.Z., Xu, N.H., Lu, T., Hong, W.J., Penuelas, J., Gillings, M., Wang, M.X., Gao, W.W., Qian, H.F., 2022. Assessment of global health risk of antibiotic resistance genes. Nature Communications 13, 1553.

Zhao, Y., Cocerva, T., Cox, S., Tardif, S., Su, J.Q., Zhu, Y.G., Brandt, K.K., 2019. Evidence for co-selection of antibiotic resistance genes and mobile genetic elements in metal polluted urban soils. Science of the Total Environment 656, 512–520.

Zhao, Y., Hu, H.W., Su, J.Q., Hao, X.L., Guo, H.M., Liu, Y.R., Zhu, Y.G., 2021. Influence of legacy mercury on antibiotic resistomes: evidence from agricultural soils with different cropping systems. Environmental Science & Technology 55, 13913–13922.

Zhao, Y., Su, J.Q., An, X.L., Huang, F.Y., Rensing, C., Brandt, K.K., Zhu, Y.G., 2018. Feed additives shift gut microbiota and enrich antibiotic resistance in swine gut. Science of the Total Environment 621, 1224–1232.

Zhou, B.R., Wang, C., Zhao, Q., Wang, Y., Huo, M.J., Wang, J.D., Wang, S.L., 2016. Prevalence and dissemination of antibiotic resistance genes and coselection of heavy metals in Chinese dairy farms. Journal of Hazardous Materials 320, 10–17.

Zhu, Y.G., Johnson, T.A., Su, J.Q., Qiao, M., Guo, G.X., Stedtfeld, R.D., Hashsham, S.A., Tiedje, J.M., 2013. Diverse and abundant antibiotic resistance genes in Chinese swine farms. Proceedings of the National Academy of Sciences of the United States of America 110, 3435–3440.