

## **Antimicrobial resistance is a health risk in Chinese cities - now it has been mapped**

Yong-Guan Zhu

1. Antimicrobial resistance (AMR) is becoming a serious urban health risk in China.
2. Unlike conventional chemical contaminants, antimicrobial resistant genes can be amplified in the environment through the spread and proliferation of bacteria and across organisms (horizontal gene transfer).
3. Urban wastewater treatment plants (WWTPs) are hotspots of AMR fueled by human consumption of antibiotics and discharge of other toxic chemicals.
4. This calls for urgent action against the dissemination of AMR through rapid urbanisation.
5. A systems approach to reduce the risk of AMR includes the development of surveillance capacities, public awareness and training, develop multi-sector action plans, and international cooperation.



## About the author

Dr Yong-Guan Zhu, Professor of biogeochemistry, environmental soil science and soil biology, is the Director General of the Institute of Urban Environment, Chinese Academy of Sciences (CAS). He has been working on the biogeochemistry of nutrients, metals and emerging pollutants and is a leader in taking multi-scale and multi-disciplinary approaches to soil and environmental problems. Before returning to China in 2002, he worked as research fellow supported by the Royal Society London, the Queen's University of Belfast, UK and as postdoctoral fellow in The University of Adelaide, Australia. He obtained his MSc from CAS in 1992 and a PhD in environmental biology from Imperial College, London in 1998. Dr Zhu is co-editor-in-chief of the journal *Environmental Technology & Innovation*, associate editor of *Environment International*, and editorial member for a several other international journals. He is a scientific committee member for the ICSU program on Human Health and Wellbeing in Changing Urban Environment, and served for nine years as a member of Standing Advisory Group for Nuclear Application, International Atomic Energy Agency. Professor Zhu is the recipient of many international and Chinese merit awards, among them the TWAS Science Award for Agricultural Science and the National Natural Science Award. Dr. Zhu has published over 300 articles and was selected as a Web of Science Highly Cited Researcher in 2016.

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Antimicrobial resistance (AMR) is the property of microorganisms (e.g., bacteria, viruses and parasites) developed under frequent exposure to antimicrobial drugs, like antibiotics, to resist them and become so-called “superbugs”. “Overuse and misuse of antimicrobial medicines accelerate the emergence of resistant microorganisms” (WHO 2015). AMR is threatening human health world-wide. The widespread use of antibiotics in humans and animals is the main selective driving force of the emergence and dissemination of AMR. Antibiotic resistance is a serious form of AMR. Antibiotic resistant pathogens now occur at high frequencies in clinical contexts. In particular, the frequent presence of multi-antibiotic resistant “superbugs” in human feces could lead to a return to the pre-antibiotic era. If the trend continues, a growing number of infections can no longer be treated using the current arsenal of drugs.

“Drug-resistant infections currently cause around 700,000 deaths worldwide annually.”

Science, 2016

Municipal wastewater treatment plants (WWTPs) receive and digest millions of tons of domestic sewage every day. Adults harbor significant quantities of resistant genes in their gut microbiome, and consequently WWTPs, especially untreated influents are likely to be a critical hub for the evolution and spread of from humans derived resistant genes into natural environments.

In China, more than 3,700 municipal WWTPs have been constructed to treat urban sewage, with a combined capacity of 157 billion liters per day. In each of these facilities, sewage from tens to hundreds of thousands of individuals creates an enormous biological reactor where bacteria and resistant genes are exposed to significant concentrations of selective agents such as antimicrobial agents, disinfectants and heavy metals. In this respect, resistant genes detected in sewage can be seen to represent the resistance burden of their urban populations. Therefore, resistance profiles in sewage reflects the structure and diversity of resistant bacteria in the gastrointestinal tracts of urban residents within the WWTP catchment. A nation-wide survey of resistance elements in sewage (untreated influent) could then provide a rapid and efficient method for assessing the burden of antibiotic resistance of urban populations.

“Antimicrobial resistance in China could cause 1 million premature deaths annually by 2050 and cost the country \$20 trillion.”

Wellcome Trust, 10. July 2017

A team of scientists from the Institute of Urban Environment, Chinese Academy of Sciences, and The University of Hong Kong, conducted a nationwide investigation in China to address the profiles of all antibiotic resistant genes (resistome) with seasons and regions. In their study, a large-scale sampling of municipal sewage from 17 major cities across China was performed. In total, 116 urban sewage samples were collected from 32 WWTPs during summer and winter, and sampling sites were specifically chosen to reflect diverse climatic conditions, economic development levels and urban geography. By combining metagenomics analyses and illumina sequencing of 16S ribosomal RNA genes, the seasonal variation and geographical distribution of the urban sewage antibiotic resistome were characterized.

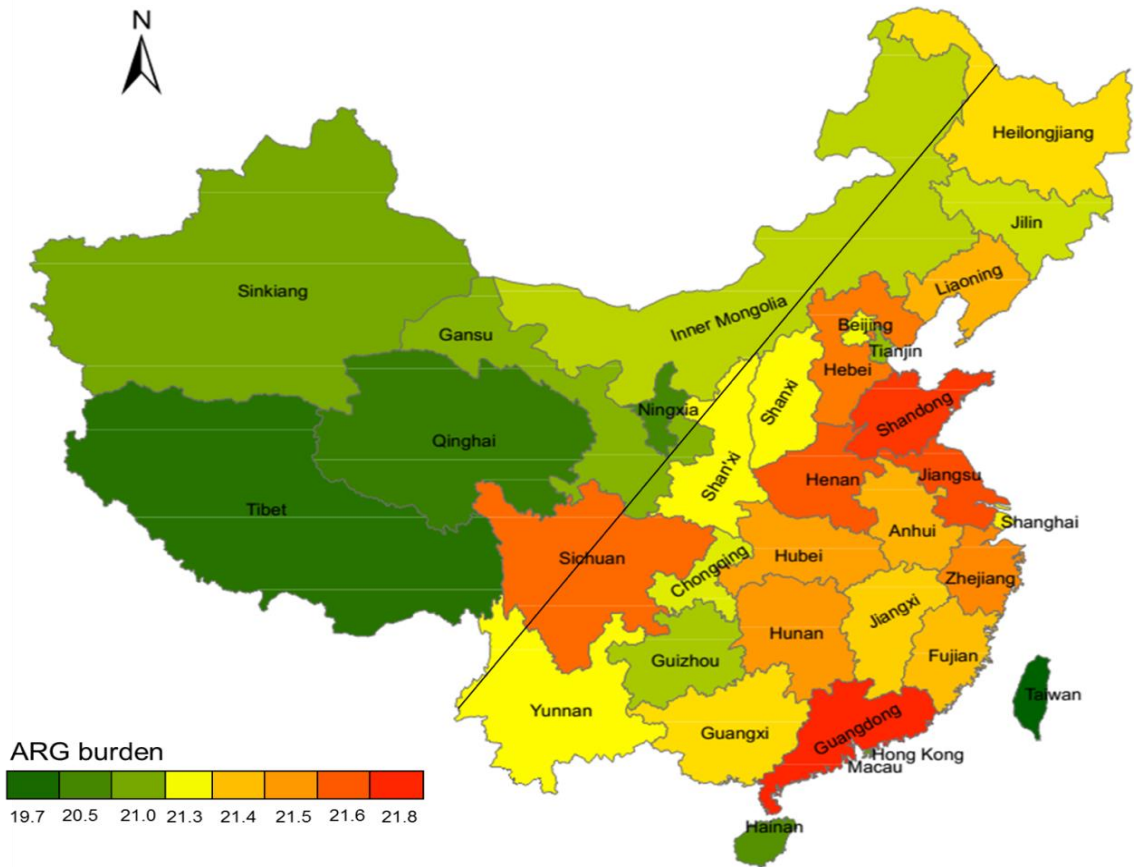


Figure: Map showing the ARG burden based on urban populations of administrative districts in China. The black line on the map refers to the Chinese demographic “Hu Huanyong line” marking the difference in the distribution of China’s population. Green signals a low and red a high burden of ARG

This study revealed that municipal sewage harbored diverse and abundant resistance genes. In total, 381 different resistance genes conferring resistance to almost all antibiotics were detected and these genes were extensively shared across China, with no geographical clustering, highlighting that municipal sewage could be a major conduit for transferring antibiotic resistance genes into the environment.

Seasonal variation in abundance of resistance genes was observed, with average concentrations of  $3.27 \times 10^{11}$  and  $1.79 \times 10^{12}$  copies/L in summer and winter, respectively. Global comparison and risk assessment are the next steps, as currently we only limited information at larger scale information. Bacterial communities did not exhibit geographical clusters, but did show a significant distance-decay relationship, which means the patterns differ more between locations further away. The researchers also found that the

core human gut microbiota was strongly associated with the shared resistome, demonstrating the potential contribution of human gut microbiota to the dissemination of resistance elements via sewage disposal. Importantly, this study observed a strong spatial dependency in the distribution of ARG abundance in various administrative areas, with two main regions separated by the demographic “Hu Huanyong line”, which is based on climatic zonation and population density. This suggests that monitoring sewage systems for ARGs could provide a real-time estimate of antibiotic resistance threats in specific areas, and this in turn could be used to inform treatments and promote antibiotic stewardship.

Detection and measurement of antimicrobial resistance are essential for understanding their potential to adversely affect human health. To obtain the surveillance data of antimicrobial resistance in urban sewage at a large scale, identifying environmental reservoirs of antimicrobial resistance and pathways that pose potential health risks to human, animals and other biota – are essential components of a systems approach to AMR.

This detailed analysis of antimicrobial resistance in Chinese urban sewage gives an indication of the magnitude of the burden imposed by resistance in China, and it should lead to increased efforts to control antibiotic resistance. Given the growing global resistance for antibiotic and documented health issues related to inappropriate use of such antibiotics, this study has major public health policy implications for countries like China. The systems approach provides a baseline for investigating environmental dissemination of resistance elements, and raises the possibility of using the abundance of resistance genes in sewage as a tool for antibiotic stewardship.

Emission of antimicrobial resistance from humans mapped for major Chinese cities revealed that urgent actions is needed to tackle the problem. New regulatory approaches to mitigate antimicrobial resistance should be developed and national and local data on antimicrobial resistance must be collected and made publicly available to enhance antimicrobial resistance surveillance systems. Antimicrobial stewardship is a critical tool for preventing and controlling antimicrobial resistance.

In August 2016, China has unveiled its national action plan for AMR. As part of a systems approach to reduce the risks of AMR, following are some actions recommended for reducing the health risks of AMR - not only for Chinese cities:

- Develop national multisector action plans
- Develop new antimicrobials
- Make sales of antimicrobial drugs by prescription only
- Increase awareness about AMR among the general public and policymakers
- Improve public information on the safe use of antimicrobial medicines
- Increase training and education for medical professionals and consumers on proper use of
- Build surveillance systems for antimicrobial resistance
- Enforce regulations on the sale of antimicrobial medicines without prescription
- Intensify international cooperation and exchanges to prevent and control AMR

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The *Urban Health and Wellbeing: a Systems Approach* (UHWB) programme, is a global science programme, of the International Council for Science (ICSU). The vision of the programme is: cities functioning as integrated complex systems which sustainably provide benefits for the health and wellbeing of its residents. It aims at (1) promoting and coordinating research, (2) developing and identifying data needs, (3) building and strengthening capacity and (4) communicating new knowledge.

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The Policy Briefs of the UHWB programme aim at highlighting and drawing attention to policy relevant findings and insights from research and researchers and communicating them with decisionmakers at all levels of society in order to encourage the co-creation of knowledge for healthy urban environments and people.



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