

Review

A Database on Antibiotics and Antibiotic Resistance in Wastewater and Solid Waste from Pharmaceutical Industry Based on a Systematic Review

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ABSTRACT

Residual antimicrobial agents in wastewater and solid waste from antimicrobial manufacturing facilities can potentially contaminate environments. The World Health Organization has established technical guidelines for managing antimicrobial resistance (AMR) in pharmaceutical wastewater and solid waste. However, the scarcity of publicly available data on antimicrobial manufacturing processes impedes the development of effective mitigation strategies. To address this knowledge gap, we developed a comprehensive database documenting antibiotics and antibiotic resistance genes (ARGs) in actual wastewater and solid waste samples, primarily fermentation residues. Through systematic review methodology, we compiled data from extensive searches of English-language article databases, including Web of Science and PubMed. The database contains data from 270 distinct samples collected across 45 fermentation residue treatment systems and 46 wastewater treatment systems, derived from 70 published English-language articles spanning 2008 to 2024. In operational pharmaceutical facilities, antibiotic concentrations ranged from 82 to 1,663 mg/L in raw wastewater and from 1,000 to 10,182 mg/kg dry matter (DM) in antibiotic fermentation residues. Various treatment technologies demonstrated significant reductions in both antibiotic concentrations and ARG levels within wastes. This database provides the first global perspective on antibiotic and ARG contamination from antibiotic production processes, supporting AMR management initiatives. It establishes a dynamic, continuously updated platform accessible to researchers and industry stakeholders via the link: <https://dash.drwater.net/antiboard/>.

Antimicrobial resistance (AMR), driven by high concentrations of active pharmaceutical ingredients

(API), poses a significant threat to disease treatment effectiveness (1–2). Pharmaceutical manufacturing processes release substantial quantities of antibiotics into the environment through wastewater and solid waste, with fermentation residue representing a major solid waste component during antibiotic production. The complex matrix of contaminants and microbiota in these waste streams presents significant management challenges. The World Health Organization (WHO) and the United Nations Environment Programme (UNEP) jointly released the *Guidance on wastewater and solid waste management for manufacturing of antibiotics* (3) in September 2024, highlighting antibiotic production's crucial role in global AMR surveillance and control.

Antibiotic manufacturing facilities require dedicated collection and treatment infrastructure for both wastewater and solid waste streams, providing opportunities to control the environmental release of antibiotics and antibiotic resistance genes (ARGs) (4–6). However, comprehensive data and scientific understanding of AMR pollution characteristics within the pharmaceutical industry remain limited. To address this knowledge gap, we developed a systematic review-based database documenting antibiotics and ARGs in pharmaceutical wastewater and solid waste streams. Fermentation residues constitute the primary solid waste generated during antibiotic production processes. The database development incorporated diverse scientific literature, including English-language review articles and research papers on treatment technologies and applications for pharmaceutical wastewater and solid waste (5,7), as well as relevant grey literature from local, national, and regional sources (8–10). China has emerged as a leader in this field, demonstrating substantial research achievements and extensive international collaboration. This database serves as an essential resource for understanding the current status of antibiotics and ARGs in pharmaceutical manufacturing while supporting enhanced management and control strategies.

LITERATURE SEARCH STRATEGY

Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (11), we conducted a comprehensive literature search using the Science Citation Index (SCI) and Social Sciences Citation Index (SSCI) databases in Web of Science (WOS) and PubMed. The search covered articles published from January 2000 to December 2023. In WOS, we employed the following search strategy: “TS = {(pharmaceutic* OR production OR fermentation) NEAR (waste* OR residue OR mycelia)} NEAR antibiotic*”, with a comparable approach used in PubMed. We supplemented these database searches with relevant grey literature (Figure 1). Using CiteSpace (12), we analyzed and visualized collaboration networks among countries, institutions, and researchers based on the 1,000 most relevant papers.

RESULTS

Analysis of publication trends revealed 2,108 unique publications following duplicate removal, demonstrating a marked increase during the

2000–2023 period (Figure 2A). Prior to 2015, research on antibiotic production wastes received limited attention, with minimal publications. From 2016 onward, publication rates exhibited a significant upward trajectory. Publication volumes in 2022 and 2023 exceeded 320 annually, representing more than a fourfold increase compared to 2015’s 79 publications. This trend indicates the growing recognition of pharmaceutical waste management as a critical research focus.

China emerged as a pioneer in addressing pharmaceutical wastewater and residue management, with Chinese researchers contributing 371 publications, substantially surpassing other nations. China’s pivotal role in international collaboration is evidenced by its high betweenness centrality (0.54), calculated from collaboration frequency. India ranked second with 87 publications (centrality 0.18), followed by the United States with 63 publications (centrality 0.35). Notably, while Iran produced 56 publications, its low centrality (0.13) indicates limited international collaboration. Conversely, Spain demonstrated strong international engagement with high centrality (0.32) despite fewer publications (Table 1).

Within China’s research landscape, the Chinese

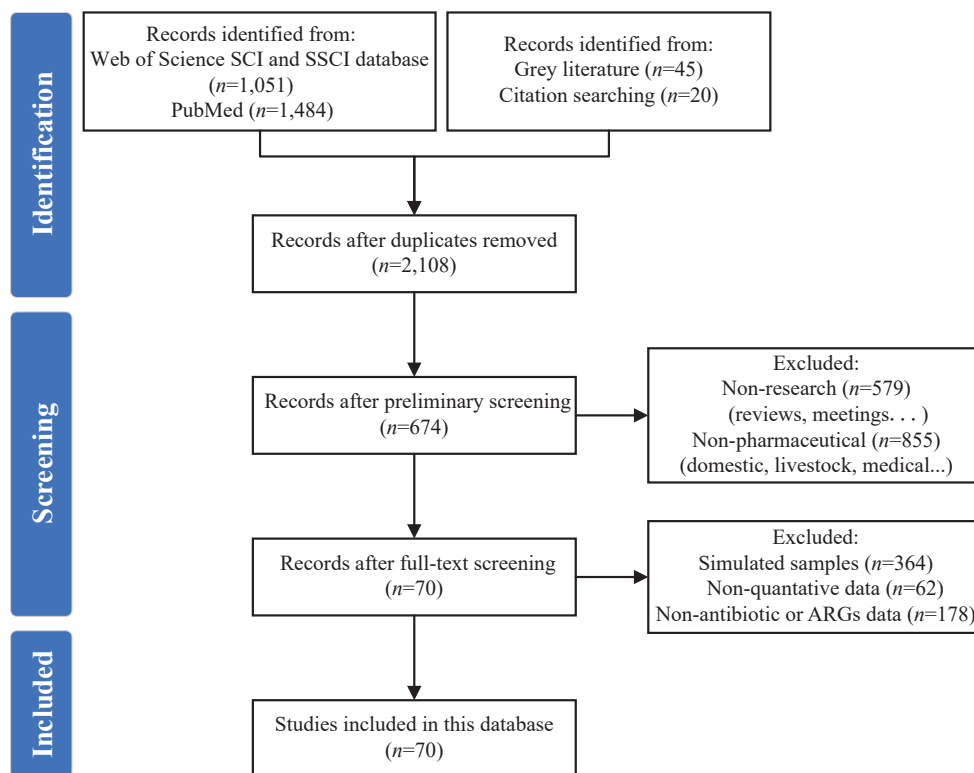


FIGURE 1. Flow diagram of the studies selection procedure. Abbreviation: ARGs=antibiotic resistance genes.

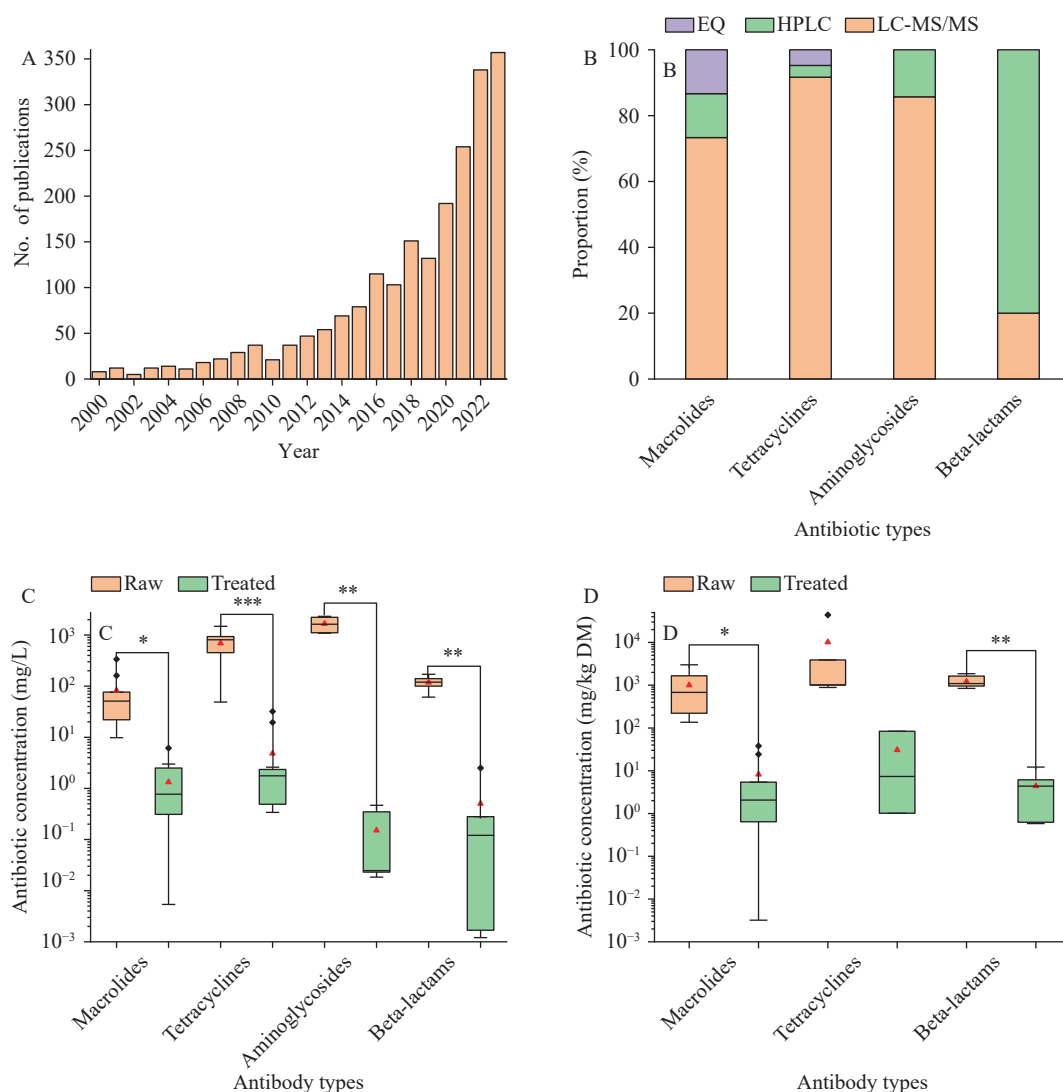


FIGURE 2. Analysis of publication trends and antibiotic measurements. (A) Annual publication numbers; (B) Distribution of antibiotic detection methods; (C) Antibiotic concentrations in pharmaceutical wastewater; (D) Antibiotic concentrations in fermentation residues.

Note: Red triangles (C, D) indicate mean values; black squares represent outliers. Statistical significance of pre- versus post-treatment concentration differences was determined using Paired-Sample t-Tests, with asterisks denoting significance levels.

Abbreviation: EQ=equivalent quantity; HPLC=high-performance liquid chromatography; LC-MS/MS=Liquid Chromatography-Mass Spectrometry/Mass Spectrometry.

Academy of Sciences (CAS) and Tsinghua University (THU) distinguished themselves through substantial publication output and high centrality metrics. The University of Chinese Academy of Sciences (UCAS) and the Research Center for Eco-Environmental Sciences (RCEES), both CAS affiliates, achieved significant research outcomes. The research group led by Min Yang and Yu Zhang has gained particular prominence, earning substantial citations for their sustained investigations into pharmaceutical wastewater and fermentation residue. In India, the

Indian Institute of Technology System (IIT System) and in Turkey, Istanbul Technical University, emerged as leading institutions. While China and India dominate bulk antibiotic production, the challenges of antibiotic pollution and AMR risks have attracted significant attention from international organizations including UNEP and WHO, as well as industry groups like the Antimicrobial Resistance Industry Alliance, resulting in comprehensive guidelines addressing pharmaceutical supply chain pollution (8,13). The IIT system in India has conducted extensive research on

local pharmaceutical wastewater treatment systems, emphasizing the crucial role of regulatory standards in AMR control (14).

Data Records

Following PRISMA guidelines, 70 papers reporting actual samples from 2008-2024 were incorporated into the database (Figure 1). The database comprises 16 comprehensive columns documenting: antibiotic and

sample types, geographical location, studied systems, treatment methodologies, experimental scale, detection methods, antibiotic concentrations, ARG testing methods and results, publication year, source ID, and reference source (Figure 3). Each entry’s source ID links directly to detailed publication information, facilitating efficient data retrieval.

The database encompasses 270 samples across five major categories: wastewater, sludge, and receiving

TABLE 1. International collaboration analysis across countries, institutions, and researchers.

Country/Institution/Author	Publications	Centrality	Year of first publication
Country			
China	371	0.54	2007
India	87	0.18	2002
Spain	33	0.32	2006
France	30	0.08	2010
Brazil	29	0.07	2009
America	63	0.35	2002
Iran	56	0.13	2014
England	23	0.22	2001
Institution			
Chinese Academy of Sciences	78	0.02	2008
Research Center for Eco-Environmental Sciences (RCEES)	41	0.08	2008
Tsinghua University	39	0.05	2013
University of Chinese Academy of Sciences	31	0.03	2017
Istanbul Technical University	16	0.08	2004
Indian Institute of Technology System (IIT System)	10	0.01	2016
Author			
Yang, Min	24	0.13	2008
Zhang, Yu	20	0.08	2008

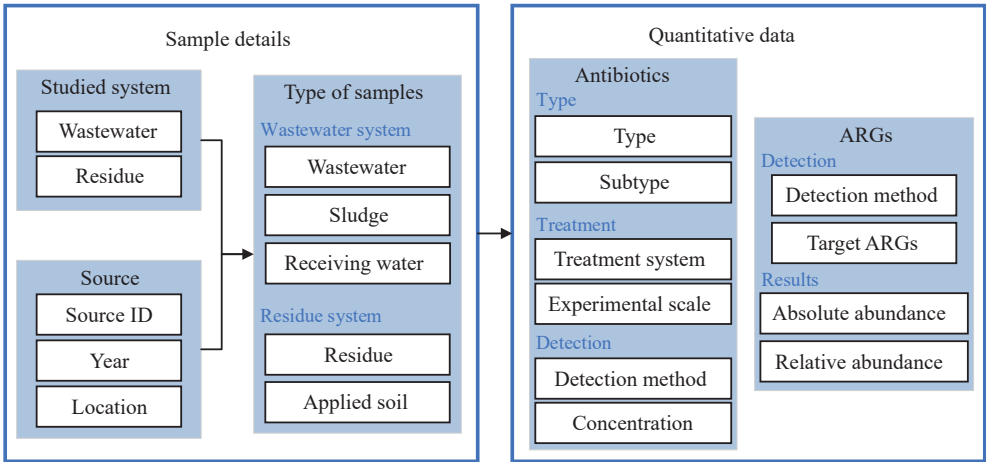


FIGURE 3. Framework of the original and quantitative samples data. Abbreviation: ARGs=antibiotic resistance genes.

water from wastewater treatment systems; and fermentation residue and applied soil from fermentation residue research systems. It contains 256 antibiotic records and 100 ARG records. The antibiotic records are distributed as follows: 96 for residues, 1 for applied soil, 126 for wastewater, 26 for sludge, and 7 for receiving water. ARG documentation includes 39 records for residues, 3 for applied soil, 31 for wastewater, 27 for sludge, with no records for receiving water. The most extensive antibiotic concentration datasets were collected in 2023 ($n=50$), 2015 ($n=30$), and 2013 ($n=21$). Similarly, ARG data peaked in 2023 ($n=28$), followed by 2019 ($n=17$) and 2013 ($n=16$). Sampling locations primarily span 14 provincial-level administrative divisions (PLADs) in China, with a concentration in the northern region due to the prevalence of antibiotic production facilities. Additional reports originated from Poland and Croatia.

The geographical distribution of pharmaceutical facilities shows a significant dispersion, with notable clustering in northern China. Manufacturing facilities in Hebei Province and Shandong Province demonstrate diverse production capabilities, manufacturing antibiotics across five major categories. Macrolide and aminoglycoside production facilities show the broadest geographical distribution, operating across six PLADs or municipalities. Tetracycline and β -lactam production facilities are distributed across five PLADs or municipalities each.

Detection Methods and Concentration of Antibiotics and ARGs

The primary quantitative methods for antibiotic detection comprise liquid chromatography-tandem mass spectrometry (LC-MS/MS) and high-performance liquid chromatography (HPLC) (Figure 2B). The selection of detection methodology is determined by the specific antibiotic type and molecular structure. Ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) is preferentially employed for macrolides, tetracyclines, and aminoglycosides due to its superior sensitivity. Conversely, HPLC enables precise separation and quantitative analysis of β -lactam antibiotics in complex matrices. Additionally, Zhang et al. (15) introduced an innovative potency assay method to evaluate residual antibacterial effects, expressed as antibiotic equivalent quantity (EQ). Compared to conventional chemical methods, the EQ

approach comprehensively accounts for the antibacterial activities of both parent compounds and their transformation products.

Antibiotic concentrations in production wastewaters were substantially elevated, with mean values ranging from 82 to 1,663 mg/L, markedly higher than the $\mu\text{g/L}$ levels typically observed in municipal and domestic wastewaters (16–18). Tetracycline and aminoglycoside antibiotics exhibited particularly high concentrations (Figure 2C). Post-treatment analysis revealed significant reduction in residual antibiotics, with mean effluent concentrations below 5.0 mg/L across various antibiotic classes. However, these levels remained substantially higher than the 12.5 $\mu\text{g/L}$ typically found in domestic wastewater treatment plant effluent (19).

Among fermentation residues, macrolides, tetracyclines, and beta-lactam antibiotics have been most extensively investigated. Raw sample concentrations averaged between 1,000 to 10,182 mg/kg dry matter (DM), substantially higher than the 4.0 mg/kg observed in municipal sewage sludge (20). Hydrothermal treatment and other remediation approaches achieved removal rates exceeding 90% (Figure 2D). Given the potential ecological risks and antimicrobial resistance concerns, fermentation residue has been classified as hazardous waste requiring efficient remediation treatment.

Researchers primarily employed quantitative PCR (qPCR) and metagenomic sequencing for ARG detection. Both production wastewater and fermentation residues exhibited significant ARG enrichment, predominantly showing resistance to the antibiotics being manufactured (Table 2). While biological treatment systems effectively removed antibiotics and certain ARGs from wastewater (5,21), treatment system sludge showed ARG enrichment, with abundance levels surpassing those found in fermentation residue from the same facility (22). ARG abundance in fermentation residues consistently reached approximately 5 log copies/mg.

Notably, treatment experiments remain predominantly confined to laboratory scale. Among research groups, the RCEES, CAS team has conducted the most extensive field studies investigating antibiotic and ARG occurrence and removal, with the explicit goal of scaling findings to pilot and full-scale applications (4,23–26).

Treatment Method and System

Biological treatment processes, particularly the

TABLE 2. Detection of antibiotic resistance genes in pharmaceutical-related matrices.

Antibiotic	Sample	Methods	Target ARGs	Abundance	Ref.
SPM	Sludge	qPCR	4 <i>erm</i> , <i>ereA</i> , <i>mphB</i> , <i>mefA</i> , <i>msrD</i>	1.4×10 ⁷ copies/mg; 4.3×10 ⁻¹ copies/16S rRNA gene	(22)
	Residue	qPCR	4 <i>erm</i> , <i>msrD</i>	1.6×10 ⁵ copies/mg; 1.6×10 ⁻³ copies/16S rRNA gene	
	Residue	qPCR	<i>ereA</i> , 2 <i>erm</i> , <i>mefA</i>	1.64×10 ⁷ copies/mL, decrease 83.6%	(38)
	Compost	qPCR	4 <i>erm</i> , <i>mefA</i> , <i>mphA</i>	Lowest in mature phase	(39)
ERY	Effluent	qPCR	5 <i>erm</i>	8 log copies/mL	(40)
	Residue	qPCR	2 <i>erm</i> , <i>ereA</i> , <i>mpfB</i> , <i>mefA</i>	1.45–5.68 log copies/mL, decreased by 96%–99% after treatment.	(41)
	Residue	qPCR	2 <i>erm</i> , <i>ereB</i>	7.42×10 ⁻⁹ –6.82×10 ⁻⁴ copies/16S rRNA gene, decreased 99% after treatment.	(42)
	Effluent	HT-PCR	3 <i>erm</i> , <i>maA/mel</i> , <i>floR</i> , <i>sul2</i> , <i>tetM</i> , <i>mefA</i>	1.8–5 log copies/mL	(43)
	Influent	qPCR	4 <i>erm</i> , 1 <i>ere</i> , 2 <i>mph</i> , 1 <i>mef</i>	4.3×10 ⁸ copies/mL	(5)
	Effluent	qPCR	4 <i>erm</i> , 1 <i>ere</i> , 2 <i>mph</i> , 1 <i>mef</i>	2.1×10 ⁷ copies/mL	
OTC	Influent	qPCR	9 <i>tet</i>	7.0×10 ⁹ copies/mL; 3.2×10 ⁰ copies/16S rRNA gene	
	Effluent	qPCR	9 <i>tet</i>	1.8×10 ⁸ copies/mL; 1.4×10 ⁰ copies/16S rRNA gene	(21)
	Residue	qPCR	9 <i>tet</i>	1.4×10 ⁵ copies/mg; 2.4×10 ⁻² copies/16S rRNA gene	
	Sludge	qPCR	5 <i>tet</i>	9–13 log copies/g dry matter	(44)
	Residue	qPCR	3 <i>tet</i>	6.5×10 ⁵ copies/mg in raw residue, decreased to 1.28×10 ⁴ copies/mg after treatment.	(45)
	Compost	Metagenomics	Multi-drugs	After composing, multiple ARGs increased by 57.38 %.	(46)
	Sludge	Metagenomics	<i>sul1</i> , <i>aph(6)-I</i> , <i>tetA</i>	Total: 2.41–6.55 copies/16S rRNA gene Tetracycline: 0.82±0.21 copies/16S rRNA gene	(47)
TC	Production wastewater	qPCR	2 <i>sul</i> , 4 <i>tet</i> , 2 <i>bla</i> , <i>ermB</i> , <i>qnrD</i>	Average (4.80 ± 12.84) × 10 ⁵ copies/mL each.	(48)
	Effluent	qPCR	2 <i>sul</i> , 3 <i>tet</i> , 2 <i>bla</i> , <i>qnrD</i>	0.4–5.1×10 ⁷ copies/mL each.	
PG	Residue	qPCR	<i>bla</i> _{TEM}	4.17±0.19 log copies/mg	(49)
	Compost	qPCR	<i>bla</i> _{TEM}	8.98±0.27 log copies/mg	

Abbreviation: SPM=spiramycin; ERY=erythromycin; OTC=oxytetracycline; TC=tetracycline; PG=penicillin; qPCR=quantitative polymerase chain reaction; ARGs=antibiotic resistance genes; Ref.=reference.

combination of anaerobic digestion and activated sludge treatment, represent the predominant approach for managing antibiotic-containing pharmaceutical wastewater (5,21,27). However, high concentrations of antibiotic residues in wastewater have been demonstrated to promote ARG development and lead to treatment system failure (4,28).

To address this challenge, pretreatment of production wastewater to remove antibiotics prior to biological treatment has emerged as the optimal strategy for controlling ARG development (8,29–30). Enhanced hydrolysis has established itself as the leading pretreatment method in full-scale pharmaceutical wastewater treatment systems, demonstrating removal efficiencies exceeding 99% for oxytetracycline (4,31–32). For fermentation residues, hydrothermal treatment has shown exceptional effectiveness in eliminating both antibiotics and ARGs, achieving approximately 90% removal efficiency (33–34).

TECHNICAL VALIDATION

To ensure data accuracy and validity across diverse reporting formats, we implemented a comprehensive validation protocol. For ARG data, we maintained distinct recording formats: specific target genes for qPCR analyses and comprehensive gene profiles for metagenomic studies. Sample-specific units were standardized according to matrix type (mass-based for solids and volume-based for liquids). We employed a dual-verification system where one researcher entered the records while a second researcher independently validated the dataset to prevent errors and eliminate duplicate entries.

USAGE NOTES

This comprehensive database encompasses 270 records documenting antibiotics and ARGs in

pharmaceutical wastewater and solid waste, developed through systematic literature review. The database is accessible through an online platform <https://dash.drwater.net/antiboard/>, providing researchers with validated scientific data for analysis and reference. The Environmental Microbiology Technology Research Group of RCEES, CAS maintains continuous data collection and performs periodic updates to the website. Future development of the database aims to enhance pharmaceutical industry management through collaborative support from pharmaceutical industry associations.

This study provides a comprehensive overview of antibiotic production industry waste research and establishes a database tracking antibiotics and ARGs in actual industrial samples. While numerous treatment technologies demonstrate promising laboratory-scale removal efficiencies for both antibiotics and ARGs, validation through full-scale implementation remains crucial. Given that India and China dominate global antimicrobial manufacturing, enhancing pollution control measures in these nations offers the greatest potential for reducing worldwide AMR risks from pharmaceutical production. The implementation of enhanced hydrolysis pre-treatment to reduce antibiotic concentrations in manufacturing wastewater has proven particularly effective in controlling AMR development during biological treatment. This approach has been successfully scaled to full-scale wastewater treatment facilities in China, positioning Chinese AMR prevention technologies at the forefront of global pharmaceutical industry practices. As the field continues to evolve, this database serves as a vital resource for researchers and industry stakeholders addressing these challenges.

In 2008, while China's Ministry of Environmental Protection established discharge limits for key pollutants in pharmaceutical wastewater, the absence of specific standards for residual antibiotics highlighted the need for further research on resistance thresholds (35). The Ministry of Ecology and Environment's 2023 technical guidelines for wastewater treatment represent progress, though many emerging technologies remain in experimental phases (10). Notably, antibiotic fermentation residues have maintained their classification as hazardous waste since their initial inclusion in the Directory of National Hazardous Wastes in 2008.

The current database iteration, while ensuring accuracy through manual literature curation, faces challenges in keeping pace with the rapidly expanding

volume of publications on pharmaceutical industry antibiotic pollution and resistance. Integration of artificial intelligence (AI), particularly Large Language Models (LLMs) and Retrieval-Augmented Generation (RAG) systems, offers potential solutions for enhancing data retrieval, automating updates, and transforming the database into a dynamic, self-updating knowledge system (36–37). Furthermore, future expansions will incorporate data from Chinese theses, dissertations, and grey literature, including relevant local, national, and regional documents, extending beyond the current English-language research paper focus.

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REFERENCES

1. Han ZM, Feng HD, Wang C, Wang XG, Yang M, Zhang Y, et al. Mitigating antibiotic resistance emissions in the pharmaceutical industry: global governance and available techniques. *China CDC Wkly* 2023;5(46):1038 – 44. <https://doi.org/10.46234/ccdcw2023.195>.
2. Hui XS, Fang WJ, Wang G, Liu HL, Dai XH. Waste recycling of antibiotic mycelial residue: the feasible harmless treatment and source control of antibiotic resistance. *J Cleaner Prod* 2023;401:136786. <https://doi.org/10.1016/j.jclepro.2023.136786>.
3. World Health Organization. Guidance on wastewater and solid waste management for manufacturing of antibiotics. Geneva: World Health Organization; 2024. Licence: CC BY-NC-SA 3.0 IGO. <https://www.who.int/publications/i/item/9789240097254>. [2024-9-13].
4. Yi QZ, Zhang Y, Gao YX, Tian Z, Yang M. Anaerobic treatment of antibiotic production wastewater pretreated with enhanced hydrolysis: simultaneous reduction of COD and ARGs. *Water Res* 2017;110:211 – 7. <https://doi.org/10.1016/j.watres.2016.12.020>.

5. Tang L, Feng HD, Luan X, Han ZM, Yang M, Zhang Y. Occurrence, distribution, and behaviors of erythromycin A, production byproducts, transformation products, and resistance genes in a full-scale erythromycin A production wastewater treatment system. *Water Res* 2023;245:120640. <https://doi.org/10.1016/j.watres.2023.120640>.
6. He YP, Tian Z, Luan X, Han ZM, Zhang Y, Yang M. Recovery of biological wastewater treatment system inhibited by oxytetracycline: rebound of functional bacterial population and the impact of adsorbed oxytetracycline on antibiotic resistance. *Chem Eng J* 2021;418:129364. <https://doi.org/10.1016/j.cej.2021.129364>.
7. Feng MM, Liu YW, Yang L, Li ZJ. Antibiotics and antibiotic resistance gene dynamics in the composting of antibiotic fermentation waste - a review. *Bioresour Technol* 2023;390:129861. <https://doi.org/10.1016/j.biortech.2023.129861>.
8. World Health Organization. Technical brief on water, sanitation, hygiene (WASH) and wastewater management to prevent infections and reduce the spread of antimicrobial resistance (AMR). Geneva: World Health Organization. 2020. <https://www.who.int/publications/i/item/9789240006416>. [2024-9-21]
9. Zhang Y, Walsh TR, Wang Y, Shen JZ, Yang M. Minimizing risks of antimicrobial resistance development in the environment from a public one health perspective. *China CDC Wkly* 2022;4(49):1105 – 9. <https://doi.org/10.46234/ccdcw2022.224>.
10. Ministry of Ecology and Environment of the People's Republic of China. Guideline on available techniques of pollution prevention and control for pharmaceutical industry—Active pharmaceutical ingredients (fermentation, chemical synthesis, extraction) and preparation categories. https://www.mee.gov.cn/ywgf/fgbz/bz/bzwb/kxxjszn/202309/t20230926_1041928.shtml. [2024-11-25]. (In Chinese).
11. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *PLoS Med* 2021;18(3):e1003583. <https://doi.org/10.1371/journal.pmed.1003583>.
12. Chen CM. CiteSpace Ii: detecting and visualizing emerging trends and transient patterns in scientific literature. *J Am Soc Inf Sci* 2006;57(3): 359 – 77. <https://doi.org/10.1002/asi.20317>.
13. AMR Industry Alliance. Minimizing risk of developing antibiotic resistance and aquatic ecotoxicity in the environment resulting from the manufacturing of human antibiotics. Geneva: AMR Industry Alliance. 2022. https://www.amrindustryalliance.org/wp-content/uploads/2022/06/AMRIA_Antibiotic-Manufacturing-Standard_EMBARGOED-UNTIL-JUN-14-8-am-EDT.pdf. [2024-12-5].
14. Kotwani A, Kapur A, Chauhan M, Gandra S. Treatment and disposal practices of pharmaceutical effluent containing potential antibiotic residues in two states in India and perceptions of various stakeholders on contribution of pharmaceutical effluent to antimicrobial resistance: a qualitative study. *J Pharm Policy Pract* 2023;16(1):59. <https://doi.org/10.1186/s40545-023-00562-z>.
15. Zhang H, Zhang Y, Yang M, Liu MM. Evaluation of residual antibacterial potency in antibiotic production wastewater using a real-time quantitative method. *Environ Sci: Processes Impacts* 2015;17(11): 1923 – 9. <https://doi.org/10.1039/C5EM00228A>.
16. Kamal A, Kanafin YN, Satayeva A, Kim J, Pouloupoulos SG, Arkhangelsky E. Removal of carbamazepine, sulfamethoxazole and aspirin at municipal wastewater treatment plant of Astana, Kazakhstan: paths to increase the efficiency of the treatment process. *J Chem Technol Biotechnol* 2024;99(11):2248 – 58. <https://doi.org/10.1002/jctb.7713>.
17. Zhang YY, Hu YF, Li XW, Gao LJ, Wang SY, Jia SY, et al. Prevalence of antibiotics, antibiotic resistance genes, and their associations in municipal wastewater treatment plants along the Yangtze River basin, China. *Environ Pollut* 2024;348:123800. <https://doi.org/10.1016/j.envpol.2024.123800>.
18. Lin Q, Yu CS, Chen KY, Yasir H, Luo AC, Liang ZW, et al. Occurrence of micropollutants in rural domestic wastewater in Zhejiang Province, China and corresponding wastewater-based epidemiology analysis. *Sci Total Environ* 2024;931:172686. <https://doi.org/10.1016/j.scitotenv.2024.172686>.
19. Hu JR, Lyu Y, Chen H, Li S, Sun WL. Suspect and nontarget screening reveal the underestimated risks of antibiotic transformation products in wastewater treatment plant effluents. *Environ Sci Technol* 2023;57(45): 17439 – 51. <https://doi.org/10.1021/acs.est.3c05008>.
20. Meng F, Sun SJ, Geng JL, Ma LX, Jiang JP, Li B, et al. Occurrence, distribution, and risk assessment of quinolone antibiotics in municipal sewage sludges throughout China. *J Hazard Mater* 2023;453:131322. <https://doi.org/10.1016/j.jhazmat.2023.131322>.
21. Liu MM, Zhang Y, Yang M, Tian Z, Ren LR, Zhang SJ. Abundance and distribution of tetracycline resistance genes and mobile elements in an oxytetracycline production wastewater treatment system. *Environ Sci Technol* 2012;46(14):7551 – 7. <https://doi.org/10.1021/es301145m>.
22. Liu MM, Ding R, Zhang Y, Gao YX, Tian Z, Zhang T, et al. Abundance and distribution of Macrolide-Lincosamide-Streptogramin resistance genes in an anaerobic-aerobic system treating spiramycin production wastewater. *Water Res* 2014;63:33 – 41. <https://doi.org/10.1016/j.watres.2014.05.045>.
23. Li D, Yang M, Hu JY, Ren LR, Zhang Y, Li KZA. Determination and fate of oxytetracycline and related compounds in oxytetracycline production wastewater and the receiving river. *Environ Toxicol Chem* 2008;27(1):80 – 6. <https://doi.org/10.1897/07-080.1>.
24. Deng YQ, Zhang Y, Gao YX, Li D, Liu RY, Liu MM, et al. Microbial Community Compositional Analysis for Series Reactors Treating High Level Antibiotic Wastewater. *Environ Sci Technol* 2012;46(2):795 – 801. <https://doi.org/10.1021/es2025998>.
25. Zhang Y, Xie JP, Liu MM, Tian Z, He ZL, van Nostrand JD, et al. Microbial community functional structure in response to antibiotics in pharmaceutical wastewater treatment systems. *Water Res* 2013;47(16): 6298 – 308. <https://doi.org/10.1016/j.watres.2013.08.003>.
26. Tian Y, Tian Z, He YP, Sun GX, Zhang Y, Yang M. Removal of denatured protein particles enhanced UASB treatment of oxytetracycline production wastewater. *Sci Total Environ* 2022;816: 151549. <https://doi.org/10.1016/j.scitotenv.2021.151549>.
27. Bengtsson-Palme J, Milakovic M, Švecová H, Ganjto M, Jonsson V, Grabic R, et al. Industrial wastewater treatment plant enriches antibiotic resistance genes and alters the structure of microbial communities. *Water Res* 2019;162:437 – 45. <https://doi.org/10.1016/j.watres.2019.06.073>.
28. Amin MM, Zilles JL, Greiner J, Charbonneau S, Raskin L, Morgenroth E. Influence of the antibiotic erythromycin on anaerobic treatment of a pharmaceutical wastewater. *Environ Sci Technol* 2006;40(12):3971 – 7. <https://doi.org/10.1021/es060428j>.
29. Grela A, Kuc J, Klimek A, Matusik J, Pamuła J, Franus W, et al. Erythromycin scavenging from aqueous solutions by zeolitic materials derived from fly ash. *Molecules* 2023;28(2):798. <https://doi.org/10.3390/molecules28020798>.
30. Liu MM, Zhang Y, Zhang H, Zhang HF, Li KX, Tian Z, et al. Ozonation as an effective pretreatment for reducing antibiotic resistance selection potency in oxytetracycline production wastewater. *Desalination Water Treat* 2017;74:155 – 62. <https://doi.org/10.5004/dwt.2017.20731>.
31. Tang M, Gu Y, Wei DB, Tian Z, Tian Y, Yang M, et al. Enhanced hydrolysis of fermentative antibiotics in production wastewater: hydrolysis potential prediction and engineering application. *Chem Eng J* 2020;391:123626. <https://doi.org/10.1016/j.cej.2019.123626>.
32. Feng HD, Hu YQ, Tang L, Tian Y, Tian Z, Wei DB, et al. New hydrolysis products of oxytetracycline and their contribution to hard COD in biological effluents of antibiotic production wastewater. *Chem Eng J* 2023;471:144409. <https://doi.org/10.1016/j.cej.2023.144409>.
33. Han ZM, Feng HD, Luan X, Shen YP, Ren LR, Deng LJ, et al. Three-year consecutive field application of erythromycin fermentation residue following hydrothermal treatment: cumulative effect on soil antibiotic resistance genes. *Engineering* 2022;15:78 – 88. <https://doi.org/10.1016/j.eng.2022.05.011>.
34. Han ZM, Luan X, Feng HD, Deng YQ, Yang M, Zhang Y. Metagenomic insights into microorganisms and antibiotic resistance genes of waste antibiotic fermentation residues along production,

- storage and treatment processes. *J Environ Sci* 2024;136:45 – 55. <https://doi.org/10.1016/j.jes.2022.10.035>.
35. Ministry of Ecology and Environment of the People's Republic of China. Discharge standard of water pollutants for pharmaceutical industry Fermentation products category. https://www.mee.gov.cn/ywgz/fgbz/bz/bzwb/shjbh/swrwpfbz/200807/t20080701_124699.shtml. [2024-11-25]. (In Chinese).
 36. Ofori-Boateng R, Aceves-Martins M, Wiratunga N, Moreno-Garcia CF. Towards the automation of systematic reviews using natural language processing, machine learning, and deep learning: a comprehensive review. *Artif Intell Rev* 2024;57(8):200. <https://doi.org/10.1007/s10462-024-10844-w>.
 37. Foppiano L, Lambard G, Amagasa T, Ishii M. Mining experimental data from materials science literature with large language models: an evaluation study. *Sci Technol Adv Mater: Methods* 2024;4(1):2356506. <https://doi.org/10.1080/27660400.2024.2356506>.
 38. Awad M, Tian Z, Gao YX, Yang M, Zhang Y. Pretreatment of spiramycin fermentation residue using hyperthermophilic digestion: quick startup and performance. *Water Sci Technol* 2018;78(9):1823 – 32. <https://doi.org/10.2166/wst.2018.256>.
 39. Wang G, Liu HL, Gong PC, Wang J, Dai XH, Wang P. Insight into the evolution of antibiotic resistance genes and microbial community during spiramycin fermentation residue composting process after thermally activated peroxydisulfate pretreatment. *J Hazard Mater* 2022;424:127287. <https://doi.org/10.1016/j.jhazmat.2021.127287>.
 40. Hua T, Li SN, Li FX, Ondon BS, Liu YWJ, Wang HN. Degradation performance and microbial community analysis of microbial electrolysis cells for erythromycin wastewater treatment. *Biochem Eng J* 2019;146: 1 – 9. <https://doi.org/10.1016/j.bej.2019.02.008>.
 41. Chu LB, Chen D, Wang JL, Yang ZL, Shen YP. Degradation of antibiotics and antibiotic resistance genes in erythromycin fermentation residues using radiation coupled with peroxymonosulfate oxidation. *Waste Manage* 2019;96:190 – 7. <https://doi.org/10.1016/j.wasman.2019.07.031>.
 42. Zhang YX, Liu HL, Xin YJ, Shen YP, Wang J, Cai C, et al. Erythromycin degradation and ERY-resistant gene inactivation in erythromycin mycelial dreg by heat-activated persulfate oxidation. *Chem Eng J* 2019;358:1446 – 53. <https://doi.org/10.1016/j.cej.2018.10.157>.
 43. Chu LB, Wang JL, Chen CH, He SJ, Wojnárovits L, Takács E. Advanced treatment of antibiotic wastewater by ionizing radiation combined with peroxymonosulfate/H₂O₂ oxidation. *J Cleaner Prod* 2021;321:128921. <https://doi.org/10.1016/j.jclepro.2021.128921>.
 44. Pei J, Yao H, Wang H, Ren J, Yu XH. Comparison of ozone and thermal hydrolysis combined with anaerobic digestion for municipal and pharmaceutical waste sludge with tetracycline resistance genes. *Water Res* 2016;99:122 – 8. <https://doi.org/10.1016/j.watres.2016.04.058>.
 45. Awad M, Tian Z, Zhang Y, Yang M, Yin WJ, Dong LP. Hydrothermal pretreatment of oxytetracycline fermentation residue: removal of oxytetracycline and increasing the potential for anaerobic digestion. *Environ Eng Res* 2020;26(4):200258. <https://doi.org/10.4491/eer.2020.258>.
 46. Chen SN, Zhong WZ, Ning ZF, Niu JR, Feng J, Qin X, et al. Effect of homemade compound microbial inoculum on the reduction of terramycin and antibiotic resistance genes in terramycin mycelial dreg aerobic composting and its mechanism. *Bioresour Technol* 2023;368: 128302. <https://doi.org/10.1016/j.biortech.2022.128302>.
 47. Tian Y, Tian Z, Feng HD, Luan X, Han ZM, Zhang Y, et al. Unveiling the threshold values of organic and oxytetracycline loadings for nitrification recovery of a full-scale pharmaceutical wastewater treatment system. *Chem Eng J* 2023;463:142487. <https://doi.org/10.1016/j.cej.2023.142487>.
 48. Hou J, Chen ZY, Gao J, Xie YL, Li LY, Qin SY, et al. Simultaneous removal of antibiotics and antibiotic resistance genes from pharmaceutical wastewater using the combinations of up-flow anaerobic sludge bed, anoxic-oxic tank, and advanced oxidation technologies. *Water Res* 2019;159:511 – 20. <https://doi.org/10.1016/j.watres.2019.05.034>.
 49. Yang L, Zhang SH, Chen ZQ, Wen QX, Wang Y. Maturity and security assessment of pilot-scale aerobic co-composting of penicillin fermentation dregs (PFDs) with sewage sludge. *Bioresour Technol* 2016;204:185 – 91. <https://doi.org/10.1016/j.biortech.2016.01.004>.