ISSN 2096-7071
CN 10-1629/R1

CHINA CDC WEEKLY

Vol. 3 No. 47 Nov. 19, 2021

中国疾病预防控制中心周报

Spread Awareness Stop Resisitance

World Antibiotic Awareness Week
November 18–24 , 2021

WORLD ANTIBIOTIC AWARENESS WEEK ISSUE

ISSN 2096-7071

This week's issue was organized by Guest Editor Yongning Wu.

Foreword

World Antimicrobial Awareness Week 2021 — Spread Awareness, Stop Resistance

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The antimicrobial resistance (AMR) Tripartite organizations — the World Health Organization (WHO), the Food and Agriculture Organization of the United Nations (FAO), and the World Organization for Animal Health (Office International des Epizooties, OIE) — are pleased to announce that the theme of World Antimicrobial Awareness Week (WAAW) 2021 will be "Spread Awareness, Stop Resistance" (*1*). China will participate in the WAAW 2021 and organize the China Antimicrobial Awareness Week (CAAW) 2021.

BACKGROUND

Celebrated between November 18–24 each year (*2*), WAAW aims to increase awareness of global AMR and to encourage best practices among the general public, healthcare workers, farmers, animal health professionals, and policymakers to avoid the further emergence and dissemination of drug-resistant infections. In May 2015, a global action plan to tackle AMR was endorsed at the World Health Assembly, supported by FAO and OIE. The first objective of the plan was to "Improve awareness and understanding of antimicrobial resistance through effective communication, education and training." To help achieve this objective, the FAO, OIE, and WHO (collectively known as the Tripartite) have jointly supported WAAW since 2015, together with the general public, students, policymakers, and professionals from various sectors across the world. The overarching slogan of World Antimicrobial Awareness Week continues to be "Antimicrobials: Handle with Care". WAAW is celebrated from November 18–24 every year, endorsing the following campaign objectives: 1) Position AMR as a globally recognized crisis with meaningful engagement across all sectors — human, animal, plant, and environment as the One Health approach, where inappropriate use of antimicrobials in both humans and animals is contributing to the problem and no sector can tackle the problem in isolation; 2) Raise awareness to protect antimicrobial sustainability through prudent and responsible use; 3) Highlight the roles and responsibilities that individuals, governments, professional societies, and organizations in human, animal, environment, and plant health play in addressing and tackling antimicrobial resistance; 4) Encourage behavioral changes that will result in the prudent use of antimicrobials across all relevant sectors and convey the message that simple and sensible actions can make a positive impact.

Tripartite guidance is designed to provide us with the essential information required to participate in the campaign with the hopes that it will help to inspire and imbue us to develop our local public awareness, initiative, and activities. The WAAW 2021 campaign will encourage stakeholders, including policymakers, healthcare providers, the general public, and livestock custodians, to recognize that everyone can be an "AMR Awareness" champion. WAAW 2021 participants are encouraged to disseminate awareness on what AMR is, share stories about its consequences, and demonstrate how the actions of individuals, families, professionals, and communities can have an impact on preventing the spread of AMR. AMR is not a pathogen problem, nor is it a pig or poultry problem, it is a "people problem," and a behavioral change in the demand for and the prescribing of antibiotics is required if the problem is to be effectively tackled. Campaigns to raise awareness, and recognition that a problem exists, are the first step towards the desired behavioral change.

China is a world leader in both human and animal healthcare and its support is essential to making this campaign a success!

Why Address AMR with the One Health Approach?

AMR occurs when bacteria, viruses, fungi, and parasites change their genetic makeup and, consequently, no longer respond to antimicrobials. AMR makes infections more challenging to treat and eradicate, and it increases the

risk of disease spread, severe illness, and death. Measures to prevent infection in humans and the subsequent requirement for antibiotics include getting vaccinated, practising safer sex, good hand hygiene, food safety practices, bolstering immune status by improved diet and wellbeing, and increasing availability of safe potable water and sanitation facilities. Historically, in food animal production, breeding decisions were based on selecting for performance traits, like weight gain, food conversion efficiency, egg production, and milk yield, but now the animal geneticists are including disease resistance traits. This coupled with improved husbandry practices, better animal welfare standards, improved nutrition, and the increased use of immunization are reducing the need for antibiotics and the associated risk of developing multidrug resistant zoonotic agents.

AMR is a complex problem affecting human, animal, plant, and environmental health and the impacts of AMR affects all four sectors and there is cross over between them. Microbes can exchange mobile genetic elements conveying disease resistance between each other making tackling this problem challenging. Therefore, addressing AMR requires a holistic and multisectoral approach — referred to as the One Health approach (*3*–*4*). This initiative is a collaborative, multisectoral, and trans-disciplinary approach recognizing the interconnections between people, animals, plants, and their shared environment. By designing and implementing multisectoral programs, policies, legislation, and research with professionals from human, terrestrial and aquatic animal and plant health, food and feed production, and the environment, AMR can be more effectively addressed and communicated to achieve better One Health outcomes (Figure 1). Each sector must play its part, and everyone has a role to play.

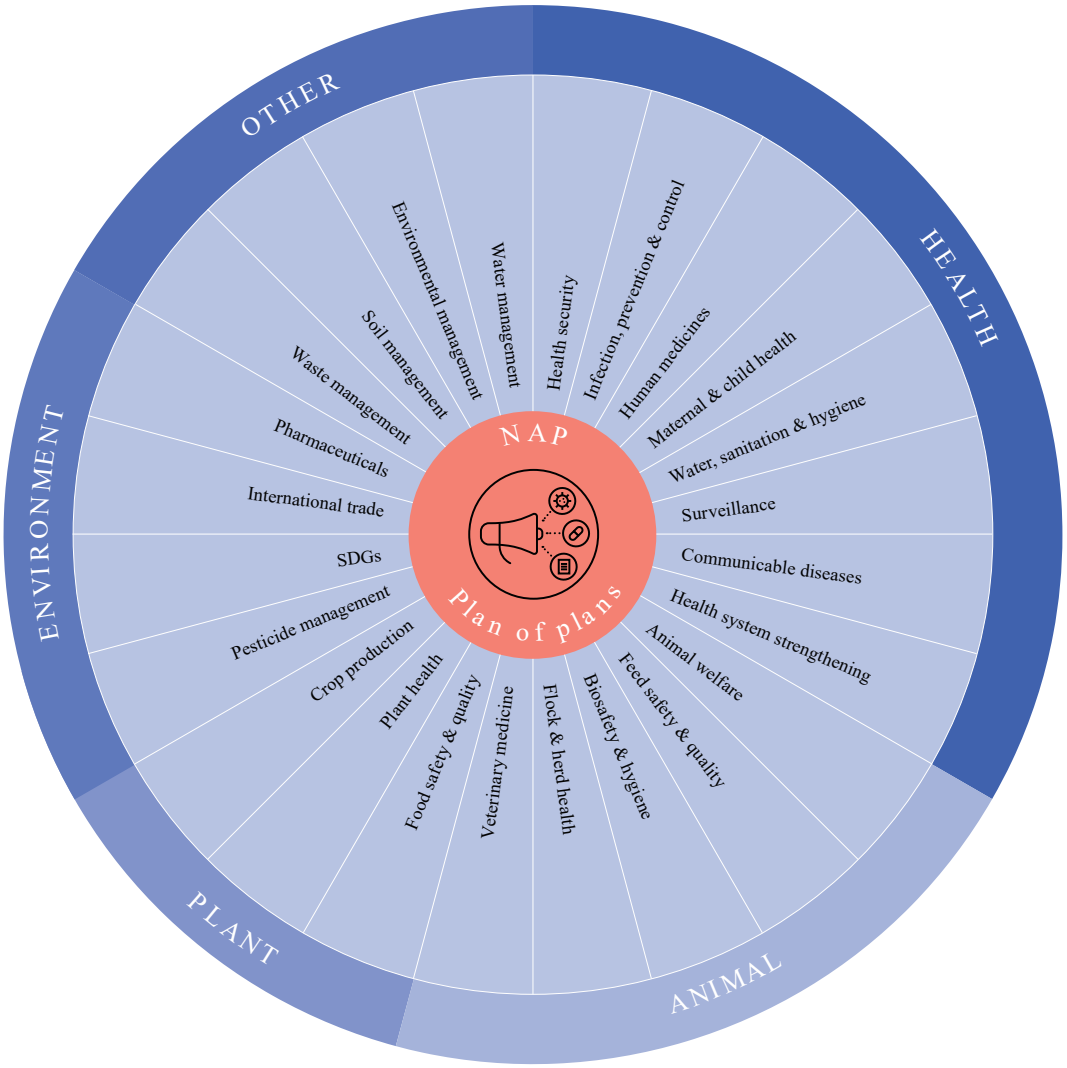

FIGURE 1. Turning plan into action: an overview for One Health approach [quoted from WHO (*8*)].
Abbreviation: SDGs=sustainable development goals; NAP=national action plans.

2021 Theme — "Spread Awareness, Stop Resistance"

As in previous years, the overall slogan for antimicrobial resistance awareness and WAAW is "Antimicrobials: Handle with Care." With the new theme of "Spread Awareness, Stop Resistance" in WAAW 2021 (*1*), we want to encourage stakeholders in human, animal, and environmental health to be "AMR Awareness" champions in their families, communities, and places of work. We hope everyone will engage with the global campaign activities and feel empowered to organize events to raise awareness as to what AMR is, and the actions of workplaces, communities, and/or government that can control the spread of AMR. We also hope you will share your personal stories so we can shift our thinking of AMR beyond the "drugs and bugs" narrative and ensure the consequences of AMR are effectively communicated to all the stakeholders. Different audiences will require different levels of detail delivered in comprehensible formats. The objective is for people everywhere to see, hear, relate to, and understand AMR as a health threat affecting our environment, animals, families, and communities and as relevant in our day-to-day lives. The big concern is that, if left unchecked, resistant microbes will develop with limited therapeutic options resulting in increased morbidity and mortality in both humans and animals and the associated costs to individuals and society. There is a limited number of new antibiotics in the research and development pipeline, therefore more powerful drugs are not the solution to the AMR crisis.

Global Action Plan and the China National Action Plan

In 2015, to advance the global and national response to AMR, the World Health Assembly issued resolution WHA68.7 calling for all Member States to develop AMR National Action Plans (NAPs) that address the 5 objectives of the Global Action Plan (GAP) by May 2017. The WHO GAP provides a framework to support countries in developing their NAPs. As of July 2021, 145 countries have developed NAPs and an additional 41 countries are currently developing a NAP. Among 145 countries, China has developed its own NAP with contributions from 14 multisectoral departments (*5*). In 2020, according to the Tripartite AMR Country Self-Assessment Survey data, approximately 20% of NAPs were fully funded and 40% had a budgeted operational plan (*6*–*7*). Embedding AMR activities in government planning and budgeting processes at the national/subnational, sectoral, and departmental levels is one strategy for progress outlined in the draft WHO implementation handbook for NAPs on AMR (Figure 2). The cost of desired actions and a cost-benefit analysis can aid policymakers and implementers in prioritizing within resource-limited settings to revise plans, as deemed necessary (e.g., the number or scale of activities can be adjusted to fit available budgets). Additional information on selecting activities in AMR NAPs is available in converting plans into action for tackling AMR (Figure 3).

Where to find the tool and who should use it

The WHO costing and budgeting tool, accompanying documentation and resources are available on the WHO AMR website (*8*). The primary audience for the WHO tool is national AMR (One Health) stakeholders. Given that the technical expertise required to develop operational plans and budgeting processes is often ministry or sector specific, costing of individual activities and components might be conducted separately by individual ministries or sectors, and subsequently combined into a single costed plan (modular approach). Although specific processes might differ depending on the country, the following steps illustrate a possible coordination plan of costing across various actors and sectors:

• Step 1: The National AMR coordinating mechanism receives/downloads the tool and resources pack and designates a (or multiple) costing coordinator(s).

• Step 2: The costing coordinator reviews this user guide and available training materials and tests the tool functionality/features. If questions arise, the costing coordinator contacts the WHO helpdesk (amrnap-helpdesk@who.int) for additional technical assistance.

• Step 3: The costing coordinator, together with the members of the national AMR coordinating mechanism agree on the process for completing the costing tool: 1) one costing tool to be filled out for all activities irrespective of sector/ministry/department; or 2) each sector/ministry/department fills out the tool separately with the designated costing coordinator. Subsequently, a lead costing coordinator will compile the information into one costed plan (modular approach).

• Step 4: The costing coordinator holds a meeting with the relevant sectors, ministries and stakeholders who will implement the costed activities selected and prioritized.

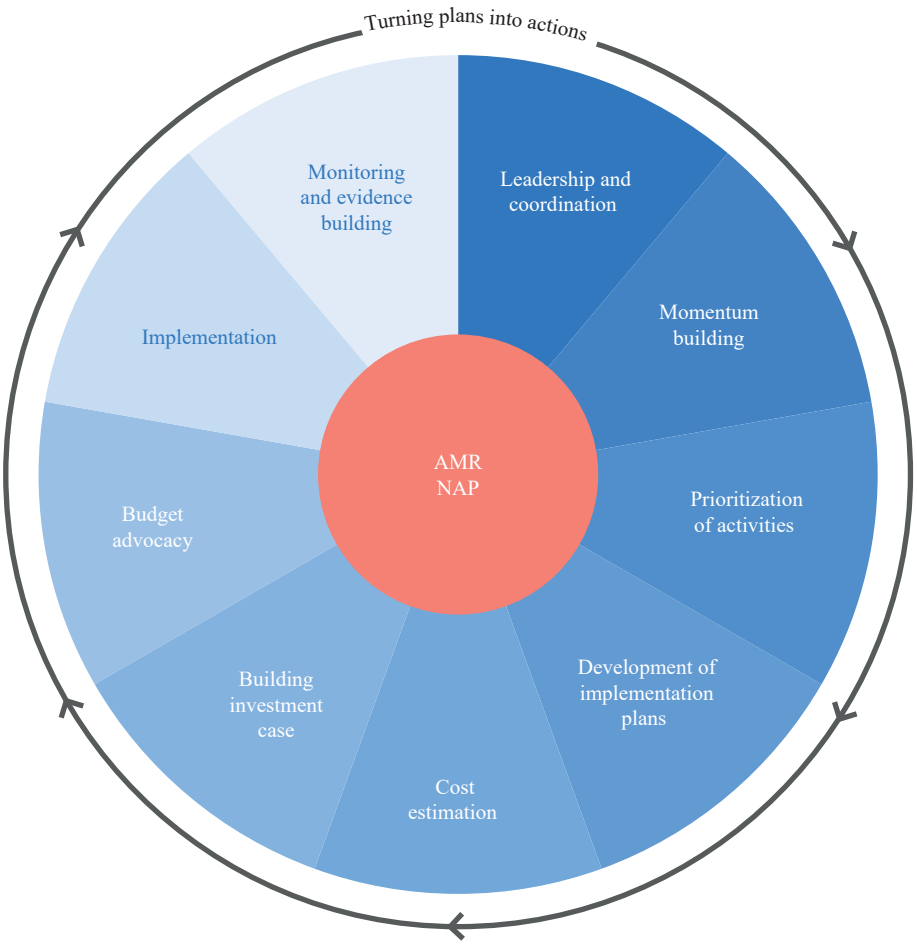

FIGURE 2. Overview of AMR NAP development and implementation [quoted from WHO (*8*)].
Abbreviations: AMR=antimicrobial resistance; NAP=national action plans.

• Step 5: The costing coordinator completes the draft costing plan based on input from the relevant sectors, ministries, and stakeholders and forwards the completed costing tool to the main costing coordinator.

• Step 6: The costing coordinator reviews the submitted data and, if errors or incomplete data are detected, requests amendments.

• Step 7: The costing coordinators from the different sectors and ministries send revised, finalized results to the lead costing coordinator.

• Step 8: The main costing coordinator combines the data from multiple costing sheets to produce a comprehensive costed plan and dashboard (modular approach).

• Step 9: The costing coordinators share the comprehensive costed plan with the relevant actors.

Overview and tool workflow completing the tool involves five key steps

Figure 4 provides an overview of key components of the workflow. These steps are:

• Step 1. NAP entry. The user specifies the NAP priorities, objectives and activities that were selected for costing.

• Step 2. Basic inputs. The user enters key parameters relevant to their country, including ministry/implementer identifiers, funding opportunities, timelines to and during implementation, and unit costs for various items.

• Step 3. Costing matrix. These tabs are automatically generated after NAP entry is completed and are used to insert sub-activities and entering units and unit costs.

• Step 4. Funding (optional). The user enters existing funds from various sources/donors/stakeholders. This step is optional but recommended and can be completed at any time after the NAP entry is complete.

• Step 5. Dashboards. The user can specify various cross-tabulations and levels of analysis to produce dashboards and visualize all data. The Dashboard tab summarizes cost data entered by the user. The Funding Dashboard tab

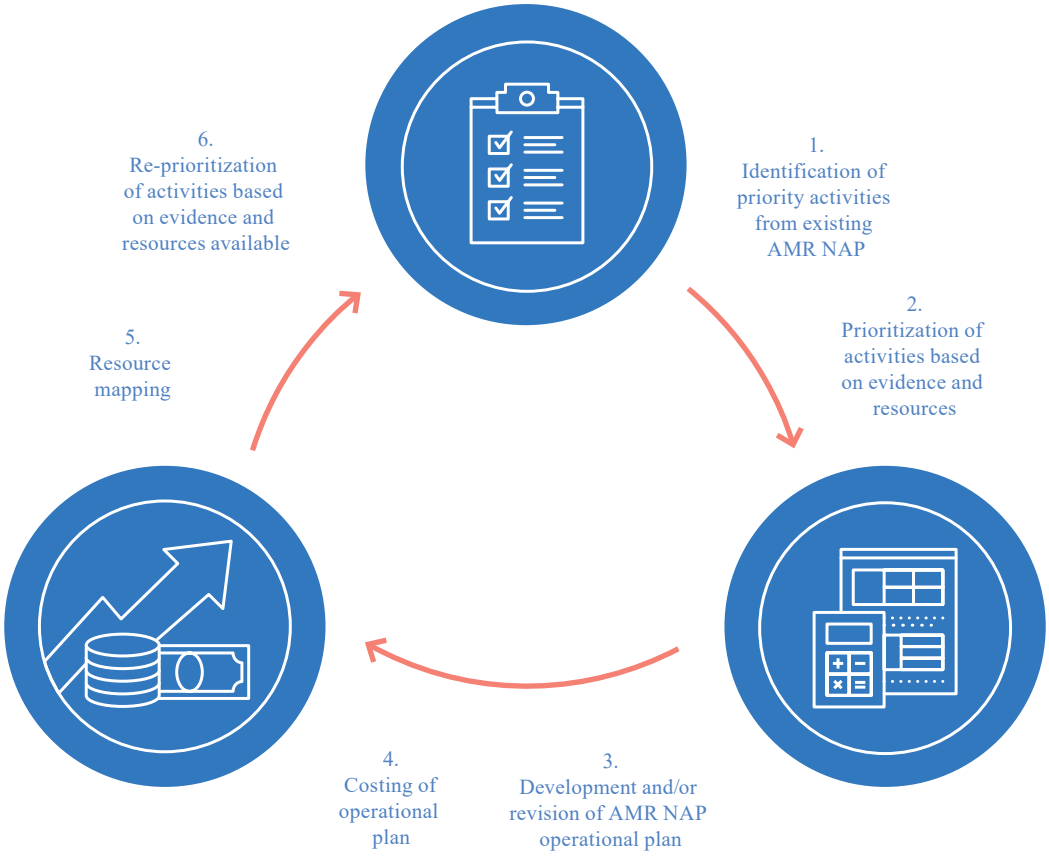

FIGURE 3. Activities' priortization of NAP for AMR with One Health approach [quoted from WHO (*8*)]. Abbreviations: AMR=antimicrobial resistance; NAP=national action plans.

combines cost and funding data (if funding data in Step 4 above have been entered) by the user.

What China should do?

In the last decade China has positioned itself as global player in trade, commerce, and international engagement. China has also proven itself to be a world leader in understanding the perils of AMR, proceeded by swiftly producing and enforcing policy. First, by recognizing the emergence of AMR driven by using colistin in farming and subsequently enforcing its withdrawal (*9*). Second, in 2020, formally announcing the ban of all antibiotics in animal feeds across all meat production; by the end of 2025, large scale farms participant in action for reducing the use of veterinary antibiotics by more than 50% (*10*). AMR is a global challenge and will require global action to tackle it. Therefore, there is an urgent need for all countries to unite and work together in the war against AMR. Whilst COVID was an abrupt earthquake, AMR is a slow but massive tsunami that will engulf all people in all countries and its current trajectory is relentless. AMR's impact, in terms of morbidity and mortality and the financial impact on societies will dwarf that of coronavirus disease 2019 (COVID-19). Furthermore, as many different microbes are involved, it will not be readily remedied by vaccines. China is assisting in the global implementation programs by working closely, and collaborating, with international partners in tackling AMR, particularly in low-middle income countries through a spirit of trust and unity. AMR has no boundaries and is blind to creed, race, and social status. China is fortunate in having high caliber scientists in the areas of microbial genetics and human and animal health who are collaborating with international colleagues and thus, China is playing a pivotal role in our global fight against our common enemy.

Funding: National Nature Science Foundation of China (NSFC) project 216812303 and Newton International Fellowship NIF\R1\192293 of Royal Society.

doi: 10.46234/ccdcw2021.241

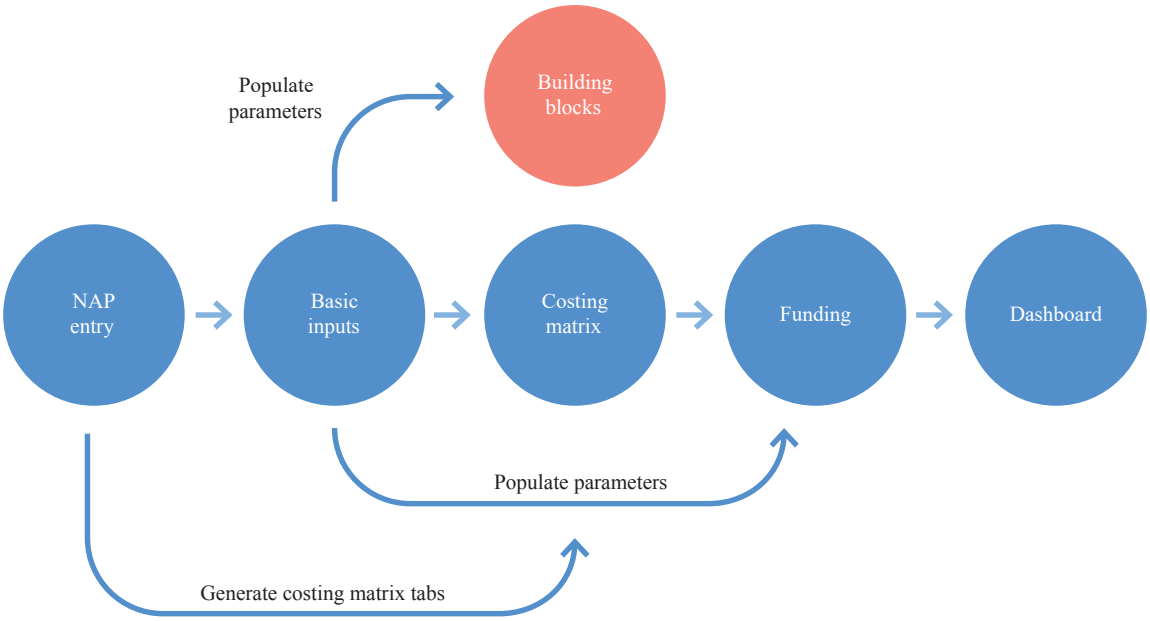

FIGURE 4. Tool workflows for NAP: from plan to action [quoted from WHO (*8*)].
Abbreviation: NAP=national action plans.

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Submitted: November 09, 2021; Accepted: November 15, 2021

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Preplanned Studies

Genomic Insight into the Antimicrobial Resistance of *Streptococcus Suis* — Six Countries, 2011–2019

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Summary

What is already known on this topic?

Streptococcus suis (*S. suis*) is a zoonotic pathogen causing disease in humans and animals, and the emergence of its increased resistance to antimicrobial agents has become a significant challenge in many countries.

What is added by this report?

Using whole genome sequencing data to accurately predict antimicrobial resistance determinants, it was found that the prevalence of antimicrobial resistance genes was higher in the pig isolates of *S. suis* than in the human isolates and that the prevalence of these genes varied with serotype.

What are the implications for public health practice?

The data regarding *S. suis* antimicrobial resistance will help guide rational drug use in the clinic to better protect the health of humans and animals.

Streptococcus suis (*S. suis*) is an important zoonotic pathogen that apart from causing huge economic losses to the global swine industry, can also cause severe illness and even death in humans. Antibiotics are commonly used to treat and control *S. suis* infections, contributing to the increasing prevalence of antimicrobial-resistant *S. suis*, which has attracted the attention of the global health community (*1*–*3*). Therefore, monitoring the prevalence of antimicrobial resistance-related genes in *S. suis* and studying its antimicrobial resistance characteristics will provide guidance for the clinical treatment of *S. suis* infections. In this study, *S. suis* isolates from 20 provincial-level administrative divisions (PLADs) in China were collected and analyzed from 2011 to 2019, together with the available *S. suis* sequencing data (with detailed host information) in the National Center for Biotechnology Information (NCBI) database, and a global surveillance of *S. suis* resistance was carried out according to several epidemiological dimensions. The results demonstrated that the prevalence of antimicrobial resistance genes in *S. suis* was generally higher in China than in other countries and that the prevalence was generally higher in the pig isolates compared to the human isolates. The prevalence of resistance genes varied with serotype; however, *erm*(B), a gene mediating macrolide resistance, and *tet*(O), a gene mediating tetracycline resistance, were both prevalent across different serotypes. The results of drug sensitivity experiments indicated a high and concerning level of antimicrobial resistance in the *S. suis* isolated in China. Therefore, public health practitioners should pay attention to the rational use of medicines, reduce the abuse of therapeutic drugs, and promote the scientific use of medicines in farming to protect the lives of animals and humans.

In this study, nasal swabs, lung, spleen, liver, and lymph nodes of healthy and diseased pigs from 20 PLADs across China were collected and analyzed. The analysis data were then combined with the *S. suis* sequencing data (with detailed host information) in the NCBI database. The samples were collected strictly according to the relevant standard protocols, as all the samples were collected using Eswab tubes containing culture media and then stored and transported appropriately to the handling laboratories using ice packs. *S. suis* isolation was performed as described in previous studies (*4*). Genomic DNA of *S. suis* was extracted using the Wizard Genomic DNA Purification Kit (Promega, Beijing, China) following the manufacturer's instructions. DNA libraries were constructed using the KAPA HyperPrep Kit Illumina platforms (Roche, Basel, Switzerland) following standard protocols and then sequenced on an Illumina HiSeq X Ten platform (Annoroad, Beijing, China). Illumina sequencing reads for each isolate were processed using Trimmomatic with an average quality cutoff of 20 (2.3 million average reads per sample). Finally, the high-quality reads were assembled as contigs of at least 500 bp with SPAdes (with parameter–careful) (version 3.13.1, St. Petersburg

Academic University, https://github.com/ablab/spades). via the Unicycler (version 0.4.7, The University of Melbourne, https://github.com/rrwick/Unicycler) assembly pipeline (*5*). The quality of the genome sequences was checked using the default settings in QUAST (version 5.0.2, St. Petersburg Academic University, https://github.com/ablab/quast) (*6*). Identification of *S. suis* serotypes was performed using the protocol described by Athey et al. (*7*). Resistance genes were identified using the SRST2 Toolkit (version 0.2.0, The University of Melbourne, http://katholt.github.io/srst2/). Minimum inhibitory concentrations were determined by the broth microdilution method according to the recommendations of the Clinical and Laboratory Standards Institute guidelines (CLSI, 2015: M100-S25).

During 2011–2019, a total of 436 *S. suis* isolates were collected from 20 PLADs in China, including 271 isolates from healthy pigs and 165 from diseased pigs (Table 1). Upon analysis, all 436 isolates were identified as *S. suis*. Genomic analysis revealed 17–1,753 contigs per isolate, with genome sizes ranging from 1,949,027 to 2,642,630 bp and an average GC content of 41.12%. Additionally, 934 sequenced *S. suis* isolates with specific host sources were screened from 2,452 isolates in the NCBI database, including 461 isolates derived from humans, 129 from healthy pigs, and 344 from diseased pigs. Altogether, 1,370 *S. suis* isolates were obtained from China, Vietnam, Thailand, the Netherlands, the United Kingdom and Japan, and majority of them were obtained during 2011-2019. A total of 27 distinct serotypes were identified from the 1,370 isolates, with the predominant serotype being serotype 2 (n=686), which accounted for 50.1% of the isolates, followed by serotype 3 (n=75, 5.5%). Furthermore, 57 (4.2%), 54 (4.0%), 50 (3.6%), 32 (2.3%), 32 (2.3%), and 29 isolates (2.1%) were identified as belonging to serotype 9, 7, 4, 1, 8, and 14, respectively.

The predicted antimicrobial resistance genes using the SRST2 Toolkit (http://katholt.github.io/srst2/) in all 1,370 *S. suis* isolates indicated that the prevalence and number of antimicrobial resistance genes were diverse among the different serotypes (Figure 1). Among all the resistance genes, *erm*(B) and *tet*(O) were highly observed in all serotypes (Figure 1A). The newly characterized *srpA* gene, which confers resistance to streptogramin A, pleuromutilins, and lincosamides, was found in 60 isolates (4.4%), mainly in serotypes 2, 3, 4, 9, 12, 21, 25, 29, 30, and 31 (dominant serotype 2) (*8*). Further, the prevalence of antimicrobial resistance genes in the isolates from China was generally higher than that in the isolates from other countries. The prevalence of antimicrobial resistance genes in human isolates was lower than that in pig isolates (Figure 1C). Drug sensitivity results showed that the antimicrobial resistance rate of *S. suis* was the highest for macrolides (91.5%) and the lowest for β-lactams (3.9%–15.4%) (Table 2), consistent with the genomic analysis results of antimicrobial resistance.

TABLE 1. Characteristics and prevalence of 436 *Streptococcus suis* from the 20 PLADs, China, 2011–2019.

PLADs	Host source (N)	
	Healthy pig	Diseased pig
Anhui	12	18
Beijing	27	0
Chongqing	28	0
Guangdong	57	0
Guizhou	1	0
Hebei	1	0
Heilongjiang	8	0
Henan	25	52
Hubei	18	22
Hunan	16	16
Inner Mongolia	1	0
Jiangsu	2	0
Jiangxi	2	19
Ningxia	1	0
Qinghai	2	0
shaanxi	0	18
Shandong	19	0
Shanxi	0	20
Sichuan	43	0
Xinjiang	8	0
Total	271	165

Note: Sequencing data obtained from the database were not shown.
Abbreviations: PLADs=provincial-level administrative divisions; N=number.

DISCUSSION

In this study, the prevalence of antimicrobial resistance genes in *S. suis* was found to differ among the isolates from different sources; the prevalence of these genes in *S. suis* was generally higher in China than in foreign countries, which may be related to

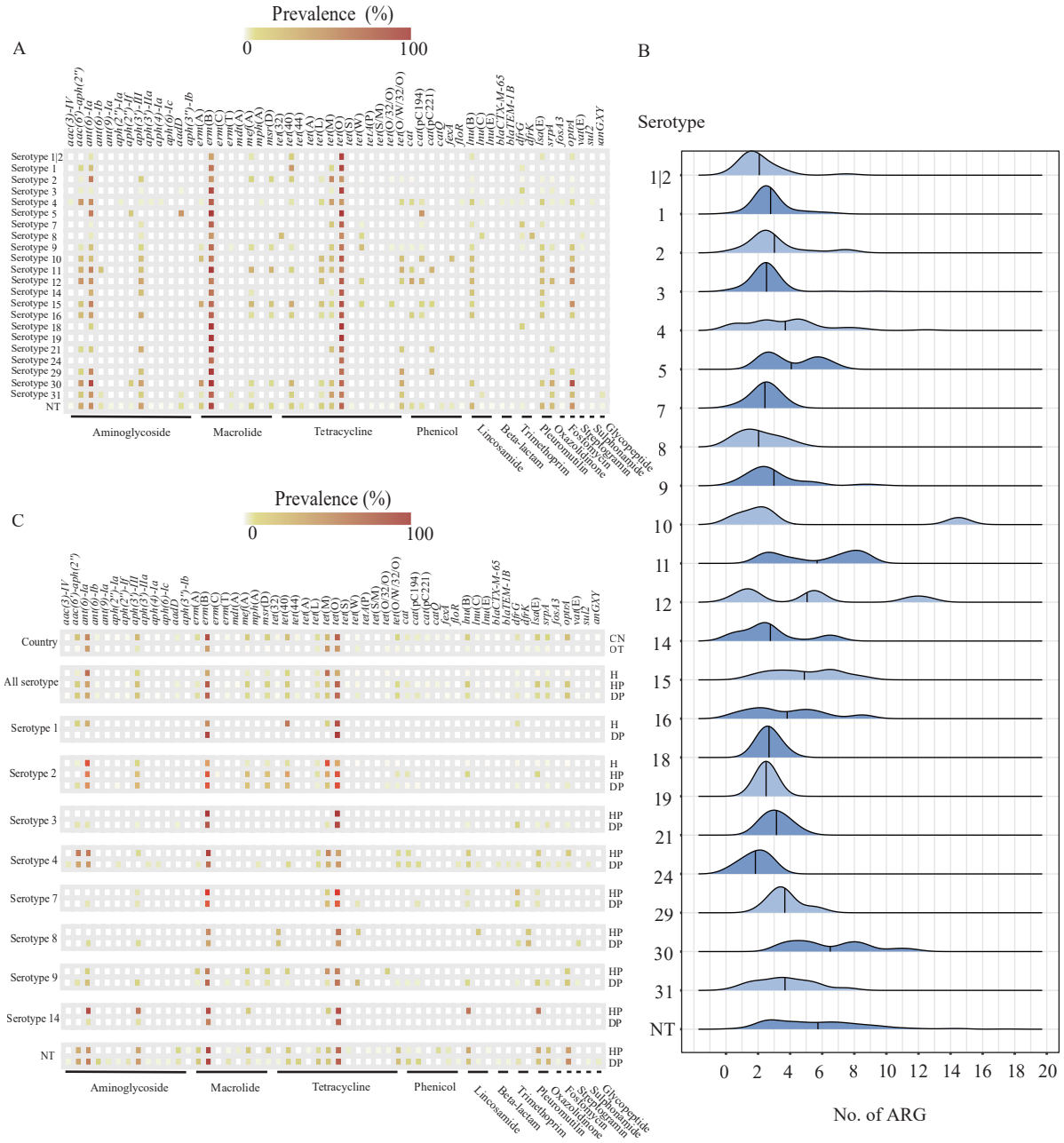

FIGURE 1. Prevalence and number of resistance genes among different serotypes in 1,370 *Streptococcus suis* isolates from 6 countries. (A) Frequencies of AMR genetic determinants within different serotypes, calculated across 22 serotypes. (B) Comparison of the number of AMR genes among the different serotypes. The median is represented by a black line. (C) Comparison of AMR gene prevalence among different countries or different hosts. The horizontal axis represents antimicrobial resistant genes and the vertical axis represents countries or host sources.

Note: In Figure 1A, cells indicate absence (white) or presence (colored by proportion) of each AMR determinant. The horizontal axis represents 54 antimicrobial resistance genes of 13 antibiotic classes, and the vertical axis represents 22 serotypes and none-type (NT), the number of which is greater than two. In Figure 1B, the median is represented by a black line. In Figure 1C, the horizontal axis represents antimicrobial resistant genes and the vertical axis represents countries or host sources.

Abbreviations: CN=China; OT=Other countries; H=Human; HP=Healthy pig; DP=Diseased pig; AMR=Antimicrobial resistance; ARG=Antibiotic resistance gene.

suboptimal drug use in breeding farms in China, indicating that the antimicrobial resistance of *S. suis* in China is a serious public health problem. With respect to the host source, the prevalence of *S. suis* antimicrobial resistance genes in the human isolates was lower than that in the pig isolates. This may be

TABLE 2. The MIC distribution of 306 *Streptococcus suis* isolated in China (n=306).

Antimicrobials	MIC values (μg/mL)														Drug resistance rate (%)
	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1,024	
Aminoglycosides[a]	2	0	0	5	15	28	68	30	18	25	15	41	51	8	58.8%
Lincosamide[b]	9	0	0	0	69	0	0	1	9	7	12	75	106	18	74.5%
Fluoroquinolones[c]	100	25	24	73	2	24	16	23	13	6	0	0	0	0	27.5%
Tetracyclines[d]	0	6	0	2	9	45	32	33	25	39	43	5	1	0	58.2%
Macrolides[e]	2	4	20	0	3	19	22	21	19	17	51	111	17	0	91.5%
Chloramphenicol[f]	0	6	3	42	64	77	25	23	36	19	9	2	0	0	37.3%
Cephalosporins[g]	163	24	26	11	6	64	9	2	1	0	0	0	0	0	3.9%
Penicillins[h]	83	28	16	32	100	26	10	4	7	0	0	0	0	0	15.4%

Note: Refer to the streptococcal drug sensitive threshold.
Drug resistance threshold (μg/mL): a≥16, b≥4, c≥2, d≥8, e≥1, f≥8, g≥8, h≥4.
Abbreviation: MIC=minimum inhibitory concentration.

because most human isolates were serotype 2 and the prevalence of antimicrobial resistance genes in serotype 2 was generally lower than that in other serotypes, though the serotype 2 isolates accounted for a large proportion of the population. In general, the prevalence of *erm*(B), which mediates macrolide resistance, and *tet*(O), which mediates tetracycline resistance, was high among the isolates from all sources; however, the prevalence of these two genes in serotype 2 was lower than that in other serotypes, although serotype 2 represents the dominant serotype of pathogenic *S. suis*. Tetracycline resistance in porcine streptococci has become a major problem worldwide and is closely related to the widespread use of tetracyclines in the pig industry. The antimicrobial resistance gene prevalence and the antimicrobial resistance phenotype of *S. suis* evaluated in this study indicate the problem of the antimicrobial resistance of *S. suis* in China to be prominent, and timely actions should be taken to avert an imminent crisis. The results further provide important guidance and reference values for clinical drug use.

The findings of this study were consistent with those of some previous studies. Hout et al. showed that among the 1,163 isolates of *S. suis* collected in the Netherlands during 2013–2015, 78.4% were resistant to tetracycline and 48.1% to clindamycin, with the resistance rate for β-lactams being less than 5% (*9*). Another study by Zhang et al. investigating the drug sensitivity of 421 *S. suis* isolates from China found that the antimicrobial resistance rates for tetracycline, macrolides, and sulfonamides were more than 60%, and the antimicrobial resistance rate for β-lactams was only 9.5% (*10*). Based on these results, β-lactam antibiotics can still be used as the drugs of choice for *S. suis* infections.

This study was subject to some limitations. While the isolates used in this study for genomic analysis covered most parts of China; the geographical locations of the isolates whose data was sourced from GenBank were not evenly distributed. In addition, most of the isolates from Vietnam belonged to serotype 2.

In summary, data of 1,370 isolates of *S. suis* from 6 countries were investigated for antimicrobial resistance and classified according to different characteristics for comparative analysis. The prevalence of macrolide and tetracycline resistance genes was the highest. The prevalence of the resistance genes varied with the source; it was lower in the human isolates of *S. suis* than in the pig isolates. Based on these findings, to limit the extensive spread of antimicrobial-resistant *S. suis*, a series of interventional policies are needed to address the impending antimicrobial resistance crisis and to develop appropriate dosing strategies for the different strains of *S. suis* with different hosts to protect the health of humans and animals under the "One Health" approach.

Acknowledgments: Research staff at College of Veterinary Medicine, China Agricultural University.

Conflicts of interest: No conflicts of interest.

Funding: Supported by the National Key Research and Development Program of China (2017YFC 1601501 and 2016YFD0501305) and Key Research and Development Program of Shandong Province (2019JZZY010719).

doi: 10.46234/ccdcw2021.242

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Submitted: October 29, 2021; Accepted: November 16, 2021

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Preplanned Studies

Prevalence of *Escherichia coli* and Antibiotic Resistance in Animal-Derived Food Samples — Six Districts, Beijing, China, 2020

Hui Li[1]; Yanchao Liu[2]; Lu Yang[1]; Xuan Wu[1]; Yige Wu[1]; Bing Shao[1,#]

Summary

What is already known about this topic?

Escherichia coli is an important hygiene indicator for animal-derived foods such as pork and chicken, and the contamination of retail meat is associated with the spread of antimicrobial resistance (AMR) and public health.

What is added by this report?

The prevalence of *E. coli* in 6 different districts of Beijing was 64.1%. The contamination of chicken was more serious than pork in Beijing. *E. coli* isolates were highly resistant to sulfonamides (87.4%). The *ampC1* and *ampC2* genes were the main antibiotic resistance genotype (94.7% and 99.4%).

What are the implications for public health practice?

This study highlights the need to strengthen the surveillance of antibiotic resistance of *E. coli* in animal-derived foods. A national or regional multicenter study is required to assess the dissemination and evolution of multidrug resistant (MDR) *E. coli* in clinical medicine and animal production for food.

Bacterial resistance has become a global problem, among which the resistance of foodborne pathogens has attracted special attention (*1*). Foodborne pathogens are currently being actively monitored for antimicrobial resistance to analyze the spread and dissemination and support the prevention and control of antimicrobial resistance. Antibiotic-resistant bacteria/genes caused by using antimicrobial drugs in the agricultural industry can spread through the food chain (*2*). In the animal breeding process, China has launched a foodborne pathogenic bacteria antimicrobial resistance monitoring program and obtained a large amount of basic data. However, we still do not fully understand the antimicrobial resistance of food contaminating bacteria in the circulation link. *Escherichia coli* (*E. coli*) bacterial infections have caused a significant increase in morbidity and mortality worldwide, threatening human health (*3*–*4*). Thus, we are using *E. coli* as a representative to investigate the antibiotic resistance of animal-derived food contaminated bacteria in six districts within Beijing. *E. coli* is also an important hygiene indicator for animal-derived foods such as pork and chicken. Previous studies have shown that retail meat is associated with the spread of *E. coli* (*5*–*6*). Therefore, strengthening the monitoring of foodborne pathogenic *E. coli* is important to protecting human health. In this study, the epidemiological surveillance and typing study of *E. coli* in retail pork and chicken from six districts (Dongcheng, Xicheng, Haidian, Fengtai, Chaoyang, and Changping) in Beijing, China, was investigated. The results demonstrated that *E. coli* contamination in chicken is more serious than that in pork, and Chaoyang District displayed the highest *E. coli* isolation rate. Antimicrobial susceptibility testing showed that foodborne *E. coli* was highly resistant to sulfonamides with a resistance rate of 87.4%. The prevalence of resistance genes *ampC1* and *ampC2* occurred in most isolates. Therefore, effective supervision of animal-derived food hygiene to control the dissemination of bacterial resistance is essential to safeguard human health.

In this study, a total of 290 raw meat samples (91 pork and 199 chicken) were randomly collected from large and small supermarkets and farmer's markets in the 6 districts of Beijing. *E. coli* were isolated using CHROMagar ECC (CHROMagar TM, Paris, France) colored medium after enrichment. The isolated strains were identified by matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS). Detailed materials and methods were provided as supporting information (Supplementary Materials, available in http://weekly.chinacdc.cn/). The gram-negative bacteria drug sensitivity plates Sensititre GNX3F (Thermo Fisher Scientific, Massachusetts, USA) were used for the antibiotic susceptibility test of

the isolated strains according to the recommendations of the Clinical and Laboratory Standards Institute guidelines (CLSI, M100-S30) (*7*) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) standards v10.0 (*8*). The microbroth dilution method was used to determine their susceptibility to 21 antimicrobial agents from 9 classes, including amikacin, gentamicin, tobramycin, doxycycline (DOX), tigecycline, minocycline, ciprofloxacin, levofloxacin, trimethoprim/sulfamethoxazole (SXT), aztreonam, imipenem, meropenem, doripenem, cefepime, ceftazidime, cefotaxime, colistin, polymyxin B, ampicillin/sulbactam, piperacillin/tazobactam, and ticarcillin/clavulanic acid. Whole genome sequencing (WGS) was conducted using an Illumina Hiseq2500 platform (Annoroad Gene Technology, Beijing, China). Multilocus sequence typing (MLST) was identified using the pMLST 2.0 database (mlst Github http://github.com/tseemann/mlst). Antimicrobial resistance genes were identified by searching the Comprehensive Antibiotic Research Database (CARD, https://card.mcmaster.ca/download). All draft genomes were used for constructing a phylogenetic tree using parsnp software (Supplemetary Materials, available in http://weekly.chinacdc.cn/ https://github.com/marbl/) (*9*), and the trees were finally visualized using the online tool iTOL (http://itol.embl.de/).

A total of 186 *E. coli* isolates (186/290, 64.1%) were collected from raw chicken and pork samples from Beijing in 2020. The highest rates (73.9%) of *E. coli* isolates were found in chicken compared to that (42.9%) in pork samples (Supplementary Table S1, available in http://weekly.chinacdc.cn/), which indicated that *E. coli* contamination in chicken was more serious than pork. For chicken, Chaoyang District displayed the highest *E. coli* isolation rate among the six examined region of Beijing, while Fengtai had the lowest isolation rate (50.0%) (Supplementary Table S1). While regarding pork, Xicheng displayed the highest *E. coli* isolation rate among the examined regions (66.7%), while Haidian and Chaoyang displayed the lowest isolation rates (33.3%).

The distributions of minimum inhibitory concentrations (MICs) and resistance rates of 186 *E. coli* isolates against 21 antimicrobial agents were shown in Table 1 and Figure 1A. Antimicrobial susceptibility tests showed that *E. coli* isolates were highly resistant to SXT (87.4%), followed by DOX (32.57%) and GEN (29.71%). Carbapenems (IMI, MERO, and DOR) had the lowest resistance rate of 4.0% (Table 1). *E. coli* isolates from six different regions represented high resistance to SXT, and Dongcheng showed 100% resistance to SXT (Figure 1B).

Comprehensive antibiotic resistome analysis using the CARD database in all 166 *E. coli* isolates indicated that diverse antimicrobial genotypes occurred in chicken and pork samples in Beijing. Among all the resistance genes, *ampC1* and *ampC2* were highly observed in all isolates (Figure 2), the detection rates were 94.7% and 99.4%, respectively. Extended-spectrum β -lactamase (ESBL)-producing strains of *E. coli* harboring CTX-M, OXA, CMY, and TEM were detected in this study. The most prevalent ESBL genes were $bla_{\text{TEM-1D}}$ (22.7%) and $bla_{\text{CTX-M-9}}$ (21.5%), followed by $bla_{\text{CTX-M-1}}$ (11.0%) and $bla_{\text{OXA-7}}$ (11.0%). Plasmid-mediated transferrable colistin resistant gene *mcr-1* was found in 22 isolates (13.3%). Most *mcr-1* gene were located on plasmid (15/22, 68.2%), and IncI2 (11/15, 73.3%) and IncY (4/15, 26.7%) were the main plasmid types. In addition, sulfonamide-resistant genes *sul1*, *sul2,* and *sul3* were also analyzed, and their detection rates were 16.9% (28 isolates), 32.5% (54 isolates), and 13.9% (23 isolates), respectively. Plasmid typing found that nine plasmid incompatibility (Inc) groups (IncFII, IncFIIp, Inc FIA, IncFIB, IncCol, IncCol156, IncX1, IncI2, and IncY) were common in these isolates. A total of 59 different STs were identified from 166 *E. coli* isolates. The most prevalent one was ST10 (22 isolates, 13.3%), followed by ST399 (11 isolates, 6.6%), and ST1434 (10 isolates, 6.0%). The remaining 56 STs were all lower than 4.2% abundance (Figure 2). Correlation analysis of antimicrobial resistance genotype and phenotype of *E. coli* isolates were shown in Supplementary Figure S1, available in http://weekly.chinacdc.cn/. Antimicrobial phenotype was consistent with resistance genotype for aminoglycosides, tetracyclines, fluoroquinolones, and lipopetides, except sulfonamides, penicillins, and carbapenems. Phylogenomic analysis revealed that all the *E. coli* isolates from animal-derived food and clinic were classified into two lineages, sharing different homologies (Supplementary Figure S2, available in http://weekly.chinacdc.cn/). Typing results showed commonality between human clinical strains, with STs 131 (especially), 297, and 2380 prominent. In addition, there was little crossover between types form

TABLE 1. Antibiotic resistant phenotype of 186 *Escherichia coli* isolates against 21 antimicrobial agents obtained from chicken and pork samples from the 6 districts, Beijing, China, 2020.

Antimicrobial classes	Antimicrobial agents	Chicken			Pork			Overall R%[§]
		S%[*]	I%[†]	R%[§]	S%[*]	I%[†]	R%[§]	
Aminoglycosides	Amikacin (AMI)	94.9	1.5	3.7	100.0	0.0	0.0	2.9
	Gentamicin (GEN)	65.4	1.5	33.1	82.1	0.0	18.0	29.7
	Tobramycin (TOB)	64.7	2.2	33.1	87.2	0.0	12.8	28.6
Tetracyclines	Doxycycline (DOX)	40.4	30.2	29.4	18.0	38.5	43.6	32.6
	Tigecycline (TGC)	98.5	0.0	1.5	94.9	0.0	5.1	2.3
	Minocycline (MIN)	83.8	11.0	5.2	64.1	12.8	23.1	9.1
Fluoroquinolones	Ciprofloxacin (CIP)	69.1	1.5	29.4	79.5	2.6	18.0	26.9
	Levofloxacin (LEVO)	73.5	2.9	23.5	79.5	7.7	12.8	21.1
Sulfonamides	Trimethoprim/sulfamethoxazole (SXT)	14.0	0.0	86.0	7.7	0.0	92.3	87.4
Penicillins	Aztreonam (AZT)	69.1	4.4	26.5	89.7	2.6	7.7	22.3
Carbapenems	Imipenem (IMI)	91.9	3.7	4.4	94.9	2.6	2.6	4.0
	Meropenem (MERO)	94.1	2.9	2.9	97.4	0.0	2.6	2.9
	Doripenem (DOR)	97.8	0.7	1.5	100.0	0.0	0.0	1.1
Cephalosporins	Cefepime (FEP)	80.9	4.4	14.7	97.4	0.0	2.6	12.0
	Ceftazidime (TAZ)	89.7	3.7	6.6	92.3	2.6	5.1	6.3
	Cefotaxime (FOT)	66.2	2.2	31.6	92.3	0.0	7.7	26.3
Lipopeptides	Colistin (COL)	80.9	2.9	16.2	92.3	5.1	2.6	13.1
	Polymixin B (POL)	69.1	15.4	15.4	82.1	15.4	2.6	12.6
β-lactam/β-lactam inhibitors	Ampicillin/sulbactam 2∶1 ratio (A/S2)	66.2	11.8	22.1	74.4	20.5	5.1	18.3
	Piperacillin/tazobactam constant 4 (P/T4)	96.3	1.5	2.2	100.0	0.0	0.0	1.7
	Ticarcillin/clavulanic acid constant 2 (TIM2)	67.7	27.2	5.2	76.9	20.5	2.6	4.6

Note: The six districts of Beijing includes Dongcheng, Xicheng, Haidian, Fengtai, Chaoyang, and Changping.
[*] S% means the percentage of isolates that were sensitive to a specific antimicrobial.
[†] I% means the percentage of isolates that were intermediate resistant to a specific antimicrobial.
[§] R% means the percent of isolates that were resistant to a specific antimicrobial.

humans, chicken, and pork, with ST10 dominated among the most common types from animal-derived foods, which is rarely found in humans (Supplementary Figure S2, available in http://weekly.chinacdc.cn/). Thus, we speculated that the risk of *E. coli* isolates passing through the food chain was relatively low.

DISCUSSION

In this study, we determined the prevalence and characteristics of foodborne pathogen *E. coli* in retail meat in six districts of Beijing, China. The prevalence of *E. coli* was 73.9% in chicken samples and 42.86% in pork. Greater contamination of chicken than pork concurs with previous findings (*10*). These results indicated that *E. coli* contamination of raw chicken in Beijing was a serious public health problem. Thus, better measures should be taken to control *E. coli* contamination in chicken. Antimicrobial susceptibility test in this study demonstrated that all the 186 *E. coli* isolates were highly resistant to at least one tested antibiotic class (sulfonamides, aminoglycosides, tetracyclines, fluoroquinolones, penicillins, carbapenems, cephalosporins, lipopeptides, and β-lactam/β-lactam inhibitors). The highest resistance to trimethoprim/sulfamethoxazole (87.4%) was observed, which might be due to sulfonamides being used widely in animal husbandry in China (*11*). Nowadays, the average resistance rates in *E. coli* to representatives of these antibiotic classes were higher than 40% (*12*). Eating retail chicken and pork without strict hygiene supervision should be avoided. These results highlight the contamination status of antibiotic resistant *E. coli* and provide an important reference value for the risk assessment and control of multidrug-resistant bacteria.

ESBL genes were located on plasmids that can be

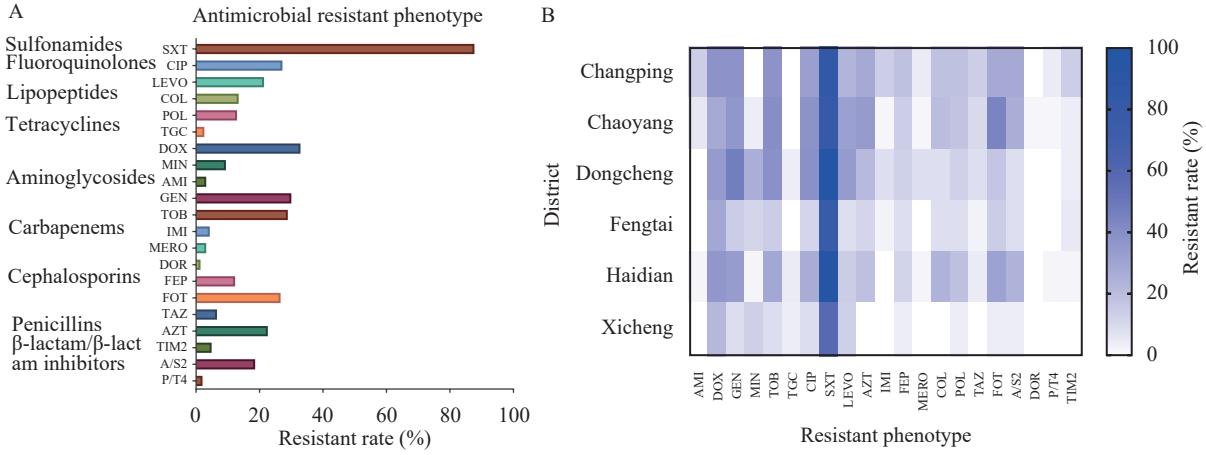

FIGURE 1. Phenotypic resistance of *Escherichia coli* isolates in raw meat sample from six districts, Beijing, China, 2020. (A) Resistant rate of all *E. coli* isolates against nine different antibiotic classes. (B) Distribution of *E. coli* resistant phenotypes from different districts in Beijing.
Note: The six districts of Beijing includes Dongcheng, Xicheng, Haidian, Fengtai, Chaoyang, and Changping.
Abbreviations: SXT=trimethoprim/sulfamethoxazole; CIP=ciprofloxacin; LEVO=levofloxacin; COL=colistin; POL=polymyxin B; TGC=tigecycline; DOX=doxycycline; MIN=minocycline; AMI=amikacin; GEN=gentamicin; TOB=tobramycin; IMI=imipenem; MERO=meropenem; DOR=doripenem; FEP=cefepime; FOT=cefotaxime; TAZ=ceftazidime; AZT=aztreonam; TIM2=ticarcillin/clavulanic acid constant 2; A/S2=ampicillin/sulbactam 2:1 ratio; P/T4=piperacillin/tazobactam constant 4.

easily transferred between and within bacterial species. In this study, the resistance gene *ampC1* and *ampC2* were highly observed in all isolates, and detection rates were 94.7%, 99.4%, respectively. However, the detection rate of *E. coli ampC* in retail chicken from 2013–2014 (45.0%) dropped to 13.4% in 2018, UK (*13*). Wu et al. (*14*) reported the ESBL gene and *mcr-1* prevalence of chicken-derived *E. coli* in many provinces in China and found the detection rate of $bla_{\text{CTX-M}}$ was 92.7%. The enrichment and changes of *E. coli ampC* resistance genes in raw meat sources in China are higher than those in other countries. With the increasing selection of β -lactam drugs, it will continue to mutate and spread in the food supply chain, causing serious public health problems. Among all the ESBL-producing *E. coli* isolates, the carrying rate of $bla_{\text{CTX-M}}$ was 33.1%, $bla_{\text{CTX-M-9}}$ and $bla_{\text{CTX-M-1}}$ were the dominant subtypes. The carrying rate of $bla_{\text{CTX-M-9}}$ was 48.7%. The ST10 is a well-known clonal lineage (mainly harboring CTX-M gene); it is also known that some of the Inc plasmids were implicated in the spread of beta-lactamases genes and other genes encoding resistance to antibiotics. Our WGS results indicated that 76 of the ESBL-producing *E. coli* isolates had 31 distinct STs, and ST10 was the most prevalent (9/76, 11.8%). Colistin serves as the "last line of defense" for the clinical treatment of gram-negative bacterial infections (*15*). With the discovery of *mcr* family, China has banned the use of colistin as a feed additive to prevent the dissemination of the gene. However, we found high levels of *mcr-1* in chicken-derived *E. coli*, which suggests that we should strengthen strict monitoring of food-borne pathogens in animal-derived foods that carry such drug-resistant genes.

This study has several limitations. The geographical distribution of the samples in this study was mainly concentrated in the central urban area, not representative of the entirety Beijing. The number of isolated strains of *E. coli* in retail pork samples was small, and strengthening the supervision of the strains in pork samples is necessary in future studies.

This study was a typical survey of the prevalence of *E. coli* in animal-derived foods in six districts of Beijing, China. *E. coli* contamination in chicken was more serious than that in pork. The isolates showed multi-drug resistance phenotypes, especially sulfonamides and tetracyclines. The β -lactamase genes *ampC1* and *ampC2* were the main drug resistance genes, and the colistin resistance gene *mcr-1* was found at a high level in chicken-derived *E. coli*. Considering the multidrug resistance of *E. coli* in animal-derived foods, especially ESBL-producing *E. coli*, continuous monitoring the emergence and spread of MDR *E. coli* would facilitate disease control and treatment. Further national or regional multicenter studies are necessary to assess the dissemination and evolution of MDR *E. coli* in both clinical medicine and food animal production in China.

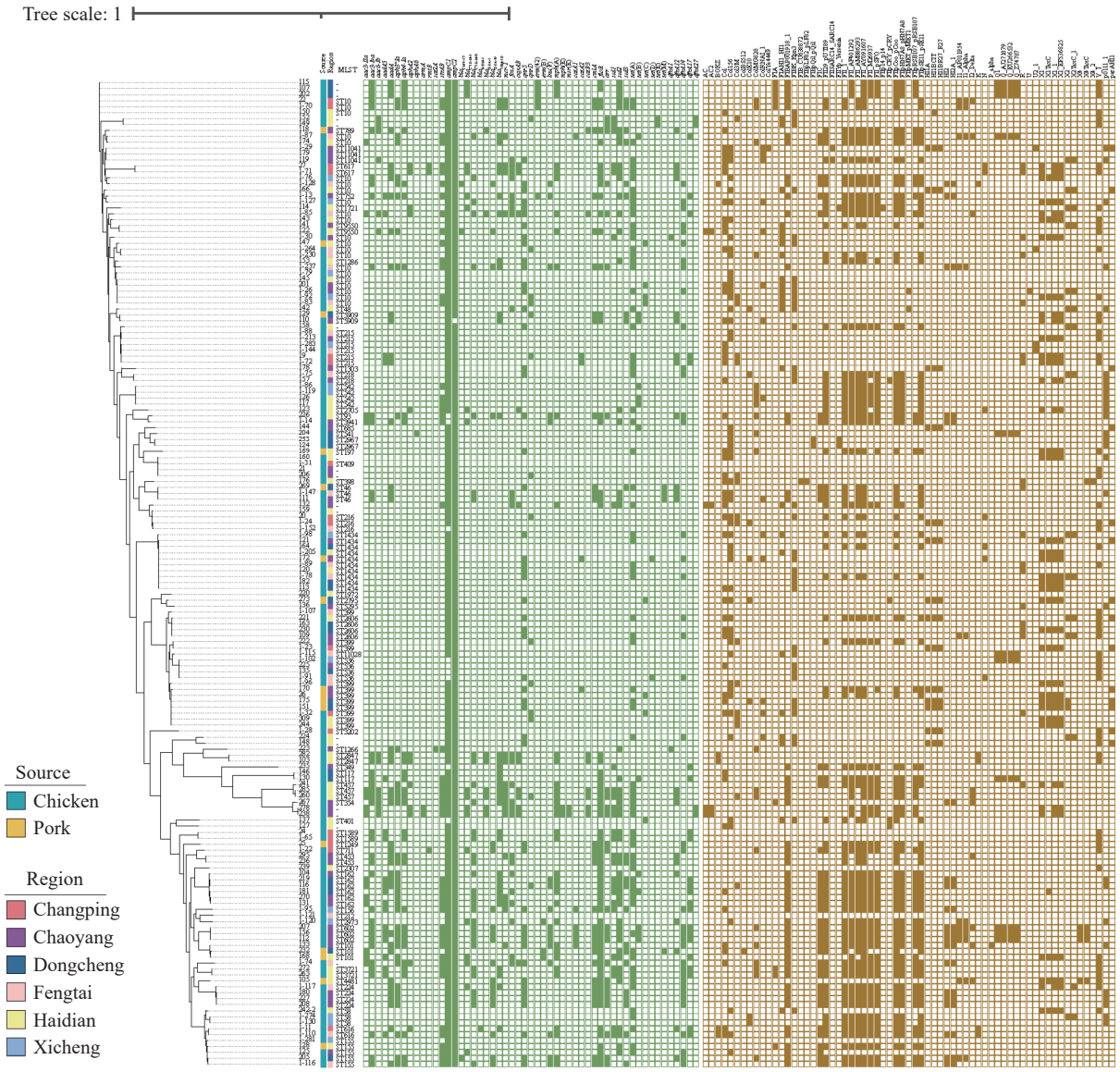

FIGURE 2. Distributions of STs, antimicrobial resistance genes, and plasmid typing among 166 *Escherichia coli* isolates from chicken and pork across the phylogenetic tree.
Note: The color strips indicate areas corresponding to the isolates. Green colored cells represent the presence of genes and white cells represent the absence of the genes. Brown colored cells represent the presence of plasmid typing and white cells represent the absence of the plasmids.

Conflicts of interest: No conflicts of interest.

Funding: This work was supported by grants from the National Key Research and Development Program of China (2018YFD0500305) and Capital Health Research and Development of Special Funding (Grant No. 2018-4-3017).

doi: 10.46234/ccdcw2021.243

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Submitted: October 30, 2021; Accepted: November 16, 2021

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SUPPLEMENTARY MATERIALS

METHODS

Sample Collection, Isolation and Identification

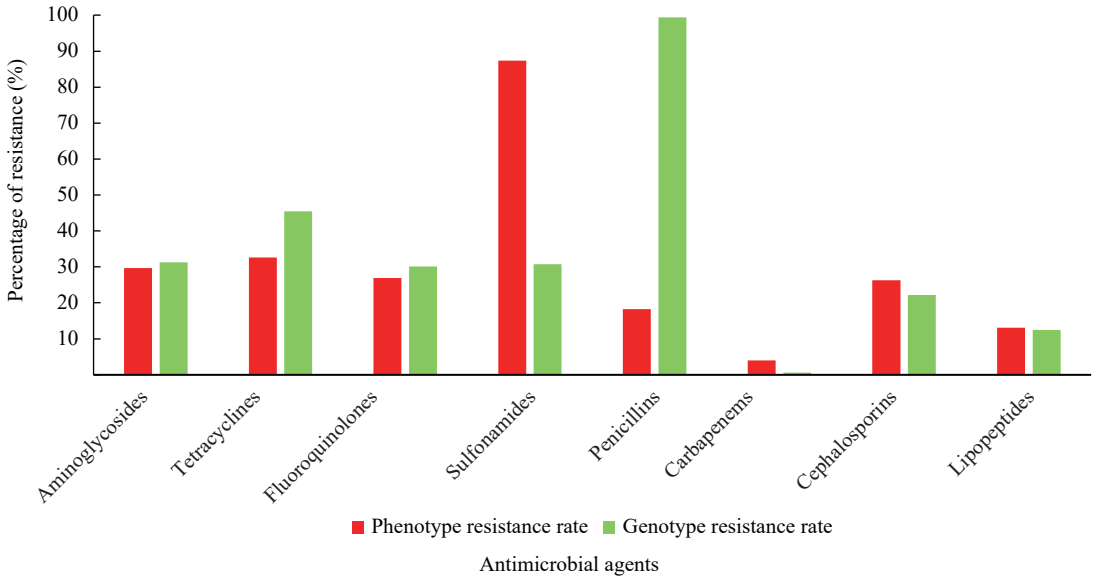
From July to October 2020, a total of 290 animal-derived food samples (91 pork and 199 chicken samples) were collected from 16 large supermarket chains and farmers' markets in 6 districts of Beijing Municipality. The specific collected samples commercially available cuts of pork meat and commercially available chicken cuts. After all samples were collected, they are collected in Labplas TWIRL'EM sterile homogeneous bags (Labplas, Canada) and brought to the laboratory for testing. A single sample was placed in a sterile sampling bag to prevent cross-contamination during sample collection. The target strains were isolated as previously described (*1*), and the brief description was shown as following: 10 mL brain heart infusion (BHI) broth (Land Bridge, Beijing, China) was used to wash the sample surface, transfer to a 10 mL EP tube, and incubation at 37 °C for 24 h. 0.5–1 mL of the enrichment culture obtained was cultured on CHROMagar^{TM} ECC medium (CHROMagar, France) and inoculated at 37 °C for 24 h. The blue colonies on the plate were further purified using Luria agar (LA) and identified by matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) mass spectrometry analysis.

Antimicrobial Susceptibility Testing

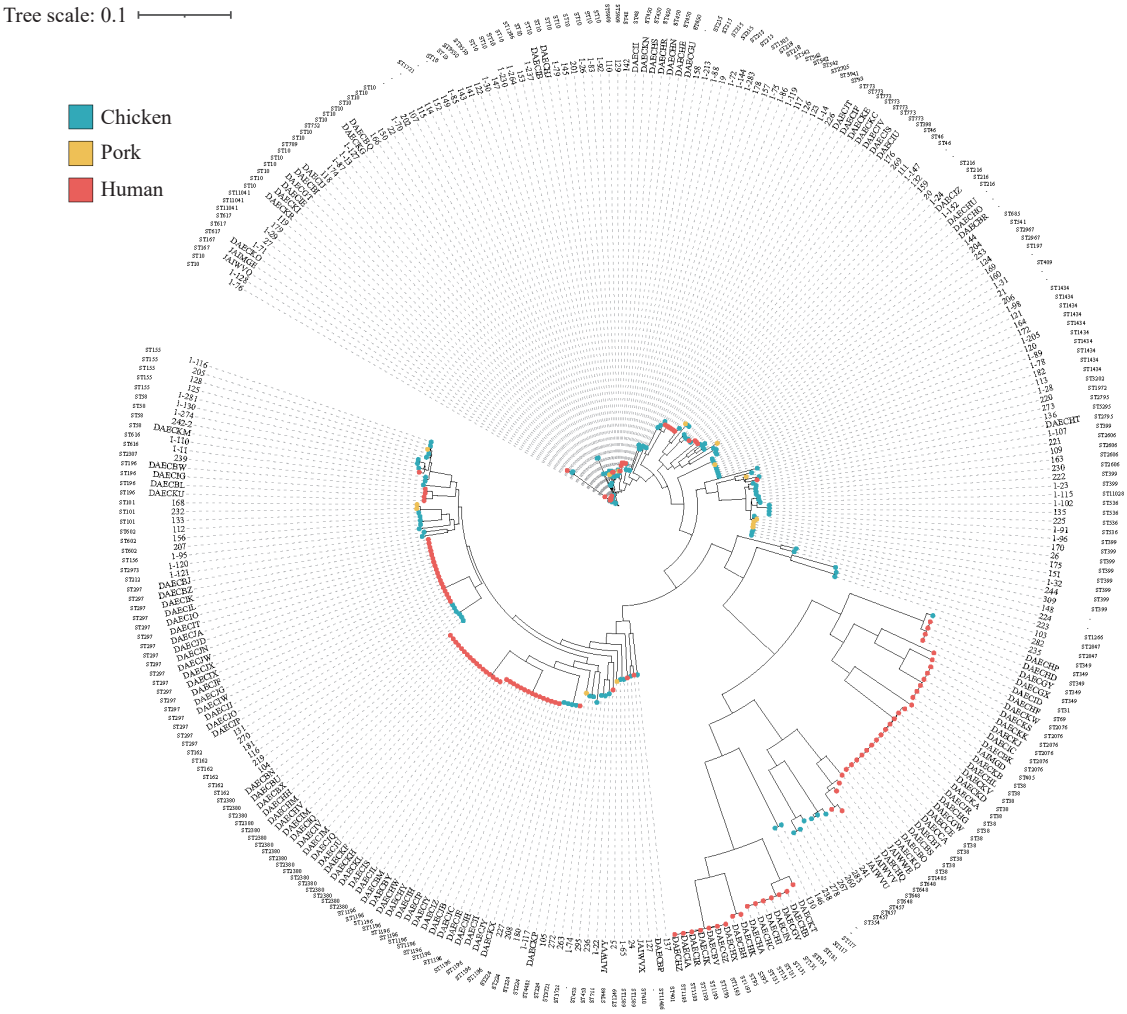
The gram-negative bacteria drug sensitivity plates Sensititre GNX3F were used for the antibiotic susceptibility test of the isolated strains according to the recommendations of the Clinical and Laboratory Standards Institute guidelines (CLSI, M100-S30) (*2*) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) standard v10.0 (*3*). *E. coli* ATCC25922 was used as the quality control strain.

Whole Genome Sequencing

Genomic DNA from *E. coli* isolates was extracted for whole genome sequencing using the Wizard Genomic DNA Purification Kit (Promega, Madison, WI, US) following the manufacturer's instructions. The DNA libraries were constructed using a KAPA Hyper Prep Kit (Roche, Basel, Switzerland). Sequencing was carried out with Illumina Novaseq 6000 platform (Illumina, San Diego, CA), which generated 150-bp paired-end reads from a library with an average insert size of 350 bp. Raw sequence data of *E. coli* isolates were assembled using SPAdes v3.13.1 (*4*) via the



SUPPLEMENTARY FIGURE S1. Correlation analysis of antimicrobial resistance genotype and phenotype of *Escherichia coli* isolates.



SUPPLEMENTARY FIGURE S2. Phylogenetic analysis of *Escherichia coli* isolates of animal-derived foods (n=166) and human clinic (n=146).
Note: A midpoint-rooted maximum-likelihood phylogenetic tree was constructed using core-genome single-nucleotide polymorphisms (SNPs).

Unicycler v0.4.7 (*5*) assembly pipeline. Additional genomes were downloaded from the National Center for Biotechnology Information (NCBI) Pathogen detection database (https://www.ncbi.nlm.nih.gov/pathogens/isolates#/search/). There were n=806 isolates retrieved with the search criteria"species_taxid:562" and "geo_loc_name: Beijing*" (*E. coli* from Beijing) on November 12th 2021. Among which, 422 clinical isolates collected from *Homo sapiens* were selected. Furthermore, 146 *E. coli* genomes collected between 2018–2021 were downloaded using collection time and WGS accession as filter criteria.

Phylogenetic Analysis

The full set of 312 genomes were used to generate a core-genome SNP alignment and construct a phylogenetic tree, using Parsnp v1.1.2 in the Harvest package (*6*). The mid-point rooted phylogenetic tree was annotated in ITOL (https://itol.embl.de/). To estimate the *E. coli* population structure, we used hierBAPS v6.0 software (*7*) to identified the Bayesian model-based population structures. BAPS groups were assigned based on single-nucleotide polymorphisms (SNPs) were identified with SAMtools v1.3.1 (*8*) using RedDog v1bata.11 (https://github.com/katholt/RedDog) pipeline in the core genome of the *E. coli* strains.

SUPPLEMENTARY TABLE S1. Characteristic and prevalence of *Escherichia coli* isolates from the 6 districts, Beijing, China, 2020.

Region	Chicken		Pork		Total isolating rate (%)
	No. of isolates	Isolating rate (%)	No. of isolates	Isolating rate (%)	
Dongcheng	18	85.7	5	41.7	63.7
Xicheng	14	73.7	8	66.7	70.2
Haidian	32	94.7	5	33.3	60.6
Fengtai	24	50.0	10	45.5	47.7
Chaoyang	43	95.6	6	33.3	65.2
Changping	16	80.0	5	41.7	67.0
Total	147	73.9	39	42.9	64.1

Note: The six districts of Beijing includes Dongcheng, Xicheng, Haidian, Fengtai, Chaoyang, and Changping. The primary objective of the present study was to investigate the isolating rate and prevalence of *E. coli* isolates in Chicken and Pork from the six districts, Beijing, China, in 2020.

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Vital Surveillances

Surveillance of Multidrug-Resistant Bacterial Infections in Non-Adult Patients — Zhejiang Province, China, 2014–2019

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ABSTRACT

Introduction: Antimicrobial resistance has become a major public health threat globally. The prevalence of multidrug-resistant (MDR) bacterial infections increased substantially among inpatients under 18 years of age in recent years. In Zhejiang Province, China, the trends of drug-resistance in non-adult patients from 2014 to 2019 were monitored, aiming to determine the variation patterns and epidemiological features of MDR strains.

Methods: Patient data were collected from the Annual Review of Hospital Infection Resistance Survey in Zhejiang Province, 2014–2019. Statistical analysis was performed to analyze the pattern of distribution of five key bacterial pathogens in different age groups, ward settings, and bloodstream infections.

Results: From 2014 to 2019, a total of 30,163 multidrug-resistant strains were identified among 212,252 clinical isolates. The prevalence of extended spectrum β-lactamase-producing Enterobacteriaceae (ESBL-E), carbapenem-resistant Enterobacteriaceae (CRE), carbapenem-resistant *Acinetobacter baumannii*, carbapenem-resistant *Pseudomonas aeruginosa* (CRPA), and methicillin-resistant *Staphylococcus aureus* (MRSA) were 40.6%, 2.3%, 14.7%, 9.0%, and 27.4%, respectively. The prevalence of these key pathogens was lower than that reported in the national surveillance system (China Antimicrobial Resistance Surveillance System and Infectious Diseases Surveillance of Pediatrics). The prevalence of ESBL-E and CRE decreased since 2015 but that of CRPA and MRSA increased from 2014 to 2018.

Conclusions: Despite an overall decrease in the prevalence of drug-resistant bacteria in 2019, the rising prevalence of MRSA and CRPA still warrant much attention. Multidrug-resistant bacteria prevention and control strategies should be adjusted in a timely manner based on the surveillance results.

The prevalence of bacterial resistance to antibiotics has risen globally since mid-1990s, posing a severe risk to public health (*1*). Multidrug-resistant (MDR) organisms, which were defined as a strain resistant to three or more classes of antimicrobial drugs within the antimicrobial spectrum, pose an increasing challenge to global health.

Despite the increasing global attention to MDR infection, little research has been conducted on MDR infections in non-adult populations. Few available data suggested that epidemiology, risk factors, and outcomes of MDR infections were comparable with those observed in adults (*2*).

Most of the MDR organisms in Chinese children showed decreasing trends in recent years, except for imipenem-resistant *Escherichia coli*, imipenem-resistant *Klebsiella pneumoniae,* and methicillin-resistant *Staphylococcus aureus* (MRSA) (*2*). It is undeniable that multidrug-resistant bacterial infections lead to longer hospital stays and higher mortality rate (*3*). Among them, carbapenem-resistant *Acinetobacter baumannii* (CRAB), carbapenem-resistant *Pseudomonas aeruginosa* (CRPA), carbapenem-resistant Enterobacteriaceae (CRE), and extended spectrum β-lactamase-producing Enterobacteriaceae (ESBL-E) were classified as critical priority pathogens and MRSA as high priority pathogen in the *Priority Pathogens List* of the World Health Organization (WHO). Infections caused by those key pathogens have aroused wide public concern.

Constant surveillance of the epidemiological trends of drug-resistant organisms is critical since MDR infections remain strongly associated with treatment failures and high mortality rates, particularly among pediatric patients. This report provides valuable information on MDR organism infections in non-adults in Zhejiang Province that could help facilitate better infection control and healthcare.

METHODS

Clinical data were obtained from the Annual Review of Hospital Infection Resistance Survey in Zhejiang Province, 2014–2019. Hospitals that participated in the study were distributed across 11 cities in Zhejiang Province: Hangzhou, Jiaxing, Huzhou, Shaoxing, Ningbo, Zhoushan, Taizhou, Jinhua, Quzhou, Lishui, and Wenzhou. Hospitals in China are classified into 3 categories (primary, secondary, and tertiary institutions) based on their medical service capacity. All the hospitals in the study were secondary or tertiary hospitals accredited to perform pathogen identification and anti-microbial susceptibility testing (Supplementary Table S1, available at http://weekly.chinacdc.cn/). The prevalence of CRE, ESBL-E, CRAB, CRPA, and MRSA isolates were determined by analyzing data exported from WHONET software (version 5.6, WHO) with SPSS software (version 23.0, SPSS Inc., Chicago, IL, USA). In group comparisons, Pearson's chi-square and Fisher's exact tests were used. In all models, there was statistical significance with $P<0.05$.

RESULTS

A total of 212,252 non-duplicate strains collected from 2014 to 2019 were analyzed in this study. Among them, 30,163 strains were found to be multidrug-resistant. These included 15,758 ESBL-producing strains of the Enterobacteriaceae family (ESBL-E, accounting for 40.6% of Enterobacteriaceae strains), 1,349 CRE (2.3% of Enterobacteriaceae), 881 CRAB (14.7% of *Acinetobacter baumannii*), 507 CRPA (9.0% of *Pseudomonas aeruginosa*), and 11,668 MRSA (27.4% of *Staphylococcus aureus*). MRSA and ESBL-E were the most common pathogens, accounting for 90.9% of all drug-resistant infections (52.2% for ESBL-E and 38.7% for MRSA infections). Sample characteristics were provided in the Supplementary Table S1.

The prevalence of CRAB, CRE, CRPA, MRSA, and ESBL-E recorded in different years were displayed in Figure 1. The prevalence of CRE decreased from 2.7% (95% CI 2.4%–3.0%) in 2016 to 2.1% (95% CI 1.9%–2.4%) in 2019, and the prevalence of ESBL-E also consistently declined from 42.7% (95% CI 41.2%–44.2%) in 2014 to 39.4% (95% CI 38.2%–40.6%) in 2019. The highest prevalence of CRAB (19.8%, 95% CI 17.6%–22.1%), was recorded in 2015, and a decrease was observed afterwards. It is worth noting that the prevalence of CRPA fluctuated during 2014–2016 and increased significantly from 7.18% (95% CI 5.2%–9.5%) in 2017 to 12.7% (95% CI 10.6%–15.0%) in 2019. MRSA appeared to be another emerging threat. The prevalence of MRSA increased significantly from 24.3% (95% CI 23.1%–25.6%) in 2014 to 29.2% (95% CI 28.2%–30.2%) in 2018 and remained at a high level (27.2%, 95% CI 26.3%–28.2%) after dropping in

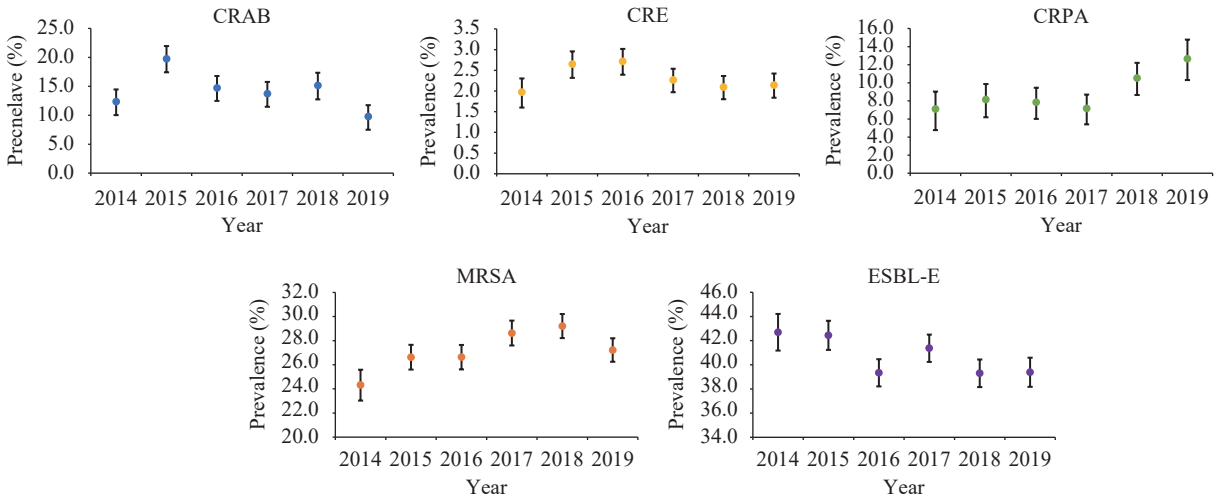

FIGURE 1. The prevalence of CRAB, CRE, CRPA, MRSA, and ESBL-E in non-adult patients — Zhejiang Province, 2014–2019.
Note: The error bars represent 95% CI of the prevalence.
Abbreviations: CRAB=carbapenem-resistant *Acinetobacter baumannii*; CRE=carbapenem-resistant Enterobacteriaceae; CRPA=carbapenem-resistant *Pseudomonas aeruginosa*; MRSA=methicillin-resistant *Staphylococcus aureus*; ESBL-E=extended-spectrum β-lactamase-producing Enterobacteriaceae.

TABLE 1. Prevalence and risk analysis of critical pathogens in intensive care unit (ICU) and non-ICU groups in non-adult patients — Zhejiang Province, 2014–2019.

Pathogens	ICU	2014				2015				2016			
		Positive	Prevalence (%) (95% CI)	Odds ratio (95% CI)	*P*	Positive	Prevalence (%) (95% CI)	Odds ratio (95% CI)	*P*	Positive	Prevalence (%) (95% CI)	Odds ratio (95% CI)	*P*
CRAB (n=889)	Yes	50	38.8 (30.3–47.7)	7.4 (4.7–11.5)	<0.001	113	50.5 (43.3–56.7)	6.7 (4.9–9.3)	<0.001	110	43.7 (37.4–50.0)	12.0 (8.2–17.5)	<0.001
	No	60	7.9 (6.1–10.0)	1		130	12.9 (10.9–15.2)	1		51	6.1 (4.5–7.9)	1	
CRE (n=6,278)	Yes	17	5.7 (3.3–8.9)	3.3 (2.0–5.6)	<0.001	54	7.1 (5.4–9.2)	3.3 (2.4–4.4)	<0.001	54	6.0 (4.5–7.7)	2.6 (1.9–3.5)	<0.001
	No	107	1.8 (1.5–2.2)	1		210	2.3 (2.0–2.6)	1		239	2.4 (2.1–2.7)	1	
CRPA (n=604)	Yes	18	31.0 (19.5–44.5)	9.4 (4.7–18.6)	<0.001	31	24.4 (24.7–45.2)	9.5 (5.6–16.1)	<0.001	30	29.1 (20.6–38.9)	7.2 (4.3–12.1)	<0.001
	No	25	4.6 (3.0–6.7)	1		43	5.3 (3.8–7.0)	1		48	5.4 (4.0–7.1)	1	
MRSA (n=4,361)	Yes	33	21.4 (15.2–28.2)	0.8 (0.6–1.2)	0.393	101	40.9 (34.7–47.3)	2.0 (1.5–2.5)	<0.001	108	41.2 (35.2–47.4)	2.0 (1.5–2.6)	<0.001
	No	1,028	24.4 (23.1–25.8)	1		1,824	26.1 (25.1–27.2)	1		1,852	26.1 (25.1–27.1)	1	
ESBL–E (n=4,124)	Yes	93	45.1 (38.2–52.2)	1.1 (0.8–1.5)	0.467	254	49.3 (44.9–53.7)	1.4 (1.1–1.6)	0.001	307	47.2 (43.3–51.1)	1.4 (1.2–1.7)	<0.001
	No	1,668	42.6 (41.0–44.1)	1		2,525	41.9 (40.6–43.1)	1		2565	38.6 (37.4–39.8)	1	

Pathogens	ICU	2017				2018				2019			
		Positive	Prevalence (%) (95% CI)	Odds ratio (95% CI)	*P*	Positive	Prevalence (%) (95% CI)	Odds ratio (95% CI)	*P*	Positive	Prevalence (%) (95% CI)	Odds ratio (95% CI)	*P*
CRAB (n=889)	Yes	86	32.2 (26.6–38.2)	6.1 (4.2–8.9)	<0.001	84	40.0 (34.2–48.0)	7.7 (5.3–11.2)	<0.001	33	24.4 (17.5–32.6)	4.4 (2.7–7.3)	<0.001
	No	55	7.2 (5.5–9.3)	1		64	8.3 (6.4–10.5)	1		45	6.8 (5.0–9.0)	1	
CRE (n=6,278)	Yes	56	5.3 (4.0–6.8)	2.8 (2.1–3.8)	<0.001	41	4.9 (3.5–6.5)	2.7 (1.9–3.8)	<0.001	38	4.7 (3.3–6.4)	2.5 (1.8–3.6)	<0.001
	No	189	1.9 (1.7–2.2)	1		174	1.8 (1.6–2.1)	1		170	1.9 (1.6–2.2)	1	
CRPA (n=604)	Yes	26	23.9 (16.2–33.0)	5.8 (3.4–9.8)	<0.001	39	33.1 (24.7–42.3)	5.6 (3.6–8.7)	<0.001	36	33.3 (24.6–43.1)	4.6 (2.9–7.3)	<0.001
	No	46	5.1 (3.8–6.8)	1		88	8.1 (6.5–9.9)	1		77	9.8 (7.8–12.1)	1	
MRSA (n=4,361)	Yes	83	29.0 (23.8–34.7)	1.0 (0.8–1.3)	0.883	123	41.4 (35.5–46.9)	1.7 (1.4–2.2)	<0.001	102	34.3 (29.0–40.0)	1.4 (1.1–1.8)	0.005
	No	2,058	28.6 (27.6–29.7)	1		2,238	28.8 (27.7–29.8)	1		2,118	27.0 (26.0–28.0)	1	
ESBL–E (n=4,124)	Yes	411	52.8 (49.2–56.3)	1.7 (1.4–1.9)	<0.001	320	53.8 (49.7–57.8)	1.9 (1.6–2.2)	<0.001	258	43.4 (39.4–47.5)	1.2 (1.0–1.4)	0.034
	No	2,630	40.0 (38.8–41.2)	1		2,464	38.0 (36.8–39.2)	1		2,263	39.0 (37.7–40.2)	1	

Abbreviations: CRAB=carbapenem-resistant *Acinetobacter baumannii*; CRE=carbapenem-resistant Enterobacteriaceae; CRPA=carbapenem-resistant *Pseudomonas aeruginosa*; MRSA=methicillin-resistant *Staphylococcus aureus*; ESBL-E=extended-spectrum β-lactamase-producing Enterobacteriaceae.

2019.

The prevalence and risk analysis of CRAB, CRE, CRPA, MRSA, and ESBL-E in ICU and non-ICU groups were described in Table 1. The prevalence and odds ratio (OR) in ICU group were significantly higher than that in non-ICU group. For CRAB, CRE, and CRPA, the prevalence and OR of ICU group were significantly higher than that in non-ICU group (P<0.001). For MRSA, the prevalence was close in ICU and non-ICU groups in 2014 and 2017, and the OR was not statistically significant in these years. For the remaining year, High prevalence and OR of MRSA in ICU group were observed (P<0.05). For ESBL-E, the prevalence in both the non-ICU group and the ICU group showed a high level, 38.0% to 42.6%, respectively. The OR in ICU group was slightly higher than that in non-ICU group.

Prevalence and risk levels of CRAB, CRE, CRPA, MRSA, and ESBL-E in different age groups were shown in Table 2. For CRAB, the age group with the lowest risk was 1 to 5 years old, and the highest risk age group was 15 to 17 years old. For CRE, the lowest risk age group in 2014 was found to be among children less than 1 year old; all the other age groups exhibited significantly higher risk (P=0.014, <0.05). The prevalence of CRPA in different age groups varied like that of CRAB during the study period, with the lowest risk age group being 1 to 5 years old, and the highest risk age group being 15 to 17 years old. For MRSA, the age group <1 years exhibited the highest risk. The age group <1 years also exhibited the highest risk of ESBL-E infection from 2014 onwards, and other age groups showed similar risk level.

Regarding antimicrobial resistance (AMR) in bloodstream infection (BSI) (Table 3), CRAB exhibited no significant difference between BSI and non-BSI consistently for six years. The risk level of CRE in BSI was significantly higher than non-blood samples (except for in 2014 and in 2018, P>0.05). For CRPA, no significant risk was found, but the prevalence decreased from 12.5% (95% CI 1.6%–38.3%) in 2014 to 3.0% (95% CI 0.1%–15.8%) in 2019. The prevalence of MRSA remained stable throughout, and the risk level in blood samples was only significantly higher than that of non-blood samples in 2015 (OR=1.4, 95% CI 1.0–2.1, P=0.037, <0.05). The prevalence of ESBL-E decreased since 2014 and there was no significant change in the risk of ESBL-E in BSI from 2015 to 2019.

CONCLUSIONS

The overall prevalence of five key pathogens were lower than that recorded in the China Antimicrobial Resistance Surveillance System (CARSS) and Infectious Diseases Surveillance of Pediatrics (ISPED). Comparison of results from ISPED 2017–2019 (*4-6*) indicated that the prevalence of CRE not only remained at a low level (2.0% to 2.7% from our data *vs*. 8.2% to 10.8% from ISPED), but also exhibited a decreasing trend since 2016 (P=0.004, <0.05). The only exception is carbapenem-resistant *Klebsiella pneumonia*, being an upward trend observable in ISPED (*6*). Though the prevalence of CRPA was lower than the data from ISPED (*5*), the prevalence has risen continuously since 2017. ESBL-E decreased since 2014 but the prevalence remained at a high level. The decrease was also observed in CRAB since 2015 and the prevalence recorded each year was lower than that of CARSS (*2*). The prevalence of MRSA kept increasing in the first few years (24.3% in 2014 to 29.2% in 2018) but then fell in 2019 (27.2%). The trend and prevalence of MRSA was in general agreement with the report of CARSS (27.5%–29.5%) (*2*). These data suggested that the prevalence of MRSA and CRPA should be prioritized due to their high prevalence and increasing trends.

Investigating the pattern of pathogens in the ICU environment, especially for MDR organisms, will help develop specific prevention and control strategies. A recent study in a tertiary teaching hospital in western China reported that *Acinetobacter baumannii* was the leading cause of infection in almost every ICU (*7*). In this study, ESBL-E was the most prevalent pathogen in ICU non-adult patients in Zhejiang Province (43.4% to 53.8%). High prevalence of CRAB, CRPA, and MRSA were also reported, suggesting a complex ICU environment. Risk analysis identified ICU admission as a risk factor for MDR infection, especially those due to CRAB (OR ranged from 4.4 to 12.0) and CRPA (OR ranged from 4.6 to 9.5). This finding is consistent with previous studies (*8–9*). Therefore, monitoring the pathogens exposure and incident infections in ICU environment is critical.

Bloodstream infections (BSIs) represent a major cause of mortality and morbidity worldwide. In addition, antimicrobial-resistant organisms, most notably MRSA and ESBL-E, have emerged as the important etiological agents of community-acquired BSI (*10*). In our study, the prevalence of ESBL-E was the most common pathogen of bloodstream infections,

TABLE 2. Prevalence and risk analysis of critical pathogen in different age groups of non-adult patients — Zhejiang Province, 2014–2019.

Pathogens	Age group, years	2014				2015				2016			
		Positive	Prevalence (%) (95% CI)	Odds ratio (95% CI)	*P*	Positive	Prevalence (%) (95% CI)	Odds ratio (95% CI)	*P*	Positive	Prevalence (%) (95% CI)	Odds ratio (95% CI)	*P*
CRAB (n=889)	<1	23	14.9 (9.7–21.6)	1.9 (1.1–3.3)	<0.001	113	28.8 (24.4–33.6)	3.0 (2.2–4.3)	<0.001	71	23.1 (18.5–28.3)	5.7 (3.5–9.2)	<0.001
	1–5	39	8.6 (6.2–11.5)	1		61	11.8 (9.1–14.8)	1		25	5.0 (3.3–7.3)	1	
	6–14	26	12.0 (8.0–17.1)	1.5 (0.9–2.5)		37	14.5 (10.4–19.4)	1.3 (0.8–2.0)		41	17.6 (12.9–23.1)	4.0 (2.4–6.8)	
	15–17	22	34.9 (23.3–48.0)	5.7 (3.1–10.6)		32	50.8 (37.9–63.6)	7.8 (4.4–13.6)		24	44.4 (30.9–58.6)	15.2 (7.8–29.7)	
CRE (n=6,278)	<1	16	1.0 (0.6–1.7)	1	0.014	82	2.8 (2.2–3.4)	1	<0.001	94	3.0 (2.4–3.6)	1	<0.001
	1–5	66	2.3 (1.8–3.0)	1.3 (1.3–4.0)		96	2.4 (1.9–2.9)	0.9 (0.6–1.2)		92	2.2 (1.8–2.7)	0.7 (0.5–1.0)	
	6–14	31	2.1 (1.4–2.9)	2.0 (1.1–3.7)		54	2.2 (1.6–2.8)	0.8 (0.5–1.1)		71	2.5 (2.2–3.2)	0.9 (0.6–1.2)	
	15–17	11	2.8 (1.4–5.0)	2.8 (1.3–6.0)		32	6.3 (4.4–8.8)	2.4 (1.6–3.6)		36	6.3 (4.4–8.5)	2.2 (1.5–3.2)	
CRPA (n=604)	<1	8	8.5 (3.7–16.1)	2.9 (1.0–7.9)	0.014	20	11.0 (6.9–16.5)	2.1 (1.1–4.1)	0.009	27	15.7 (10.6–22.0)	3.4 (1.9–6.2)	<0.001
	1–5	8	3.1 (1.4–6.1)	1		20	5.5 (3.4–8.3)	1		21	5.2 (3.3–7.9)	1	
	6–14	13	6.4 (3.5–10.7)	2.1 (0.9–5.2)		23	7.8 (5.0–11.5)	1.5 (0.8–2.7)		24	7.2 (4.7–10.5)	1.4 (0.8–2.6)	
	15–17	14	26.9 (15.6–41.0)	11.4 (4.5–28.9)		11	16.4 (8.5–27.5)	3.4 (1.5–7.5)		6	7.1 (2.7–14.9)	1.4 (0.5–3.6)	
MRSA (n=4,361)	<1	330	36.8 (33.6–40.0)	3.5 (2.3–5.2)	<0.001	497	30.9 (28.6–33.2)	1.3 (1.0–1.6)	<0.001	531	27.8 (25.8–29.9)	1.1 (0.8–1.4)	0.308
	1–5	465	22.6 (20.8–24.5)	1.7 (1.2–2.6)		924	26.0 (24.6–27.5)	1.0 (0.8–1.3)		890	26.8 (25.3–28.4)	1.1 (0.8–1.3)	
	6–14	236	19.7 (17.5–22.1)	1.5 (1.0–2.2)		418	24.0 (22.0–26.1)	0.9 (0.7–1.2)		456	25.1 (23.2–27.2)	0.9 (0.7–1.2)	
	15–17	30	14.4 (9.9–19.9)	1		86	26.2 (21.5–31.3)	1		83	26.2 (21.4–31.4)	1	
ESBL–E (n=4,124)	<1	556	53.0 (49.9–56.1)	2.0 (1.5–2.7)	<0.001	1,002	52.1 (49.8–54.4)	2.0 (1.6–2.6)	<0.001	1025	44.8 (42.8–46.9)	1.6 (1.2–2.0)	<0.001
	1–5	738	40.2 (38.0–42.5)	1.2 (0.9–1.6)		1,004	39.4 (37.5–41.3)	1.2 (0.9–1.5)		970	36.7 (34.9–38.6)	1.1 (0.9–1.4)	
	6–14	383	38.0 (35.0–41.1)	1.1 (0.8–1.5)		665	37.6 (35.4–39.9)	1.1 (0.9–1.4)		762	37.4 (35.3–39.6)	1.2 (0.9–1.5)	
	15–17	84	35.9 (29.8–42.4)	1		108	35.2 (29.8–40.8)	1		115	33.9 (28.9–39.2)	1	

TABLE 2. (Continued)

Pathogens	Age group, years	2017				2018				2019			
		Positive	Prevalence (%) (95% CI)	Odds ratio (95% CI)	*P*	Positive	Prevalence (%) (95% CI)	Odds ratio (95% CI)	*P*	Positive	Prevalence (%) (95% CI)	Odds ratio (95% CI)	*P*
CRAB (n=889)	<1	41	14.6 (10.7–19.3)	1.8 (1.1–2.9)	<0.001	27	11.9 (8.0–16.8)	1.4 (0.8–3.2)	<0.001	16	8.2 (4.8–13.0)	0.9 (0.5–1.7)	<0.001
	1–5	35	8.8 (6.2–12.0)	1		39	8.9 (6.4–11.9)	1		31	9.0 (6.2–12.5)	1	
	6–14	38	14.1 (10.2–18.9)	1.7 (1.0–2.8)		42	18.4 (13.6–24.1)	2.3 (1.4–3.7)		19	8.8 (5.4–13.3)	1.0 (0.5–1.8)	
	15–17	27	33.8 (23.6–45.2)	5.3 (3.0–9.4)		40	48.2 (37.1–59.4)	9.5 (5.6–16.4)		12	28.6 (15.7–44.6)	4.0 (1.9–8.7)	
CRE (n=6,278)	<1	83	2.7 (2.1–3.3)	1	0.002	74	2.2 (1.8–2.8)	1	<0.001	75	2.4 (1.9–3.0)	1	0.014
	1–5	70	1.8 (1.4–2.2)	0.7 (0.5–0.9)		55	1.5 (1.2–2.0)	0.7 (0.5–1.0)		59	1.8 (1.4–2.3)	0.7 (0.5–1.1)	
	6–14	68	2.1 (1.7–2.7)	0.8 (0.6–1.1)		59	2.1 (1.6–2.7)	0.9 (0.7–1.3)		53	1.9 (1.4–2.5)	0.8 (0.5–1.1)	
	15–17	24	4.0 (2.6–5.9)	1.5 (1.0–2.4)		27	4.6 (3.0–6.6)	2.1 (1.3–3.3)		21	3.8 (2.3–5.7)	1.6 (1.0–2.6)	
CRPA (n=604)	<1	14	7.9 (4.4–12.8)	1.8 (0.8–3.6)	0.007	24	10.6 (6.9–15.2)	1.5 (0.8–2.5)	<0.001	14	8.4 (4.7–13.7)	0.9 (0.5–1.7)	0.001
	1–5	18	4.7 (2.8–7.3)	1		33	7.5 (5.2–10.4)	1		33	9.4 (6.6–13.0)	1	
	6–14	28	7.8 (5.2–11.0)	1.7 (0.9–3.2)		38	8.9 (6.4–12.1)	1.2 (0.7–2.0)		50	16.4 (12.5–21.1)	1.9 (1.2–3.0)	
	15–17	12	15.6 (8.3–25.6)	3.8 (1.7–8.2)		32	28.1 (20.1–37.3)	4.8 (2.8–8.3)		16	22.2 (13.3–33.6)	2.7 (1.4–5.3)	
MRSA (n=4,361)	<1	638	32.1 (30.1–34.2)	1.3 (1.0–1.7)	0.001	709	31.5 (29.6–33.5)	1.1 (0.9–1.4)	0.041	597	29.5 (27.5–27.5)	1.1 (0.9–1.4)	0.074
	1–5	890	27.4 (25.9–29.0)	1.1 (0.8–1.4)		939	28.4 (26.9–30.0)	1.0 (0.8–1.2)		933	26.4 (25.0–27.9)	1.0 (0.8–1.2)	
	6–14	534	27.5 (25.5–29.5)	1.1 (0.8–1.4)		599	28.0 (26.1–29.9)	0.9 (0.7–1.2)		586	26.4 (24.6–28.3)	1.0 (0.7–1.2)	
	15–17	79	26.3 (21.4–31.7)	1		114	29.5 (25.0–34.3)	1		104	27.3 (22.9–32.1)	1	
ESBL–E (n=4,124)	<1	1030	47.7 (25.5–49.8)	1.5 (1.2–1.9)	<0.001	969	42.4 (40.4–44.5)	1.5 (1.2–1.9)	<0.001	891	42.8 (40.7–45.0)	1.5 (1.2–1.9)	<0.001
	1–5	968	39.1 (37.2–41.1)	1.1 (0.9–1.3)		935	39.8 (37.8–41.8)	1.4 (1.1–1.7)		718	38.0 (35.8–40.2)	1.2 (1.0–1.6)	
	6–14	899	38.6 (36.6–40.6)	1.1 (0.8–1.3)		759	36.5 (34.4–38.6)	1.2 (0.9–1.5)		789	38.4 (36.2–40.5)	1.3 (1.0–1.6)	
	15–17	144	37.3 (32.5–42.3)	1		121	32.6 (27.9–37.6)	1		123	33.2 (28.4–38.2)	1	

Abbreviations: CRAB=carbapenem-resistant *Acinetobacter baumannii*; CRE=carbapenem-resistant Enterobacteriaceae; CRPA=carbapenem-resistant *Pseudomonas aeruginosa*; MRSA=methicillin-resistant *Staphylococcus aureus*; ESBL-E=extended-spectrum β-lactamase-producing Enterobacteriaceae.

TABLE 3. Prevalence and risk analysis of critical pathogen in BSI non-adult patients — Zhejiang Province, 2014–2019.

BSI		2014				2015				2016			
		Positive	Prevalence (%) (95% CI)	Odds ratio (95% CI)	*P*	Positive	Prevalence (%) (95% CI)	Odds ratio (95% CI)	*P*	Positive	Prevalence (%) (95% CI)	Odds ratio (95% CI)	*P*
CRAB (n=889)	Yes	5	23.8 (8.2–47.2)	2.3 (0.8–6.3)	0.202	6	20.0 (7.7–38.6)	1.0 (0.4–2.5)	0.973	5	20.0 (6.8–40.7)	1.5 (0.5–4.0)	0.641
	No	105	12.1 (10.0–14.5)	1		237	19.8 (17.5–22.1)	1		156	14.6 (12.5–16.9)	1	
CRE (n=6,278)	Yes	6	2.3 (0.8–4.8)	1.2 (0.5–2.6)	0.737	23	4.8 (3.1–7.1)	1.9 (1.2–3.0)	0.003	23	4.3 (2.8–6.5)	1.7 (1.1–2.6)	0.018
	No	118	2.0 (1.6–2.3)	1		241	2.5 (2.2–2.9)	1		270	2.6 (2.3–3.0)	1	
CRPA (n=604)	Yes	2	12.5 (1.6–38.3)	1.9 (0.4–8.7)	0.722	7	14.9 (6.2–28.3)	2.1 (0.9–4.8)	0.145	3	13.0 (2.8–33.6)	1.8 (0.5–6.2)	0.587
	No	41	7.0 (5.0–9.3)	1		67	7.8 (6.1–9.8)	1		75	7.7 (6.1–9.6)	1	
MRSA (n=4,361)	Yes	25	29.1 (19.8–39.9)	1.3 (0.8–2.1)	0.301	49	34.3 (26.5–42.7)	1.4 (1.0–2.1)	0.037	56	31.5 (24.7–38.8)	1.3 (0.9–1.8)	0.141
	No	1,036	24.2 (23.0–25.5)	1		1876	26.5 (25.5–27.5)	1		1904	26.5 (25.5–27.6)	1	
ESBL–E (n=4,124)	Yes	91	53.8 (46.0–61.5)	1.6 (1.2–2.2)	0.003	102	37.9 (32.1–44.0)	0.8 (0.6–1.1)	0.125	143	41.6 (36.3–47.0)	1.1 (0.9–1.4)	0.386
	No	1,670	42.2 (40.7–43.8)	1		2,677	42.6 (41.4–43.9)	1		2,729	39.2 (38.1–40.4)	1	

BSI		2017				2018				2019			
		Positive	Prevalence (%) (95% CI)	Odds ratio (95% CI)	*P*	Positive	Prevalence (%) (95% CI)	Odds ratio (95% CI)	*P*	Positive	Prevalence (%) (95% CI)	Odds ratio (95% CI)	*P*
CRAB (n=889)	Yes	7	26.9 (11.6–47.8)	2.4 (1.0–5.8)	0.091	9	33.3 (16.5–54.0)	2.9 (1.3–6.6)	0.016	3	16.7 (3.6–41.4)	1.9 (0.5–6.6)	0.554
	No	134	13.4 (11.3–15.7)	1		139	14.6 (12.4–17.0)	1		75	9.6 (7.6–11.9)	1	
CRE (n=6,278)	Yes	29	5.9 (4.0–8.4)	2.9 (2.0–4.4)	<0.001	14	3.0 (1.6–4.9)	1.5 (0.8–2.5)	0.174	18	4.3 (2.6–6.8)	2.2 (1.3–3.6)	0.002
	No	216	2.1 (1.8–2.4)	1		201	2.1 (1.8–2.4)	1		190	2.0 (1.8–2.4)	1	
CRPA (n=604)	Yes	3	13.6 (2.9–34.9)	2.1 (0.6–7.2)	0.442	3	9.4 (2.0–25.0)	0.9 (0.3–2.9)	1	1	3.0 (0.1–15.8)	0.2 (0.0–1.5)	0.153
	No	69	7.0 (5.5–8.8)	1		124	10.6 (8.9–12.5)	1		112	13.0 (10.9–15.5)	1	
MRSA (n=4,361)	Yes	33	25.8 (18.5–34.3)	0.9 (0.6–1.3)	0.471	52	34.9 (27.3–43.1)	1.3 (0.9–1.8)	0.123	41	29.3 (21.9–37.6)	1.1 (0.8–1.6)	0.581
	No	2,108	28.7 (27.7–29.7)	1		2,309	29.1 (28.1–30.1)	1		2179	27.2 (26.2–28.2)	1	
ESBL–E (n=4,124)	Yes	145	43.4 (38.0–48.9)	1.1 (0.9–1.4)	0.44	134	41.6 (36.2–47.2)	1.1 (0.9–1.4)	0.385	117	41.2 (35.4–47.2)	1.1 (0.8–1.4)	0.522
	No	2,896	41.3 (40.1–42.4)	1		2,650	39.2 (38.0–40.4)	1		2,404	39.3 (38.1–40.5)	1	

Abbreviations: BSI=blood stream infection; CRAB=carbapenem-resistant *Acinetobacter baumannii*; CRE=carbapenem-resistant Enterobacteriaceae; CRPA=carbapenem-resistant *Pseudomonas aeruginosa*; MRSA=methicillin-resistant *Staphylococcus aureus*; ESBL-E=extended-spectrum β-lactamase-producing Enterobacteriaceae.

followed by MRSA. The results agreed with the observations from a population-based and large multicenter cohort study in the US and Europe (*11*). The high prevalence of ESBL-E may be related to inappropriate antibiotic use. One study showed that clinical isolation of ESBL-producing *E. coli* or ESBL-producing *Klebsiella* spp. was closely linked to the third-generation cephalosporin treatment (*12*).

In China, third-generation cephalosporin is the most common antibiotics to treat infections in neonates and older children and therefore may be overused in hospitals (*13*). MRSA is another critical pathogen associated with significant clinical morbidity and mortality. The prevalence of MRSA in adults is stable in Zhejiang Province and is similar to that in children (from 33.0% in 2014 to 29.8% in 2017) according to the China Antimicrobial Surveillance Network (*14*). In addition, the MDR pathogens responsible for BSI vary significantly in different regions in China. The predominant pathogen of BSI in our study is ESBL-E, whereas MRSA was the predominant BSI pathogen in Hubei Province (*15*). Risk analysis indicated that BSI had been a risk factor for CRE infection for many years, but a significant difference was not observed among other bacterial groups.

Surveillance carried out in Zhejiang Province indicated that great attention should be paid to MDR organisms, especially for CRPA and MRSA. Some measures should be taken to alleviate the threat of AMR. On the one hand, for hospital-acquired infections, it is necessary to monitor the ICU environment, where broad-spectrum antibiotic use and the presence of MDR bacteria are common. On the other hand, antimicrobial stewardship programs should be advocated, especially for antibiotic prescription in the community since, in accordance with China Health Care Policy, pediatric patients were referred to community hospitals first, where the misuse and overuse of antibiotics occur frequently. Encouragingly, the government of China has started explorations of AMR. In 2016, National Action Plan for Containing Antibacterial Resistance (2016–2020) was published, aiming at reducing antimicrobial resistance through the synergy between national, regional, and local levels. Surveillance of MDR pathogens in clinical patients is necessary for monitoring AMR.

There were some limitations in this surveillance study. First, due to the differences in medical conditions, data collected from hospitals in rural areas might be lower than the actual value. Second, symptomatic patients were more likely to visit medical institutions compared with asymptomatic ones, which may lead to selection bias. Finally, the lack of available data on antibiotic prescription in the community may influence the analysis of community-sourced infection.

In conclusion, conducting surveillance of multidrug-resistant bacterial infections in non-adult patients to depict the prevalence and variation trends will support better diagnosis and clinical treatment.

doi: 10.46234/ccdcw2021.244

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Submitted: September 05, 2021; Accepted: November 16, 2021

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SUPPLEMENTARY TABLE S1. Statistical summary of patient recruitment data collected during the study period of 2014–2019, Zhejiang Province.

Item	All years (n=125), No. (%)	2014 (n=42), No. (%)	2015 (n=79), No. (%)	2016 (n=88), No. (%)	2017 (n=84) No. (%)	2018 (n=84), No. (%)	2019 (n=94), No. (%)
Age							
<1 year	53,809 (25.4)	4,754 (21.0)	8,735 (24.7)	9,576 (22.8)	10,001 (25.8)	11,081 (30.0)	9,662 (26.3)
1–5 year	95,639 (45.1)	11,212 (49.4)	16,420 (46.5)	20,701 (49.1)	16,570 (42.8)	15,054 (40.8)	15,682 (42.7)
6–14 year	52,815 (24.9)	5,437 (24.0)	8,516 (24.1)	9,786 (23.3)	10,361 (26.8)	9,060 (24.6)	9,655 (26.3)
15–17 year	9,989 (4.7)	1,286 (5.7)	1,658 (4.7)	1,865 (4.4)	1,762 (4.6)	1,702 (4.6)	1,716 (4.7)
Outpatient/inpatient							
Outpatient	24,185 (11.4)	3,556 (15.7)	4,385 (12.4)	4,265 (10.2)	4,230 (10.9)	3,093 (8.4)	4,656 (12.7)
Inpatient	188,067 (88.6)	19,133 (84.3)	30,944 (87.6)	37,663 (89.8)	34,464 (89.1)	33,804 (91.6)	32,059 (87.3)
No. of hospital beds							
<800	26,322 (12.4)	1,314 (5.8)	4,416 (12.5)	4,918 (11.7)	5,219 (13.7)	4,225 (11.5)	6,158 (16.8)
≥800	185,930 (87.6)	21,375 (94.5)	30,913 (87.5)	37,010 (88.3)	33,403 (86.3)	32,672 (88.5)	30,557 (83.2)
Hospital rank							
Tertiary-A hospital	156,016 (73.5)	17,635 (77.7)	26,093 (73.9)	27,505 (65.6)	29,127 (75.3)	28,410 (77.0)	27.246 (74.2)
Tertiary-B hospital	42,189 (19.9)	5,054 (22.3)	7,138 (20.2)	11,400 (27.2)	6,990 (18.1)	6,079 (16.5)	5,528 (15.1)
Secondary-A hospital	13,207 (6.2)	0	1,968 (5.6)	2,898 (6.9)	2,328 (6.2)	2,188 (5.9)	3,771 (10.3)
Secondary-B hospital	840 (0.4)	0	130 (0.4)	125 (0.3)	195 (0.5)	220 (0.5)	170 (0.5)
Location							
Northern plain	107,262 (50.5)	10,680 (47.1)	19,092 (54.0)	22,730 (54.2)	19,801 (51.2)	17,734 (48.1)	17,225 (46.9)
Coastal area	77,764 (36.3)	9,229 (40.7)	11,990 (33.9)	13,689 (32.6)	13,591 (35.1)	14,759 (40.0)	14,506 (39.5)
Inland area	27,226 (12.8)	2,780 (12.3)	4,247 (12.0)	5,509 (13.1)	5,302 (13.7)	4,404 (11.9)	4,984 (13.6)
City							
Hangzhou	57,054 (26.9)	2,839 (12.5)	10,477 (29.7)	10,346 (24.7)	12,219 (31.6)	11,090 (30.1)	10,083 (27.5)
Jiaxing	30,029 (14.1)	5,427 (23.9)	5.766 (16.3)	5,105 (12.2)	5,163 (13.3)	4,107 (11.1)	4,461 (12.2)
Huzhou	3,946 (1.9)	955 (4.2)	882 (2.5)	832 (2.0)	291 (0.8)	215 (0.6)	771 (2.1)
Shaoxing	16,233 (7.6)	1,459 (6.4)	1,967 (5.6)	6,447 (15.3)	2,128 (5.5)	2,322 (6.3)	1,910 (5.2)
Ningbo	17,265 (8.1)	689 (3.0)	3,134 (8.9)	3,325 (7.9)	3,101 (8.0)	3,470 (9.4)	3,546 (9.7)
Taizhou	18,172 (8.6)	2,031 (9.0)	1,549 (4.4)	3,462 (8.3)	3,072 (7.9)	4,169 (11.3)	3,889 (10.6)
Wenzhou	39,903 (18.8)	6,076 (26.8)	6,943 (19.7)	6,473 (15.4)	7,056 (18.2)	6,690 (18.1)	6,665 (18.2)
Zhoushan	2,424 (1.1)	433 (1.9)	364 (1.0)	429 (1.0)	362 (0.9)	430 (1.2)	406 (1.1)
Jinhua	13,874 (6.5)	1,701 (7.5)	2,330 (6.6)	3,259 (7.8)	3,157 (8.2)	1,768 (4.8)	1,659 (4.5)
Lishui	8,476 (4.0)	516 (2.3)	1,436 (4.1)	1,291 (3.1)	1,232 (3.2)	1,619 (4.4)	2,182 (6.5)
Quzhou	4,876 (2.3)	563 (2.5)	481 (1.4)	595 (2.3)	913 (2.4)	1,017 (2.8)	943 (2.6)

Indexed by PubMed Central (PMC) and Emerging Sources Citation Index (ESCI).

The inauguration of *China CDC Weekly* is in part supported by Project for Enhancing International Impact of China STM Journals Category D (PIIJ2-D-04-(2018)) of China Association for Science and Technology (CAST).

CCDC weekly

Vol. 3 No. 47 Nov. 19, 2021

Responsible Authority
National Health Commission of the People's Republic of China

Sponsor
Chinese Center for Disease Control and Prevention

Editing and Publishing
China CDC Weekly Editorial Office
No.155 Changbai Road, Changping District, Beijing, China
Tel: 86-10-63150501, 63150701
Email: weekly@chinacdc.cn

CSSN
ISSN 2096-7071
CN 10-1629/R1