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Antimicrobial prescribing for children in China: data from point prevalence surveys in 18 tertiary centres in China in 2016–2017

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ABSTRACT

Objectives The reports on evaluating the classification of antibiotic agents prescribed for Chinese children by combining WHO's and China's administrative categories were rare. This study aimed to investigate the pattern of antimicrobial agents prescribing for Chinese children in 2016.

Settings 18 tertiary centres from nine provinces located in northern, southern, eastern and western China.

Participants The antimicrobial prescribing data from the children admitted in medical wards, surgical wards and intensive care units were collected and analysed. A total of 3680 antibiotic prescriptions for Chinese children were included in the analysis.

Primary and secondary outcome measures One-day point-prevalence surveys (PPSs) on antimicrobial prescribing were conducted among hospitalised children in China between 1 February 2016 and 28 February 2017. Five hospitals participated in the first PPS, 13 hospitals in the second PPS, 17 hospitals in the third PPS and 18 hospitals in the fourth PPS. Patterns of antibiotic use with a drug utilisation of 90%, Anatomical Therapeutical Chemical Classification, WHO Access, Watch and Reserve (AWaRe) (version 2019) and antibiotic classification in China were described retrospectively.

Results A total of 4442 children and 3680 antibiotic prescriptions for Chinese children were included in the analysis. 2900 (65.3%) children received at least one ongoing antibiotic during the survey days. On the basis of WHO AWaRe classification, the proportion of antibiotics in the Watch group was 76.5% (2814/3680). According to the Management of Antibiotic Classification in China, 56.8% (2089/3680) and 16.1% (594/3680) of antibiotic prescriptions in the Restricted group and the Special group, respectively, were included into broad-spectrum antibiotics. The most common indication for antibiotics was bacterial lower respiratory tract infection (2044/3680, 55.5%).

Conclusions The use of broad-spectrum antibiotics was frequent and excessive in hospitalised children in China in 2016.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This study was a multicentre survey covering nine provinces and increasing representativeness.
- ⇒ This study focused on describing the classification pattern of antibiotic prescriptions in clinical practice in Chinese children in terms of both the WHO access, watch and reserve and the Management of Antibiotic Classification in China, which were different.
- ⇒ It was difficult to determine appropriateness of antibiotic use because of lack of microbiology and antimicrobial susceptibility results and detailed patient characteristics.

INTRODUCTION

Antimicrobial resistance is a threat to society, the economy and life in the 21st century. Exposure to antibiotics is associated with the development of antimicrobial resistance. Broad-spectrum antibiotics have higher resistance potential and should be prioritised as key targets of local and national stewardship programmes and monitoring.

In response to increasing antimicrobial resistance, WHO adopted a global action plan on antimicrobial resistance, and one of objectives is to optimise the use of antimicrobial medicines. In December 2011, the National Health Commission of the People's Republic of China launched a special campaign to improve the use of antibiotic agents, which produced remarkable achievements. The antibiotic utilisation rate declined from 76.0% (30568/40221) to 50.3% (35493/70544) and antibiotic use density from 38.4 to 19.4 defined daily dose (DDDs)/100 bed-days before (2010–2011) and after (2016–2017) antimicrobial stewardship programme. These two indicators of antimicrobial management had both been greatly reduced following this campaign.[1] However, these two indicators (ie, antibiotic usage rate and antibiotic use density) do not reflect the types of antimicrobial agents that are used. Hence, these indicators cannot be used as metrics to assess the classifications of antibiotics. In the past 10 years, more attention has been paid to the antibiotic usage rate and total antibiotic consumption, both of which have consequently been reduced in China. However, the proportion of bacteria producing extra-broad-spectrum β lactamases and carbapenem-resistant organisms are high and have been increasing year by year.[2] Therefore, it is particularly important to assess the relative use of broad-spectrum antibiotics by children in China. The 21st WHO Expert Committee on the Selection and Use of Essential Medicines divided antibacterial agents for children with the most frequent and severe bacterial infections into three groups: Access, Watch and Reserve (AWaRe). AWaRe classification was established in 2017 and revised in 2019 to include also antibiotics not listed on the WHO Model List of Essential Medicines.[3]

Under the guidance of the National Health Commission of the People's Republic of China, the provinces have formulated that antibacterial drugs be divided into specific subgroups. According to safety, efficacy, bacterial resistance and price, antibacterial drugs are divided into three levels of subgroups: Unrestricted, Restricted and Special group.[4]

Both the AWaRe classification and China's administrative categories of antibiotics, as simple metrics for antimicrobial stewardship, may help to estimate the relative use of narrow-spectrum and broad-spectrum antibiotics prescribed for children in clinical practice in China. Currently, no previous studies have reported changes in antibiotic usage patterns before and after the implementation of special campaign by the national antimicrobial stewardship in 2011.

In the present study, the types of antimicrobial agents were analysed by China's administrative categories of antibiotics and the WHO Essential Medicines List of AWaRe to determine antibiotic patterns in 2016 in Chinese children.

METHODS

Data collection

Four 1 day point-prevalence surveys (PPS) were completed in February–March 2016, May–June 2016, September–October 2016 and December 2016 through February 2017. A total of 18 hospitals from nine provinces from northern, southern, eastern and western China joined in this project in China. Children (age range: birth to 18 years old) who were hospitalised in participating hospitals were included in this survey. Thirteen children's hospitals, paediatric wards from two general hospital and three women and children's healthcare centres participated into this cross-sectional study. All participating hospitals were tertiary. Each participating hospital assigned a physician to collect and upload data to a web-based electronic data collection system. Indications for antibiotics would be determined by the main diagnoses in the hospital records. The case report form for data collection was fully structured to ensure the standardisation and completeness of data entry. All the doctors who collected the data were trained to understand the definitions of each field before they started collecting data, and they would receive research project documents. The antimicrobial prescribing data from the children admitted in medical wards (general paediatric wards and special medical wards including respiratory, infectious diseases and neonatology wards), surgical wards and intensive care units (ICUs) (neonatal intensive care units and paediatric intensive care units) were collected and analysed. The participation in this study was voluntary.

A web-based electronic data capture (https://pidrg-database.sgul.ac.uk/redcap/) was used to collect data and all participating centres logged into this database and entered their data online. This survey collected detailed information of patients who were prescribed antibiotics and the antimicrobial agents that they used (as well as their doses and routes of administration). Five hospitals participated in the first PPS, 13 hospitals in the second PPS, 17 hospitals in the third PPS and 18 hospitals in the fourth PPS. Five hospitals participated in all of four PPSs, eight hospitals in three PPSs, four hospitals in two PPSs and one hospital in only one PPS.

Only systemic antibiotics—such as intravenous, intramuscular and oral antibiotics—were included in this study, while inhaled or skin application antibiotics were excluded. For example, gentamicin was included when administered intramuscularly, where as it was excluded when it was inhaled.

Antifungal, antiviral or antituberculous agents (rifampicin, isoniazid, pyrazinamide and ethambutol) were excluded when the data were analysed. When rifampicin was combined with other antitubercular agents such as isoniazid, pyrazinamide or ethambutol, it was considered as antitubercular agent. Otherwise, rifampicin was considered as an antibacterial drug.

Statistical analysis

We described patterns of antibiotic use with a drug utilisation 90%, defined as the number of antibiotics that accounted for 90% of the total antibiotics prescriptions.[5] Antibiotic prescriptions were classified on the basis of the Anatomical Therapeutical Chemical Classification (ATC Classification), WHO AWaRe and antibiotic classification in China were supplied by the detailed antibiotics in each category.

According to ATC classification, the antibiotics were classified into macrolides, penicillins, penicillins plus enzyme inhibitors, first-generation cephalosporins, second-generation cephalosporins, third-generation cephalosporins (with or without enzyme inhibitor), fourth-generation cephalosporins, carbapenems, glycopeptides, fluoroquinolones and aminoglycosides.

The WHO Essential Medicines for Children defines antibiotics into three groups: Access, Watch, and Reserve antibiotics.[3] The Access group includes antibiotics that are widely available, affordable and reliable and are recommended as the first or second choice for common infectious diseases. The Watch group includes antibiotics that have higher resistance potential and are only recommended as first choice or second choice treatments for a limited number of specific infectious syndromes. The Reserve group includes antibiotics that should be tailored to highly specific patients and settings, when all alternatives have failed or are not suitable.[3] The antibiotics included in WHO Essential Medicines List for Children were shown in online supplemental table 1.[6]

In China's administrative categories of antibiotics, antibacterial drugs are divided into the following three levels of subgroups based on some factors such as safety, efficacy, bacterial resistance and price: Unrestricted, Restricted and Special groups.[4] The Unrestricted group contains narrow-spectrum antibiotics that are safe, affordable and effective for common infections. The Restricted group antibiotics have a higher potential bacterial resistance and/or a higher price. The Special group includes antibiotics that can cause adverse effects, are expensive and/or induce multidrug resistance probably. The Special group antibiotic lists in different hospitals in China were the same. However, the Unrestricted group and Restricted group antibiotic lists were based on the province and similar. The Unrestricted group and Restricted group antibiotic lists in this study were integrated from Shenzhen Children's Hospital (located in southern China) and Tianjin Children's Hospital (located in northern China) catalogues. A list of Unrestricted, Restricted and Special group of antibiotics in China for this study was shown in online supplemental table 2. The WHO AWaRe classification and matched China classification of antibiotics were described in online supplemental table 3.

For the statistical analysis, Microsoft Excel 2007 (Microsoft Corporation, Washington, USA) and SPSS V.22.0 (IBM) were used.

Patient and public involvement

Patients or the public were not involved in the design, or conducting, or reporting or dissemination plans of this survey.

RESULTS

Antimicrobial prescription patterns based on antimicrobial agents and ATC classification in 2016

In the PPS in 2016, a total of 4442 children and 3680 antibiotic prescriptions for Chinese children were included in the analysis. Two thousand nine hundred (65.3%) children received at least one ongoing antibiotic during the survey days. The characteristics of participating hospitals by frequency of antibiotic prescriptions in 2016 are shown in table 1.

The five most common classes of antimicrobials prescribed for children in 2016 were third-generation cephalosporins (1372, 37.3%), beta lactam-beta lactamase inhibitors (636, 17.3%), macrolides (593, 16.1%), carbapenems (373, 10.1%) and second-generation cephalosporins (227, 6.2%) (figure 1).

In 2016, the top five antimicrobials prescribed for children—which accounted for 48.4% of all antimicrobial use—were azithromycin (411, 11.2%), amoxicillin and enzyme inhibitors (374, 10.2%), latamoxef (346, 9.4%), ceftriaxone (327, 8.9%) and ceftizoxime (324, 8.8%) (figure 2).

In the top 10 antimicrobial agents, only two agents that were amoxicillin and enzyme inhibitor (374, 10.2%) and piperacillin and enzyme inhibitor (151, 4.1%) were included into penicillins. Penicillins without enzyme inhibitors including benzylpenicillin, oxacillin and other penicillins only accounted for 3.9% (142/3680).

Four agents accounting for 32.0% (1176/3680) were included in the third-generation cephalosporins. The antimicrobial agent prescribed commonly in the third-generation cephalosporins was latamoxef (346, 9.4%), which was not included in the WHO Essential Medicines List.

Meropenem and vancomycin were classified into Watch group based on WHO AWaRe classification and the Special group based on the Management of Antibiotic Classification in China accounted for 8.4% (308/3680) and 3.3% (120/3680).

One thousand and thirty-four antibiotic prescriptions were used for children in the ICUs, 635 for neonates in neonatal ICUs and 399 for children in paediatric ICUs. The top three antimicrobials prescribed for children and neonates in ICUs were meropenem (179/1034, 17.3%), amoxicillin and enzyme inhibitors (153/1034, 14.8%), and latamoxef (93/1034, 9.0%). The three most common classes of antimicrobials prescribed for children and neonates in ICUs that accounted for 71.0% were third-generation cephalosporins (317/1034, 30.7%), carbapenems (207/1034, 20.0%) and beta lactam-beta lactamase inhibitors (210/1034, 20.3%). In neonatal ICUs, the top three antimicrobials prescribed were amoxicillin and enzyme inhibitors (147/635, 23.1%), meropenem (111/635, 17.5%) and latamoxef (77/635, 12.1%). In PICUs, the top three antimicrobials prescribed were meropenem (68/399, 17.0%), cefoperazone/sulbactam (54/399, 13.5%) and vancomycin (48/399, 12.0%).

Antibiotic classes prescribed pattern based on the WHO Access/Watch/eserve group

According to the WHO AWaRe, 66 antibiotic agents were included in the survey in 2016. There were 19 (28.8%) agents in the Access group, accounting for 15.0% (552/3680) of antibiotic prescriptions. There were 39 (59.1%) agents in the Watch group, accounting for 76.5% (2814/3680) of antibiotic prescriptions. There were four (6.1%) agents in the Reserve group, accounting for 1.6% (58/3680) of antibiotic prescriptions. There were two (3.0%) agents in the not-recommended group, accounting for 6.6% (242/3680) of antibiotic prescriptions. In ICUs (n=1034), there were 234 (22.6%) prescriptions in the Access group, 692 (66.9%) in the Watch group and 18 (1.7%) in the Reserve group.

Table 1 The characteristics of participating hospitals by frequency of antibiotic prescriptions in 2016

Hospital	City	Total beds	Total patients	Patients prescribed antibiotics	Rates of antibiotic therapy (%)	Types of antibiotics	Frequency of antibiotics prescriptions	No. of antibiotic prescriptions/ patients prescribed antibiotics
H1	Beijing	613	582	495	85.1	24	689	1.4
H2	Beijing	98	96	60	62.5	6	90	1.5
H3	Beijing	70	65	48	73.8	8	55	1.1
H4	Chongqing	307	282	145	51.4	24	178	1.2
H5	Shanghai	162	136	91	66.9	22	122	1.3
H6	Guangdong	95	90	65	72.2	11	90	1.4
H7	Guangdong	353	346	173	50.0	21	218	1.3
H8	Shandong	381	389	239	61.4	23	302	1.3
H9	Shandong	698	559	345	61.7	22	424	1.2
H10	Shanghai	108	108	106	98.1	12	166	1.6
H11	Guangdong	253	230	72	31.3	18	83	1.2
H12	Guangdong	307	274	146	53.3	19	158	1.1
H13	Zhejiang	204	196	158	80.6	20	188	1.2
H14	Jilin	104	112	90	80.4	11	127	1.4
H15	Shanghai	231	231	128	55.4	18	164	1.3
H16	Tianjin	273	272	212	77.9	7	244	1.2
H17	Shaanxi	187	183	171	93.4	22	198	1.2
H18	Zhejiang	291	291	156	53.6	23	184	1.2
Total		4735	4442	2900	65.3	66	3680	1.3

There were 66 types of antimicrobial agents in total, and 20 (30.3%) antimicrobial agents accounted for 90% of antimicrobial use.

In the watch group (n=2814), azithromycin accounting for 14.6% (411/2814) was the antibiotic most commonly used, followed by latamoxef (346/2814, 12.3%), ceftriaxone (327/2814, 11.6%), ceftizoxime (324/2814, 11.5%) and meropenem (308/2814,10.9%). The detailed antibiotic types in every group based on the WHO AWaRe classifications were shown in table 2.

Antibiotic classes prescribed pattern based on China's administrative categories of antibiotics

According to the Management of Antibiotic Classification in China, 67 antibiotic agents were included in the survey in 2016. There were 17 (25.4%) types of antibiotic agents in the Unrestricted group, accounting for 24.1% (886/3680) of antimicrobial prescriptions. There were 21 (31.3%) types of antimicrobial agents in the Restricted group, accounting for 56.8% (2089/3680) of antibiotic prescriptions. There were seven (10.4%) types of antibiotic agents in the Special group, accounting for 16.1% (594/3680) of antibiotic prescriptions. In ICUs (n=1034), there were 139 (13.4%) prescriptions in the Unrestricted group, 520 (50.3%) in the Restricted group and 328 (31.7%) in the Special group. Forty-seven (4.5%) antibiotic prescriptions for children and neonates in the ICUs were in the unclassified group.

In the Special group, antimicrobials that were strictly regulated, meropenem (308/594, 51.9%) and vancomycin (120/594, 20.2%) were the commonly two antibiotics prescribed. The detailed antibiotic types in every group based on the antibiotic classification in China are shown in table 3.

Indications for antibiotics in this study

The most common indications for antibiotics in Chinese children in this study were proven or probable bacterial lower respiratory tract infection (2044/3680, 55.5%), followed by upper respiratory infections (283/3680, 7.7%) and sepsis (240/3680, 6.5%). A percentage of 64.0 of antibiotic prescriptions were for respiratory tract infection including lower and upper tract infection. The antibiotic prescriptions for invasive infections like sepsis, central nervous system infection, cardiac infections, catheter-related blood stream infection and joint/bone infection only accounted for 12.3%. The detailed reasons for antimicrobial prescribing in Chinese children were shown in table 4.

The top five antibiotic agents for proven or probable bacterial lower respiratory tract infection were azithromycin (236/2044, 11.5%), latamoxef (225/2044, 11.0%), amoxicillin and enzyme inhibitors (200/2044,

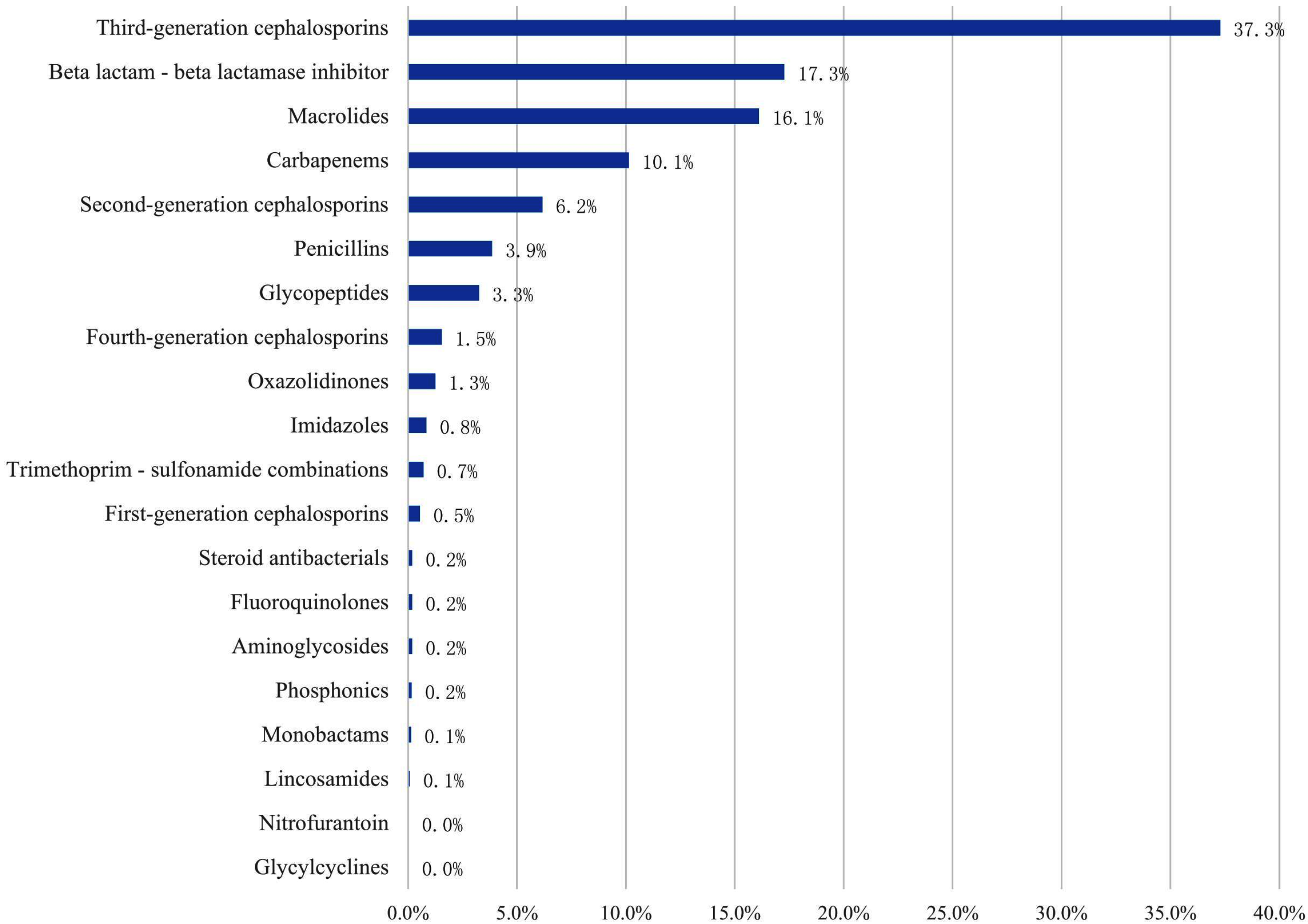

Figure 1 Proportion of prescribed antibiotics (ATC classification) among Chinese children (%). ATC classification, Anatomical Therapeutical Chemical classification.

9.8%), ceftriaxone (197/2044, 9.6%) and ceftizoxime (188/2044, 9.2%).

DISCUSSION

A special campaign to improve the use of antimicrobial agents, which launched by the National Health Commission of the People's Republic of China, have reduced the usage of antimicrobial agents and concomitantly reduced bacterial resistance.[1] After implementation of the antimicrobial stewardship programme, the antibiotic prescription rate in China has been far lower than that of many developing countries and has been close to that of developed countries in North America and Europe.[7–9]

In 2016, we participated in a study collecting the antibiotic prescribing data in children and neonates globally. The study showed that China has the second highest percentage of Watch antibiotics use (74.1%), which may lead to higher potential antimicrobial resistance and should be used as a key target of stewardship.[10] In our present study, the proportion of the watch group was 76.5% in 2016. Among the top five most commonly prescribed antibiotics in 2016, four types of antibiotics belonged to the Watch group, accounting for 38.26% of antibiotic use in China, which was far higher than that in all other regions including Africa (26.3%), the Americas (12.0%) and Europe (7.9%), while only one type of antibiotic belonged to the Access group, accounting for 10.16% of antibiotic use. The proportion of penicillins prescribed for Chinese children was far lower than that for other countries, and no aminoglycosides were in the top five antibiotics.[10]

The low use of penicillins and nearly no use of aminoglycosides may be related to antimicrobial management policies in China. A skin test must be performed before intravenous or oral penicillins are prescribed.[11] In some hospitals where skin tests are not required when oral penicillins are prescribed, the proportion of prescribed cephalosporins have been substantially decreased.[12] Only moderate risk patients need to be evaluated with penicillin skin testing for penicillins prescribing, not all of patients must be performed skin test before penicillins prescribing.[13 14]

Gentamicin is the first-line antibiotic recommended for children and neonates with common infections by international guidelines and WHO recommendations.[15] Gentamicin was prohibited for children under 6 years old

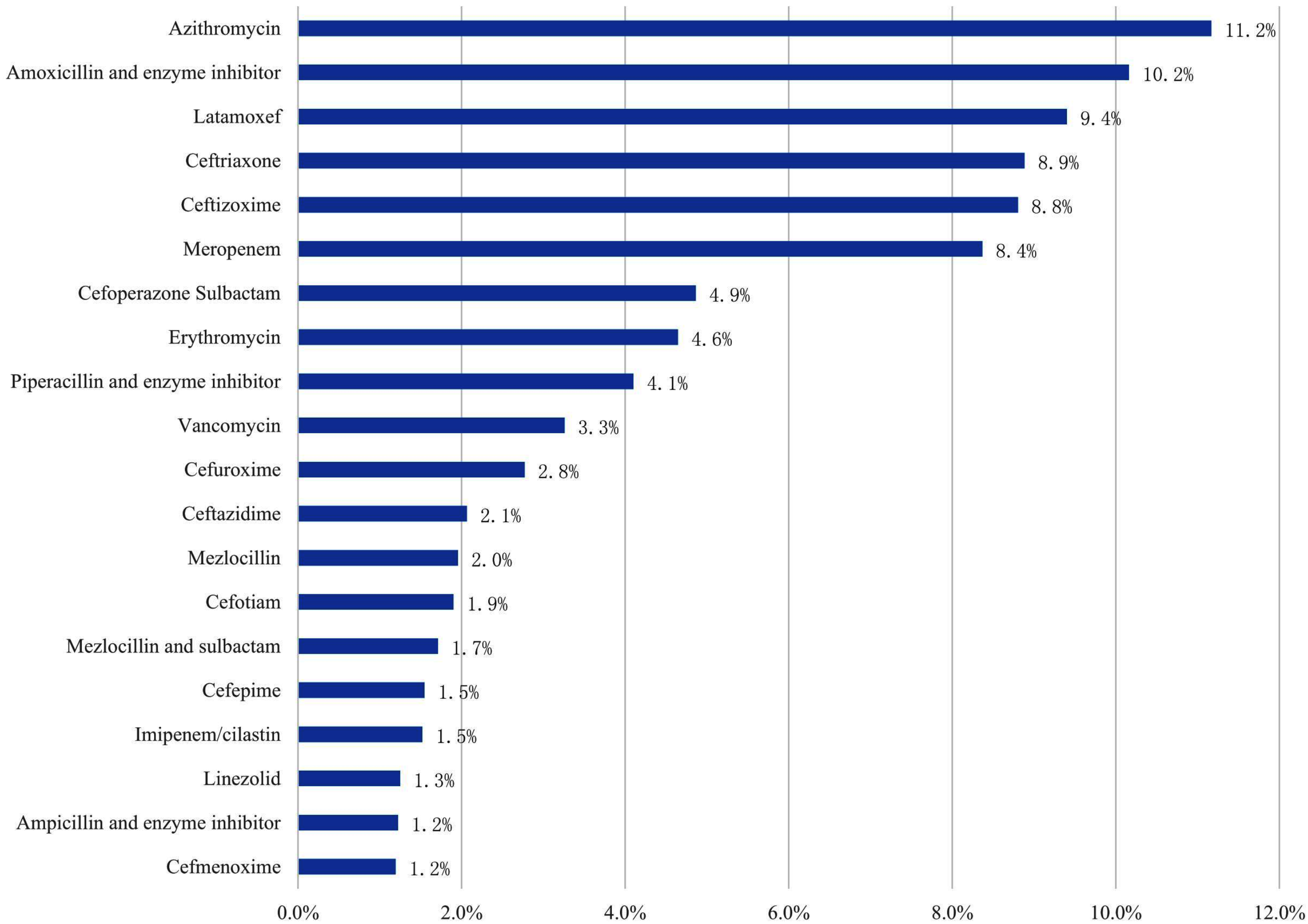

Figure 2 Patterns of antibiotic prescribing to Chinese children by drug utilisation 90%.

in China because of its potential to cause deafness and hearing impairments.[16] The ototoxicity of gentamicin was associated with genetic susceptibility. Mutations in the mitochondrial *12SrRNA (MTRNR1)*, particularly the *A1555G* mutation, was considered highly associated with the ototoxic effect of aminoglycosides.[17] The Chinese newborns were with 0.12% (18/14913) carrier rate of *A1555G* mutation that was lower to the carrier rate 0.19% (18/9371) in European children.[18 19] There are no enough evidence for gentamicin forbidden in Chinese children and neonates. In the future, some surveys on association between deafness in children and gentamicin prescribing should be done.

In 2016, the proportion of third-generation cephalosporins in China was 37.3% and higher than those in other countries. In a survey in the USA from 2016 to 2017, there was one antibiotic (ceftriaxone) that belonged to third-generation cephalosporins accounting for 9.2% of antimicrobial use.[9] In 2012, a survey focusing on paediatric inpatients in Australia revealed that the proportion of third-generation cephalosporins was less than 10%.[20]

The most common bacteria causing infections in children are *Haemophilus influenzae* and *Streptococcus pneumoniae*. Third-generation cephalosporins that are recommended for pathogens such *as H. influenzae* and *S. pneumoniae* are resistant to penicillins, as well as first-generation and second-generation cephalosporins. In 2016, the resistance rates of *H. influenzae* isolated from children for different agents were as follows: ampicillin (52.9%), cefuroxime (30.8%) and ampicillin clavulanate (15.9%). The penicillin non-sensitivity rate to *S. pneumoniae* was 18.2%.[21] The antimicrobial resistance of penicillins did not increase greatly and was not more than 30%. So, penicillins with or without enzyme inhibitors should be recommended as the primary antimicrobials for infections in children. Many infections by penicillin non-susceptible pneumococci may still be treated with penicillins if adequate doses are given.

Probable overuse of third-generation cephalosporins caused high resistance of common pathogens. Fu *et al*[22] reported the antimicrobial resistance of clinical strains isolated from children in China, the resistance of *Escherichia coli* and *Klebsiella pneumoniae* to ceftriaxone were 52.3% and 56.1%.

Based on antibacterial agent management in China, the proportion of antibiotics included in the Special group was 16.1% (594/3680) in 2016. The most commonly prescribed class of antibiotics in the Special group was carbapenems. Carbapenems, as a kind of extra-broad-spectrum antibiotic, should be prioritised as key targets

Table 2 Antibiotics (WHO AWaRe classification) prescribing to Chinese children by drug utilisation 90% in 2016

Access (552)		Watch (2814)		Reserve (58)		Not recommended (242)		Unclassified (n=14)	
Amoxicillin and enzyme inhibitor	67.8%	Azithromycin	14.6%	Linezolid	79.3%	Cefoperazone Sulbactam	74.0%	Ornidazole	78.6%
Ampicillin and enzyme inhibitor	8.2%	Latamoxef	12.3%	Fosfomycin	10.3%	Mezlocillin and sulbactam	26.0%	Ticarcillin and enzyme inhibitor	21.4%
Benzylpenicillin	8.0%	Ceftriaxone	11.6%	Aztreonam	8.6%				
Sulfamethoxazole and trimethoprim	4.7%	Ceftizoxime	11.5%						
Metronidazole	3.6%	Meropenem	10.9%						
		Erythromycin	6.1%						
		Piperacillin and enzyme inhibitor	5.4%						
		Vancomycin	4.3%						
		Cefuroxime	3.6%						
		Ceftazidime	2.7%						
		Mezlocillin	2.6%						
		Cefotiam	2.5%						
		Cefepime	2.0%						

AWaRe classification, access/watch/reserve classification.

Table 3 Antibiotics (China classification) prescribing to Chinese children by drug utilisation 90% in 2016

Unrestricted (n=886)		Restricted (n=2089)		Special (n=594)		Unclassified (n=111)	
Ceftriaxone	36.9%	Amoxicillin and enzyme inhibitor	17.9%	Meropenem	51.9%	Cefminox	14.4%
Erythromycin	19.3%	Latamoxef	16.6%	Vancomycin	20.2%	Cefbuperazone	12.6%
Azithromycin(oral)	17.9%	Ceftizoxime	15.5%	Cefepime	9.6%	Ornidazole	9.9%
Cefuroxime	11.5%	Azithromycin (IV)	12.1%	Imipenem/cilastin	9.4%	Azidocillin	9.0%
Benzylpenicillin	5.0%	Cefoperazone Sulbactam	8.6%			Cefamandole	9.0%
		Piperacillin and enzyme inhibitor	7.2%			Cefaloridine	8.1%
		Ceftazidime	3.6%			Cefoxitin	5.4%
		Mezlocillin	3.4%			Aztreonam	4.5%
		Cefotiam	3.4%			Amikacin	3.6%
		Mezlocillin and sulbactam	3.0%			Levofloxacin	3.6%
						Panipenem and betamipron	2.7%
						Ticarcillin and enzyme inhibitor	2.7%
						Ceftezole	2.7%
						Tobramycin	2.7%

Table 4 Indications for antimicrobial prescribing in Chinese children

Indications for antimicrobial prescribing	Frequency	Percentage
Proven or probable bacterial lower respiratory tract infection (LRTI)	2044	55.5
Upper respiratory infections (URTIs)	283	7.7
Sepsis	240	6.5
Central nervous system (CNS) infection	193	5.2
Other	188	5.1
Gastrointestinal tract infections	158	4.3
Newborn prophylaxis for newborn risk factors	134	3.6
Treatment for surgical disease	74	2.0
Fever of unknown origin	56	1.5
Unknown	46	1.3
Skin/soft tissue infections	43	1.2
Prophylaxis for surgical disease	40	1.1
Prophylaxis for medical problems	39	1.1
Febrile neutropenia/fever	37	1.0
Viral coinfection with bacteria LRTI	29	0.8
Urinary tract infections	27	0.7
Cardiac infections	13	0.4
Newborn prophylaxis for maternal risk factors	13	0.4
Lymphadenitis	8	0.2
Decolonisation for bacterial carrier	6	0.2
Joint/bone infections	5	0.1
Probable or proven catheter related	3	0.1
Acute otitis media	1	0.0
Total	3680	100

*'Other' in the 'Indications for antimicrobial prescribing' column refers to indications for antibiotics that are not in the indications list designed for the survey.

of local and national stewardship programmes and monitoring. Furthermore, carbapenems should be used for children infected by *Enterobacterales* producing extra-spectrum broad lactamases (ESBLs), as well as for *Pseudomonas aeruginosa*. As the data in this study showed, the proportion of carbapenems prescribed for children in China was 10.14% in 2016 and higher than that in Europe and North America.[23] The rapidly increasing proportion of carbapenem-resistant organisms in both adults and children may be caused by the extensive use of carbapenems. In adults in China, *E. coli* resistant to meropenem increased from 0.2% in 2005 to 2.3% in 2017, while *Klebsiella* spp. resistant to meropenem increased from 0.6% in 2005 to 23.1% in 2017.[24] The prevalence of carbapenem-resistant organisms in Chinese children is more common and serious than that found in adults.

For children with *Enterobacterales* infections producing ESBLs, piperacillin and tazobactam are viable alternatives to carbapenems and keep low resistance rate to *E. coli* (3.9%) *and K. pneumoniae* (22.2%) in the survey of antimicrobial resistance profile of clinical isolates in paediatric hospitals in China in 2019.[22] In this study, the piperacillin and tazobactam used for infections in Chinese children only accounted for 4.1% and less than half of carbapenems.

Since 2017, there have been continuous actions to promote the rational use of antibiotic agents, such as multidisciplinary cooperation of pharmacology, microbiology and clinical medicine, monitor of antimicrobial resistance, evaluation of antibiotic prescriptions and so on. The appropriateness of antibiotic prescribing for children will be improved.

The strengths of this study lie in the collaboration of 18 hospitals located in nine provinces that contributed the largest dataset of antibiotic prescriptions from China in children and neonates. The inclusion of children from different wards increased the generalisability. This study described the distribution of different types of antibiotic agents in clinical practice in children 5 years later after special action for antimicrobial stewardship in China, which has been promoted strongly since 2011. To our knowledge, our present study is the first to have analysed the distribution of antibiotic agents in Chinese children in terms of both the WHO AWaRe and the Management of Antibiotic Classification in China, which were different. Because of the simplicity and high feasibility of the PPS, it may be useful as a means for continuous monitoring of antibiotic use over time.

The present study had several limitations. The PPS in 2016 only collected antibacterial prescriptions for 4 days, and only a subset of departmental data were enrolled in the survey, which may have underestimated antibiotic use. Furthermore, the hospitals that participated in this survey were children's specialised hospitals within regional centres that may prescribe a higher percentage of broader spectrum antibiotics compared with that of other types of hospitals. Third, it was difficult to determine appropriateness of antibiotic use because of lack of microbiology and antimicrobial susceptibility results and detailed patient characteristics.

CONCLUSION

In this study, it was found that in 2016—5 years after the promotion of special action for antimicrobial stewardship in China—the proportions of broad-spectrum antibiotics in the Watch group, as well as in the Restricted and Special groups in China were far higher than other countries. Therefore, it is time to pay more attention to the different types of antibiotic agents that are used and to encourage the prescription of narrow-spectrum antibiotics to mitigate the further development of antibiotic resistance.

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Ethics approval Every child was given a non-identifiable serial number, which was automatically generated by the survey system. The ethics committees at Shenzhen Children's Hospital approved the procedures in this study (Reference Number: 2018015). Written informed consent from participate was gived by the participants before data collection. Participants gave informed consent to participate in the study before taking part.

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