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Antimicrobial stewardship in children in China: It is time to consider the category of antibiotic agents

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Title: Antimicrobial stewardship in children in China: It is time to concern the category of antibiotic agents

Running title: Antibiotic prescribing pattern in Chinese children

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The ethics committees at Shenzhen Children's Hospital approved the procedures in this study and patients and public were involved in the design, reporting and dissemination plans. The protocol of this study was in accordance with the principles of the Declaration of Helsinki.

Competing interests

The authors have declared no conflict of interest.

Consent for publication

Not applicable.

Author contributions

YY, JZ, WZ, YZ, JD were responsible for the study concept and design. YY organized all hospitals to collect data. JZ, WZ, XM, LT and DT collected the data of antibiotic prescriptions. JZ and KW contributed to the data management and analyses. JZ and WZ contributed to the interpretation of data and writing of the manuscript. YY, YZ, KS and JD revised the manuscript. All authors reviewed and agreed the final manuscript.

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Antimicrobial stewardship in children in China: It is time to concern the category of agents

Abstract

Objectives: Broad spectrum antibiotics have a potentially greater influence on antibiotic resistance. The reports on evaluating the classification of antibiotic agents prescribed for Chinese children by combining metrics were rare. The World Health Organization's (WHO) Essential Medicines List Access, Watch, and Reserve (AWaRe) classification and the Management of Antibiotic Classification in China could facilitate simple metrics to show the proportion of broad spectrum antibiotics. This study aimed to investigate the pattern of antimicrobial agents prescribing for Chinese children in 2016 after the implementation of the National Special Rectification Activities on Clinical Antibiotic Use in 2011.

Settings: 18 secondary centers 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 was collected and analyzed. 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 in hospitalized children in China between February 1, 2016, and February 28, 2017. Patterns of antibiotic use by using a drug utilization (DU) of 90%, Anatomical Therapeutical Chemical Classification (ATC Classification), WHO AWaRe, and antibiotic classification in China were described.

Results: On the basis of WHO AWaRe classification, the proportion of antibiotics in the Watch group belonged to broad spectrum antibiotics was 76.48%. According to the Management of Antibiotic Classification in China, antibiotic prescriptions in the restricted group and the special group included into broad spectrum antibiotics were 56.77% and 16.14%.

Conclusions: The proportion of broad-spectrum antibiotics included in the Watch group and the special group was high in 2016. Combining the AWaRe classification and the Management of Antibiotic Categories in China may provide a simple metric to

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evaluate appropriate antibiotic use.

Keywords: Antibiotic; Children; Antibiotic stewardship; WHO Essential Medicines list for children; China;

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Strengths and limitations of this study

1. This study was a multi-center survey covering nine provinces and had better representativeness.

2. This study focused on describing the classification pattern of antibiotic prescriptions in clinical practice in Chinese children in terms of both the WHO AWaRe and the Management of Antibiotic Classification in China which were different.

3. The majority of hospitals that participated in this survey were tertiary children's specialized hospitals and a higher percentage of broader-spectrum antibiotics may be showed.

4. It was difficult to determine appropriateness of antibiotic use because of lack of microbiology and antimicrobial susceptibility results and detailed patient characteristics.

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1. 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 prioritized as key targets of local and national stewardship programs and monitoring.

In response to increasing antimicrobial resistance, World Health Organization adopted a global action plan on antimicrobial resistance and one of objective is to optimize 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 utilization rate and antibiotic-use density have both been greatly reduced following this campaign [1]. However, these two indicators (i.e., 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 ten years, more attention has been paid to the antibiotic usage rate and total antibiotic consumption and 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.

In 2017, 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), with the goals of improved clinical outcomes and reduced potential antimicrobial resistance. In 2019, the group of the Essential Medicines List (EML) was revised and classified most antibiotics used globally into AWaRe groups[3]. The Access group includes antibiotics that are readily available, affordable, and reliable, and are recommended as the first-line treatment for common infectious diseases. The Watch group includes antibiotics that have higher resistance potential, and are only recommended as first- or second-choice treatments for a limited number of indications. The Reserve group includes

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antibiotics that should only be used when other alternatives are inadequate or have already failed.

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 factors such as safety, efficacy, bacterial resistance, and price, antibacterial drugs are divided into the following three levels of subgroups: unrestricted, restricted, and special group [4]. The unrestricted group includes antibiotics that are safe, affordable, and effective, with little impact on bacterial resistance. The restricted group includes antibiotics that have a higher potential bacterial resistance and/or a higher price. The special group includes antibiotics that can induce serious adverse effects, are expensive, and/or have a high probability of inducing bacterial resistance. The antimicrobial stewardship management committee has limited different levels of antimicrobial agents that are authorized to be prescribed by doctors with different professional titles.

Both the AWaRe classification and Management of Antibiotic Classification in China, 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 analyzed by the Management of Antibiotic Classification in China and the WHO Essential Medicines List of AWaRe to determine antibiotic patterns in 2016 in Chinese children.

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2. Methods

2.1. Data collection

Four one-day point-prevalence surveys 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 hospitalized in participating hospitals were included in this survey. Thirteen children's hospitals, pediatric wards from 2 general hospital and 3 women and children's healthcare centers participated into this cross-sectional study. All participating hospitals were tertiary. The antimicrobial prescribing data from the children admitted in medical wards (general pediatric wards and special medical wards including respiratory, infectious diseases and neonatology wards), surgical wards and intensive care units (Neonatal intensive care units and Pediatric intensive care units) was collected and analyzed. The participation in this study was voluntary. The children from different wards would help to reduce potential bias.

A web-based Electronic Data Capture (https://pidrg-database.sgul.ac.uk/redcap/) was used to collect data and all participating centers 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). The characteristics of participating hospitals by frequency of antibiotic prescriptions in 2016 are shown in Supplementary Table 1.

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 analyzed. When rifampicinwas 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.

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The ethics committees at Shenzhen Children's Hospital approved the procedures in this study. The protocol of this study was in accordance with the principles of the Declaration of Helsinki.

2.2. Statistical analysis

We described patterns of antibiotic use by using a drug utilization (DU) of 90%, defined as the number of antibiotics that accounted for 90% of the total antibiotics prescriptions. 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 special group antibiotic lists in different hospitals in China were the same. But 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) catalogs. A list of unrestricted, restricted, and special group of antibiotics in China for this study was shown in Supplementary Table 2. The WHO AWaRe classification and matched China classification of antibiotics were described in Supplementary Table 3.

For the statistical analysis, Microsoft Excel 2007 (Microsoft Corporation, WA, United States of America) and SPSS 22.0(IBM, Chicago, United States of America) were used.

Patient and public involvement

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

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3. Results

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

In the point-prevalence survey in 2016, a total of 3680 antibiotic prescriptions for Chinese children were included in the analysis. There were 66 types of antimicrobial agents in total, and 20 (29.41%) antimicrobial agents accounted for 90 percent of antimicrobial use.

The five most common classes of antimicrobials prescribed for children in 2016 were third-generation cephalosporins (37.28%), beta lactam-beta lactamase inhibitors (17.28%), macrolides (16.11%), carbapenems (10.14%) and second-generation cephalosporins (6.17%) (Figure 1 Proportion of prescribed antibiotics (ATC classification) among Chinese children(%)).

In 2016, the top-five antimicrobials prescribed for children—which accounting for 48.42% of all antimicrobial use—were azithromycin (11.17%), amoxicillin and enzyme inhibitors (10.16%), latamoxef (9.40%), ceftriaxone (8.89%) and ceftizoxime (8.80%)(Figure 2 Patterns of antibiotic prescribing to Chinese children by drug utilization 90%).

In the top-ten antimicrobial agents, only two agents which were Amoxicillin and enzyme inhibitor(10.16%) and Piperacillin and enzyme inhibitor(4.10%) were included into penicillins. Penicillins without enzyme inhibitors including Benzylpenicillin, Oxacillin and other penicillins only accounted for 3.86%.

Four agents accounting for 31.96% were included in the third-generation cephalosporins. The antimicrobial agent prescribed commonly in the third-generation cephalosporins was latamoxef (9.40%), which was not included in the WHO Essential Medicines List.

Meropenem and vancomycin classified into Watch group based on WHO AWaRe classification and the special group based on the Management of Antibiotic Classification in China accounted for 8.37% and 3.26%.

3.2. Antibiotic classes prescribed pattern based on the WHO

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Access/Watch/Reserve group

According to the WHO AWaRe, 66 antibiotic agents were included in the survey in 2016. There were 19(28.79%) agents in the Access group, accounting for 15.00% of antibiotic prescriptions. There were 39(59.09%) agents in the Watch group, accounting for 76.48% of antibiotic prescriptions. There were four (6.06%) agents in the Reserve group, accounting for 1.58% of antibiotic prescriptions. There were two (3.03%) agents in the not-recommended group, accounting for 6.58% of antibiotic prescriptions.

In the Watch group, azithromycin accounting for 14.61% was the antibiotic most commonly used, followed by latamoxef(12.30%), ceftriaxone(11.62%), ceftizoxime(11.51%), meropenem(10.95%). The detailed antibiotic types in every group based on the WHO AWaRe classifications were shown in Table 1.

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Table 1 Antibiotics(WHO AWaRe classification) prescribing to Chinese children by drug utilization 90% in 2016

Access(552)		Watch(2814)		Reserve(58)		Not recommended(242)		Unclassified(n=14)	
Amoxicillin and enzyme inhibitor	67.75%	Azithromycin	14.61%	Linezolid	79.31%	Cefoperazone Sulbactam	73.97%	Ornidazole	78.57%
Ampicillin and enzyme inhibitor	8.15%	Latamoxef	12.30%	Fosfomycin	10.34%	Mezlocillin and sulbactam	26.03%	Ticarcillin and enzyme inhibitor	21.43%
Benzylpenicillin	7.97%	Ceftriaxone	11.62%	Aztreonam	8.62%				
Sulfamethoxazole and trimethoprim	4.71%	Ceftizoxime	11.51%						
Metronidazole	3.62%	Meropenem	10.95%						
		Erythromycin	6.08%						
		Piperacillin and enzyme inhibitor	5.37%						
		Vancomycin	4.26%						
		Cefuroxime	3.62%						
		Ceftazidime	2.70%						
		Mezlocillin	2.56%						
		Cefotiam	2.49%						
		Cefepime	2.03%						

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3.3. Antibiotic classes prescribed pattern based on the Management of Antibiotic Classification in China

According to the Management of Antibiotic Classification in China, 67 antibiotic agents were included in the survey in 2016. There were 17(25.37%) types of antibiotic agents in the unrestricted group, accounting for 24.08% of antimicrobial prescriptions. There were 21(31.34%) types of antimicrobial agents in the restricted group, accounting for 56.77% of antibiotic prescriptions. There were seven (10.45%) types of antibiotic agents in the special group, accounting for 16.14% of antibiotic prescriptions.

In the special group antimicrobials which were strictly regulated, meropenem(51.85%) and vancomycin(20.20%) were the commonly two antibiotics prescribed. The detailed antibiotic types in every group based on the antibiotic classification in China are shown in Table 2.

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Table 2 Antibiotics(China classification) prescribing to Chinese children by drug utilization 90% in 2016

Unrestricted(n=886)		Restricted(n=2089)		Special(n=594)		Unclassified(n=111)	
Ceftriaxone	36.91%	Amoxicillin and enzyme inhibitor	17.90%	Meropenem	51.85%	Cefminox	14.41%
Erythromycin	19.30%	Latamoxef	16.56%	Vancomycin	20.20%	Cefbuperazone	12.61%
Azithromycin(oral)	17.95%	Ceftizoxime	15.51%	Cefepime	9.60%	Ornidazole	9.91%
Cefuroxime	11.51%	Azithromycin（IV）	12.06%	Imipenem/cilastin	9.43%	Azidocillin	9.01%
Benzylpenicillin	4.97%	Cefoperazone Sulbactam	8.57%			Cefamandole	9.01%
		Piperacillin and enzyme inhibitor	7.23%			Cefaloridine	8.11%
		Ceftazidime	3.64%			Cefoxitin	5.41%
		Mezlocillin	3.45%			Aztreonam	4.50%
		Cefotiam	3.35%			Amikacin	3.60%
		Mezlocillin and sulbactam	3.02%			Levofloxacin	3.60%
						Panipenem and betamipron	2.70%
						Ticarcillin and enzyme inhibitor	2.70%
						Ceftezole	2.70%
						Tobramycin	2.70%

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3.4 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, 55.54%), followed by upper respiratory infections (283, 7.66%) and sepsis(240, 6.52%). 64.02% 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 12.34%. The detailed reasons for antimicrobial prescribing in Chinese children were shown in Table 3.

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Table 3 Indications for antimicrobial prescribing in Chinese children

Indications for antimicrobial prescribing	Frequency	Percentage%
Proven or probable Bacterial lower respiratory tract infection(LRTI)	2,044	55.54
Upper Respiratory Infections (URTI)	283	7.66
Sepsis	240	6.52
Central Nervous System (CNS) infection	193	5.24
Other	188	5.11
Gastrointestinal tract infections	158	4.29
Newborn Prophylaxis for Newborn Risk factors	134	3.64
Treatment for Surgical disease	74	2.01
Pyrexia of Unknown Origin (PUO)	56	1.52
Unknown	46	1.25
Skin/Soft Tissue Infections (SSTI)	43	1.17
Prophylaxis for Surgical disease	40	1.09
Prophylaxis for Medical problems	39	1.06
Febrile neutropenia/Fever	37	1.01
Proven or probable Viral LRTI	29	0.79
Urinary Tract Infections (UTI)	27	0.73
Cardiac Infections	13	0.35
Newborn Prophylaxis for Maternal Risk factors	13	0.35
Lymphadenitis	8	0.22
Decolonization for Bacterial Carria	6	0.16
Joint/Bone Infections	5	0.14
Probable or Proven Catheter-related	3	0.08
Acute Otitis Media (AOM)	1	0.03
Total	3680	100

"Other" in the "Indications for antimicrobial prescribing" column refers to indications for antibiotics which is not in the indications list designed for the survey.

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4. 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. A survey was conducted in Yuying Children's Hospital of Wenzhou Medical University, located in the Zhejiang province in Southeastern China, from 2010 to 2017. Data on antimicrobial prescription usage showed that the antibiotic prescription rate declined from 55.2% to 23.1% in outpatient departments, 75.6% to 35.1% in emergency departments, and 76% to 50.3% in inpatient departments. DDDs decreased from 38.43/100 to 19.41/100 patient-days. The detection rates of extended-spectrum β-lactamases-producing *Escherichia coli* decreased from 75.4% to 46.7%, whereas detection rates of *Klebsiella pneumonia* decreased from 78.7% to 32.5%[1]. After implementation of the antimicrobial stewardship program, 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[5-7].

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[8]. In our present study 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[8].

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

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intravenous or oral penicillins are prescribed [9]. Due to this inconvenience and the fear of penicillin-induced allergy, the use of penicillin has been greatly limited while cephalosporins and macrolides have been commonly prescribed due to no skin test being required. In some hospitals where skin tests are not required when oral penicillins are prescribed, the proportion of prescribed cephalosporins have been substantially decreased [10]. Only moderate-risk patients who have urticaria or other pruritic rashes and reactions with features of IgE-mediated reactions need to be evaluated with penicillin skin testing for penicillins prescribing, not all of patients must be performed skin test before penicillins prescribed[11, 12]. Even though pregnant women with a history of penicillin allergy are recommended to undergo skin testing for evaluating the possibility of penicillins prescribing. Penicillin skin testing for all patients prescribed penicillins increases the workload of nurses and barriers to use of penicillins and will reduce penicillins prescriptions. Moreover, unnecessary penicillin skin testing increases the false positive cases and prevents patients from receiving penicillin treatment. In the future, multi-center researches should be conducted to evaluate the necessity of penicillin skin testing for all patients and decrease the barriers for penicillins usage. Penicillins used for common infections in children which are available, cheap, less side effects can be used rationally for infections in children in China.

Gentamicin is the first-line antibiotic recommended for children and neonates with common infections by international guidelines and WHO recommendations [13]. Gentamicin was prohibited for children under six years old in China in the clinical specification of common ototoxic medicines in 1999, published by the Ministry of Health of the People's Republic of China, as a strategy for preventing deafness and hearing impairments [14]. The ototoxicity of gentamicin also associated with genetic susceptibility. Mutations in the mitochondrial *12SrRNA(MTRNR1)*, particularly the A1555G mutation was considered highly associated with the ototoxic effect of aminoglycosides[15]. The Chinese newborns with 0.12% (18/14913) carrier rate of A1555G mutation was lower to the carrier rate 0.19% (18/9371) in European children [16, 17]. There are no reasons for gentamicin forbidden in Chinese children and neonates. In the future, some surveys on association between deafness in children and gentamicin

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prescribing should be done. If no relationship would be proven, gentanmicin will should be recommended to treat gram-negative bacteria infections in children and reduce third-generation cephalosporins and carbapenems which are easier to promote the antimicrobial resistance.

The proportion of the Watch group was 76.48% in 2016. Based on antibacterial-agent management in China, the special group of antibiotics included carbapenems and glycopeptides was 16.14% in 2016. According to this analysis, the most antibiotic classes prescribed were third-generation cephalosporins, carbapenems and macrolides. In 2016, the proportion of third-generation cephalosporins in China was 37.28% and higher than those in other countries. Among the five most commonly used antibiotics, three (latamoxef, ceftriaxone and ceftizoxime) belonged to third-generation cephalosporins and accounted for 27.09% of antimicrobial use in 2016. In a survey in the United States from 2016 to 2017, there was one antibiotic (ceftriaxone) that belonged to third-generation cephalosporins accounting for 9.2% of antimicrobial use [7]. In 2012, a survey focusing on paediatric inpatients in Australia revealed that the proportion of third-generation cephalosporins was less than 10% [18].

The most common bacteria causing infection in children are *Haemophilus influenzae* and *Streptococcus pneumoniae*. Third-generation cephalosporins that are recommended for pathogens such *as Haemophilus influenzae* and *Streptococcus pneumoniae* are resistant to penicillins, as well as first-generation and second-generation cephalosporins. In 2016, the resistance rates of *Haemophilus influenzae* isolated from children for different agents were as follows: ampicillin (52.9%), cefuroxime (30.8%), ampicillin sulbactam (24.0%), and ampicillin clavulanate (15.9%). The penicillin non-sensitivity rate to *Streptococcus pneumoniae* was 18.2% [19]. The antimicrobial resistance of penicillins, as well as first-generation and second-generation cephalosporins, did not increase greatly and was not more than thirty percent, if the resistance rate of antimicrobials were more than 30% and the antimicrobials will not be recommended as the first-line antibiotics for infections. So, there was no more reason for promoting the use of more third-generation cephalosporins. Penicillins with or without enzyme inhibitors should be recommended as the primary antimicrobials for

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infections in children.

It was probable that the third-generation cephalosporins in Chinese children were overused. Abuse of third-generation cephalosporins caused common pathogens with the high resistance to cephalosporins. Fu P, et al reported the antimicrobial resistance of clinical isolates in children in China, the resistance of *E.coli.* and *Klebsiella pneumonia* to ceftriaxone were 52.3% and 56.1%[20].

Carbapenems as a kind of extra broad spectrum antibiotic are classified into the Watch group based on the WHO AWaRe and into the special group in the Management of Antibiotic Classification in China and should be prioritized as key targets of local and national stewardship programs and monitoring. Furthermore, carbapenems should be used for children infected by *Enterobacteriaceae* producing extra-spectrum broad lactamases (ESBLs), as well as for *Pseudomonas aeruginosa* that is resistant to third-generation cephalosporins. As the data in this study showed, the proportion of carbapenems prescribed for children in China was 10.14% in 2016 and higher than in Europe and North America [21].

Furthermore, it is likely that carbapenems are overused. 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[22]. The prevalence of carbapenem-resistant organisms in Chinese children is more common and serious than that found in adults. The overall prevalence of carbapenem-resistant *Enterobacteriaceae* increased from 3.0% in 2005 to 10.2% in 2017; additionally, *E.coli* resistant to carbapenems increased from 1.1% in 2005 to 3.9% in 2017; finally, *Klebsiella pneumonia* resistant to carbapenems increased from 2.2% in 2005 to 25.4% in 2017[2].

For children with *Enterobacteriaceae* infections producing ESBLs, piperacillin and tazobactam are viable alternatives to carbapenems and keep low resistance rate to *E.coli*(3.9%) *and Klebsiella pneumonia*(22.2%) in the survey of Antimicrobial resistance profile of clinical isolates in pediatric hospitals in China in 2019[20]. In this

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study, the piperacillin and tazobactam used for infections in Chinese children only accounted for 4.1% and less than half of carbapenems.

In this study, we found that azithromycin belonged to macrolides was the commonest antibiotic prescribed for children, accounting for 11.7% of total antimicrobial prescriptions. The high azithromycin prescribing promoted the resistance to a lot of pathogens like *Mycoplasma pneumoniae*, *Bordetella pertussis* and other microorganisms. Antimicrobial susceptibility of *Mycoplasma pneumonia* isolates from different regions of China showed that the general macrolides resistance rate was 79.7% and 100% in some cities[23].

Different from high Macrolide-resistance of *Mycoplasma pneumonia* in China, the resistance were very low in some countries. A study on resistance of *M. pneumonia* isolated from United States, Macrolide-resistant *M. pneumonia* was detected in 37(8.3%) specimens in the 446 *M. pneumonia*- positive specimens from 9 states between 2012 and 2018[24]. *Streptococcus pneumonia* and *Streptococcus pyogenes* were the common pathogens caused invasive or non-invasive infections in children. In the monitor of antimicrobial resistance of clinical isolates in children in China, the resistance rates of *Streptococcus pneumonia* to erythromycin and clindamycin were 97.7% and 93.5%. *Streptococcus pyogenes* to erythromycin and clindamycin were 95.7% and 93.8%. It was probable high resistance of common pathogens to macrolides related to overuse of this class of antibiotics[20]. In Europe, only sporadic *Bordetella pertussis* isolates which were resistant to macrolides were reported[25]. In China, however, the picture has been significantly different. The rate of resistance to macrolides was over than 90% in Beijing[26].

There are a number of reasons for the high prescription rate of macrolides in China. Macrolides have lower allergy risk with no need for skin testing, and are readily available in general pharmacies. They are also easier to be taken. For example, azithromycin is only taken once daily. Misunderstanding of positive IgM or IgG which can last months as the evidence of *mycoplasma pneumoniae* infection would prolong the duration of azithromycin treatment to months. On the one hand, the overuse of

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macrolides such as azithromycin leads to the further aggravation of antimicrobial resistance. In addition, higher resistance will lead to poor clinical efficacy.

The antimicrobial resistance pattern of macrolides such as azithromycin should be reported to doctors at regular intervals, indicating that the majority of many bacteria are resistance to macrolides. In addition to it, the diagnosis of pathogens like *mycoplasma pneumoniae* infection should be standardized and the antibody of *mycoplasma pneumoniae* alone cannot be used as the diagnostic basis and monitoring indicators of efficacy. Efforts can be made to reduce the consumption of macrolides such as azithromycin.

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. This study described the distribution of different types of antibiotic agents in clinical practice in children five 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 analyzed 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 point-prevalence survey, it may be useful as a means for continuous monitoring of antibiotic use over time.

The present study had several limitations. The point-prevalence survey in 2016 only collected antibacterial prescriptions for four 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 specialized hospitals within regional centers that may prescribe a higher percentage of broader-spectrum antibiotics compared to that of other types of hospitals. Thirdly, it was difficult to determine appropriateness of antibiotic use because of lack of microbiology and antimicrobial susceptibility results and detailed patient characteristics.

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5. Conclusion

In this study, it was found that in 2016—five years after the promotion of special action for antimicrobial stewardship in China—the proportions of broad-spectrum antibiotics in the Watch group (based on the WHO AWaRe classification), as well as in the restricted and special groups (based on the Management of Antibiotic Classification) 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. The WHO AWaRe classification and the Management of Antibiotic Classification in China are two complementary types of category management that may be useful for evaluating the effectiveness of antimicrobial stewardship.

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Figure 1 Proportion of prescribed antibiotics(ATC classification) among Chinese children（%）

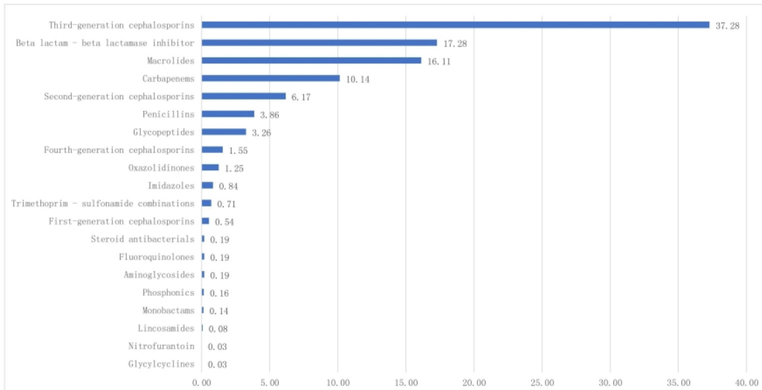

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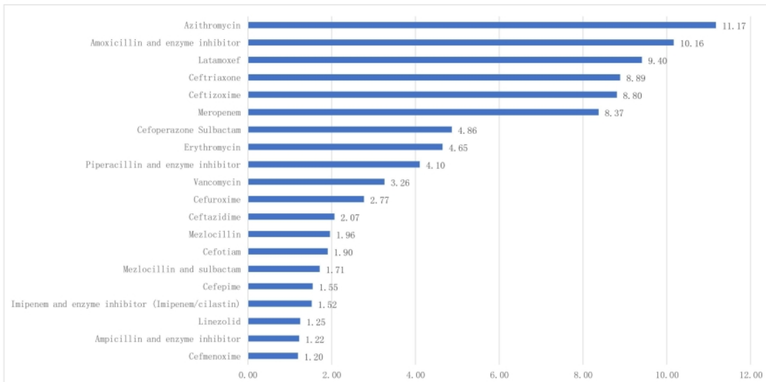
Figure 2 Patterns of antibiotic prescribing to Chinese children by drug utilization 90%



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

Hospital	City	Types of antibiotics	Frequency of Antibiotics prescriptions
Beijing Children's Hospital Affiliated to Capital Medical University	Beijing	24	689
Beijing Obstetric and GynocologyHospital,Capital Medical University	Beijing	6	90
Capital Institute of Pediatrics	Beijing	8	55
Chongqing Children's Hospital	Chongqing	24	178
Fudan University Pediatric Hospital	Shanghai	22	122
Guangdong Provincal Women and Children Health Care Hospital	Guangzhou	11	90
Guangzhou Women and Children's Medical Center	Guangzhou	21	218
Jinan Children's Hospital	Jinan	23	302
Shandong Provincial Qianfoshan hospital, Shandong University	Qianfoshan	22	424
Shanghai Children's Hospital	Shanghai	12	166
Shenzhen Baoan Women and Children's Hospital	Shenzhen	18	83
Shenzhen Children's Hospital	Shenzhen	19	158
The Children's Hospital Zhejiang University School of Medicine	Zhejiang	20	188
The first Hospital of Jilin University	Changchun	11	127
The Shanghai Children's Medical Center of Shanghai Jiaotong University	Shanghai	18	164
Tianjin Children's Hospital	Tianjin	7	244
Xi'An Children's Hospital	Xi'An	22	198
Yuying Children's Hospital of Wenzhou Medical University	Wenzhou	23	184

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Supplementary table 3 A list of unrestricted, restricted, and special groups of antibiotics in China

Unrestricted antibiotics
Cefazolin
cefadroxil
Metronidazole
Clindamycin
Azithromycin
Erythromycin
Clarithromycin
Roxithromycin
Acetylkitasamycin
Erythromycin estolate
Nitrofurantoin
Amoxicillin
Ampicillin
Benzylpenicillin
Penicillins
Benzathine benzylpenicillin
Fosfomycin
Cefaclor
Cefuroxime
Ceftriaxone
Sulfamethoxazole and trimethoprim
Restricted antibiotics
Amoxicillin and enzyme inhibitor
Piperacillin and enzyme inhibitor
Mezlocillin and sulbactam
Ampicillin and enzyme inhibitor
Amoxicillin clavulinic acid
Ampicillin and Sulbactam
Piperacillin/Tazobactam
Chloramphenicol
Azithromycin
Fusidic acid
Mezlocillin
Piperacillin
Cefatrizine
Cefathiamidine
Cefotiam
Latamoxef
Cefpodoxime
Cefdinir
Cefodizime
Cefmenoxime

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Cefixime
Ceftazidime
Cefoperazone
Cefoperazone Sulbactam
Ceftizoxime
Cefotaxime
Cefpiramide
Cefetamet
Special group antibiotics
Ertapenem
Meropenem
Lmipenem and enzyme inhibitor (Imipenem/cilastin)
Linezolid
Tigecycline
Vancomycin
Teicoplanin
Cefotaxime Sulbactam
Cefepime
Unclassified antibiotics
Azidocillin
Azlocillin
Sulbenicillin
Oxacillin
Furbucillin
Ampicloxacillin
Fluloxacillin amoxicillin
Cloxacillin
Oxacillin
Amikacin
Tobramycin
Netilmicin
Sisomicin
Neomycin
Streptomycin
Micronomicin
Aztreonam
Ornidazole
Panipenem and betamipron
Ticarcillin and enzyme inhibitor
Piperacillin and Sulbactam
Cefbuperazone
Cefmetazole
Cefamandole
Cefminox

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Cefoxitin
Cefonicid
Cefprozil
Cefradine
Ceftezole
Cefazedone
Cefaloridine
Ciprofloxacin
Ofloxacin
Levofloxacin
norfloxacin
Pipemidic acid
Josamycin
ErythromycinEthylsuccinate
Lincomycin
Polymyxin E
Doxycycline

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Supplementary table 3 A list of antimicrobial agents prescribed in this study based on WHO AWaRe classification and Management of Antibiotic Classification in China

Antibiotic	WHO AWaRe	Antibiotic classification in China
Amikacin	Access	Unclassified
Amoxicillin	Access	Unrestricted
Amoxicillin and enzyme inhibitor	Access	Restricted
Ampicillin	Access	Unrestricted
Ampicillin and enzyme inhibitor	Access	Restricted
Azidocillin	Access	Unclassified
Azithromycin(IV)	Watch	Restricted
Azithromycin(Oral)	Watch	Unrestricted
Azlocillin	Watch	Unclassified
Aztreonam	Reserve	Unclassified
Benzylpenicillin	Access	Unrestricted
Cefaclor	Watch	Unrestricted
Cefaloridine	Access	Unclassified
Cefamandole	Watch	Unclassified
Cefatrizine	Access	Restricted
Cefazedone	Access	Unclassified
Cefazolin	Access	Unrestricted
Cefbuperazone	Watch	Unclassified
Cefdinir	Watch	Restricted
Cefepime	Watch	Special
Cefixime	Watch	Restricted
Cefmenoxime	Watch	Restricted
Cefmetazole	Watch	Unclassified
Cefminox	Watch	Unclassified
Cefodizime	Watch	Restricted
Cefoperazone	Watch	Restricted
Cefoperazone Sulbactam	not recommended	Restricted
Cefotaxime	Watch	Restricted
Cefotiam	Watch	Restricted
Cefoxitin	Watch	Unclassified
Cefpodoxime	Watch	Restricted
Cefradine	Access	Unclassified
Ceftazidime	Watch	Restricted
Ceftezole	Access	Unclassified
Ceftizoxime	Watch	Restricted
Ceftriaxone	Watch	Unrestricted
Cefuroxime	Watch	Unrestricted
Ciprofloxacin	Watch	Unclassified
Clarithromycin	Watch	Unrestricted
Clindamycin	Access	Unrestricted

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Ertapenem	Watch	Special
Erythromycin	Watch	Unrestricted
Fosfomycin	Reserve	Unrestricted
Fusidic acid	Watch	Restricted
Imipenem/cilastin	Watch	Special
Latamoxef	Watch	Restricted
Levofloxacin	Watch	Unclassified
Linezolid	Reserve	Special
Meropenem	Watch	Special
Metronidazole	Access	Unrestricted
Mezlocillin	Watch	Restricted
Mezlocillin and sulbactam	not recommended	Restricted
Nitrofurantoin	Access	Unrestricted
Ofloxacin	Watch	Unclassified
Ornidazole	Unclassified	Unclassified
Oxacillin	Access	Unclassified
Panipenem and betamipron	Watch	Unclassified
Piperacillin	Watch	Restricted
Piperacillin and enzyme inhibitor	Watch	Restricted
Roxithromycin	Watch	Unrestricted
Sulbenicillin	Watch	Unclassified
Sulfamethoxazole and trimethoprim	Access	Unrestricted
Ticarcillin and enzyme inhibitor	Unclassified	Unclassified
Tigecycline	Reserve	Special
Tobramycin	Watch	Unclassified
Vancomycin	Watch	Special

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STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	5
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	5
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	7
Objectives	3	State specific objectives, including any prespecified hypotheses	8
Methods			
Study design	4	Present key elements of study design early in the paper	9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	9
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	9
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	10
Bias	9	Describe any efforts to address potential sources of bias	9
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	NA
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10
		(*b*) Describe any methods used to examine subgroups and interactions	10
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	11
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11
		(b) Indicate number of participants with missing data for each variable of interest	11
Outcome data	15*	Report numbers of outcome events or summary measures	11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11

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		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	21
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-19
Generalisability	21	Discuss the generalisability (external validity) of the study results	20
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Antimicrobial prescribing for children in China, data from point prevalence surveys in 18 tertiary centers in China in 2016-2017

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Title: Antimicrobial prescribing for children in China, data from point prevalence surveys in 18 tertiary centers in China in 2016-2017

Running title: Antibiotic prescribing pattern in Chinese children

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Antimicrobial prescribing for children in China, data from point prevalence surveys in 18 tertiary centers in China in 2016-2017Abstract

Objectives: The reports on evaluating the classification of antibiotic agents prescribed for Chinese children by combining World Health Organization'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 centers 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 was collected and analyzed. 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 hospitalized children in China between February 1, 2016, and February 28, 2017. Six 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 utilization (DU) of 90%, Anatomical Therapeutical Chemical Classification (ATC Classification), WHO 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%. According to the Management of Antibiotic Classification in China, 56.8% and 16.1% 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 (55.5%).

Conclusions: The proportion of broad-spectrum antibiotics included in the Watch group and the special group was high and there was overuse in hospitalized children in China in 2016.

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Keywords: Antibiotic; Children; Antibiotic stewardship; WHO Essential Medicines list for children; China;

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Strengths and limitations of this study

1. This study was a multi-center survey covering nine provinces and increasing representativeness.

2. This study focused on describing the classification pattern of antibiotic prescriptions in clinical practice in Chinese children in terms of both the WHO AWaRe and the Management of Antibiotic Classification in China which were different.

3. It was difficult to determine appropriateness of antibiotic use because of lack of microbiology and antimicrobial susceptibility results and detailed patient characteristics.

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1. 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 prioritized as key targets of local and national stewardship programs and monitoring.

In response to increasing antimicrobial resistance, World Health Organization adopted a global action plan on antimicrobial resistance and one of objectives is to optimize 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 utilization rate declined from 76.0% to 50.3% and antibiotic-use density from 38.43 to 19.41. These two indicators of antimicrobial management had both been greatly reduced following this campaign. [1]. However, these two indicators (i.e., 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 ten years, more attention has been paid to the antibiotic usage rate and total antibiotic consumption, both 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. In 2017, 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). In 2019, the group of the Essential Medicines List (EML) was revised and classified most antibiotics used globally into AWaRe groups[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

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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 analyzed by China's administrative categories of antibiotics and the WHO Essential Medicines List of AWaRe to determine antibiotic patterns in 2016 in Chinese children.

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2. Methods

2.1. Data collection

Four one-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 hospitalized in participating hospitals were included in this survey. Thirteen children's hospitals, pediatric wards from 2 general hospital and 3 women and children's healthcare centers 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 standardization 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 pediatric wards and special medical wards including respiratory, infectious diseases and neonatology wards), surgical wards and intensive care units (Neonatal intensive care units and Pediatric intensive care units) was collected and analyzed. The participation in this study was voluntary. The children from different wards would help to reduce potential bias.

A web-based Electronic Data Capture (https://pidrg-database.sgul.ac.uk/redcap/) was used to collect data and all participating centers 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). Six 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.

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

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was excluded when it was inhaled.

Antifungal, antiviral or antituberculous agents (rifampicin, isoniazid, pyrazinamide and ethambutol) were excluded when the data were analyzed. 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.

The ethics committees at Shenzhen Children's Hospital approved the procedures in this study. The protocol of this study was in accordance with the principles of the Declaration of Helsinki.

2.2. Statistical analysis

We described patterns of antibiotic use with a drug utilization (DU) 90%, defined as the number of antibiotics that accounted for 90% of the total antibiotics prescriptions. 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 readily 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- or second-choice treatments for a limited number of indications. The Reserve group includes antibiotics that should only be used when other alternatives are inadequate or have already failed.

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,

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bacterial resistance, and price: Unrestricted, Restricted, and Special group [4]. The Unrestricted group includes antibiotics that are safe, affordable, and effective, with little impact on bacterial resistance. The Restricted group includes antibiotics that have a higher potential bacterial resistance and/or a higher price. The Special group includes antibiotics that can induce serious adverse effects, are expensive, and/or have a high probability of inducing bacterial resistance. The Special group antibiotic lists in different hospitals in China were the same. But 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) catalogs. A list of Unrestricted, Restricted, and Special group of antibiotics in China for this study was shown in Supplementary Table 1. The WHO AWaRe classification and matched China classification of antibiotics were described in Supplementary Table 2.

For the statistical analysis, Microsoft Excel 2007 (Microsoft Corporation, WA, United States of America) and SPSS 22.0(IBM, Chicago, United States of America) 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.

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3. Results

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

In the point-prevalence survey in 2016, 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. The characteristics of participating hospitals by frequency of antibiotic prescriptions in 2016 are shown in Table 1.

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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

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There were 66 types of antimicrobial agents in total, and 20 (29.4%) antimicrobial agents accounted for 90 percent of antimicrobial use.

The five most common classes of antimicrobials prescribed for children in 2016 were third-generation cephalosporins (37.3%), beta lactam-beta lactamase inhibitors (17.3%), macrolides (16.1%), carbapenems (10.1%) and second-generation cephalosporins (6.2%) (Figure 1 Proportion of prescribed antibiotics (ATC classification) among Chinese children).

In 2016, the top-five antimicrobials prescribed for children—which accounted for 48.42% of all antimicrobial use—were azithromycin (11.17%), amoxicillin and enzyme inhibitors (10.16%), latamoxef (9.40%), ceftriaxone (8.89%) and ceftizoxime (8.80%)(Figure 2 Patterns of antibiotic prescribing to Chinese children by drug utilization 90%).

In the top-ten antimicrobial agents, only two agents which were Amoxicillin and enzyme inhibitor(10.16%) and Piperacillin and enzyme inhibitor(4.10%) were included into penicillins. Penicillins without enzyme inhibitors including Benzylpenicillin, Oxacillin and other penicillins only accounted for 3.86%.

Four agents accounting for 31.96% were included in the third-generation cephalosporins. The antimicrobial agent prescribed commonly in the third-generation cephalosporins was latamoxef (9.40%), which was not included in the WHO Essential Medicines List.

Meropenem and vancomycin classified into Watch group based on WHO AWaRe classification and the special group based on the Management of Antibiotic Classification in China accounted for 8.37% and 3.26%.

1034 antibiotic prescriptions were used for children in the Intensive Care Units (ICU), 635 for neonates in neonatal ICUs and 399 for children in pediatric ICUs. The top-three antimicrobials prescribed for children and neonates in ICUs were meropenem (179, 17.3%), amoxicillin and enzyme inhibitors (153, 14.8%), and latamoxef (93, 9.0%). The three most common classes of antimicrobials prescribed for children and neonates in ICUs which accounted for 71.0% were third-generation cephalosporins (317, 30.7%), carbapenems (207, 20.0%) and beta lactam-beta lactamase inhibitors (210,20.3%), macrolides (16.1%), and second-generation cephalosporins (6.2%). In NICUs, the top-

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three antimicrobials prescribed were amoxicillin and enzyme inhibitors (147, 23.1%), meropenem (111, 17.5%), and latamoxef (77, 12.1%). In PICUs, the top-three antimicrobials prescribed were meropenem (68, 17.0%), cefoperazone/sulbactam inhibitors (54, 13.5%), and vancomycin (48, 12.0%).

3.2. Antibiotic classes prescribed pattern based on the WHO Access/Watch/Reserve 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% of antibiotic prescriptions. There were 39(59.1%) agents in the Watch group, accounting for 76.5% of antibiotic prescriptions. There were four (6.1%) agents in the Reserve group, accounting for 1.58% of antibiotic prescriptions. There were two (3.0%) agents in the not-recommended group, accounting for 6.58% of antibiotic prescriptions. In ICUs, 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. In addition to that, 8.2% of antibiotic prescriptions including cefoperazone/sulbactam and mezlocillin/sulbactam were in the not-recommended group.

In the Watch group, azithromycin accounting for 14.6% was the antibiotic most commonly used, followed by latamoxef(12.3%), ceftriaxone(11.6%), ceftizoxime(11.5%), meropenem(11.0%). The detailed antibiotic types in every group based on the WHO AWaRe classifications were shown in Table 2.

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Table 2 Antibiotics(WHO AWaRe classification) prescribing to Chinese children by drug utilization 90% in 2016. AWaRe classification, Access/Watch/Reserve classification

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%						

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3.3. 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% of antimicrobial prescriptions. There were 21(31.3%) types of antimicrobial agents in the restricted group, accounting for 56.8% of antibiotic prescriptions. There were seven (10.4%) types of antibiotic agents in the special group, accounting for 16.1% of antibiotic prescriptions. In ICUs, 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. 47(4.5%) antibiotic prescriptions for children and neonates in the ICUs were in the Unclassified group.

In the Special group antimicrobials which were strictly regulated, meropenem(51.9%) and vancomycin(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.

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Table 3 Antibiotics(China classification) prescribing to Chinese children by drug utilization 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.[illegible]%	Cefminox	14.4%
Erythromycin	19.3%	Latamoxef	16.6%	Vancomycin	20.[illegible]%	Cefbuperazone	12.6%
Azithromycin(oral)	17.9%	Ceftizoxime	15.5%	Cefepime	9.[illegible]%	Ornidazole	9.9%
Cefuroxime	11.5%	Azithromycin（IV）	12.1%	Imipenem/cilastin	9.[illegible]%	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%

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3.4 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, 55.5%), followed by upper respiratory infections (283, 7.7%) and sepsis (240, 6.5%). 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 12.34%. 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, 11.5%), latamoxef (225, 11.0%), amoxicillin and enzyme inhibitors (200, 9.8%), ceftriaxone (197, 9.6%) and ceftizoxime (188, 9.2%).

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Table 4 Indications for antimicrobial prescribing in Chinese children

Indications for antimicrobial prescribing	Frequency	Percentage%
Proven or probable Bacterial lower respiratory tract infection(LRTI)	2,044	55.5
Upper Respiratory Infections (URTI)	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
Pyrexia of Unknown Origin (PUO)	56	1.5
Unknown	46	1.3
Skin/Soft Tissue Infections (SSTI)	43	1.2
Prophylaxis for Surgical disease	40	1.1
Prophylaxis for Medical problems	39	1.1
Febrile neutropenia/Fever	37	1.0
Proven or probable Viral LRTI	29	0.8
Urinary Tract Infections (UTI)	27	0.7
Cardiac Infections	13	0.4
Newborn Prophylaxis for Maternal Risk factors	13	0.4
Lymphadenitis	8	0.2
Decolonization for Bacterial Carrier	6	0.2
Joint/Bone Infections	5	0.1
Probable or Proven Catheter-related	3	0.1
Acute Otitis Media (AOM)	1	0.0
Total	3680	100

"Other" in the "Indications for antimicrobial prescribing" column refers to indications for antibiotics which is not in the indications list designed for the survey.

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4. 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. A survey was conducted in Yuying Children's Hospital of Wenzhou Medical University, located in the Zhejiang province in Southeastern China, from 2010 to 2017. Data on antimicrobial prescription usage showed that the antibiotic prescription rate declined from 55.2% to 23.1% in outpatient departments, 75.6% to 35.1% in emergency departments, and 76% to 50.3% in inpatient departments. DDDs decreased from 38.43/100 to 19.41/100 patient-days. The detection rates of extended-spectrum β-lactamases-producing *Escherichia coli* decreased from 75.4% to 46.7%, whereas detection rates of *Klebsiella pneumonia* decreased from 78.7% to 32.5% [1]. After implementation of the antimicrobial stewardship program, 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[5-7].

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[8]. In our present study 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 [8].

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

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intravenous or oral penicillins are prescribed [9]. In some hospitals where skin tests are not required when oral penicillins are prescribed, the proportion of prescribed cephalosporins have been substantially decreased [10]. 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[11, 12].

Gentamicin is the first-line antibiotic recommended for children and neonates with common infections by international guidelines and WHO recommendations [13]. Gentamicin was prohibited for children under six years old in China in the clinical specification of common ototoxic medicines in 1999, published by the Ministry of Health of the People's Republic of China, as a strategy for preventing deafness and hearing impairments [14]. The ototoxicity of gentamicin also associated with genetic susceptibility. Mutations in the mitochondrial *12SrRNA(MTRNR1)*, particularly the A1555G mutation was considered highly associated with the ototoxic effect of aminoglycosides[15]. 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 [16, 17]. There are no reasons 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.

The proportion of the Watch group was 76.5% in 2016. Based on antibacterial-agent management in China, the Special group of antibiotics included carbapenems and glycopeptides was 16.14% in 2016.

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 United States from 2016 to 2017, there was one antibiotic (ceftriaxone) that belonged to third-generation cephalosporins accounting for 9.2% of antimicrobial use [7]. In 2012, a survey focusing on pediatric inpatients in Australia revealed that the proportion of third-generation cephalosporins was less than 10% [18].

The most common bacteria causing infection in children are *Haemophilus influenzae* and *Streptococcus pneumoniae*. Third-generation cephalosporins that are recommended for pathogens such *as Haemophilus influenzae* and *Streptococcus*

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pneumoniae are resistant to penicillins, as well as first-generation and second-generation cephalosporins. In 2016, the resistance rates of *Haemophilus 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 *Streptococcus pneumoniae* was 18.2% [19]. The antimicrobial resistance of penicillins, as well as first-generation and second-generation cephalosporins, did not increase greatly and was not more than thirty percent. 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.

It was probable that the third-generation cephalosporins in Chinese children were overused. Abuse of third-generation cephalosporins caused common pathogens with the high resistance to cephalosporins. Fu P, et al reported the antimicrobial resistance of clinical isolates in children in China, the resistance of *E.coli.* and *Klebsiella pneumonia* to ceftriaxone were 52.3% and 56.1%[20].

Carbapenems as a kind of extra broad spectrum antibiotic are classified into the Watch group based on the WHO AWaRe and into the Special group and should be prioritized as key targets of local and national stewardship programs and monitoring. Furthermore, carbapenems should be used for children infected by *Enterobacterales* producing extra-spectrum broad lactamases (ESBLs), as well as for *Pseudomonas aeruginosa* that is resistant to third-generation cephalosporins. 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 [21]. 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[22]. 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

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tazobactam are viable alternatives to carbapenems and keep low resistance rate to *E.coli*(3.9%) *and Klebsiella pneumoniae*(22.2%) in the survey of Antimicrobial resistance profile of clinical isolates in pediatric hospitals in China in 2019[20]. In this study, the piperacillin and tazobactam used for infections in Chinese children only accounted for 4.1% and less than half of carbapenems.

In this study, we found that azithromycin belonged to macrolides was the commonest antibiotic prescribed for children, accounting for 11.7% of total antimicrobial prescriptions. The high azithromycin prescribing promoted the resistance to a lot of pathogens like *Mycoplasma pneumoniae*, *Bordetella pertussis* and other microorganisms. Antimicrobial susceptibility of *Mycoplasma pneumoniae* isolates from different regions of China showed that the general macrolides resistance rate was 79.7% and 100% in some cities [23].

Different from high Macrolide-resistance of *Mycoplasma pneumoniae* in China, the resistance were very low in some countries. Macrolide-resistant *M. pneumoniae* was detected in 8.3% of specimens in the United States, between 2012 and 2018[24]. In the monitor of antimicrobial resistance of clinical isolates in children in China, the resistance rates of *Streptococcus pneumoniae* to erythromycin and clindamycin were 97.7% and 93.5%. It was probable high resistance of common pathogens to macrolides related to overuse of this class of antibiotics [20]. In Europe, only sporadic *Bordetella pertussis* isolates which were resistant to macrolides were reported [25]. In China, however, the picture has been significantly different. The rate of resistance to macrolides was over than 90% in Beijing [26].

There are a number of reasons for the high prescription rate of macrolides in China. Macrolides have lower allergy risk with no need for skin testing, and are readily available in general pharmacies. Misunderstanding of positive IgM or IgG which can last months as the evidence of *mycoplasma pneumoniae* infection would prolong the duration of azithromycin treatment to months. On the one hand, the overuse of macrolides such as azithromycin leads to the further aggravation of antimicrobial resistance and poor clinical efficacy.

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Since 2017, there have been continuous actions to promote the rational use of antibiotic agents, such as multi-disciplinary 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. This study described the distribution of different types of antibiotic agents in clinical practice in children five 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 analyzed 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 point-prevalence survey, it may be useful as a means for continuous monitoring of antibiotic use over time.

The present study had several limitations. The point-prevalence survey in 2016 only collected antibacterial prescriptions for four 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 specialized hospitals within regional centers that may prescribe a higher percentage of broader-spectrum antibiotics compared to that of other types of hospitals. Thirdly, it was difficult to determine appropriateness of antibiotic use because of lack of microbiology and antimicrobial susceptibility results and detailed patient characteristics.

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5. Conclusion

In this study, it was found that in 2016—five 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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Author contributions

YY, JZ, WZ, YZ, JD were responsible for the study concept and design. YY organized all hospitals to collect data. JZ, WZ, XM, LT and DT collected the data of antibiotic prescriptions. JZ and KW contributed to the data management and analyses. JZ and WZ contributed to the interpretation of data and writing of the manuscript. YY, YZ, KS and JD revised the manuscript. All authors reviewed and agreed the final manuscript.

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Competing interests

The authors have declared no conflict of interest.

Consent for publication

Not applicable.

Data availability statement

No additional data available.

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

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

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Figure 1 Proportion of prescribed antibiotics(ATC classification) among Chinese children（%）

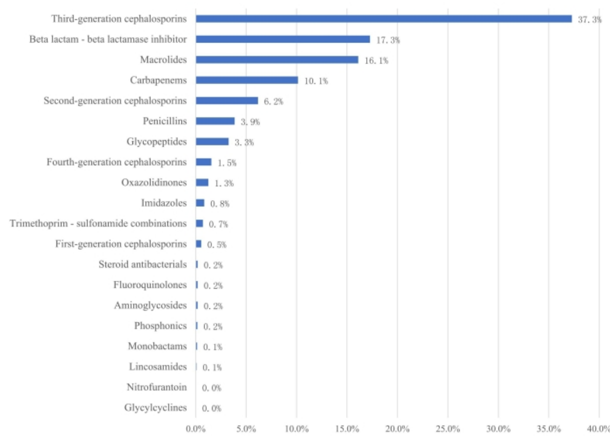

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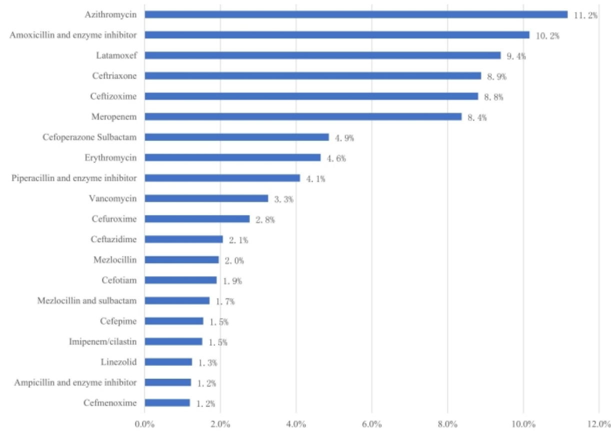
Figure 2 Patterns of antibiotic prescribing to Chinese children by drug utilization 90%



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Supplementary table 1 A list of Unrestricted, Restricted, and Special groups of antibiotics in China

Unrestricted antibiotics
Cefazolin
cefadroxil
Metronidazole
Clindamycin
Azithromycin
Erythromycin
Clarithromycin
Roxithromycin
Acetylkitasamycin
Erythromycin estolate
Nitrofurantoin
Amoxicillin
Ampicillin
Benzylpenicillin
Penicillins
Benzathine benzylpenicillin
Fosfomycin
Cefaclor
Cefuroxime
Ceftriaxone
Sulfamethoxazole and trimethoprim
Restricted antibiotics
Amoxicillin and enzyme inhibitor
Piperacillin and enzyme inhibitor
Mezlocillin and sulbactam
Ampicillin and enzyme inhibitor
Amoxicillin clavulinic acid
Ampicillin and Sulbactam
Piperacillin/Tazobactam
Chloramphenicol
Azithromycin
Fusidic acid
Mezlocillin
Piperacillin
Cefatrizine
Cefathiamidine
Cefotiam
Latamoxef
Cefpodoxime
Cefdinir
Cefodizime
Cefmenoxime

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Cefixime
Ceftazidime
Cefoperazone
Cefoperazone Sulbactam
Ceftizoxime
Cefotaxime
Cefpiramide
Cefetamet
Special group antibiotics
Ertapenem
Meropenem
Lmipenem and enzyme inhibitor (Imipenem/cilastin)
Linezolid
Tigecycline
Vancomycin
Teicoplanin
Cefotaxime Sulbactam
Cefepime
Unclassified antibiotics
Azidocillin
Azlocillin
Sulbenicillin
Oxacillin
Furbucillin
Ampicloxacillin
Fluloxacillin amoxicillin
Cloxacillin
Oxacillin
Amikacin
Tobramycin
Netilmicin
Sisomicin
Neomycin
Streptomycin
Micronomicin
Aztreonam
Ornidazole
Panipenem and betamipron
Ticarcillin and enzyme inhibitor
Piperacillin and Sulbactam
Cefbuperazone
Cefmetazole
Cefamandole
Cefminox

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Cefoxitin
Cefonicid
Cefprozil
Cefradine
Ceftezole
Cefazedone
Cefaloridine
Ciprofloxacin
Ofloxacin
Levofloxacin
norfloxacin
Pipemidic acid
Josamycin
ErythromycinEthylsuccinate
Lincomycin
Polymyxin E
Doxycycline

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Supplementary table 2 A list of antimicrobial agents prescribed in this study based on WHO AWaRe classification and China's administrative categories

Antibiotic	WHO AWaRe	Antibiotic classification in China
Amikacin	Access	Unclassified
Amoxicillin	Access	Unrestricted
Amoxicillin and enzyme inhibitor	Access	Restricted
Ampicillin	Access	Unrestricted
Ampicillin and enzyme inhibitor	Access	Restricted
Azidocillin	Access	Unclassified
Azithromycin(IV)	Watch	Restricted
Azithromycin(Oral)	Watch	Unrestricted
Azlocillin	Watch	Unclassified
Aztreonam	Reserve	Unclassified
Benzylpenicillin	Access	Unrestricted
Cefaclor	Watch	Unrestricted
Cefaloridine	Access	Unclassified
Cefamandole	Watch	Unclassified
Cefatrizine	Access	Restricted
Cefazedone	Access	Unclassified
Cefazolin	Access	Unrestricted
Cefbuperazone	Watch	Unclassified
Cefdinir	Watch	Restricted
Cefepime	Watch	Special
Cefixime	Watch	Restricted
Cefmenoxime	Watch	Restricted
Cefmetazole	Watch	Unclassified
Cefminox	Watch	Unclassified
Cefodizime	Watch	Restricted
Cefoperazone	Watch	Restricted
Cefoperazone Sulbactam	not recommended	Restricted
Cefotaxime	Watch	Restricted
Cefotiam	Watch	Restricted
Cefoxitin	Watch	Unclassified
Cefpodoxime	Watch	Restricted
Cefradine	Access	Unclassified
Ceftazidime	Watch	Restricted
Ceftezole	Access	Unclassified
Ceftizoxime	Watch	Restricted
Ceftriaxone	Watch	Unrestricted
Cefuroxime	Watch	Unrestricted
Ciprofloxacin	Watch	Unclassified
Clarithromycin	Watch	Unrestricted
Clindamycin	Access	Unrestricted

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Ertapenem	Watch	Special
Erythromycin	Watch	Unrestricted
Fosfomycin	Reserve	Unrestricted
Fusidic acid	Watch	Restricted
Imipenem/cilastin	Watch	Special
Latamoxef	Watch	Restricted
Levofloxacin	Watch	Unclassified
Linezolid	Reserve	Special
Meropenem	Watch	Special
Metronidazole	Access	Unrestricted
Mezlocillin	Watch	Restricted
Mezlocillin and sulbactam	not recommended	Restricted
Nitrofurantoin	Access	Unrestricted
Ofloxacin	Watch	Unclassified
Ornidazole	Unclassified	Unclassified
Oxacillin	Access	Unclassified
Panipenem and betamipron	Watch	Unclassified
Piperacillin	Watch	Restricted
Piperacillin and enzyme inhibitor	Watch	Restricted
Roxithromycin	Watch	Unrestricted
Sulbenicillin	Watch	Unclassified
Sulfamethoxazole and trimethoprim	Access	Unrestricted
Ticarcillin and enzyme inhibitor	Unclassified	Unclassified
Tigecycline	Reserve	Special
Tobramycin	Watch	Unclassified
Vancomycin	Watch	Special

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STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	5
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	5
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	8
Objectives	3	State specific objectives, including any prespecified hypotheses	8
Methods			
Study design	4	Present key elements of study design early in the paper	10
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	10
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	10
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	10
Bias	9	Describe any efforts to address potential sources of bias	10
Study size	10	Explain how the study size was arrived at	10
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	NA
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	11
		(*b*) Describe any methods used to examine subgroups and interactions	10
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	13
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	13-21
		(b) Indicate number of participants with missing data for each variable of interest	13-21
Outcome data	15*	Report numbers of outcome events or summary measures	13-21

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Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	13-21
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	22
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	26
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-19
Generalisability	21	Discuss the generalisability (external validity) of the study results	27
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Antimicrobial prescribing for children in China, data from point prevalence surveys in 18 tertiary centers in China in 2016-2017

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Title: Antimicrobial prescribing for children in China, data from point prevalence surveys in 18 tertiary centers in China in 2016-2017

Running title: Antibiotic prescribing pattern in Chinese children

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Antimicrobial prescribing for children in China, data from point prevalence surveys in 18 tertiary centers in China in 2016-2017

Abstract

Objectives: The reports on evaluating the classification of antibiotic agents prescribed for Chinese children by combining World Health Organization'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 centers 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 was collected and analyzed. 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 hospitalized children in China between February 1, 2016, and February 28, 2017. Six 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 utilization (DU) of 90%, Anatomical Therapeutical Chemical Classification (ATC Classification), WHO 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

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hospitalized children in China in 2016.

Keywords: Antibiotic; Children; Antibiotic stewardship; WHO Essential Medicines list for children; China;

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Strengths and limitations of this study

1. This study was a multi-center survey covering nine provinces and increasing representativeness.

2. This study focused on describing the classification pattern of antibiotic prescriptions in clinical practice in Chinese children in terms of both the WHO AWaRe and the Management of Antibiotic Classification in China which were different.

3. It was difficult to determine appropriateness of antibiotic use because of lack of microbiology and antimicrobial susceptibility results and detailed patient characteristics.

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1. 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 prioritized as key targets of local and national stewardship programs and monitoring.

In response to increasing antimicrobial resistance, World Health Organization adopted a global action plan on antimicrobial resistance and one of objectives is to optimize 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 utilization rate declined from 76.0% (30568/40221) to 50.3% (35493/70544) and antibiotic-use density from 38.4 to 19.4 DDDs (Defined Daily Dose) /100 bed-days before (2010-2011) and after (2016-2017) antimicrobial stewardship program. These two indicators of antimicrobial management had both been greatly reduced following this campaign [1]. However, these two indicators (i.e., 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 ten years, more attention has been paid to the antibiotic usage rate and total antibiotic consumption, both 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

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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 analyzed by China's administrative categories of antibiotics and the WHO Essential Medicines List of AWaRe to determine antibiotic patterns in 2016 in Chinese children.

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2. Methods

2.1. Data collection

Four one-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 hospitalized in participating hospitals were included in this survey. Thirteen children's hospitals, pediatric wards from 2 general hospital and 3 women and children's healthcare centers 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 standardization 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 pediatric wards and special medical wards including respiratory, infectious diseases and neonatology wards), surgical wards and intensive care units (Neonatal intensive care units and Pediatric intensive care units) was collected and analyzed. 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 centers 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, thirteen hospitals in the second PPS, seventeen hospitals in the third PPS, and eighteen 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.

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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 analyzed. 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.

2.2. Statistical analysis

We described patterns of antibiotic use with a drug utilization (DU) 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- 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 showed in Supplementary 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 group [4]. The

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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 multi-drug resistance probably. The Special group antibiotic lists in different hospitals in China were the same. But 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) catalogs. A list of Unrestricted, Restricted, and Special group of antibiotics in China for this study was shown in Supplementary Table 2. The WHO AWaRe classification and matched China classification of antibiotics were described in Supplementary Table 3.

For the statistical analysis, Microsoft Excel 2007 (Microsoft Corporation, WA, United States of America) and SPSS 22.0(IBM, Chicago, United States of America) 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.

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3. Results

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

In the point-prevalence survey in 2016, 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. The characteristics of participating hospitals by frequency of antibiotic prescriptions in 2016 are shown in Table 1.

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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

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

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 Proportion of prescribed antibiotics (ATC classification) among Chinese children).

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 Patterns of antibiotic prescribing to Chinese children by drug utilization 90%).

In the top-ten antimicrobial agents, only two agents which 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 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).

1034 antibiotic prescriptions were used for children in the Intensive Care Units (ICU), 635 for neonates in neonatal ICUs and 399 for children in pediatric 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 which accounted for 71.0% were third-generation cephalosporins (317/1034, 30.7%), carbapenems (207/1034, 20.0%) and

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beta lactam-beta lactamase inhibitors (210/1034, 20.3%). In NICUs, 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 inhibitors (54/399, 13.5%), and vancomycin (48/399, 12.0%).

3.2. Antibiotic classes prescribed pattern based on the WHO Access/Watch/Reserve 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.

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%), meropenem(308/2814,10.9%). The detailed antibiotic types in every group based on the WHO AWaRe classifications were shown in Table 2.

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Table 2 Antibiotics(WHO AWaRe classification) prescribing to Chinese children by drug utilization 90% in 2016. AWaRe classification, Access/Watch/Reserve classification

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%						

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3.3. 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. 47(4.5%) antibiotic prescriptions for children and neonates in the ICUs were in the Unclassified group.

In the Special group antimicrobials which 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.

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Table 3 Antibiotics(China classification) prescribing to Chinese children by drug utilization 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	51.7%	Cefminox	14.4%
Erythromycin	19.3%	Latamoxef	16.6%	Vancomycin	20.7%	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%

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3.4 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%). 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, 9.8%), ceftriaxone (197/2044, 9.6%) and ceftizoxime (188/2044, 9.2%).

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Table 4 Indications for antimicrobial prescribing in Chinese children

Indications for antimicrobial prescribing	Frequency	Percentage%
Proven or probable Bacterial lower respiratory tract infection(LRTI)	2,044	55.5
Upper Respiratory Infections (URTI)	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
Pyrexia of Unknown Origin (PUO)	56	1.5
Unknown	46	1.3
Skin/Soft Tissue Infections (SSTI)	43	1.2
Prophylaxis for Surgical disease	40	1.1
Prophylaxis for Medical problems	39	1.1
Febrile neutropenia/Fever	37	1.0
Viral co-infection with bacteria LRTI	29	0.8
Urinary Tract Infections (UTI)	27	0.7
Cardiac Infections	13	0.4
Newborn Prophylaxis for Maternal Risk factors	13	0.4
Lymphadenitis	8	0.2
Decolonization for Bacterial Carrier	6	0.2
Joint/Bone Infections	5	0.1
Probable or Proven Catheter-related	3	0.1
Acute Otitis Media (AOM)	1	0.0
Total	3680	100

"Other" in the "Indications for antimicrobial prescribing" column refers to indications for antibiotics which is not in the indications list designed for the survey.

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4. 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 program, 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 six years old in China because of its potential to cause deafness and hearing impairments [16]. The ototoxicity of gentamicin

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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 United States 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 pediatric 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 Haemophilus influenzae* and *Streptococcus pneumoniae* are resistant to penicillins, as well as first-generation and second-generation cephalosporins. In 2016, the resistance rates of *Haemophilus 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 *Streptococcus pneumoniae* was 18.2% [21]. The antimicrobial resistance of penicillins, did not increase greatly and was not more than thirty percent. 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 P, et al reported the antimicrobial resistance of clinical strains isolated from children in China, the resistance of *E.coli.* and *Klebsiella pneumoniae* to ceftriaxone were 52.3% and 56.1% [22].

Based on antibacterial-agent management in China, the proportion of antibiotics

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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 prioritized as key targets of local and national stewardship programs 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 Klebsiella pneumoniae*(22.2%) in the survey of Antimicrobial resistance profile of clinical isolates in pediatric 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 multi-disciplinary 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 generalizability. This study described the distribution of different types of antibiotic agents in clinical practice in children five years later after special action for

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antimicrobial stewardship in China, which has been promoted strongly since 2011. To our knowledge, our present study is the first to have analyzed 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 point-prevalence survey, it may be useful as a means for continuous monitoring of antibiotic use over time.

The present study had several limitations. The point-prevalence survey in 2016 only collected antibacterial prescriptions for four 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 specialized hospitals within regional centers that may prescribe a higher percentage of broader-spectrum antibiotics compared to that of other types of hospitals. Thirdly, it was difficult to determine appropriateness of antibiotic use because of lack of microbiology and antimicrobial susceptibility results and detailed patient characteristics.

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5. Conclusion

In this study, it was found that in 2016—five 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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Author contributions

YY, JZ, WZ, YZ, JD were responsible for the study concept and design. YY organized all hospitals to collect data. JZ, WZ, XM, LT and DT collected the data of antibiotic prescriptions. JZ and KW contributed to the data management and analyses. JZ and WZ contributed to the interpretation of data and writing of the manuscript. YY, YZ, KS and JD revised the manuscript. All authors reviewed and agreed the final manuscript.

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Competing interests

The authors have declared no conflict of interest.

Consent for publication

Not applicable.

Data availability statement

Data are available from the corresponding author upon reasonable request.

Ethics approval

Every patient record was given a unique non-identifiable serial survey number in a hospital, which was automatically generated by the survey system. The ethics

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committees at Shenzhen Children's Hospital approved the procedures in this study (Reference Number: 2018015). Written informed consent from participate was provided by the participants before data collection.

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

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

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Figure 1 Proportion of prescribed antibiotics(ATC classification) among Chinese children（%）

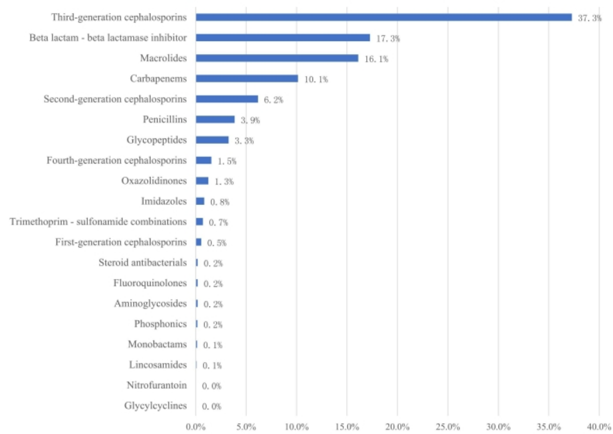

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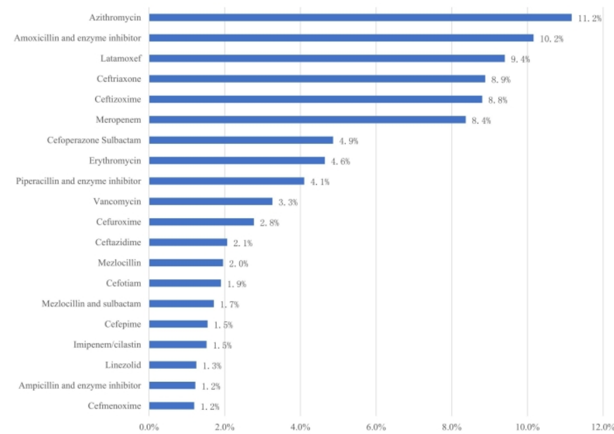
Figure 2 Patterns of antibiotic prescribing to Chinese children by drug utilization 90%



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Supplementary table 1 The antibiotics included in WHO Essential Medicines List for Children by AWaRe group

Access antibiotics
Amikacin
Amoxicillin
Amoxicillin/clavulanic Acid
Ampicillin
Benzathine benzylpenicillin
Benzylpenicillin
Cefalexin
Cefazolin
Chloramphenicol
Clindamycin
Cloxacillin
Doxycycline
Gentamicin
Metronidazole
Nitrofurantoin
Phenoxymethylpenicillin
Spectinomycin
Procaine benzylpenicillin
Sulfamethoxazole/trimethoprim
Watch antibiotics
Azithromycin
Cefixime
Cefotaxime
Ceftazidime
Ceftriaxone
Cefuroxime
Ciprofloxacin
Clarithromycin
Meropenem
Piperacillin/tazobactam
Vancomycin (IV)
Vancomycin (oral)
Reserve antibiotics
Ceftazidime-avibactam
Colistin
Fosfomycin (IV)
Linezolid
Meropenem-vaborbactam
Plazomicin
Polymyxin B

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Supplementary table 2 A list of Unrestricted, Restricted, and Special groups of antibiotics in China

Unrestricted antibiotics
Cefazolin
cefadroxil
Metronidazole
Clindamycin
Azithromycin
Erythromycin
Clarithromycin
Roxithromycin
Acetylkitasamycin
Erythromycin estolate
Nitrofurantoin
Amoxicillin
Ampicillin
Benzylpenicillin
Penicillins
Benzathine benzylpenicillin
Fosfomycin
Cefaclor
Cefuroxime
Ceftriaxone
Sulfamethoxazole and trimethoprim
Restricted antibiotics
Amoxicillin and enzyme inhibitor
Piperacillin and enzyme inhibitor
Mezlocillin and sulbactam
Ampicillin and enzyme inhibitor
Amoxicillin clavulinic acid
Ampicillin and Sulbactam
Piperacillin/Tazobactam
Chloramphenicol
Azithromycin
Fusidic acid
Mezlocillin
Piperacillin
Cefatrizine
Cefathiamidine
Cefotiam
Latamoxef
Cefpodoxime
Cefdinir
Cefodizime
Cefmenoxime

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Cefixime
Ceftazidime
Cefoperazone
Cefoperazone Sulbactam
Ceftizoxime
Cefotaxime
Cefpiramide
Cefetamet
Special group antibiotics
Ertapenem
Meropenem
Lmipenem and enzyme inhibitor (Imipenem/cilastin)
Linezolid
Tigecycline
Vancomycin
Teicoplanin
Cefotaxime Sulbactam
Cefepime
Unclassified antibiotics
Azidocillin
Azlocillin
Sulbenicillin
Oxacillin
Furbucillin
Ampicloxacillin
Fluloxacillin amoxicillin
Cloxacillin
Oxacillin
Amikacin
Tobramycin
Netilmicin
Sisomicin
Neomycin
Streptomycin
Micronomicin
Aztreonam
Ornidazole
Panipenem and betamipron
Ticarcillin and enzyme inhibitor
Piperacillin and Sulbactam
Cefbuperazone
Cefmetazole
Cefamandole
Cefminox

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Cefoxitin
Cefonicid
Cefprozil
Cefradine
Ceftezole
Cefazedone
Cefaloridine
Ciprofloxacin
Ofloxacin
Levofloxacin
norfloxacin
Pipemidic acid
Josamycin
ErythromycinEthylsuccinate
Lincomycin
Polymyxin E
Doxycycline

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Supplementary table 3 A list of antimicrobial agents prescribed in this study based on WHO AWaRe classification and China's administrative categories

Antibiotic	WHO AWaRe	Antibiotic classification in China
Amikacin	Access	Unclassified
Amoxicillin	Access	Unrestricted
Amoxicillin and enzyme inhibitor	Access	Restricted
Ampicillin	Access	Unrestricted
Ampicillin and enzyme inhibitor	Access	Restricted
Azidocillin	Access	Unclassified
Azithromycin(IV)	Watch	Restricted
Azithromycin(Oral)	Watch	Unrestricted
Azlocillin	Watch	Unclassified
Aztreonam	Reserve	Unclassified
Benzylpenicillin	Access	Unrestricted
Cefaclor	Watch	Unrestricted
Cefaloridine	Access	Unclassified
Cefamandole	Watch	Unclassified
Cefatrizine	Access	Restricted
Cefazedone	Access	Unclassified
Cefazolin	Access	Unrestricted
Cefbuperazone	Watch	Unclassified
Cefdinir	Watch	Restricted
Cefepime	Watch	Special
Cefixime	Watch	Restricted
Cefmenoxime	Watch	Restricted
Cefmetazole	Watch	Unclassified
Cefminox	Watch	Unclassified
Cefodizime	Watch	Restricted
Cefoperazone	Watch	Restricted
Cefoperazone Sulbactam	not recommended	Restricted
Cefotaxime	Watch	Restricted
Cefotiam	Watch	Restricted
Cefoxitin	Watch	Unclassified
Cefpodoxime	Watch	Restricted
Cefradine	Access	Unclassified
Ceftazidime	Watch	Restricted
Ceftezole	Access	Unclassified
Ceftizoxime	Watch	Restricted
Ceftriaxone	Watch	Unrestricted
Cefuroxime	Watch	Unrestricted
Ciprofloxacin	Watch	Unclassified
Clarithromycin	Watch	Unrestricted
Clindamycin	Access	Unrestricted

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Ertapenem	Watch	Special
Erythromycin	Watch	Unrestricted
Fosfomycin	Reserve	Unrestricted
Fusidic acid	Watch	Restricted
Imipenem/cilastin	Watch	Special
Latamoxef	Watch	Restricted
Levofloxacin	Watch	Unclassified
Linezolid	Reserve	Special
Meropenem	Watch	Special
Metronidazole	Access	Unrestricted
Mezlocillin	Watch	Restricted
Mezlocillin and sulbactam	not recommended	Restricted
Nitrofurantoin	Access	Unrestricted
Ofloxacin	Watch	Unclassified
Ornidazole	Unclassified	Unclassified
Oxacillin	Access	Unclassified
Panipenem and betamipron	Watch	Unclassified
Piperacillin	Watch	Restricted
Piperacillin and enzyme inhibitor	Watch	Restricted
Roxithromycin	Watch	Unrestricted
Sulbenicillin	Watch	Unclassified
Sulfamethoxazole and trimethoprim	Access	Unrestricted
Ticarcillin and enzyme inhibitor	Unclassified	Unclassified
Tigecycline	Reserve	Special
Tobramycin	Watch	Unclassified
Vancomycin	Watch	Special

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STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	7
Objectives	3	State specific objectives, including any prespecified hypotheses	8
Methods			
Study design	4	Present key elements of study design early in the paper	9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	9
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	10
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	10
Bias	9	Describe any efforts to address potential sources of bias	10
Study size	10	Explain how the study size was arrived at	10
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	NA
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	11
		(*b*) Describe any methods used to examine subgroups and interactions	11
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	12
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	13-20
		(b) Indicate number of participants with missing data for each variable of interest	13-20
Outcome data	15*	Report numbers of outcome events or summary measures	13-20

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Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	13-20
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	21-24
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	25
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	26
Generalisability	21	Discuss the generalisability (external validity) of the study results	26
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	27

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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