

ORIGINAL RESEARCH

Shanghai Parents' Perception And Attitude Towards The Use Of Antibiotics On Children: A Cross-Sectional Study

This article was published in the following Dove Press journal: Infection and Drug Resistance

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Background: Parents play an important role in the management of their children's illnesses, including in decisions concerning how and whether to use antibiotics. This study aims to assess the knowledge and attitude towards antibiotics usage among young parents from different areas in Shanghai and to identify contributing factors of antibiotics usage that are comprehensible for parents.

Methods: A cross-sectional study was conducted at vaccination clinics of three community health centers from April to June 2017. Primary guardians who took children for vaccination under the national expanded immunization program were invited to participate.

Results: Of the 1368 young parents interviewed, 78.4% of them have taken their children for medical treatment, and 68.9% of their children have taken antibiotics. Parents with education level of senior high school (OR=1.850, 95% CI: 1.214–2.818), or university/college, or above (OR=3.950, 95% CI: 2.604–5.991), and parents with high-income (OR=1.360, 95% CI: 1.013–1.827) have better comprehension of antibiotics. It is found that parents who deny the existence of antibiotic abuse in China (OR=1.857, 95% CI: 1.100–3.135), who have lower income (OR=1.536, 95% CI: 1.074–2.197) and who have antibiotics prescribed by doctors (OR=1.473, 95% CI: 1.048–2.070) are associated with those incorrect practices.

Conclusion: Lack of knowledge and poor perception of antibiotics usage are found among young parents in Shanghai. Intervention should be conducted to publicize the rational use of antibiotics, reduce the rate of inappropriate behaviors and limit the sale of antibiotics.

Keywords: antimicrobial resistance, KAP, China, urban area

Background

The discovery of antibiotics was a milestone in human history. Countless lives in the previous decades were saved after this medical revolution. However, antimicrobial resistance (AMR) is rapidly becoming one of the most serious threats to public health. AMR occurs naturally, but the misuse of antibiotics on humans and animals is accelerating the process and occurring everywhere in the world. AMR leads to longer hospital stays, higher medical costs, increased mortality, and decreased effectiveness of treatment. Amany of the medical breakthroughs since the last century could be wiped out because of the spreading of AMR. Tackling antibiotic resistance is a high priority for WHO and many governments.

China is the largest producer and consumer of antibiotics among countries in the world. The total human usage of antibiotics in China was estimated to be approximately 77,760 tons in 2013, which was 23 times more than that in the US.⁷ As a

result of antibiotic abuse and misuse, China has the world's most rapid growth of antibiotic resistance. In 2009, Heddini et al found that more than 60% of *Staphylococcus aureus* isolated from Chinese patients were methicillin-resistant, much higher than that in 2000 (40%). Meanwhile, the proportion of *Streptococcus pneumonia* isolated from Chinese patients that are resistant to macrolide topped 70%. Antibiotics are also regarded as a panacea in many primary health-care centers in China. Doctors might overprescribe antibiotics due to lack of knowledge of its rational use. A recent review shows that in China 83.7% of all patients with upper respiratory tract infections (URTI) have been prescribed with antibiotics. However, most URTIs are caused by viruses, which do not respond to antibiotics.

Children are more susceptible to respiratory tract infection and certain other infections. 12 In developed countries, a preschool infant experiences an average of 6-10 viral infections annually. 13 Parents' practices on how to use antibiotics have important effects on the management of children's illnesses. 14 For example, parents' high expectations of quick relief of symptoms and recovery of their children would impose further pressure on doctors to prescribe more antibiotics in order to make treatments more immediately effective.⁸ Parents' knowledge and attitudes towards antibiotics usage have huge impact on their practices. Previous studies observed the connection between parents' low level of knowledge about the use of antibiotics and the high prevalence of parents self-medicating their children with antibiotics in rural China. 14,15 However, there is little research on the perception and attitude of parents from more developed areas in China.

This study aims to assess the knowledge and attitude towards antibiotics usage among young parents in different areas in Shanghai, to identify contributing factors of antibiotics usage for parents, and to provide information for further health education in Shanghai.

Methods

Study Sites

Shanghai is one of the richest areas in China and its gross domestic product (GDP) ranked 1st in the country in 2016. Three communities, Tangqiao (TQ), Huacao (HC), and Gangyan (GY), were purposefully selected for the study based on their location and economic development level in Shanghai. TQ belongs to Pudong New District and its per capita gross domestic product (GDP) was US\$25,365 in

2016. HC belongs to Minhang District and its per capita GDP was US\$12,429 in 2016. GY belongs to Chongming District. Chongming District is on the edge of Shanghai and its per capita GDP was US\$6,664 in 2016. 16

The survey was conducted in the vaccination clinic of community health centers, the only one in each community, in each study site from April to June of 2017. Parents who took children for vaccination under the national expanded immunization program were invited to participate.

Data Instrument And Collection

Face-to-face questionnaire interviews were used to collect data. The questionnaire was developed by Professor Biao Xu and the research team in the School of Public Health of Fudan University in China. 14 The questionnaire collected information on: (1) demographic characteristics of the child and socioeconomic information of the parents; (2) the parents' knowledge and attitudes on antibiotic use, including basic concepts of antibiotics, indications of antibiotic use, administration of antibiotics. AMR and other side effects; (3) parents' experiences and practices of purchasing antibiotics without a prescription and (4) parents' experience and practices of self-medicating children with antibiotics. In total, the nine investigators, three physicians from each vaccination clinic, all of whom were responsible for the investigation. All of them had been trained by the School of Public Health of Fudan University before the investigation began.

Data Analysis

Parents' knowledge on antibiotics was scored from 14 selected questions, with one point for each correct answer. The scores ranged from 0 to 14, with scores above the median score deemed as being knowledgeable about antibiotics. Those who have at least one unfit behavior were defined as having inappropriate practices. To determine unfit behavior, we used the 4 questions below: (1) If I want my child to take antibiotics, I will ask the doctor directly, (2) When I want my child to take antibiotics, the dose is generally smaller than that required by the instructions, (3) When I want my child to take antibiotics, the dose is generally larger than that required by the instructions. (4) I will stock some antibiotics at home for my child.

The database was established using Epidata 3.0.1. SPSS for Windows ver. 17.0 (SPSS, Chicago, IL, USA) issued for data analysis. Means, medians, proportions and 95% confidence intervals (95% CIs) are calculated as

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descriptive statistics. The student's t-test, ANOVA and Chi-square test were used to compare the differences among subgroups. Logistic regression analysis was used to identify the factors associated with knowledge level and behavior. Confounding variables were defined as those resulting in ≥10% of change in the parameter with the estimation of the variable of interest when the potential confounder is added to the logistic regression model. Statistical significance is considered to be at p<0.05.

Ethical Statement

Written consent was obtained from all participants after the study was described in the initial face-to-face interview. Approval of this study was obtained from the Ethics Committee of Zhongshan Hospital, Fudan University (B2017-036).

Results

Characteristics Of Participants

A total of 1423 questionnaires were collected and 55 questionnaires were excluded because their completion rate was less than 90%. In the remaining 1368 questionnaires, 482 (33.9%) were from TQ, 481 (33.8%) were from HC, and 405 (32.3%) were from GY. Among the respondents, 33.1% were male, with the mean age being 33.2 years old. Parents from TQ had higher educational level and higher income level compared with those from HC and GY. The coverage of health insurance was higher in TQ than in HC (97.3% vs 91.7%, P<0.001) and GY (97.3% vs 93.8%, P=0.011). Parents from HC are more likely to have more than one child than those from TQ (43.6% vs 23.3%, P<0.001) and GY (43.6% vs 22.6%, P<0.001) (Table 1).

Use Of Antibiotics

In the six months before the interview, 78.4% of the respondents had taken their children to hospital. The median number of medical treatments received was 2, varying from 1 to 3. In those past six months, 68.9% of the respondents said that a doctor had prescribed antibiotics for their children, with the median number of prescriptions being 1 and varying from 0 to 2. As high as 27.2% of the parents had purchased antibiotics by themselves in the past 12 months and retail pharmacy (62.2%) was the main channel for them. As high as 41.8% of the parents had self-medicated their children with antibiotics without prescriptions from doctors in the last 12 months. The main

reasons cited for parents to self-medicate their children were: "Some antibiotics previously prescribed by physicians for the similar symptoms were left over at home (55.9%)" and "Children's condition was not serious enough (38.3%)". Parents who had purchased antibiotics by themselves were also more likely to self-medicate their children (49.0% vs 11.1%, P<0.001)

Knowledge Around The Appropriate Use Of Antibiotics And Antibiotics Resistance

As shown in Table 2, 46.5% of the participants think that antibiotics and anti-inflammatory drugs are same drugs. Only 27.4% of the participants know that antibiotics could not cure infections caused by viruses. The majority of participants (83.5%) believe that common cold does not require using antibiotics while 81.2% feel that antibiotics is not necessary when a child has a fever. More than half (60.6%) of the parents believe that antibiotics should be withdrawn as soon as the symptoms disappear. As high as 36.7% of the parents think that administration of multiple antibiotics would have better effects than a single one, and 24.6% of the parents prefer expensive antibiotics. About 29.2% of the parents believe that antibiotics can prevent the common cold.

The median score of parents for the 14 questions about antibiotics knowledge is 10, and 36% of them have higher levels of antibiotics usage knowledge. The proportion of parents with better antibiotics usage knowledge in TQ is significantly higher (51.7%) compared to those in HC (25.6%, P<0.001) and GY (29.6%, P<0.001). From multiple logistic regression analysis, we identified that parents with senior high school education (OR=1.850, 95% CI: 1.214–2.818) or college/university education and above (OR=3.950, 95% CI: 2.604-5.991) are more likely to have better knowledge of antibiotics usage than those with junior high school education or below. That is to say, the higher the parents' education level, the higher their level of knowledge about antibiotics usage will be. High-income parents also tend to have better knowledge of antibiotics (OR=1.360, 95% CI: 1.013-1.827) (Table 3).

Awareness And Attitudes Towards Antibiotics

As high as 71.6% of the parents agree that overuse of antibiotics does exist in China. Only 22.8% of the parents think that they are very knowledgeable about antibiotics while more than nine out of ten (90.4%) respondents are willing to receive more guidance on how to use antibiotics

Table I Characteristics Of Participants

	TQ, n (%)	HC, n (%)	GY, n (%)	P	
Number of participants	482(35.2)	481(35.2)	405(29.6)		
Gender				0.002	
Female	349(72.4)	317(65.9)	249(61.5)		
Male	133(27.6)	164(34.1)	156(38.5)		
Age of parents				<0.001	
≤20	0(0.0)	3 (0.6)	I (0.2)		
21–30	51(10.8)	280(58.2)	158(39.0)		
31–40	380(78.8)	175(36.4)	210(51.9)		
>40	51(10.6)	23(4.8)	36(8.9)		
Age of children				0.010	
<	9(1.9)	12(2.5)	13(3.2)		
I-6	469(97.3)	469(97.5)	386(95.3)		
7–12	1(0.2)	0(0.0)	6(1.5)		
>13	3(0.6)	0(0.0)	(0.3)		
Education level of parents				<0.001	
Primary school	0(0.0)	5(1.0)	10(2.5)		
Junior high school	18(3.7)	209(43.5)	113(27.9)		
Senior high school	34(7.1)	140(29.1)	147(36.3)		
Bachelor	339(70.3)	121(25.2)	131(32.3)		
Master and above	91(18.9)	6(1.2)	4(1.0)		
Number of children				<0.001	
One	353(76.7)	265(56.4)	312(77.4)		
More than one	107(23.3)	205(43.6)	91(22.6)		
Health insurance				0.001	
With	469(97.3)	441(91.7)	380(93.8)		
Without	13(2.7)	40(8.3)	25(6.2)		

Table 2 Parents' Correct Response To Questions Related To Knowledge Of Antibiotic Use

Questions		Correct Response	
	n	%	
Antibiotics and anti-inflammatory drugs are the same drugs.	635	46.5	
2. Antibiotics can cure infections caused by virus.	374	27.4	
3. Antibiotics should only be obtained with a doctor's prescription.	1077	78.8	
4. Antibiotics should be administered in all cases, once a child has fever.	1109	81.2	
5. If a child suffers from a cough, running nose, and a sore throat, it will be cured more quickly if he/she receives antibiotic as early as possible.	977	71.6	
6. In most cases, it is not necessary to treat a common cold with antibiotics.	1141	83.5	
7. Taking antibiotics in advance can protect children from a common cold.	967	70.8	
8. Administration of multiple antibiotics has better effects than a single one.	864	63.3	
9. The more expensive the antibiotic, the more effective it will be.	1030	75.4	
10. Antibiotics should be withdrawn as soon as the symptoms disappear	538	39.4	
11. Overuse of antibiotics increases the risk of antibiotic resistance.	958	70.2	
11. Antibiotics do not have side effects	1120	82.1	
12. Scientists can always produce new antibiotics.	323	23.7	
13. It is dangerous to children if pathogens become resistant to antibiotics.	925	67.7	

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Table 3 Factors Associated With Better Knowledge Of The Uses Of Antibiotics

Factors		n	Better Knowledge		cOR (95% CI)	aOR (95% CI)
			n	%		
Study sites	CM HC TQ	405 481 482	120 123 249	29.6 25.6 51.7	0.816(0.607–1.097) 2.538(1.922–3.352)*	0.963(0.682–1.361) 1.157(0.781–1.712)
Gender	Male Female	453 915	144 348	31.8 38.0	1.317(1.037–1.672)*	1.227(0.912–1.652)
Education	Secondary school or below High school College or above	355 321 692	54 83 355	15.2 25.9 51.3	1.944(1.326–2.850)* 5.872(4.239–8.133)*	1.850(1.214–2.818)* 3.950(2.604–5.991)*
Number of children	One More than one	624 403	214 117	34.3 29.0	0.784(0.598–1.028)	0.948(0.700-1.284)
Income	Low High	589 770	152 338	25.8 43.9	2.249(1.782–2.840)*	1.360(1.013–1.827)*
Insurance	Without With	78 1290	12 480	15.4 37.2	3.259(1.744–6.091)*	1.744(0.872–3.487)
Age of parents					1.039(1.021–1.056)*	1.015(0.993–1.038)

Note: *P<0.05.

correctly. Most of the parents (71.1%) are willing to follow doctors' advice completely. Only a few parents (9.0%) are dissatisfied if the doctors do not prescribe antibiotics. As high as 9.7% of the respondents are willing to use antibiotics by intravenous infusion. A majority of parents (90.6%) think that doctors should determine the etiological agent before prescribing (Figure 1).

Practices Of Using Antibiotics

As high as 19.3% of the respondents would ask doctors to prescribe antibiotics. Nearly half (48.5%) of the parents would use lower dose of antibiotics than required by the instructions with consideration of safety, while 8.9% of the

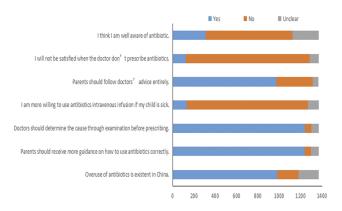


Figure 1 Parents' attitude towards antibiotics.

parents would choose a higher dose. More than a third of the respondents (35.9%) are likely to store antibiotics at home. Parents who would use a lower dose of antibiotics than required by the instructions (48.1% vs 24.3%, P<0.001) are more likely to store antibiotics at home.

We divided parents into two groups: Group One includes those report no use of antibiotics on their children and Group Two includes those with at least one instance of antibiotic use on their children. Multiple logistic regression results showed that the probability of having one or more instances of antibiotic use among parents from HC is 2.054 (OR=2.054, 95% CI: 1.217–3.467) times higher than parents from TQ. Denying the existence of antibiotic abuse in China (OR=1.857, 95% CI: 1.100–3.135), lower income (OR=1.536, 95% CI: 1.074–2.197) and having received prescription of antibiotics from doctors (OR=1.473, 95% CI: 1.048–2.070) are risk factors for those practices (Table 4).

Discussion

From our study, we found that there are misconceptions and lack of basic knowledge about the antibiotic resistance and the usage and administration of antibiotics.

Use Of Antibiotics

In our study, we find that antibiotics use is widespread over all three study sites. As high as 68.9% of the

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Table 4 Factors Associated With Practices Of Incorrect Uses Of Antibiotics

Factors		n	Have Prac	e tices	cOR (95% CI)	aOR (95% CI)
			n	%		
Age of parents						0.977(0.953-1.001)
Age of child						0.935(0.854–1.025)
Study sites	TQ HC CM	482 481 405	331 380 322	68.7 79.0 79.5	1.770(1.300–2.410)* 1.716(1.282–2.298)*	2.054(1.217–3.467)* 1.565(0.968–2.529)
Gender	Male Female	453 915	364 669	80.4 73.1	0.665(0.506–0.875)*	0.761(0.532–1.089)
Education	Secondary school or below High school College or above	355 321 692	279 249 505	78.6 77.6 73.0	0.942(0.654–1.357) 0.736(0.543–0.997)*	0.900(0.563–1.439) 1.384(0.826–2.319)
Number of child	One More than one	624 403	476 319	76.3 79.2	1.181(0.872–1.599)	1.197(0.847–1.693)
Income	Low High	589 770	459 567	77.9 73.6	1.264(0.982–1.627)	1.536(1.074–2.197)*
Insurance	Without With	78 1290	63 970	80.8 75.2	0.722(0.405–1.285)	0.588(0.273-1.269)
Better knowledge of antibiotics	Without With	876 492	696 337	79.5 68.5	0.562(0.437–0.723)*	0.771(0.530–1.123)
Know that antibiotics can only be prescribed by a doctor	No	289	229	79.2		
	Yes	1077	804	74.7	0.772(0.563-1.058)	0.735(0.470–1.149)
Having received prescription of antibiotics from doctors	No	535	379	70.8		
	Yes	673	527	78.3	1.486(1.144–1.930)*	1.473(1.048–2.070)*
Approving the existence of antibiotic abuse	Yes No Unknown	980 200 188	728 166 139	74.3 83.0 73.9	1.690(1.138–2.511)* 0.982(0.688–1.401)	1.857(1.100–3.135)* 0.751(0.456–1.239)
Well aware of antibiotic knowledge	No Yes Unknown	812 311 244	616 226 191	75.9 72.7 78.3	0.876(0.629-1.138) 1.147(0.813-1.618)	0.880(0.584–1.326) 1.073(0.677–1.700)

Note: *P<0.05.

respondents claimed that they had received antibiotics from doctors in the previous 6 months. Although recall bias might impact our result, we still believe that the improper prescription of antibiotics is a severe problem in Shanghai.

As high as 41.8% of the parents had self-medicated their children with antibiotics without prescription from doctors in the last 12 months. This rate is lower than that conducted in a previous study in rural China (62.0%),14 but higher than that in a research in Lithuania (31.0%). 17 The main reasons are: "The situation is not serious enough." and "Some antibiotics previously prescribed by doctors are left over". Only a few parents chose reasons like "do not have enough money to go to hospital", which is comparable to results found in a previous study in Thailand. 18 As high as 27.2% of the parents had purchased

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antibiotics by themselves in the last 12 months. A recent study in Saudi Arabia found that due to insufficient policies, 63.6% of the participants were reported to have purchased antibiotics without prescriptions from doctors at a rate higher than that found in our study (27.2%). Although antibiotic sales in retail pharmacies are not within the jurisdiction of government regulation, 20 retail pharmacy is still the main channel for parents to purchase antibiotics in China. Both self-medication and purchase of antibiotics without a prescription would cause irrational use of antibiotics. It is essential to publicize the harm of self-medication, to strengthen the supervision of pharmacies and to limit the sale of antibiotics.

Misconception Of Antibiotics

Our study shows that parents in Shanghai are not quite knowledgeable about antibiotic usage. Only 36.0% of them answered more than 10 questions correctly, and some of them had misinterpretation about the use of antibiotics. It is a major misconception that antibiotics can treat viral infections. Previous research in Poland found that the vast majority of respondents (80%) thought that antibiotics "kill" bacteria while at the same time 60% of the respondents believed that antibiotics "kill" viruses as well.²¹ Hawking et al found in their qualitative study²² that most parents could not tell the difference between viral and bacterial infections. In our study, we also found that 72.7% of the parents believed that antibiotics could treat viral infections. Thus, it is essential for us to strengthen the public knowledge of the difference between viral and bacterial infection for parents.

WHO suggests that patients should always take the full prescription, even if they feel better earlier. However, our study found that more than 60% of the participants reported believing that antibiotics should be withdrawn as soon as the symptoms disappear. A similar finding was reported by WHO in 2015, citing that Chinese respondents (53%) are more likely to stop taking antibiotics when they feel better. A previous study conducted at Xi'an Jiaotong University found that more than 50% of the students agreed that the use of antibiotics could be stopped as soon as symptoms disappear and nearly 30% of the students were uncertain about the answer to this question. ²³

Another interesting finding is that the majority of the respondents (76.3%) think that new antibiotics can always be developed by scientists. However, low return of the investment, unpredictable and often arduous pathways of

approval by regulatory agencies have caused many pharmaceutical companies to leave the antibiotics market.²⁴ The Infectious Disease Society of America (IDSA) reported that only a single new antibiotic had been approved by the Food and Drug Administration (FDA) since 2010.²⁵ As the development of new antibiotics is not optimistic, the thought that 'new antibiotics can always be developed by scientists' should be corrected.

On multivariate regression, the results show that the higher the educational level of parents, the higher level of their antibiotic knowledge; this is comparable to the results of many other studies. 26-30 The possible reason might be that parents with higher levels of education have more access to knowledge and information. Furthermore, parents with higher educational levels have more opportunities to learn about the use of antibiotics. On the other hand, parents with lower educational levels have fewer opportunities to acquire knowledge on and information about antibiotic use. In our study, the respondents with higher income are shown to have a higher level of antibiotic knowledge, which is similar to the findings of a previous study.²⁷ Compared with parents from TO and GY, the rate of correct answers to questions related to knowledge of antibiotic use among parents from HC is the lowest. We found that the rate of correct answers from parents in TQ was lower than that of GY, which might be due to the fact that HC community has more immigrant communities compared to GY.

Our study shows that 71.6% of the parents believe that overuse of antibiotics does exist in China; this rate is higher than that from previous researches conducted in rural China (61.0%)¹⁴ and in Malaysia (67.5%),²⁷ but lower than that from a study in Sweden (94.0%).³¹ This rate is alarming because Shanghai is one of the richest areas in China and the situation might be more serious in other areas.

As high as 70.2% of the parents agree that antibiotics resistance is caused by excessive use of antibiotics. Antibiotics resistance will lead to longer hospital stays, increased patient mortality and increased health-care costs, especially for children.³² In addition, children are more vulnerable than adults, and more than two-thirds of child-hood mortality is related to infections.⁵ Unfortunately, one-third of parents do not think that it is dangerous if the pathogens become resistant to antibiotics. It is essential to increase awareness of the seriousness of antibiotics resistance, especially in parents.

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Awareness And Practices Of Antibiotics Use

In general, it is reported that AMR mainly results from incompliance with treatment, uncompleted treatment, irregular treatment, and inadequate dosage.³³ In our research, a higher percentage of parents choose a lower dose of antibiotics compared to those who choose a higher dose of antibiotics to treat their child. This result is comparable to that of a previous study in Shandong province, China. 15 The result may be attributed to a Chinese traditional concept that any drug does harm to people's health to some extent. However, lower dose of antibiotics will prolong the treatment course, increase the risk of AMR and treatment failure. A total of 35.9% of the parents had stored antibiotics at home for future need. In addition, we found that parents who use a lower dose of antibiotics than that required by the instructions have a higher probability of storing antibiotics at home. Thus, antibiotics would be left over due to the lower dose used, and then these left-over antibiotics would be stored at home for future, unprescribed use. Therefore, it is essential to ask parents to follow the correct dose on the instructions. After adjusting the confounding factors, logistic regression analysis found that parents from HC are more likely to have irrational practices than parents from TQ. This is in line with the above result of parents' knowledge of antibiotic and the main reason is that HC has one of the largest immigrant communities in Shanghai. Parents who have received prescriptions of antibiotics from doctors in the previous 6 months are more likely to have those behaviors, which indicates that it is essential to restrict the prescriptions of antibiotics. Reducing the opportunity of parents' contact with antibiotics may be an effective way to decrease the rate of irrational antibiotic usage.

Conclusion

In conclusion, this study revealed incomplete knowledge and poor understanding of antibiotic usage among parents in Shanghai, especially in the HC area. The prescription of antibiotics from doctors may impact parents' practice of using antibiotics on children. Intervention should be conducted to regulate the prescriptions of antibiotics, advocate for rational use of antibiotics by parents to reduce inappropriate behaviors and limit the sale of antibiotics in retail pharmacies.

Abbreviations

AMR, antimicrobial resistance; cOR, crude odds ratio; aOR, adjusted odds ratio; CI, confidence interval; TQ, Tangqiao; HC, Huacao; GY, Gangyan.

Availability Of Data And Materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval And Consent Of Participant

Written consent was obtained from all participants after the study was described in the initial face-to-face interview. Approval of this study was obtained from the Ethics Committee of Zhongshan Hospital, Fudan University (B2017-036).

Acknowledgments

The author is grateful to those staff members from the three community health centers for their help in conducting the questionnaire. We greatly appreciate April Ai-Rou Qian (a rising Junior in the Molecular Biology and Biochemistry department at Middlebury College, USA) for her time and efforts to revise the manuscript.

Author Contributions

Jian Wang, Yuchao Sheng and Qi Zhao participated in the study design, data collection, analysis and the writing of manuscript. Jun Ni, Jianyu Zhu, Zhigang Zhou, Tianwei Liu, and Xiaoying Zhang participated in the data collection. All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Funding

This study was supported by The Fourth Round of Three-Year Public Health Action Plan of Shanghai, China, NO.15GWZK0101.

Disclosure

The authors report no conflicts of interest in this work.

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