BMJ Open

Leftover antibiotics encourage self-medication with antibiotics for children: a cross-sectional study from three Chinese provinces

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-033679
Article Type:	Original research
Date Submitted by the Author:	31-Aug-2019
Complete List of Authors:	Sun, Chenhui; Zhejiang University, School of Medicine, Institute of Social and Family Medicine Hu, Yanhong; The University of Melbourne, Murdoch Children's Research Institute Wang, Xiaomin; Zhejiang University, School of Medicine, Institute of Social and Family Medicine Lu, Jingjing; Zhejiang University, School of Medicine, Institute of Social and Family Medicine Lin, Leesa; London School of Hygiene and Tropical Medicine, Department of Public Health, Environments and Society, Faculty of Public Health and Policy; Harvard Medical School, Department of Global Health and Social Medicine Zhou, Xudong; Zhejiang University, School of Medicine, Institute of Social and Family Medicine
Keywords:	antimicrobial resistance, children, self-medication with antibiotics, leftover antibiotics

Title page

Leftover antibiotics encourage self-medication with antibiotics for children: a cross-sectional study from three Chinese provinces

Corresponding author:

Xudong Zhou

Institute of Social and Family Medicine, School of Medicine, Zhejiang University, 866 Yuhangtang Rd., Hangzhou, Zhejiang, 310058, P.R. China.

Email: zhouxudong@zju.edu.cn

Phone: 86-571-88208221

First author:

Chenhui Sun

Institute of Social and Family Medicine, School of Medicine, Zhejiang University, 866 Yuhangtang Rd., Hangzhou, Zhejiang, 310058, P.R. China.

Email: sunchenhui@zju.edu.cn

Second author:

Yanhong Jessika Hu

Murdoch Children's Research Institute, University of Melbourne. Royal Children's Hospital, Flemington Rd, Parkville VIC 3052

Email: huhubest@gmail.com

Xiaomin Wang

Institute of Social and Family Medicine, School of Medicine, Zhejiang University, 866 Yuhangtang Rd., Hangzhou, Zhejiang, 310058, P.R. China.

Email: xiaominwang2018@zju.edu.cn

Jingjing Lu

Institute of Social and Family Medicine, School of Medicine, Zhejiang University, 866 Yuhangtang Rd., Hangzhou, Zhejiang, 310058, P.R.China.

Email: jingjinglu@zju.edu.cn

Leesa Lin

1. Department of Public Health, Environments and Society, Faculty of Public Health and Policy, London School of Hygiene & Tropical Medicine, 15-17 Tavistock PL, Kings Cross, London WC1H9SH, UK;

2. Department of Global Health and Social Medicine, Harvard Medical School, 641 Huntington Avenue, Boston, MA 02215, USA

Email: leesaklin@gmail.com

Word count: 3814

ABSTRACT

Objectives To investigate leftover antibiotics and their influence on self-medication with antibiotics (SMA) for Chinese children, and further explore the different impacts of leftovers from two main sources: previous prescriptions and non-prescription purchases.

Design A cross-sectional questionnaire study.

Setting The participants were approached through kindergartens and primary schools as well as in vaccination clinics.

Participants A total of 9526 parents from three Chinese provinces whose children were 0-13 completed the survey.

Outcome measures The prevalence of keeping antibiotics at home for children and the proportion of leftover antibiotics from two main sources were measured by a self-administrated questionnaire. Logistic regression models were established to examine the association between keeping antibiotics at home and SMA for children, specifically the risks of leftovers from two main sources.

Results Overall, 4580 (48.1%) reported keeping antibiotics at home for children. Among those who had leftovers, 2891 (63.1%) reported that their leftovers came from previous prescriptions and 1619 (35.3%) reported their leftovers came from non-prescription purchases. Keeping antibiotics at home was significantly associated with SMA for children (aOR=4.91, 95% CI 3.84–6.28). Particularly, compared with parents who did not keep antibiotics at home, parents who kept leftover antibiotics from previous prescriptions or those whose leftovers came from non-prescription purchases were 3.80 times (95% CI 2.89–5.00) and 6.45 times (95% CI 4.89–8.51) more likely to engage in SMA for children respectively.

Conclusions Keeping antibiotics at home for children was pervasive in China. Most leftovers came from previous prescriptions, while those from pharmacies had a higher risk of SMA for children. Educational campaign on appropriate antibiotic use for the public and reinforcement on supervision for sales of antibiotics in pharmacies in China can help to reduce leftover antibiotics and the risk of SMA for children.

Keywords: antimicrobial resistance; children; self-medication with antibiotics; leftover antibiotics

Strengths and limitations

- This survey had a large sample size which spanned three Chinese provinces with differing economic development levels and including urban as well as rural areas.
- Our study firstly explored the different impacts of the leftover antibiotics from two main sources (previous prescriptions and non-prescription purchases from pharmacies) on SMA for children.

- Only parents were recruited as respondents for our study, contexts in which grandparents or others acted as children's caregivers were not included.
- Other sources of leftover antibiotics (1.6%) aside from previous prescriptions and non-prescription purchases were not investigated in this study.

INTRODUCTION

Antimicrobial resistance (AMR) is a growing health concern which the World Health Organization (WHO) lists as one of the top ten threats to public health worldwide.[1,2] Widespread antibiotic misuse increases selection pressure for mutated strains of microbes thereby accelerating the development of AMR.[3] The spread of AMR renders routine treatments for infectious diseases such as pneumonia ineffective[4,5] thereby increasing mortality rates from common diseases and deepening the financial burden of public health systems as they struggle to find new and more effective treatment options.[1]

Human antibiotic misuse plays a leading role in the development of AMR.[3,6] Self-medication with antibiotics (SMA) is a common form of antibiotic misuse which leads to a plethora of nefarious outcomes including AMR.[7-9] SMA occurs worldwide; with a rate of 3.1% among European adults in the past 12 months[10] and 85.5% among Nigerian undergraduates within the past two-three months.[11] In China, the prevalence of SMA was reported to be 40% among undergraduates[12] and 38% among urban children[13] in the past six months.

Keeping antibiotics at home increases the likelihood of SMA.[14] One study reported that 50% of antibiotics used in self-medication were leftovers.[15] In developed countries, leftover antibiotics originate almost entirely from previous prescriptions due to strict regulations on the retail sale of antibiotics,[16,17] while leftovers in developing countries also include non-prescription antibiotics purchased from pharmacies.[12,18] It is assumed that leftover antibiotics from the above two sources might have different impacts on SMA.[19]

Antibiotic misuse in children is especially pervasive;[20] 10% of Greek parents[21] and 60% of Mongolian parents admitted to having self-medicated their children with antibiotics in the past two weeks.[22] The rate of SMA for children over the past year in Chinese rural areas reached as high as 62%.[23] Keeping antibiotics at home can facilitate SMA for children.[22] Two studies in China found that parents who kept antibiotics at home were 2.8[23] and 6.3[13] times more likely to engage in SMA for children than parents who did not. However, no study thus far has investigated the different impacts of leftovers from previous prescriptions and leftovers from pharmacies, which have further implications for intervention strategies. Moreover, existing studies were limited by the relatively long recall periods of their questionnaires, their small sample sizes, and their limited geographical locations. Additionally, little attention has been paid to SMA for children for prophylaxis in China; this practice is widespread in developing countries.[24] Therefore, our study aims to: 1) assess the situation of keeping antibiotics at home for children and the influencing factors of this behavior; 2) explore the association between keeping antibiotics at home and SMA for children (remedial and prophylactic), as well as the impacts of leftover antibiotics from two different sources.

METHODS

Study design and participants

Data for this study came from a cross-sectional survey conducted in three provinces in China between June 2017 and April 2018. These three provinces were selected according to their geographical locations and GDP (Gross Domestic Product) per capita to encompass eastern (Zhejiang, ranked 5th), central-northwestern (Shaanxi, ranked 12th), and southwestern (Guangxi, ranked 26th) regions with significant differences in socioeconomic development levels.[25]

Multi-stage stratified cluster random sampling was adopted to ensure the representativeness of data from diverse Chinese parents whose children were between 0 and 13 years old. In each province, a prefecture-level city was randomly selected and within each city an urban and rural district were randomly chosen as sampling sites. Corresponding with our target age group, a complete roster including kindergartens, primary schools, and medical facilities was obtained. At each site, a cluster of kindergartens and primary schools were randomly selected, and all parents whose children aged 4 to 13 were sampled. Parents of children aged 0 to 3 were recruited from vaccination clinics of the medical facilities where up to 99% of children under 3 years old were covered as they must receive government subsidized vaccinations.[26]

Study measurement

A self-administered questionnaire which consisted of two main sections was utilized: 1) socio-demographic characteristics including the parents' sex, education level, average monthly household income, location of residence, medical background, as well as their children's age and sex; 2) whether the respondents (i) engaged in SMA when children fell ill in the past month, (ii) engage in SMA for children for prophylaxis in the past year, (iii) kept leftover antibiotics (not for current use) at home for children, and if so, where the leftovers came from. The questionnaire was based on literature review,[23,27-29] modified by qualitative interviews, and finalized after a pilot test.

Data collection

The questionnaire was easily accessed telephonically by scanning a QR code which led to a survey on WenJuanXing (the Chinese version of Survey Monkey).[30] The first page of the questionnaire provided a brief introduction assuring the anonymity of respondents as well as their right to withdraw from the study at any time.

The parents who acted as the main caregiver and health decision-maker for the child were invited to fill out the questionnaire. Parents whose children aged 0-3 were surveyed in vaccination clinics of local medical facilities where their children had to wait before receiving vaccinations and then stay for 30 minutes of

observation after being vaccinated. While parents waited for their children to be vaccinated, our research assistants: 1) distributed informative leaflets about the survey, 2) introduced the survey, and 3) obtained signed consent forms from participants. Parents completed the survey after their children had received their vaccinations. Parents whose children aged 4-13 were surveyed in kindergartens and primary schools with the help of teachers. Teachers distributed the QR code and sent consent forms to children's parents. Parents who agreed to participate signed the consent form and completed the questionnaire.

Statistical analyses

Data were analyzed using the SPSS version 24.0 (SPSS Inc., Chicago, IL, USA). Chi-square tests and t-tests were conducted to compare the socio-demographic characteristics and prevalence of SMA for children between parents who kept antibiotics at home for children and those who did not. Logistic regression was used to identify factors associated with keeping antibiotics at home for children. Two other logistic regression models were established to further explore associations between keeping antibiotics at home and SMA for children (when they were sick and for prophylaxis). In Model 1, responses to *keeping antibiotics at home for children* were simply divided into Yes or No, while in Model 2 it was divided into three subgroups according to the sources of leftover antibiotics: group 1 = no; group 2 = yes, previously prescribed by doctors; group 3 = yes, previously purchased from pharmacies. A statistical significance level of $p<0.05$ was applied.

Public involvement statement

Members of the public were involved in the development of our survey by participating in qualitative interviews as stakeholders, which helped tailor the questionnaire to the local Chinese context. In addition, 315 respondents contributed to the pilot study to improve the instrument and enhance better validity. All respondents were informed that their answers would be valuable to scientific research and policy decisions which in turn benefit their children.

RESULTS

Basic information of the sample

A total of 9526 questionnaires were collected with a response rate of 88.7%. The number of respondents in three provinces (Zhejiang, Shaanxi, and Guangxi) were 2924, 3355, and 3247 respectively (30.7% vs. 35.2% vs. 34.1%). Mothers accounted for the majority of respondents (7283, 76.5%). There were slightly more male children than females (4943, 51.9% vs. 4583, 48.1%), and the mean age of children was 5.8 years old (SD=3.6). Slightly less than half of the respondents had college and above levels of education (4242, 44.5%). More than half of the respondents had an average household income of 5000 RMB (US$ 769) or less per month (4991,

52.4%), and more than half were urban residents (5265, 55.3%). A small proportion (1122, 11.8%) of the respondents had a medical background.

Almost half of the respondents (4580, 48.1%) kept antibiotics at home for children. 2891 (63.1%) reported that their leftover antibiotics came from previous medical prescriptions while 1619 (35.3%) reported that their leftovers had been purchased from pharmacies without prescription. Among all the respondents, 3579 (37.6%) reported their children fell ill within the month before the survey. The most common illnesses were cold (2938, 82.1%), sore throat (1707, 47.7%), and fever (1108, 31.0%). To manage these illnesses, 1944 (54.3%) self-treated their children, of whom 621 (31.9%) used antibiotics. Moreover, 1983 (20.8%) of all respondents reported that they had engaged in SMA for children for prophylaxis in the past year.

Sociodemographic characteristics and antibiotic use behaviors of parents

As shown in Table 1, significant differences were found regarding sex, highest education level, average household income per month, province, residence and medical background between respondents who kept antibiotics at home for children and those who did not ($p < 0.001$). The rates of SMA for children when they were sick and for prophylaxis were both significantly higher in the respondents who kept antibiotics at home for children ($p < 0.001$).

Table 1. Characteristics and behaviors of parents stratified by keeping antibiotics at home for children (n=9526)

	Keep antibiotics at home			
	No (n=4946) n(%)	Yes (n=4580) n(%)	χ^2/t	p
Sex of Caregiver			17.04	< 0.001
Male	1250(25.3)	993(21.7)		
Female	3696(74.7)	3587(78.3)		
Sex of Child			1.784	0.182
Male	2599(52.5)	2344(51.2)		
Female	2347(47.5)	2236(48.8)		
Age of Child Mean(SD)	5.6(0.5)	6.0(0.5)	5.454	< 0.001
Parents' Highest Level of Education			77.43	< 0.001
Middle school and below	1493(30.2)	1026(22.4)		
High school	1400(28.3)	1365(29.8)		
College and above	2053(41.5)	2189(47.8)		
Average Household Income (RMB, monthly)			47.62	< 0.001
< 3000(US$461)	1228(24.8)	874(19.1)		
3000-5000 (US$462–769)	1455(29.4)	1434(31.3)		

5001-10000(US$770–1538)	1394(28.2)	1355(29.6)		
> 10000(US$1538)	869(17.6)	917(20.0)		
Province			228.9	< 0.001
Zhejiang	1591(32.2)	1333(29.1)		
Shaanxi	1405(28.4)	1950(42.6)		
Guangxi	1950(39.4)	1297(28.3)		
Residence			31.76	< 0.001
Rural	2349(47.5)	1912(41.7)		
Urban	2597(52.5)	2668(58.3)		
Parents with Medical Background			65.85	< 0.001
No	4491(90.8)	3913(85.4)		
Yes	455(9.2)	667(14.6)		

	SMA for Children Yes[n(%)]	χ^2/t	*p*	**SMA for Children for Prophylaxis** Yes[n(%)]	χ^2/t	*p*
Keeping Antibiotics for Children at Home		187.5	< 0.001		481.9	< 0.001
No	108(17.4)			595(30.0)		
Yes	513(82.6)			1388(70.0)		

Factors associated with keeping antibiotics at home for children

As Table 2 shows, mothers (aOR=1.17, 95% CI 1.06–1.29) and respondents with higher education levels (aOR=1.34, 95% CI 1.20–1.51; aOR=1.50, 95% CI 1.33–1.70) were more likely to keep antibiotics at home for children. Respondents from Shaanxi (aOR=1.96, 95% CI 1.75–2.20) and respondents with medical backgrounds (aOR=1.54, 95% CI 1.35–1.75) had greater odds of keeping antibiotics at home for children.

Table 2. Factors associated with keeping antibiotics at home for children (*n*=9526)

Independent Variables	**aOR (95% CI)**
Sex of Caregiver	
Male	Ref
Female	1.17(1.06,1.29)**
Sex of Child	
Male	Ref
Female	1.04(0.96,1.13)
Age of Child	1.05(1.04,1.07)***
Parents' Highest Level of Education	
Middle school and below	Ref
High school	1.34(1.20,1.51)***
College and above	1.50(1.33,1.70)***

Average Household Income (RMB, monthly)	
< 3000(US$461)	Ref
3000-5000 (US$462–769)	1.22(1.08,1.38)**
5001-10000(US$770–1538)	1.17(1.02,1.33)*
> 10000(US$1538)	1.36(1.16,1.60)***
Province	
Zhejiang	Ref
Guangxi	1.00(0.89,1.13)
Shaanxi	1.96(1.75,2.20)***
Residence	
Rural	Ref
Urban	1.03(0.94,1.13)
Parents with Medical Background	
No	Ref
Yes	1.54(1.35,1.75)***

*p＜0.05,**p＜0.01,***p＜0.001; Ref: reference group; aOR: adjusted odds ratio

The association between keeping antibiotics at home and SMA for children

Among 1927 parents who self-medicated their children in the last month (Model 1), those who kept antibiotics at home for children were nearly five times (aOR=4.91, 95% CI 3.84–6.28) more likely to engage in SMA for children than those who did not. Model 2 illustrates that parents who had leftover antibiotics which came from previous prescriptions and which were purchased from pharmacies without prescription were 3.80 times (95% CI 2.89–5.00) and 6.45 times (95% CI 4.89–8.51) more likely to engage in SMA for children than those who did not keep antibiotics at home (Table 3).

Table 3. The association between keeping antibiotics at home and SMA for children when they fell sick (*n*=1927)[1]

Independent Variables	Model 1 aOR (95% CI)	Model 2 aOR (95% CI)
Sex of Caregiver		
Male	Ref	Ref
Female	1.23(0.93,1.62)	1.28(0.97,1.69)
Sex of Child		
Male	Ref	Ref
Female	0.95(0.77,1.18)	0.95(0.77,1.17)
Age of Child	1.03(0.99,1.06)	1.02(0.99,1.06)
Parents' Highest Level of Education		
Middle school and below	Ref	Ref
High school	0.81(0.60,1.11)	0.79(0.58,1.08)
College and above	0.72(0.52,0.99)*	0.71(0.52,0.98)*
Average Household Income (RMB, monthly)		

< 3000(US$461)	Ref	Ref
3000-5000(US$462–769)	0.92(0.68,1.24)	0.94(0.69,1.27)
5001-10000(US$770–1538)	0.65(0.46,0.91)*	0.66(0.47,0.94)*
> 10000(US$1538)	0.76(0.50,1.16)	0.78(0.51,1.20)
Province		
Zhejiang	Ref	Ref
Guangxi	1.91(1.38,2.65)***	1.69(1.21,2.35)**
Shaanxi	2.63(1.91,3.60)***	2.41(1.75,3.31)***
Residence		
Rural	Ref	Ref
Urban	0.97(0.77,1.23)	0.96(0.76,1.21)
Parents with Medical Background		
No	Ref	Ref
Yes	0.71(0.52,0.97)*	0.71(0.52,0.98)*
Keeping Antibiotics at Home for Children		
No	Ref	-
Yes	4.91(3.84,6.28)***	-
Keeping Antibiotics at Home for Children		
No	-	Ref
Yes, previously prescribed by doctors	-	3.80(2.89,5.00)***
Yes, previously purchased from pharmacies	-	6.45(4.89,8.51)***

[1] 17 of 1944 respondents who self-treated their children in the past month kept antibiotics from other sources except the two main ones (previous prescriptions or pharmacies), leaving 1927 for analysis in the regression models. *p＜0.05,**p＜0.01,***p＜0.001; Ref: reference group; aOR: adjusted odds ratio.

The association between keeping antibiotics at home and SMA for children for prophylaxis

Among 9 456 respondents (Model 1), those who kept antibiotics at home for children were 3.16 times (95% CI 2.83–3.53) more likely to prophylactically engage in SMA for children than those who did not keep antibiotics at home. Model 2 illustrates that parents who had leftover antibiotics which came from previous prescriptions and which were purchased from pharmacies without prescription were 2.96 times (95% CI 2.62–3.34) and 3.53 times (95% CI 3.07–4.05) more likely to engage in SMA for children for prophylaxis than those who did not keep antibiotics at home (Table 4).

Table 4. The association between keeping antibiotics at home and prophylactic SMA for children(n=9456)[2]

Independent Variables	Model 1 aOR (95% CI)	Model 2 aOR (95% CI)
Sex of Caregiver		
Male	Ref	Ref
Female	0.83(0.74,0.94)**	0.83(0.74,0.94)**
Sex of Child		
Male	Ref	Ref
Female	1.06(0.96,1.18)	1.06(0.96,1.18)

Age of Child	1.01(1.00,1.03)	1.01(1.00,1.03)
Parents' Highest Level of Education		
Middle school and below	Ref	Ref
High school	0.97(0.84,1.12)	0.97(0.84,1.11)
College and above	0.85(0.73,0.99)*	0.84(0.72,0.98)*
Average Household Income (RMB, monthly)		
< 3000(US$461)	Ref	Ref
3000-5000(US$462–769)	0.93(0.80,1.08)	0.93(0.80,1.08)
5001-10000(US$770–1538)	0.90(0.76,1.06)	0.90(0.76,1.06)
> 10000(US$1538)	0.84(0.68,1.03)	0.84(0.69,1.04)
Province		
Zhejiang	Ref	Ref
Shaanxi	1.59(1.38,1.84)***	1.56(1.35,1.80)***
Guangxi	1.00(0.86,1.17)	0.97(0.83,1.13)
Residence		
Rural	Ref	Ref
Urban	0.94(0.84,1.06)	0.94(0.84,1.06)
Parents with Medical Background		
No	Ref	Ref
Yes	0.62(0.52,0.75)***	0.62(0.52,0.75)***
Keeping Antibiotics at Home for Children		
No	Ref	-
Yes	3.16(2.83,3.53)***	-
Keeping Antibiotics at Home for Children		
No	-	Ref
Yes, previously prescribed by doctors	-	2.96(2.62,3.34)***
Yes, previously purchased from pharmacies	-	3.53(3.07,4.05)***

[2] 70 of 9526 respondents kept antibiotics from other sources except the two main ones (previous prescriptions or pharmacies), leaving 9456 for analysis in the regression models. *p < 0.05,**p < 0.01,***p < 0.001; Ref: reference group; aOR: adjusted odds ratio.

DISCUSSION

To the best of our knowledge, this is the first study covering both rural and urban Chinese populations to investigate parental behaviors of keeping antibiotics at home for children and its association with SMA for sick children and for prophylaxis. This is also the first study to identify the two main sources of leftover antibiotics for children: previous prescriptions and non-prescription purchases. We found that keeping antibiotics at home for children is a widespread practice in China, which increases chances of parents engaging in SMA for their children. In this study, leftover antibiotics from previous prescriptions accounted for a larger proportion of total in-home antibiotics; however, leftovers which originated from non-prescription purchase had a higher risk of

SMA for children. These findings demand targeted intervention programs aiming at reducing leftover antibiotics and enhancing appropriate antibiotic use for children.

The prevalence of keeping antibiotics for children varies greatly across China. Rates of antibiotics kept at home by parents or caregivers in central rural, eastern rural, and urban China were reported as 75%,[23] 32%,[28] and 25%[13] respectively, and in our study as 48.1%. Unlike previous studies, our results are based on data from disparate locations thereby providing a broader picture of the prevalence of leftover antibiotics in China. Compared with similar studies conducted overseas, the rate in China is higher than that reported in Trinidad and Tobago (21.8%)[31] but lower than that in Mongolia (58.4%)[22].

As is consistent with our results, previous studies have proven that keeping antibiotics at home could increase the likelihood of parents engaging in SMA for children.[13,22,23] It has been found that people tend to use the same drug when they confronted similar symptoms based on their experiences.[32] Recent evidence also shows that parents who keep antibiotics at home prefer to self-medicate their children rather than directly seeking advice from a medical professional.[13] Therefore, leftover antibiotics at home facilitate parents' deleterious practice of SMA for children by referring to previous practices. One survey in China even reported that among parents who kept antibiotics at home, 97% used the leftovers for their children on a second occasion.[28]

Overall, 63.1% leftover antibiotics we found came from previous prescriptions. This result differs from a study of Chinese university students which identified non-prescription pharmaceutical purchases as the main source of leftover antibiotics.[19] This discrepancy could be attributed to the long-term impact of previous "one child" policy,[33] which has made the child become the focus of the entire family. When children suffered from illness, parents preferred to seek official medical advice for assurance even after self-medication. In this study, there were 69.2% parents who engaged in hospital visits (not shown in tables) while the rate among university students was only 27.4%.[27] In addition, medications are dispensed in fixed packages rather than exact doses in China.[14] High consultation rates and inadequate dispensing systems explain the origin of most leftover antibiotics for children – previous prescriptions. Moreover, non-compliance could also be responsible for a large portion of leftovers[28] since many children fail to complete the course of treatment because their parents incorrectly accuse antibiotics for the side effects of other drugs taken at the same time.[34]

In this study, only one-third of leftover antibiotics for children came from pharmacies. However, one should note that this kind of leftovers shows higher risks of SMA for children. In China, although a prescription-only regulation for antibiotics at retail pharmacies has been in place since 2004,[35] it still remains easy for parents to purchase antibiotics without prescriptions due to the lack of an effective monitoring system for sales of

antibiotics. As one multi-center survey in urban China concluded, 55.9% pharmacies sold non-prescription antibiotics for pediatric diarrhea.[36] Furthermore, previous studies found that antibiotics purchased from pharmacies without prescription strongly contributed to the problem of SMA for children,[13,37] and most leftover antibiotics from pharmacies were kept for future use.[18] In contrast, as discussed above, leftover antibiotics from previous prescriptions were usually unintentionally left and not necessarily meant to be used on a second occasion.[38] This finding reinforces our belief that China needs to more strongly enforce regulations prohibiting non-prescription sales of antibiotics through a supervisory system of antibiotic sales at retail pharmacies.

In line with previous evidence,[19] parents with medical backgrounds were more likely to keep antibiotics at home for children; however, they were also less likely to engage in SMA for children. A possible explanation could be that parents with medical backgrounds had easier access to antibiotics. One study found that some pharmacists helped their families to obtain non-prescription antibiotics.[39] On the other hand, parents with medical backgrounds might keep stand-by antibiotics since they believed that they have the capacity to handle some of their children's illnesses. However, most conditions in this study were self-limited diseases which didn't need antibiotic therapy. Parents with medical backgrounds could be aware of that, thus they were more likely to self-treat their children without antibiotics.

Our findings have several important implications for medical practitioners and policy makers. For the supply side, closer supervision of sales of antibiotics at retail pharmacies is urgently needed; the dispensing system of medication in healthcare institutions needs reformation. For the demand side, it is essential to provide public education programs which teach appropriate knowledge and skills to manage common self-limited juvenile diseases, which may help reduce the rates of unnecessary hospital visits and improper antibiotic use. Furthermore, collecting and recycling programs for leftover antibiotics could be useful in China, as these have been proven successful in reducing leftover antibiotics elsewhere.[40,41]

Our study has several limitations. First, this study only recruited parents, which excluded situations when grandparents or others acted as children's primary caregivers. Second, the study relied on self-reports of parents, which undoubtedly reflected their misunderstanding of antibiotics.[12,13] This means that they might have over- or under-estimated the rates at which they use or keep antibiotics, however , we tried to minimize this bias by a brief explanation about antibiotics in the questionnaire. Third, our study cannot show the direct relation between leftover antibiotics and SMA for children, instead only a strong association has been found. Specific sources of leftover antibiotics used in SMA should be investigated in future studies. Fourth, our findings only focus on the impact of leftover antibiotics from two main sources because others represent a very small proportion (1.6%) in

China. This might not be the case in other countries so that future studies are needed to convey more pictures of leftover antibiotics.

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of School of Public Health, Zhejiang University (reference number: ZGL201706-2).

Acknowledgments

We thank the staff of medical facilities and teachers for their help during data collection. We also acknowledge all the parents who participated in the study. We especially appreciate Théo Storella for editing and polishing this paper.

Contributors

CS analyzed the data and drafted the manuscript. YH revised the manuscript critically for important intellectual content. XZ and XW led the design of the study. XZ is the PI of the study and participated in the coordination of data collection and critical review of the manuscript. XM, JL and LL participated in critical review of the manuscript. All authors read and approved the final manuscript.

Funding

Zhejiang University Zijin Talent Programme.

Competing interests

All authors declare no competing interests.

Data sharing statement

The data-sets analyzed during this study are available from the corresponding author on reasonable request.

REFERENCES

1 O'Neill J. Antimicrobial resistance: tackling a crisis for the health and wealth of nations. 2014 https://amr-review.org/sites/default/files/AMR%20Review%20Paper%20-%20Tackling%20a%20crisis%20for%20the%20health%20and%20wealth%20of%20nations_1.pdf (accessed 19 July 2019).

2 Organization W H. Ten threats to global health in 2019. 2019. https://www.who.int/emergencies/ten-threats-to-global-health-in-2019 (accessed 19 July 2019).

3 Laxminarayan R, Duse A, Wattal C, et al. Antibiotic resistance—the need for global solutions[J]. *Lancet Infect Dis* 2013;13(12):1057-1098.

4 Feikin DR, Schuchat A, Kolczak M, et al. Mortality from invasive pneumococcal pneumonia in the era of antibiotic resistance, 1995-1997[J]. *American journal of public health* 2000;90(2):223-229.

5 Flandrois JP, Lina G, Dumitrescu O. MUBII-TB-DB: a database of mutations associated with antibiotic resistance in Mycobacterium tuberculosis[J]. *BMC bioinformatics* 2014;15(1): 107.

6 Davies J, Davies D. Origins and evolution of antibiotic resistance. *Microbiol Mol Biol Rev* 2010;74(3): 417–433.

7 Al Akhali KM, Alzomar AK, Khan NA, et al. Misuse of antibiotics and awareness of antibiotic hazard among the public and medical professionals in Thamar province, in republic of Yemen[J]. *Pharmacie Globale* 2013;4(1): 1-4.
8 Awad A, Aboud EA. Knowledge, attitude and practice towards antibiotic use among the public in Kuwait. *PLoS One* 2015;10(2):e0117910.
9 Li LJ, Wang PS. Self-medication with antibiotics: a possible cause of bacterial resistance[J]. *Med Hypotheses* 2005;5(65): 1000-1001.
10 Grigoryan L, Burgerhof JGM, Haaijer-Ruskamp FM, et al. Is self-medication with antibiotics in Europe driven by prescribed use?[J]. *J Antimicrob Chemother* 2007;59(1):152-156.
11 Badger-Emeka LI, Emeka PM, Okosi M. Evaluation of the extent and reasons for increased non-prescription antibiotics use in a University town, Nsukka Nigeria[J]. *Int J Health Sci* 2018;12(4):11.
12 Lv B, Zhou Z, Xu G, et al. Knowledge, attitudes and practices concerning self-medication with antibiotics among university students in western China[J]. *Trop Med Int Health* 2014;19(7):769-779.
13 Chang J, Lv B, Zhu S, et al. Non-prescription use of antibiotics among children in urban China: a cross-sectional survey of knowledge, attitudes, and practices[J]. *Expert Rev Anti Infect Ther* 2018;16(2):163-172.
14 Kardas P, Pechère JC, Hughes DA, et al. A global survey of antibiotic leftovers in the outpatient setting[J]. *Int J Antimicrob Agents* 2007;30(6):530-536.
15 Ocan M, Obuku EA, Bwanga F, et al. Household antimicrobial self-medication: a systematic review and meta-analysis of the burden, risk factors and outcomes in developing countries[J]. *BMC Public Health* 2015;15(1): 742.
16 Grigoryan L, Haaijer-Ruskamp FM, Burgerhof JGM, et al. Self-medication with antimicrobial drugs in Europe[J]. *Emerg Infect Dis* 2006;12(3): 452-459.
17 Richman PB, Garra G, Eskin B, et al. Oral antibiotic use without consulting a physician: a survey of ED patients[J]. *Am J Emerg Med* 2001;19(1):57-60.
18 Jassim AM. In-home Drug Storage and Self-medication with Antimicrobial Drugs in Basrah, Iraq[J]. *Oman Med J* 2010;25(2):79-87.
19 Wang X, Lin L, Xuan Z, et al. Keeping antibiotics at home promotes self-medication with antibiotics among Chinese University Students[J]. *Int J Environ Res Public Health* 2018;15(4): 687.
20 Li R, Xiao F, Zheng X, et al. Antibiotic misuse among children with diarrhea in China: Results from a national survey[J]. *PeerJ* 2016;4:e2668.
21 Panagakou SG, Spyridis N, Papaevangelou V, et al. Antibiotic use for upper respiratory tract infections in children: A cross-sectional survey of knowledge, attitudes, and practices (KAP) of parents in Greece[J]. *BMC Pediatr* 2011;11(1):60.
22 Togoobaatar G, Ikeda N, Ali M, et al. Survey of non-prescribed use of antibiotics for children in an urban community in Mongolia[J]. *Bull World Health Organ* 2010;88(12):930-936.
23 Yu M, Zhao G, Lundborg CS, et al. Knowledge, attitudes, and practices of parents in rural China on the use of antibiotics in children: a cross-sectional study[J]. *BMC Infect Dis* 2014;14(1):112.
24 Alhomoud F, Aljamea Z, Almahasnah R, et al. Self-medication and self-prescription with antibiotics in the Middle East—do they really happen? A systematic review of the prevalence, possible reasons, and outcomes[J]. *Int J Infect Dis* 2017;57:3-12.
25 China. N. National Bureau of Statistics China http://data.stats.gov.cn/english/ (accessed 19 July 2019).
26 China. N. National Bureau of Statistics China http://www.stats.gov.cn/tjsj/zxfb/201710/t20171026_1546618.html (accessed 19 July 2019)
27 Wang X, Peng D, Wang W, et al. Massive misuse of antibiotics by university students in all regions of China: implications for national policy[J]. *Int J Antimicrob Agents* 2017;50(3):441-446.
28 Ding L, Sun Q, Sun W, et al. Antibiotic use in rural China: a cross-sectional survey of knowledge, attitudes and self-reported practices among caregivers in Shandong province[J]. *BMC Infect Dis* 2015;15(1):576.
29 Cantarero-Arévalo L, Hallas MP, & Kaae S. Parental knowledge of antibiotic use in children with respiratory infections: a systematic review[J]. *Int J Pharm Pract* 2017;25(1):31-49.
30 Wen Juan Xing. https://www.wjx.cn (accessed 23 July 2019).
31 Parimi N, Pereira LMP, Prabhakar P. Caregivers' practices, knowledge and beliefs of antibiotics in paediatric upper respiratory tract infections in Trinidad and Tobago: a cross-sectional study[J]. *BMC Fam Pract* 2004；5(1):28.
32 Jin C, Ely A, Fang L, et al. Framing a global health risk from the bottom-up: User perceptions and practices around antibiotics in four villages in China[J]. *Health Risk Soc* 2011;13(5):433-449.
33 Feng XT, Poston Jr DL, Wang XT. China's One-Child Policy and the Changing Family[J]. *J Comp Fam Stud* 2014;45(1):17-29.
34 Wun YT, Lam TP, Lam KF, et al. Antibiotic use: do parents act differently for their children?[J]. *Int J Clin Pract* 2012;66(12):1197-1203.

35 State Food and Drug Administration. The five prescription sales only antibacterial released by SFDA. 2003. http://www.nmpa.gov.cn/WS04/CL2196/323380.html (accessed 19 July 2019).
36 Chang J, Ye D, Lv B, et al. Sale of antibiotics without a prescription at community pharmacies in urban China: a multicentre cross-sectional survey[J]. *J Antimicrob Chemother* 2017;72(4):1235-1242.
37 Bi P, Tong S, Parton KA. Family self-medication and antibiotics abuse for children and juveniles in a Chinese city[J]. *Soc Sci Med* 2000;50(10):1445-1450.
38 Agarwal S, Yewale VN, Dharmapalan D. Antibiotics Use and Misuse in Children: A Knowledge, Attitude and Practice Survey of Parents in India[J]. *J Clin Diagn Res* 2015;9(11):SC21.
39 Dameh M, Norris P, Green J. New Zealand pharmacists' experiences, practices and views regarding antibiotic use without prescription[J]. *J Prim Health Care* 2012;4(2):131-140.
40 Thach AV, Brown CM, Pope N. Consumer perceptions about a community pharmacy-based medication take back program[J]. *J Environ Manage* 2013;127:23-27.
41 Lauer MF, Kettell BD, Davis MH. Environments and health: leftover drugs in the water supply: don't flush those pills![J]. *American Journal of Nursing* 2010;110(8):46-49.

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	1, 3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
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	6-7
Bias	9	Describe any efforts to address potential sources of bias	6-7
Study size	10	Explain how the study size was arrived at	N/A
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	N/A
		(*c*) Explain how missing data were addressed	N/A
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	N/A
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	7
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7-8
		(b) Indicate number of participants with missing data for each variable of interest	N/A
Outcome data	15*	Report numbers of outcome events or summary measures	8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear	9-12

		which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
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	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
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	15

*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.

BMJ Open

The influence of leftover antibiotics on self-medication with antibiotics for children: a cross-sectional study from three Chinese provinces

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-033679.R1
Article Type:	Original research
Date Submitted by the Author:	04-Nov-2019
Complete List of Authors:	Sun, Chenhui; Zhejiang University, School of Medicine, Institute of Social and Family Medicine Hu, Yanhong; The University of Melbourne, Murdoch Children's Research Institute Wang, Xiaomin; Zhejiang University, School of Medicine, Institute of Social and Family Medicine Lu, Jingjing; Zhejiang University, School of Medicine, Institute of Social and Family Medicine Lin, Leesa; London School of Hygiene and Tropical Medicine, Department of Public Health, Environments and Society, Faculty of Public Health and Policy; Harvard Medical School, Department of Global Health and Social Medicine Zhou, Xudong; Zhejiang University, School of Medicine, Institute of Social and Family Medicine
Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Public health
Keywords:	antimicrobial resistance, children, self-medication with antibiotics, leftover antibiotics

Title page

The influence of leftover antibiotics on self-medication with antibiotics for children: a cross-sectional study from three Chinese provinces

First author:

Chenhui Sun

Institute of Social and Family Medicine, School of Medicine, Zhejiang University, 866 Yuhangtang Rd., Hangzhou, Zhejiang, 310058, P.R. China.

Email: sunchenhui@zju.edu.cn

Second author:

Yanhong Jessika Hu

Murdoch Children's Research Institute, University of Melbourne. Royal Children's Hospital, Flemington Rd, Parkville VIC 3052

Email: huhubest@gmail.com

Xiaomin Wang

Institute of Social and Family Medicine, School of Medicine, Zhejiang University, 866 Yuhangtang Rd., Hangzhou, Zhejiang, 310058, P.R. China.

Email: xiaominwang2018@zju.edu.cn

Jingjing Lu

Institute of Social and Family Medicine, School of Medicine, Zhejiang University, 866 Yuhangtang Rd., Hangzhou, Zhejiang, 310058, P.R.China.

Email: jingjinglu@zju.edu.cn

Leesa Lin

1. Department of Public Health, Environments and Society, Faculty of Public Health and Policy, London School of Hygiene & Tropical Medicine, 15-17 Tavistock PL, Kings Cross, London WC1H9SH, UK;

2. Department of Global Health and Social Medicine, Harvard Medical School, 641 Huntington Avenue, Boston, MA 02215, USA

Email: leesaklin@gmail.com

Corresponding author:

Xudong Zhou

Institute of Social and Family Medicine, School of Medicine, Zhejiang University, 866 Yuhangtang Rd.,

Hangzhou, Zhejiang, 310058, P.R. China.

Email: zhouxudong@zju.edu.cn

Phone: 86-571-88208221

Word count: 3929

ABSTRACT

Objectives To investigate leftover antibiotics and their influence on self-medication with antibiotics (SMA) for Chinese children, and further explore the different influences of leftovers from two main sources: previous prescriptions and pharmaceutical purchases.

Design A cross-sectional questionnaire study.

Setting The participants were approached through kindergartens and primary schools as well as in vaccination clinics.

Participants A total of 9526 parents from three Chinese provinces whose children were 0-13 completed the survey.

Outcome measures The prevalence of keeping antibiotics at home for children and the proportion of leftover antibiotics from two main sources were measured by a self-administrated questionnaire. Logistic regression models were established to examine the association between keeping antibiotics at home and SMA for children, specifically the risks of leftovers from two main sources.

Results Overall, 4580 (48.1%) reported keeping antibiotics at home for children. Among those who had leftovers, 2891 (63.1%) reported that their leftovers came from previous prescriptions and 1619 (35.3%) reported their leftovers came from pharmaceutical purchases. Mothers, older age of child, higher household income, higher education level, and medical background were significantly associated with keeping antibiotics at home. Keeping antibiotics at home was significantly associated with SMA for children (aOR=4.91, 95% CI 3.84–6.28). Particularly, compared with parents who did not keep antibiotics at home, parents who kept leftover antibiotics from previous prescriptions or those whose leftovers came from pharmaceutical purchases were 3.80 times (95% CI 2.89–5.00) and 6.45 times (95% CI 4.89–8.51) more likely to engage in SMA for children respectively.

Conclusions Keeping antibiotics at home for children was pervasive in China. Most leftovers came from previous prescriptions, while those from pharmacies had a higher risk of SMA for children.

Keywords: antimicrobial resistance; children; self-medication with antibiotics; leftover antibiotics

Strengths and limitations

- This survey had a large sample size which spanned three Chinese provinces with differing economic development levels and including urban as well as rural areas.
- Our study firstly explored the different influences of the leftover antibiotics from two main sources (previous prescriptions and pharmaceutical purchases) on SMA for children.

- Only parents were recruited as respondents for our study, contexts in which grandparents or others acted as children's caregivers were not included.
- Other sources of leftover antibiotics (1.6%) aside from previous prescriptions and pharmaceutical purchases were not investigated in this study.

INTRODUCTION

Antimicrobial resistance (AMR) is a growing health concern which the World Health Organization (WHO) lists as one of the top ten threats to public health worldwide.[1,2] Widespread antibiotic misuse increases selection pressure for mutated strains of microbes thereby accelerating the development of AMR.[3] The spread of AMR renders routine treatments for infectious diseases such as pneumonia ineffective[4,5] thereby increasing mortality rates from common diseases and deepening the financial burden of public health systems as they struggle to find new and more effective treatment options.[1]

Human antibiotic misuse plays a leading role in the development of AMR.[3,6] Self-medication with antibiotics (SMA) is a common form of antibiotic misuse which leads to a plethora of nefarious outcomes including AMR.[7-9] SMA occurs worldwide; with a rate of 3.1% among European adults in the past 12 months[10] and 85.5% among Nigerian undergraduates within the past two-three months.[11] In China, the prevalence of SMA was reported to be 40% among undergraduates[12] and 38% among urban children[13] in the past six months.

Keeping antibiotics at home increases the likelihood of SMA.[14] One study reported that 50% of antibiotics used in self-medication were leftovers.[15] In developed countries, leftover antibiotics originate almost entirely from previous prescriptions due to strict regulations on the retail sale of antibiotics,[16,17] while leftovers in developing countries also include non-prescription antibiotics purchased from pharmacies.[12,18] It is assumed that leftover antibiotics from the above two sources might have different influences on SMA.[19]

Antibiotic misuse in children is especially pervasive;[20] 10% of Greek parents[21] and 60% of Mongolian parents admitted to having self-medicated their children with antibiotics in the past two weeks.[22] The rate of SMA for children over the past year in Chinese rural areas reached as high as 62%.[23] Keeping antibiotics at home can facilitate SMA for children.[22] Two studies in China found that parents who kept antibiotics at home were 2.8[23] and 6.3[13] times more likely to engage in SMA for children than parents who did not. However, no study thus far has investigated the different influences of leftovers from previous prescriptions and leftovers from pharmacies, which have further implications for intervention strategies. Moreover, existing studies were limited by the relatively long recall periods of their questionnaires, their small sample sizes, and their limited geographical locations. Additionally, little attention has been paid to SMA for children for prophylaxis in China; this practice is widespread in developing countries.[24] Therefore, our study aims to: 1) assess the situation of keeping antibiotics at home for children and the influencing factors of this behavior; 2) explore the association between keeping antibiotics at home and SMA for children (remedial and prophylactic), as well as the influences of leftover antibiotics from two different sources.

METHODS

Study design and participants

Data for this study came from a cross-sectional survey conducted in three provinces in China between June 2017 and April 2018. These three provinces were selected according to their geographical locations and GDP (Gross Domestic Product) per capita to encompass eastern (Zhejiang, ranked 5th), central-northwestern (Shaanxi, ranked 12th), and southwestern (Guangxi, ranked 26th) regions with significant differences in socioeconomic development levels.[25]

To ensure an adequate sample size for the subgroup analyses, we aimed to survey ca. 3000 parents per province with an even distribution in urban and rural areas. Multi-stage stratified cluster random sampling was adopted to ensure the representativeness of data from diverse Chinese parents whose children were between 0 and 13 years old. In each province, a prefecture-level city was randomly selected and within each city an urban and a rural district were randomly chosen as sampling sites. At each site, a certain number of kindergartens, primary schools and vaccination clinics were randomly selected as clusters according to their size or daily flow to meet the target sample size. All parents of children at the age of 4 to 13 who attended those kindergartens and primary schools, and all parents who took their children under 3 to those vaccination clinics during working days were sampled. In China, children are required to be fully vaccinated for school enrollment and up to 99% of children under 3 years old were covered by government subsidized vaccinations.[26,27]

Study measurement

A self-administered questionnaire (see online supplementary file) which consisted of two main sections was utilized: 1) socio-demographic characteristics including the parents' sex, education level, average monthly household income, location of residence, medical background, as well as their children's age and sex; 2) whether the respondents (i) engaged in SMA when children fell ill in the past month, (ii) engaged in SMA for children for prophylaxis in the past year, (iii) kept leftover antibiotics (not for current use) at home for children at the time of survey, and if so, where the leftovers came from. The questionnaire was based on literature review,[23,28-30] modified by qualitative interviews, and finalized after a pilot test.

Data collection

The questionnaire was easily accessed through a smartphone by scanning a QR Code (Quick Response Code) which led to a survey on WenJuanXing (the Chinese version of Survey Monkey).[31] The first page of the questionnaire provided a brief introduction assuring the anonymity of respondents as well as their right to withdraw from the study at any time. Additionally, it is explained during introduction that the questions

only involve the child who was receiving vaccination or attending the kindergarten/primary school if the participant had more than one child.

The parents who acted as the main caregiver and health decision-maker for the child were invited to fill out the questionnaire. Parents whose children aged 0-3 were surveyed in vaccination clinics during their waiting time. Our research assistants: 1) distributed informative leaflets about the survey, 2) introduced the survey, and 3) obtained signed consent forms from participants. Parents scanned the QR Code with smart phones and completed the survey after vaccination. Parents whose children aged 4-13 were surveyed in kindergartens and primary schools with the help of teachers. Teachers distributed the QR Code and sent consent forms to children's parents. Parents who agreed to participate signed the consent form and completed the questionnaire.

Statistical analyses

Data were analyzed using the SPSS version 24.0 (SPSS Inc., Chicago, IL, USA). Chi-square tests and t-tests were conducted to compare the socio-demographic characteristics and prevalence of SMA for children between parents who kept antibiotics at home for children and those who did not. Logistic regression was used to identify factors associated with keeping antibiotics at home for children. Two other logistic regression models were established to further explore associations between keeping antibiotics at home and SMA for children (when they were sick and for prophylaxis). In Model 1, responses to *keeping antibiotics at home for children* were simply divided into Yes or No, while in Model 2 it was divided into three subgroups according to the sources of leftover antibiotics: group 1 = no; group 2 = yes, previously prescribed by doctors; group 3 = yes, previously purchased from pharmacies. A statistical significance level of $p<0.05$ was applied.

Public involvement statement

Members of the public were involved in the development of our survey by participating in qualitative interviews as stakeholders, which helped tailor the questionnaire to the local Chinese context. In addition, 315 respondents contributed to the pilot study to improve the instrument and enhance better validity. All respondents were informed that their answers would be valuable to scientific research and policy decisions which in turn benefit their children.

RESULTS

Basic information of the sample

A total of 9526 questionnaires were collected with a response rate of 88.7%. The number of respondents in three provinces (Zhejiang, Shaanxi, and Guangxi) were 2924, 3355, and 3247 respectively (30.7% vs. 35.2% vs. 34.1%). Mothers accounted for the majority of respondents (7283, 76.5%). There were slightly more male

children than females (4943, 51.9% vs. 4583, 48.1%), and the mean age of children was 5.8 years old (SD=3.6). Slightly less than half of the respondents had college and above levels of education (4242, 44.5%). More than half of the respondents had an average household income of 5000 RMB (US$ 769) or less per month (4991, 52.4%), and more than half were urban residents (5265, 55.3%). A small proportion (1122, 11.8%) of the respondents had a medical background.

Almost half of the respondents (4580, 48.1%) kept antibiotics at home for children. 2891 (63.1%) reported that their leftover antibiotics came from previous medical prescriptions while 1619 (35.3%) reported that their leftovers had been purchased from pharmacies. Among all the respondents, 3579 (37.6%) reported their children fell ill within the month before the survey. The most commonly reported illnesses were cold (2938, 82.1%), sore throat (1707, 47.7%), and fever (1108, 31.0%). To manage these illnesses, 1944 (54.3%) self-treated their children, of whom 621 (31.9%) used antibiotics. Moreover, 1983 (20.8%) of all respondents reported that they had engaged in SMA for children for prophylaxis in the past year.

Sociodemographic characteristics and antibiotic use behaviors of parents

As shown in Table 1, significant differences were found regarding sex, highest education level, average household income per month, province, residence and medical background between respondents who kept antibiotics at home for children and those who did not ($p<0.001$). The rates of SMA for children when they were sick and for prophylaxis were both significantly higher in the respondents who kept antibiotics at home for children ($p<0.001$).

Table 1. Characteristics and behaviors of parents stratified by keeping antibiotics at home for children (n=9526)

	Keep antibiotics at home			
	No (n=4946) n(%)	Yes (n=4580) n(%)	χ^2/t	p
Sex of Caregiver			17.04	< 0.001
Male	1250(25.3)	993(21.7)		
Female	3696(74.7)	3587(78.3)		
Sex of Child			1.784	0.182
Male	2599(52.5)	2344(51.2)		
Female	2347(47.5)	2236(48.8)		
Age of Child. Mean(SD)	5.6(0.5)	6.0(0.5)	5.454	< 0.001
Parents' Highest Level of Education			77.43	< 0.001
Middle school and below	1493(30.2)	1026(22.4)		
High school	1400(28.3)	1365(29.8)		
College and above	2053(41.5)	2189(47.8)		

Average Household Income (RMB, monthly)			47.62	< 0.001
< 3000(US$461)	1228(24.8)	874(19.1)		
3000-5000 (US$462–769)	1455(29.4)	1434(31.3)		
5001-10000(US$770–1538)	1394(28.2)	1355(29.6)		
> 10000(US$1538)	869(17.6)	917(20.0)		
Province			228.9	< 0.001
Zhejiang	1591(32.2)	1333(29.1)		
Shaanxi	1405(28.4)	1950(42.6)		
Guangxi	1950(39.4)	1297(28.3)		
Residence			31.76	< 0.001
Rural	2349(47.5)	1912(41.7)		
Urban	2597(52.5)	2668(58.3)		
Parents with Medical Background			65.85	< 0.001
No	4491(90.8)	3913(85.4)		
Yes	455(9.2)	667(14.6)		

	SMA for Children	χ^2/t	*p*	**SMA for Children for Prophylaxis**	χ^2/t	*p*
	Yes[n(%)]			Yes[n(%)]		
Keeping Antibiotics for Children at Home		187.5	< 0.001		481.9	< 0.001
No	108(17.4)			595(30.0)		
Yes	513(82.6)			1388(70.0)		

Factors associated with keeping antibiotics at home for children

As Table 2 shows, mothers (aOR=1.17, 95% CI 1.06–1.29) and respondents with higher education levels (aOR=1.34, 95% CI 1.20–1.51; aOR=1.50, 95% CI 1.33–1.70) were more likely to keep antibiotics at home for children. Respondents from Shaanxi (aOR=1.96, 95% CI 1.75–2.20) and respondents with medical backgrounds (aOR=1.54, 95% CI 1.35–1.75) had greater odds of keeping antibiotics at home for children.

Table 2. Factors associated with keeping antibiotics at home for children (*n*=9526)

Independent Variables	**aOR (95% CI)**
Sex of Caregiver	
Male	Ref
Female	1.17(1.06,1.29)**
Sex of Child	
Male	Ref
Female	1.04(0.96,1.13)

Age of Child	1.05(1.04,1.07)***
Parents' Highest Level of Education	
Middle school and below	Ref
High school	1.34(1.20,1.51)***
College and above	1.50(1.33,1.70)***
Average Household Income (RMB, monthly)	
< 3000(US$461)	Ref
3000-5000 (US$462–769)	1.22(1.08,1.38)**
5001-10000(US$770–1538)	1.17(1.02,1.33)*
> 10000(US$1538)	1.36(1.16,1.60)***
Province	
Zhejiang	Ref
Guangxi	1.00(0.89,1.13)
Shaanxi	1.96(1.75,2.20)***
Residence	
Rural	Ref
Urban	1.03(0.94,1.13)
Parents with Medical Background	
No	Ref
Yes	1.54(1.35,1.75)***

*p＜0.05,**p＜0.01,***p＜0.001; Ref: reference group; aOR: adjusted odds ratio

The association between keeping antibiotics at home and SMA for children

Among 1927 parents who self-medicated their children in the last month (Model 1), those who kept antibiotics at home for children were nearly five times (aOR=4.91, 95% CI 3.84–6.28) more likely to engage in SMA for children than those who did not. Model 2 illustrates that parents who had leftover antibiotics which came from previous prescriptions and which were purchased from pharmacies were 3.80 times (95% CI 2.89–5.00) and 6.45 times (95% CI 4.89–8.51) more likely to engage in SMA for children than those who did not keep antibiotics at home (Table 3).

Table 3. The association between keeping antibiotics at home and SMA for children when they fell sick (*n*=1927)[1]

Independent Variables	Model 1 aOR (95% CI)	Model 2 aOR (95% CI)
Sex of Caregiver		
Male	Ref	Ref
Female	1.23(0.93,1.62)	1.28(0.97,1.69)
Sex of Child		
Male	Ref	Ref
Female	0.95(0.77,1.18)	0.95(0.77,1.17)
Age of Child	1.03(0.99,1.06)	1.02(0.99,1.06)
Parents' Highest Level of Education		

Middle school and below	Ref	Ref
High school	0.81(0.60,1.11)	0.79(0.58,1.08)
College and above	0.72(0.52,0.99)*	0.71(0.52,0.98)*
Average Household Income (RMB, monthly)		
< 3000(US$461)	Ref	Ref
3000-5000(US$462–769)	0.92(0.68,1.24)	0.94(0.69,1.27)
5001-10000(US$770–1538)	0.65(0.46,0.91)*	0.66(0.47,0.94)*
> 10000(US$1538)	0.76(0.50,1.16)	0.78(0.51,1.20)
Province		
Zhejiang	Ref	Ref
Guangxi	1.91(1.38,2.65)***	1.69(1.21,2.35)**
Shaanxi	2.63(1.91,3.60)***	2.41(1.75,3.31)***
Residence		
Rural	Ref	Ref
Urban	0.97(0.77,1.23)	0.96(0.76,1.21)
Parents with Medical Background		
No	Ref	Ref
Yes	0.71(0.52,0.97)*	0.71(0.52,0.98)*
Keeping Antibiotics at Home for Children		
No	Ref	-
Yes	4.91(3.84,6.28)***	-
Keeping Antibiotics at Home for Children		
No	-	Ref
Yes, previously prescribed by doctors	-	3.80(2.89,5.00)***
Yes, previously purchased from pharmacies	-	6.45(4.89,8.51)***

[1] 17 of 1944 respondents who self-treated their children in the past month kept antibiotics from other sources except the two main ones (previous prescriptions or pharmacies), leaving 1927 for analysis in the regression models. *p<0.05,**p<0.01,***p<0.001; Ref: reference group; aOR: adjusted odds ratio.

The association between keeping antibiotics at home and SMA for children for prophylaxis

Among 9 456 respondents (Model 1), those who kept antibiotics at home for children were 3.16 times (95% CI 2.83–3.53) more likely to prophylactically engage in SMA for children than those who did not keep antibiotics at home. Model 2 illustrates that parents who had leftover antibiotics which came from previous prescriptions and which were purchased from pharmacies were 2.96 times (95% CI 2.62–3.34) and 3.53 times (95% CI 3.07–4.05) more likely to engage in SMA for children for prophylaxis than those who did not keep antibiotics at home (Table 4).

Table 4. The association between keeping antibiotics at home and prophylactic SMA for children(n=9456)[2]

Independent Variables	Model 1 aOR (95% CI)	Model 2 aOR (95% CI)
Sex of Caregiver		
Male	Ref	Ref

Female	0.83(0.74,0.94)**	0.83(0.74,0.94)**
Sex of Child		
Male	Ref	Ref
Female	1.06(0.96,1.18)	1.06(0.96,1.18)
Age of Child	1.01(1.00,1.03)	1.01(1.00,1.03)
Parents' Highest Level of Education		
Middle school and below	Ref	Ref
High school	0.97(0.84,1.12)	0.97(0.84,1.11)
College and above	0.85(0.73,0.99)*	0.84(0.72,0.98)*
Average Household Income (RMB, monthly)		
< 3000(US$461)	Ref	Ref
3000-5000(US$462–769)	0.93(0.80,1.08)	0.93(0.80,1.08)
5001-10000(US$770–1538)	0.90(0.76,1.06)	0.90(0.76,1.06)
> 10000(US$1538)	0.84(0.68,1.03)	0.84(0.69,1.04)
Province		
Zhejiang	Ref	Ref
Shaanxi	1.59(1.38,1.84)***	1.56(1.35,1.80)***
Guangxi	1.00(0.86,1.17)	0.97(0.83,1.13)
Residence		
Rural	Ref	Ref
Urban	0.94(0.84,1.06)	0.94(0.84,1.06)
Parents with Medical Background		
No	Ref	Ref
Yes	0.62(0.52,0.75)***	0.62(0.52,0.75)***
Keeping Antibiotics at Home for Children		
No	Ref	-
Yes	3.16(2.83,3.53)***	-
Keeping Antibiotics at Home for Children		
No	-	Ref
Yes, previously prescribed by doctors	-	2.96(2.62,3.34)***
Yes, previously purchased from pharmacies	-	3.53(3.07,4.05)***

[2] 70 of 9526 respondents kept antibiotics from other sources except the two main ones (previous prescriptions or pharmacies), leaving 9456 for analysis in the regression models. *p < 0.05,**p < 0.01,***p < 0.001; Ref: reference group; aOR: adjusted odds ratio.

DISCUSSION

To the best of our knowledge, this is the first study covering both rural and urban Chinese populations to investigate parental behaviors of keeping antibiotics at home for children and its association with SMA for sick children and for prophylaxis. This is also the first study to identify the two main sources of leftover antibiotics for children: previous prescriptions and pharmaceutical purchases. We found that keeping antibiotics at home for children is a widespread practice in China, which increases chances of parents engaging in SMA for their

children. In this study, leftover antibiotics from previous prescriptions accounted for a larger proportion of total in-home antibiotics; however, leftovers which originated from pharmaceutical purchase had a higher risk of SMA for children. These findings indicate an urgent need for intervention programs on reducing leftover antibiotics and enhancing appropriate antibiotic use for children.

The prevalence of keeping antibiotics for children varies greatly across China. Rates of antibiotics kept at home by parents or caregivers in central rural, eastern rural, and urban China were reported as 75%,[23] 32%,[29] and 25%[13] respectively, and in our study as 48.1%. Unlike previous studies, our results are based on data from disparate locations thereby providing a broader picture of the prevalence of leftover antibiotics in China. Compared with similar studies conducted overseas, the rate in China is higher than that reported in Trinidad and Tobago (21.8%)[32] but lower than that in Mongolia (58.4%).[22]

As is consistent with our results, previous studies have proven that keeping antibiotics at home could increase the likelihood of parents engaging in SMA for children.[13,22,23] It has been found that people tend to use the same drug when they confronted similar symptoms based on their experiences.[33] Recent evidence also shows that parents who keep antibiotics at home prefer to self-medicate their children rather than directly seeking advice from a medical professional.[13] Therefore, leftover antibiotics at home facilitate parents' deleterious practice of SMA for children by referring to previous practices. One survey in China even reported that among parents who kept antibiotics at home, 97% used the leftovers for their children on a second occasion.[29]

Overall, 63.1% leftover antibiotics we found came from previous prescriptions. This result differs from a study of Chinese university students which identified non-prescription pharmaceutical purchases as the main source of leftover antibiotics.[19] In this study, there were 69.2% parents who engaged in hospital visits (not shown in tables) while the rate among university students was only 27.4%.[28] In addition, medications are dispensed in fixed packages rather than exact doses in China.[14] High consultation rates and inadequate dispensing systems explain the origin of most leftover antibiotics for children – previous prescriptions. Moreover, non-compliance could also be responsible for a large portion of leftovers[29] since many children fail to complete the course of treatment because their parents incorrectly accuse antibiotics for the side effects of other drugs taken at the same time.[34]

In this study, only one-third of leftover antibiotics for children came from pharmacies. However, one should note that this kind of leftovers shows higher risks of SMA for children. In China, although a prescription-only regulation for antibiotics at retail pharmacies has been in place since 2004,[35] it still remains easy for parents to purchase antibiotics without prescriptions due to the lack of an effective monitoring system for sales of

antibiotics. As one multi-center survey in urban China concluded, 55.9% pharmacies sold non-prescription antibiotics for pediatric diarrhea.[36] Another nationwide study also reported that nearly 70% university students who succeeded in pharmaceutical purchases of antibiotics had no prescription at all[28]. It can be inferred that substantial leftover antibiotics from pharmacies in our study had been purchased without prescription. Furthermore, previous studies found that antibiotics purchased from pharmacies without prescription strongly contributed to the problem of SMA for children,[13,37] and most leftover antibiotics from pharmacies were kept for future use.[18] In contrast, as discussed above, leftover antibiotics from previous prescriptions were usually unintentionally left and not necessarily meant to be used on a second occasion.[38] This finding reinforces our belief that China needs stronger regulations on prohibiting non-prescription sales of antibiotics at retail pharmacies.

In line with previous evidence,[19] parents with medical backgrounds were more likely to keep antibiotics at home for children; however, they were also less likely to engage in SMA for children. A possible explanation could be that parents with medical backgrounds had easier access to antibiotics. One study found that some pharmacists helped their families to obtain non-prescription antibiotics.[39] On the other hand, parents with medical backgrounds might keep stand-by antibiotics since they believed that they have the capacity to handle some of their children's illnesses. However, most conditions in this study were self-limited diseases which did not need antibiotic therapy. Parents with medical backgrounds could be aware of that, thus they were more likely to self-treat their children without antibiotics. Additionally, mothers were less likely to engage in SMA for children for prophylaxis in our study, which might be attributed to their role of the main caregiver and health decision maker in the family.**Error! Bookmark not defined.** However, this predictor was not significant in remedial use, which deserves further investigation.

Our findings have several important implications for medical practitioners and policy makers. For the supply side, close supervision of sales of antibiotics at retail pharmacies is urgently needed; the dispensing system of medication in healthcare institutions needs reformation so that patients get a precise dosage of antibiotics. For the demand side, it is essential to provide public education programs which teach appropriate knowledge and skills to manage common self-limited juvenile diseases, which may help reduce the rates of unnecessary hospital visits and improper antibiotic use. Furthermore, collecting and recycling programs for leftover antibiotics could be useful in China, as these have been proven successful in reducing leftover antibiotics elsewhere.[40,41]

Our study has several limitations. First, this study only recruited parents, which excluded situations when grandparents or others acted as children's primary caregivers. Second, the study relied on self-reports of parents,

which undoubtedly reflected their misunderstanding of antibiotics.[12,13] This means that they might have over- or under-estimated the rates at which they use or keep antibiotics, however , we tried to minimize this bias by a brief explanation about antibiotics in the questionnaire. Third, our study cannot show the direct relation between leftover antibiotics and SMA for children, instead only a strong association has been found. Specific sources of leftover antibiotics used in SMA should be investigated in future studies. Fourth, our findings only focus on the influence of leftover antibiotics from two main sources because others represent a very small proportion (1.6%) in this study. This might not be the case in other countries so that future studies are needed to convey more pictures of leftover antibiotics.

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of School of Public Health, Zhejiang University (reference number: ZGL201706-2).

Acknowledgments

We thank the staff of medical facilities and teachers for their help during data collection. We also acknowledge all the parents who participated in the study. We especially appreciate Théo Storella for editing and polishing this paper.

Contributors

CS analyzed the data and drafted the manuscript. YH revised the manuscript critically for important intellectual content. XZ and XW led the design of the study. XZ is the PI of the study and participated in the coordination of data collection and critical review of the manuscript. XM, JL and LL participated in critical review of the manuscript. All authors read and approved the final manuscript.

Funding

Zhejiang University Zijin Talent Programme.

Competing interests

All authors declare no competing interests.

Data sharing statement

The data-sets analyzed during this study are available from the corresponding author on reasonable request.

REFERENCES

1 O'Neill J. Antimicrobial resistance: tackling a crisis for the health and wealth of nations. 2014 https://amr-review.org/sites/default/files/AMR%20Review%20Paper%20-%20Tackling%20a%20crisis%20for%20the%20health%20and%20wealth%20of%20nations_1.pdf (accessed 19 July 2019).

2 Organization W H. Ten threats to global health in 2019. 2019. https://www.who.int/emergencies/ten-threats-to-global-health-in-2019 (accessed 19 July 2019).
3 Laxminarayan R, Duse A, Wattal C, et al. Antibiotic resistance—the need for global solutions[J]. *Lancet Infect Dis* 2013;13(12):1057-1098.
4 Feikin DR, Schuchat A, Kolczak M, et al. Mortality from invasive pneumococcal pneumonia in the era of antibiotic resistance, 1995-1997[J]. *American journal of public health* 2000;90(2):223-229.
5 Flandrois JP, Lina G, Dumitrescu O. MUBII-TB-DB: a database of mutations associated with antibiotic resistance in Mycobacterium tuberculosis[J]. *BMC bioinformatics* 2014;15(1): 107.
6 Davies J, Davies D. Origins and evolution of antibiotic resistance. *Microbiol Mol Biol Rev* 2010;74(3): 417–433.
7 Al Akhali KM, Alzomar AK, Khan NA, et al. Misuse of antibiotics and awareness of antibiotic hazard among the public and medical professionals in Thamar province, in republic of Yemen[J]. *Pharmacie Globale* 2013;4(1): 1-4.
8 Awad A, Aboud EA. Knowledge, attitude and practice towards antibiotic use among the public in Kuwait. *PLoS One* 2015;10(2):e0117910.
9 Li LJ, Wang PS. Self-medication with antibiotics: a possible cause of bacterial resistance[J]. *Med Hypotheses* 2005;5(65): 1000-1001.
10 Grigoryan L, Burgerhof JGM, Haaijer-Ruskamp FM, et al. Is self-medication with antibiotics in Europe driven by prescribed use?[J]. *J Antimicrob Chemother* 2007;59(1):152-156.
11 Badger-Emeka LI, Emeka PM, Okosi M. Evaluation of the extent and reasons for increased non-prescription antibiotics use in a University town, Nsukka Nigeria[J]. *Int J Health Sci* 2018;12(4):11.
12 Lv B, Zhou Z, Xu G, et al. Knowledge, attitudes and practices concerning self-medication with antibiotics among university students in western China[J]. *Trop Med Int Health* 2014;19(7):769-779.
13 Chang J, Lv B, Zhu S, et al. Non-prescription use of antibiotics among children in urban China: a cross-sectional survey of knowledge, attitudes, and practices[J]. *Expert Rev Anti Infect Ther* 2018;16(2):163-172.
14 Kardas P, Pechère JC, Hughes DA, et al. A global survey of antibiotic leftovers in the outpatient setting[J]. *Int J Antimicrob Agents* 2007;30(6):530-536.
15 Ocan M, Obuku EA, Bwanga F, et al. Household antimicrobial self-medication: a systematic review and meta-analysis of the burden, risk factors and outcomes in developing countries[J]. *BMC Public Health* 2015;15(1): 742.
16 Grigoryan L, Haaijer-Ruskamp FM, Burgerhof JGM, et al. Self-medication with antimicrobial drugs in Europe[J]. *Emerg Infect Dis* 2006;12(3): 452-459.
17 Richman PB, Garra G, Eskin B, et al. Oral antibiotic use without consulting a physician: a survey of ED patients[J]. *Am J Emerg Med* 2001;19(1):57-60.
18 Jassim AM. In-home Drug Storage and Self-medication with Antimicrobial Drugs in Basrah, Iraq[J]. *Oman Med J* 2010;25(2):79-87.
19 Wang X, Lin L, Xuan Z, et al. Keeping antibiotics at home promotes self-medication with antibiotics among Chinese University Students[J]. *Int J Environ Res Public Health* 2018;15(4): 687.
20 Li R, Xiao F, Zheng X, et al. Antibiotic misuse among children with diarrhea in China: Results from a national survey[J]. *PeerJ* 2016;4:e2668.
21 Panagakou SG, Spyridis N, Papaevangelou V, et al. Antibiotic use for upper respiratory tract infections in children: A cross-sectional survey of knowledge, attitudes, and practices (KAP) of parents in Greece[J]. *BMC Pediatr* 2011;11(1):60.
22 Togoobaatar G, Ikeda N, Ali M, et al. Survey of non-prescribed use of antibiotics for children in an urban community in Mongolia[J]. *Bull World Health Organ* 2010;88(12):930-936.
23 Yu M, Zhao G, Lundborg CS, et al. Knowledge, attitudes, and practices of parents in rural China on the use of antibiotics in children: a cross-sectional study[J]. *BMC Infect Dis* 2014;14(1):112.
24 Alhomoud F, Aljamea Z, Almahasnah R, et al. Self-medication and self-prescription with antibiotics in the Middle East—do they really happen? A systematic review of the prevalence, possible reasons, and outcomes[J]. *Int J Infect Dis* 2017;57:3-12.
25 China. N. National Bureau of Statistics China http://data.stats.gov.cn/english/ (accessed 19 July 2019).
26 China. The State Council. The Ordinance on the Management of Vaccine and Immunizatio. 2005. http://www.gov.cn/zhengce/content/2008-03/28/content_6250.htm (accessed 9 October 2019)
27 China. N. National Bureau of Statistics China http://www.stats.gov.cn/tjsj/zxfb/201710/t20171026_1546618.html (accessed 19 July 2019)
28 Wang X, Peng D, Wang W, et al. Massive misuse of antibiotics by university students in all regions of China: implications for national policy[J]. *Int J Antimicrob Agents* 2017;50(3):441-446.

29 Ding L, Sun Q, Sun W, et al. Antibiotic use in rural China: a cross-sectional survey of knowledge, attitudes and self-reported practices among caregivers in Shandong province[J]. *BMC Infect Dis* 2015;15(1):576.
30 Cantarero-Arévalo L, Hallas MP, & Kaae S. Parental knowledge of antibiotic use in children with respiratory infections: a systematic review[J]. *Int J Pharm Pract* 2017;25(1):31-49.
31 Wen Juan Xing. https://www.wjx.cn (accessed 23 July 2019).
32 Parimi N, Pereira LMP, Prabhakar P. Caregivers' practices, knowledge and beliefs of antibiotics in paediatric upper respiratory tract infections in Trinidad and Tobago: a cross-sectional study[J]. *BMC Fam Pract* 2004；5(1):28.
33 Jin C, Ely A, Fang L, et al. Framing a global health risk from the bottom-up: User perceptions and practices around antibiotics in four villages in China[J]. *Health Risk Soc* 2011;13(5):433-449.
34 Wun YT, Lam TP, Lam KF, et al. Antibiotic use: do parents act differently for their children?[J]. *Int J Clin Pract* 2012;66(12):1197-1203.
35 State Food and Drug Administration. The five prescription sales only antibacterial released by SFDA. 2003. http://www.nmpa.gov.cn/WS04/CL2196/323380.html (accessed 19 July 2019).
36 Chang J, Ye D, Lv B, et al. Sale of antibiotics without a prescription at community pharmacies in urban China: a multicentre cross-sectional survey[J]. *J Antimicrob Chemother* 2017;72(4):1235-1242.
37 Bi P, Tong S, Parton KA. Family self-medication and antibiotics abuse for children and juveniles in a Chinese city[J]. *Soc Sci Med* 2000;50(10):1445-1450.
38 Agarwal S, Yewale VN, Dharmapalan D. Antibiotics Use and Misuse in Children: A Knowledge, Attitude and Practice Survey of Parents in India[J]. *J Clin Diagn Res* 2015;9(11):SC21.
39 Dameh M, Norris P, Green J. New Zealand pharmacists' experiences, practices and views regarding antibiotic use without prescription[J]. *J Prim Health Care* 2012;4(2):131-140.
40 Thach AV, Brown CM, Pope N. Consumer perceptions about a community pharmacy-based medication take back program[J]. *J Environ Manage* 2013;127:23-27.
41 Lauer MF, Kettell BD, Davis MH. Environments and health: leftover drugs in the water supply: don't flush those pills![J]. *American Journal of Nursing* 2010;110(8):46-49.

Questionnaire

Part I Social demographic characteristics

If you have more than one child, the child you refer to in the text is the child who is taking vaccination at the vaccination point or studying at the current kindergarten/at the current elementary school.

Q1. Gender of the child:

1 Male 2 Female

Q2. Birth date of the child:

Q3.1. You currently have_____child/children?

Q3.2. （The child you refer to in the text）He/She is your _____ (rank) child?

Q4. You are the child's:

1 Father 2 Mother

Q5. Who is the major caregiver of this child at home?

1 Father 2 Mother 3 Grandpa 4 Grandma 5 Others

Q6. Your education level:

1 Primary school or below 2 Middle school

3 High school/Secondary Technical school 4 College/Junior College

5 Postgraduate or above

Q7. Your spouse's education level:

1 Primary school or below 2 Middle school

3 High school/Secondary Technical school 4 College/Junior College

5 Postgraduate or above

Q8. Your are living in:

1 Rural areas 2 Urban areas

Q9. Do you have medical education background?

1 Yes 2 No

Q10. Does your spouse have medical education background?

1 Yes 2 No

Q11. When the child is sick, will the elderly at home participate in the treatment decision?

1 Never 2 Sometimes 3 Often 4 Always

Q12. Your family average monthly income (RMB):

1 ＜3000 2 3001-5000 3 5001-10000

4 10001-20000 5 ＞20000

Part II Medicine related knowledge

Q13. Antibiotics are effective for viral infections.

1 Yes 2 No 3 Don't know

Q14. Antibiotics are an anti-inflammatory drug.

1 Yes 2 No 3 Don't know

Q15. The more frequently people use antibiotics, the harder it is to cure the bacteria infections.

1 Yes 2 No 3 Don't know

Q16. Excessive use of antibiotics can lead to bacterial antibiotic resistance.

1 Yes 2 No 3 Don't know

Q17. Expensive antibiotics are more effective than cheaper antibiotics.

1 Yes 2 No 3 Don't know

Q18. Excessive use of antibiotics is a serious problem in China.

1 Yes 2 No 3 Don't know

Q19. Bacterial antibiotic resistance in China will become a serious problem.

1 Yes 2 No 3 Don't know

Q20. New antibiotics are more effective than old antibiotics.

1 Yes 2 No 3 Don't know

Q21. Antibiotic abuse can produce super bacteria.

1 Yes 2 No 3 Don't know

Q22.1. Do you think the following drugs are antibiotics or not? (Penicillin drugs such as amoxicillin)

1 Yes 2 No 3 Don't know

Q22.2. Do you think the following drugs are antibiotics or not? (Cephalosporins such as cefaclor/ceftus sodium)

1 Yes 2 No 3 Don't know

Q22.3. Do you think the following drugs are antibiotics or not? (Non-steroidal drugs such as ibuprofen/merlin/aspirin)

1 Yes 2 No 3 Don't know

Q22.4. Do you think the following drugs are antibiotics or not? (Dexamethasone/prednisone and other steroids)

1 Yes 2 No 3 Don't know

Q22.5. Do you think the following drugs are antibiotics or not? (Quinolones such as ofloxacin/norfloxacin)

1 Yes 2 No 3 Don't know

Q22.6. Do you think the following drugs are antibiotics or not? (Macrolides such as azithromycin/roxithromycin)

1 Yes 2 No 3 Don't know

Q23.1. Do you think you antibiotics is appropriate when your child has the following symptoms or diseases? (Sore throat)

1 Yes 2 No 3 Don't know

Q23.2. Do you think you antibiotics is appropriate when your child has the following symptoms or diseases? (Cold/cough/runny)

1 Yes 2 No 3 Don't know

Q23.3. Do you think you antibiotics is appropriate when your child has the following symptoms or diseases? (Diarrhea)

1 Yes 2 No 3 Don't know

Q23.4. Do you think you antibiotics is appropriate when your child has the following symptoms or diseases? (Fever)

1 Yes 2 No 3 Don't know

Q23.5. Do you think you antibiotics is appropriate when your child has the following symptoms or diseases? (Otitis media/ear canal inflammation)

1 Yes 2 No 3 Don't know

Q24. Using antibiotics can boost your child's cold recovery.

1 Yes 2 No 3 Don't know

Q25. Using antibiotics can alleviate your child's cold symptoms.

1 Yes 2 No 3 Don't know

Q26. If your child needs antibiotics, the infusion method should be preferred.

1 Yes 2 No 3 Don't know

Q27. Antibiotics should be stopped immediately when the child's condition improves.

1 Yes 2 No 3 Don't know

Q28. If antibiotics are used unreasonably, there will be fewer and fewer effective antibiotics in the future.

1 Yes 2 No 3 Don't know

Q29. Antibiotics are effective for children's viral infections.

1 Yes 2 No 3 Don't know

Part III Antibiotic use behavior

Q30. Has your child been sick in the past month?

1 Yes 2 No (Jump to Q42)

If so, what was the child's most recent illness or what symptoms?

Q31.0. Cold (Runny nose, cough):

1 Yes 2 No (Jump to Q31.2)

Q31.1. If so, the cold has continued for _____ days and has not improved.

Q31.2. Fever:

1 Yes 2 No (Jump to Q31.3)

Q31.21. If so, the fever is up to _____° C

Q31.22. and continued for_____ days and has not improved.

Q31.3. Sore throat:

1 Yes 2 No (Jump to Q31.4)

Q31.31. If so, the sore throat has continued for _____ days and has not improved.

Q31.4. Diarrhea:

1 Yes 2 No (Jump to Q31.5)

Q31.41. If so, the diarrhea has continued for _____ days and has not improved.

Q31.5. Otitis media:

1 Yes 2 No (Jump to Q31.6)

Q31.51. If so, the otitis media has continued for _____ days and has not improved.

Q31.6. Other symptoms

1 Yes 2 No

Q32. Was the illness/symptom treated?

1 Yes 2 No (Jump to Q42)

Q33. If treated, was it self-medication or treated at hospital?

1 Self-medication (Jump to Q33134)

2 Self-medication without effects, then being treated at hospital (Jump to Q33234)

3 Being treated at hospital (Jump to Q36.1)

Q33134. During the self-medication, did you use antibiotics for your child?

1 Yes (Jump to Q34.1) 2 No (Jump to Q42)

Q33234. During the self-medication, did you use antibiotics for your child?

1 Yes (Jump to Q34.1) 2 No (Jump to Q36.1)

Q34.1. If so, please tell us the drug name or trade name of the antibiotics you used_____.

Q35. Where do the antibiotics for self-medication come from?

1 Home storage antibiotics 2 From pharmacies

3 From other people 4 Other

Q36.1. If being treated at hospital, which kinds of medical institutions did you go (You may choose more than one options)? (Private Clinics)

1 No 2 Yes

Q36.2. If being treated at hospital, which kinds of medical institutions did you go (You may choose more than one options)? (Community health service centres/stations)

1 No 2 Yes

Q36.3. If being treated at hospital, which kinds of medical institutions did you go (You may choose more than one options)? (County/district hospital)

1 No 2 Yes

Q36.4. If being treated at hospital, which kinds of medical institutions did you go (You may choose more than one options)? (Provincial/municipal hospitals)

1 No 2 Yes

Q37. Did the doctor give the child antibiotics at the medical institution?

1 Yes 2 No (Jump to Q42)

Q37.1. If so, please tell us the drug name or trade name of the antibiotics you used_____.

Q38. If the doctor prescribed antibiotics to the child, was it oral or infusion?

1 Oral 2 Infusion 3 Both

Q39. Did you stop the antibiotics as soon as your child got better (oral or infusion)?

1 Yes 2 No

Q40. Did you ask the doctor for antibiotics (oral or infusion) when you took you child to hospital this time?

1 Yes, and I asked for infusion antibiotics. 2 Yes, and I asked for oral antibiotics.

3 No (Jump to Q42)

Q41. Did the doctor meet your requirements for antibiotics (oral or infusion)?

1 Yes 2 No

Q42. Are there any antibiotics kept at home for the child?

1 Yes (Jump to Q44) 2 No

Q43. If so, where do they come from?

1 Previous antibiotic prescription left-overs

2 Previous purchase left-overs from pharmacies

3 Got them from other people 4Other

Q44. During the past year, did you ask your children to take antibiotics prophylactically (eg, when your children's classmates were having a cold or flu) ?

1 Yes 2 No

Q45.1. As parents, how can you acquire knowledge and skills to deal with your children's illness including cold, fever, and diarrhea? (Medical advice)

1 No 2 Yes

Q45.2. As parents, how can you acquire knowledge and skills to deal with your children's illness including cold, fever, and diarrhea? (Personal/relatives' experience)

1 No 2 Yes

Q45.3. As parents, how can you acquire knowledge and skills to deal with your children's illness including cold, fever, and diarrhea? (Television)

1 No 2 Yes

Q45.4. As parents, how can you acquire knowledge and skills to deal with your children's illness including cold, fever, and diarrhea? (Internet)

1 No 2 Yes

Q45.5. As parents, how can you acquire knowledge and skills to deal with your children's illness including cold, fever, and diarrhea? (Radio)

1 No 2 Yes

Q45.6. As parents, how can you acquire knowledge and skills to deal with your children's illness including cold, fever, and diarrhea? (Newspapers/books)

1 No 2 Yes

Q45.7. As parents, how can you acquire knowledge and skills to deal with your children's illness including cold, fever, and diarrhea? (Weibo, Wechat, QQ)

1 No 2 Yes

Q45.8. As parents, how can you acquire knowledge and skills to deal with your children's illness including cold, fever, and diarrhea? (Other)

1 No 2 Yes

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	1, 3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
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	6-7
Bias	9	Describe any efforts to address potential sources of bias	6-7
Study size	10	Explain how the study size was arrived at	N/A
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	N/A
		(*c*) Explain how missing data were addressed	N/A
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	N/A
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	7
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7-8
		(b) Indicate number of participants with missing data for each variable of interest	N/A
Outcome data	15*	Report numbers of outcome events or summary measures	8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear	9-12

		which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
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	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
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	15

*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.