PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	The influence of leftover antibiotics on self-medication with antibiotics for children: a cross-sectional study from three Chinese provinces
AUTHORS	Sun, Chenhui; Hu, Yanhong; Wang, Xiaomin; Lu, Jingjing; Lin, Leesa; Zhou, Xudong

VERSION 1 – REVIEW

REVIEWER	Jie Chang Xi'an Jiaotong University
REVIEW RETURNED	07-Oct-2019

GENERAL COMMENTS	The work conducted by Sun and Prof Zhou and colleagues is very interesting as well as an important topic, that they tried to establish an empirical link between storing leftover antibiotics in households and self-medication with antibiotics among young children and particularly tried to assess the different impact between leftover antibiotics from previous prescriptions and community pharmacies on SMA in the same sample. Another added value in this study is that the authors differentiate remedial use and prophylaxis use of antibiotics, which is rare in early studies on this topic in China. The article is well-written and easy to follow. I enjoyed reading it quite much and learned a lot. The survey was well organized to achieve a large sample size with very high respondent rate from different provinces in different regions in China. The methods used were suitable. Therefore, I do not have any major points for this paper, but only several minor suggestions. Minor point In line 108, the authors stated “multi-stage stratified cluster random sampling” was used for sampling, but information about how were the clusters (i.e. kindergartens, primary schools) sampled was missing. In lines 113-115, the parents of children under-3 were reached at vaccination clinics in this study, and I understand it might be the best way to conduct a survey like this among children younger than the kindergartens' enrollment age in China. But how was the sampling process in this specific study population, was it different from those sampled from kindergartens and primary schools? I think it would be better to expressly state this more clearly. Moreover, was the survey conducted at vaccination clinics mobile phone-based too? Line 115, in the sentence “...they must receive government subsidized...”, “must” is too strong here — I think in the law it is stated that residents should take the vaccines if they are among the targeted population, and fully vaccinated according to the EPI schedule in children is a requisite for primary school enrollment in China.

	Line 121. Is there a timeframe when asked people whether had kept antibiotics at home or not? If so, I think the time should also be a 1-year recall period to justify the association analysis between keeping leftovers and SMA is based on the same cross-section. And how was the question framed? – the current description is not clear enough – was the question specified onto children's use purpose or not? The questionnaire used in this study should be attached as an appendix. Line 125. Should specify what QR stands for first. Lines 231-233. Here, please delete the speculative statements regarding the differences in sources of antibiotics for SMA between children and college students in China. the explanation here has not been assessed with this study, and I think it also has not been supported by cited literature. Lines 240-250. I think it would be better to point out that there was a possible potential proportion of the antibiotics from pharmacies were dispensed without prescriptions -- dispensed from pharmacies doesn't mean dispensed without a prescription. Line 273. "because others represent a very small proportion (1.6%) in China"— please provide a reference here. I believe some more discussion on the differences in multivariable analyses results between remedial use and prophylactic use could be interesting and improve the depth and hence the quality of the paper.

REVIEWER	Nick Daneman Sunnybrook Health Sciences Centre, University of Toronto, Canada
REVIEW RETURNED	07-Oct-2019

GENERAL COMMENTS	The investigators report a cross-sectional multi-stage stratified cluster random sampling survey study in 3 provinces in China (n=9526 parents; response rate 89%), in which they test for an association between left-over antibiotic medications (kept by nearly half of parents) and the report of self medication of children. Leftover medications were significantly associated with self medication - and this association was strongest for those obtained directly from pharmacies rather than by prescription. Comments and questions: -abstract: there are interesting results in the manuscript (Table 2) related to the predictors of keeping antibiotics at home for children; I think it would be worth highlighting some of these in the abstract results section. -I'm confused by the number of survey respondents. The abstract says 9526 people were surveyed of which 88.7% responded; there are 9526 responses described in the tables; line 196 describes 9456 respondents. -were there any differences between survey respondents and non-respondents (or is impossible to assess)? -did the survey inquire specifically about left-over antibiotics that were intended for the child, or does it also include left-over antibiotics that were prescribed for other household members including the parents? -were the parents that self-medicated children for acute recent illnesses, also more likely to provide prophylaxis within the past 12 months? -Many of the predictors of leftover medications were not predictors of self-medication. It might be interesting to do an additional analysis restricted only to those parents with leftover antibiotics at

	home, and then to analyze the predictors of self-medicating versus not self-medicating children among this subset.

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

Reviewer Name: Jie Chang

Institution and Country: Xi'an Jiaotong University

Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below

1. The work conducted by Sun and Prof Zhou and colleagues is very interesting as well as an important topic, that they tried to establish an empirical link between storing leftover antibiotics in households and self-medication with antibiotics among young children and particularly tried to assess the different impact between leftover antibiotics from previous prescriptions and community pharmacies on SMA in the same sample. Another added value in this study is that the authors differentiate remedial use and prophylaxis use of antibiotics, which is rare in early studies on this topic in China. The article is well-written and easy to follow. I enjoyed reading it quite much and learned a lot. The survey was well organized to achieve a large sample size with very high respondent rate from different provinces in different regions in China. The methods used were suitable. Therefore, I do not have any major points for this paper, but only several minor suggestions.

Minor point

In line 108, the authors stated “multi-stage stratified cluster random sampling” was used for sampling, but information about how were the clusters (i.e. kindergartens, primary schools) sampled was missing.

We have specified the description of how the clusters were sampled:

“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.”

2. In lines 113-115, the parents of children under-3 were reached at vaccination clinics in this study, and I understand it might be the best way to conduct a survey like this among children younger than the kindergartens' enrollment age in China. But how was the sampling process in this specific study population, was it different from those sampled from kindergartens and primary schools? I think it would be better to expressly state this more clearly. Moreover, was the survey conducted at vaccination clinics mobile phone-based too?

The sampling process for parents of children under three was partially different from that for parents of school-age children, though both followed the multi-stage stratified cluster random sampling strategy. In kindergartens and primary schools, parents were indirectly recruited through teachers and students who were approached simultaneously. While in vaccination clinics, we contacted all parents (who met the criteria) face-to-face during business days. All surveys were mobile phone-based. We have specified related information according to your advice as below.

“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.”

3. Line 115, in the sentence “...they must receive government subsidized...”, “must” is too strong here — I think in the law it is stated that residents should take the vaccines if they are among the targeted population, and fully vaccinated according to the EPI schedule in children is a requisite for primary school enrollment in China.

We have amended it accordingly.

“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 [1,2].”

References

[1]. China. The State Council. The Ordinance on the Management of Vaccine and Immunization. 2005. http://www.gov.cn/zhengce/content/2008-03/28/content_6250.htm (accessed 9 October 2019)
[2]. China. N. National Bureau of Statistics China http://www.stats.gov.cn/tjsj/zxfb/201710/t20171026_1546618.html (accessed 19 July 2019)

4. Line 121. Is there a timeframe when asked people whether had kept antibiotics at home or not? If so, I think the time should also be a 1-year recall period to justify the association analysis between keeping leftovers and SMA is based on the same cross-section. And how was the question framed? – the current description is not clear enough – was the question specified onto children’s use purpose or not? The questionnaire used in this study should be attached as an appendix.

Our pilot study indicated that keeping leftover antibiotics behavior, which is different from direct use of antibiotics, is a continuous behavior without particular precondition. Therefore, we did not set a timeframe in the formal survey. We asked whether there were antibiotics kept at home for children use at the survey time. The question was framed “Are there any antibiotics kept at home for the child?”

The question was specified onto children’ use purpose and “the child” referred to the one who was receiving vaccination or attending the kindergarten/primary school. To avoid potential misunderstandings, we have added the following information in the “Data collection” section:

“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 questionnaire is attached.

5. Line 125. Should specify what QR stands for first.

QR Code stands for quick response code. We have amended it accordingly.

6. Lines 231-233. Here, please delete the speculative statements regarding the differences in sources of antibiotics for SMA between children and college students in China. the explanation here has not been assessed with this study, and I think it also has not been supported by cited literature.

We have deleted the statements you mentioned.

7. Lines 240-250. I think it would be better to point out that there was a possible potential proportion of the antibiotics from pharmacies were dispensed without prescriptions -- dispensed from pharmacies doesn't mean dispensed without a prescription.

We really appreciate your academic rigor. We have amended it accordingly:

"It can be inferred that substantial leftover antibiotics from pharmacies in our study had been purchased without prescription."

We also removed expressions like *without prescription/ non-prescription* when referring to pharmaceutical purchase in our results.

8. Line 273. "because others represent a very small proportion (1.6%) in China"— please provide a reference here.

Actually, this proportion (1.6%) is one of the results from our study. We have changed the expression "in China" to "in this study" for avoiding such misunderstanding.

9. I believe some more discussion on the differences in multivariable analyses results between remedial use and prophylactic use could be interesting and improve the depth and hence the quality of the paper.

We agree that the difference between remedial and prophylactic use deserves further investigation although it is not one of our main focuses in this study. Our results showed two main differences.

1) Mothers were less likely to engage in prophylactic use but the association in remedial use was not significant. We have added this point in the discussion:

"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[1]. However, this predictor was not significant in remedial use, which deserves further investigation."

2) Parents from Shaanxi province were significantly associated with remedial use while the association both existed for parents from Shaanxi and Guangxi in prophylactic use. This point was discussed in another paper focusing on the regional disparities (unpublished data).

Reference:

[1]. 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.

Reviewer: 2

Reviewer Name: Nick Daneman

Institution and Country: Sunnybrook Health Sciences Centre, University of Toronto, Canada

Please state any competing interests or state 'None declared': None Declared

Please leave your comments for the authors below

The investigators report a cross-sectional multi-stage stratified cluster random sampling survey study in 3 provinces in China (n=9526 parents; response rate 89%), in which they test for an association between left-over antibiotic medications (kept by nearly half of parents) and the report of self-medication of children. Leftover medications were significantly associated with self-medication - and this association was strongest for those obtained directly from pharmacies rather than by prescription.

Comments and questions:

1. -abstract: there are interesting results in the manuscript (Table 2) related to the predictors of keeping antibiotics at home for children; I think it would be worth highlighting some of these in the abstract results section.

We have added the following predictors in the abstract:

"Mothers, older age of child, higher household income, higher education level, and medical background were significantly and positively associated with keeping antibiotics at home."

2. -I'm confused by the number of survey respondents. The abstract says 9526 people were surveyed of which 88.7% responded; there are 9526 responses described in the tables; line 196 describes 9456 respondents.

Sorry to confuse you, but 9526 was the number of parents who actually returned a valid questionnaire, which means the response rate has been considered.

There were 70 respondents whose leftover antibiotics came from other sources besides previous prescriptions and pharmaceutical purchase, which were excluded in the two regression models (9526-70 = 9456). You can also refer to the caption below Table 4.

3. -were there any differences between survey respondents and non-respondents (or is impossible to assess)?

It is a pity that we did not conduct a further analysis to find out the differences between survey respondents and non-respondents. However, according to the feedback from our RAs who conducted the face-to-face investigation in the vaccination clinics, most non-respondents could not spare time to fill in the questionnaire because they were busy comforting their babies after vaccination. The response rate of our study is 88.7%, which is relatively high.

4. -did the survey inquire specifically about left-over antibiotics that were intended for the child, or does it also include left-over antibiotics that were prescribed for other household members including the parents?

This survey inquired specifically about the leftover antibiotics that were intended for the child. The exact question in the questionnaire was “Are there any antibiotics kept at home for the child?”.

5. -were the parents that self-medicated children for acute recent illnesses, also more likely to provide prophylaxis within the past 12 months?

Table A. The association between SMA for children for prophylaxis and SMA for children when they fell sick

Independent Variables	**aOR (95% CI)**
SMA for Children	
No	Ref
Yes	2.18(1.73,2.74)***

***p＜0.001; Ref: reference group; aOR: adjusted odds ratio.

As shown in Table A, there was a positive association between the remedial use and prophylactic use. However, we did not include it in the manuscript since the current topic is the influence of leftover antibiotics. We still appreciate your valuable hints for future research.

6. -Many of the predictors of leftover medications were not predictors of self-medication. It might be interesting to do an additional analysis restricted only to those parents with leftover antibiotics at home, and then to analyze the predictors of self-medicating versus not self-medicating children among this subset.

Table B. Factors associated with SMA among parents keeping antibiotics at home for children (*n*=4039)[a]

Independent Variables	**aOR (95% CI)**
Sex of Caregiver	

Male	Ref
Female	1.14(0.84,1.57)
Sex of Child	
Male	Ref
Female	0.80(0.63,1.02)
Age of Child	1.02(0.98,1.06)
Parents' Highest Level of Education	
Middle school and below	Ref
High school	0.66(0.45,0.97)
College and above	0.62(0.42,0.91)
Average Household Income (RMB, monthly)	
< 3000(US$461)	Ref
3000-5000 (US$462–769)	0.90(0.62,1.30)
5001-10000(US$770–1538)	0.70(0.46,1.04)
> 10000(US$1538)	0.82(0.50,1.34)
Province	
Zhejiang	Ref
Guangxi	1.93(1.33,2.81)***
Shaanxi	2.76(1.94,3.93)***
Residence	
Rural	Ref
Urban	0.97(0.74,1.26)
Parents with Medical Background	
No	Ref
Yes	0.66(0.47,0.93)*

[a] 541 of 4580 respondents who reported keeping antibiotics at home for children didn't engage in self-medicating children, leaving 4039 for analysis in the regression models. *p＜0.05,**p＜0.01,***p＜0.001; Ref: reference group; aOR: adjusted odds ratio

Thanks for your advice. We have analyzed the predictors of self-medicating children with antibiotics among parents keeping leftover antibiotics at home for children (Table B). The results showed that 1) parents from less developed provinces (Guangxi and Shaanxi) were significantly and positively associated with self-medicating children with antibiotics, 2) parents with medical background were less likely to self-medicating children with antibiotics.

Our research team has already drafted another paper on the regional differences of antibiotics use among parents. Therefore, we did not want to overlap the point in this manuscript. The influence of medical background has been mentioned in the Discussion part – “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.”.

VERSION 2 – REVIEW

REVIEWER	Jie Chang Xi'an Jiaotong University
REVIEW RETURNED	09-Nov-2019

GENERAL COMMENTS	The authors have addressed the issues raised.

REVIEWER	Nick Daneman Sunnybrook Health Sciences Centre, University of Toronto
REVIEW RETURNED	04-Nov-2019

GENERAL COMMENTS	The authors have addressed all of my questions.