A systematic review of antibiotic utilization in China

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Objectives: Reliable data about antibiotic utilization in the large pharmaceutical market of the world’s most populous country, the People’s Republic of China, are in short supply. Although many primary studies have investigated the use of antibiotics in China, most of the relevant studies were published in the Chinese language. This systematic review aims to summarize reported percentages of outpatient encounters resulting in the prescription of antibiotics in China.

Methods: We systematically searched and reviewed studies of antibiotic prescribing patterns in China, published in Chinese or English between 2000 and August 2012. The study quality was assessed and the overall percentage of outpatient encounters resulting in the prescription of antibiotics was calculated using random-effects meta-analysis. Subgroup analyses were conducted to investigate heterogeneity across studies.

Results: We included 57 eligible studies (with a total of 556,435 outpatient encounters). The overall percentage of outpatients prescribed antibiotics was 50.3% (95% CI: 47.4%–53.1%). Of the outpatients prescribed antibiotics, 74.0% (95% CI: 71.3%–76.6%) were prescribed one antibiotic, 23.3% (95% CI: 21.1%–25.7%) were prescribed two antibiotics and 2.0% (95% CI: 1.3%–2.8%) were prescribed three or more antibiotics. The proportion of antibiotic utilization differed greatly across hospital levels and geographical regions and fluctuated over time.

Conclusions: The percentage use of antibiotics is high in China. The excessive use of antibiotics is particularly more problematic in lower-level hospitals and in less developed western China. The implementation and impact of the national efforts to control the excessive use of antibiotics should be appropriately evaluated.

Keywords: antibiotic prescription, usage, pharmacoepidemiology

Introduction

Resistance to antibiotics is a growing public health problem, leading to a delay in the administration of effective therapy, increased costs, morbidity and mortality. The widespread inappropriate use of antibiotics is considered as one of the important causes of the development of antibiotic resistance. A crucial strategy to control antibiotic resistance is to reduce the excessive and inappropriate use of antibiotics in practice.

The percentage use of antibiotics has been employed as a key indicator for assessing whether the use of antibiotics is likely appropriate. Since the 1980s, there have been many studies of the use of antibiotics in practice. The WHO systematically reviewed information on the use of antibiotics gathered from different countries in 1988, 2004 and 2011. Because the use of antibiotics may be more problematic in developing countries, WHO published a book entitled Medicines Use in Primary Care in Developing and Transitional Countries. According to this WHO report, the percentage use of antibiotics was on average up to 40%–50% in developing countries and this range of percentages remained unchanged over time.

Although there have been many studies of the use of antibiotics worldwide, available data from studies in China are very limited. The 2004 World Medicines Situation Report pointed out that reliable data about antibiotic utilization in the large pharmaceutical market of the world’s most populous country, the People’s Republic of China, were in short supply.

Recently, the number of published studies of the use of antibiotics in China has greatly increased. However, most of the relevant studies were published in the Chinese language, with only a few published in English. These studies presented high degrees of variability in terms of findings, settings and other study characteristics.

To overcome the perceived shortage of research evidence on the use of antibiotics in China, we conducted a systematic review of studies of the use of antibiotics in China. We summarized the proportion of antibiotic use in outpatients and investigated causes of heterogeneity in findings across individual studies.
Methods
We followed the Meta-analysis of Observational Studies in Epidemiology guidelines to report the present meta-analysis.16

Search strategy
To identify relevant studies, we searched five Chinese biomedical databases and PubMed (1946-) up to 1 August 2012. Additional studies were identified by cross-referencing.

The five Chinese databases are the Chinese Biomedical Literature database, China National Knowledge Infrastructure, VIP Information/Chinese Scientific Journals database and WANFANG database (Chinese Medicine Premier). The Chinese databases were searched using the following terms (in Chinese): ‘prescription’, ‘antimicrobial’, ‘antibacterial’ and ‘antibiotic’.

PubMed was searched using the following terms: (antibacterial [Title/Abstract] OR antibiotic [Title/Abstract] OR antimicrobial [Title/Abstract] OR antibiotics [Title/Abstract]) AND (China [Title/Abstract] OR Chinese [Title/Abstract]) Limits Activated: Humans, English.

Identification of relevant studies was carried out by one researcher and checked by two other researchers. Titles and abstracts yielded by searching bibliographic databases were examined first. Then, the full publications of possibly relevant studies based on titles and abstracts were retrieved and examined for inclusion or exclusion.

Inclusion and exclusion criteria
We included observational studies, published in Chinese or English between 2000 and 1 August 2012, which reported the percentage use of antibiotics in mainland China. For a study to be included, it should have used WHO/International Network for the Rational Use of Drugs (INRUD) methods and followed the guideline recommended by WHO to determine what antimicrobial agents can be counted as antibiotics for prescribing indicators analysis.17 Percentage use of antibiotics is defined as the percentage of outpatient encounters with antibiotics prescribed. In addition, the study must provide the following information: enrolment time, study site, the total number of sampled outpatient encounters, the number of outpatient encounters with one antibiotic, and the number of outpatient encounters with two antibiotics and with more than two antibiotics. For duplicate publications of the same study, the version published first or published in English was included. Review articles, congress abstracts and data from the regions of China other than the mainland (Taiwan, Hong Kong and Macao) were excluded.

To analyse the overall utilization of antibiotics and minimize potential bias, outpatient encounters must be randomly sampled from clinical departments. Studies of a single clinical department (such as paediatrics or the dental department) were excluded.

Quality assessment of included studies
The methodological quality of the included studies was assessed based on the WHO/INRUD methods.17 We considered six criteria for quality assessment:

(i) Whether a study defined drugs to be regarded as antibiotics according to WHO/INRUD indicator methodology.
(ii) Whether the type of health facility was specified. The prescribing indicators were designed for use in healthcentres, dispensaries or hospital outpatient departments.
(iii) Whether the types of included prescribing encounters were defined. Studies of prescribing indicators should be restricted to a sample of general illness encounters.
(iv) Whether data collection methods were described. For example, data may be collected retrospectively or prospectively.

(v) Whether the sample size was adequate. There should be ≥600 outpatient encounters included in an adequate cross-sectional study.
(vi) Whether the statistical methods were appropriate according to WHO/INRUD indicator methodology.

Each criterion was given one point if a study satisfied the WHO’s recommendation. Two independent reviewers assessed the quality of the included studies. We considered studies that scored five or higher as ‘high quality’, scored three or four as ‘moderate quality’ and scored two or lower as ‘low quality’. Quality assessment scores of the included studies are shown in Table S1 (available as Supplementary data at JAC Online).

Data extraction
We extracted the following data from included studies: first author and year of publication, enrolment time, sample size (the number of outpatient encounters), the number of outpatient encounters with one antibiotic, the number of outpatient encounters with two antibiotics and with more than two antibiotics, and study settings, populations and regions. The frequency of each antibiotic category prescribed was also extracted.

Statistical analysis
In developing countries, WHO/INRUD methods were often used to evaluate the situation of medicine use and the percentage use of antibiotics was a key indicator. We adopted this indicator to analyse antibiotic utilization in China. To indicate the extent of the combination of antibiotics, we analysed the proportion of outpatient encounters with one, two and three or more antibiotics prescribed. Subgroup analyses were performed with respect to study period, geographical area, hospital level and study quality. Studies were divided into three geographical regions: eastern, central and western. Chinese hospitals are divided into three levels (level 1, level 2 and level 3 hospitals). Level 3 hospitals are the highest level with the best medical equipment and technology, while level 1 hospitals include community healthcentres and township hospitals.

Data analyses were conducted using STATA/IC (version 12.1 for Windows). Meta-analyses were conducted using Freeman–Tukey transformed proportions and the pooled estimates were back-transformed to ordinary proportions.18 Heterogeneity across the studies was tested using the Q test and I² test. The random-effects model was used. Egger’s weighted regression methods were used to assess publication bias.

Results
The process of study identification and inclusion is shown in Figure 1. A total of 2998 articles were identified by literature search. After excluding irrelevant studies based on titles and abstracts, 219 articles were retrieved for detailed full-text evaluation. There were 57 studies, 2 in English and 55 in Chinese, that met the inclusion criteria. The main characteristics of the included studies are shown in Table S2 and Table S3 (both available as Supplementary data at JAC Online). According to quality assessment scores, there were 18 high-quality studies, 33 moderate-quality studies and 6 low-quality studies.

Figure 2 shows the percentage use of antibiotics reported in the included studies. The percentage of outpatient encounters resulting in the prescription of antibiotics was on average 50.3% (95% CI: 47.4%–53.1%) (Table 1). Of the outpatients prescribed antibiotics in China, 74.0% were prescribed one antibiotic, 23.3% were prescribed two antibiotics and 2.0% were prescribed three or more antibiotics (Table 2).

Heterogeneity across studies was statistically significant in the overall and subgroup analyses, presented in Table 1 and Table 2.
The funnel plot was statistically significantly asymmetric (Egger's test \( P = 0.031 \)) (Figure 3). The reported proportion of antibiotic use was not associated with the study quality score (data not shown).

In subgroup analyses, the percentage use of antibiotics was observed to vary by hospital level, geographical region and study period (Table 1). Lower-level hospitals tended to report higher antibiotic utilization than higher-level hospitals, although the differences between hospital levels were not statistically significant. The percentage of outpatient encounters resulting in the prescription of antibiotics was on average 47.1% in level 3 hospitals, 49.2% in level 2 hospitals and 53.4% in level 1 hospitals (Table 1). Antibiotic utilization in eastern China (47.3%) was lower than that in the western region (57.4%) and central region (50.3%); the difference
Figure 2. Reported percentage use of antibiotics in China, sorted by hospital level. One included study (a092 - Yongbin Li) was conducted in three different regions in 2009 and one was divided into three subgroup studies. The letters e, c, and w after the years (‘2009e’, ‘2009c’, ‘2009w’) represent eastern China, central China and western China, respectively. See Table S2 (available as Supplementary data at JAC Online).
between the western and eastern subgroups was statistically signific-
(P=0.003). The percentage of antibiotic utilization fluctuated
over time; it declined between 2005 and 2007 and then
increased between 2007 and 2009 (Table 1).

<table>
<thead>
<tr>
<th>Year of study</th>
<th>Number of studies</th>
<th>n/N</th>
<th>Percentage of antibiotic use (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010 and after</td>
<td>8</td>
<td>22111/46045</td>
<td>45.7 (39.3, 52.2)</td>
</tr>
<tr>
<td>2009</td>
<td>11</td>
<td>57641/124667</td>
<td>52.4 (46.4, 58.3)</td>
</tr>
<tr>
<td>2008</td>
<td>10</td>
<td>56125/133032</td>
<td>47.6 (42.5, 52.7)</td>
</tr>
<tr>
<td>2007</td>
<td>8</td>
<td>55475/127462</td>
<td>41.8 (35.6, 48.3)</td>
</tr>
<tr>
<td>2006</td>
<td>9</td>
<td>15113/31576</td>
<td>50.7 (38.4, 62.9)</td>
</tr>
<tr>
<td>2005</td>
<td>5</td>
<td>25217/45929</td>
<td>57.5 (48.6, 66.1)</td>
</tr>
<tr>
<td>2004 or before</td>
<td>9</td>
<td>28820/47724</td>
<td>57.2 (48.7, 65.5)</td>
</tr>
<tr>
<td>2009</td>
<td>10</td>
<td>56125/133032</td>
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</tr>
<tr>
<td>2004 or before</td>
<td>9</td>
<td>28820/47724</td>
<td>57.2 (48.7, 65.5)</td>
</tr>
</tbody>
</table>

The proportion of outpatient encounters with one antibiotic pre-
scribed in eastern China (75.8%) was higher than that in central (74.4%) and western (69.4%) China, while the proportion of out-
patient encounters with two antibiotics prescribed was 22.2% in
the eastern region, 21.8% in the central region and 26.9% in the
western region, although the differences between the regions were statistically non-significant. However, hospitals in the
western region reported a significantly higher proportion of outpa-
tients with three or more antibiotics prescribed than hospitals in
eastern China (P=0.03). Level 3 hospitals reported a significantly higher proportion of outpatient encounters with one antibiotic pre-
scribed (P<0.01) and a lower proportion of outpatient encounters with two antibiotics prescribed (P<0.01) than level 1 or level 2 hos-
pitals (Table 2).

### Discussion

Based on data from 57 studies that included a total of 556435 out-
patient encounters, this systematic review found that the propor-
tion of antibiotic use in China is high and excessive. More than
half of the outpatient visits in China resulted in prescription of anti-
biotics and a quarter of the outpatient prescriptions of antibiotics contained two or more antibiotics. In addition, hospitals in
western China or primary care centres (level 1 hospitals) tend to
be associated with higher antibiotic use than hospitals in eastern
China and high-level hospitals.

Although an international standard for the percentage use of
antibiotics has not been empirically established, WHO recom-
pended that the proportion of antibiotic use should not be
>30%. The percentage use of antibiotics in China (50.3%) is
much higher than this recommended level and higher than in
many other countries. For example, the percentage use of antibiot-
ic in the USA was 15.3% in the USA and the average percentage use of anti-
biotics in developing countries was 40%–50%. As the primary health-
care facilities in China cover a large number of patients, the excessive use of anti-
biotics in primary healthcare causes a waste of health resources and the development of antibiotic resistance. Therefore, it is neces-
sary to take measures to control the overuse of antibiotics in
primary healthcare facilities in China.

The excessive utilization of antibiotics may be associated with
the training and experiences of doctors and the knowledge and at-
titude of patients towards antibiotics, as well as financial incen-
tives. Doctors in level 3 hospitals have a higher level of education and better training than those in lower-level hospitals. The
improved training could help clinicians recognize the importance of the rational use of antibiotics. The differences in the training
of doctors may also explain the observed difference between the
regions. Doctors in the eastern region may on average have more
training than those in the central and western regions. In addition,
the use of antibiotics is influenced by financial incentives. Many

### Table 1. Percentage use of antibiotics in outpatients: the overall estimate and subgroups by region, year of enrolment and hospital level

<table>
<thead>
<tr>
<th>Region</th>
<th>Number of studies</th>
<th>n/N</th>
<th>Percentage of antibiotic use (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>overall</td>
<td>60</td>
<td>260502/556435</td>
<td>50.3 (47.4, 53.1)</td>
</tr>
<tr>
<td>eastern China</td>
<td>32</td>
<td>94592/216905</td>
<td>47.3 (43.1, 51.6)</td>
</tr>
<tr>
<td>central China</td>
<td>13</td>
<td>25344/53825</td>
<td>50.3 (42.5, 57.9)</td>
</tr>
<tr>
<td>western China</td>
<td>15</td>
<td>72173/132505</td>
<td>57.4 (52.2, 62.5)</td>
</tr>
<tr>
<td>Year of study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2010 and after</td>
<td>8</td>
<td>22111/46045</td>
<td>45.7 (39.3, 52.2)</td>
</tr>
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<td>2009</td>
<td>11</td>
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<td>2008</td>
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<td>2007</td>
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<td>2006</td>
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<td>2005</td>
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</tr>
<tr>
<td>2004 or before</td>
<td>9</td>
<td>28820/47724</td>
<td>57.2 (48.7, 65.5)</td>
</tr>
</tbody>
</table>

The difference between the western and eastern region subgroups was statistically significant (P=0.003). The percentage of antibiotic use in 2007 was statistically significantly lower than that in 2004, 2005 and 2009. The differences between hospital levels were statistically non-significant.
studies found that economic stimulus may induce doctors to prescribe excessive antibiotics. It is possible that, as compared with doctors in lower-level hospitals and the western region, doctors in level 3 hospitals and prosperous eastern China have relatively high incomes with a reduced need to generate incomes by excessively prescribing antibiotics.

The reported percentages of antibiotic utilization in China have been fluctuating over time, which is different from the situation in other developing countries where it remained stable over time. The percentage use of antibiotics declined from 57.2% in 2004 to 41.8% in 2007; it then increased to 52.4% in 2009 and 45.7% in 2010 (Table 1). These changes in the use of antibiotics in China over time might be associated with the implementation of some national healthcare policies. In 2003, the Chinese government introduced a new community-based rural health insurance, the New Cooperative Medical Scheme (NCMS). The NCMS began in 305 pilot counties and was then implemented to all rural areas in China. In 2007, China began to promote the Urban Resident Basic Medical Insurance (URBMI) and in 2009 it was implemented nationwide. Studies have shown that medical insurance could induce healthcare consumption. The increase of antibiotic utilization may follow the introduction of NCMS and URBMI. However, the increase in antibiotic use caused by the new medical insurance schemes may have been interrupted by the Chinese health authority's effort to curb the excessive use of antibiotics. The Ministry of Health of China promulgated ‘Guidelines on the Clinical Application of Antibiotics’ in 2004 and ‘Guidelines on Prescription Management’ in 2006, which explicitly stated that the percentage of patients prescribed antibiotics should be 50%. The Ministry also issued ‘Prescription Management and Evaluation Standards in Clinical Practice’ in 2010. The guidelines may have reduced antibiotic usage in China. It is worthy to note that the Ministry of Health of China issued a ‘National Plan to Rectify the Clinical Application of Antibiotics’, which has come into effect since 1 August 2012. It is too early to know the full impact of the national plan on antibiotic utilization.

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>n/N</th>
<th>Proportion (%) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>With one antibiotic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Region</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eastern China</td>
<td>32</td>
<td>71446/94592</td>
</tr>
<tr>
<td>central China</td>
<td>13</td>
<td>18408/25344</td>
</tr>
<tr>
<td>western China</td>
<td>15</td>
<td>53839/72173</td>
</tr>
<tr>
<td>Hospital level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>level 3 hospitals</td>
<td>20</td>
<td>54815/68879</td>
</tr>
<tr>
<td>level 2 hospitals</td>
<td>16</td>
<td>29559/39758</td>
</tr>
<tr>
<td>level 1 hospitals</td>
<td>24</td>
<td>111021/151865</td>
</tr>
<tr>
<td><strong>With two antibiotics</strong></td>
<td>60</td>
<td>61427/260502</td>
</tr>
<tr>
<td>Region</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eastern China</td>
<td>32</td>
<td>21821/94592</td>
</tr>
<tr>
<td>central China</td>
<td>13</td>
<td>6375/25344</td>
</tr>
<tr>
<td>western China</td>
<td>15</td>
<td>16540/72173</td>
</tr>
<tr>
<td>Hospital level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>level 3 hospitals</td>
<td>20</td>
<td>12816/68879</td>
</tr>
<tr>
<td>level 2 hospitals</td>
<td>16</td>
<td>9302/39758</td>
</tr>
<tr>
<td>level 1 hospitals</td>
<td>24</td>
<td>39309/151865</td>
</tr>
<tr>
<td><strong>With three or more antibiotics</strong></td>
<td>57a</td>
<td>3903/162088</td>
</tr>
<tr>
<td>Region</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eastern China</td>
<td>31</td>
<td>1617/82481</td>
</tr>
<tr>
<td>central China</td>
<td>12</td>
<td>519/16398</td>
</tr>
<tr>
<td>western China</td>
<td>14</td>
<td>1767/63209</td>
</tr>
<tr>
<td>Hospital level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>level 3 hospitals</td>
<td>20</td>
<td>1215/68879</td>
</tr>
<tr>
<td>level 2 hospitals</td>
<td>16</td>
<td>1196/39758</td>
</tr>
<tr>
<td>level 1 hospitals</td>
<td>21</td>
<td>1492/53451</td>
</tr>
</tbody>
</table>

As compared with level 1 and level 2 hospitals, level 3 hospitals were associated with a statistically significantly higher proportion of one antibiotic (P < 0.01) and a statistically significantly lower proportion of two antibiotics (P < 0.01). The proportion of outpatients prescribed three or more antibiotics by western region hospitals was statistically higher than that by eastern region hospitals (P = 0.03).

*aOne included study (a092–Yongbin Li), which had three subgroup studies, did not report the number of outpatients with three or more antibiotics. See Table S1 (available as Supplementary data at JAC Online).
Conclusion

The percentage use of antibiotics in China is much higher than the recommended level. Antibiotic prescribing in China varies across hospital levels and geographical regions. The percentage use of antibiotics in China has been fluctuating over time, which may be associated with changes in national healthcare policies. The impact of the national efforts to control the excessive use of antibiotics needs to be appropriately evaluated.

Funding

This study was carried out as part of our routine work.

Transparency declarations

None to declare.

Author contributions

Z. L. and X. Y. conceived the idea and prepared a draft review protocol. Y. G. and X. T. conducted the literature search. Y. W., S. C. and J. L. collected articles. X. Y. extracted data from the included studies. S. C. and J. L. checked the extracted data. X. Y. and Y. G. analysed the data and prepared the manuscript. Z. L., S. C., F. S., Y. W. and X. T. helped with results interpretation and critically commented on and revised the manuscript. All authors reviewed the study findings and read and approved the final version before submission. Z. L. is guarantor of the paper.

Access to data

All the data in this review are from publicly published papers. The corresponding author, Z. L., had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Supplementary data

Tables S1, S2 and S3 are available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/).

References


17 WHO. How to Investigate Drug Use in Health Facilities: Selected Drug Use Indicators. EDM Research Series no. 007, 1993.


