Developing comprehensive and integrated health system reform policies to improve use of medicines
Sun, Jing

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2015

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):
Sun, J. (2015). Developing comprehensive and integrated health system reform policies to improve use of medicines [Groningen]: University of Groningen

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

Take-down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.
The Effects of Clinical Interventions on Use of Medicines with a Focus on Antibiotics

3.2 Changes in patterns of antibiotic use in Chinese public hospitals (2005–2012) and a benchmark comparison with Sweden in 2012

Jing Sun
Siping Dong
Xiao Shen
Meng Li
Liu He
Shuyan Guo
Gunilla Skoog
Grape Malin
Cars Otto

Journal of Global Antimicrobial Resistance (2015), http://dx.doi.org/10.1016/j.jgar.2015.03.001
ABSTRACT

The changes in the patterns of antibiotic use in Chinese hospitals before and after intensive nationwide interventions are reported, and compared with Chinese national targets and antibiotic use in Swedish hospitals. Chinese data were collected quarterly and yearly from selected patient prescriptions/medical records and medicines inventory control systems from 15 hospitals (2005-2012). Swedish data were extracted from a 2010 point prevalence survey and 2009-2012 sales data from seven university hospitals. An interrupted time series with segmented regression analysis was used to measure changes in the patterns of antibiotic use in Chinese hospitals before and after the 2011 interventions. Following the 2011 interventions, significant reductions of antibiotic use in Chinese hospitals were seen: the proportion of prescriptions with antibiotics decreased 4.7% (p=0.03), and the proportion of medical records with antibiotic prescription decreased 7.3% (p=0.04). The proportions of prescriptions and medical records with antibiotic in Chinese hospitals in 2012 was 10% and 50%, respectively, and remained much higher than Swedish hospitals (1.1% in DDDs for outpatients and 34% in number of patients for inpatients). Inpatient consumption in Chinese hospitals significantly dropped from 910 DDD/1 000 inpatient days in 2008 to 473 in 2012 (588 in Swedish hospitals). Antibiotics are being used less frequently in Chinese hospitals, broad spectrum antibiotics are still preferred, and overall usage is higher than Sweden. A significant reduction of overall inpatient antibiotic consumption was observed the 2011 interventions. It is not possible to identify whether the changes have resulted in less inappropriate antibiotic use. Further studies are needed.
INTRODUCTION

Over-prescription of antimicrobials and increasing antimicrobial resistance are major public health issue in China as well as a significant challenge to global health. The World Health Assembly called member states to promote rational antibiotic use to contain antimicrobial resistance. As a result, the Chinese government have issued and implemented a number of policies.

To assess the impact of these actions, a study was undertaken as part of the Plan of Action for Sino-Swedish Health Cooperation 2011-2014. The collaboration aims to apply Swedish expertise in promoting appropriate use of antibiotics and to motivate the ongoing work in China. Sweden has been used as a benchmark because of its well-established and effective policies and legislation on antibiotic use. Sweden was also one of the first countries to initiate a cross-stakeholder cooperation for the containment of antibiotic resistance (Swedish strategic programme against antibiotic resistance, STRAMA). These long-term and structured interventions have proved a success, as Sweden has a low use of antibiotics and resistance rates.

The health systems of China and Sweden are very different, Sweden being a country with a small population (9.5 million) compared with China (1.3 billion). Swedish hospitals are largely publicly owned and the primary healthcare system is universal and effective. Most patients enter the health system via the primary care. In contrast, the capacity of the primary healthcare providers is still under development in China, especially in the extensive rural areas that lack skilled staff and modern equipment. Healthcare delivery relies predominantly on hospital-based care, with public tertiary hospitals being the main healthcare providers. Primary care institutions do not play a dominant role in providing outpatient services, and most patients directly accessing hospitals even for common diseases, as evidenced by only 41% of outpatient visits being provided by primary care in 2012.

This study measured the changes in patterns of antibiotic use and inpatient consumption in Chinese public general tertiary hospitals from 2005 to 2012, which covered the period before and after the 2011 interventions. The 2012 observations in Chinese hospitals were also compared with the Chinese national targets and Swedish hospitals.

Policy impact analysis in China usually uses simple before and after comparison. Rigorous research studies using more sophisticated methods that can make more precise measurement of policy impact are few. To our knowledge, this is the first assessment of the effect of interventions has on antibiotic use using a longitudinal study with interrupted time series data and segmented regression analysis. This methodology is the strongest quasi-experimental design to evaluate longitudinal effects of time-delimited interventions.
Chapter 3

MATERIALS AND METHODS

Study design
Changes in the patterns of antibiotic use in Chinese hospitals before and after the 2011 interventions (during March 2005 to December 2012) were measured and the 2012 observations in Chinese hospitals were compared with the Chinese national targets\textsuperscript{16,17} and with Swedish hospitals.

The 2011 interventions were the most intensive and far-reaching initiative of the Ministry of Health aimed to improve antibiotic use in hospitals. Following extensive advocacy and mobilization across the country, all levels of governments officially announced the interventions in written documents, and circulated the documents to each hospital. The internationally accepted concept of “antibiotic stewardship” was integrated into these measures. Many coordinated measures were taken,\textsuperscript{16-18} including (a) setting targets; (b) strengthening accountability; (c) auditing clinical indications for antibiotic use; (d) building the capacity of infection control; (e) defining the prescribing of specific antimicrobials for different levels of professionals in clinical practice; (f) restricting the number of agents prescribed; (g) conducting regular antimicrobial resistance monitoring with an alert system for multi-resistance; (h) organizing guideline training; (i) conducting a monthly outpatient prescription and inpatient medical record audits, identifying the prescribers who are continuously not able to achieve the targets set by an individual hospital, and revoking prescribing rights for the frequent outliers; (j) setting up monitoring networks across hospitals and regions to share information at national and local levels; (k) carrying out unannounced inspections at the targeted public hospitals; and (l) sharing good practice. Specific targets were set by the Ministry of Health as follows: the proportions of outpatient (OP) prescriptions and inpatient (IP) medical records with the prescription of antibiotics to be <20\% and <60\%, respectively. All antibiotic prophylaxis should be given before incision (except for Cesarean section) and patients receiving antibiotic prophylaxis should not be >24 h (except certain specific conditions), and the total IP consumption of antibiotics for systemic use (J01) to be <400 DDD/1 000 inpatient days.

Outcome measures
Severn indicators to measure the pattern of antibiotic use in hospitals were defined: (a) the proportion of OP prescriptions given for at least one antibiotic (including oral and parenteral); or (b) one parenteral antibiotic prescribed; (c) the proportion of IP medical records with a prescription for at least one antibiotic; or (d) one parenteral antibiotic prescribed; (e) the proportion of patients receiving antibiotic prophylaxis before incision; (f) the proportion of patients given antibiotic prophylaxis for >24 hours; and (g) the total IP antibiotic consumption (DDD/1 000 inpatient days).

“Inpatient days” were calculated by multiplying the annual total number of hospital discharges (ranging between 15,425-193,000 in various study hospitals during 2005-2012) with the mean number
of days of hospitalization (discharge date minus admission date for admitted patients in each study hospital; for patients who were discharged on the same day of hospitalization, the number will be regarded as 1. IP antibiotic consumption was measured for antibiotics for systemic use (J01), and specific Anatomical Therapeutic Chemical (ATC) 3 and ATC 4 classes. These classes include penicillins (J01C), quinolones (J01M), 1st-4th generation cephalosporins (J01DB-DE), carbapenems (J01DH), and macrolides (J01FA), of which the Chinese antibiotic classification system and the ATC system are similar to each other.

**Study population, setting, and data source**

**China**
The 35 hospitals, all public general tertiary hospitals of the National Antimicrobial Clinical Use and Resistance Monitoring Network (which started to collect antibiotic clinical data in 2005), were categorized by geographic regions (six in total across the country). Two member hospitals from each region were chosen, which were located in a city with a mean income level for each region. In addition one was added to each of the three regions with the highest populations. The 15 targeted hospitals had 600-4300 beds, 2800-12600 daily OP and emergency visits, and 91-375 daily discharges.

Longitudinal data for antibiotic use (indicators a-f) were extracted from selected prescriptions and medical records from the 15 study hospitals. In each hospital, 100 prescriptions, 15 surgical records and 15 non-surgical records were randomly selected from the OP adult prescriptions given on the 16th and patients discharged during 11th-20th of the first month of each quarter during 2005-2010 and of each month during 2011-2012. In each quarter during 2005-2010, a total of 1500 prescriptions, 225 surgical records and 225 non-surgical records were randomly selected. In each quarter during 2011-2012, a total of 4500 prescriptions, 675 surgical records and 675 non-surgical records were selected. Following the practice of the national monitoring network, the departments of emergency, pediatrics, infectious diseases, and care for senior government officials were excluded from the sampling of OP prescriptions. Antibiotic consumption pressures (indicator g) were collected annually from the medicines inventory control systems of the 15 studied hospitals (2005-2012).

**Sweden**
The 2009-2012 annual sales data were collected from all seven public tertiary hospitals in Sweden (university hospitals, 550-2000 beds) to measure the IP antibiotic consumption. OP antibiotic and parenteral antibiotic use and IP antibiotic consumption data for indicators a, b, and g were extracted from 2012 sales data of the seven university hospitals. Data for IP antibiotics and parenteral antibiotic use, proportion of patients given antibiotic prophylaxis for >24 hours for indicators c, d, f were obtained from the most recent 2010 point prevalence survey.
Data analysis
The quarterly antibiotic use data collected from the OP prescription and IP medical record data for the Chinese hospitals was plotted (March 2005 to December 2012) (Fig. 1). Annual antibiotic consumption for Chinese and Swedish hospitals during 2005–2012 for systemic use and for specific ATC categories as DDD/1 000 inpatient days and proportions consumed are shown in Fig. 2.

Fig. 1 Proportions of (A) outpatient prescriptions of antibiotic and (B) inpatient medical records with antibiotic, and (C) proportions of surgical patients given antibiotic prophylaxis before incision and for a duration of >24 h in Chinese hospitals. Data source: selected outpatient prescriptions and inpatient medical records from 15 Chinese public tertiary general hospitals.
Fig. 2 Inpatient antibiotic (J01 systemic use) consumption by Anatomical Therapeutic Chemical (ATC) categories in (A) Chinese and (B) Swedish hospitals. Sources: (1) China: medicines inventory control systems of 15 Chinese public general tertiary hospitals; (2) Sweden: sales data of seven Swedish university hospitals. Notes: (1) The ATC classes not measured (J01A, J01B, J01DF, J01DI, J01E, J01FF, J01FG, J01G, J01MB and J01X) are included as ‘Others’ in the bar; (2) Inpatient antibiotic consumption pressure is calculated as defined daily doses (DDD) per 1000 inpatient days.

Longitudinal time series quarterly data were analyzed using a segmented linear regression model to assess changes in levels and trends after the 2011 interventions in Chinese hospitals. Time series data analysis statistical software can control for auto correlated errors, which controls for secular trends and can also adjust for potential serial correlation of the data. Although the announcement of the interventions was issued in April 2011, implementation started in August 2011. Considering that the study collected quarterly data from Chinese hospitals in 2011, September 2011 was adopted as the starting time point of the interventions for conducting segmented regression analysis. Changes in trends before and after September 2011 and the change in levels in September 2011 were compared using Stata 12.0 (StataCorp LP, College Station, TX).
Data for China and Sweden were compared using 2012 indicators (a–g) for Chinese hospitals, and the 2012 Swedish sales data and 2010 point prevalence survey data. Using 2012 indicators (a–g) for Chinese hospitals, and the 2012 Swedish sales data and 2010 point prevalence survey data.

RESULTS

Changes in antibiotic use in Chinese hospitals before and after the introduction of the 2011 interventions

The proportion of OP prescriptions with parenteral antibiotics was stable at < 6% (Fig. 1). With the exception of antibiotic prophylaxis, which increased from 40 to 50% (pre-2011) to 50-60% (post-2011), all other indicators steadily decreased, as did OP prescriptions (20% to 10%). The proportion of IP medical records with antibiotics and parenteral antibiotics both decreased from 60 to 80% to around 50%. The proportion of patients given antibiotic prophylaxis for >24 h decreased from 70 to 90% to 60%.

Data are also presented on the trends in IP consumption of some targeted antibiotic ATC classes (Fig. 2). Consumption of antibiotics for systemic use (J01) was highest in 2008, thereafter decreasing afterwards, particularly during 2011-2012, as did other classes.

Segmented regression analysis of the quarterly data (Table 1) showed that, before September 2011, OP and IP antibiotics use (indicators a and c), IP parenteral antibiotic use (indicator d), and patients given antibiotic prophylaxis for >24 hours (indicator f) had already decreased significantly, (p=0.004, p=0.002, p<0.001 and p<0.001, respectively) from the start of the study. OP parenteral antibiotic use (indicator b) steadily increased and antibiotic prophylaxis given before incision (indicator e) steadily decreased.

In September 2011, the proportion of OP prescriptions given for at least one antibiotic (indicator a) and the proportion of IP medical records with at least one antibiotic (indicators b) significantly dropped by 4.7% (p=0.03, 95% CI [-8.91%, -0.56%]) and 7.3% (p=0.04, 95% CI -14.2 to -0.4), respectively. The proportion of IP medical records with at least one parenteral antibiotic prescribed (indicator d) and the proportion of antibiotic prophylaxis duration>24 h (indicator f) both dropped significantly by 8.6% (p=0.03, 95% CI -16.1% to -1.1%; and p=0.003, 95% CI 13.9% to 3.3%), respectively. The proportion of OP prescriptions given with at least one parenteral antibiotic (indicator b) and the proportion of antibiotic prophylaxis given before incision (indicator e) steadily decreased.

After September 2011, antibiotic prophylaxis duration>24 h (indicator f) significantly decreased (p=0.002), the other indicators not changing significantly.

We also observed the trends of IP consumption pressures of the targeted antibiotic ATC classes, as
shown in Fig. 2. The consumption pressure of antibiotics for systemic use (J01) reached the highest level in 2008, shifted to decrease afterwards, and decreased faster during 2011-2012. Other classes had similar trend changes. After September 2011, antibiotic prophylaxis of duration >24 h (indicator f) significantly decreased (P = 0.002), with the other indicators not changing significantly.

Segmented regression analysis of the quarterly data (Table 1) showed that, before September 2011 OP and IP antibiotics use (indicators a and c), IP parenteral antibiotics use (indicator d), and antibiotic prophylaxis duration >24 hours (indicator f) already decreased significantly, (p=0.004, p=0.002, p<0.000 and p<0.000). OP parenteral antibiotics use (indicator b) steadily increased, but antibiotic prophylaxis before incision (indicator e) steadily decreased.

In September 2011, the proportion of OP prescriptions given for at least one antibiotic (indicator a) and the proportion of IP medical records with at least one antibiotic (indicators b) significantly dropped 4.7% (p=0.03, 95% CI [−8.9%, −0.6%]) and 7.3% (p=0.04, 95% CI [−14.2%, −0.4]), respectively. The proportion of IP medical records with at least one parenteral antibiotic prescribed (indicator d) and the proportion of antibiotic prophylaxis duration >24 hours (indicator f) both significantly dropped 8.6% (p=0.03, 95% CI [−16.1%, −1.1%]) and (p=0.003, 95% CI [−13.9%, −3.3%]), respectively. The proportion of OP prescriptions given for at least one parenteral antibiotic (indicator c) and the proportion of antibiotic prophylaxis before incision (indicator e) steadily decreased.

After September 2011, antibiotic prophylaxis duration >24 hours (indicator f) significantly decreased (p=0.002), with the other indicators did not changing significantly.

**Comparison of antibiotic use in Chinese and Swedish hospitals**

Table 2 shows that 10% of OP prescriptions and 50% of IP medical records include a prescription for antibiotics in Chinese hospitals. These are below the Chinese national targets (<20% and <60%) but higher than Swedish hospitals (1.1% and 34%). Use of parenteral antibiotics for OP prescriptions (2%) and IP (46%) in Chinese hospitals is much higher than Swedish hospitals (0.001% and 15%). The use of antibiotic prophylaxis is much poorer in China compared to Sweden, with only 55% of prophylaxis being given before incision and 56% of prophylaxis having a duration >24 h. Both values are above the Chinese national targets are much worse than Swedish hospitals (1.1% and 34%). IP antibiotic consumption for systemic use (J01) in Chinese hospitals was 473 DDD/1000 inpatient days, which is higher than the Chinese national target (<400 DDD/1000 inpatient days) but lower than Swedish hospitals (588 DDD/1000 inpatient days).
Table 1  Segmented regression analysis results comparing antibiotic use before, during, and after the 2011 nationwide interventions in China, 2005–2012

<table>
<thead>
<tr>
<th>Independent Variables</th>
<th>Coefficient(^a)</th>
<th>SE</th>
<th>P-value(^b)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) % of OP prescriptions with antibiotics</td>
<td>Constant (\beta_0)</td>
<td>22.8</td>
<td>0.8</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Secular trend (\beta_1)</td>
<td>−0.2</td>
<td>0.05</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>Change in level (\beta_2)</td>
<td>−4.7</td>
<td>2.0</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>Change in trend (\beta_3)</td>
<td>−0.4</td>
<td>0.5</td>
<td>0.4</td>
</tr>
<tr>
<td>(b) % of OP prescriptions with parenteral antibiotics</td>
<td>Constant (\beta_0)</td>
<td>2.6</td>
<td>0.7</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>Secular trend (\beta_1)</td>
<td>0.04</td>
<td>0.05</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td>Change in level (\beta_2)</td>
<td>−0.7</td>
<td>1.1</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>Change in trend (\beta_3)</td>
<td>−0.1</td>
<td>0.3</td>
<td>0.7</td>
</tr>
<tr>
<td>(c) % of IP medical records with antibiotics</td>
<td>Constant (\beta_0)</td>
<td>74.7</td>
<td>1.4</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Secular trend (\beta_1)</td>
<td>−0.3</td>
<td>0.09</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>Change in level (\beta_2)</td>
<td>−7.3</td>
<td>3.4</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>Change in trend (\beta_3)</td>
<td>−1.5</td>
<td>0.8</td>
<td>0.07</td>
</tr>
<tr>
<td>(d) % of IP medical records with parenteral antibiotics</td>
<td>Constant (\beta_0)</td>
<td>75.2</td>
<td>1.5</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Secular trend (\beta_1)</td>
<td>−0.4</td>
<td>0.1</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Change in level (\beta_2)</td>
<td>−8.6</td>
<td>3.7</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>Change in trend (\beta_3)</td>
<td>−1.3</td>
<td>0.9</td>
<td>0.14</td>
</tr>
<tr>
<td>(e) % of antibiotic prophylaxis before incision</td>
<td>Constant (\beta_0)</td>
<td>42.8</td>
<td>3.7</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Secular trend (\beta_1)</td>
<td>−0.06</td>
<td>0.2</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td>Change in level (\beta_2)</td>
<td>5.0</td>
<td>6.0</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td>Change in trend (\beta_3)</td>
<td>1.7</td>
<td>1.6</td>
<td>0.3</td>
</tr>
<tr>
<td>(f) % of antibiotic prophylaxis duration &gt; 24h</td>
<td>Constant (\beta_0)</td>
<td>95.6</td>
<td>1.1</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Secular trend (\beta_1)</td>
<td>−0.8</td>
<td>0.07</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Change in level (\beta_2)</td>
<td>−8.6</td>
<td>2.6</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>Change in trend (\beta_3)</td>
<td>−2.2</td>
<td>0.6</td>
<td>0.002</td>
</tr>
</tbody>
</table>

SE, standard error; CI, confidence interval; OP, outpatient; IP, inpatient.

Notes:

a \(\beta_0\) is the intercept of the pre-intervention trend line (value of the variable at the start of the observation); \(\beta_1\) is the slope of the pre-intervention trend line (the baseline trend); \(\beta_2\) is the immediate post-intervention absolute change (immediate effect of the intervention); \(\beta_3\) is the change of the post-intervention trend; and \(\beta_1 + \beta_3\) is the slope of the post-intervention trend line.

b Bold signifies statistically significant coefficient (P < 0.05).

We found that the patterns of IP consumption of different categories of antibiotics were quite different between Chinese and Swedish hospitals. In Chinese hospitals, IP consumption of antibiotics for systemic use (J01) sharply dropped from 819 DDD/1 000 inpatient days in 2010 to
Table 2 Comparison of antibiotic use patterns and consumption pressure in Chinese public general tertiary hospitals with the Chinese national targets and the Swedish levels in 2012

<table>
<thead>
<tr>
<th>Outcome measures</th>
<th>15 Chinese public general tertiary hospitals</th>
<th>Chinese national targets(^a)</th>
<th>Seven Swedish university hospitals</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) Proportion of OP(^1) prescriptions with antibiotics</td>
<td>10% (n=18,000, SD=1.14,95% CI [7.96%, 12.83%])</td>
<td>&lt;20%</td>
<td>1.1(^b)c</td>
</tr>
<tr>
<td>(b) Proportion of OP(^2) prescriptions with parenteral antibiotics</td>
<td>2% (n=18,000, SD=0.55,95% CI [0.99%, 3.34%])</td>
<td>NA</td>
<td>0.001(^c)</td>
</tr>
<tr>
<td>(c) Proportion of IP(^1) medical records with antibiotics</td>
<td>50% (n=5,400, SD=2.0,95% CI [37.96%, 64.17%])</td>
<td>&lt;60%</td>
<td>34(^a)</td>
</tr>
<tr>
<td>(d) Proportion of IP(^1) medical records with parenteral antibiotics</td>
<td>46% (n=5,400, SD=1.96,95% CI [42.26%, 50.67%])</td>
<td>NA</td>
<td>15(^a)</td>
</tr>
<tr>
<td>(e) Proportion of antibiotic prophylaxis before incision</td>
<td>55% (n=1,708, SD=7.51,95% CI [39.29%,71.51%])</td>
<td>100% (except cesarean)</td>
<td>NA</td>
</tr>
<tr>
<td>(f) Proportion of antibiotic prophylaxis duration&gt;24h</td>
<td>56% (n=1,708, SD=8.11,95% CI [38.5%, 73.28%])</td>
<td>Generally&lt;24h (except specific conditions)</td>
<td>33(^a)</td>
</tr>
<tr>
<td>(g) Total IP consumption of antibiotics for systematic use (J01)</td>
<td>473 DDD/1,000 inpatient days (n=15, SD=28.96, Median=464.43)</td>
<td>&lt;400</td>
<td>588 DDD/1,000 inpatient days(^c)</td>
</tr>
<tr>
<td>IP Consumption of penicillins (J01C)</td>
<td>51 DDD/1,000 inpatient days (10.82% of J01) (n=15, SD=7.68, Median=40.00)</td>
<td>NA</td>
<td>263 DDD/1,000 inpatient days(^c) (44.73% of J01)</td>
</tr>
<tr>
<td>IP Consumption of quinolones (J01M)</td>
<td>51 DDD/1,000 inpatient days (n=15, SD=6.05, Median=47.93)</td>
<td>NA</td>
<td>58 DDD/1,000 inpatient days(^c)</td>
</tr>
<tr>
<td>IP Consumption of 1st generation cephalosporins (J01DB)</td>
<td>44 DDD/1,000 inpatient days (n=15, SD=4.92, Median=44.75)</td>
<td>NA</td>
<td>5 DDD/1,000 inpatient days(^c)</td>
</tr>
<tr>
<td>IP Consumption of 2(^{nd}) generation cephalosporins (J01DC)</td>
<td>82 DDD/1,000 inpatient days (n=15, SD=8.07, Median=73.74)</td>
<td>NA</td>
<td>13 DDD/1,000 inpatient days(^c)</td>
</tr>
<tr>
<td>IP Consumption of 3(^{rd}) generation cephalosporins (J01DD)</td>
<td>105 DDD/1,000 inpatient days (22.24% of J01) (n=15 hospitals, SD=14.72, Median=93.91)</td>
<td>NA</td>
<td>53 DDD/1,000 inpatient days(^c) (9.01% of J01)</td>
</tr>
<tr>
<td>IP Consumption of 4(^{th}) generation cephalosporins (J01DE)</td>
<td>19 DDD/1,000 inpatient days (n=15, SD=5.11, Median=16.96)</td>
<td>NA</td>
<td>0(^c)</td>
</tr>
</tbody>
</table>

OP, outpatient; IP, inpatient; S.D., standard deviation; CI, confidence interval; N/A, not available (no specific target); DDD, defined daily doses.

Notes:
- a Ministry of Health of P.R China.
- b in DDD.
- c 2012 sales data.
- d 2010 Swedish Strategic Programme against Antibiotic Resistance (STRAMA) point prevalence survey data.
473 in 2012. Table 2 shows that in 2012, the IP consumption of third-generation of cephalosporins (J01DD) reached 105 DDD/1 000 inpatient days (22.2% of J01), while that of the penicillins (J01C) was 51 DDD/1 000 inpatient day (10.8% of J01). Conversely, in Swedish hospitals, IP consumption of all these categories were stable throughout 2005–2012, ranging between 572 and 645 DDD/1 000 inpatient days. J01C was the major antibiotic group consumed during 2005–2012, with an IP consumption of 263 DDD/1 000 inpatient days in 2012 (44.7% of J01), while that of J01DD was only 55 DDD/1 000 inpatient days (9.0% of J01) (Table 2).

**DISCUSSION**

**Changes in antibiotic use in Chinese hospitals before and after the introduction of the 2011 interventions**

From the outcome indicators of antibiotic use (a–f), we found that antibiotic prescription in Chinese hospitals was falling before the 2011 interventions. The segmented regression analysis also confirmed this finding. An explanation may be that the Ministry of Health had issued a series of regulations since 2002, which will have probably had an impact. The regulations included the requirement to establish a hospital Drug and Therapeutics Committee in 2002,20 strengthened regulations on prescriptions,21 guidelines for antimicrobial use in 2004,22 the establishment of a use and resistance monitoring network in 2005,23 improving antibiotic prophylaxis for surgery in 2008 and 2009 and developing guidelines for prescription audits in 2010.24

Although the 2011 interventions effected immediate and significant reductions in antimicrobial use, we could not conclude that the effects were solely caused by the 2011 interventions, because these indicators already had significantly decreased baseline trends.

Using the internationally recognized standard for comparative drug utilization research (ATC/DDD systems), we found more subtle trends in indicator g. The IP consumption of antibiotics for systemic use (J01) decreased in 2008 and further decreased following the 2011 interventions. Until December 2012, it quickly dropped to almost one-half of the highest level. Broad-spectrum antibiotics always dominated prescribing during 2005–2012, and reached a peak in 2012. Conversely, the consumption of narrow-spectrum antibiotics continuously decreased during 2005–2012.

**Comparison of antibiotic use in Chinese and Swedish hospitals**

IP antibiotic consumption of Swedish hospitals has been well controlled at a stable level over time and, like most of other EU countries, penicillins (J01C) are always the most frequently used antibiotics.25 In contrast, IP antibiotic consumption in Chinese hospitals dropped sharply from an unacceptably high level to the equivalent to the 2012 Swedish level. The absolute values of each studied ATC category all decreased. The proportion of the third-generation of cephalosporins (J01DD) prescribed to all prescribed antibiotics for systemic use (J01) did not change and it was the dominant class, whereas
penicillins (J01C) fell throughout the period.

The significant reductions in OP and IP antibiotic do not address the more appropriate use. However, there are achievements measured against a background of an unacceptable baseline. Even though the proportions of OP & IP antibiotic use achieved the national targets following the 2011 interventions (there were no targets for parenteral antibiotics use), antibiotic prophylaxis usage and practice still falls short of the national targets as well as Swedish usage.

It is concerning that Chinese hospitals still use more broad-spectrum antibiotics than narrow-spectrum antibiotics, and that such preferences did not change. Broad-spectrum antibiotics have been generally regarded by many Chinese doctors and the general public as the more efficient treatment to address all kinds of infections. There is also a reluctance to use diagnostics and a heavy reliance on empirical treatment. The second factor is that the Chinese guideline requires allergy test for penicillins (excluding a few oral formulations).26 Chinese doctors tend to avoid skin testing procedures and are averse to any potential risk of dispute with the patient due to allergy, which contrasts with most other countries where a negative allergy history is accepted.26 Resistance rates in China are much higher than Sweden and prescribers believe immediate use of broad-spectrum agents give the best empirical cover. Greater availability of resistance data should encourage the use of narrow-spectrum agents.

Although overuse of antibiotics had been reduced in Chinese hospitals through the joint efforts during 2002-2011, the Chinese national targets are yet to be met and there is a significant gap compared with Swedish hospitals. The primary care system in China was not as effective as in Sweden, particularly for patient referred to hospital. Despite efforts to build the capacity in the primary care in China, patients still prefer to directly seek hospital care due to a lack of trust, no compulsory referral mechanism, and a weak referral capacity in primary care. Approximately 60% of the medicines market is dominated by tertiary hospitals in China,27,28 and Chinese patients will always go directly to tertiary hospitals for common diseases. In Sweden, primary care forms the foundation of the healthcare system. Although there is no formal gate-keeping role for primary care in most county councils, it plays an important role in guiding the patient to the right care within the health system.2,21 It might be inferred that Chinese patients require less intensive antibiotic treatment than the patients in the equivalent Swedish settings, which should lead to a lower consumption in China. Alternatively, Swedish IP consumption data were collected from the sales data, which might be higher than the data collected from medicines procurement and inventory management systems leading to the apparent anomaly.

Chinese and Swedish hospitals have opposing trends for the use of narrow-and broad-spectrum antibiotics but similar IP antibiotic (for systemic use) consumption. Such a contradiction could be explained by the 2011 interventions causing a rapid significant reduction in overall antibiotic consumption. The high rate of antibiotic use might be due to unnecessary treatment of minor illnesses and non-bacterial infections, combined with under-treating serious bacterial infections due to tight restrictions on antibiotic use. Further studies are needed in China to investigate guideline compliance...
and hospital-acquired infection rates. In addition, as our consumption measurement does not include OP and community pharmacies, we do not know if IP antibiotic use was shifted to OP or over-the-counter sales.

Another reason should be considered is that, the Chinese longitudinal data of antibiotic use indicators (a–f) might be an underestimate as they did not include data from departments with a potential high use (e.g. infectious diseases).

Ideally, we would have used the existing Chinese national monitoring network data to conduct this study. However, due to the unavailability of the national data, we had to conduct a sampling study whilst social, demographic, and economic characteristics of different geographic areas were considered in selecting hospitals. The hospitals were all part of a special national monitoring network and may be atypical.

The internationally recognized DDD/ATC system was used in our comparisons of patterns of antibiotic use between China and Sweden. However, the Chinese medicines classification system is different from the ATC system, and different prescribed doses are used in different countries. We only targeted the antibiotic categories that were similar between the Chinese system and ATC system to attempt to reduce this bias.

There are also some limitations in the Swedish data. Unlike the IP consumption data collected in China, we extracted sales data of antibiotics to the hospital wards were extracted, but not what was actually used by the patients. This may result in an overestimate of antibiotic use in Sweden. In addition, due to the limitation of Swedish data availability (consumption data only in 2009-2012, IP antibiotics use only in 2010), these do not exactly match with the years of the Chinese data (consumption data in 2005-2012, IP antibiotics use data in 2012).

Segmented regression analysis of interrupted time series data is the strongest, quasi-experimental design to evaluate longitudinal effects of time-delimited interventions. This evidence would be stronger if a control setting was available. Due to the restriction of data availability, we were not able to obtain control data.

Data from our study do not enable us to understand whether the changes in China have resulted in less inappropriate antibiotic use, or whether antibiotics use has been shifted from IP to other sources. Some intervention strategies such as "revoking prescription rights of the frequent outliers" may lead to that appropriate antibiotic use being denied. Sophisticated policies are needed to guide antibiotic use rather than simple restriction of use. There is also a clear need to obtain better surveillance of both antibiotic resistance and usage to guide future interventions.
REFERENCES


