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

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The Effects of Clinical Interventions on Use of Medicines with a Focus on Antibiotics


Jing Sun

ABSTRACT

To systematically review intervention studies on antibiotic prophylaxis in clean or clean-contaminated surgery in Chinese hospitals from 2000 to 2012. Published peer reviewed articles, unpublished documents and reports, and gray literatures were identified through searching CNKI, CBM, VIP, PubMed (MEDLINE), WHO database, and the official websites of the Ministry of Health of China, provincial health authorities and medical university internal publications. Eighty-two studies were identified. Circulation and localization of central rules, regulations and guidelines; clinical pharmacists’ involvement; technical, administrative, and managerial strategies were the mostly adopted interventions. Except one study, all claimed effectiveness of interventions. Limited effects were observed for non-indicated clean surgery. Huge gaps still existed between the international agreed guidelines and the claimed best performance following interventions. The following were critical to have more effective interventions: recognition, acceptance, and enforcement strategies of rules, regulations, and guidelines; intervention persistence and intensity; health information system; removal of health system perverse incentives; patient–doctor relationship; public education; and access to unbiased medicines information. A total 4 of 82 studies were pre–post studies with control; all others were simple pre–post studies without control. Simple measurement of the outcome indicators as an average for pre–post intervention groups and changes in between failed to distinguish the real intervention effect from confounding factors, and failed to adjust underlying trends. Interventions on surgical antibiotic prophylaxis in Chinese hospitals during 2000–2012 brought limited positive effects. There are still huge gaps between the Chinese situation and internationally agreed standards. More advanced study methodologies are needed to have better documentation of evidence of the most effective interventions.
BACKGROUND

World Health Assembly (WHA) resolutions urged member states to formulate measures to promote appropriate and cost-effective use of antibiotics.1 The National Health and Family Planning Commission of P.R. China (formerly named the Ministry of Health, MoH) committed to this. They developed series regulations and rules on medicines use in health facilities. These included regulations on health facility pharmacy,2 retail pharmacies sell antimicrobials with prescriptions,3 national standard clinical guidelines for antibiotics use,4 national antimicrobials clinical use and resistance monitoring network in hospitals,5 standardized format of prescription and procedure of dispensing,6 and restriction of antimicrobials stocked and used in different levels of public health facilities in 2012.7

Meanwhile, the World Health Organization (WHO) and the Chinese government jointly conducted interventions on antibiotics use in hospitals across China. Antibiotic prophylaxis in surgery was prioritized due to its severe inappropriate use in Chinese hospitals.8 Beijing, Zhuhai, Guangdong, Jiangxi, Anhui, and Guangxi9-14 reported the above interventions accordingly. Some local authorities followed this and conducted similar interventions to improve antibiotic prophylaxis in surgery.

MATERIALS AND METHODS

This study systematically identified and studied published peer reviewed articles, unpublished documents and reports, and gray literatures about antibiotic prophylaxis in clean or clean-contaminated surgery in Chinese hospitals during 2000–2012, and analyzed the effects of reported interventions and study methods, and the key determinants of antibiotic prophylaxis in surgery in Chinese hospitals.

Published peer reviewed articles were identified through searching CNKI, CBM, and VIP. Four Chinese terms were used to search the title, abstract and key words: prevention, antibiotics, antimicrobials, and intervention. Considering the possible difference between Chinese and English meaning of the same word, and only targeting studies about China, three English terms were used in searching the title and abstract of PubMed (MEDLINE): antibiotic prophylaxis, intervention, China. The study also reviewed reference lists of published articles to obtain earlier relevant articles.

In addition to peer reviewed literature, this study performed a systematic review of published and unpublished reports and documents. Chinese materials were obtained from the MoH and its working arms, such as the national antibiotics clinical use monitoring network, and other relevant research organizations. We searched the official website of MoH, provincial health authorities and medical university internal publications (including master and PhD thesis). English materials were obtained from WHO database of studies on use of medicines in developing and transitional countries. This database includes systematically
extracted information from published and unpublished articles and reports. It also contains information on interventions on medicines use reported by these studies. All studies in this database were published during 1990–2009. It has not been updated since 2009. Several relevant project reports of WHO country cooperation projects in China were identified through this way.

RESULTS

As showed in Table 1, 82 published studies were identified, which included eight articles of gray literatures (five in Chinese, three in both English and Chinese), and 74 peer reviewed articles (72 in Chinese, two in English). These articles contained studies about interventions on antibiotic prophylaxis in clean or clean-contaminated surgery in Chinese hospitals during 2000–2012. According to the infection control categories defined by the MoH, \(^{15}\) 58 targeted category I incision (clean surgery), and 24 targeted category I and II incision (clean-contaminated surgery). A total 3 of 82 reviewed studies were published before 2005. The earliest published articles came from Beijing \(^{9,10}\) and Guangdong \(^{11,12,16,17}\) supported by WHO. A total 59 of 82 articles were published during 2010–2012, and came from provinces which participated in a WHO supported project. \(^{10,12,14}\)

<table>
<thead>
<tr>
<th>Category</th>
<th>(n)</th>
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</thead>
<tbody>
<tr>
<td>Language</td>
<td></td>
</tr>
<tr>
<td>Grey literature</td>
<td>8</td>
</tr>
<tr>
<td>Chinese</td>
<td>5</td>
</tr>
<tr>
<td>Both English and Chinese</td>
<td>3</td>
</tr>
<tr>
<td>Peer review articles</td>
<td>74</td>
</tr>
<tr>
<td>Chinese</td>
<td>72</td>
</tr>
<tr>
<td>English</td>
<td>2</td>
</tr>
<tr>
<td>Timing</td>
<td></td>
</tr>
<tr>
<td>2000-2004</td>
<td>3</td>
</tr>
<tr>
<td>2005-2009</td>
<td>20</td>
</tr>
<tr>
<td>2010-2012</td>
<td>59</td>
</tr>
<tr>
<td>Targeted surgery</td>
<td></td>
</tr>
<tr>
<td>Clean surgery</td>
<td>58</td>
</tr>
<tr>
<td>Clean-contaminated surgery</td>
<td>24</td>
</tr>
</tbody>
</table>

All interventions were in public hospitals. As showed in Table 2, 81 of 82 reviewed articles were research articles, \(^{9,11,16,21}\) and one was review paper containing evidence from other articles and reports. \(^{18}\)

A total 4 of 81 research articles were pre–post studies with control. \(^{13,14,19,20}\) A total 77 of 81 articles were simple pre–post studies without control. Although they named pre-group (non-intervention) as control group, they only measured the outcome indicators as an average for pre-group (non-
intervention) before interventions, and for post-group (intervention) after interventions, and calculated changes in between.

A total of 77 simple pre–post studies assessed the difference between pre-group (non-intervention group) and post-group (intervention group) in terms of age, sex, and severity of diseases, or designed appropriate data collection plan to avoid seasonal variations.

As shown in Table 3, a total 18 of 81 studies adopted rule, regulation and guideline approach. Circulation and localization of centrally developed rules, regulations and guidelines were common approaches; others were guideline training course and examination, newsletter and broader circulation, and experience sharing with other hospitals.

A total 41 of 81 studies used clinical pharmacist to conduct interventions. Clinical pharmacist worked on-site with surgeons to decide antibiotics selection, dosage and strength, administration route and time, and took joint ward rounds. They collected drug utilization data, evaluated the degree of guideline compliance, gave feedback and recommendations to surgeons regularly.

A total 12 of 81 studies introduced electronic prescription and medical record management system. Electronic prescription and medical record management system were developed to achieve real time monitoring and evaluation of antibiotics use, and electronic control of antibiotics use (alert to non-compliance prescriptions).

A total 12 of 81 studies adopted administrative and managerial strategy. Restriction of antibiotics prescribing rights of surgeons based on levels of technical skills; strengthening the accountability of hospital managers and department directors through signing commitment documents; setting up antibiotics clinical use supervision group under the leadership of hospital managers; integrating antibiotics use performance assessment into quality of care accreditation process; naming, shaming and economic punishment to bad performances, praising and rewarding to good performances.
Table 3 Intervention approach

<table>
<thead>
<tr>
<th>Intervention approach</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rules, regulations and guidelines approach</td>
<td>18</td>
</tr>
<tr>
<td>Clinical pharmacist</td>
<td>41</td>
</tr>
<tr>
<td>Electronic prescription and medical record management system</td>
<td>12</td>
</tr>
<tr>
<td>Administrative and managerial strategy</td>
<td>12</td>
</tr>
</tbody>
</table>

As shown in Table 4, all studies selected the following measurements based on Chinese national guidelines: antibiotics selection and changing, dose, solvent, admission routes and timing, and combination. A total 17 of 81 measured surgical site infection rate. A total 5 of 81 studies assessed adverse drug reaction rate. A total 34 of 81 studies counted medical and medicines expenditures. A total 9 of 81 studies compared duration of hospitalization.

Table 4 Outcome measurement

<table>
<thead>
<tr>
<th>Outcome measurement</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics selection and changing, dose, solvent, admission routes and timing, combination</td>
<td>81</td>
</tr>
<tr>
<td>Surgical site infection rate</td>
<td>17</td>
</tr>
<tr>
<td>Adverse drug reaction rate</td>
<td>5</td>
</tr>
<tr>
<td>Medical and medicines expenditures</td>
<td>34</td>
</tr>
<tr>
<td>Duration of hospitalization</td>
<td>9</td>
</tr>
</tbody>
</table>

As showed in Table 5, only one study claimed failure in improving antibiotic prophylactic in a Chinese hospital, all others concluded effectiveness of interventions. There were limited effects on non-indicated clean surgery, especially clean-contaminated surgery. This was because that surgeon concerned about failure to control hygiene risks in operating theatres, and patients’ complains in case of having infections.

A total 24 of 81 studies reported that the proportion of clean surgery used antibiotics reduced from 21.3–100% to 3.2–90%; 18,23,25,35,37,41,44–46,56,58,66,74–76,79,80,84–89 9 of 81 reported that the proportion of antibiotic prophylaxis <2 hours before incision increased from 7.7–60% to 31–92%; 18,23,25,37,45,47,60,72,77,88 5 of 81 reported that the proportion of antibiotic prophylaxis <24 hours increased from 0–5% to 46–81%; 34,45,47,76,90 2 of 81 reported that the proportion of cases used no antibiotics after operation increased from 0–62% to 39–96%; 36,91 26 of 81 reported that the number of days for antibiotic prophylaxis reduced from 2–16 to <24 hours; 11,12,18,23,34,38,42–49,52,56–58,60,65,69,70,72,81 9 of 81 reported that the proportion of combination therapy reduced from 4–100% to 0–21%; 11,12,23,41,48,55,58,67,75 7 of 81 reported that the number of days for hospitalization reduced from 6–16 to 2–6.
The Effects of Clinical Interventions on Use of Medicines with a Focus on Antibiotics

Table 6 Quantitative intervention effect of three controlled studies

<table>
<thead>
<tr>
<th>Included study</th>
<th>Indicator</th>
<th>Intervention group</th>
<th></th>
<th></th>
<th>Control group</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Pre-intervention</td>
<td>Post-intervention</td>
<td>Pre-intervention</td>
<td>Post-intervention</td>
<td></td>
</tr>
<tr>
<td>WHO Project(^{13}) &amp; Zheng(^{14})</td>
<td>Rationality scores of indicated clean surgery with antibiotic prophylaxis</td>
<td>55.4(^{a})</td>
<td>77(^{b})</td>
<td>57.6(^{a})</td>
<td>64.3(^{b})</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Proportion of non-indicated clean surgery admitted no antibiotics</td>
<td>61.9(^{c})</td>
<td>60.9(^{d})</td>
<td>84.4(^{c})</td>
<td>59.1(^{d})</td>
<td></td>
</tr>
<tr>
<td>Sun(^{20})</td>
<td>Proportion of non-indicated clean surgery with antibiotic prophylaxis</td>
<td>75(^{e})</td>
<td>32.56(^{e})</td>
<td>44.23(^{f})</td>
<td>42.05(^{f})</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Proportion of clean surgery admitted no antibiotics after operation</td>
<td>0.96%</td>
<td>39.5%</td>
<td>0</td>
<td>1.1%</td>
<td></td>
</tr>
</tbody>
</table>

Notes:

a. t-test P > 0.05, no significant difference between intervention and control group pre intervention.

b. t-test P < 0.05, significant difference between intervention and control group post intervention.

c. Chi2-test P < 0.05, significant difference between intervention and control group pre intervention.

d. Chi2-test P > 0.05, no significant difference between intervention and control group post intervention.

e. P < 0.05, significant difference of intervention group pre and post intervention.

f. P > 0.05, no significant difference of control group pre and post intervention.

Table 5 Outcome of intervention

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Outcome</th>
<th>No. of research articles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall effect of intervention</td>
<td>Effective</td>
<td>80/81</td>
</tr>
<tr>
<td>% of clean surgery used antibiotics</td>
<td>Reduced from 21%-100% to 3%-90%</td>
<td>24/81</td>
</tr>
<tr>
<td>% of antibiotic prophylaxis 0.5-2h before incision</td>
<td>Increased from 7.7%-60% to 31%-92%</td>
<td>9/81</td>
</tr>
<tr>
<td>% of antibiotic prophylaxis &lt;24 h</td>
<td>Increased from 0-5% to 46%-81%</td>
<td>5/81</td>
</tr>
<tr>
<td>% of cases used no antibiotics after operation</td>
<td>Increased from 0-62% to 39%-96%</td>
<td>2/81</td>
</tr>
<tr>
<td>No. of days for antibiotic prophylaxis</td>
<td>Reduced from 2-16 to &lt;24 h</td>
<td>26/81</td>
</tr>
<tr>
<td>% of combination therapy</td>
<td>Reduced from 4%-100% to 0-21%</td>
<td>9/81</td>
</tr>
<tr>
<td>No. of days for hospitalization</td>
<td>Reduced from 6-16 to 2-6</td>
<td>7/81</td>
</tr>
</tbody>
</table>

The outcome reported by the three controlled studies was summarized as showed in Table 6. The WHO supported project\(^{13}\) and Zheng\(^{14}\) found that, the rationality scores of indicated clean surgery with antibiotic prophylaxis of the intervention group increased from 55.4 to 77.0, and that of the control group also increased from 57.6 to 64.3.
Chapter 3

The difference between the intervention and control group was not significant before interventions (p>0.05), but was significant following interventions (p<0.05). This implied positive effect of interventions on increasing the rationality scores of indicated clean surgery with antibiotic prophylaxis.

The proportion of non-indicated clean surgery with antibiotic prophylaxis of the intervention group slightly dropped from 61.9% to 60.9%, while that of the control group significantly dropped from 84.4% to 59.1%. The difference between the intervention and control groups was significant before intervention (p<0.05), but was not significant (p>0.05) following interventions. This indicated other factors to affect surgeons' decision on antibiotics use for non-indicated clean surgery, such as health system problems and patients' expectations. Sun\textsuperscript{20} considered similarity

Table 7 Surgical prophylaxis guidelines & reported best performance after intervention in Chinese hospitals

<table>
<thead>
<tr>
<th>Key indicators</th>
<th>World Alliance for Patient Safety (2\textsuperscript{nd} edition)\textsuperscript{92}</th>
<th>Scottish NHS Guideline July 2008\textsuperscript{93}</th>
<th>Chinese National Guideline 2008\textsuperscript{4}</th>
<th>Reported best performance after intervention in Chinese hospitals</th>
</tr>
</thead>
<tbody>
<tr>
<td>General principle</td>
<td>NA</td>
<td>Grades of recommendations based on levels of evidence</td>
<td>Not recommended in general, except high risk factors</td>
<td>32.6%-39.1% non-indicated clean surgery with antibiotic prophylaxis\textsuperscript{14,20}</td>
</tr>
<tr>
<td>Timing</td>
<td>Within the hour before incision</td>
<td>Intravenously ≤30 minutes before the skin is incised</td>
<td>0.5-2 hours before surgery</td>
<td>31.4%-92.4% antibiotic prophylaxis 0.5-2 hours before surgery\textsuperscript{33,36,45,73}</td>
</tr>
<tr>
<td>Dosage and duration</td>
<td>NA</td>
<td>Single standard dose is sufficient under most circumstances. Additional dosage may be indicated for longer surgery or shorter-acting agents, and intra-operative blood loss in adults (&gt;1,500 ml)/children (25 ml/kg) after fluid replacement. Duration&lt;24 hours</td>
<td>Single dose for clean surgery &lt;2 hours. 2\textsuperscript{nd} dose could be given when surgery &gt;3 hours or blood loss &gt;1,500 ml. Duration&lt;24 hours, could be prolonged to 48 hours for specific circumstances</td>
<td>39.5%-96% of clean surgery with no antibiotic prophylaxis after operation\textsuperscript{30,34} average number of days for antibiotic prophylaxis was 4.1±2.9 (X ± SD)\textsuperscript{53,54}</td>
</tr>
<tr>
<td>Medicines choice</td>
<td>NA</td>
<td>Narrow spectrum, less expensive antibiotics should be the first choice.</td>
<td>Effectiveness, safety, convenience, and cost should be considered</td>
<td>2nd &amp; 3rd generations of cephalosporins were the most commonly used antibiotics\textsuperscript{22,34,47,80,79}</td>
</tr>
</tbody>
</table>
of the studied cases in the control and intervention groups. Proportion of clean surgery with antibiotic prophylaxis of the intervention group significantly decreased from 100% to 60.5% (p<0.05), while that of the control group changed from 100% to 98.9% (p>0.05). Proportion of clean surgery without antibiotic prophylaxis after operation of the intervention group significantly increased from 1.0% to 39.5% (p<0.05), while that of the control group changed from 0 to 1.1% (p>0.05). Proportion of non-indicated clean surgery with antibiotic prophylaxis of the intervention group significantly reduced from 75.0% to 32.6% (p<0.05), while that of the control group changed from 44.2% to 42.1% (not significant, p> 0.05).

The best performances claimed by the reviewed studies were compared with the international guideline, the internationally recognized national guideline, and the Chinese national guideline in Table 7. Although Chinese national guideline recommends that antibiotic prophylaxis is not necessary for non-indicated clean surgery, 32.6–39.1% of them still used antibiotics; 31.4–92.4% cases were in line with the recommendation of international and national guidelines: antibiotic prophylaxis 0.5–2 hours before incision; 39.5–96.0% of clean surgery did not use antibiotics after operation, the average number of days using antibiotics was 4.1 ± 2.9 (X ± SD), although both the Scottish and Chinese national guideline recommend that single standard dose is sufficient under most circumstances, and duration for antibiotic prophylaxis should <24 hours for special cases; Narrow spectrum antibiotics were recommended by the Scottish Guideline, Class II and III generations of cephalosporin were the most commonly used antibiotics.

DISCUSSION

Intervention effect evaluation criteria
Even though the Chinese guideline is generally not as stringent as the international/internationally recognized national guidelines, huge gaps still existed between the Chinese guideline and the claimed best performances following interventions. This indicates that, the situations after intervention are still not optimistic.

Lessons learnt from the reviewed literature
According to the experiences summarized by the reviewed literature, the following aspects are critical to have more effective interventions:

Enforcement of rules and regulations and guidelines
The MoH of China issued a series of rules and regulations and guidelines. Most of them were general principles but not operational details. Putting them into good practice in hospitals was problematic without effective implementing strategies. Identification and recognition of centrally issued rules and regulations and guidelines based on actual situation, and developing operational implementation strategies were crucial for better enforcement.13,14,18,27,48
Chapter 3

Acceptance and compliance of guidelines
Contradictions exist among guidelines issued by different government agencies and professional associations. Well organized expert consultation process and standardized evidence-based mechanism for guideline development are premise for more authoritative guideline and better acceptance and compliance at local levels.14,18

Intervention intensity
Promoting appropriate use of antibiotics requires continued efforts, one-time project based intervention, or pure executive order won’t have sustainable effects.11–14,18,25,35,38,59 Continued efforts with repeated MTP circles have better effects on changing prescribing behaviors than pure guideline circulation and training.11–14,20,22,23,34,35,37,44,45,55,56 Naming and shaming, economic punishment for bad performances, praising and rewarding to good performances are helpful for better guideline compliance.19,23,26,29,57,59–65

Health information system
Electronic prescribing management system enables real time monitoring of antibiotics prescribing, timely alert of prescriptions not complied with guidelines, and easy utilization analysis. It is an efficient tool for easy regular monitoring, data collection, evaluation, feedback, and information sharing.16,19–22,25,27,42,43,53,57,58

Health system problems
Technical interventions have limited effect in convincing surgeons not to use antibiotics for non-indicated cases. Complicated problems exist which are beyond the knowledge and prescribing habits of surgeons. Perverse incentives in health systems have driven doctors to use expensive and broad spectrum antibiotics even for non-indicated cases.18 These perverse incentives include prices of both labor and skill extensive medical services are set by the government far below the real cost, surgeons have to rely on selling medicines and diagnostic tests to collect revenue and to compensate low salary.

Patient–doctor relationship
Poor accessibility and affordability to quality care and low formal salary but heavy workload have brought huge pressures to both patients and doctors. Such pressures lead to deteriorated patient–doctor relationship. Placing the responsibility of proof on doctors in medical disputes about unexpected infections may also be a factor for inappropriate antibiotic prophylaxis. Surgeons are risk-averse for those clean contaminated surgeries, and high risk ones, such as cesarean section.11,12,14,18,20,23,39,58,62

Public education
Public education on prudent use of antibiotics is weak.9,14,18,20,70 General public always have
incorrect perceptions about antibiotic use for cold, cough, fever, and other non-bacterial infections. People always regard the brand new and broad-spectrum antibiotics as “big guns.”

**Unbiased medicines information**
Clinical pathway and guideline are just newly introduced and not yet accepted nationwide. Timely access to evidence-based medicines information has been weak in less developed areas. There is no well recognized, officially launched, friendly and public accessed channels for evidence-based medicines information dissemination.\(^{14,18}\)

**Intervention effect evaluation method**
Making conclusions on successfulness of intervention needs rigorous research methods. There is a need for adopting more advanced method for policy impact analysis. Lots of studies claimed positive effects. However, simple pre–post study without control failed to distinguish the real intervention effect from the confounding factors. Simple before-after comparison without consideration of difference between pre-group (non-intervention) and post group (intervention) and seasonal variations, could not adjust underlying trends. In addition, calculating average outcome measurement for pre–post groups, and not using advanced statistical techniques (such as segmented regression) to analyze the data, was a rough estimation rather than an accurate quantification.

**CONCLUSION**
Interventions on antibiotic prophylaxis in clean and clean contaminated surgery in Chinese hospitals during 2000–2012 brought limited positive effects. There are gaps between the Chinese situation and international standards. It is not yet a time for concluding a successfulness of these interventions. Simple pre–post study without a well designed control group might not be appropriate for drawing any conclusions of the intervention effect. The most outstanding problem for interventions is non-indicated antibiotic prophylaxis. This indicates that there might be complex factors which affected surgeons’ antibiotic prophylaxis decision making, such as health system problems and patients’ expectations. More comprehensive approaches and continued efforts are needed. More advanced methodologies are needed to better document evidences for the most effective interventions, and to inform the policy makers more effectively.

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