Pharmacopoeial quality of antimicrobial drugs in southern China

Antimicrobial drugs are the most counterfeit or substandard drugs worldwide. The pharmacopoeial quality of these drugs in China is of special concern because China is the second producer, after India, of most counterfeit or substandard drugs in the global market. The antimicrobials circulating in China are produced by local, joint-venture, or foreign pharmaceuticals. There were 4875 local pharmaceutical manufacturers in China in 2013, most of which were small-sized or medium-sized. Although the central government aimed to minimise the number of pharmaceutical manufacturers and to improve drug quality by increasing the severity of punishment for forgery, the progress has been slow with only minor changes in the related policies and surveillance on pharmaceutical manufacturers and 414 840 pharmacies across China. Loose regulations and laws (eg, the maximum penalty of 1000 RMB [1 RMB≈0·1 GBP] for the sale of prescription drugs without prescription) greatly contribute to the great increase in non-prescription antimicrobial drugs and underline the problem of drug resistance in China. Moreover, storage conditions in domestic pharmacies are usually suboptimal with unknown effects on the pharmacopoeial quality of medicines.

The reported prevalence of counterfeit or substandard medicines is 1–2% on the China Food and Drug Administration (CFDA) website; one available official report cites the prevalence of counterfeit or substandard antimicrobials in 2007 as 1·9%, which is much lower than the 22–38% prevalence reported in other low-income and middle-income countries. Therefore, in a cross-sectional study, we independently investigated the pharmacopoeial quality of five common antimicrobial drugs (amoxicillin, azithromycin, cefuroxime axetil, levofloxacin, and metronidazole) from community pharmacies in Shantou, southern China, with a population of 5·1 million.

We selected the five antimicrobial drugs representing common antimicrobial classes—penicillins, macrolides, cephalosporins, quinolones, and imidazoles—because they were (1) commonly used in hospitals and community pharmacies, (2) sensitive to degrade under unsatisfied storage conditions, (3) frequently reported to have no active ingredient, and/or (4) included in the National Essential Drug List of China, as described previously. Of note, levofloxacin and cefuroxime axetil were first and third among the top 10 consumed antimicrobials in 360 hospitals in China during 2005–08.

In this cross-sectional study (May–July, 2013), our study staff purchased 506 antimicrobial samples without prescriptions and without informing the purpose of purchase from 115 rural and urban community pharmacies, representing 4·1% of all community pharmacies in Shantou. We used stratified random sampling by district (depending on the total numbers of pharmacies and populations in districts) to select the pharmacies, ensuring the coverage of all seven districts in Shantou.

Following the Chinese Pharmacopeia (Version 2010), we validated the pharmacopoeial quality of the samples using high-performance liquid chromatography (HPLC) in the Bio-analytical Laboratory of Shantou University Medical College (Shantou, China). Reference standard antimicrobial drugs were purchased from the National Institutes for Food and Drug Control, China. Assays were conducted in triplicate runs for each sample, blinded to packaging, and mean value was reported as the active pharmaceutical ingredient (API) of each sample. An antimicrobial sample was regarded as poor quality if its actual amount of API was lower than 90% or higher than 110% of the labelled amount (except for metronidazole, for which the limits were <93% or >107%).

A sample containing the wrong type of API or no API was considered counterfeit, on the basis of WHO’s definition of counterfeit medicines. We used a χ² test, a t-test, and a rank-sum test for the analyses through SPSS statistics (v17.0). Our results are reported according to the MEDQUARG guidelines where possible.

The APIs of five antimicrobials are shown in table 1. The tested antimicrobial samples were made in the mainland China, Hong Kong, Japan, USA, and UK, and registered with CFDA. Of 506 samples, 77 (15%) failed to meet the Chinese Pharmacopoeia standard limits in HPLC tests and 60 (78%) of these samples had an API lower than the labelled amount (table 2). All the poor-quality antimicrobials were from the mainland China (table 2). The poor-quality antimicrobials represented 65 (57%) of all 115 sampled pharmacies.

The number of pharmaceutical manufacturers that produced the

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mean actual content (SD)*</th>
<th>Range</th>
<th>IQR</th>
<th>Chinese Pharmacopoeia (2010) standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin</td>
<td>94·1% (5·1)</td>
<td>74·3–122·0</td>
<td>91·8–96·6</td>
<td>90·0–110·0</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>101·3% (7·9)</td>
<td>84·5–122·9</td>
<td>96·9–102·6</td>
<td>90·0–110·0</td>
</tr>
<tr>
<td>Cefuroxime axetil</td>
<td>97·9% (2·9)</td>
<td>90·4–103·9</td>
<td>95·8–100·3</td>
<td>90·0–110·0</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>98·7% (4·1)</td>
<td>83·5–110·2</td>
<td>96·1–101·5</td>
<td>90·0–110·0</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>93·4% (1·8)</td>
<td>84·1–98·1</td>
<td>92·1–94·5</td>
<td>93·0–107·0</td>
</tr>
</tbody>
</table>

* Compared with reference standard antimicrobial drugs.

Table 1: Active pharmaceutical ingredients of the antimicrobial drugs determined by high-performance liquid chromatography (n=506)
samples was 34 for amoxicillin, 30 for azithromycin, 12 for cefuroxime axetil, 39 for levofloxacin, and ten for metronidazole. The poor-quality rates of individual antimicrobials were as follows: amoxicillin (15%, 17 of 114), azithromycin (17%, 16 of 92), cefuroxime axetil (0%, 0 of 91), levofloxacin (3%, three of 101), and metronidazole (38%, 41 of 108). The poor-quality rates associated with the formulation were 16% (43 of 273) for tablets, 32% (20 of 62) for dispersible tablets, and 8% (14 of 167) for capsules.

All antimicrobials were lightweight-protected in the pharmacies, but temperature and humidity were unregulated, and accordingly the indoor temperature at the time of sampling in most pharmacies (mean 30.6°C [SD 2.6]) was higher than the recommended storage temperature (25°C). The prices of poor-quality antimicrobials were significantly lower than those of standard-quality antimicrobials (mean 0.6 RMB [SD 0.9] per tablet or capsule vs 1.2 RMB [1-2], p<0.0001), mostly contributed by poor-quality metronidazole.

As the first independent (non-government sponsored) study on the pharmacopeial quality of antimicrobials in China, the overall prevalence of poor-quality antimicrobials (15%) herein was much higher than that reported by CFDA in 2007 (1.9%). These poor-quality antimicrobials could be due to poor quality control in the domestic pharmaceutical industry. All the poor-quality antimicrobials were made by domestic pharmaceutical manufacturers, which are mostly small-sized or medium-sized. 40% of the poor-quality antimicrobials were produced by one medium-sized listed company.

The true influence of storage conditions on the tested drugs remains uncertain because we could not verify the long-term storage conditions of drugs in the pharmacies. High temperature (up to 40°C in summer) and high relative humidity seen in Shantou could probably influence the quality of amoxicillin, which is sensitive to storage conditions. Besides, low price or profit at the expense of quality control in manufacturing process could have compromised the drug quality in the case of metronidazole.

As to the consequences, whereas the higher API can potentially cause adverse drug events, a lower API such as that observed with the majority (78%) of poor-quality antimicrobials in this study could lead to treatment failure and drug resistance. Also, the poor-quality rate (15%) of these common and freely circulating antimicrobials and high proportion (57%) of sampled pharmacies (4% of all community pharmacies in Shantou) selling poor-quality medicines can be translated into high public health risk in China.

This study had limitations. Due to lack of official reference antimicrobials and their package inserts for some samples (particularly those made in mainland China), we could not validate the regulatory status of our samples. Since the failure rate of drugs might vary greatly with different sample collection methods and validation methods, essays, or cutoff values for drug-quality determination in different pharmacopeias, the comparison between our results and others should be interpreted with caution.

In summary, this study shows high rates of poor-quality common antimicrobials (metronidazole in particular) made and circulating in China, with potential risks of public health and drug resistance. The current antimicrobial policies and surveillance need fresh reconsideration to ensure the quality of antimicrobial drugs in China.

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