Epidemiology and control of multidrug-resistant tuberculosis in China

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CHAPTER 5

AVAILABILITY OF SECOND-LINE DRUGS AND ANTI-TUBERCULOSIS DRUG SUSCEPTIBILITY TESTING IN CHINA: A SITUATIONAL ANALYSIS

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ABSTRACT

Objective: To assess the availability of second line drugs (SLDs) and the use of susceptibility testing (DST) results for treatment of tuberculosis (TB) in China.

Design: Cross sectional survey in 4675 health care facilities, 1960 of which have a dedicated TB clinic, in 12 provinces in China.

Results: More than 70% of TB clinics at provincial and prefecture level had at least one SLD available, compared to 41.8% of facilities at county/district level. The proportion of facilities at provincial, prefecture, and county level with any fluoroquinolone was respectively 74.1%, 64.9%, and 34.5%. Sputum culture was performed at 6.0% of TB clinics at county level, 37.5% at prefecture and 59.3% at provincial level, while DST was performed only at the prefecture (28.6%) and provincial (44.4%) level. Only 18% of the facilities that used SLD for the treatment of multidrug-resistant TB (MDR-TB) designed treatment regimens based on DST results.

Conclusion: SLDs are widely available in China for the treatment of both TB and other infectious diseases. To prevent development of resistance of Mycobacterium tuberculosis resistance to SLDs, the availability of SLDs should be limited and they should be used with caution in the treatment of MDR-TB.

Key words: tuberculosis; second-line drugs; drug-resistance; MDR-TB; XDR-TB
In Beijing, China, ministers of health and other representatives from countries with a high incidence of multi- and extensively drug resistant tuberculosis (MDR-/XDR-TB) met in April 2009 to address the alarming threat of MDR-/XDR-TB. The meeting resulted in a call for action that included ensuring a sufficient supply of quality-assured first- and second-line medicines for TB treatment, and recommending the use of fixed-dose combination drugs within a management system that promotes treatment adherence.1

Treatment of TB that is resistant to the most effective first-line drugs (FLDs), rifampicin (RMP) and isoniazid (INH; i.e., MDR-TB), requires treatment with the less effective and more toxic second-line drugs (SLDs).2 Successful treatment becomes even more difficult when MDR-TB strains acquire resistance to SLDs as well.3 XDR-TB, which, in addition to being MDR, is also resistant to SLDs (any fluoroquinolone [FQ], and at least one of three injectable SLDs—kanamycin [KM], amikacin [AMK] and capreomycin [CPM]), has emerged worldwide, including in China.4-6 The results of the first national survey, performed in 2007, reported an overall MDR-TB prevalence of 8.3%, of which 8% were XDR-TB.7 TB resistant to all available SLDs has been reported by TB hospitals in China.5,8

Most of the drugs used in standard TB treatment are used exclusively for TB: only RMP is also indicated for staphylococcal and Legionella infections.9 Among the SLDs, aminoglycosides (KM and AMK) and FQs are also active against bacteria other than mycobacteria. Use of these broader-spectrum antibiotics in the treatment of TB patients without achieving cure, or use in undiagnosed TB patients, may lead to drug-resistant TB or delays in the diagnosis of TB.10-12 Treatment with FQs has also been associated with nosocomial spread of FD-resistant pneumococcal infections.13 This highlights the importance of the prudent use of antibiotics in the treatment of TB and all other bacterial infections.

The World Health Organization (WHO) PMDT guidelines for the programmatic management of drug-resistant tuberculosis recommend treatment with ≥4 drugs with certain, or almost certain, effectiveness.2 Programmatic management of drug-resistant TB (PMDT), including SLD treatment, is being implemented in several pilot areas in China. DST is routinely performed for MDR-TB suspects only at these pilot sites and in a few well-developed areas of China. Standardised TB treatment by the National
TB Programme (NTP) outside these pilot sites depends on FLDs only, which are not effective in the treatment of MDR-TB. Considering the high number of MDR-TB patients, the current standardised regimen is expected to fail often.\textsuperscript{14}

To date, no data are available on the use of SLDs for the treatment of TB in China; only a few small studies on SLD use for TB treatment have been published in national journals.\textsuperscript{15, 16} In the present survey, we inventoried the use of SLDs in general and specifically for TB treatment in various different health care facilities at different levels in China. We also assessed the availability of DST in TB clinics. Our findings may be used to, where necessary, to guide policies regarding the prudent use of SLDs and DST in China, to prevent the development of further drug resistance.

**METHODS**

**TB CONTROL SYSTEM IN CHINA**

At all administrative levels in China—at the national, provincial, prefecture and district/county levels—one TB centre is responsible for implementing the NTP at its own level. An outline of the TB control system in China at all levels is shown in Figure 1. The National Center for TB Control and Prevention (NCTB), part of the China Centers for Disease Control and Prevention (CDC), is responsible for implementing the NTP.
Figure 1. Framework of the NTP in China. CDC = Centers for Disease Control and Prevention; TB = tuberculosis; NTP = National TB Control Programme.
At the peripheral level, the NTP is represented by self-governed TB centres and TB centres embedded within the CDC or other facilities.

Approximately 50% of the TB centres under the CDC at the provincial and prefecture levels do not diagnose and treat patients themselves, but supervise TB control at lower levels. Most CDC TB centres at the county/district level have out-patient TB clinics. TB centres in hospitals and self-governed TB centres often also have in- and out-patient departments for other respiratory and infectious diseases.

According to NTP guidelines, township hospitals and village-level health stations have part-time staff designated for managing TB patients and referring TB suspects to the TB centre for diagnosis. General hospitals are required to refer TB suspects or patients to a TB centre. However, some general hospitals have TB beds for treating patients with severe complications or treatment-related side effects. In general, TB hospitals and hospitals specialising in infectious diseases that have a TB department diagnose and treat TB patients themselves and refer them to a TB centre after discharge.

SAMPLING
Provinces of China were categorized into three regions: the eastern, middle and western region. Four provinces from each region with a relatively high human resource capacity and the willingness to participate were included in the study. In each province, the TB centre, the TB hospital and the three largest general hospitals at the provincial level; in each prefecture, the TB centre, the largest TB hospital (if more than one) and the two largest general hospitals; and in each county/district the TB centre, the largest general hospital and 1-2 central township hospitals (the largest hospitals at the township level) were selected.

DATA COLLECTION
Interviews were held from July to November 2008 with the heads of the TB clinic, pharmacy, laboratory, and/or respiratory disease departments of each selected health care facility to obtain information on the availability and use of 10 classes of SLDs for TB treatment and all other indications in the last year. SLDs included were para-aminosalicylic acid (PAS), KM, AMK, CPM, ofloxacin (OFX), levofl oxacin (LVX), ciprofl oxacin (CFX), moxifl oxacin (MFX), prothionamide (PTH) and cycloserine (CS). Use of sputum smear examination, sputum culture and DST against FLDs/SLDs
and quality assurance for these laboratory tests were assessed. We also requested details of SLD-containing treatment regimens from facilities that mentioned using SLDs for TB treatment.

The provincial TB centres organised TB staff at different levels to hold interviews with the heads of the above-mentioned departments. Five per cent (5%) of the questionnaires were randomly rechecked by interviewing central-level staff by telephone; rechecking gave almost identical results.

DATA MANAGEMENT AND ANALYSIS
Data were double entered using EpiData 3.1 (EpiData Association, Odense, Denmark, 2003-2008), and discrepancies were checked against the raw data. Analyses were performed using SPSS 13.0 (Statistical Package for the Social Sciences, Chicago, IL, USA).

ETHICAL ISSUES
The research project was approved by the Chinese Ethical Committee for TB Operational Research, Beijing.

RESULTS

HEALTH CARE FACILITIES
In total, 4782 facilities in 12 provinces, including 156 prefectures, 1362 counties/districts and 1943 towns, were covered by the survey. Of these 4782 facilities, 4675 (97.8%) treated patients, and of these 1960 (41.0%) had an in- and/or out-patient clinic for treatment of TB patients.

USE OF SECOND-LINE DRUGS IN TB CLINICS AND GENERAL HOSPITALS
SLDs were more often available for treatment at provincial and prefecture level than at county/district level. More than 70% of the TB clinics at the provincial and prefecture levels had at least one SLD available, compared to 41.8% of clinics at the county/district level. AMK was the most widely available injectable SLD, while LFX was the most widely available FQ. CS was not available at any facility (Table 1).
SLDs were available in 34.4-49.0% of the CDC TB centres and general hospitals at the county/district-level (Table 2) compared to 60.9-70.1% of self-governed TB centres. TB centres in CDC-designated hospitals specialising in TB and chest diseases and general hospitals at the provincial and prefecture levels had at least one SLD at their disposal for treatment. All classes of SLD were widely available at the non-NTP TB hospitals and hospitals specialising in infectious diseases.

SLD availability for all indications in the general and township (non-NTP) hospitals is described in Table 3. Most of these hospitals do not have TB clinics, and TB patients make up only a small proportion of all patients. At least one SLD was available in all the general hospitals and in 70% of the township hospitals. FQs and AMK were the most widely available SLD at all levels; KM was also almost always available, but only at the provincial/prefecture level.

**TB diagnostics in health care facilities with an out- and/or in-patient TB clinic**

More facilities at the provincial and prefecture levels had TB diagnostic tests available than those at the county and district levels. At the county/district level, 80.2% of the facilities could perform smear microscopy; sputum culture was mainly performed at the prefecture and provincial levels, while DST was performed only at the prefecture and provincial levels (Table 4). External quality assurance (EQA) was in place for around 15% of the health care facilities that performed sputum culture and DST for FLDs (Table 5).

We requested information on SLD-containing regimens from the 905 facilities that indicated using SLDs for TB treatment: 198 (21.9%) facilities for new cases, 421 (46.5%) for retreatment cases and 292 (32.3%) for (suspected) MDR-TB cases. For new and retreatment cases, most facilities used one or two SLDs in their treatment regimens. For the treatment of MDR-TB, 104 (35.6%) facilities used one or two classes of SLD (Figure 2). Only a small proportion of the facilities that used SLDs and provided information on regimens relied on DST to formulate the regimen: 12% for new cases, 10% for retreatment cases and 18% for MDR-TB cases.
Table 1. Availability of SLDs for treatment of TB patients in 1960 health care facilities with an out- and/or in-patient TB clinic, by hierarchical level

<table>
<thead>
<tr>
<th>Hospital</th>
<th>n*</th>
<th>Any SLD</th>
<th>PAS</th>
<th>KM</th>
<th>AMK</th>
<th>CPM</th>
<th>Any FQ</th>
<th>OFX</th>
<th>LVX</th>
<th>CFX</th>
<th>MFX</th>
<th>PTH</th>
<th>CS</th>
</tr>
</thead>
<tbody>
<tr>
<td>General hospital (provincial/prefecture level)</td>
<td>302</td>
<td>100</td>
<td>100</td>
<td>23.8</td>
<td>98.7</td>
<td>99.7</td>
<td>5.0</td>
<td>100</td>
<td>57.3</td>
<td>28.5</td>
<td>7.0</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>General hospital (county/district level)</td>
<td>1058</td>
<td>99.2</td>
<td>99.2</td>
<td>12.9</td>
<td>15.5</td>
<td>60.1</td>
<td>3.3</td>
<td>53.3</td>
<td>98.8</td>
<td>52.4</td>
<td>5.7</td>
<td>2.6</td>
<td>0.0</td>
</tr>
<tr>
<td>Township hospital</td>
<td>1943</td>
<td>70.3</td>
<td>70.3</td>
<td>2.6</td>
<td>12.6</td>
<td>52.7</td>
<td>1.5</td>
<td>51.7</td>
<td>61.1</td>
<td>50.5</td>
<td>1.0</td>
<td>0.3</td>
<td>0.0</td>
</tr>
</tbody>
</table>

* FQ.

SLD = second line drug; PAS = para-aminosalicylic acid; KM = kanamycin; AMK = amikacin; CPM = capreomycin; FQ = fluoroquinolone; OFX = ofloxacin; LVX = levofloxacin; CFX = ciprofloxacin; MFX = moxifloxacin; PTH = prothionamide; CS = cycloserine.
Table 2. Availability of SLDs for TB treatment in 1960 different health care facilities with an out- and/or in-patient TB clinic

<table>
<thead>
<tr>
<th>Facility</th>
<th>n</th>
<th>Any SLD</th>
<th>PAS</th>
<th>KM</th>
<th>AMK</th>
<th>CPM</th>
<th>Any FQ</th>
<th>OFX*</th>
<th>LVX*</th>
<th>CFX*</th>
<th>MFX*</th>
<th>PTH</th>
<th>CS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TB centers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDC at provincial/prefecture levels</td>
<td>49</td>
<td>49.0</td>
<td>49.0</td>
<td>2.0</td>
<td>16.3</td>
<td>10.2</td>
<td>38.8</td>
<td>4.1</td>
<td>38.8</td>
<td>0</td>
<td>2.0</td>
<td>32.7</td>
<td>0.0</td>
</tr>
<tr>
<td>CDC at county/district level</td>
<td>945</td>
<td>34.4</td>
<td>26.3</td>
<td>1.5</td>
<td>9.8</td>
<td>3.6</td>
<td>26.1</td>
<td>6.6</td>
<td>24.1</td>
<td>2.1</td>
<td>0.3</td>
<td>18.6</td>
<td>0.0</td>
</tr>
<tr>
<td>Self-governed</td>
<td>157</td>
<td>70.1</td>
<td>56.7</td>
<td>6.4</td>
<td>45.2</td>
<td>19.7</td>
<td>59.9</td>
<td>17.2</td>
<td>58.0</td>
<td>4.5</td>
<td>1.3</td>
<td>44.6</td>
<td>0.0</td>
</tr>
<tr>
<td>Designated TB and chest disease hospitals</td>
<td>139</td>
<td>64.7</td>
<td>34.5</td>
<td>12.2</td>
<td>38.1</td>
<td>3.6</td>
<td>59.7</td>
<td>33.8</td>
<td>56.1</td>
<td>13.7</td>
<td>7.2</td>
<td>17.3</td>
<td>0.0</td>
</tr>
<tr>
<td><strong>Hospitals</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TB and special infectious hospital</td>
<td>67</td>
<td>100</td>
<td>85.1</td>
<td>83.6</td>
<td>95.5</td>
<td>55.2</td>
<td>100</td>
<td>53.7</td>
<td>100</td>
<td>14.9</td>
<td>16.4</td>
<td>74.6</td>
<td>0.0</td>
</tr>
<tr>
<td>General hospital at provincial/prefecture levels</td>
<td>116</td>
<td>62.9</td>
<td>40.5</td>
<td>9.5</td>
<td>35.3</td>
<td>4.3</td>
<td>52.6</td>
<td>29.3</td>
<td>50.9</td>
<td>11.2</td>
<td>4.3</td>
<td>17.2</td>
<td>0.0</td>
</tr>
<tr>
<td>General hospital at county/district level</td>
<td>487</td>
<td>44.4</td>
<td>18.5</td>
<td>6.2</td>
<td>27.3</td>
<td>1.6</td>
<td>39.4</td>
<td>19.8</td>
<td>37.4</td>
<td>9.2</td>
<td>1.4</td>
<td>4.7</td>
<td>0.0</td>
</tr>
</tbody>
</table>

*FQ.
†TB centres participate in the National TB Programme (see Figure 1), while hospitals do not.
SLD = second-line drug; TB = tuberculosis; PAS = para-aminosalicylic acid; KM = kanamycin; AMK = amikacin; CPM = capreomycin; FQ = fluoroquinolone; OFX = ofloxacin; LVX = levofloxacin; CFX = ciprofloxacin; MFX = moxifloxacin; PTH = prothionamide; CS = cycloserine; CDC = China Centers for Disease Control and Prevention.
Table 3. Availability of SLDs for the treatment of all indications in general and township hospitals

<table>
<thead>
<tr>
<th>Hospital</th>
<th>n†</th>
<th>Any SLD</th>
<th>PAS</th>
<th>KM</th>
<th>AMK</th>
<th>CPM</th>
<th>Any FQ</th>
<th>OFX</th>
<th>LVX</th>
<th>CFX</th>
<th>MFX</th>
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<td>100</td>
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<td>23.8</td>
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<td>99.7</td>
<td>5.0</td>
<td>55.3</td>
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<td>1943</td>
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<td>2.6</td>
<td>12.6</td>
<td>52.7</td>
<td>1.5</td>
<td>51.7</td>
<td>61.1</td>
<td>50.5</td>
<td>1.0</td>
<td>0.3</td>
<td>0.0</td>
</tr>
</tbody>
</table>

* Includes 588 hospitals that have a TB clinic (included in Tables 1 and 2).

SLD = second-line drug; PAS = para-aminosalicylic acid; KM = kanamycin; AMK = amikacin; CPM = capreomycin; FQ = fluoroquinolone; OFX = ofloxacin; LVX = levofloxacin; CFX = ciprofloxacin; MFX = moxifloxacin; PTH = prothionamide; CS = cycloserine.
Table 4. Availability of TB diagnostics in health care facilities with an out- and/or in-patient TB clinic, by hierarchical level.

<table>
<thead>
<tr>
<th>Level</th>
<th>Health care facilities with TB clinic n(%)</th>
<th>Health care facilities with TB clinic using SLDs n(%)</th>
<th>Smear n(%)</th>
<th>Culture n(%)</th>
<th>FLD DST n(%)</th>
<th>SLD DST n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Province</td>
<td>27 (39.7)</td>
<td>20 (74.1)</td>
<td>22 (81.5)</td>
<td>16 (59.3)</td>
<td>12 (44.4)</td>
<td>6 (22.2)</td>
</tr>
<tr>
<td>Prefecture</td>
<td>248 (54.9)</td>
<td>180 (72.6)</td>
<td>209 (84.3)</td>
<td>93 (37.5)</td>
<td>71 (28.6)</td>
<td>28 (11.3)</td>
</tr>
<tr>
<td>County/district</td>
<td>1685 (72.7)</td>
<td>705 (41.8)</td>
<td>1352 (80.2)</td>
<td>101 (6.0)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

TB = tuberculosis; SLD = second-line drug; FLD = first-line drug; DST = drug susceptibility testing.

Figure 2. Distribution of the number of SLDs used in treatment regimens, including SLDs for new, previously treated and (suspected) MDR-TB patients in facilities that reported using SLDs for TB treatment. SLD = second-line drug; MDR-TB = multidrug-resistant tuberculosis.

Table 5. Availability of TB diagnostics and external quality assurance in 1960 health care facilities with out- and/or in-patient TB clinics.

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Facilities n(%)</th>
<th>External quality assurance n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smear</td>
<td>1583 (80.8)</td>
<td>733 (46.3)</td>
</tr>
<tr>
<td>Culture</td>
<td>210 (10.7)</td>
<td>34 (16.2)</td>
</tr>
<tr>
<td>FLD DST</td>
<td>83 (4.2)</td>
<td>11 (13.2)</td>
</tr>
<tr>
<td>SLD DST</td>
<td>34 (1.7)</td>
<td>2 (5.9)</td>
</tr>
</tbody>
</table>

TB = tuberculosis; FLD = first-line drug; DST = drug susceptibility testing; SLD = second-line drug.
DISCUSSION

This situation analysis is the first large-scale investigation of the availability of SLDs and diagnostic possibilities for TB in China. The results show that 1) SLDs are widely available in China for the treatment of both TB and other diseases; 2) only a fraction of the facilities that diagnose and treat (drug-resistant) TB patients use DST to guide their choice of treatment regimen; and 3) EQA is rarely performed for culture and DST, while for smear microscopy it is conducted in about half the facilities. Current practice regarding SLD use was observed to be widely divergent from national policy, which prescribes standardised regimens that include only FLDs for both new and retreatment patients. The type and level of health care facility were more important predictors of SLD availability than whether or not they were part of the NTP (i.e., TB centres).

Where SLDs were available for the treatment of MDR-TB, fewer than three classes of SLDs were available in as many as a third of the facilities. We know, from provincial drug resistance surveys in China, that most MDR-TB patients are resistant to at least one other FLD (in addition to INH and RMP), and furthermore, that baseline resistance to SLDs is common, especially in retreatment and MDR-TB patients. For example, in Henan Province, the prevalence of OFX and AMK resistance was respectively 13% and 7% in new, 27% and 21% in retreatment, and 48% and 48% in MDR-TB patients. Regimens should contain at least four drugs with (almost) certain effectiveness to improve the chances of success and prevent amplification of resistance. If the availability and use of SLDs are not changed to meet this minimum requirement, further resistance may be created, potentially leading to XDR-TB.

There are several limitations to our study. The main limitation is that clinics were not randomly selected, and that the largest hospitals were included. Larger hospitals are expected to have greater access to SLDs, which would overestimate SLD availability in our study compared to the national average. However, as SLDs are widely available at all levels, we do not expect this to affect our results greatly. Furthermore, larger hospitals generally treat more patients and thus expose more patients to SLDs. TB centres may be expected to have provided underestimates of SLD availability, as SLD use is not recommended by the NTP. This would mean that actual availability is higher than reported here. Another limitation is that we were unable to obtain precise information on the exact quantities used, but only whether SLDs were available at all.
We requested data on actual use (amount of drugs used in the previous year and actual treatment regimens) but did not receive this, probably because data on amounts used are not easily available and due to reluctance to provide information on regimens that do not follow national policy. We also could not obtain information on why SLDs were used for certain patients. As only a small fraction of the facilities using SLDs provided information on treatment regimens, the results provided may not be representative of all TB clinics.

Due to the low response on treatment regimens, the first author (HG) collected additional data during monitoring visits on the regimens used in the TB hospitals. As these are not part of the NTP, they are expected to provide the most reliable information on regimens used. SLDs were included in the regimen in 83% of 177 reviewed new cases, and in 92% of 96 retreatment cases. In general, in regimens containing SLDs, one or two SLDs were used (96% and 69%, respectively). We do not know whether these results represent other TB facilities, but they do support the findings from this survey on the number of SLDs used in regimens and they indicate that SLDs are used almost routinely for TB treatment in TB hospitals.

Although PMDT has been implemented in China at some pilot sites at the prefecture level, rapid scale-up to the rest of the country is highly desirable. The slow pace of implementation is due to a lack of capacity in some settings: lack of laboratories for diagnosing MDR-TB, problems with the procurement of expensive SLDs, lack of properly trained personnel capable of managing MDR-TB and a lack of infection control in high-density settings. As expansion to the country/district level is not feasible in the near future, we recommend that MDR-TB designated hospitals should be rolled out at the prefecture level to enable expansion of PMDT at the fastest pace possible. Prefectures that do not meet the criteria for the implementation of PMDT should first receive capacity-building support on programmatic management and laboratory and clinical aspects. For lower level TB centres and hospitals, training should ensure adherence to treatment guidelines. At the same time, quality assured DST for FLDs should be rolled out to health care facilities at the provincial and prefecture levels. Drug resistance surveillance and survey results may guide the development of adjusted standardised retreatment regimens, including SLDs, for settings where DST against SLDs is not performed.
CONCLUSIONS

Drugs designated as SLDs for the treatment of TB are widely available in China for the treatment of both TB and other diseases. However, their use is rarely based on DST results. Moreover, testing is rarely quality assured. Measures to limit the irrational use of SLDs should be implemented, monitoring of SLD use should be strengthened and implementation of quality-assured DST and PMDT needs to be scaled up urgently in China to prevent rising drug resistance.

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