

Effect of a comprehensive programme to provide universal access to care for sputum-smear-positive multidrug-resistant tuberculosis in China: a before-and-after study



Renzhong Li*, Yunzhou Ruan*, Qiang Sun*, Xiexiu Wang, Mingting Chen, Hui Zhang, Yanlin Zhao, Jin Zhao, Cheng Chen, Caihong Xu, Wei Su, Yu Pang, Jun Cheng, Junying Chi, Qian Wang, Yunting Fu, Shitong Huan, Lixia Wang, Yu Wang, Daniel P Chin*



Summary

Background China has a quarter of all patients with multidrug-resistant tuberculosis (MDRTB) worldwide, but less than 5% are in quality treatment programmes. In a before-and-after study we aimed to assess the effect of a comprehensive programme to provide universal access to diagnosis, treatment, and follow-up for MDRTB in four Chinese cities (population 18 million).

Methods We designated city-level hospitals in each city to diagnose and treat MDRTB. All patients with smear-positive pulmonary tuberculosis diagnosed in Center for Disease Control (CDC) clinics and hospitals were tested for MDRTB with molecular and conventional drug susceptibility tests. Patients were treated with a 24 month treatment package for MDRTB based on WHO guidelines. Outpatients were referred to the CDC for directly observed therapy. We capped total treatment package cost at US\$4644. Insurance reimbursement and project subsidies limited patients' expenses to 10% of charges for services within the package. We compared data from a 12 month programme period (2011) to those from a retrospective survey of all patients with MDRTB diagnosed in the same cities during a baseline period (2006–09).

Findings 243 patients were diagnosed with MDRTB or rifampicin-resistant tuberculosis during the 12 month programme period compared with 92 patients (equivalent to 24 per year) during the baseline period. 172 (71%) of 243 individuals were enrolled in the programme. Time from specimen collection for resistance testing to treatment initiation decreased by 90% (from median 139 days [IQR 69–207] to 14 days [10–21]), the proportion of patients who started on appropriate drug regimen increased 2.7 times (from nine [35%] of 26 patients treated to 166 [97%] of 172), and follow-up by the CDC after initial hospitalisation increased 24 times (from one [4%] of 23 patients to 163 [99%] of 164 patients). 6 months after starting treatment, the proportion of patients remaining on treatment increased ten times (from two [8%] of 26 patients to 137 [80%] of 172), and 116 (67%) of 172 patients in the programme period had negative cultures or clinical–radiographic improvement. Patients' expenses for hospital admission after MDRTB diagnosis decreased by 78% (from \$796 to \$174), reducing the ratio of patients' expenses to annual household income from 17.6% to 3.5% ($p < 0.0001$ for all comparisons between baseline and programme periods). However, 36 (15%) patients did not start or had to discontinue treatment in the programme period because of financial difficulties.

Interpretation This comprehensive programme substantially increased access to diagnosis, quality treatment, and affordable treatment for MDRTB. The programme could help China to achieve universal access to MDRTB care but greater financial risk protection for patients is needed.

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Introduction

Multidrug-resistant tuberculosis (MDRTB; defined as tuberculosis resistant to both isoniazid and rifampicin) is a global public health problem.¹ In 2009, the World Health Assembly (WHA) passed a resolution urging countries by 2015 to provide all patients with tuberculosis with appropriate care to prevent, diagnose, and treat the disease.² In 2014, the WHA adopted this resolution as part of WHO's post-2015 tuberculosis control strategy.³ However, only a handful of countries seem on track to achieve universal access to MDRTB care by 2015.⁴

The gap to achieve universal access is especially large in India and China, two countries with nearly half of the world's MDRTB cases.⁴ Among the barriers to the scale-up of care for MDRTB are the low number of patients diagnosed, poor quality of treatment, high cost of treatment, and inadequate financing for scale-up.^{5–8} Unless these barriers are addressed in a comprehensive manner, countries are unlikely to achieve universal access to care by 2015.

Although China has achieved impressive reductions in tuberculosis prevalence and mortality during the past

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*Contributed equally

National Center for Tuberculosis Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing, China (R Li MS, Y Ruan PhD, M Chen MS, H Zhang PhD, Y Zhao PhD, J Zhao MS, C Chen MS, C Xu MS, W Su MS, Y Pang PhD, J Cheng MS, J Chi MS, Q Wang MS, Y Fu MS, L Wang MS, Y Wang PhD); Center for Health Management and Policy, Shandong University, Jinan, Shandong, China (Q Sun PhD); Chinese Anti-tuberculosis Association, Beijing, China (X Wang MS); and Bill & Melinda Gates Foundation, China Office, Beijing, China (D P Chin MD, S Huan MS)

Correspondence to:
Dr Yu Wang, Chinese Center for Disease Control and Prevention, Beijing 102206, China
wangyu@chinacdc.cn

20 years, MDRTB has become a serious issue, with more than 100 000 cases developing each year—roughly a quarter of the world's total.^{9,10} In 2011, only 3% of estimated new MDRTB cases were diagnosed and reported and 2% were placed on quality treatment programmes.³ Many patients with tuberculosis, including those with MDRTB, are treated in China's public hospital system. However, these patients are often given non-standard drug regimens,¹¹ resulting in poor treatment outcomes, amplification of drug resistance, and opportunities for further transmission to other individuals. Furthermore, in view of the low protection from financial risk resulting from illness in China,¹² patients with MDRTB almost certainly experience catastrophic health expenses, although this occurrence has not been documented.

Against this backdrop are new opportunities to improve access to care for MDRTB in China. New molecular diagnostics, which have simplified testing for drug resistance, are now available.^{13,14} More importantly, China's health reform efforts aim to improve access to quality health care and increase protection from financial risk. These reforms, including expansion of health insurance coverage, strengthening of primary health care and public health, and reform of public hospitals, have the potential to improve quality of care for MDRTB and provide the financing needed for universal access to care.^{12,15}

Under the guidance of the Chinese Ministry of Health (now known as the National Health and Family Planning Commission [NHFPCC]), we developed a comprehensive programme to provide universal access to care for MDRTB. In an uncontrolled before-and-after study, we aimed to evaluate access to diagnosis, access to quality treatment, and affordability of treatment for MDRTB after implementation of this programme.

Methods

Study design and participants

We selected four medium-size, third-tier cities in China (based on their economic development) to implement our programme. The cities are Hohhot (Inner Mongolia, northern China), Kaifeng (Henan, central China), Lianyungang (Jiangsu, eastern China), and Yongchuan (Chongqing municipality, western China); further details are provided in the appendix. Their size, economic development, and geographic spread make them fairly representative of the situation throughout the country. In 2011, the four cities had a total population of 18 million people residing in 15 urban districts and 17 rural counties. For our programme, we grouped Chongqing's Yongchuan County with four surrounding counties and categorised them as a city unit because Yongchuan is the referral centre for patients with tuberculosis from these other counties, and is one of the larger counties in Chongqing.

All cities have implemented the WHO-recommended directly observed therapy strategy for several years as part

of the Chinese National Tuberculosis Control Program. The baseline period was from Jan 1, 2006, to Oct 31, 2009. The comprehensive programme started at different timepoints between Jan 1, 2011, and May 1, 2011. We included patients with multidrug-resistant or rifampicin-resistant tuberculosis who were consecutively diagnosed in a 12-month period after the programme began in each of the cities.

The study was reviewed and approved by the Tuberculosis Operational Research Ethics Review Committee of the Chinese Ministry of Health. For the comprehensive programme, all patients signed informed consent before the start of treatment.

Programme

We developed a comprehensive programme to expand access to diagnosis, quality treatment, and affordable treatment of MDRTB. Table 1 shows the details of this programme along with information about the previous programme. In each city, we designated one city-level hospital to be responsible for the diagnosis and treatment of MDRTB and other complicated forms of tuberculosis. We equipped the laboratories in these hospitals with rapid molecular testing for isoniazid and rifampicin resistance with the Genechip (Capitabio, Beijing, China), which is only approved for testing of smear-positive or culture-positive specimens. We trained staff in these hospital laboratories to do molecular tests and conventional drug susceptibility tests (for both first-line and second-line tuberculosis drugs).¹⁶ We established collaborative mechanisms between the hospital, the Center for Disease Control and Prevention (CDC), and community health-centre systems to ensure that patients, clinical specimens, and patients' information were not lost as they moved between these systems.

We used a pre-payment mechanism to finance a standard package of services for MDRTB on the basis of WHO guidelines (table 1).¹⁷ The total cost of the clinical package was capped at US\$4644. We used government insurance funding, supplemented by project funding, to limit patient expenses to 10% of package costs. We also developed a public health package of services to better ensure all patients obtained diagnosis and treatment follow-up. These measures included transportation of specimens, free rapid testing for resistance, cash transfer to patients for transportation costs and nutritional supplements, and subsidy for provision of directly observed therapy. We provided roughly \$100 000 in project funding to each city for this package of services and for laboratory equipment, laboratory renovation, staff training, and supervision activities.

Procedures

For the comprehensive programme, we prospectively collected data about patients' characteristics, diagnosis, treatment, follow-up during treatment, treatment outcome, reason for failure to start or continue treatment,

See Online for appendix

hospitalisation charges, insurance payment, and expenses. Because HIV testing is not routinely done in the national tuberculosis control programme, we collected self-reported information about HIV status. In our programme cities, we also retrospectively collected data about all patients diagnosed with MDRTB from Jan 1, 2006, to Oct 31, 2009. In Hohhot, Kaifeng, and Lianyungang, only one hospital in each city (all at the city level) did drug susceptibility testing for *Mycobacterium tuberculosis*; none of the hospitals in Yongchuan did such testing. We reviewed laboratory records in the three hospitals and identified patients with tuberculosis resistant to both isoniazid and rifampicin. Then we reviewed available hospital records of these patients to collect information about diagnosis, treatment, and cost of hospitalisation for these patients.

An expert committee reviewed treatment information to determine whether the drug regimens used were consistent with WHO recommendations.¹⁷ We also reviewed records of the local CDCs to determine if patients were referred to or followed up by the public health system. We also attempted to contact all patients for an in-person interview to collect information about treatment expenses, income, treatment follow-up, and outcome after hospital discharge. Additionally, we collected information about how the cities did diagnosis, treatment, patient referral and follow-up, and insurance reimbursement for MDRTB during 2006–09 (table 1). Financial data were collected in renminbi and then converted to US dollars for analysis. Because the exchange rate decreased during and between our baseline and programme period, we chose to use ¥6.46 to \$1.00

	Baseline approach, 2006–09	Programme approach, 2011
Diagnosis		
CDC	No sputum culture or conventional DST done to diagnose drug resistance	All patients with smear-positive disease had their specimens sent to designated hospital for DST
Hospital	Sputum culture and conventional DST done when patients could pay for them; culture and conventional DST available only in three of four cities	All smear-positive specimens from hospital or CDC patients had rapid molecular testing for rifampicin resistance done at designated city-level hospital for MDRTB diagnosis and treatment; culture and conventional DST for first-line and second-line tuberculosis drugs done on specimens with rifampicin resistance
System linkages	None	Smear-positive sputum specimens transported from CDC to hospital; hospitals notified CDC of resistance testing results
Treatment		
CDC	No MDRTB treatment; all patients with tuberculosis given standard first-line drug treatment (6 month regimen for new cases and 8 month regimen for previously treated cases on the basis of WHO recommendations)	Patients with rifampicin-resistant tuberculosis sent to designated city-level hospital for treatment; patients without rifampicin resistance continued standard first-line drug treatment at CDC
Hospital	Second-line drugs frequently used, with or without documentation of drug resistance; no standard drug regimens or service package for MDRTB; patients admitted to hospital for treatment if they could pay	Patients with rifampicin-resistant tuberculosis (on the basis of rapid molecular testing) started on standard second-line drug regimen as part of a standard treatment package with a clinical algorithm*; as part of standard MDRTB treatment package, all patients initially admitted to hospital for treatment and discharged when stable; if conventional DST later showed patients to not have isoniazid resistance, treatment modified for treatment of mono-rifampicin-resistant tuberculosis*; if second-line-drug DST showed patient had XDRTB or pre-XDRTB, patient switched to another drug regimen*
System linkages	None	After receiving results of resistance testing from hospital, CDC located patients needing MDRTB treatment and referred them to hospital; hospital notified CDC about whether patient arrived at hospital; if patient did not show up at hospital, CDC worked with community or township health centres to track down patients and send them to hospital
Follow-up after hospitalisation		
CDC	No routine follow-up of patients discharged from hospital	Follow-up of all patients with MDRTB after discharge from hospital, then referral of patients to community health-care providers for DOT; follow-up of patients to ensure they returned to hospital for regular outpatient follow-up
Community health centres	Not routinely involved with follow-up of patients discharged from hospital	After referral from CDC, health-care providers at urban community health centres, rural township health centres, and village clinics followed up patients with MDRTB and provided DOT until treatment completion and helped to ensure patients returned to hospital for regular follow-up
Hospital	Patients asked to return to hospital for outpatient follow-up; no systematic follow-up if patient did not return	As part of standard treatment package, patients with MDRTB returned to hospital for regular outpatient follow-up and treatment (every month for first 6 months, then every other month until treatment completion)
System linkages	Hospitals did not routinely notify CDC at time of discharge and refer patients for outpatient follow-up	Hospital notified CDC at time of patient discharge; patients referred to CDC for outpatient follow-up; CDC follow-up for all patients with MDRTB who were referred at the time of hospital discharge; then referral of patients to community health-care providers for DOT; if patients did not return to hospital for regular outpatient follow-up, hospital contacted CDC to trace patient

(Table 1 continues on next page)

	Baseline approach, 2006–09	Programme approach, 2011
(Continued from previous page)		
Cost of services to patients		
CDC	CDC did not provide services for MDRTB	Transport of sputum specimens for resistance testing and the testing itself, including molecular testing and DST if necessary, provided free of charge to patients
Hospital	All services required fee-for-service payment by patients first, then patients sought insurance reimbursement; reimbursement from the three government insurance programmes varies but generally is <30% for inpatient tuberculosis services because second-line drugs are not reimbursable; very limited reimbursement for outpatient services†	A standard MDRTB treatment package negotiated with all three government insurance programmes provided 24 months of treatment (including inpatient and outpatient services and second-line drugs) capped at a total cost of US\$4644†; for services in the MDRTB treatment package, patient payment capped at a maximum of 10% of charges or \$464; insurance covered 40–50% of charges (exact percentages varied by programme and city) with remainder paid by project funding; quality of MDRTB care monitored by CDC; for services outside of the standard MDRTB treatment package, insurance coverage variable but generally about 40%, the rest paid for by patients
Other payments	..	Patients given transportation subsidy of \$15.50 for each outpatient visit to hospital; health-care providers at community health centres, township health centres, and village clinics given a total of \$15.50 per month per patient for providing DOT
<p>MDRTB=multidrug-resistant tuberculosis. CDC=Center for Disease Control and Prevention. DST=drug susceptibility testing. XDRTB=extensively drug-resistant tuberculosis. DOT=directly observed therapy. *All patients with MDRTB started on amikacin, levofloxacin, pyrazinamide, aminosalicylic acid (also known as p-aminosalicylic acid), and prothionamide for 6 months, then levofloxacin, pyrazinamide, aminosalicylic acid, and prothionamide for 18 months. If a patient had a history of previous treatment with an earlier-generation quinolone (eg, ofloxacin, levofloxacin) or amikacin, then moxifloxacin or capreomycin, respectively, were used instead. Those diagnosed with mono-rifampicin resistance were switched to treatment with amikacin, levofloxacin, pyrazinamide, isoniazid, and ethambutol for 6 months, then levofloxacin, pyrazinamide, isoniazid, and ethambutol for 12 months. Those diagnosed with XDRTB were switched to treatment with pyrazinamide, capreomycin, moxifloxacin, aminosalicylic acid, prothionamide, clarithromycin, and amoxicillin-clavulanate for 12 months, then pyrazinamide, moxifloxacin, aminosalicylic acid, prothionamide, clarithromycin, and amoxicillin-clavulanate for 18 months. †There are three government insurance schemes in China: the New Cooperative Medical Scheme for rural residents, the Urban Resident Basic Medical Insurance for urban residents, and the Urban Employee Basic Medical Insurance for urban employees.</p>		
Table 1: Comparison of baseline and programme approaches to MDRTB care		

(the average exchange rate in 2011) for all conversions to eliminate bias from a changing exchange rate.

Statistical analysis

We used a before-and-after analytical approach to assess changes in diagnosis, treatment, and affordability of treatment for MDRTB. One measure of affordability is the percentage of annual household income used to pay for a patient's hospitalisation expenses. We used government data to determine the annual household income for an urban or rural resident in each city; income data for the baseline and pilot period are from 2008 and 2011, respectively. We used rifampicin-resistant tuberculosis cases in the programme period as the comparison group for MDRTB cases in the baseline period, because rifampicin-resistant and MDRTB cases were treated and managed the same way in our programme. We defined time to MDRTB diagnosis as the number of days from submission of specimens for resistance testing to reporting of multidrug or rifampicin resistance back to the submitting institution. We compared continuous variables using Student's *t* test and categorical variables using Pearson χ^2 tests or Fisher's exact tests; two-sided tests with 95% CI were used in all comparisons. Data were entered independently by two people using EpiData software (version 3.1). Statistical analyses were done with SAS version 17.2.

Role of the funding source

Funding was provided by the governments in the four cities and the Bill & Melinda Gates Foundation. The Chinese CDC operates under the general guidance of the

Ministry and was responsible for the design, implementation, and analysis of the study. The Bill & Melinda Gates Foundation participated in analysing the data and preparing the publication. RL, DPC, YR, and QS had complete access to all the data and had responsibility for the decision to submit for publication.

Results

During the baseline period (2006–09), 92 patients were diagnosed with MDRTB in our programme area, averaging 24 patients per year. Eight patients received treatment as outpatients only, no medical records were kept on them, and they were never admitted to hospital. The remaining 84 patients had inpatient records. We reviewed the inpatient medical records of 81 patients (three records could not be located) and interviewed 44 patients. 79 (98%) of 81 patients had smear-positive disease.

In the four cities that implemented our comprehensive programme, 10 106 patients were diagnosed with pulmonary tuberculosis (including 2816 patients with smear-positive disease) over a 12 month period. We collected sputum specimens from 2365 (84%) patients and submitted them for rapid testing of rifampicin resistance. Of these specimens, 2244 (95%) had testing results and 243 (10%) were identified as rifampicin-resistant tuberculosis. In Hohhot, only 305 (52%) of 581 patients had sputum submitted for rapid testing, much lower than the 2060 (92%) of 2235 patients in the other three cities ($p<0.0001$; appendix). These missing data, along with insufficient quantity of sputum remaining after smear examination, accounted for

most of the 16% of patients without specimens submitted.

Of the 243 patients with rifampicin-resistant tuberculosis, 226 (93%) had drug susceptibility test results for isoniazid and 144 were found to have isoniazid resistance; therefore, 6% of individuals with sputum collected were documented to have MDRTB. 172 (71%) patients gave informed consent and were enrolled into our treatment programme. Among those enrolled, second-line results for drug susceptibility test were available for 163 (95%) patients. Of these individuals, ten (6%) had resistance to both ofloxacin and kanamycin (extensively drug-resistant tuberculosis [XDRTB]); another 30 (18%) had resistance to ofloxacin only, and seven (4%) had resistance to kanamycin only. HIV testing was not routinely done but each patient was asked about whether they were HIV positive. All patients self-reported as HIV negative.

Although the two patient cohorts had similar age and gender distributions (table 2), they had several important differences. The programme cohort had significantly more rural residents (as suggested by their insurance source) and most were initially seen in the CDC system. On the basis of self-reported annual household income, rural patients had lower income than urban patients (median \$330 [IQR 114–381] vs \$916 [521–1118], $p < 0.0001$) and CDC patients had lower income than hospital patients (\$315 [129–383] vs \$639 [186–774], $p < 0.0001$). Therefore, our programme patients were probably much poorer than our baseline patients.

The time taken to diagnose MDRTB decreased from a median of 60 days (IQR 40–80) to 7 days (IQR 5–9; difference 88%; table 3). For CDC patients, time to diagnosis included 3 days (IQR 2–5) for sputum specimens to be transported to the hospital.

55 (68%) of 81 patients with hospital records in the baseline cohort were admitted to hospital and placed on tuberculosis treatment after specimens were collected for drug susceptibility testing but before results became available (table 3). By the time a diagnosis of MDRTB became available, 13 patients were still in hospital and thus continued on treatment; however, 42 patients had already been discharged. Of the 26 patients not in hospital at time of diagnosis (including those discharged or not admitted to hospital during diagnosis), 13 were admitted for treatment. Therefore 26 (32%) of 81 patients with inpatient records in the baseline cohort were treated after diagnosis of MDRTB. We could not systematically collect information about why patients were not treated after a diagnosis of MDRTB. Anecdotally, hospital workers cited inability to locate patients and patients' inability to pay for treatment as the main reasons.

In our programme, 172 (71%) of 243 patients started tuberculosis treatment after a diagnosis of MDRTB or rifampicin-resistant tuberculosis, a proportional increase of 2.2 times (32% vs 71%) compared with baseline.

Because of rapid molecular testing, no patients were admitted to hospital and then discharged before diagnosis of rifampicin resistance. 71 (29%) patients did not enrol in our programme because of financial

	Baseline period, 2006–09 (n=92)	Programme period, 2011 (n=243)	p value*
Age (years)	0.64
15–29	11 (12%)	42 (17%)	..
30–44	22 (24%)	61 (25%)	..
45–59	28 (30%)	93 (38%)	..
≥60	20 (22%)	47 (19%)	..
Unknown†	11 (12%)	0 (0%)	..
Gender	0.16
Male	65 (71%)	176 (72%)	..
Female	16 (17%)	67 (28%)	..
Unknown†	11 (12%)	0 (0%)	..
Insurance	<0.0001
Urban workers	26 (28%)	18 (7%)	..
Urban residents	3 (3%)	23 (9%)	..
Rural	11 (12%)	135 (56%)	..
Other	12 (13%)	6 (2%)	..
None	27 (29%)	27 (11%)	..
Unknown†‡	13 (14%)	34 (14%)	..
Years in education
0	NA	33 (14%)	..
1–6	NA	57 (23%)	..
7–9	NA	85 (35%)	..
>9	NA	35 (14%)	..
Unknown‡	NA	33 (14%)	..
Employment status
Employed	NA	45 (19%)	..
Unemployed	NA	170 (70%)	..
Unknown‡	NA	28 (11%)	..
Household income per year (¥)§
0–3000	NA	42 (17%)	..
3000–5000	NA	53 (22%)	..
5000–10 000	NA	35 (14%)	..
>10 000	NA	74 (30%)	..
Unknown‡	NA	39 (16%)	..
Patient category
New	NA	67 (28%)	..
Relapse	NA	69 (28%)	..
Initial treatment failure	NA	16 (7%)	..
Retreatment failure or chronic case	NA	77 (32%)	..
Other	NA	14 (6%)	..

Data are n (%) unless otherwise stated. NA=not applicable. *Statistical test for a categorical table. †Information unknown from the baseline cohort because medical records were not available from three inpatients and all eight outpatients. ‡Information unknown from pilot cohort because these patients were not enrolled into the treatment programme and thus were not interviewed. §Equivalent to US\$0–464, \$465–774, \$775–1548, and >\$1548.

Table 2: Patients' characteristics

	Baseline period, 2006–09	Programme period, 2011	p value
Patients with a diagnosis of MDRTB or rifampicin-resistant tuberculosis	92	243	..
CDC patients	0	152 (63%)	<0.0001
Hospital patients	92 (100%)	91 (37%)	<0.0001
Treatment before and after diagnosis			
Patients with treatment information available*	81	243	..
Treated while waiting for result of resistance testing	55 (68%)	0	<0.0001
Treated after diagnosis of MDRTB or rifampicin-resistant tuberculosis	26 (32%)	172 (71%)	<0.0001
Initial treatment during hospitalisation after diagnosis			
Patients admitted for treatment after diagnosis†	26	171	..
Started on initial standardised treatment regimen for MDRTB‡	9 (35%)	165 (96%)	<0.0001
Treatment results during hospitalisation for treatment after diagnosis†			0.11§
Patients admitted for treatment after diagnosis	26	171	..
Discharged on treatment	23 (88%)	164 (96%)	..
Died on treatment	0	1 (1%)	..
Discontinued treatment because of side-effects	3 (12%)	4 (2%)	..
Discontinued treatment because of financial difficulties	0	2 (1%)	..
Follow-up of patients discharged on treatment			
Hospitalised patients discharged on treatment	23	164	..
Referred to CDC for follow-up	0	164 (100%)	<0.0001
Successfully followed up by CDC	1 (4%)	163 (99%)	<0.0001
Placed on DOT in community	0	156 (95%)	<0.0001
Treatment outcome at 6 months for patients treated after diagnosis			<0.0001§
Patients started on treatment after diagnosis	26	172	..
Still on treatment	2 (8%)	137 (80%)	..
Died	6 (23%)	7 (4%)	..
Defaulted from treatment¶	12 (46%)	3 (2%)	..
Transferred out	0	2 (1%)	..
Discontinued treatment because of side-effects	2 (8%)	10 (6%)	..

(Table 3 continues on next page)

difficulties (26 patients), being too sick or old (16 patients), death before treatment could start (seven patients), distrust of hospital (seven patients), non-qualification for programme because they were non-resident (six patients), miscellaneous reasons (six patients), or reasons not determined (three patients).

Among those who were treated after diagnosis, the median time from collection of specimen for resistance testing to treatment initiation was 139 days (IQR 69–207) in the baseline cohort and 14 days (IQR 10–21) in the programme cohort (a decrease of 90%; table 3). Among those treated after a diagnosis of MDRTB or rifampicin-resistant tuberculosis, the proportion placed on an appropriate initial second-line drug regimen for tuberculosis increased by 2.7 times from 35% of patients (9/26) to 96% (165/172). Among all diagnosed patients with treatment information available (irrespective of treatment initiation), the proportion who started on an appropriate drug regimen after diagnosis of MDRTB or rifampicin-resistant tuberculosis increased by 6.2 times from 11% of patients (9/81) in the baseline cohort to 68% (165/243) in the programme cohort. Of the ten patients in the

programme cohort with XDRTB, nine were switched to an effective treatment regimen a median of 45 days (IQR 45–54) after starting treatment for MDRTB. Similarly, of the 37 patients with pre-extensive drug resistance—ie, those with resistance to either ofloxacin or kanamycin, but not both—35 were switched to an effective regimen for their disease a median of 55 days (IQR 47–64) after starting treatment for MDRTB.

At the time of discharge from hospital for MDRTB treatment, none of the baseline patients was referred to the local CDC for follow-up in the community or placed on directly observed therapy, although one patient presented himself at the CDC after discharge. By contrast, all 164 programme patients were referred at discharge, 163 (99%) were successfully followed up by the CDC, and 156 (95%) were placed on directly observed therapy in the community.

Among patients with MDRTB who started treatment, the proportion still on treatment 6 months after treatment initiation was 8% of patients (2/26) in the baseline cohort and 80% (137/172) in the programme cohort (table 3). This improvement was due to a 91% reduction in the proportion of patients who died or

	Baseline period, 2006–09	Programme period, 2011	p value
(Continued from previous page)			
Discontinued treatment because of financial difficulties	0	8 (5%)	..
Discontinued for other reasons	4 (15%)	5 (3%)	..
Sputum culture conversion at 6 months			
Patients started on treatment after diagnosis	NA	172	..
Culture-negative	NA	108 (63%)	..
Culture-positive	NA	18 (10%)	..
No sputum	NA	8 (5%)	..
Sputum not checked	NA	3 (2%)	..
Days from specimen collection for resistance testing to diagnosis**			
CDC patients	NA	8 (6–11)	..
Hospital patients	60 (40–80)	6 (3–8)	<0.0001
All patients	60 (40–80)	7 (5–9)	<0.0001
Days from diagnosis to start of treatment††			
CDC patients	NA	7 (5–12)	..
Hospital patients	57.5 (0–113)	4 (2–11)	<0.0001
All patients	57.5 (0–113)	6 (3–12)	<0.0001
Days from specimen collection for resistance testing to start of treatment††			
CDC patients	NA	14 (11–21)	..
Hospital patients	139 (69–207)	12 (8–21)	<0.0001
All patients	139 (69–207)	14 (10–21)	<0.0001
Data are n, n (%), or median (IQR). NA=not applicable. CDC=Center for Disease Control and Prevention. DOT=directly observed therapy. MDRTB=multidrug-resistant tuberculosis. *Of the 92 baseline patients, treatment information unavailable from three inpatients and eight patients who were treated only as outpatients. †Of the 172 patients treated during the programme period, one was treated exclusively as an outpatient. ‡Pending results from drug susceptibility testing for second-line drugs, patients started on an initial empiric drug regimen for MDRTB treatment that is consistent with WHO guidelines. §p value for all percentage comparisons. ¶Lost to follow-up and interrupted treatment for at least two consecutive months. Seven patients had both clinical and chest radiographic improvement; one had no change in chest radiograph. **Information about baseline patients is based on 55 patients with complete information on date when specimen was sent for drug susceptibility testing. ††For patients started on treatment after diagnosis of MDRTB or rifampicin-resistant tuberculosis.			

Table 3: Diagnosis, treatment, and follow-up of patients with MDRTB or rifampicin-resistant tuberculosis

defaulted from treatment (from 18 [69%] of 26 to 10 [6%] of 165). Among programme patients, seven (4%) died, ten (6%) discontinued treatment because of side-effects, and eight (5%) discontinued treatment because of financial difficulties. Overall, at 6 months, 108 (63%) of 172 programme patients had negative sputum cultures and eight (5%) had clinical–radiographic improvements even though they had no sputum. The proportion of patients still on treatment at 6 months was lower in Yongchuan than in the other three cities (29 [67%] of 43 vs 108 [84%] of 129, $p=0.022$; appendix).

Among all programme patients diagnosed with rifampicin resistance or MDRTB (irrespective of whether they were treated or not), 36 (15%) did not start or could not continue treatment because of financial difficulties and 15 (6%) died within 6 months. However, the actual proportion of deaths might be higher because another 16 patients were too sick or old to start treatment.

Our programme eliminated the need for hospital admission while waiting for results of resistance testing. During the baseline period, median out-of-pocket patient expenses for this hospitalisation were \$846, which was 21% of the annual household income in our programme area (table 4). Using 10% and 20% of annual household

income as the threshold for catastrophic health expenses,¹⁸ we calculated that 80% (44/55) and 38% (21/55) of patients, respectively, had catastrophic health expenses for this hospital admission alone.

Our programme also reduced the median cost of hospital admission after diagnosis of MDRTB by 30% (\$1135 to \$800; table 4). Because of increased insurance reimbursement and project subsidy, patients' out-of-pocket expenses for this hospital admission were only \$174, which was 3.5% of the annual household income during the programme period. Our programme reduced the proportion of patients with catastrophic health expenses for this hospital admission from 58% (15/26) to 6% (10/171; $p<0.0001$) when 10% of household income was used as the catastrophic threshold,¹⁸ and from 42% (11/26) to 1% (2/171; $p<0.0001$) when the 20% threshold was used.¹⁹ Overall, 68 baseline patients were admitted to hospital during diagnosis, after diagnosis, or both. Of these patients, 56 (82%) had catastrophic expenses from these hospital admissions for the 10% threshold and 33 (49%) had catastrophic health expenses for the 20% threshold.

Because patients' actual household incomes might be lower than average among residents in their cities, we

	Baseline period, 2006–09	Programme period, 2011	p value
Hospitalisation pending results of resistance testing			
Number of patients	55
Average charges per patient (US\$)	1207 (814–1421)
Average number of hospital days per patient	35.6 (22.5–40.5)
Average charges per hospital day (\$)	34 (29–44)
Payment for hospitalisation			
Average insurance payment (\$)	361 (244–425)*
Average insurance payment as a proportion of total payment	29.9%
Average patient out-of-pocket payment (\$)	846 (571–996)
Average patient out-of-pocket payment as a proportion of total payment	70.1%
Patient payment as a proportion of annual household income†	21.0% (10.7–26.9)
Hospitalisation for MDRTB treatment after diagnosis			
Number of patients	26	171	..
Average charges per patient (\$)	1135 (351–1612)	800 (363–993)	0.034
Average number of hospital days per patient	30.5 (8–45)	39 (23–51.5)	0.082
Average charges per hospital day (\$)	37 (26–51)	20 (12–25)	0.001
Payment for hospitalisation			
Average insurance payment (\$)	339 (105–482)*	350 (126–463)	<0.0001
Average insurance payment as a proportion of total payment	29.9%	43.8%	
Average patient out-of-pocket payment (\$)	796 (246–1130)	174 (57–174)	<0.0001
Average patient out-of-pocket payment as a proportion of total payment	70.1%	21.8%	
Average project payment (\$)	..	275 (131–346)	..
Average project payment as a proportion of total payment	..	34.4%	..
Patient payment as a proportion of annual household income†	17.6% (6.2–26.8)	3.5% (1.1–3.9)	<0.0001

Data are median (IQR) unless otherwise stated. MDRTB=multidrug-resistant tuberculosis. *Percent of hospitalisation charges paid by insurance comes from the median percentage ascertained from interview of 44 patients in baseline period. †Each patient's payment for the hospitalisation is divided by the average annual household income of an urban or rural resident in each city for each time period, which is then averaged for all patients.

Table 4: Hospitalisation charges, payment, and financial burden on patients

reanalysed the percentage of patients with catastrophic health expenses using data for patients' self-reported household income. For the hospital admission after a diagnosis of MDRTB, 95 (57%) of our programme patients had catastrophic health expenses (using the 10% threshold). Although self-reported income data are difficult to verify, these results suggest the use of average household income among all residents could lead to underestimation of those with catastrophic expenses.

Of the total hospitalisation charges, \$619 (77%) was for services within the MDRTB treatment package. For charges within the package, patients paid only \$65 (11%) and insurance paid \$278 (45%). For charges outside of the MDRTB treatment package, patients paid an average of \$110 (61%). Overall, 68% of all patient expenses were for services outside of the MDRTB treatment package.

We also reanalysed the financial data using only patients from the three cities that had baseline patients with MDRTB. All of the reductions documented in the four-city analysis were greater in the three-city analysis.

Discussion

This before-and-after analysis of a comprehensive programme shows how China can provide universal access to MDRTB care by simultaneously expanding access to diagnosis, quality treatment, and more affordable care of MDRTB. To our knowledge it is the first programme to demonstrate how the key barriers to MDRTB care can be effectively addressed with new molecular diagnostics, quality treatment, system linkages to ensure continuity of care, and financing by government insurance schemes (panel). Our results are particularly applicable to middle-income countries that have most of the global burden of MDRTB but need to rely on domestic resources to scale-up care for the disease.^{34,35}

Our comprehensive programme successfully expanded access to the diagnosis of smear-positive MDRTB. In a 1 year period, the programme successfully tested 84% of all smear-positive patients with tuberculosis in our programme area for MDRTB or rifampicin resistance. As a result, the programme identified ten times more patients needing treatment for MDRTB than were identified during the baseline period, including many more poor rural patients who would not have been diagnosed without the programme. The programme would have identified even more patients if not for a major problem with submission of sputum specimens in one city and insufficient remaining quantity of sputum after sputum examination in some patients. These problems can be addressed by use of a diagnostic such as Xpert MTB/RIF (Cepheid, Sunnyvale, CA, USA) to replace smear examination in diagnosis of tuberculosis and provide testing of rifampicin resistance—all with the same specimen—at a county-level or district-level laboratory. In our analysis we grouped patients with rifampicin-resistant tuberculosis with those with MDRTB because they need the same treatment. By providing free testing of resistance to all CDC patients, our programme increased access to diagnosis and eventual treatment of MDRTB for poor, rural patients who would otherwise not have made it to a city-level hospital for diagnosis.

Our programme substantially reduced the time to diagnosis of and treatment initiation for smear-positive MDRTB. Reduction of time to treatment initiation is important because a high proportion of patients with MDRTB are lost to follow-up or die while waiting for their diagnosis, especially in high-HIV-prevalence settings.^{36–38} The programme reduced the time to diagnose MDRTB by nearly 90%, from 57 days to 7 days. The programme also reduced the time to treatment initiation by 90%, from 139 days to 14 days. As a result,

the proportion of patients who started treatment after diagnosis more than doubled.

To our knowledge, findings from only two studies have shown the time to treatment initiation when a molecular diagnostic was used to diagnose MDRTB.^{29,30} The investigators reported a treatment delay of 50–55 days for patients with smear-positive MDRTB and attributed it to both laboratory and system delays. The time to treatment initiation for MDRTB in our programme was substantially shorter than the delay reported in these studies. The availability of molecular testing partly accounted for this decrease. But equally important was our effort to implement new linkage mechanisms between the CDC and the hospital systems, which improved, for example, specimen transportation, reporting of test results, and CDC referral of patients with MDRTB to hospitals. Although simple, these system linkages were very important to the success of our programme.

Our comprehensive programme also expanded access to quality treatment for MDRTB. Among those started on treatment, our programme increased the proportion who started on an initial WHO-recommended drug regimen from a third to nearly all patients. If a programme expands access to treatment but initial treatment quality is poor, both patients and the public at large could be harmed by the development of more serious forms of drug-resistant tuberculosis, such as XDRTB.^{39,40} Through the use of a clinical pathway, with CDC staff monitoring adherence to clinical protocols, our programme largely eliminated the use of improper initial treatments. Additionally, we used drug susceptibility testing to identify patients with XDRTB and eventually started them on appropriate treatment.

Improvement in treatment quality extended to follow-up in the community. At the time of hospital discharge, our programme referred all patients to the local CDC for outpatient follow-up and directly observed therapy. Such referrals and follow-up are examples of effective system linkages, which were not in place during the baseline period. In a meta-analysis, directly observed therapy and follow-up by a community health worker were associated with decreased risk of defaulting from treatment for MDRTB.²⁰ We also provided transportation and food subsidies. Thus, our programme incorporated several best practices of community care for patients with tuberculosis.

Because of improved treatment quality, our programme substantially improved treatment outcome at the end of 6 months. The proportion of patients still on treatment at 6 months increased nine times, mainly due to a 90% reduction in the proportion of patients who defaulted or died. Only 2% of our patients had defaulted by 6 months, which compares favourably with the 15% proportion of treatment default reported in other treatment programmes for MDRTB (even though these programmes measured default over 18–24 months of

Panel: Research in context

Systematic review

We reviewed the scientific literature on multidrug-resistant tuberculosis (MDRTB) and molecular diagnosis, treatment, and affordability of care. We used as our starting point five systematic reviews and meta-analyses on molecular diagnostics for MDRTB published between 2008 and 2014, and five systematic reviews and meta-analyses on MDRTB treatment published between 2009 and 2013.^{13,20–28} We supplemented these by searching PubMed with the terms “multidrug-resistant tuberculosis” for English-language articles published from Jan 1, 2010, to Jan 31, 2014. We looked for articles relevant to our topics of interest. Additionally, using PubMed, we looked for English-language articles published from Jan 1, 2000, to Jan 31, 2014, containing the terms “multidrug-resistant tuberculosis” and any of the following: “insurance”, “financial protection”, “affordability”, “patient cost”, “economic burden”, or “universal access”.

Interpretation

There are many publications about molecular testing for drug-resistant tuberculosis, but they exclusively describe test performance in laboratory or field conditions. There are also publications comparing time to diagnosis for molecular versus conventional drug susceptibility tests. However, we found only two studies that compared time to treatment initiation for MDRTB for cases diagnosed with molecular versus conventional drug susceptibility tests.^{29,30} There are many publications on MDRTB treatment. All of them are observational studies and reported treatment outcome for patient cohorts in a variety of settings. We did not find any publications that compared treatment outcome for MDRTB diagnosed with molecular versus conventional drug susceptibility tests. There are several descriptions of successful programme models for MDRTB. Most publications came from programme models in Russia, Peru, and the Philippines.^{31–33} These programmes were initially called directly observed therapy, short-course plus and later changed to be known as programmatic management of drug-resistant tuberculosis (PMDT). We did not find any publications on use of insurance funding for or affordability of MDRTB treatment. Many of the programme components believed to be important for a successful PMDT have been reported previously. However, very few studies quantified the effectiveness of system linkages such as patient referral or follow-up as in our study. In addition, our study is the first to report the effects of molecular diagnostics on patient outcome and financial burden, and also the first to describe the use of a pre-payment mechanism for MDRTB.

treatment).²⁰ Overall, nearly 70% of our patients had documented improvement by 6 months after starting treatment, similar to other quality treatment programmes for MDRTB globally.^{21,22}

Before our programme, out-of-pocket expenses for MDRTB treatment were very high. While awaiting results of conventional drug susceptibility test, most baseline patients with MDRTB were admitted to hospital for a month and at discharge paid more than \$800 in medical expenses. When a confirmed diagnosis of MDRTB became available another month later, only a third of these patients received MDRTB treatment and were admitted to hospital; they paid a further \$800 in medical expenses. The out-of-pocket expenses for each of these hospitalisations were roughly 20% of the annual household income of local residents. When a household's health expenses reach 10% of its annual income, the World Bank considers this catastrophic.¹⁸ Among baseline patients who were hospitalised during the diagnostic or early treatment period, or both, over

80% had catastrophic health expenses. Even if one uses 20% of household income as a more conservative threshold,¹⁹ half of these patients had catastrophic expenses.

Our comprehensive programme successfully reduced patient expenses for MDRTB treatment and made treatment more affordable. Through the use of rapid resistance testing and improved referral between the CDC and hospital systems, our programme eliminated the need for hospitalisation pending results of resistance testing, thus reducing patient expenses. Our programme also reduced the patient expenses for treatment after MDRTB diagnosis. We achieved this by using a standard MDRTB treatment package of services to control medical cost, capping the charges for the 2-year treatment course at \$4644, and reducing patient expenses to 10% of the medical charges for the treatment package through increased insurance funding and project funding. As a result, the patient expenses for hospitalisation after MDRTB diagnosis were reduced to \$174, which was only 3.5% of the annual household income for residents in our study area. This greatly reduced the percentage of patients with catastrophic health expenses for initial hospital treatment of MDRTB.

Although we improved the affordability of MDRTB treatment, it is unlikely that our programme eliminated catastrophic health expenses for those with MDRTB. An important finding in our study was that 15% of patients in our programme could not start or had to discontinue MDRTB treatment because of financial difficulties. Our analysis of patient expenses for MDRTB did not include expenses for treatment of comorbidities and non-medical costs of illness such as lost income and transportation cost.⁴¹ Additionally, many patients had already incurred substantial expenses for unsuccessful treatments in the past. Therefore the cumulative expenses incurred could have reached catastrophic level for many more patients. Furthermore, we used the average household income of local residents to calculate catastrophic health expenses when patients with tuberculosis are generally poorer. Therefore we could have underestimated the proportion of patients with catastrophic health expenses.

On the basis of results from this programme, the NHFPC has secured funding to scale-up different aspects of this programme nationwide, thus enhancing its sustainability. First, free MDRTB testing with molecular diagnostics will be expanded to more than 30% of Chinese cities in 2014. Second, our standard package of MDRTB care has been adopted for nationwide use. Third, the NHFPC has already designated MDRTB as one of eight priority diseases eligible for 70% reimbursement in the government's rural insurance programme. However, because our results showed that insurance reimbursement for MDRTB should exceed 90%, the NHFPC has tapped

into the country's social protection fund for the poorest segment of the population and is using it to provide additional financial assistance for the poorest patients. Nevertheless, more funding will be needed to ensure the sustainability of this programme, including, for instance, funding for training, laboratory renovation, and cash transfer payments to patients for transportation and nutrition supplements.

Our study has important lessons for other countries with high MDRTB burden as they seek to expand access to MDRTB care. First, our programme demonstrated that the benefits of molecular diagnostics for MDRTB extended beyond making a more rapid diagnosis. Molecular testing also shortened the time to treatment initiation, reduced loss to follow-up after diagnosis, and increased affordability of treatment. Second, an effective MDRTB programme should include government funding for public health elements that can ensure universal diagnosis, system linkages, and continuity of care. In our programme, these elements included specimen transport, free testing for tuberculosis resistance, following up of patients in the community, directly observed therapy, and cash transfer to patients for transportation fees and nutritional supplements. Governments should separately fund these items as a form of public good. Third, the use of a pre-payment mechanism to finance MDRTB treatment can facilitate access by minimising medical expenses at the point of care and reduce catastrophic health expenses. To our knowledge this programme is the first to describe how a government insurance scheme can finance an effective MDRTB treatment programme. However, our use of initial hospitalisation for all patients with MDRTB may not apply to all settings. China has sufficient hospital beds to accommodate a scale-up of this programme, but other countries might not.

Our study has several limitations. First, the programme identified smear-positive but not smear-negative MDRTB cases because the Genechip diagnostic can only be used in smear-positive or culture-positive specimens. However, our programme has all the other elements needed to expand treatment to these smear-negative MDRTB cases. For instance, the current insurance reimbursement for MDRTB is not restricted to individuals with smear-positive disease, nor are any of the other programme activities such as initiation of a WHO-recommended treatment regimen or successful referral for follow-up in the community. Therefore, once a reliable rapid test to detect rifampicin resistance in smear-negative specimens is available in China, our programme can easily expand to cover all MDRTB cases. Second, the use of a before-and-after study design means that temporal improvements in quality of health services or the involvement of researchers (the so-called Hawthorne effect) could have resulted in some of the improvements in this study; our study also did not include contemporaneous controls. Third, the amount

and quality of our baseline data were restricted by the information available in hospital records, by difficulty in locating patients for interview, and by recall bias. For example, HIV-positivity could have been biased by self-report. However, better-quality data are unlikely to change our key findings and conclusions. Fourth, there was substantial delay in provision of patients with XDRTB with appropriate treatment. In the future, the availability of rapid resistance testing to other key second-line tuberculosis drugs will ensure that those with XDRTB in our programme are started on appropriate treatment much earlier.

Finally, the results of this programme are striking when viewed from a population-based perspective. Before our programme, in a population of 18 million people, we identified only two patients with MDRTB over a period of nearly 4 years who were properly diagnosed, started on appropriate treatment, and still on treatment 6 months later—an average of less than one patient per year. Our programme increased the number of such patients more than 100 times. On the one hand, this scenario provides a glimpse into why MDRTB is such a serious public health problem in China. On the other, it shows the potential of our comprehensive programme to substantially reduce the morbidity, mortality, and transmission of MDRTB in a country with one of the largest MDRTB epidemics in the world.

Contributors

All authors participated in the design of the study and were involved in the implementation of the study. Data analysis was done by LR, YR, SQ, and DPC. DPC wrote the first draft of the paper and all authors reviewed and provided input into the final submitted version.

Declaration of interests

We declare no competing interests.

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