

## Screening of patients with tuberculosis for diabetes mellitus in China

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### Abstract

**OBJECTIVE** There is a high burden of both diabetes (DM) and tuberculosis (TB) in China, and this study aimed to assess feasibility and results of screening patients with TB for DM within the routine healthcare setting of six health facilities.

**METHOD** Agreement on how to screen, monitor and record was reached in May 2011 at a stakeholders' meeting, and training was carried out for staff in the six facilities in July 2011. Implementation started in September 2011, and we report on 7 months of activities up to 31 March 2012.

**RESULTS** There were 8886 registered patients with TB. They were first asked whether they had DM. If the answer was no, they were screened with a random blood glucose (RBG) followed by fasting blood glucose (FBG) in those with RBG  $\geq 6.1$  mm (one facility) or with an initial FBG (five facilities). Those with FBG  $\geq 7.0$  mm were referred to DM clinics for diagnostic confirmation with a second FBG. Altogether, 1090 (12.4%) patients with DM were identified, of whom 863 (9.7%) had a known diagnosis of DM. Of 8023 patients who needed screening for DM, 7947 (99%) were screened. This resulted in a new diagnosis of DM in 227 patients (2.9% of screened patients), and of these, 226 were enrolled to DM care. In addition, 575 (7.8%) persons had impaired fasting glucose (FBG 6.1 to  $<7.0$  mm). Prevalence of DM was significantly higher in patients in health facilities serving urban populations (14.0%) than rural populations (10.6%) and higher in hospital patients (13.5%) than those attending TB clinics (8.5%).

**CONCLUSION** This pilot project shows that it is feasible to screen patients with TB for DM in the routine setting, resulting in a high yield of patients with known and newly diagnosed disease. Free blood tests for glucose measurement and integration of TB and DM services may improve the diagnosis and management of dually affected patients.

**keywords** tuberculosis, diabetes mellitus, screening, China

### Introduction

China is a country with 1.3 billion people (or 18.5% of the world population) and has the second largest number of tuberculosis (TB) cases (estimated at 0.9–1.2 million per annum) in the world (WHO 2011a). China follows the 'DOTS' model for TB control and, over the last 20 years, has had much success in reducing the burden of disease

caused by TB. Case detection rates are above 85%, and treatment success rates in patients with new smear-positive pulmonary tuberculosis (PTB) are above 90%. However, TB is still a major public health problem, and rates of multidrug resistant TB (MDR-TB = resistance to both isoniazid and rifampicin) are high, with 6% of new cases and 26% of retreatment cases estimated to have MDR-TB (WHO 2011a).

As a consequence of population growth, ageing, changed lifestyle and urbanisation, the country has also witnessed an escalating epidemic of diabetes mellitus (DM) (Danaei *et al.* 2011; International Diabetes Federation 2011; Alcorn & Ouyang 2012). Available data suggest that an estimated 10% of people above the age of 15 years have DM, with about half of those in rural areas and one-third in urban areas being unaware of the problem. A recent study in a nationally representative sample of over 46 000 adults confirms these estimates, giving a figure of 92 million adults with DM and 148 million with pre-diabetes (Yang *et al.* 2010).

A number of literature reviews, including systematic reviews and meta-analyses, have shown that people with DM have a significantly increased risk of developing active TB, which is 2–3 times higher than in those with no DM (Stevenson *et al.* 2007; Jeon & Murray 2008; Dooley & Chaisson 2009; Ruslami *et al.* 2010). DM patients with TB also appear to experience worse treatment outcomes than patients with no DM, with delays in sputum culture conversion, an increased risk of death and an increased risk of recurrent disease after successful completion of treatment (Baker *et al.* 2011). Despite a good national TB programme, it is likely that in a country such as China, the diabetes epidemic is hampering TB control efforts. Currently, routine screening and reporting of patients with TB for DM in China does not take place even though the links between the two diseases are recognised.

In high HIV–TB burden countries, HIV testing and counselling is the gateway to HIV prevention and care for co-infected patients with TB, and the ways by which this screening and reporting are performed have largely been worked out (Harries *et al.* 2011). Given the current burden of DM in China, patients with TB would merit being screened for DM. A recently launched World Health Organization (WHO)-Union Framework for Collaborative activities to reduce the dual burden of DM and TB recommends bidirectional screening of the two diseases (WHO & IUATLD 2011). However, how this is best performed and carried out in routine healthcare settings is not known, and this knowledge gap needs to be addressed (Jeon *et al.* 2010).

In China, a standardised procedure for screening patients with TB for DM, a monitoring tool linked to the TB registration system and quarterly system of reporting were developed and agreed upon in the first half of 2011 with implementation starting in the second half of the year. This article describes the implementation, monitoring, results and challenges of screening patients with TB for DM within routine healthcare settings in the country.

## Methods

This was a prospective observational implementation project carried out in six TB clinics/hospitals within the routine health services in China.

As a result of support from the World Diabetes Foundation (WDF), a national stakeholders meeting was held in Beijing, China, in May 2011, between the Union, WHO, the World Diabetes Foundation (WDF) and national diabetes, non-communicable disease and TB authorities to review and discuss linkages between DM and TB, the need for bidirectional screening and the WHO-Union Collaborative Framework. Broad guidelines for how the screening should be performed were worked out: five sites were selected for screening patients with DM for TB (the subject of a different paper), and 6 different sites were selected for screening patients with TB for DM. These six sites were Xinjiang Chest Hospital; Anding District CDC TB Clinic; Number 1 and Number 2 TB Clinics of Guangzhou Chest Hospital; Shandong Chest Hospital; and Shenyang Chest Hospital (Figure 1). Details of the hospitals and TB clinics are shown in Table 1. The TB clinic/hospitals were selected because of their geographical locations (north-west [Xinjiang Chest Hospital and Anding District CDC], north-east [Shenyang Chest Hospital], south [Guangzhou Chest Hospital], east [Shandong Chest Hospital]), high prevalence of pulmonary TB in the surrounding communities and urban–rural mix.

In July 2011, a training workshop was held with healthcare staff from the six sites to share standardised guidelines for screening and referral of patients, and monitoring and reporting the data. Registers and cohort reporting forms were developed and printed and distributed to the study sites. Staff officers returned to their health facilities and provided in-service training for staff working in the clinics. Implementation of activities started in September 2011. It was agreed that data would be reported in quarterly cohorts: Q3-2011 (September); Q4-2011 (October to December); and Q1-2012 (January to March).

Patients included all persons aged 15 years and older who were consecutively diagnosed and registered with TB from 1 September 2011 up to 31 March 2012.

Every patient with confirmed TB started anti-TB treatment immediately. Treatment regimens and anti-TB drug formulations were in accordance with those recommended by WHO (WHO 2009) and in line with National TB Control Guidelines (Ministry of Health and Chinese Centre on TB Control and Prevention 2008). The screening for DM followed national guidelines that stipulate that a fasting blood glucose (FBG) is carried out using venous plasma and biochemical analyser with cut-off thresholds in



**Figure 1** Map of China indicating where the six facilities are situated.

**Table 1** Details of the six hospitals involved in the pilot study in China

	Xinjiang Chest Hospital	Anding District CDC TB Clinic	Number 1 Clinic of Guangzhou Hospital	Number 2 Clinic of Guangzhou Hospital	Shandong Chest Hospital	Shenyang Chest Hospital
Number of Hospital Beds	300	0	0	0	680	800
Number of daily outpatient visits	170	20	200	100	200	450
Number of daily TB patient visits	110	20	200	100	100	40
Number of TB doctors	139	2	16	9	30	72
Number of TB Nurses	167	0	31	20	72	144
Main source of patients	Rural	Rural	Urban and migrant population	Urban and migrant population	Urban and rural	Urban
Sites to where DM suspects are referred	DM/TB clinic at the same hospital	Dingxi Number 2 Hospital	Hospital authorised by medical insurance contract	Hospital authorised by medical insurance contract	Jinan Central Hospital	DM/TB clinic at the same hospital
Distance of DM clinic from TB clinic (Km)	Not applicable	1.0	Variable	Variable	0.5	Not applicable

TB, tuberculosis; DM, diabetes mellitus.

line with those recommended by the WHO (WHO 2006). In brief, FBG  $\geq 7.0$  mm (126 mg/dl) indicates DM; FBG of between 6.1 and  $<7.0$  mm (110 to  $<126$  mg/dl) indicates

impaired fasting glucose; FBG  $< 6.1$  mm (110 mg/dl) is normal. Sites determined whether to (i) first screen patients with a random blood glucose (RBG) followed by FBG at

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the next visit if the RBG was  $\geq 6.1$  mm (110 mg/dl) or (ii) screen patients just with FBG. If patients with TB were found to have FBG  $\geq 7.0$  mm, the patients were referred to diabetes services for a definitive diagnosis of DM by measuring a second FBG, and if this was  $\geq 7.0$  mm, the diagnosis was confirmed (although it was understood that this diagnosis may include stress-induced temporary hyperglycaemia). Tests for blood glucose had to be paid for by the patient (about USD\$1.6–1.8 per test). Whether DM was confirmed or excluded at the diabetes clinic, the patients were referred back to the TB clinic for continued anti-TB treatment.

Tuberculosis patients with newly diagnosed DM were to be enrolled into DM care. Patients with TB with known DM were already in diabetes care, but if their blood glucose levels were high at the time of TB registration, they were referred back for better management.

A parallel register (Figure 2) was developed for recording data about whether the patient was already known to have DM and was under DM care. If the patient had no known history of DM, screening was carried out with RBG/FBG as described earlier. Patients with newly diagnosed DM were to be enrolled to diabetes services, and this information was captured in the parallel register. The DM register was linked to the patient TB register through the TB registration number, which was recorded in both sets of documents.

Standardised quarterly report forms were developed and used for the recording of screening data. These were compiled by TB clinic staff 30 days after the end of the quarter to allow for the collection of data from diabetes clinics. Reports were kept at the facilities and also sent to

the Union China Office and TB clinical centre of the China Centre for Disease Control (CDC) for collation. Supervision and site visits were carried out by staff of the Union China Office and the TB clinical centre of the China CDC early on during the period of the study.

Individual patient data were received and cross-checked by staff of the Union China Office and the TB clinical centre of the China CDC, then double entered to an EXCEL file and analysed. Comparisons between groups were made using the chi-squared test, and odds ratios (OR) were calculated where appropriate with 95% confidence intervals (CI). The level of significance was set at 5%.

National authorities in China stipulated that this was a pilot project aiming to test the feasibility of the DM screening approach amongst patients with TB with a view to learning lessons for national scale up. As such, formal ethics approval in China was deemed not to be necessary. However, permission to use, report and publish the collected data was obtained from the Union Ethics Advisory Group, Paris, France.

**Results**

In Number 2 TB Clinic of Guangzhou Chest Hospital, screening was carried out first with RBG followed by FBG for those with a blood glucose  $\geq 6.1$  mm (110 mg/dl). Results for the three quarterly periods combined are shown in Table 2. All 541 patients were screened according to guidelines: 3.3% of patients had a known diagnosis of DM and were receiving DM care, and 3.2% of those tested had a new diagnosis of DM. All patients with newly diagnosed DM were enrolled to DM care. Five patients

Quarter and Year	TB Reg. Number	Name	Known DM Y/N	Screen with RBG Date	Result of RBG	Screen with FBG Date	Result of FBG	New DM Y/N	Known or New DM Y/N	New or Known DM referred to DM care Date	New DM enrolled to DM care Date

**Figure 2** Register of Diabetes (DM) screening in patients with TB. Ten rows per page (therefore ten patients per page). DM, diabetes mellitus; TB, tuberculosis; RBG, Random Blood Glucose; FBG, Fasting Blood Glucose. If answer to ‘Known DM’ is No, then screen for DM. If RBG  $\geq 6.1$  mm (110 mg/dl), do second screen with FBG at next visit. If FBG  $\geq 7.0$  mm (126 mg/dl), then refer to DM services for the confirmation of diagnosis of DM. Refer all new patients with Diabetes and known patients with Diabetes to Diabetes care.

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had impaired FBG with blood glucose levels between 6.1 and <7.0 mm.

In the other five clinics/hospitals, screening was carried out with an initial FBG. Results for the facilities and for the three quarterly periods combined are shown in Table 3. Of 8345 patients, 10.1% had a known diagnosis of DM and were receiving DM care. Of the remaining 7500 patients, 7361 (98%) were screened with FBG. One hundred thirty-nine patients refused to be screened for reasons not formally ascertained. Of those screened, 282 were found to have FBG  $\geq 7.0$  mm of whom 210 (2.9% of those screened) were confirmed to have DM on subsequent testing at the diabetes clinic. All patients with newly diagnosed DM except one were enrolled in DM care. Five hundred seventy patients had impaired FBG with blood glucose levels between 6.1 and <7.0 mm.

In the three facilities serving a predominately urban population (Shenyang and the two clinics of Guangzhou), the prevalence of DM (new and known) was 13.8%, which was significantly higher than in the two facilities serving a predominantly rural population (Anding and Xinjiang) where the prevalence of DM (new and known) was 10.6% [OR 1.35, 95% CI 1.16–1.57,  $P < 0.001$ ]. In the one facility with a mixed urban–rural population (Shandong), the prevalence of DM (new and known) was 8.8%. In the

three hospitals, the prevalence of DM (new and known) was 12.9%, which was significantly higher than the DM prevalence of 8.5% found in the three TB clinics (OR 1.61, 95% CI 1.30–2.00,  $P < 0.001$ ).

Results for DM screening and diagnosis in patients with TB for quarter 3-2011, quarter 4-2011 and quarter 1-2012 for all six facilities combined are shown in Table 4. In total, there were 8886 patients consecutively registered for TB, of whom 1090 (12.4%) were diagnosed with DM (863 with known DM and 227 with new DM). Although no action was taken on patients with FBG between 6.1 and <7.0 mm, 575 (7.8%) of 7884 patients with TB screened had FBG results in this range, indicating they had impaired fasting blood glucose. For each of the quarters, between 9% and 10% of patients were found to have a known diagnosis of DM, over 98% of patients not known to have DM were screened, and of those screened between 2.5% and 3.5% were found to have newly diagnosed DM. Although some of these proportions between the quarters were statistically different, these were not of clinical or public health significance.

## Discussion

This is the first study reported from China about routine implementation of screening patients with TB for DM. The overall prevalence of DM in patients with TB was 12.4%. Health facilities serving urban populations and hospitals had a higher prevalence of DM compared with health facilities serving rural populations and clinics, respectively. The majority of patients were already known to have DM, probably a high proportion compared with many other high TB burden countries. However, nearly 3% of those screened were found to have new DM, and if it had not been for the screening process, these patients would not have been identified. If DM screening was scaled up nationwide and implemented at the high levels of performance achieved in this pilot project, a prevalence of 3% of 1 million patients with TB translates to 30 000 new DM cases diagnosed each year, which is an important contribution to case finding of DM.

If this pilot project was scaled up countrywide, another 78 000 (7.8%) new cases could be identified as having impaired fasting glucose, an indicator for future high risk of DM and also future morbidity such as stroke (Lee *et al.* 2012; Perreault *et al.* 2012). While some of this may be attributed to stress hyperglycaemia because of TB comorbidity, it is nonetheless an indicator of future risk. Lifestyle counselling, health promotion and follow-up may prevent or delay the onset of DM in a substantial number of these cases (Perreault *et al.* 2012). Given that patients with TB anyway are counselled on healthy diet, avoidance of

**Table 2** Screening patients with TB for DM at Number 2 Clinic in Guangzhou Chest Hospital: data combined for the three quarters

Registered patients with TB screened for and diagnosed with DM	Number
Number of patients with TB registered over the three quarters	541
Number (%) with known diagnosis of DM	18 (3.3%)
Number needing to be screened with RBG	523
Number (%) screened with RBG	523 (100%)
Number with RBG $\geq 6.1$ mm and needing to be screened with FBG	54
Number screened with FBG	54 (100%)
FBG results	
FBG < 6.1 mm	32
FBG 6.1 to 7.0 mm	5
FBG $\geq 7.0$ mm	17
Number with FBG $\geq 7.0$ mm referred to DM services	17
Number (%) newly diagnosed with DM*	17 (3.2%)
Number (%) patients with newly diagnosed DM enrolled to DM care	17 (100%)
Number (%) with known or newly diagnosed DM	35 (6.5%)

TB, tuberculosis; DM, diabetes mellitus; RBG, random blood glucose; FBG, fasting blood glucose.

\*Percentage of screened patients with TB with a new diagnosis of DM.

**Table 3** Screening patients with TB for DM at the five other health facilities in China: data combined for the three quarters

Registered patients with TB screened and diagnosed with DM	Anding TB Clinic	No. 1. Clinic Guangzhou	Shandong Hospital	Shenyang Hospital	Xinjiang Hospital	Total
Number of patients with TB registered over the three quarters	185	545	1060	4240	2315	8345
Number (%) with known diagnosis of DM	6 (3.2%)	46 (8.4%)	64 (6.0%)	533 (12.6%)	196 (8.5%)	845 (10.1%)
Number needing to be screened with FBG	179	499	996	3707	2119	7500
Number screened with FBG	168 (93.9%)	493 (98.8%)	995 (99.9%)	3586 (96.7%)	2119 (100%)	7361 (98.1%)
FBG results						
FBG < 6.1 mm	149	438	896	3082	1944	6509
FBG 6.1 to 7.0 mm	15	37	67	336	115	570
FBG ≥ 7.0 mm	4	18	32	168	60	282
Number with FBG ≥ 7.0 mm referred to DM services	4	18	32	168	60	282
Number (%) newly diagnosed with DM*	2 (1.2%)	18 (3.7%)	29 (2.9%)	101 (2.8%)	60 (2.8%)	210 (2.9%)
Number (%) patients with newly diagnosed DM enrolled to DM care	2 (100%)	17 (94%)	29 (100%)	101 (100%)	60 (100%)	209 (99.5%)
Number (%) with known or newly diagnosed DM	8 (4.3%)	64 (11.9%)	93 (8.8%)	634 (15.4%)	256 (11.1%)	1055 (13.0%)

TB, tuberculosis; DM, diabetes mellitus; RBG, random blood glucose; FBG, fasting blood glucose.

\*Percentage of screened patients with TB with a new diagnosis of DM.

**Table 4** Screening of patients with TB for DM in quarter 3-2011, quarter 4-2011, and quarter 1-2012: data combined for the 6 facilities

Registered patients with TB screened and diagnosed with DM	Q3-2011	Q4-2011	Q1-2012	Total
Number of patients with TB registered in the quarter	1406	3676	3804	8886
Number with known diagnosis of DM	132 (9.4%)	344 (9.4%)	387 (10.2%)	863 (9.7%)
Number who should have been screened for DM (either RBG or FBG)	1274	3332	3417	8023
Number who were screened for DM (either RBG or FBG)	1270 (99.7%)	3311 (99.4%)	3366 (98.6%)	7947 (99.1%)
Number newly diagnosed with DM*	33 (2.6%)	78 (2.4%)	116 (3.4%)	227 (2.9%)
Number with known or newly diagnosed DM	165 (11.4%)	422 (11.5%)	503 (13.4%)	1090 (12.4%)

TB, tuberculosis; DM, diabetes mellitus; RBG, random blood glucose; FBG, fasting blood glucose

\*Percentage of screened patients with TB with a new diagnosis of DM.

smoking, harmful use of alcohol and increasing outdoor physical activity, linking this advice at no or marginal additional costs would be beneficial in an overall public health strategy to prevent DM.

While the prevalence rate of 12.4% DM amongst patients with TB found in this study is 28% higher than the 9.7% prevalence of DM reported in the large China national survey (Yang *et al.* 2010), the latter was based on a 2-h 75-g oral glucose tolerance test rather than FBG. In the national survey by Yang *et al.*, 47% of patients with a diagnosis of DM had normal FBG, and by extrapolation, this suggests that the TB cohorts would have had about twice the prevalence of DM as the general adult population if they had been screened with an oral glucose tolerance

test. Similarly, the 7.8% rate of impaired fasting glucose in patients with TB is more than 3 times higher than in the national study. Any serious comparisons would require further adjustments for age, body mass index and socio-economic status that influence DM prevalence – all likely to be lower for the TB cohort than the general population. Such comparative analysis needs further data extraction and research and was not the purpose of this study.

All new patients were enrolled to DM care. Although data were not formally captured in this study, round table discussions with healthcare staff indicated that those with known DM were already in care and those with elevated blood glucose levels were referred back earlier to their diabetes services for improved treatment and management.

Again, if screening was scaled up nationally, this would mean 124 000 patients with DM (known and new) being referred for care and treatment of their endocrine disease, which would not only benefit their diabetes but might improve TB treatment outcomes.

Screening procedures, either by RBG followed by FBG or initially by FBG alone, were equally acceptable in each of the sites, and the few patients who did not undergo blood tests either felt they were well enough not to need further blood tests or were concerned about costs of laboratory investigations. There appeared to be no particular problems with TB healthcare staff collecting data on blood glucose results, and some initial problems with understanding how the quarterly forms should be completed were solved through site supervision that took place just before the end of the first quarter.

One of the important problems with the screening process, which is undertaken soon after TB registration and at the start of anti-TB treatment, is that TB may induce infection-related hyperglycaemia. In four studies assessing blood glucose levels at multiple points during the course of anti-TB treatment (Kishore *et al.* 1973; Goyal *et al.* 1978; Singh *et al.* 1984; Oluboyo & Erasmus 1990), the prevalence of hyperglycaemia decreased over time, leading to the suggestion that screening should occur later on or after TB treatment has been completed or false-positive DM diagnoses might occur. This may be the explanation of why some patients initially found to have FBG  $\geq 7.0$  mm were not confirmed as having DM with subsequent tests. However, we feel it is better to err on the side of over-diagnosis of DM and screen, diagnose and refer earlier on in the course of TB treatment because this allows opportunities to intervene and better control DM and influence TB treatment outcomes. We are unsure of the implications or the best management approach for the significant number of patients with TB (nearly 8%) with impaired FBG, and this is an area needing further research. Providing lifestyle counselling as indicated above is one such credible option.

Although referral of TB cases for the confirmation of diagnosis and enrolment into DM care was managed well in this pilot project, this is an area in need of improvement. In the context of HIV-associated TB, different geographical locations of HIV and TB clinics pose problems for the timely referral of cases for appropriate care and management (Lawn & Wood 2012), while integration of services appears to be the most efficient model both from the health services' and patients' point of view (Howard & El-Sadr 2010). Given the scale of the two diseases in China, colocation and integration of services should be considered with TB healthcare staff cross-trained in DM care and management so that dually affected patients can be cared for within the same clinic until their

TB disease is cured. This approach would also best fit China's current strategy of decentralisation where at the primary healthcare level, the two diseases would be managed within the same clinic.

The strengths of this study are that we implemented screening within the routine system, and no special budget was set aside for the implementation of this activity. The six sites have already decided to continue with the current approach, and other sites are being considered for the expansion of this screening activity. In our opinion, this approach provides substantial public health benefits, not least of which is the start of cooperation and collaboration between communicable disease and non-communicable disease programmes. The cost of the blood test for glucose measurement, although only between USD \$1.6 and 1.8, is still an issue, and we would like to advocate that for patients with TB, who often come from poor communities, these costs are met by the health services rather than out of pocket for the patient.

Limitations include some of the problems discussed above, such as the difficulties in knowing whether a high FBG in the context of TB means true DM disease or infection-induced hyperglycaemia. Further research in this area, possibly with tests such as glycosylated haemoglobin (HbA<sub>1C</sub>) or oral glucose tolerance tests, is needed. Measurement of HbA<sub>1C</sub> provides an index of blood glucose levels over a period of 2–3 months and is not subject to the rapid swings that can occur with random and fasting blood glucose measurements (International Expert Committee 2009; Kumar *et al.* 2010; WHO 2011b). Further prospective research is also needed to assess the effect of better DM control on TB treatment outcomes and whether this leads to a decrease in the reported risk of recurrent TB (Baker *et al.* 2011).

## Conclusion

With the launch of the WHO and Union Collaborative Framework for the care and control of Diabetes and Tuberculosis, it is important that countries with a high dual burden of the two diseases work out how best to screen for each disease and manage detected cases within the routine health services. Screening for DM in TB clinics should lead to better and earlier detection of DM, earlier and better treatment of DM (which might have gone unrecognised) and improved clinical outcomes on anti-TB treatment. This pilot project shows the way and should be of benefit not only for China but also for the global community.

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