## **RESEARCH ARTICLE**

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# Multidrug-resistant tuberculosis (MDR-TB) disease burden in China: a systematic review and spatio-temporal analysis

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#### **Abstract**

**Background:** Surveillance data on the proportion of incident TB cases with MDR was limited and there is no systematic study of MDR-TB in China to date. Our aim was to estimate MDR-TB disease burden in 2012 and change trends during 2003–2012 using spatio-temporal systematic analysis.

**Methods:** We systematically searched Chinese and English databases for primary articles and reviews that contain MDR-TB survey data about China during the period of 2003–2012. We estimated the proportion of incident TB cases with MDR in cities which had no data to report in 2012 by Kriging spatial interpolation analysis. The primary outcomes were the proportion of incident TB cases with MDR at 2012 and the change trend during 2003–2012.

**Results:** Total 487 articles met the screening criteria, including 450 in Chinese and 37 in English, and have been used in analysis. The proportion of incident TB cases with MDR among all cases in 2012 showed clear geographic differences. From 2003 to 2012, the proportion of incident TB cases with MDR in all, new and previously treated TB cases were higher during 2006–2009 and significantly lower during 2010–2012 in comparison with the period during 2003–2005 (*P* < 0.0167). The estimated median proportion of incident TB cases with MDR among all cases, as well as in new and previously treated cases in 2012 was 12.8% (IQR 9.8–17.3%), 5.4% (4.5–7.3%) and 28.5% (20.5–30.9%) respectively, which led to an estimate of 121,600 (IQR93,000–164,350) MDR-TB cases in China.

**Conclusions:** This estimate of MDR-TB burden is considerably higher than data reported by the Chinese fifth national tuberculosis epidemiological sampling survey in 2010 but close to the WHO report, which implies that detailed investigations of MDR-TB burden in China is needed. This research provides data to guide public health decisions at various scales; methods described here can be extended to estimate of the other chronic diseases as well.

**Keywords:** Multidrug-resistant tuberculosis (MDR-TB), Disease burden, Spatio-temporal analysis, Systems analysis, Kriging interpolation

#### **Background**

Based on data emerging from drug resistance surveys and continuous surveillance among notified TB cases, the Global Tuberculosis Report suggested that, globally, an estimated 3.3% of new TB cases and 20% of previously treated cases were infected with Multidrug-resistant tuberculosis (MDR-TB) in 2014 [1]. An estimated 480,000

The Chinese government has been involved in extensive efforts to prevent and control MDR-TB. In 2006, China initiated the fifth round of the Global Fund

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people who developed MDR-TB and 190,000 people died of MDR-TB; with more than half of them (54%) occurring in India, China and the Russian Federation. The number of MDR-TB patients in China followed India and ranked second in the world. The report estimated that 5.7% (4.5–7.0%) incident TB cases with MDR among new cases and 26%(22–30%) among previously treated cases in China [1].

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tuberculosis (TB) project in Hebei, Jilin, Jiangsu, Yunnan, Guangxi, Sichuan, and Shaanxi province to target at MDR-TB specifically [2]. During 2007–2008, the Ministry of Health organized a nationwide baseline survey for TB drug resistance [3], and the results indicated that the prevalence of MDR-TB was 8.32% (95%CI, 7.13 to 9.70) with 120,000 new MDR-TB cases occurring every year, which estimated about 110,000(95%CI, 97,000 to 130,000) new MDR-TB cases occurring every year, which accounted for about a quarter of the globally total number of new MDR-TB cases in a year. The fifth national tuberculosis epidemiological sampling survey in 2010 suggested that the total proportion of incident TB cases with MDR was 6.8%, with 5.4% of new cases and 15.4% of previously treated cases [4].

MDR-TB patients need at least 24 months of treatment in general and the severe cases may need 36 months of treatment, however, the cure rate is only around 50 to 60% [5–8], which makes the economic burden of MDR-TB as high as 10–100 times comparing with non MDR-TB cases [9, 10]. MDR-TB takes longer to treat with second-line drugs, which are more expensive and have more side-effects [11].

Therefore, to control the proportion of incident TB cases with MDR is a top public health priority in China [12].

However, very few cases were tested for TB sensitivity at present time in China, for example, only 280 cases completed TB sensitivity test in the fifth national tuberculosis epidemiological sampling survey in 2010 [4], indicating the survey may not represent whole MDR-TB epidemic. Another important nationwide baseline survey for TB drug resistance in 2007–2008 has lasted 7 years [3], so reliable estimate of the proportion of incident TB cases with MDR is essential to prevent and control MDR-TB. Spatio-temporal analysis refers to the spatial distribution and changing trends with time of the proportion of incident TB cases with MDR [13]. In this study, we aimed to update the estimate of MDR-TB burden in China by a spatio-temporal systematic analysis across 2003–2012.

#### Methods

MDR-TB is defined as TB disease caused by organisms that are resistant to isoniazid and rifampicin, two major first-line anti-TB drugs. We divided MDR-TB case into three groups: all cases, new cases, and previously treated cases. The new case is defined as a patient who has received no or less than 1 month of anti-tuberculosis treatment, the previously treated case is defined as a patient who has been treated for 1 month or longer using anti-tuberculosis medication, and the all case was defined as an MDR-TB case regardless of the treatment history [5].

The proportion of incident TB cases with MDR equaled the number of MDR divided by the total number of culture-positive mycobacterium tuberculosis (MTB), multiplied by 100%. We have calculated it for three groups (all, new, and previously treated cases) based on the articles reports respectively.

### Data source and study design

We systematically searched Chinese CNKI, WANGFANG DATA, VIP databases and English PubMed, and Web of Science databases for primary articles and reviews. The search keywords were 'multidrug-resistant tuberculosis' or 'drug-resistant tuberculosis' (Appendix 1). We contacted authors for additional information if the information in the articles was not clearly presented.

MDR-TB burden was analyzed and evaluated by fivesteps. First, we acquired and screened the proportion of incident TB cases with MDR at provincial and city level respectively through articles retrieval. Second, we classified the proportion of incident TB cases with MDR into three groups (all cases, new cases and the previously treated cases) at the provincial and city level. Third, we estimated the proportion of incident TB cases with MDR based on provincial level. If this data was absent in certain regions in 2012, we used data from 2011 or 2010 considering of 2-3 years treatment duration for MDR-TB and the proportion was unlikely to change significantly within 2–3 years. Fourth, we estimated the proportion in cities during 2012 using the Kriging spatial interpolation analysis method. The primary outcomes were the proportion of incident TB cases with MDR in 2012 and the change trend during 2003–2012.

## Selection and exclusion criteria

Below we describe the selection criteria for the study. The study area included China's provinces and cities; we considered studies from Jan. 1, 2003 to Dec. 31, 2012. Second, articles was required to include survey time, area, the number of TB cases which tested for TB resistance, MDR-TB case numbers, resistance test methods and standards of classification. When several surveys were all conducted in same area, we kept only the most informative one.

We excluded the articles which contained duplicate information, or the sample size less than 50. We also excluded the articles describing tests that were carried out for specific populations, such as the elderly, children, prisoners and migrants; the articles describing MDR-TB patient co-infected with other diseases, such as HIV, and diabetes also were also excluded.

Data extracted from each article included: survey area, time of the drug resistance test, number of TB cases which received drug susceptibility testing for isoniazid and rifampicin, the number of MDR-TB cases. MDR-TB data was further classified into all cases, new cases and the previously treated case respectively.

Two investigators were independently responsible for data selection, exclusion, and extraction; if there was disagreement, a discussion to agreement would follow; if this failed, a third person was invited to make the judgment.

#### Statistical analysis

There were abundant dataset in the eastern and central areas of China, so we estimated the proportion of incident TB cases with MDR at city level (or scale) which had not been report in 2012 by Kriging spatial interpolation analysis in those areas. Kriging spatial interpolation analysis is a classical geostatistical analysis method and based on rules of space at correlation quantize between the sample points, which we can calculate the proportion of incident TB cases with MDR for no data area by using the known sample points area [14-16], the cross validation method can improve the accuracy of prediction. There are scarce data available in the western area, therefore, the spatial interpolation analysis was conducted only in eastern and central area, and used the provincial data in the western areas to estimate the MDR-TB for nationwide.

Considering the stability of the proportion of incident TB cases with MDR at a short period and the data is rarely in same area in different year during 2003-2012, so we classified the 10 years into three periods: 2003-2005, 2006-2009and 2010-2012. There are two reasons that the years 2005 and 2009 were chosen to define the time periods: in 2002, the largest TB project worldwide was launched by the Chinese government to reinvigorate DOTS, and the government (national, provincial, and rural counties) increased funding on TB control nationwide from 2003 [2, 17]; in 2005, China fulfilled its commitment to the WHO to detecting 70% of all new smear-positive cases and to successfully treat 85% of these cases nationwide; On July. 13, 2009, the Ministry of Health of China and the Bill & Melinda Gates Foundation initiated a TB control project in Beijing [17]. Therefore, the years 2003, 2005 and 2009 indicate meaningful time points for TB prevention and control in China.

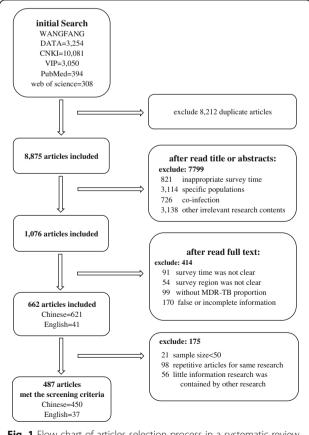
Change of the proportion of incident TB cases with MDR in the three periods was examined separately using the multiple chi-square tests using SPSS 22.0 (IBM). The P-value has a new criterion in the multiple testing, our article involves three pairs comparisons, so the criterion was 0.05/3 = 0.167, when P < 0.167, we could get the conclusion: the differences were significant.

#### Results

Total 487 articles met the screening criteria, with 450 in Chinese and 37 in English (Fig. 1), among them, 288 were concerned new cases of MDR-TB, 297 reported previously treated cases of MDR-TB and 436 involved all cases of MDR-TB. Table 1 demonstrated the spatial distribution of articles in 31 provinces (see detail distribution of the number of TB and MDR-TB cases in 31 provinces in Appendix 2).

The median of estimated the proportion of incident TB cases with MDR among all cases, new cases and previously treated cases in 2012 was 12.8% (IQR 9.8–17.3%), 5.4% (4.5–7.3%) and 28.5% (20.5–30.9%) respectively, the number of TB cases was 0.95million in 2012 according to the data from The Data-center of China Public Health Science (Chinese Center for Disease Control and Prevention, CDC), which led to an estimate of 121,600 (IQR93,000–164,350) MDR-TB cases in China.

Figure 2a, b and c showed the proportion of incident TB cases with MDR among all cases based on city level (scale); among them, Fig. 2a showed the proportion of incident TB cases with MDR obtained from articles reports, the white blank areas refer to no data available;



**Fig. 1** Flow chart of articles selection process in a systematic review of the proportion of incident TB cases with MDR in China

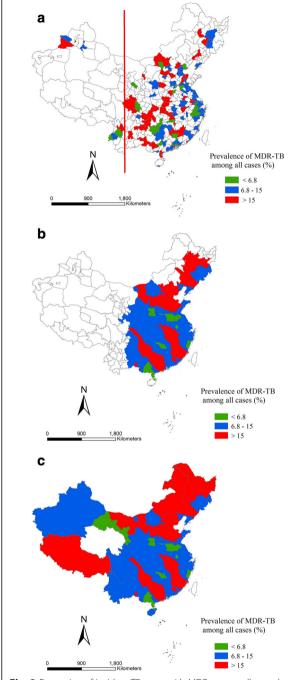
Table 1 the number of articles, the proportion of incident TB cases with MDR in 31 provinces

Area	Articles num	nber		the proportion of incident TB cases with MDR (%)				
	all cases new cases		previously treated cases	all cases	new cases	previously treated cases		
Anhui	23	8 8		15.04 4.5		35.61		
Beijing	13	10	11	27.82	11.36	35.09		
Chekiang	38	31	33	6.6	2.97	28.62		
Chongqing	11	7	6	17.72	5.5	26.06		
Fujian	15	13	12	9.77	4.63	19.69		
Gansu	1	1	1	4.2	3.52	4.67		
Guangdong	29	24	24	9.31	6.07	31.11		
Guangxi	15	13	14	10.8	4.63	25.53		
Guizhou	15	7	8	15.64	4.64	31.14		
Hainan	1	1	1	13.49	5.1	29.91		
Hebei	15	11	10	12.34	5.33	36.37		
Heilongjiang	10	8	7	15.1	6.96	30.2		
Henan	27	16	16	11.08	4.03	19.45		
Hubei	18	14	17	24.27	4.47	22.37		
Hunan	16	10	9	10.59	4.75	28.87		
Jiangsu	30	22	22	16.92	5.5	29.3		
Jiangxi	8	4	5	17.36	9.35	21.16		
Jilin	13	5	6	18.59	2.94	13.71		
Liaoning	11	10	9	17.41	6.52	29.36		
Mongolia	4	2	2	29.03	7.38	39.71		
Ningxia	7	4	4	9.56	7.69	28.4		
Qinghai	0	0	0	nodata	nodata	nodata		
Shaanxi	10	4	6	12.02	7.74	12.09		
Shandong	22	12	12	12.99	5.73	32.64		
Shanghai	21	11	13	7.1	3.38	20.28		
Shanxi	8	5	5	12.68	4.43	43.02		
Sichuan	18	9	10	8.47	4.62	28.22		
Tianjin	7	6	6	13.64	9.09	22.73		
Tibet	1	1	1	29.8	20.69	56.6		
Xinjiang	20	12	12	8.63	7.21	11.82		
Yunnan	9	7	7	10	12	14		

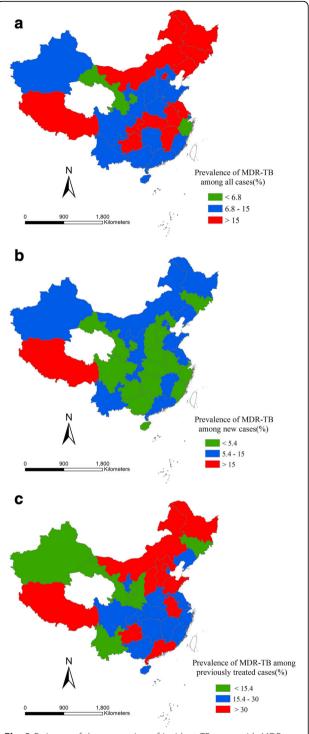
Fig. 2b presented the Kriging interpolation results. We used Ordinary Kriging method and selected Exponential Function as covariance model according the characteristics of data and this model have a higher accuracy after we tried other models, the case of 127(59%) areas were used to estimate the overall numbers of cases. We did the Kriging interpolation analysis only in eastern and central area (right side of red line in Fig. 2a) since fewer dataset was available in western areas; Fig. 2c showed that the proportion of incident TB cases with MDR in nationwide, We used the provincial data in Fig. 3 to make up the west blank area to estimate the proportion of incident TB cases with MDR

in nationwide. Therefore, the proportion of incident TB cases with MDR of western regions in Fig. 2c was the provincial data from Fig. 3a, and the proportion of incident TB cases with MDR of eastern and central area in Fig. 2c was the Kriging interpolation result from Fig. 2b. All spatial analysis was run in ArcGIS 10.2 (ESRI).

There was a clearly geographic difference of the proportion of incident TB cases with MDR among all cases in 2012 at provincial level (scale), with 4.2–6.8% in 2 provinces, 6.8–15% in other 16 provinces and 15–30% in 12 provinces (Fig. 3a). For the new cases, the proportion was 3–5.4% in 15 provinces,



**Fig. 2** Proportion of incident TB cases with MDR among all cases based on city level. **a** Proportion of incident TB cases with MDR obtained from articles reports, the white blank areas refer to no data available. **b** Kriging interpolation result. We did the Kriging interpolation analysis only in eastern and central area (right side of red line in Fig. 2a) since fewer data was available in western areas. **c** Estimate the proportion of incident TB cases with MDR in nationwide. We used the provincial date in Fig. 3 to make up the west blank area to estimate the proportion of incident TB cases with MDR in nationwide. Therefore, the proportion of incident TB cases with MDR of western region in Fig. 2c was the provincial data from Fig. 3a, and the proportion of incident TB cases with MDR of eastern and central area in Fig. 2c was the Kriging interpolation result from Fig. 2b

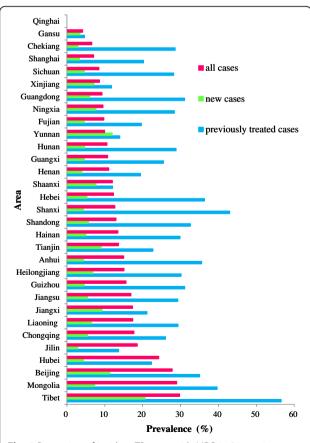


**Fig. 3** Estimate of the proportion of incident TB cases with MDR based on provincial level. **a** Proportion of incident TB cases with MDR among all cases. **b** Proportion of incident TB cases with MDR among new cases. **c** Proportion of incident TB cases with MDR among previously treated cases

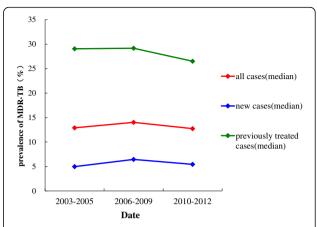
5.4–15% in 14 provinces and 15–21% in 1 province (Fig. 3b). For the previously treated cases, 4.6–15.4% in 5 provinces, 15.4–30% in 15 provinces and 30–57% in 10 provinces (Fig. 3c). It is unclear whether Tibet should be included in the high burden region for new, previously treated and all cases, as only one article report in Tibet was found, which included 198 cases (see detail in Fig. 4, Table 1).

During the period from 2003 to 2012, the proportion of incident TB cases with MDR among all, new and previously treated TB cases were all higher during 2006–2009 period and significantly lower during 2010–2012 period compared with 2003–2005 (P < 0.167), the proportion of incident TB cases with MDR among previously treated cases was statistically significant higher than that of new cases (P < 0.167). (Fig. 5, Tables 2 and 3).

Complete dataset available only on 26 provinces out of 31 provinces around the country; and those datasets were used to represent nationwide data. The spatial distribution maps concerning the three groups in three periods are presented in Figs. 6, 7, and 8.



**Fig. 4** Proportion of incident TB cases with MDR in 31 provinces among all cases, new cases, previously treated cases



**Fig. 5** Change trend of the proportion of incident TB cases with MDR. The blue line showed the change trend among new cases in three periods (2003–2005, 2006–2009, 2010–2012); The green line showed the change trend among previously treated TB cases in three periods; The red line showed the change trend among all cases in three periods

## **Discussion and conclusions**

The study results indicate that the proportion of incident TB cases with MDR in China is higher than other international regions [1]. Factors contributing to the high burden may include economic development, poor knowledge and side effects of TB treatment, poor quality DOTS, lack of coordination of medical services, unsatisfactory supervision of treatment and poor infection control [18–21].

The estimates results in our study are higher than the results in the fifth national tuberculosis epidemiological sampling survey in 2010 [4] (12.8vs.6.8% in all cases, 5.4 vs.5.4% in new TB cases; 28.5 vs.15.4% in the previously treated cases). The difference may be due to small sampling size in the sample survey which only provided susceptible test for 280 TB cases, including 241 new cases and 39 previously treated cases.

While, our estimated the proportion of incident TB cases with MDR among new cases and previously treated cases were close to the result from Global tuberculosis Report in 2013, 5.4% (4.5–7.3%) vs. 5.7% (4.5–7.0%) in new TB cases; 28.5% (20.5–30.9%) vs.26% (22–30%) in the previously treated cases. There was no information concerning the proportion of incident TB cases with MDR among all cases in Global tuberculosis Report [1].

It is not a surprise that, our study reveals substantial spatial differences in MDR-TB burden, consistent with previous work [17]. We believe that the difference might be linked to factors including local economy, education, population density and mobility, ethnic minority populations, and distribution of relevant diseases (such as

Date	all cases					new cases				previously treated cases					
	Article number	TB cases	MDR cases	Proportion (%)	IQR (%)	Article number	TB cases	MDR cases	Proportion (%)	IQR (%)	Article number	TB cases	MDR cases	Proportion (%)	IQR (%)
2003- 2005	92	61,363	7,846	12.89	9.21– 19.5	70	36,707	2,039	4.98	3.6- 8.64	65	10,983	3,001	29.06	20.2- 42.65
2006- 2009	181	129,058	18,807	14.02	11.23- 19.78	105	42,743	3,056	6.45	5.18– 10.58	105	16,875	5,022	29.17	25.24– 37.02
2010- 2012	167	132,929	16,725	12.74	9.6– 18.88	112	67,927	3,348	5.44	4.41- 7.72	124	23,304	5,783	26.51	19.6– 30.21

Table 2 The number of articles, TB cases, MDR-TB cases, the proportion of incident TB cases with MDR in three periods

HIV/AIDS) based on geographic features. The high burden provinces, Guangdong, Anhui, Jiangsu and Hebei are good examples for relevant disease of AIDS and density of population [22]. Guangdong has much more complicated factors, such as large migrant population [23].

Our study also indicates that the proportion of incident TB cases with MDR among all TB cases had a significantly higher during 2006-2009 periods and then showed a decreased change during 2010-2012 compared with 2003-2005. The high rate of discovery of TB cases stimulated by the TB project worldwide and the Chinese government's commitment to detecting 70% of all new smear-positive cases and successfully treat 85% of these cases nationwide contribute to the increase of proportion during 2006-2009. This increase is clearly resulted from the significant efforts of the Chinese government to prevent and control TB by launching a series of policies in past decades, and not a real aggravation of MDR-TB burden in China [17]. Following the implementation of policies concerning TB prevention and control, a decline of the proportion of incident TB cases with MDR would be expected.

The proportion of incident TB cases with MDR differed significantly among the three groups. The new case group was an epidemiological index which better reflect the effectiveness of TB control in recent times. The previously treated case group was a mixed index which is a reflection of both TB control conditions and treatment efficacy in the past [24]. According our estimates, in the past 10 years, our

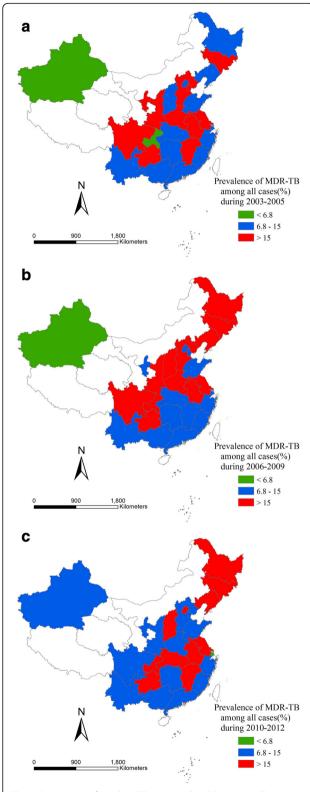
research results show that the proportion of incident TB cases with MDR among new cases has only little change, among previously treated case was shown to be on the decline, but the proportion was extremely higher than that of new cases. Therefore, we should strengthen the drug management of MDR-TB patients, and programmatic management of multidrug-resistant tuberculosis (MDR-TB), including standardized high quality DST for patients, especially in high MDR-TB burden regions [25].

Our study has several strengths. First, the search strategy covered several databases and reported in two languages which involved all provinces except for Qinghai; in addition data for Hong Kong, Taiwan and Macao were also unavailable, which reveals national MDR-TB burden. Second, we propose a spatial systematic analysis by using Kriging's interpolation method which relies on available data and predict the absence of data from some cities in China. Such analysis would improve local estimates as well as reduce uncertainty in regional and national estimates. The national quantitative map presented here illustrates distribution of the proportion of incident TB cases with MDR. This study is the first attempt to quantify the national burden of MDR-TB in China.

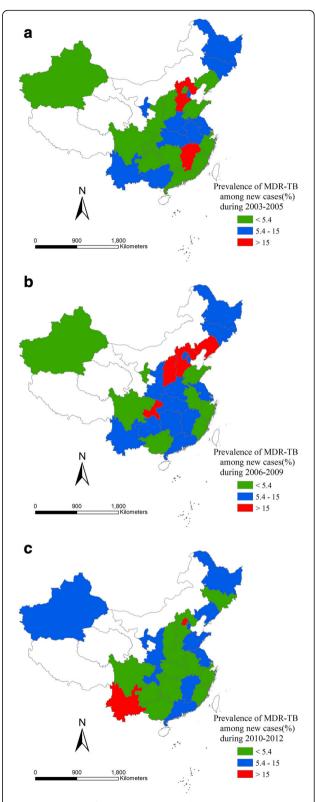
Although we used the strict search strategy and quality control as soon as possible, there still maybe some potential (major) source of bias in this article. First, the DOTS strategy has a significant impact on the prevalence of MDR-TB, although China has realized 100% complete coverage for DOTS strategy in 2007 [26], the implement quality of DOTS strategy have differences in

**Table 3** The chi square test results of three periods in three groups

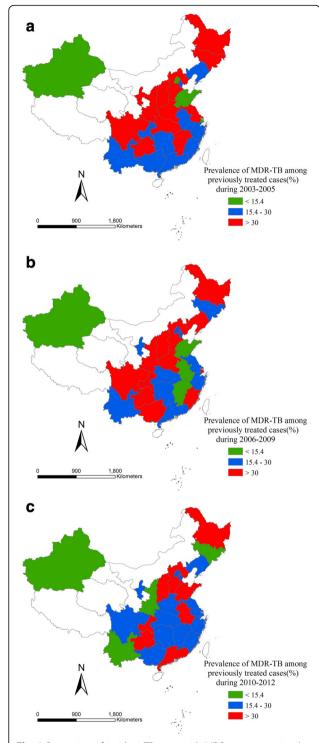
Date	All cases		New cases		The previously treated cases		
	$\chi^2$	P value	$\chi^2$	P value	$\chi^2$	P value	
2003–2005 compared with 2006–2009	110.242	0.000	83.841	0.000	19.252	0.000	
2006–2009 compared with 2010–2012	221.338	0.000	237.354	0.000	121.712	0.000	
2003–2005 compared with 2010–2012	1.586	0.208	19.121	0.000	24.652	0.000	



**Fig. 6** Proportion of incident TB cases with MDR among all cases in three periods. **a** Proportion of incident TB cases with MDR among all cases in 2003–2005. **b** Proportion of incident TB cases with MDR among all cases in 2006–2009. **c** Proportion of incident TB cases with MDR among all cases in 2010–2012



**Fig. 7** Proportion of incident TB cases with MDR among new cases in three periods. **a** Proportion of incident TB cases with MDR among new cases in 2003–2005. **b** Proportion of incident TB cases with MDR among new cases in 2006–2009. **c** Proportion of incident TB cases with MDR among new cases in 2010–2012



**Fig. 8** Proportion of incident TB cases with MDR among previously treated cases in three periods. **a** Proportion of incident TB cases with MDR among previously treated cases in 2003–2005. **b** Proportion of incident TB cases with MDR among previously treated cases in 2006–2009. **c** Proportion of incident TB cases with MDR among previously treated cases in 2010–2012

different areas of China, especially in the poor economic areas [27, 28]; Second, since eligible published reports were not available for all of the 31 provinces/ municipalities, and not every study explored MDR-TB in all three groups and three periods, therefore, we only carried out change trend analysis in the data rich area and spatial interpolation analysis in central and eastern regions based on city scale; Third, due to the geographical, historical and cultural factors [29, 30], few articles reports about the proportion of TB cases with MDR in the Western areas of China, and the missing data of western regions may affect the reliability of our study result, therefore, we have to use provincial centers data to estimate the entire province based on there was no other data sources in these areas; Without long-term nationwide surveillance data, the results obtained here are so far the best data source to show the proportion of incident TB cases with MDR among China in the past 10 years.

These bias will hopefully encourage other investigators to conduct further prospective studies, which include the collection of high quality epidemiological and microbiological surveillance data, the monitoring of change trends of the proportion of incident TB cases with MDR, and the detection of key groups of people for further research and improved TB control in the future [21].

Our research concerning the proportion of incident TB cases with MDR provides an initial assessment of the MDR-TB disease burden in China. Although research is limited by the data source, it sheds light on the prevalence and change trends of the proportion in China. Detailed investigations of MDR-TB burden are needed in China; this research provides a valuable tool to guide public health decisions at various scales and can be extended to estimates of the other chronic diseases.

# **Appendix 1**Search strategy

We applied the PRISMA guidelines for this systematic review.

We systematically searched Chinese CNKI, WANG-FANG DATA, VIP databases and English PubMed, and Web of Science databases for primary articles and reviews. The search keyword was 'multidrug-resistant tuberculosis' or 'drug-resistant tuberculosis'. In fact, in the process of search, we search all articles contains 'multidrug-resistant tuberculosis' or 'drug-resistant tuberculosis' in the full text to avoid miss articles. Articles were also searched manually and, if required and when it was feasible, authors were contacted directly for unpublished data and additional information.

## Appendix 2

**Table 4** Distribution of the number of cases

Areas	date	TB Case			MDR-TB Case			
		all	new	previously treated	all	new	previously treated	
Anhui	2012	7,388	2,599	994	1,111	117	354	
Beijing	2012	417	88	57	116	10	20	
Chekiang	2012	11,216	9,439	1,887	740	280	540	
Chongqing	2012	6,054	2,091	495	1,073	115	129	
Fujian	2012	4,462	1,834	523	436	85	103	
Gansu	2012	834	341	493	35	12	23	
Guangdong	2012	7,033	4,758	1,305	655	289	406	
Guangxi	2012	3,111	2,181	936	336	101	239	
Guizhou	2012	2,481	474	334	388	22	104	
Hainan	2012	126	1,196	341	17	61	102	
Hebei	2012	3,971	2,927	866	490	156	315	
Heilongjiang	2012	1,437	819	351	217	57	106	
Henan	2012	3,502	1,813	622	388	73	121	
Hubei	2012	5,938	2,060	2,097	1,441	92	469	
Hunan	2012	1,180	547	239	125	26	69	
Jilin	2012	1,818	102	890	338	3	122	
Jiangsu	2012	9,058	5,531	1,536	1,533	304	450	
Jiangxi	2012	1,365	813	189	237	76	40	
Liaoning	2012	2,860	1,580	780	498	103	229	
Mongolia	2012	2,556	610	1,040	742	45	413	
Ningxia	2012	2,092	91	169	200	7	48	
Qinghai	2012	nodata	nodata	nodata	nodata	nodata	nodata	
Shaanxi	2012	1,165	4,238	513	140	328	62	
Shandong	2012	3,379	646	432	439	37	141	
Shanghai	2012	13,934	9,702	1,277	990	328	259	
Shanxi	2012	891	609	172	113	27	74	
Sichuan	2012	2,656	2,012	489	225	93	138	
Tianjin	2012	1,393	385	88	190	35	20	
Tibet	2012	198	116	53	59	24	30	
Xinjiang	2012	1,714	749	533	148	54	63	
Yunnan	2012	694	152	36	113	7	5	

# **Appendix 3**List of references for the 487 studies

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#### Abbreviations

CDC: Chinese Center for Disease Control and Prevention; CNKI: China National Knowledge Infrastructure; DOTS: Directly-Observed Treatment Strategy; ESRI: Environmental Systems Research Institute; MDR-TB: Multidrugresistant tuberculosis; MTB: Mycobacterium tuberculosis; TB: Tuberculosis; WHO: World Health Organization

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#### Availability of data and materials

All data analyzed during this study are included in the published articles which all listed in Appendix 3, and the further datasets were available from the corresponding author on reasonable request.

#### Authors' contributions

Professor ZHL and ZWJ designed this work; PPD analyzed the data and wrote the draft; ZHL, ZWJ, XWL and PPD explained the results; ZHL, ZWJ and PPD wrote the final manuscript; PPD prepared the protocol for the review. All authors agreed to submit the paper. All authors contributed to critical revision of the article, and approved the final version.

#### Competing interests

We declared we have no conflicts of interest.

#### Consent for publication

Not applicable

#### Ethics approval and consent to participate

The work is based on data from public publication, and did not access individual information, so we could not pursue ethics approval and consent. We added ethics declaration.

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