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Supplementary appendix

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ONLINE SUPPLEMENT

SUPER-BUGS THREATEN GLOBAL TB CONTROL: FROM EXTENSIVELY DRUG-RESISTANT (XDR-TB) TO UNTREATABLE TUBERCULOSIS – STATE OF THE ART

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Molecular epidemiology of XDR and TDR tuberculosis

Intensive longitudinal studies have demonstrated that treatment in the absence of routine drug susceptibility testing was the underlying cause of the emergence of XDR-TB in different settings in South Africa [1, 2]. This in turn was exacerbated by the implementation of the WHO-recommended standardised MDR treatment regimen, which failed to recognise the association between ethambutol [3, 4], pyrazinamide [5, 6] and ethionamide resistance [7] and MDR-TB. These programmatic errors have led to the selection of distinct XDR-TB strain genotypes in the different South African provinces [8-11] and in Portugal [12]. Subsequent to the emergence of XDR-TB, these strains were transmitted in settings where diagnostic delay prevents the implementation of effective treatment and where infection control measures are inadequate [13]. The theme of the emergence of XDR-TB followed by transmission was common to most of the countries where molecular epidemiological studies have been done (Table 1E). Nevertheless, a number of studies reported that XDR-TB was primarily acquired, possibly reflecting failure of the current policies and protocols to initially test and treat, and cure cases adequately (Table 1E). Despite improving our understanding of the mechanisms driving the XDR-TB epidemic in the respective countries, it is not clear whether this information has influenced TB control policy, except in KwaZulu-Natal [14].

XDR-TB and resistance beyond XDR-TB in India and China

MDR-TB has been reported from every country in the world surveyed with a recent WHO study reporting that global rates of MDR-TB are currently at their highest [15]. 36% of the world's total population and 50% of the world's MDR-TB population reside in China and India and hence this section will focus on these two vast countries (see Table 3 in the main paper summarizing the disease burden and outcomes).

China: Estimates of the extent of drug resistance in China were limited in the past by local or regional surveys not truly representative of such a vast country. In 2012 the Chinese Center for Disease Control and Prevention (CDC) conducted a national survey of DR-TB in 2012 by sampling 70 clusters nationwide (4606 patients) with all the provinces contributing at least one cluster [16]. 5.7% of newly diagnosed and 25.6% of previously treated patients had MDR-TB. Among those with MDR-TB, 8.3% of new cases (95% CI, 2.9 to 13.6) and 8.0% of previously treated patients (95% CI, 2.2 to 13.9) had XDR-TB. This translates into ~120,000 MDR and ~10,000 XDR-TB cases per year in China, confirming the severity of China's MDR-TB problem. The Ministry of Health responded to these alarming figures by strengthening the reporting, referral, and follow up of patients seen in the hospital system.

India: In India, the situation is less clear because of the lack of national surveillance data and "official" figures are at variance with estimates in the private sector. In the latest WHO global resistance report, MDR-TB rates were reported at 2-3% in new cases and 12-17% in retreatment cases [17]. However, these estimates are based on small sample sizes and come from sentinel centers where program performance may exceed what is routinely encountered elsewhere. For example, at a private referral hospital in Mumbai, the corresponding MDR-TB rates for new and retreatment cases run at 30% and 60% [18]. The WHO report reveals that XDR-TB prevalence rates amongst retreatment cases is ~0.5%, yet in the first report of XDR-TB from Mumbai in 2006, 11% of all MDR samples sent to a private mycobacterial laboratory were XDR-TB [19]. Recently, a study from a tertiary private hospital in Mumbai attracted intense global attention documenting the first four Indian patients whose isolates were resistant to all drugs tested (TDR-TB) [20]. Several factors including inappropriate treatment may underpin the emergence of DR-TB in this setting. In the public sector category 1 (2HREZ/4RH) treatment failures,

instead of receiving DST and an appropriate regimen, were until recently inappropriately put on category 2 (2HREZS/1HREZ/5HRE) treatment for a further 8 months, which in essence adds a single new drug (streptomycin) to a clearly failing regimen. In India's huge and unregulated private sector (70% of hospitals and 76% of doctors) Second line drugs have been used inappropriately over the last two decades by a wide range of non-specialists without any government control. A recent audit of the MDR-TB prescriptions written out by 106 private doctors practicing in Dharavi, Asia's largest slum, revealed that 97% of all prescribed regimens were so inadequate that amplification of MDR to XDR-TB was highly likely [21]. Typical of many resource-poor settings including Africa, infrastructure, patient isolation, and infection control measures are severely lacking (Figure 2 is typical of a congregate ward setting in which patients reside).

Table 1E. Transmission dynamics and genotyping data from XDR-TB from different geographical regions.

Continent	Country	Region	Study period	Number of XDR cases	Number of TDR cases	Genotyping method(s) used	Genotypes present	Number of isolates	% Clustering (transmission)	Interpretation of results	Data used to construct Figure 1	Reference
Africa	South Africa	Gauteng, Limpopo, Mpumalanga and North West	June 2007 to January 2008	24		Spoligotyping, MIRU-VNTR typing	Beijing LAM T EAI S X H	6 3 3 6 2 3 1	N/A	XDR-TB is endemic in the region and only low levels of transmission were observed	Yes	A1
Africa	South Africa	Western Cape, Eastern Cape, KwaZulu-Natal and Gauteng	August 2000-2010 (Western Cape), July 2008-November 2009 (Eastern Cape), KwaZulu-Natal (May 2005-April 2006) and Gauteng (March 2004-December 2007)	224		Spoligotyping	**Western Cape** Beijing (typical) Beijing (atypical) LAM T U X Orphan **Eastern Cape** Beijing (atypical) LAM S Orphan **KwaZulu-Natal** LAM T S Orphan	 37 57 2 5 1 1 2 89 1 1 3 18 2 2 3	N/A	Endemic spread of MDR-TB or pre-XDR followed by acquisition of resistance to generate XDR-TB. Additional spread through migration	Yes	A2

Africa	South Africa	North West (gold mine)	January 2003 to November 2005	5		IS*6110* DNA fingerprinting, Spoligotyping, MIRU typing	LAM X H	1 3 1	0/5 (0%)	Amplification of resistance due to diagnostic delay and inappropriate treatment	No	A3
Africa	South Africa	KwaZulu-Natal	N/A	9		Whole genome sequencing	LAM	9	9/9 (100%)	Clonal transmission of XDR-TB	No	A4
Africa	South Africa	KwaZulu-Natal	June 2005 to June 2006	14		Spoligotyping	N/A	N/A	N/A	Reinfection with XDR-TB strains indicating transmission of XDR-TB	No	A5
Africa	South Africa	Gauteng, Limpopo, Mpumalanga, Nort West, Eastern Cape, Western Cape and Free State	June 2005 to December 2006	41		Spoligotyping	Beijing LAM T EAI X H S Orphan	14 5 4 4 1 2 1 10	15/41 (37%)	XDR-TB was endemic in all regions tested. Transmission was low implying acquisition of resistance	No	A6
Africa	South Africa	KwaZulu-Natal	January 2005 to March 2006	46		Spoligotyping	LAM (not defined)	39 7	N/A	Extensive transmission of XDR-TB	No	A7
Africa	South Africa	Western Cape	August 2002 to February 2008	52		IS*6110* DNA fingerprinting, targeted DNA sequencing	Beijing LAM S X	45 1 1 5	19%	Transmission of MDR-TB followed by acquisition of second-line resistance leading to the emergence of XDR-TB	No	A8

Africa	South Africa	Western Cape	N/A	4		Whole genome sequencing	N/A	N/A	N/A	Transmission of MDR-TB followed by acquisition of second-line resistance leading to the emergence of XDR-TB	No	A9
Africa	South Africa	Eastern Cape	July 2008 to July 2009	108	9	IS*6110* DNA fingerprinting, spoligotyping, targeted DNA sequencing	Beijing (atypical) LAM MANU S T	103 2 1 1 1	88/108 (81%)	Endemic spread of pre-XDR-TB followed by acquisition of resistance to generate XDR-TB and subsequent transmission	No	A10
Africa	Ethiopia	Addis Ababa	December 2005 to August 2006	2		spoligotyping	T	2	N/A	XDR-TB was emerging	Yes	A11
Americas	Argentina	Salta, Rosario, Buenos Aires, Mar del Plata	January 2003 to December 2009	53		IS*6110* DNA fingerprinting, spoligotyping	LAM T H Orphan	8 2 21 22	31/53 (58%)	XDR-TB was emerging and being transmitted	Yes	A12
Asia	Nepal	Country-wide	2007 to 2010	13		Spoligotyping, VNTR typing	Beijing CAS T Orphan	9 1 2 1	4/13 (31%)	XDR-TB was emerging and being transmitted	Yes	A13
Asia	China	Hong Kong	1997 to 2006	20		IS*6110* DNA fingerprinting	N/A	N/A	13/20 (65%)	Community transmission of XDR-TB	No	A14
Asia	China	Xinjiang province, Shihezi		2		MIRU-VNTR typing	N/A	N/A	N/A	Not described	Yes	A15

Asia	China	Jiangxi	January 2010 to June 2011	16		MIRU-VNTR typing, DNA sequencing	N/A	N/A	0/16 (0%)	XDR-TB was emerging through acquisition of resistance	No	A16
Asia	China	Shanghai	March 2004 to November 2007	11		VNTR typing	Beijing orphan	10 1	8/11 (73%)	XDR-TB was primarily transmitted	Yes	A17
Asia	China	Country wide	January 2002 to December 2005	13		MIRU-VNTR typing, targeted DNA sequencing	Beijing T	10 3	2/13 (15%)	XDR-TB was emerging through acquisition of resistance followed by limited transmission	Yes	A18
Asia	Cambodia	Not given	May 2007 and June 2009	1		Spoligotyping, targeted DNA sequencing	EAI	1	N/A	Not described	Yes	A19
Asia	Pakistan	Country wide	2006 to 2009	57		Spoligotyping, MIRU-VNTR typing	Beijing CAS T EAI U X Orphan	5 33 4 1 2 1 11	0/57 (0%)	XDR-TB was emerging through acquisition of resistance	Yes	A20
Asia	Pakistan	Country wide	2006 to 2009	50 (previously described isolates Hasan *et al*.)		Spoligotyping, targeted DNA sequencing	N/A	N/A	N/A	N/A	No	A21
Asia	Taiwan	Country wide	May 2007 to Dec 2008	43		Spoligotyping	Beijing LAM T EAI H Orphan	22 2 1 8 2 8	N/A	Not described	Yes	A22

Asia	India	Mumbai	January 28 to March 2009	150		Spoligotyping, targeted DNA sequencing	Beijing CAS T EAI H Family 35	94 21 20 13 1 1	93/150 (62%)	XDR-TB was emerging and being transmitted	Yes	A23
Asia	Japan	Osaka	April 2000 to March 2007	36		MIRU-VNTR typing	N/A	N/A	N/A	Not described	No	A24
Asia	Japan	Country wide (drug resistance survey)	June 2002 and November 2002	17		IS*6110* DNA fingerprinting, spoligotyping, VNTR typing	Beijing LAM T Orphan	8 3 2 4	12/17 (57%)	XDR-TB was emerging and being transmitted	Yes	A25
Asia	Japan	Osaka	2001 to 2004	29		IS*6110* DNA fingerprinting, MIRU-VNTR typing	N/A	N/A	20/29 (69%)	XDR-TB was emerging and being transmitted	No	A26
Middle East	Iran	Tehran	October 2006 to October 2008	8	15	Spoligotyping and VNTR typing	Beijing CAS EAI H	5 4 5 9	0/23 (0%)	XDR-TB was emerging through acquisition of resistance	Yes	A27
Middle East	Iran	Country wide (drug resistance survey)	January 2003 to January 2005	12		IS*6110* DNA fingerprinting, spoligotyping	EAI H	4 8	12/12 (100%)	XDR-TB transmission was identified in known contacts	Yes	A28
Europe	France	Marseilles	Case report	1		Targeted DNA sequencing	N/A	N/A	N/A	Previously treated in Russia prior to being diagnosed with XDR-TB in France (Immigration)	No	A29
Europe	Portugal	Lisbon	1997 and 2009	30		MIRU-VNTR typing	LAM	30	30/30 (100)	On-going transmission of XDR-TB	No	A30
Europe	Portugal	Lisbon	2001 to 2006	57		MIRU-VNTR typing	LAM	57	N/A	On-going transmission of XDR-TB	Yes	A31

Europe	Portugal	Lisbon	2005	26		MIRU-VNTR	LAM	26	73% (new cases)	On-going transmission of XDR-TB	No	A32
Europe	Poland	Drug Resistance Survey	1997 to 2004	1		Spoligotyping	N/A	N/A	N/A	Not described	No	A33
Europe	Poland	Drug Resistance Survey	2000 to 2008	18	1 pre-TDR	Spoligotyping and MIRU-VNTR typing	Beijing T U H Orphan	2 12 1 2 2	10/19 (53%)	XDR-TB was emerging and being transmitted	Yes	A34

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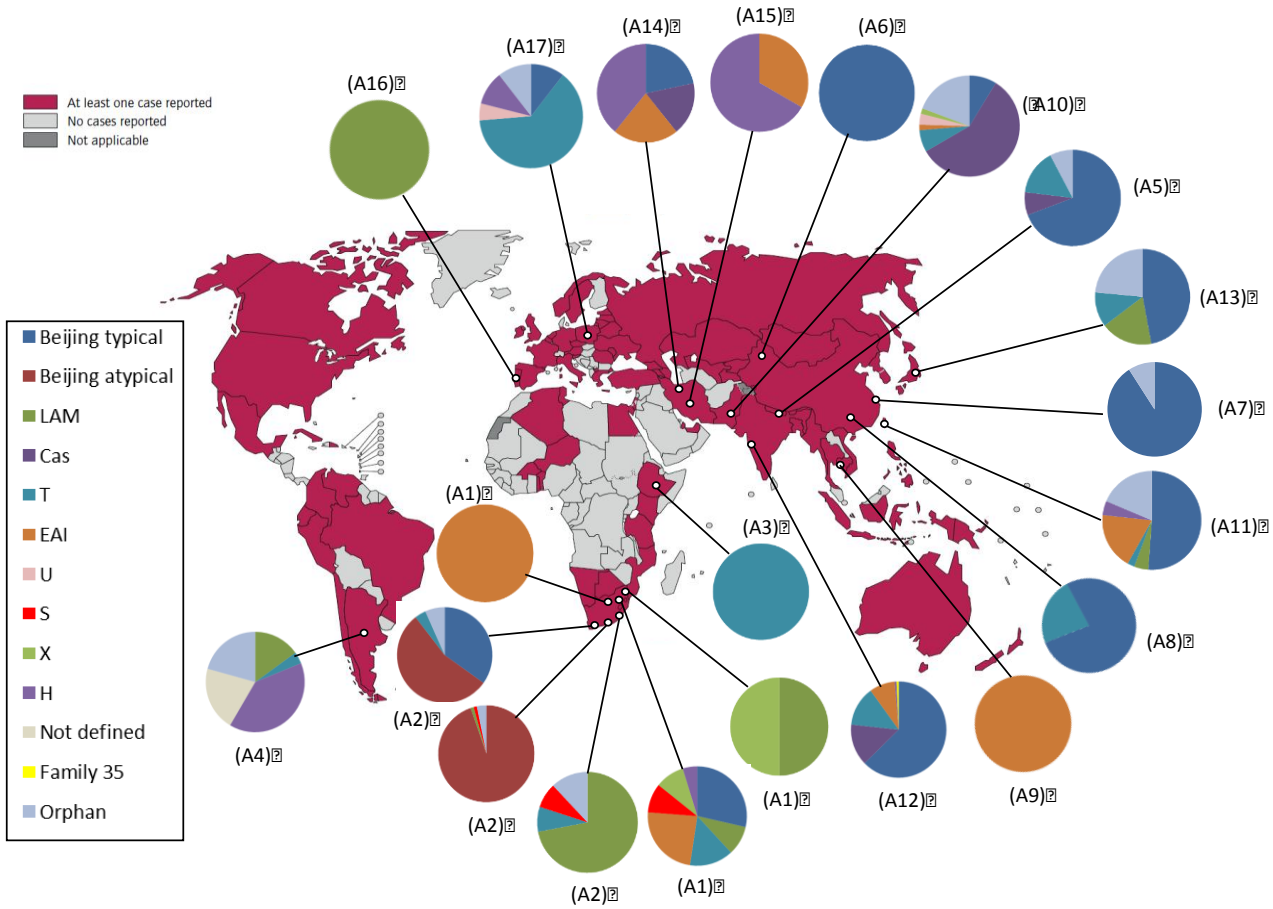
A1 [10], A2 [8], A3 [1], A4 [22], A5 [23], A6 [9], A7 [24], A8 [25], A9 [26], A10 [27], A11 [28], A12 [29], A13 [30], A14 [31], A15 [32], A16 [33], A17 [34], A18 [35], A19 [36], A20 [37], A21 [38], A22 [39], A23 [40], A24 [41], A25 [42], A26 [43], A27 [44], A28 [45], A29 [46], A30 [47], A31 [48], A32 [12], A33 [49], A34 [50]

Figure 1. Global distribution of XDR-TB genotypes overlaid onto the WHO map of the 84 countries which have reported XDR-TB cases [51]. The colour specific segments in each of the pie charts reflect the proportion of isolates with a defined genotype for each country or region: South Africa [8, 10], Ethiopia[28], Argentina [29], Portugal [47], Poland [50], Iran [44, 45], Pakistan [37], India [40], Nepal [30], Cambodia [36], China [33-35], Taiwan [39], Japan [42] (Table 2). Beijing genotype strains from South Africa were sub-classified as typical and atypical to demonstrate regional differences in the population structure of XDR-TB.



A1 [10], A2 [8], A3 [28], A4 [29], A5 [30], A6 [32], A7 [34], A8 [35], A9 [36], A10 [37], A11 [39], A12 [40], A13 [42], A14 [44], A15 [45], A16 [48], A17 [50]

Table: Comparison of the disease burden and outcomes between the global TB super-powers

	India	**China**
Population	1241 million	1348 million
TB prevalence	3,100,000	1,400,000
TB incidence	2,200,000	1,000,000
TB mortality	300,000	47,000
Total MDR-TB	66,000	61,000
MDR rate in new cases	1·7%	5·66%
MDR rate in previously treated cases	14·7%	25·6%

Source: Global Tuberculosis Report 2012: WHO.[1]

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