Increased resistance to second-line anti-TB drugs in Belgium from 2001 to 2008

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BELTA

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TB is decreasing, MDR is not increasing

TB case notification in Belgium has been decreasing slowly from 12.9 per 100,000 in 2001 to 9.7 per 100,000 in 2007 (***figure 1***). The data from the 2008 TB register are not yet available.

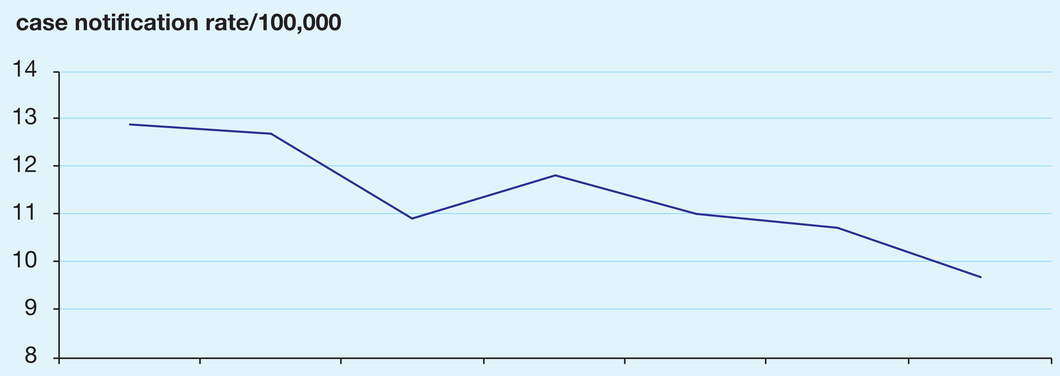

Figure 1. *TB case notification rate (all cases) in Belgium 2001-2007*

During this same period, MDR TB had been expected to increase, but it has remained fairly stable (***figure 2***) with an average of 16 cases per year. The proportion of MDR among the total number of TB cases fluctuated around 1.3%, with a range of 0.9%-1.7%, and among the TB cases who were tested for drug sensitivity it fluctuated around 1.9%, with a range of 1.2%-2.7%.

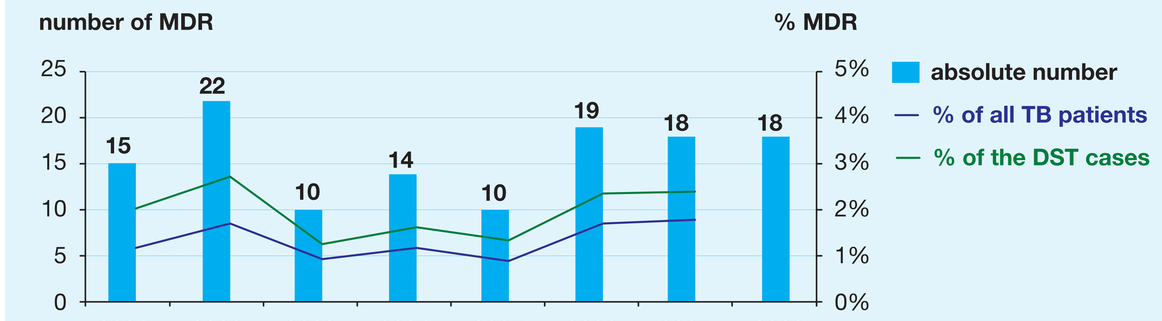

Figure 2. *MDR TB cases diagnosed in Belgium 2001-2008, in absolute numbers, as a percentage of the total number of TB patients and as a percentage of the patients for whom drug sensitivity testing (DST) was performed*

Resistance to first-line drugs has been stable, resistance to second-line drugs is on the rise

From 2001 to 2008, a total of 126 MDR cases were diagnosed. Testing for first-line drug resistance was done systematically. For the sake of simplicity, streptomycin (up to 2006) and rifabutin are included with the first-line drugs. The proportion of MDR cases resistant to ethambutol (75%), pyrazinamide (58%), streptomycine (69%) and rifabutin (77%) did not vary much over the years. (***figure 3***)

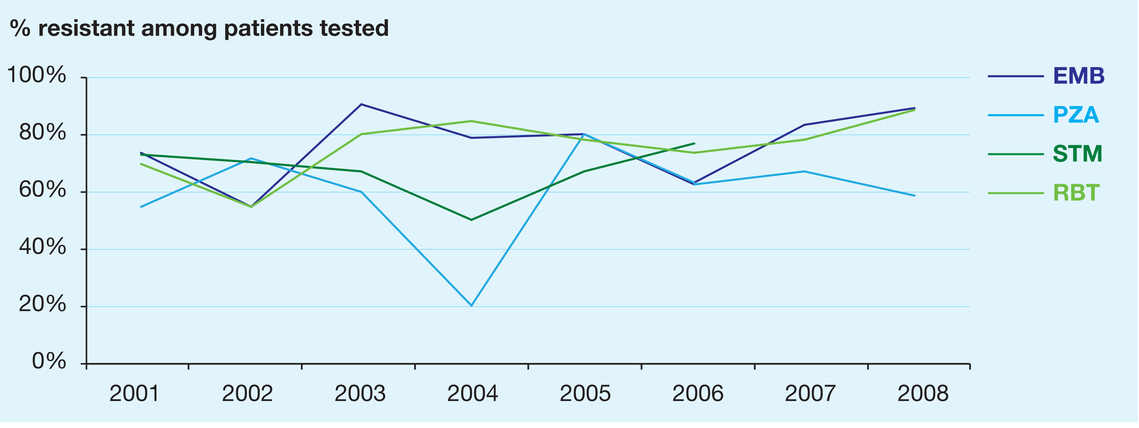

Figure 3. *Resistance to ethambutol (EMB), pyrazinamide (PZA), streptomycine (STM) en rifabutine (RBT) among the MDR patients in Belgium 2001-2008 who were tested for sensitivity to the drug*

The proportion of MDR patients with resistance to one or more second-line drugs never exceeded 20% from 2001 to 2007, but it reached 50% in 2008. (***figure 4***)

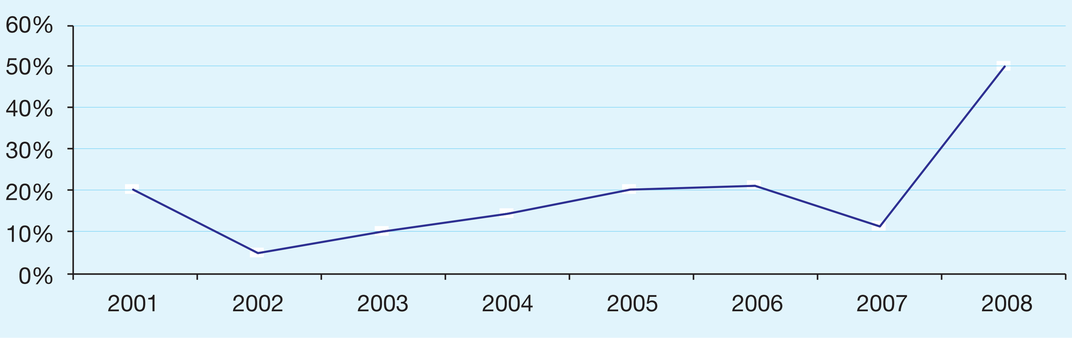

Figure 4. *Percentage of MDR patients with resistance to one or more second-line drugs in Belgium 2001-2008*

Testing for resistance to the second-line drugs amikacin, fluoroquinolones and thionamides was done systematically. Resistance has increased over the years, especially since 2006 (***figure 5***). In 2008, 39% of the MDR cases tested were resistant to amikacin, 17% to the fluoroquinolones and 50% to the thionamides. Cycloserin was tested as well but the results are considered unreliable and are not included in the analysis. Resistance to PAS was present in 75% of the patients tested but this is not shown in the graph because the proportion of patients tested was small (22%).

Prior to 2007, the proportion of MDR cases tested for capreomycin and linezolid was very low, but in 2008, it reached 56% and 78% respectively, with 50% being resistant to capreomycin and 7% (this represents 1 case) to linezolid. (***figure 5***)

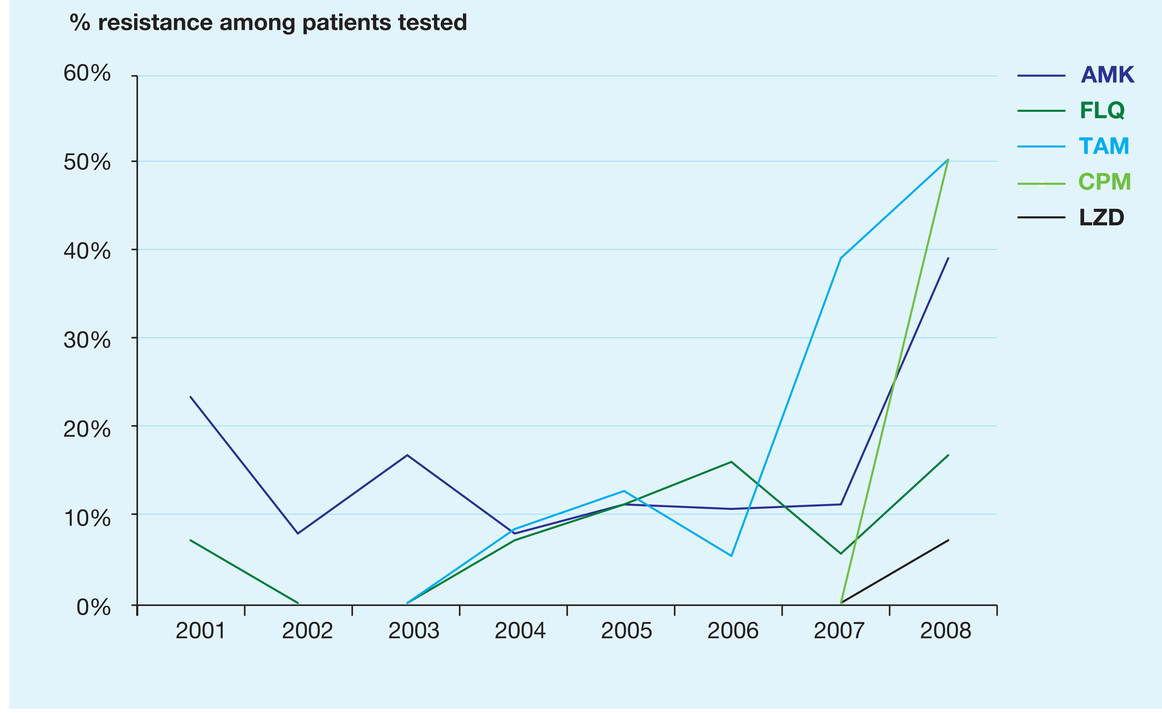

Figure 5. *Resistance to amikacin (AMK), fluoroquinolones (FLQ)), thionamides (TAM), capreomycin (CPM) and linezolid (LZD) among the MDR patients in Belgium 2001-2008 who were tested for sensitivity to the drug*

XDR and other second line drug resistance patterns

In absolute numbers, 24 out of 126 MDR patients 2001-2008 presented with resistance to second-line drugs. Five among them were XDR: one patient in 2001 (retrospective diagnosis), one in 2006, one in 2007 and two in 2008. Second-line resistance other than XDR increased considerably in 2008. (***figure 6***)

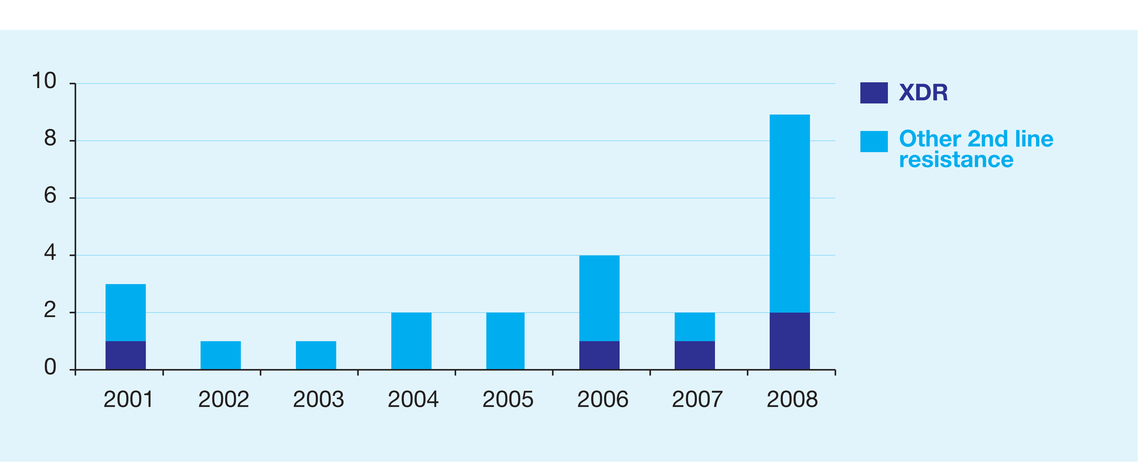

Figure 6. *Absolute numbers of MDR patients in Belgium 2001-2008 with resistance to second-line drugs, according to resistance pattern:*
- *XDR (extremely drug resistant TB) = MDR TB with additional resistance to at least one of the injectable second-line drugs (amikacin or capreomycin) as well as to the fluoroquinolones*
- *Other 2nd-line resistance = MDR TB with additional resistance to one or more second-line drugs but not corresponding to the definition of XDR*

Most patients with second-line drug resistance (63%) come from the former Soviet Union, mainly from Chechnya (***table 1***). All XDR and 54% of all patients with second-line drug resistance come from only 2 countries, the Russian Federation and Georgia. If Romania is added, 67% come from only 3 countries.

Country of origin			All MDR			XDR	All patients with second-line resistance			
Ex-USSR	Russian Federation	Chechnya	16	13%	32%	3	8	33%	54%	63%	67%
		Rest	4	3%			2				
	Georgia		6	5%		2	3				
	7 other countries		14	11%			2		8%		
Romania			6	5%			3		13%		
Congo			18	14%			2		25%		
Belgium			19	15%			2				
21 other countries			43	34%			2				
Total			126			5	24				

Table 1. *Country of origin of the MDR patients in Belgium 2001-2008 with second-line drug resistance*

Treatment outcome of the MDR TB patients in Belgium

Prior to 2005, most MDR patients, including those with second-line drug resistance, were treated with pyrazinamide, ethambutol if sensitive, amikacin, a fluoroquinolone, and a thionamide if indicated. In December 2005, the BELTA-TBnet project was created. It ensured that all TB drugs were available at no cost to the patient, including those drugs that were not reimbursed by the health insurance or that had to be imported from abroad. This resulted in an increase of the use of capreomycin and especially cycloserin and linezolid. (***figure 7***)

Figure 7. *Percentage of the MDR patients diagnosed since 2005 who have been treated with a specific second-line drug*

The availability of the more expensive second-line drugs had a beneficial effect on the treatment outcome of the MDR patients (***table 2***). The table compares the treatment outcome of the MDR patients treated prior to and after the start of the BELTA-TBnet project. The 2007 cohort has not been included since many of those patients had not yet completed their treatment. Both groups are comparable in terms of age, sex, country of origin and social situation. The difference in treatment success is statistically significant (p = 0.0355, Fisher's exact test, 2-tailed).

Treatment outcome	MDR patients treated after the start of BELTA-TBnet		MDR patients treated prior to the start of BELTA-TBnet	
	n	%	n	%
Succes	22	88%	39	63,9%
Death	0	-	9	14,8%
Default	2	8,0%	11	18,0%
Transfer out	1	4,0%	1	1,6%
Total	25		61	

Table 2. *Treatment outcome of the MDR TB patients in the 2001-2006 cohorts in Belgium (excluding the patients whose diagnosis had been modified and those who had not completed treatment on 31/12/08)*

The BELTA-TBnet project also had an impact on the treatment outcome of the patients with second-line resistance. Of the 8 patients treated prior to the start of the project, only 1 was cured, 2 defaulted, and 5 died. Of the 16 patients treated since the start of the project, none have died. Only 4 have completed their treatment, but all 4 are cured, including 1 who was XDR.

Conclusion

The BELTA-TBnet project ensures that all MDR TB patients in Belgium receive the best possible treatment. This results in improved treatment outcomes and limits the transmission of multidrug resistant bacilli. Genotyping of all MDR strains in Belgium has demonstrated that not one single case of transmission from an allochthonous patient to the autochthonous population has occurred.

While the overall burden of MDR is not seen to be increasing, the resistance patterns among MDR cases become more severe. New drugs with different modes of action from the existing ones must be developed and be made available urgently. If not, MDR may become untreatable.

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