

## LETTER

## Multidrug-resistant tuberculosis: resistance rates to first and reserve antituberculosis drugs in the UK in 2008/9 and the role of rapid molecular tests for drug resistance

At the Health Protection Agency National Mycobacterium Reference Laboratory (HPA NMRL) between January 2008 and December 2009, we evaluated in patients with multidrug-resistant tuberculosis (MDRTB; isolates resistant to rifampicin and isoniazid) the rate of resistance to other first-line drugs (ethambutol and pyrazinamide) and to reserve drugs and the role of rapid molecular tests for rifampicin (and MDRTB) resistance.

MDRTB is difficult to manage—drugs are toxic, less effective and costly. Further problems arise from extensively drug-resistant tuberculosis (XDRTB); MDRTB isolates resistant to a quinolone and any of the injectable drugs (amikacin, capreomycin, kanamycin). Effective management of MDRTB/XDRTB depends on drug sensitivity test (DST) results to the remaining first-line and reserve drugs.

We have previously demonstrated that our national 'fastrack' molecular tuberculosis and rifampicin resistance identification service significantly reduces time for detection compared with bacteriological culture.

Overall, *Mycobacterium tuberculosis* complex is detected 15.2 days earlier than gold standard automated liquid culture methods and rifampicin resistance 30.7 days earlier.<sup>1–3</sup>

During 2008, 53 UK cases of MDRTB were reported by the HPA,<sup>4</sup> of which the NMRL identified 47 (89%). The NMRL identified a further 65 cases of MDRTB during 2009. Of the 112 MDRTB cases, 107 (96%) patients had a complete DST profile for all 11 drugs tested, and 87 (78%) isolates were initially identified as MDRTB by 'fastrack'.

Fifty-one of the 107 isolates (48%) were resistant to rifampicin and isoniazid alone of the first-line drugs (table 1, group 1); 17 (33%) were additionally resistant to one reserve drug, ie, only 34 isolates (67%) were sensitive to all reserve drugs. In the remaining 56 isolates (52%), resistance to rifampicin and isoniazid was combined with resistance to another first-line drug (table 1, group 2), and 34 of these (61%) were additionally resistant to a reserve drug; 22 isolates (39%) were sensitive to all reserve drugs. Almost half (48%) of all MDRTB isolates were resistant to at least one reserve drug and 21% were resistant to all four first-line drugs.

Our results show multidrug-resistant isolates with resistance to one or more of the remaining first-line drugs increases the likelihood of resistance to reserve drugs. In table 1, the rate of resistance to any second-line drug was significantly greater in group 2 (61%) than in group 1 (33%) (Fisher's exact test  $p=0.0065$ ). Our findings justify a policy of using the 'fastrack' approach and, when

rifampicin resistance has been detected and a culture obtained, of setting up DST to all first and reserve drugs immediately and simultaneously (rather than the conventional approach of DST for reserve drugs only when MDRTB is detected phenotypically). The NMRL has recently added a similar test for resistance to isoniazid and the introduction of genotypic tests for XDRTB would be highly desirable. This policy would greatly accelerate the return of DST results to relevant clinics, reducing the time for the instigation of appropriate management, helping to reduce any increasing prevalence of MDRTB.

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**Competing interests** None.

**Contributors** SLM was responsible for the drug sensitivity tests. FAD was responsible for policy development and is the guarantor. DCSH and NS developed the database for assessing the drug resistance patterns in MDRTB cases. All authors participated in the study design, had full access to all of the data and take full responsibility for the integrity and interpretation of the results and writing of the manuscript. All authors approved the final manuscript.

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**Table 1** MDRTB and additional drug resistances: years 2008 and 2009 (complete drug profiles)

	2008 + 2009	
	N	%
Total MDRTB strains with complete DST profile	107	100%
Group 1		
MDRTB (R+H)	51	48%
MDRTB (R+H)+resistance to any reserve drug*	17	33%
MDRTB (R+H)+sensitivity to all reserve drugs*	34	67%
Group 2		
MDRTB (R+H)+/or E+/or Z	56	52%
MDRTB (R+H)+/or E+/or Z+resistance to reserve any drugs*	34	61%
MDRTB (R+H)+sensitivity to all reserve drugs*	22	39%
Resistance to first-line drugs		
Ethambutol	48	45%
Pyrazinamide	30	28%
Resistance to reserve drugs		
Injectables†	6	6%
Quinolones‡	21	20%
Prothionamide	41	38%
Streptomycin	68	64%
XDR	3	3%

In multidrug-resistant tuberculosis (MDRTB) isolates the rate of resistance to any reserve drug was significantly greater when accompanied by resistance to another first line drug (group 2 vs group 1) (Fisher's exact test  $p=0.0065$ ).

\*Reserve drugs: amikacin, capreomycin, kanamycin, moxifloxacin, ofloxacin and prothionamide (streptomycin is not included).

†Any of amikacin, capreomycin and kanamycin.

‡Ofloxacin and/or moxifloxacin.

DST, drug sensitivity test; E, ethambutol; H, isoniazid; R, rifampicin; XDR, extensively drug resistant; Z, pyrazinamide.