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Rifampicin-resistant *Mycobacterium tuberculosis*: susceptibility to isoniazid and other anti-tuberculosis drugs

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Abstract

Based on data from 14 Supranational Tuberculosis (TB) Reference Laboratories worldwide, the proportion of rifampicin-resistant isolates that were isoniazid-susceptible by phenotypic drug-susceptibility tests varied widely (0.5%–11.6%). Rifampicin-resistant isolates that were isoniazid-susceptible had significantly lower rates of resistance to other first-line and second-line anti-TB drugs (except rifabutin) compared to multidrug-resistant isolates. Rifampicin resistance is not always a good proxy for a presumptive diagnosis of multidrug-resistant tuberculosis, which has implications for use of molecular assays that identify only rifampicin resistance-associated DNA mutations.

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Disclaimer: The conclusions and interpretations of data presented in this report are solely those of the authors and do not necessarily represent an official position of the CDC or World Health Organization.

Keywords

tuberculosis; rifampicin resistance; molecular diagnostic tests; drug resistance

Molecular tests greatly expedited the detection of *M. tuberculosis* complex (MTB) and rifampicin (RMP) resistance. Recently WHO endorsed use of an automated rapid molecular assay Xpert® MTB/RIF for the detection of MTB and RMP-resistance.[1] RMP-resistance is frequently associated with concomitant isoniazid (INH) resistance,[2] and thus is considered by many to be a proxy for multidrug-resistant (MDR) tuberculosis (TB); however, this association may vary widely between countries and patient groups.[3] The WHO/IUATLD Global Project on Anti-tuberculosis Drug Resistance Surveillance (Global Project)[2, 4–6] documented a low overall prevalence of non-MDR RMP-resistance using as a denominator all TB cases, but little has been evaluated about the proportion of RMP-resistant isolates that are INH-susceptible using as a denominator all RMP-resistant cases. This latter proportion should be assessed when considering use of RMP-resistance as a proxy for MDR-TB.

Global Project data demonstrates that the proportion of RMP-resistant isolates that are INH-susceptible can be substantial, >40% of new cases in low MDR-TB prevalence settings, but even in high MDR-TB burden settings ~14% of new RMP-resistant cases remain INH-susceptible.[7] Preliminary results of an analysis of U.S. TB surveillance data indicates 22% of reported RMP-resistant isolates are INH-susceptible.[8] An Xpert® MTB/RIF implementation study demonstrated that even among MDR-TB suspect patients, 6.8% of RMP-resistant cases were INH-susceptible.[9] Treating all RMP-resistant patients as though they have MDR-TB would deprive the INH-susceptible cases of one of the most effective bactericidal and least expensive TB drugs. Furthermore, little is known about the association between RMP-resistance and second-line drug resistance, especially when isolates are INH-susceptible. A better understanding of these issues is urgent to guide recommendations for treatment of patients with RMP-resistance found by any molecular method such as the Xpert® MTB/RIF.

To address these questions, we analyzed drug-susceptibility test (DST) results from a collaborative study by the U.S. Centers for Disease Control and Prevention, the WHO and the Supranational Reference Laboratories (SRLs).[10] Our objectives were to (1) describe the proportion of MTB RMP-resistant isolates that are susceptible to INH by geographic region, and (2) compare proportions of resistance to other first-line and second-line drugs between RMP-resistant/INH-susceptible and MDR-TB isolates.

The study

We conducted a retrospective analysis of data reported from 14 SRLs, representing cultures from 112 TB laboratories in 80 countries, including phenotypic DST results for MTB isolates that had been tested for resistance to first-line and second-line drugs during 2000–2004.[10]

The SRL in the Republic of Korea routinely performs DSTs to first-line and second-line drugs on all initial culture-positive TB isolates in the country, thus data were considered to

be representative of TB in Korea. Data from the other 13 SRLs included isolates from their own and other countries that were submitted for various purposes, including clinical confirmation, surveillance, and quality assurance; specimens from those SRLs were considered a convenience sample biased toward a higher prevalence of MDR. For this reason, we distinguish DST results from Korea and the other SRLs.

In total, 17,946 isolates were included in analysis, 3,851 (21.5%) were resistant to RMP; 292/3,851 (7.6%) were INH-susceptible (Table 1). The proportion of all RMP-resistant isolates that were INH-susceptible ranged from 0.5% in Northern Africa/Middle East to 11.6% of isolates from Korea. Isolates that were RMP-resistant/INH-susceptible had significantly lower rates of resistance to other first-line and second-line drugs (except rifabutin) compared to MDR-TB isolates (Table 2).

Conclusions

We found that the proportion of INH-susceptibility among isolates with RMP-resistance varied by region and this proportion could depend on whether the samples were representative or “convenience”. RMP-resistant/INH-susceptible isolates were significantly more likely to be susceptible to all other anti-TB drugs tested (except rifabutin) compared to MDR-TB isolates.

The reliability of using molecular testing for RMP-resistance to diagnose MDR-TB will be driven by two components: the positive predictive value (PPV) of RMP-resistance as detected by the assay (which is tied to local prevalence of RMP-resistance, sensitivity and specificity), and the proportion of RMP-resistant isolates that are INH-resistant. Therefore, PPV of RMP-resistance will be diminished in countries/settings with a low prevalence of MDR-TB or among low MDR-TB risk patient groups. Targeted molecular testing of high MDR-TB risk groups should increase pre-test probability and improve PPV. On the other side, our and other[7] data suggest that in certain countries/settings among patients with a high *a priori* probability of MDR-TB, RMP-resistance may be a reliable proxy marker for MDR. Further, our analysis suggests that in patients with RMP-resistant TB, INH susceptibility may correlate with susceptibility to other anti-TB drugs, and this knowledge might help in planning more effective treatment regimens.

Our analysis has limitations. We did not have information about the reasons that isolates were submitted to the SRL; however, it is likely this represents a sampling bias, given the greater probability of MDR-TB; thus, our results probably underestimate the proportion of RMP-resistant/INH-susceptible isolates. We did not have information on previous TB treatment history, thus we could not stratify resistance rates for new and re-treatment cases. No clinical information was provided, including HIV status of patients; in some areas DST is more often done in HIV-infected TB patients and it was previously shown that in some settings RMP-resistance/INH-susceptibility is associated with HIV-infection.[8, 11] Lastly, conventional growth-based DST is imperfect, and underscores the increasing need to adjudicate results with genetic data.

Despite these limitations, our analysis provides data important for implementation and use of rapid molecular tests for RMP-resistance. Additional research focused on regional epidemiology of drug-resistant TB; association between RMP-resistance, MDR and second-line drug resistance; and between RMP-resistance and HIV status in specific settings will ensure optimal use of rapid RMP-resistance testing. DST to other drugs including INH should be done if RMP-resistance is detected. If a substantial proportion of RMP-resistant TB is INH-susceptible in a given population, including INH in empiric treatment regimens triggered by RMP-resistance may be superior to omitting. Research is needed to compare outcomes and costs of treatment of RMP-resistant/INH-susceptible and MDR-TB. Rapid molecular tests for MTB and RMP-resistance are much anticipated, potentially revolutionary advances in the fight against MDR-TB, and much needed operations research will help maximize their impact.

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Table 1

Isoniazid (INH) susceptibility among rifampicin (RMP)-resistant isolates, by geographic region, 2000–2004[£]

Geographic region	Isolates with any resistance to RMP/Total isolates tested (%)		INH susceptibility among isolates with any RMP resistance	
			Susceptible to INH	Resistant to INH (MDR-TB[*])
	n/N	(%)	n (%)	n (%)
Republic of Korea	1,469/11,939	(12.3)	171 (11.6)	1,298 (88.4)
Latin America[¥]	508/799	(63.6)	39 (7.7)	469 (92.3)
Industrialized nations[¥¥]	869/2,709	(32.1)	61 (7.0)	808 (93.0)
Sub-Saharan Africa[**]	89/373	(23.9)	6 (6.7)	83 (93.3)
Asia (except Republic of Korea) [†]	284/389	(73.0)	8 (2.8)	276 (97.2)
Eastern Europe[††]	430/1,178	(36.5)	6 (1.4)	424 (98.6)
Northern Africa and Middle East[***]	202/559	(36.1)	1 (0.5)	201 (99.5)
Total	3,851/17,946	(21.5)	292 (7.6)	3,559 (92.4)

[£] All reported drug susceptibility test results are based on phenotypic culture-based methods.[10]

[*] MDR-TB was defined as resistance to at least INH and RMP.

[¥] Argentina, Bolivia, Brazil, Chile, Costa Rica Ecuador, El Salvador, Guatemala, Guyana, French Guyana, Mexico, Peru.

[¥¥] Australia, Belgium, Canada, Germany, France, Ireland, Portugal, Spain, United Kingdom, USA.

[**] Botswana, Burundi, Cameroon, Central African Republic, Cote d'Ivoire, Kenya, Madagascar, Rwanda, South Africa, Senegal, Uganda.

[†] Bangladesh, Fiji, Indonesia, Papua New Guinea, Thailand, East Timor.

[††] Azerbaijan, Armenia, Czech Republic, Republic of Georgia, Kazakhstan, Russia.

[***] Afghanistan, Algeria, Egypt, Tunisia, Djibouti.

Table 2

Resistance to first-line and second-line drugs among RMP-resistant isolates, stratified by INH susceptibility, 2000–2004[£]

Drug	Republic of Korea, N=1,469					Other than Korea, N=2,382				
	RMP-resistant, INH-susceptible		MDR-TB		p-value[††]	RMP-resistant, INH-susceptible		MDR-TB		p-value[††]
	n/N[*]	%	n/N[*]	%		n/N[*]	%	n/N[*]	%	
First-line drugs										
EMB	19/171	11.1	817/1,298	62.9	<.001	4/121	3.3	1,236/2,261	54.7	<.001[†]
STM	7/171	4.1	322/1,298	24.8	<.001	22/121	18.2	1,701/2,261	75.2	<.001
PZA	36/171	21.1	723/1,298	55.7	<.001	6/66	9.1	577/1,217	47.4	<.001
Second-line drugs										
≥1 SLD	18/171	10.5	614/1,298	47.3	<.001	12/120	10.0	896/2,233	40.1	<.001
FQ	12/171	7.0	421/1,298	32.4	<.001	5/117	4.3	234/2,107	11.1	0.02[†]
AG	8/171	4.7	186/1,298	14.3	<.001	2/113	1.8	438/2,148	20.4	<.001[†]
CAP	1/171	0.6	103/1,298	7.9	<.001[†]	1/90	1.1	173/1,420	12.2	<.001[†]
PAS[**]	4/171	2.3	284/1,298	21.9	<.001[†]	1/82	1.2	158/1,521	10.4	.004[†]
CS[**]	0/171	0	76/1,298	5.9	0.001[†]	0/70	0	63/1,228	5.1	.04[†]
ETH[**]	1/171	0.6	209/1,298	16.1	<.001[†]	5/95	5.3	388/1,867	20.8	<.001[†]
RBT	n/a		n/a			47/66	71.2	536/786	68.2	0.61

Notes.

[£]All reported drug susceptibility test results are based on phenotypic culture-based methods.[10]

[*]Denominator is number of isolates tested for this drug, which vary for laboratories other than those in the Republic of Korea (for laboratories other than Korea drug susceptibility testing to the second-line drugs was usually limited to isolates from patients known or suspected to have drug-resistant TB[10]).

[††]P-values reported for chi-square test unless noted otherwise.

[†]P-values are Fisher's exact test.

RMP=rifampicin; INH=isoniazid; EMB=Ethambutol; STM=Streptomycin; PZA=Pyrazinamide; SLD=Second-line drug; FQ=Fluoroquinolones; AG=Aminoglycosides; CAP=Capreomycin; PAS=Para-aminosalicylic acid; CS=Cycloserine; ETH=Ethionamide; RBT=Rifabutin.

[**]Consensus has not been reached on methods and drug concentrations for testing of PAS, CS, ETH.