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SHORT COMMUNICATION

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

E. V. Kurbatova,* J. S. Cavanaugh,* N. S. Shah,† A. Wright,‡ H. Kim,§ B. Metchock,* A. Van Deun,¶ L. Barrera,# F. Boulahbal, E. Richter,†† N. Martín-Casabona,‡‡ F. Arias,§§ I. Zemanova,¶¶ F. Drobniewski,## A. Santos Silva,*** C. Coulter,††† R. Lumb,‡‡‡ J. P. Cegielski***

***Centers for Disease Control and Prevention, Atlanta, Georgia, †Division of General Internal Medicine, Albert Einstein College of Medicine, Bronx, New York, USA; ‡World Health Organization, Geneva, Switzerland; §Korean Institute of Tuberculosis, Seoul, Republic of Korea; ¶Institute of Tropical Medicine, Antwerp, Belgium; #National Institute of Infectious Diseases, Buenos Aires, Argentina; **Institut Pasteur d'Algérie, Algiers, Algeria; ††National Reference Center for Mycobacteria, Borstel, Germany; ‡‡Hospital Universitaris Vall d'Hebron, Barcelona, Spain; §§Institute of Public Health of Chile, Providencia Santiago, Santiago, Chile; ¶¶National Institute of Public Health, Scrobarova, Czech Republic; ##Health Protection Agency, London, UK; ***National Institute of Health, Porto, Portugal; †††Queensland Mycobacterium Reference Laboratory, Brisbane, Queensland, ‡‡‡Institute of Medical and Veterinary Science, Adelaide, South Australia, Australia**

SUMMARY

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

KEY WORDS: tuberculosis; rifampicin resistance; molecular diagnostic tests; drug resistance

MOLECULAR TESTS have greatly expedited the detection of *Mycobacterium tuberculosis* complex and rifampicin (RMP) resistance. The World Health Organization (WHO) recently endorsed the use of an automated rapid molecular assay, Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA), for the detection of *M. tuberculosis* and RMP resistance.[1] RMP resistance is frequently associated with concomitant isoniazid (INH) resistance,[2] and is thus considered by many to be a proxy for multidrug-resistant tuberculosis (MDR-TB); however, this association may vary widely between countries and patient groups.[3] The WHO/International Union Against Tuberculosis and Lung Disease 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 is known 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 using RMP resistance as proxy for MDR-TB.

Global Project data demonstrate that the proportion of RMP-resistant isolates that are INH-susceptible can be substantial. In low MDR-TB prevalence settings this represents >40% of new cases, but even in high MDR-TB burden settings ~14% of new RMP-resistant cases remain INH-susceptible.[7] Preliminary results of an analysis of US TB surveillance data indicate that 22% of reported RMP-resistant isolates are INH-susceptible (Sharling et al. unpublished data). An Xpert® MTB/RIF implementation study demonstrated that, even among MDR-TB suspect patients, 6.8% of RMP-resistant cases were INH-susceptible.[8] Treating all RMP-resistant patients as though they have MDR-TB would deprive the INH-susceptible cases of one of the most effective and least expensive bactericidal anti-tuberculosis drugs. Furthermore, little is known about the association between RMP resistance and resistance to second-line drugs, particularly when the isolates are INH-susceptible. A better understanding of these issues is urgently required to guide recommendations for treatment of patients with RMP resistance found by molecular methods such as the Xpert® MTB/RIF test.

To address these questions, we analyzed drug sus-

EVK and JSC are first authors.

Correspondence to: Ekaterina V Kurbatova, International Research and Programs Branch, Division of Tuberculosis Elimination, CDC, Mailstop E-10, 1600 Clifton Road NE, Atlanta, Georgia 30333, USA. Tel: (+1) 404 639 2017. Fax: (+1) 404 639 1566. e-mail: ekurbatova@cdc.gov

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ceptibility testing (DST) results from a collaborative study by the US Centers for Disease Control and Prevention, the WHO and the Supranational Reference Laboratories (SRLs).[9] Our objectives were 1) to describe the proportion of *M. tuberculosis* RMP-resistant isolates that were susceptible to INH by geographic region, and 2) to compare the proportions of resistance to other first-line and second-line drugs between RMP-resistant, INH-susceptible and MDR-TB isolates.

METHODS

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 *M. tuberculosis* isolates that had been tested for resistance to first- and second-line drugs during 2000–2004.[9]

The SRL in the Republic of Korea routinely performs DST against first- and second-line drugs on all initial culture-positive TB isolates in the country; data were thus 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-TB. For this reason, we have made a distinction between DST results from Korea and those from the other SRLs.

IRB approval

The original study was approved by the Institutional Review Board (IRB) of the US Centers for Disease Control and Prevention (CDC). Secondary analysis of these data received non-research determination by the US CDC IRB.

RESULTS

Of 17 946 isolates included in the analysis, 3851 (21.5%) were resistant to RMP; 292/3851 (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 the isolates from Korea. Isolates that were RMP-resistant, INH-susceptible had significantly lower rates of resistance to other first- and second-line drugs (except rifabutin [RFB]) than MDR-TB isolates (Table 2).

DISCUSSION

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

Table 1 INH susceptibility among RMP-resistant isolates by geographic region, 2000–2004*

Geographic region	Isolates with any resistance to RMP/total isolates tested *n/N* (%)	INH susceptibility among isolates with any RMP resistance	
		INH-susceptible *n* (%)	INH-resistant (MDR-TB†) *n* (%)
Republic of Korea	1469/11 939 (12.3)	171 (11.6)	1298 (88.4)
Latin America‡	508/799 (63.6)	39 (7.7)	469 (92.3)
Industrialized countries§	869/2709 (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**	430/1178 (36.5)	6 (1.4)	424 (98.6)
Northern Africa and Middle East††	202/559 (36.1)	1 (0.5)	201 (99.5)
Total	3851/17 946 (21.5)	292 (7.6)	3559 (92.4)

*All reported drug susceptibility testing results are based on phenotypic culture-based methods.[10]
†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, United States.
¶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.
INH = isoniazid; RMP = rifampicin; MDR-TB = multidrug-resistant tuberculosis.

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. The PPV of RMP resistance will therefore be lower 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. However, our data, and those of others,[7] suggest that in certain countries/settings among patients with a high a priori probability of MDR-TB, RMP resistance may be a reliable proxy for MDR-TB. Furthermore, our analysis suggests that in patients with RMP-resistant TB, INH susceptibility may correlate with susceptibility to other anti-tuberculosis drugs, and this knowledge might help in planning more effective treatment regimens.

Our analysis has limitations. We did not have information on the reason why isolates were submitted to the SRL. It is likely that this led to sampling bias, given the greater probability of MDR-TB. Our results thus probably underestimate the proportion of RMP-resistant, INH-susceptible isolates. As we did not have information on previous TB treatment history, we could not stratify resistance rates for new and re-treatment cases. Furthermore, no clinical information was provided, including human immunodeficiency virus (HIV) status of patients. In some areas, DST is performed more often in HIV-infected TB patients,

Table 2 Prevalence of resistance to first- and second-line drugs among RMP-resistant isolates, stratified by INH susceptibility, 2000–2004*

	Republic of Korea (n = 1469)			Other than Korea (n = 2382)		
Drug	RMP-resistant, INH-susceptible n/N† (%)	MDR-TB n/N† (%)	P value‡	RMP-resistant, INH-susceptible n/N† (%)	MDR-TB n/N† (%)	P value‡
First-line drugs						
EMB	19/171 (11.1)	817/1298 (62.9)	<0.001	4/121 (3.3)	1236/2261 (54.7)	<0.001§
SM	7/171 (4.1)	322/1298 (24.8)	<0.001	22/121 (18.2)	1701/2261 (75.2)	<0.001
PZA	36/171 (21.1)	723/1298 (55.7)	<0.001	6/66 (9.1)	577/1217 (47.4)	<0.001
SLD						
⩾1 SLD	18/171 (10.5)	614/1298 (47.3)	<0.001	12/120 (10.0)	896/2233 (40.1)	<0.001
FQ	12/171 (7.0)	421/1298 (32.4)	<0.001	5/117 (4.3)	234/2107 (11.1)	0.02§
AG	8/171 (4.7)	186/1298 (14.3)	<0.001	2/113 (1.8)	438/2148 (20.4)	<0.001§
CPM	1/171 (0.6)	103/1298 (7.9)	<0.001§	1/90 (1.1)	173/1420 (12.2)	<0.001§
PAS¶	4/171 (2.3)	284/1298 (21.9)	<0.001§	1/82 (1.2)	158/1521 (10.4)	0.004§
CS¶	0/171	76/1298 (5.9)	0.001§	0/70	63/1228 (5.1)	0.04§
ETH¶	1/171 (0.6)	209/1298 (16.1)	<0.001§	5/95 (5.3)	388/1867 (20.8)	<0.001§
RFB	NA	NA		47/66 (71.2)	536/786 (68.2)	0.61

* All reported DST results are based on phenotypic culture-based methods.[9]
† Denominator is number of isolates tested for this drug, which varies for laboratories other than those in the Republic of Korea (for laboratories other than Korea, DST against second-line drugs was usually limited to isolates from patients known or suspected to have drug-resistant TB).[10]
‡ χ^2 test, unless otherwise noted.
§ Fisher's exact test.
¶ Consensus has not been reached on methods and drug concentrations for testing of PAS, CS and ETH.
RMP = rifampin; INH = isoniazid; MDR-TB = multidrug-resistant tuberculosis; EMB = ethambutol; SM = streptomycin; PZA = pyrazinamide; SLD = second-line drug; FQ = fluoroquinolones; AG = aminoglycosides; CPM = capreomycin; PAS = para-aminosalicylic acid; CS = cycloserine; ETH = ethionamide; RFB = rifabutin; NA = not available; DST = drug susceptibility testing.

and it was previously shown that RMP resistance + INH susceptibility is associated with HIV infection in some settings.[8,10] Lastly, conventional growth-based DST is imperfect, and underscores the increasing need to adjudicate results with genetic data.

Despite these limitations, our analysis provides important information for the implementation and use of rapid molecular tests for RMP resistance. Additional research focused on the regional epidemiology of drug-resistant TB, on the association between RMP resistance, MDR-TB and second-line drug resistance and on the association between RMP resistance and HIV status in specific settings will ensure optimal use of rapid RMP resistance testing. DST against other drugs, including INH, should be performed if RMP resistance is detected. If a substantial proportion of RMP-resistant TB is INH-susceptible in a given population, the inclusion of INH in empiric treatment regimens triggered by RMP resistance may be preferable to omitting it. Research is needed to compare the outcomes and costs of treatment of RMP-resistant, INH-susceptible and MDR-TB. Rapid molecular tests for *M. tuberculosis* 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.

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 Centers for Disease Control and Prevention or the World Health Organization.

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RÉSUMÉ

On note de larges variations (0,5–11,6%) de la proportion d'isolats résistants à la rifampicine (RMP) chez qui une sensibilité à l'isoniazide (INH) est démontrée par des tests phénotypiques de sensibilité aux médicaments en se basant au niveau mondial sur les données de 14 laboratoires supranationaux de référence de tuberculose (TB). Dans les isolats résistants à la RMP et sensibles à l'INH, on note des taux significativement plus bas de résistance à l'égard des autres médicaments antituberculeux de première et de deuxième ligne (à l'exception de la rifabutine) par comparaison aux isolats multirésistants. La résistance à la RMP ne constitue pas toujours une bonne approche d'un diagnostic probable de TB à germes multirésistants, ce qui a des implications pour l'utilisation de tests moléculaires n'identifiant que les mutations de l'ADN associées à la résistance à la RMP.

RESUMEN

Los datos de 14 laboratorios supranacionales de tuberculosis (TB) alrededor del mundo permitieron poner en evidencia una gran variabilidad en la proporción de aislados resistentes a rifampicina (RMP), que exhiben un fenotipo sensible a isoniazida (INH) en las pruebas de sensibilidad a los medicamentos (de 0,5% a 11,6%). Estos aislados resistentes a RMP y sensibles a INH presentaron una tasa significativamente más baja de resistencia a otros medicamentos antituberculosos de primera y segunda línea (con la excepción de la rifabutina) que los aislados multidrogorresistentes. La resistencia a RMP no siempre constituye un buen criterio sustitutivo en la presunción diagnóstica de TB multidrogorresistente. Esta observación tiene repercusiones sobre el uso de las pruebas moleculares que solo detectan las mutaciones del ácido desoxirribonucleico que se asocian con la resistencia a RMP.