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Global isoniazid resistance patterns in rifampin-resistant and rifampin-susceptible tuberculosis

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Summary

Following WHO's endorsement of the Xpert® MTB/RIF assay, which rapidly and simultaneously diagnoses tuberculosis (TB) and detects resistance to rifampin (RIF), the question arises to what extent RIF resistance is an adequate marker for multidrug-resistant (MDR) TB. A retrospective analysis of data from >81 countries and subnational settings demonstrated that >40% of RIF resistant isolates from new TB cases did not display resistance to isoniazid (INH) in settings with relatively low MDR-TB prevalence (1/3 of all countries and subnational settings). Results indicated the need for INH susceptibility testing in addition to RIF susceptibility testing.

Keywords

tuberculosis; rifampin resistance; Xpert MTB/RIF assay

Introduction

In December 2010, the World Health Organization (WHO) endorsed a new, automated nucleic acid amplification test for rapidly and simultaneously diagnosing tuberculosis (TB) and detecting DNA mutations associated with resistance to rifampin (RIF).[1] By targeting a well-defined segment of the *rpoB* gene, the Xpert® MTB/RIF assay detects >95% of RIF resistance among clinical isolates.[2, 3] Resistance to at least RIF and isoniazid (INH), the two most important anti-TB drugs, defines multidrug-resistant (MDR) TB. Therefore, the question naturally arises to what extent rifampin resistance is an adequate marker for MDR-TB. In other words, for patients with Xpert® MTB/RIF results indicating RIF-resistant TB, what proportion would be treated incorrectly by excluding INH from the treatment regimen? And what proportion would be classified incorrectly as MDR-TB for case registration and surveillance purposes?

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Conflict of Interest. All authors declare no conflict of interest.

IRB approval. The Institutional Review Board (IRB) review was not required for this study which was a retrospective analysis of publicly available aggregate data.

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 CDC.

Methods

This is a retrospective analysis of publicly available aggregate data as reported by the WHO/International Union Against Tuberculosis and Lung Diseases (IUATLD) Global Project on Anti-Tuberculosis Drug Resistance Surveillance (DRS) from 1994 to 2007.[4–7] Drug susceptibility test (DST) results from 35, 58, 77 and 81 countries and subnational settings were collected from the 1997, 2000, 2004, and 2008 reports, respectively.

Data were collected and cases were defined according to the WHO guidelines for surveillance of drug resistance in tuberculosis.[4–7] The main principles include: 1) representative sampling of TB patients in the geographical setting under evaluation; 2) clearly distinguishing the treatment history of the patient (i.e. never treated or previously treated) to allow correct interpretation of the data; and 3) quality-assured laboratory testing. [7]

When a country or region had multiple years of surveillance data available, the two most recent surveillance years were averaged. For analysis, countries and subnational settings were grouped into even tertiles (each containing 1/3 of the countries/subnational settings providing data) according to the prevalence of MDR-TB among total isolates tested. The countries and regions were pooled within each tertile to determine aggregate drug resistance rates.

Results

Table 1 displays trends in INH susceptibility of isolates, given resistance to RIF according to levels of MDR-TB. Of the 181,657 tested isolates from new cases, 5,303 (2.9%) were resistant to RIF. As the prevalence of MDR-TB in each cohort increased, the percentage of INH-susceptible isolates decreased (low MDR-TB prevalence cohorts: 43.3% of RIF-resistant isolates were INH susceptible, medium: 24.4%, high: 14.0%). A similar trend was observed among previously treated and combined cases. Of the 36,338 tested isolates from previously treated cases, 8,412 (23.1%) displayed resistance to RIF with less overall susceptibility to isoniazid compared to isolates from new cases (low: 24.0%, medium: 12.5%, high: 8.5%). Of the 221,084 isolates from combined cases, 12,562 (5.7%) were resistant to RIF. A decrease in the frequency of INH susceptibility with increased MDR-TB prevalence was also observed in the combined cases (low: 26.5%, medium: 19.2%, high: 9.8%).

Table 2 displays the trends in INH susceptibility of isolates given susceptibility to RIF. The majority of all isolates were susceptible to RIF among all case types (new cases: 97.1%, retreatment cases: 76.9%, combined cases: 94.3%). Of the new cases, the percentage of isolates resistant to INH increased as MDR-TB prevalence increased (low: 3.5%, medium: 5.3%, high: 11.1%). A parallel trend in INH resistance given RIF susceptibility was observed in previously treated and combined cases.

Discussion

These results indicate that RIF resistance is not accompanied by INH resistance in >40% of new cases from countries/subnational settings in the lowest tertile of MDR-TB prevalence. Among the 1/3 of countries or settings in the middle tertile, >24% of RIF-resistant new TB cases have INH-susceptible TB. Even among previously treated cases, in whom INH resistance is more prevalent, dropping INH from the treatment regimen based on Xpert® results for RIF resistance would deprive too many patients of this crucial anti-TB drug. Based on this analysis, we would recommend classifying such patients as having RIF-resistant TB, not MDR-TB, and we would recommend including INH in the treatment regimen at least until INH resistance is demonstrated by phenotypic DST and/or molecular methods.

Among RIF-susceptible isolates, INH resistance was identified in ~5%–15%, again reinforcing the need for testing for INH resistance in addition to testing for RIF resistance to prevent the development of RIF resistance in cases resistant to INH.

These findings have important limitations. While WHO has published the results of the global drug resistance surveys, the sampling weights and survey design specifications were not available to us. The fifth volume of drug resistance survey results covering 2008–2010 did not have sufficient detail to be included in this analysis.[8] Reported DST results for INH generally are based on low-level INH resistance (0.2 mcg/ml in solid media, 0.1 mcg/ml in liquid media) and therefore may overestimate the prevalence of clinically relevant INH resistance.[9] Because of imperfect specificity of phenotypic RIF susceptibility testing, it is possible that some RIF-resistant cases were falsely positive, which may overestimate the magnitude of the non-MDR RIF resistance problem as estimated from these data.

These findings add to previous reports on epidemiology of drug-resistant TB by focusing on the prevalence of INH susceptibility among RIF-resistant cases, rather than comparing the prevalence of MDR-TB with the prevalence of RIF-monoresistance among all TB cases. Secondly, we divided countries/settings into equal tertiles of MDR-TB prevalence, rather than arbitrary prevalence criteria based on round numbers, so that countries with low versus medium versus high prevalence of MDR-TB would be equally represented in the results.

In summary, the reliability of RIF-resistance as a proxy for multidrug resistance depends on the epidemiology of drug-resistant TB in the region. In settings with low MDR-TB prevalence, the positive predictive value of RIF-resistance detected by Xpert® is diminished. Xpert® findings of RIF-resistance should be confirmed by conventional DST, and susceptibility to INH should be determined as rapidly as possible. INH should be included in the treatment regimen at least until INH resistance is proven. Cases should be registered as RIF-resistant TB based on Xpert® or other molecular test giving only RIF results and not as MDR-TB.

References

1. World Health Organization. Rapid Implementation of the Xpert MTB/RIF diagnostic test. Geneva, Switzerland: 2011.

2. Boehme CC, et al. Rapid molecular detection of tuberculosis and rifampin resistance. N Engl J Med. 2010; 363(11):1005–15. [PubMed: 20825313]
3. Boehme CC, et al. Feasibility, diagnostic accuracy, and effectiveness of decentralised use of the Xpert MTB/RIF test for diagnosis of tuberculosis and multidrug resistance: a multicentre implementation study. Lancet. 2011; 377(9776):1495–505. [PubMed: 21507477]
4. Aziz, MA., et al. WHO. Anti-tuberculosis drug resistance in the world: third global report. WHO; Geneva: 2004.
5. Espinal, MA., et al. Anti-tuberculosis drug resistance in the world: report no. 2. WHO; 2000.
6. Pablos-Mendez, A., et al. Anti-tuberculosis drug resistance in the world. WHO; Geneva: 1997.
7. Wright, A.; Zignol, M. Anti-tuberculosis drug resistance in the world: fourth global report. WHO/IUATLD; Geneva: 2008.
8. World Health Organization. Multidrug and extensively drug-resistant TB (M/XDR-TB) 2010 Global Report on Surveillance and Response. Geneva, Switzerland: 2010.
9. World Health Organization. Anti-tuberculosis drug resistance in the world: fourth global report. Geneva, Switzerland: 2008.

Table 1

Global isoniazid (INH) resistance patterns given resistance to rifampin (RIF), by MDR-TB prevalence tertiles (% MDR-TB of those tested) based on WHO/IUTLD Global DRS data 1994–2007[1].

MDR-TB prevalence cohort[2, 3]	# of settings represented	Isolates with any resistance to RIF/total tested		Isolates resistant to RIF	
				Susceptible to INH (% of any RIF resistance)	Resistant to INH (% of any RIF resistance)
		n/N	%	n (%)	n (%)
New cases					
Low (<0.78%)	45	374/47,744	0.8	162 (43.3)	212 (56.7)
Medium (0.78–2.40%)	47	1,566/87,806	1.8	382 (24.4)	1,184 (75.6)
High (≥2.40%)	46	3,363/46,107	7.3	472 (14.0)	2,891 (86.0)
Total	138	5,303/181,657	2.9	1,016 (19.2)	4,287 (80.8)
Retreatment cases					
Low (<6.61%)	42	462/7,662	6.0	111 (24.0)	351 (76.0)
Medium (6.61–17.46%)	44	1,642/13,283	12.4	205 (12.5)	1,437 (87.5)
High (≥17.46%)	43	6,308/15,393	41.0	534 (8.5)	5,774 (91.5)
Total	129	8,412/36,338	23.1	850 (10.1)	7,562 (89.9)
Combined (new & retreatment) cases					
Low (<1.47%)	41	1,432/100,004	1.4	365 (26.5)	1,067 (73.5)
Medium (1.47–4.58%)	43	1,852/59,854	3.1	337 (19.2)	1,515 (80.8)
High (≥4.58%)	41	9,278/61,226	15.2	913 (9.8)	8,365 (90.2)
Total	125	12,562/221,084	5.7	1,615 (12.9)	10,947 (87.1)

[1] Global DRS report #5, 2008–2010, did not provide enough detail to be included in these data

[2] Cohorts formed from country or subnational region data enumerated in the DRS data

[3] For sites providing prevalence data in two or more years, the two more recent values were averaged

Table 2

Global isoniazid resistance patterns given susceptibility to rifampin, by MDR-TB prevalence tertiles (% MDR-TB of those tested) based on WHO/IUATLD Global DRS data 1994–2007[1]

MDR-TB prevalence cohort[2, 3]	# of settings represented	Isolates without any resistance to RIF/total tested		Isolates susceptible to RIF	
				Susceptible to INH (% of any RIF susceptible)	Resistant to INH (% of any RIF susceptible)
		n/N	%	n (%)	n (%)
New cases					
Low (<0.78%)	45	47,370/47,744	99.2	45,691 (96.5)	1,679 (3.5)
Medium (0.78–2.40%)	47	86,240/87,806	98.2	81,676 (94.7)	4,564 (5.3)
High (≥2.40%)	46	42,744/46,107	92.7	37,997 (88.9)	4,747 (11.1)
Total	138	176,354/181,657	97.1	165,364 (92.8)	10,990 (7.2)
Retreatment cases					
Low (<6.61%)	42	7,200/7,662	94.0	6,479 (90.0)	721 (10.0)
Medium (6.61–17.46%)	44	11,641/13,283	87.6	10,457 (89.8)	1,184 (10.2)
High (≥17.46%)	43	9,085/15,393	59.0	6,991 (77.0)	2,094 (33.0)
Total	129	27,926/36,338	76.9	23,927 (84.7)	3,999 (15.3)
Combined (new & retreatment) cases					
Low (<1.47%)	41	98,572/100,004	98.6	93,213 (94.6)	5,359 (5.4)
Medium (1.47–4.58%)	43	58,002/59,854	96.9	54,777 (94.4)	3,225 (5.6)
High (≥4.58%)	41	51,948/61,226	84.8	44,409 (85.5)	7,539 (14.5)
Total	125	208,522/221,084	94.3	192,399 (92.3)	16,123 (7.7)

[1] Global DRS report #5, 2008–2010, did not provide enough detail to be included in these data

[2] Cohorts formed from country or subnational region data enumerated in the DRS data

[3] For sites providing prevalence data in two or more years, the two more recent values were averaged