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How is Xpert MTB/RIF being implemented in 22 high tuberculosis burden countries?

To the Editor:

Accurate and rapid diagnosis is crucial for tuberculosis control by ensuring a timely start to treatment and reducing transmission. In 2012, almost one third of tuberculosis cases were not diagnosed and/or reported to national tuberculosis programmes (NTPs), and <25% of estimated incident multidrug-resistant (MDR) cases were diagnosed [1]. Xpert MTB/RIF (Cepheid, Sunnyvale, CA, USA), a nucleic acid amplification test, was recommended in 2010 by the World Health Organization (WHO) for detection of HIV-associated

pulmonary tuberculosis and rifampicin resistance [2]. In 2013, the test was recommended for detection of paediatric tuberculosis and some forms of extrapulmonary tuberculosis (EPTB), as well as an initial test to replace smear microscopy [3].

Following these recommendations, modules and cartridges have been procured in increasing numbers. As of June 30, 2014, 15 846 Xpert modules and 7.5 million cartridges were procured by 104 countries at concessional prices [4], yet the potential market is much larger [5]. Although general policies regarding Xpert in the 22 high-burden countries (HBCs) have been summarised [1] and some experiences from early Xpert implementers are available [6, 7], a more comprehensive analysis of NTPs' policies and implementation of Xpert has not been performed.

To assess the current landscape of implementation of Xpert, we designed a standardised questionnaire that was sent to NTPs in 22 HBCs that account for 80% of tuberculosis cases globally. We contacted NTP managers and representatives with responsibilities relating to Xpert. Questionnaires were completed from January to July 2014, with follow-ups to ensure completion and clarify any ambiguities. Questions covered the following topics: funding sources, instrument placement, access in the private sector, testing algorithms, result reporting and treatment decisions for rifampicin-resistant results. Additionally, to better assess the scale of implementation, we analysed publicly available Xpert procurement data [4].

As shown in table 1, of the 22 HBCs, 19 (86%) reported an existing national plan or policy pertaining to Xpert. Seven (32%) of the 22 countries reported the use of domestic funding for Xpert procurement. However, only Brazil and Russia currently fund all Xpert testing with domestic resources, while the majority of HBCs rely on some of the 16 international donor groups identified. As many as six external donors were reported in some countries, suggesting a strong need for in-country coordination.

Until June 2014, of the 7.5 million cartridges procured through public sector pricing, HBCs procured 6.4 million (85%). Of those, 4.2 million (66%) of cartridges were procured by South Africa alone, which along with China, India and Brazil, account for 80% of total HBC procurement. The ratio of smear volumes for initial diagnosis [5] to the number of Xpert cartridges procured during a roughly similar time period was used as an approximate index of Xpert market penetration in the public sector. The ratio in South Africa was 1.6, significantly lower than most other HBCs where approximately 40–70 smears were performed for each Xpert. Evidently, wide-scale implementation of Xpert has only occurred in South Africa, while other HBCs continue to rely heavily on smear microscopy.

While all countries reported deployment of Xpert in the public sector, only five (23%) reported public–private partnerships around Xpert testing, the initiatives to promote the collaboration between private and public health providers in the delivery of tuberculosis care; an additional eight (36%) use Xpert in other private-sector settings. As Xpert was initially recommended for use at district and subdistrict laboratories [8], eight (36%) countries reported the deployment of Xpert at microscopy or peripheral health centres, showing promising progress. 18 (82%) reported deployment at district and subdistrict levels, and 17 (77%) reported deployment at reference or centralised laboratories. Although a previous study showed that Xpert implementation is feasible in some primary care facilities [9], the current infrastructure in HBCs might not be adequate for wide-scale coverage [10].

With respect to testing algorithms, only South Africa, Brazil and Russia recommend Xpert for all people suspected of having tuberculosis. Additionally, Brazil reported plans to replace smear microscopy with Xpert in 92 cities across the country. Although all HBCs recommend Xpert as an initial test for drug-resistant tuberculosis (DR-TB), eligibility criteria vary among them. Four countries recommend Xpert only for patients with suspected drug resistance, although in Pakistan and Bangladesh, Xpert is also being used for general tuberculosis case finding at selected sites [7]. The remaining 19 HBCs recommend Xpert among HIV-infected patients, although in Thailand and Uganda, Xpert is recommended only after negative smear results, against WHO recommendations. However, given the limited number of cartridges procured outside South Africa, actual application of these algorithms is likely to be limited. Testing strategies focusing on the detection of drug resistance among retreatment cases only identify a fraction of total new MDR cases in most countries and will limit the ability to scale-up DR-TB treatment programmes. Ultimately, countries have to work towards universal drug susceptibility testing (DST) as outlined in the Global Plan and Post-2015 Global TB Strategy [11, 12], but this will require greater resources.

While updated policy guidance on Xpert for the diagnosis of paediatric tuberculosis and EPTB was only issued in October 2013, 14 (59.1%) countries already reported recommending Xpert in children suspected of having tuberculosis. The use of Xpert for EPTB diagnosis was recommended in four (18%) countries.

WHO developed new recording and reporting recommendations in 2013 largely in response to the introduction of new molecular tests [13]. 14 (64%) countries recommended recording Xpert-positive results as bacteriologically positive, while three (14%) reported having no standards for reporting at this

TABLE 1 Policy and implementation data on Xpert MTB/RIF from 22 high tuberculosis (TB) burden countries

Country (WHO classification)	Estimated HIV+ TB cases[#] n	Estimated MDR-TB among notified TB cases[#] n	Total MDR cases that are new TB cases[#,¶] %	Xpert policy	Cartridges procured[§] n	Smear/ Xpert cartridge ratio[f]	Modules procured[§] n	Availability in private sector	Algorithm	SLT initiation	
										Patients with high risk of DR	Patients with low risk of DR
Afghanistan	310	1150	65	N	570 (460)	37.0	6	N	DR	Treat w/DST	Treat w/ DST
Bangladesh (HDR)	240	4200	45	Y	114 910 (96 300)	15.0	376	Y w/PPM	DR	Treat no DST	Treat w/ DST
Brazil (HTH)	16 000	1710	50	Y	290 930 (256 670)	6.2	716	Y w/o PPM	All EPTB Children	Under revision	
Cambodia (HTH)	2700	386	85	Y	57 640 (20 690)	21.1	96	N	DR HIV+	Treat w/DST	Wait
China (HDR, HTH)	7300	60 000	82	Y	240 000 (227 560)	74.3	3812	Y w/o PPM	DR	Treat no DST	Wait
DR Congo (HDR, HTH)	16 000	2860	73	Y	67 740 (24 780)	31.2	110	N	DR HIV+	Treat w/DST	Treat w/DST
Ethiopia (HDR, HTH)	23 000	2080	77	Y	37 040 (12 680)	378.5	104	Y w/o PPM	DR HIV+ Children	Treat no DST	Treat w/o DST
India (HDR, HTH)	130 000	64 000	33	Y	379 200 (232 150)	71.5	598	Y w/PPM	DR HIV+ Children	Treat w/DST	Wait
Indonesia (HDR, HTH)	7500	6800	85	Y	52 950 (41 250)	39.3	284	Y w/PPM	DR HIV+	Treat w/DST	Wait
Kenya (HTH)	45 000	2780	65	Y	147 950 (81 010)	47.6	370	Y w/PPM	DR HIV+ Children	Treat w/DST	Wait
Mozambique (HTH)	83 000	1940	72	Y	76 020 (31 700)	6.2	108	N	DR HIV+ Children	Treat w/DST	Treat w/DST
Myanmar (HDR, HTH)	19 000	6100	80	Y	72 520 (40 100)	23.2	164	N	DR HIV+ Children	Wait	Wait
Nigeria (HDR, HTH)	46 000	3600	69	Y	76 840 (38 080)	27.8	400	Y w/PPM	DR HIV+ EPTB	Wait	Wait
Pakistan (HDR)	3800	11 400	68	Y	98 200 (45 860)	31.0	294	Y w/PPM	DR HIV+ EPTB	Treat w/DST	Wait for 2nd Xpert
Philippines (HDR)	460	15 300	55	Y	71 780 (34 350)	41.9	404	Y w/PPM	DR HIV+ EPTB Children	Wait	Wait
Russia (HDR, HTH)	9300	45 000	44	N	15 490 (2 950)	2386.4	58	N	All	Treat w/DST	Treat w/DST
	330 000	8100	43	Y		1.6	4132	Y w/o PPM		Treat w/DST	Wait

Continued

TABLE 1 Continued

Country (WHO classification)	Estimated HIV$^+$ TB cases[#] n	Estimated MDR-TB among notified TB cases[#] n	Total MDR cases that are new TB cases[#,¶] %	Xpert policy	Cartridges procured[§] n	Smear/ Xpert cartridge ratio[f]	Modules procured[§] n	Availability in private sector	Algorithm	SLT initiation	
										Patients with high risk of DR	Patients with low risk of DR
South Africa (HDR, HTH)					4 228 480 (2 312 280)						
Tanzania	32 000	500	100	Y	113 550 (56 640)	12.0	192	N	ALL EPTB Children DR, Unknown HIV$^+$	Treat w/o DST	Wait
Thailand (HTH)	12 000	1760	45	Y	24 560 (10 330)	123.9	85	Y w/o PPM	Children DR HIV$^+$	Treat w/DST	Wait
Uganda (HTH)	35 000	1010	53	Y	84 560 (50 340)	4.1	266	N	(smear$^-$) DR HIV$^+$	Treat w/ or w/o DST[##]	Wait
Vietnam (HDR, HTH)	9300	3800	55	Y	54 930 (31 130)	62.6	158	Y w/o PPM	(smear$^-$) DR HIV$^+$	Treat w/DST	Wait
Zimbabwe (HTH)	55 000	930	61	Y	146 340 (83 590)	0.6	300	N	Children DR Unknown HIV$^+$ Children	Under revision	

WHO: World Health Organization; MDR: multidrug-resistant; SLT: second-line treatment; DR: drug resistance; HDR: high MDR-TB burden; HTH: high TB/HIV burden; N: no; Y: yes; PPM: private–public mix initiatives (initiatives encouraged by WHO to promote the collaboration between private and public health providers in the delivery of TB care); EPTB: extrapulmonary TB HIV$^+$ (smear$^-$): HIV$^+$ patients presumed to have TB but with a negative smear; DST: drug susceptibility testing; wait: do not start until DR is confirmed. [#]: in 2012 [1]. [¶]: rather than retreatment TB patients. [§]: accumulated procurement until June 30, 2014 (and the accumulated procurement in the past 12 months) [4], under concessional pricing; the data do not include private sector procurement. [f]: ratio of the numbers of smears performed in high-burden countries for initial diagnosis to the numbers of Xpert cartridges procured in the same country; the annual smear volumes were collected for the year 2012 [5], the numbers of Xpert cartridges procured were for the last 12 months (July 2013 to June 2014). [##]: in Uganda, DR-TB contacts with TB symptoms require no confirmation before initiating SLT (w/o DST), while the other Xpert RIF-resistant patients suspected to have DR-TB will start on SLT with confirmatory DST.

time. These findings demonstrate progress after some early implementers documented challenges around unclear and inconsistent reporting [7].

Initial WHO guidance for treatment decisions for patients with rifampicin resistance but not at risk for DR-TB recommended follow-up DST using another method, citing poor positive predictive values for Xpert [2]. Recent evidence suggests that using phenotypic DST as the reference standard misses some rifampicin-resistant cases [14]. Currently, WHO recommends that a rifampicin-resistant Xpert result for persons suspected of having DR-TB is sufficient to initiate second-line treatment (SLT) [3]. Most countries initiate SLT for those with risk factors for drug resistance (without confirmation or while waiting for confirmation of Xpert results), while three (14%) require confirmatory DST prior to SLT initiation. For patients at low risk of drug resistance, 13 (59%) countries require confirmatory DST before initiating SLT. A number of countries reported that current guidelines are under review and likely to change as more evidence becomes available.

Overall, we found the uptake of WHO guidelines on Xpert has been relatively quick compared with other guidelines on new tuberculosis diagnostics, such as light-emitting diode microscopy or same-day smear diagnosis. However, previous studies [7] suggest the implementation of Xpert in the field may deviate from stated national policy, and we found current Xpert testing is mainly donor-funded, mostly limited to district or reference laboratories, and primarily used in patients suspected of having DR-TB, and to a lesser extent among persons suspected of HIV-associated tuberculosis. Models suggest that more restrictive implementation strategies might limit the impact of Xpert [15]. Therefore, we hope these results will serve to raise awareness about the need for more ambitious testing algorithms (*e.g.* universal DST) and implementation for greater impact, acknowledging this will only be possible with much greater investments in improved tuberculosis diagnosis and care from both donors and domestic funding.

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Xpert MTB/RIF implementation is mainly donor-funded, focused on DST and is not widely used outside South Africa http://ow.ly/CK4NS

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A mutation associated with clofazimine and bedaquiline cross-resistance in MDR-TB following bedaquiline treatment

To the Editor:

The world-wide increase in the incidence of multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) poses a major clinical challenge. The treatment outcome of MDR-TB and XDR-TB patients is often poor and unsuccessful in the absence of an optimal number of active drugs [1]. Novel antituberculous compounds are urgently required and only very few, such as bedaquiline, have recently been approved for tuberculosis treatment [2]. In a recent phase 2b clinical trial that was based on a 160 newly diagnosed MDR-TB patients, the addition of bedaquiline to a preferred background regimen for 24 weeks resulted in faster culture conversion and significantly more culture conversion at 120 weeks compared with the control group. However, there were more deaths in the bedaquiline than in the placebo group and half of these patients died due to tuberculosis. So far, it is unclear whether the death of any of these patients may have been associated with diminished susceptibility to bedaquiline [3].

Our study indicates that emergence of drug resistance to bedaquiline is already an ongoing threat, as we provide *in vivo* evidence of acquired resistance due to a mutation in an efflux pump-related gene, and its association with clofazimine and bedaquiline cross resistance in an *Mycobacterium tuberculosis* isolate from a patient with MDR-TB. In January 2011, a Tibetan refugee hospitalised with bilateral cavernous chest radiograph abnormality was diagnosed with MDR-TB at the Swiss Reference Center for Mycobacteria, Zurich, Switzerland. The *M. tuberculosis* isolate from the patient showed resistance to isoniazid, rifampicin, pyrazinamide, ethionamide, linezolid, moxifloxacin and streptomycin by quantitative drug susceptibility testing (DST) in the BACTEC MGIT 960 system (Becton-Dickinson Inc., East Rutherford, NJ, USA) (table 1) [4]. In line with the DST results, a combined and directly observed antituberculous therapy was initiated with cycloserine, capreomycin, para-aminosalicylic acid (PAS) and ethambutol. Published evidence indicates that treatment outcome of patients with MDR-TB whose isolates show resistance either to pyrazinamide or fluoroquinolones is poor in the absence of an adequate number of active drugs [5, 6]. In order to strengthen the efficacy of therapy with the less potent second-line drugs, the patient received bedaquiline on a compassionate basis between September 2011 and February 2012. Culture conversion was confirmed at the end of October 2011. The patient remained culture negative and therapy was terminated in March 2013.

In August 2013, the patient was re-admitted with fever, cough and acid-fast bacillus-positive sputum microscopy. Therapy was re-initiated with cycloserine, capreomycin, PAS, ethambutol, clofazimine and inhaled amikacin. Re-application for bedaquiline treatment was rejected by the manufacturer on the basis that the patient had already received treatment on a compassionate basis for 6 months. DST of the relapse isolate in 2013 confirmed the previous resistance pattern but, to our surprise, revealed additional resistance to clofazimine. The 2011 isolate was susceptible to clofazimine (table 1). Most notably, the patient never received clofazimine. Genotyping using 24-locus mycobacterial interspersed repetitive unit variable number tandem repeats did not identify differences between the post-relapse and the previous isolates from 2011, indicating a common clonal origin of these isolates [7]. Recently, Hartkoorn *et al.* [8] described a mechanism of cross-resistance between clofazimine and bedaquiline in *in vitro*-selected