Implementation of Xpert MTB/RIF in 22 high tuberculosis burden countries: are we making progress?

To the Editor:

By the end of 2016, approximately 23 million Xpert MTB/RIF® (Xpert) cartridges for tuberculosis (TB) diagnosis had been procured by the public sector in 130 countries at concessional pricing [1], but smear microscopy continues to be the most widely used test for TB [2]. To understand the true market penetration of Xpert in TB high burden countries (HBCs), we surveyed National TB Programmes (NTPs) or their partnering organisations in 22 HBCs to obtain Xpert data from 2015 and to assess dynamic trends from 2014 to 2015. These 22 countries had been previously surveyed by us in 2014 [3]. Q1

A questionnaire based on our previous studies [3, 4] was sent to representatives of each NTP or partnering organisation. Survey questions included smear usage, algorithms, Xpert placement in healthcare system, and Xpert cartridge and module procurement. Survey responses regarding procurement of cartridges were compared with 2015 procurement data obtained from Cepheid, *via* FIND. There was large variability between the two datasets, and four countries were unable to provide the data. To ensure consistency, we reported the cartridge procurement data from FIND for 2015, except for China, for which Cepheid data were not available, thus survey data were reported. World Health Organization (WHO) data were used to report country algorithms for 2015 except for Afghanistan, for which WHO data were not available [5], thus survey data were reported. Questionnaires were completed from September 2016 to February 2017. If responses were unclear, the respondent was re-contacted for clarification. Q2

Following the methodology of Qin *et al.*, a ratio was calculated that compared total smear volumes for initial diagnosis in 2015 with the number of Xpert cartridges procured in 2015 for each country [3]. This smear/Xpert ratio was used to represent Xpert market penetration in the public sector, and was compared with the smear/Xpert ratios from 2014. The percentage change in ratio from 2014 to 2015 was calculated for each country. Changes in diagnostic algorithms and level of placement of GeneXpert were also assessed.

In 2015, a total of 6.2 million cartridges were procured by 22 HBCs under concessional pricing, an increase from 4.8 million in 2014. South Africa, which for the past 4 years has been responsible for the majority of procurement, had a decrease in its share of cartridge procurement from 63% to 45% in 2015, despite remaining the highest procurer of cartridges for any one country (2 777 190 cartridges).

As seen in table 1 and figure 1, 19 out of the 22 HBCs (82%) had a decrease in their smear/Xpert ratios between 2014 and 2015, while Afghanistan, Zimbabwe and the Democratic Republic of the Congo (DRC) had an increase in their ratios. A decrease in ratio signifies an increased use in Xpert compared with smear microscopy for the diagnosis of TB. The median smear/Xpert ratio of countries decreased from 32.60 (Q1: 14.28, Q3: 58.85) in 2014 to 9.08 (Q1: 3.74, Q3: 26.64) in 2015. In 2014, five countries had a smear/Xpert ratio <10, 11 countries had a ratio of 10–50, three countries had a ratio of 51–100 and three had a ratio of >100. In comparison, in 2015, 13 countries had a smear/Xpert ratio <10, six countries had a ratio of 10–50, one country had a ratio of 51–100 and two countries had a ratio >100. The two countries with a ratio larger than 100 were Russia and the DRC. Further research is needed to understand the reasons for the low penetration of Xpert.

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Cite this article as: Cazabon D, Suresh A, Oghor C, *et al*. Implementation of Xpert MTB/RIF in 22 high tuberculosis burden countries: are we making progress? *Eur Respir J* 2017; 0: 1700918 [https://doi.org/10.1183/13993003.00918-2017].

TABLE 1 Policy and implementation data on Xpert MTB/RIF from 22 high tuberculosis (TB) burden countries in 2015

Country (WHO classification)	Cartridges procured[#] n	Modules procured[#] n	Initial smears[¶]	Smear/Xpert cartridge ratio[+]	Change in smear/Xpert ratio 2014–2015 %	Algorithm[§]
Thailand	45 190	120	192 585	4.26	−96.56	HIV+, DR, children, EPTB
South Africa	2 777 190	9	164 735	0.06	−96.29	All, HIV+, DR, children, EPTB
Nigeria	152 450	377	165 968	1.09	−96.08	HIV+, DR, children, EPTB
Kenya	199 150	252	570 000	2.86	−93.99	HIV+, DR, children, EPTB
Ethiopia	165 300	36	4 600 000	27.83	−92.65	HIV+, DR, children, EPTB
India	766 860	140	7 026 841	9.16	−87.18	HIV+, DR, children, EPTB
Philippines	169 200	516	1 628 642	9.63	−77.03	HIV+, DR, children, EPTB
Pakistan	181 800	106	1 384 621	7.62	−75.43	HIV+, DR, children, EPTB
Vietnam	88 400	84	1 651 749	18.68	−70.15	HIV+, DR, children, EPTB
China	220 000[f]	3600[f]	5 079 636	23.09	−68.92	DR
Myanmar	110 800	132	850 000	7.67	−66.93	HIV+, DR, EPTB[##]
Cambodia	38 300	135	344 345	8.99	−57.39	HIV+, DR, EPTB
Mozambique	66 550	128	207 441	3.12	−49.72	HIV+, DR, children, EPTB
Russia	4550	NA	6 096 500	1339.89	−43.85	All, children, HIV+, DR, EPTB
Brazil	207 350	280	820 000	3.95	−36.22	All, HIV+, DR, children, EPTB
United Republic of Tanzania	33 990	64	362 054	10.65	−11.24	All, HIV+, DR, children, EPTB
Uganda	84 280	24	309 068	3.67	−10.56	HIV+, DR, children
Bangladesh	116 800	2	3 615 109	30.95[¶¶]	−8.97	HIV+, DR, EPTB
Indonesia	70 000	88	2 678 829	38.27	−2.62	HIV+, DR, children, EPTB
Afghanistan	4450	20	437 688	98.36	165.83	HIV+, DR[++]
Zimbabwe	75 570	180	224 284	2.97	394.65	HIV+, DR, children, EPTB
DR Congo	12 800	46	2 760 000	215.63	591.11	DR

[#]: accumulated procurement in 2015 (data from FIND). [¶]: for those countries that were not able to stratify total smears for initial diagnosis and treatment monitoring we assumed that, on average, 76% of the total sputum smears were performed for initial diagnosis (the average proportion reported by 16 countries able to stratify smears) [4]. [+]: 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 and the numbers and the numbers of Xpert cartridges procured were collected for 2015. [§]: national policy stipulating Xpert MTB/RIF as the initial diagnostic test for: all: all people presumed to have TB; DR: people at risk of drug resistant TB; EPTB: extrapulmonary TB using selected specimens; HIV+: people at risk of HIV-associated TB; children: children presumed to have TB. [f]: FIND data not available. [##]: Yangon region is testing Xpert MTB/RIF for all registered TB cases; extrapulmonary TB specimen is cerebrospinal fluid only. [¶¶]: 2014 smear/Xpert ratio for Bangladesh [3] corrected to 34.06. [++]: World Health Organization (WHO) data not available; 2015 Afghanistan survey data was used. [§§]: Tanzania could only provide total smear positive TB cases, so an estimate of initial smears was based on the average proportion of total smears performed for initial diagnosis reported by Kenya and Zimbabwe, countries with a TB burden similar to that of Tanzania.

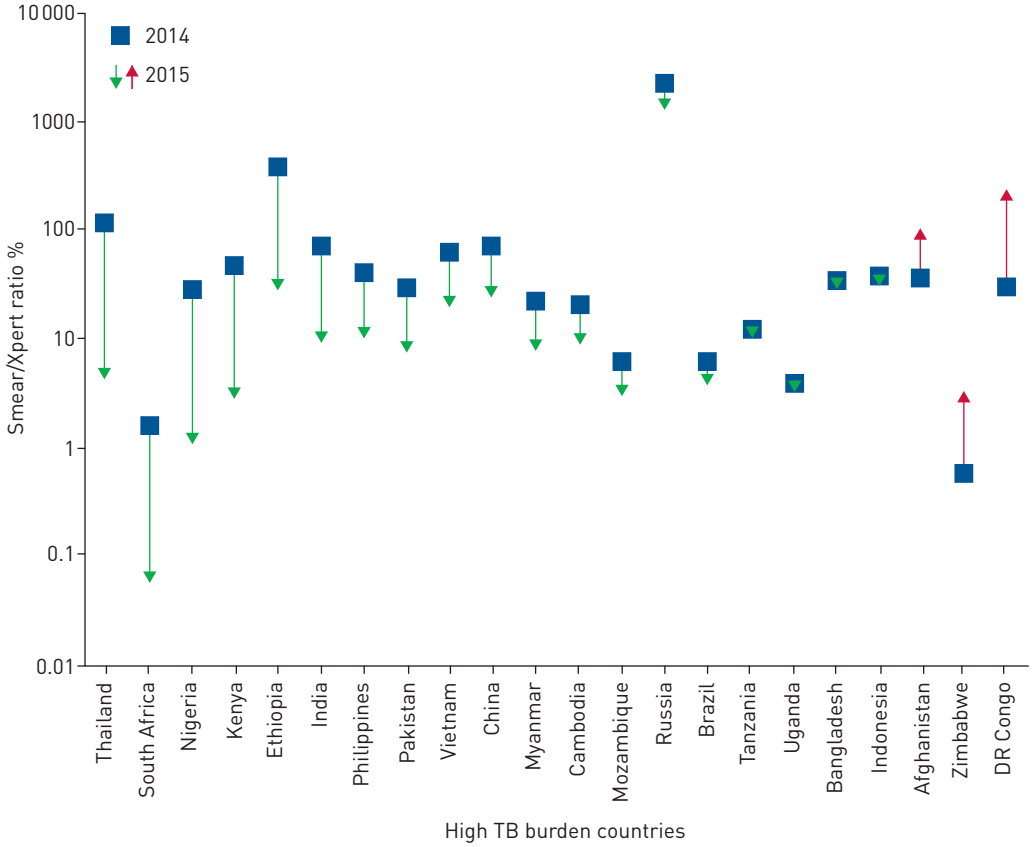

FIGURE 1 Uptake of Xpert MTB/RIF in 22 high tuberculosis (TB) burden countries in 2015, listed by greatest decrease in smear/Xpert ratio from 2014–2015. Arrows represent percentage changes in smear/Xpert ratios from 2014–2015. Trends moving closer to 0 (decreasing ratio) signify a greater use of Xpert compared to smear microscopy for the diagnosis of TB. Trends moving away from 0 (increasing ratio) signify a greater use of smear microscopy compared to Xpert for the diagnosis of TB.

Of the 22 countries surveyed, 18 (82%) have expanded their algorithms since early 2014. Seventeen countries (77%) had Xpert as an initial test for all children presumed to have TB in 2015, compared with 14 (64%) in 2014 [3]. Furthermore, 18 (82%) countries now include Xpert testing for extrapulmonary TB (EPTB), compared with four (18%) in 2014 [3]. In 2015, 20/22 (91%) countries had what can be considered decentralised placement of Xpert (being placed in either district/sub-district health centres or microscopy centres). This number increased from 2014, when only 18/22 (82%) countries had decentralised placement.

Thailand, South Africa, Nigeria and Kenya had the largest decrease in their smear/Xpert ratios since 2014. In 2015, the four countries had decentralised placement of Xpert. They also all had Xpert included widely in their diagnostic algorithms, using Xpert as the initial diagnostic testto diagnose pulmonary TB and rifampicin resistance in people living with HIV, children, those at risk of multidrug resistant TB (MDR-TB) and those at risk of EPTB. To ensure coverage of these WHO-recommended groups, Thailand added Xpert testing for children and those at risk for EPTB to its algorithm since 2014, Nigeria added children, and Kenya added those at risk of EPTB. South Africa was already using Xpert to test all individuals presumed to have TB in 2014, and made no changes to their algorithm in 2015.

Smear/Xpert ratios increased in DRC, Zimbabwe and Afghanistan between 2014 and 2015. All three countries reported centralised placement of Xpert (in regional or national labs only). Survey responses as well as recent studies suggest that challenges with sputum transportation and limited testing algorithms might be contributing to the observed trends [6]. It was also reported that during early implementation of Xpert in 2014, certain areas in Zimbabwe performed multiple Xpert tests on the same individual. In these cases, a decrease in redundant cartridge usage in 2015, rather than an increase in smear usage, could contribute to an increase in ratio [7].

A limitation to our study is that only public sector data were utilised and therefore it may not be representative of all smears performed and all cartridges procured within each country. In India, for

example, approximately half the TB cases are managed in the private sector and are not necessarily captured under the Revised National Tuberculosis Control Programme (RNTCP) TB notification system [8]. Including the private sector in future studies would enable a more complete analysis. It is also worth noting that countries such as India have invested heavily in Xpert since 2015, and these recent trends are not captured in our analysis. For example, in 2016, the RNTCP procured 500 GeneXpert machines, expanding the rapid molecular diagnostic facilities to 628 laboratories [9]. Another limitation is that procurement data do not necessarily reflect the actual utilisation, and we could not separate volumes of cartridges procured by donors (*e.g.* Global Fund) from those procured by others. Under-utilisation of GeneXpert has been reported in many countries due to challenges such as cost and infrastructure [10].

While our study focused on the 22 HBCs to allow for comparison of 2015 status with previous studies, three new HBC lists of 30 countries each (or 48 countries in total), accounting for TB, TB/HIV and MDR-TB, have been defined by the WHO as part of the End TB Strategy [11]. It would be useful to expand the current analysis to all these countries in future.

In summary, implementation of Xpert in 22 HBCs has progressed well since 2014, although much more can be done to reach scale [2]. The median smear/Xpert ratio decreased from 23.5 to 9.1, 82% of countries expanded their algorithms to include more WHO-recommended groups, and 9% of countries further decentralised Xpert placement in healthcare systems compared with 2014. While we cannot conclude that the performance of HBCs in this study resulted from specific changes in policies, algorithms or level of placement, our study presents a dynamic picture of how countries are advancing in the uptake of Xpert, and identifies countries that may require more support.

Danielle Cazabon[1], Anita Suresh[1], Collins Oghor[2], Zhi Zhen Qin[3], Sandra V. Kik[4], Claudia M. Denkinger[5] and Madhukar Pai[1,6]

[1]McGill International TB Centre, McGill University, Montreal, QC, Canada. [2]Faculty of Medicine, McGill University, Montreal, QC, Canada. [3]Stop TB Partnership, Geneva, Switzerland. [4]KNCV Tuberculosis Foundation, The Hague, Netherlands. [5]FIND, Geneva, Switzerland. [6]Dept of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, QC, Canada.

Correspondence: Madhukar Pai, McGill University, Dept of Epidemiology and Biostatistics, 1020 Pine Ave West, Montreal, QC H3A 1A2, Canada. E-mail: madhukar.pai@mcgill.ca

Received: May 04 2017 | Accepted after revision: May 31 2017

Support statement: This study was funded by the Foundation for Innovative New Diagnostics. Funding information for this article has been deposited with the Crossref Funder Registry.

Conflict of interest: Disclosures can be found alongside this article at erj.ersjournals.com

Acknowledgements: We are grateful to survey respondents from 22 countries for their time and support. This work was supported by a FIND-McGill Partnership grant.

References

1 World Health Organization. Status of Xpert MTB/RIF testing capacity and cartridge procurements as of December 2016. Geneva, WHO, 2017. www.who.int/tb/areas-of-work/laboratory/status_xpert_rollout_dec_2016.pdf?ua=1 Date last accessed: April 17, 2017.
2 Pai M, Furin J. Tuberculosis innovations mean little if they cannot save lives. *eLife* 2017; 6: e25956.
3 Qin ZZ, Pai M, Van Gemert W, *et al.* How is Xpert MTB/RIF being implemented in 22 high tuberculosis burden countries? *Eur Respir J* 2015; 45: 549–554.
4 Kik SV, Denkinger CM, Chedore P, *et al.* Replacing smear microscopy for the diagnosis of tuberculosis: what is the market potential? *Eur Respir J* 2014; 43: 1793–1796.
5 World Health Organization. Global Tuberculosis Report. Geneva, WHO, 2016. www.who.int/tb/publications/global_report/gtbr2016_executive_summary.pdf?ua=1 Date last accessed: April 17, 2017.
6 Mbonze NB, Tabala M, Wenzi LK, *et al.* Xpert® MTB/RIF for smear-negative presumptive TB: impact on case notification in DR Congo. *Int J Tuberc Lung Dis* 2016; 20: 240–246.
7 Charambira K, Ade S, Harries AD, *et al.* Diagnosis and treatment of TB patients with rifampicin resistance detected using Xpert(®) MTB/RIF in Zimbabwe. *Public Health Action* 2016; 6: 122–128.
8 Satyanarayana S, Nair SA, Chadha SS, *et al.* From where are tuberculosis patients accessing treatment in India? Results from a cross-sectional community based survey of 30 districts. *PLoS One* 2011; 6: e24160.
9 Revised National TB Programme. TB India 2017. Annual Status Report. New Dehli: Central TB Division, Directorate General of Health Services; 2017. http://tbcindia.nic.in/WriteReadData/TB%20India%202017.pdf Date last accessed: April 24, 2017.
10 Creswell J, Codlin AJ, Andre E, *et al.* Results from early programmatic implementation of Xpert MTB/RIF testing in nine countries. *BMC Infect Dis* 2014; 14: 2.
11 World Health Organization Strategic and Technical Advisory Group for TB (STAG-TB). Use of high burden country lists for TB by WHO in the post-2015 era. Geneva, WHO, 2015, www.who.int/entity/tb/publications/global_report/high_tb_burdencountrylists2016-2020.pdf?ua=1 Date last accessed: April 17, 2017.

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Q1 Please give manufacturer's details for Xpert MTB/RIF.

Q2 Please define FIND.

Q3 The final footnote item was not mentioned in the original table (only in the legend). Please indicate which part of the table the note refers to.