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RESEARCH ARTICLE

REVISED Market penetration of Xpert MTB/RIF in high tuberculosis burden countries: A trend analysis from 2014 - 2016 [version 2; peer review: 4 approved]

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Abstract

Background: Xpert® MTB/RIF, a rapid tuberculosis (TB) molecular test, was endorsed by the World Health Organization in 2010. Since then, 34.4 million cartridges have been procured under concessional pricing. Although the roll out of this diagnostic is promising, previous studies showed low market penetration.

Methods: To assess 3-year trends of market penetration of Xpert MTB/RIF in the public sector, smear and Xpert MTB/RIF volumes for the year 2016 were evaluated and policies from 2014-2016 within 22 high-burden countries (HBCs) were studied. A structured questionnaire was sent to representatives of 22 HBCs. The questionnaires assessed the total smear and Xpert MTB/RIF volumes, number of modules and days of operation of GeneXpert machines in National TB Programs (NTPs). Data regarding the use of NTP GeneXpert machines for other diseases and GeneXpert procurement by other disease control programs were collected. Market penetration was estimated by the ratio of total sputum smear volume for initial diagnosis divided by the number of Xpert MTB/RIF tests procured in the public sector.

Results: The survey response rate was 21/22 (95%). Smear/Xpert ratios decreased in 17/21 countries and increased in four countries, since 2014. The median ratio decreased from 32.6 (IQR: 44.6) in 2014 to 6.0 (IQR: 15.4) in 2016. In 2016, the median GeneXpert utilization was 20%, however seven countries (7/19; 37%) were running tests for other diseases on their NTP-procured GeneXpert systems in 2017, such as HIV, hepatitis-C virus (HCV), *Chlamydia trachomatis*, and *Neisseria gonorrhoeae*. Five (5/15; 33%) countries reported GeneXpert procurement by HIV or HCV programs in 2016 and/or 2017.

Conclusions: Our results show a positive trend for Xpert MTB/RIF market

Open Peer Review

Reviewer Status ✓ ✓ ✓ ✓

	Invited Reviewers			
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REVISED **version 2** published 18 Sep 2018				
version 1 published 25 Jul 2018	✓ report	✓ report	✓ report	✓ report

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penetration in 21 HBC public sectors. However, GeneXpert machines were under-utilized for TB, and inadequately exploited as a multi disease technology.

Any reports and responses or comments on the article can be found at the end of the article.

Keywords
tuberculosis, diagnostics, market penetration, Xpert MTB/RIF, access

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Competing interests: SK and CD are employed by FIND. FIND is a not-for-profit foundation that supports the evaluation of publicly prioritized tuberculosis assays and the implementation of WHO-approved (guidance and prequalification) assays using donor grants. FIND has product evaluation agreements with several private sector companies, including Cepheid Inc, that design diagnostics and related products for treatment of tuberculosis and other diseases. These agreements strictly define FIND's independence and neutrality vis-a-vis the companies whose products get evaluated and describe roles and responsibilities. MP previously consulted for the Bill & Melinda Gates Foundation. He serves on the Access Advisory Committee of FIND, Geneva. The other authors have no conflicts to disclose.

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REVISED **Amendments from Version 1**

This revised manuscript incorporates the changes suggested by our reviewers. We have provided more specific details for our results and edited our discussion section accordingly. Minor grammatical edits have also been made.

See referee reports

Introduction

Tuberculosis (TB), caused 1.7 million deaths in 2016, surpassing human immunodeficiency infection and acquired immune deficiency syndrome (HIV/AIDS) as the leading cause of death. The World Health Organization (WHO) reported 10.4 million new TB cases in 2016, with 87% of them occurring in 30 high TB burden countries (HBCs).

The WHO endorsed the Xpert® MTB/RIF assay (Xpert MTB/RIF; Cepheid, Sunnyvale, CA, USA) for TB in 2010. By the end of 2017, 34.4 million Xpert MTB/RIF reagent cartridges had been procured in the public sector under concessional pricing[1]. Xpert Ultra, a test with a higher sensitivity than Xpert MTB/RIF, was released in 2017 and also endorsed by the WHO[2].

While the roll out of these diagnostic tools is promising, previous analyses from Qin *et al.* in 2014 and Cazabon *et al.* in 2015 showed low market penetration in comparison to the conventional sputum smear microscopy test - there were 32.6 and 9.1 sputum smears for every Xpert MTB/RIF test procured in 2014 and 2015, respectively[3,4]. To assess 3-year trends in the public sector, we evaluated the smear and Xpert MTB/RIF volumes for the year 2016 and studied changes in Xpert MTB/RIF market penetration and policies from 2014–2016 within 22 HBCs.

Methods

A structured questionnaire (Supplementary File 1) was created based on two previous studies[3,4], and sent via e-mail to staff members of Ministries of Health, National TB Programs (NTP), National Reference Laboratories and TB research institutes of 22 HBCs, as defined by WHO prior to 2015[5]. A maximum of two staff members were contacted per HBC. A response was taken as consent to participate in this study. Ethics approval was not obtained, as this was a market research study on test volumes, and no human subject data were collected.

The survey included questions about smear volumes (stratified by smears used for initial diagnosis vs. treatment monitoring), the number of Xpert MTB/RIF tests conducted in the country, the number of days of operation of NTP GeneXpert machines, and the number of NTP GeneXpert modules in operation, all for the year 2016. The questionnaire also included questions on implementation of Xpert Ultra, the use of NTP GeneXperts for other diseases (e.g. HIV), and other programme procurement of GeneXpert in the year 2017.

Data on Xpert MTB/RIF cartridge procurement was obtained from Cepheid, via Foundation for Innovative New Diagnostics (FIND) and WHO-recommended TB rapid diagnostics (WRD) algorithms were obtained from WHO[1]. WRDs include Xpert MTB/RIF and TB-LAMP (loop-mediated isothermal amplification)[1]; however based on expert knowledge of limited LAMP adoption to date and to allow comparisons with previous years, we assumed WRDs to be represented by Xpert MTB/RIF only.

Data were collected between November 2017 and March 2018. Participants were contacted via e-mail a maximum of three times to respond. If any clarification was required, the participant was contacted.

Xpert MTB/RIF market penetration, estimated by the ratio of total sputum smear volume for initial diagnosis divided by the number of Xpert MTB/RIF tests procured in the public sector, was calculated for 2016 in each country (smear/Xpert ratio;[4]) and compared to the same ratio in 2014 and 2015. A decreasing ratio signified a greater use of Xpert compared to smear microscopy for the diagnosis of TB. The median smear/Xpert ratio was calculated for 2016 and compared to prior years.

To calculate the percent utilization of GeneXpert for TB diagnosis in the public sector, the actual number of Xpert MTB/RIF tests conducted in 2016 was compared to the full capacity of GeneXpert for TB diagnosis during the same year. Full capacity of GeneXpert for TB diagnosis was calculated using the following assumptions; an 8-hour workday and 2 hours to run each Xpert MTB/RIF test, i.e. 4 tests per module per working day. This was multiplied by the number of operating days of GeneXpert in 2016. Data were entered and tabulated using Excel 2016.

Results

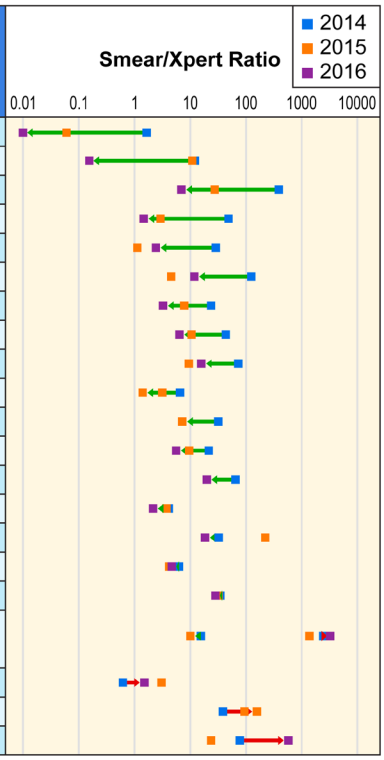
Data from Cepheid and WHO reports were available for all 22 HBCs. Our survey response rate was 21/22 (95%). All missing values were marked as "not available" (NA) and were removed from descriptive analyses.

In 2016, 6.9 million Xpert MTB/RIF cartridges had been procured globally in the public sector under concessional pricing, compared to 4.8 million in 2014. In the 22 HBCs that we studied, a total of 5.8 million Xpert MTB/RIF cartridges were procured in 2016. According to the WHO Global TB Report, 10/22 (48%) countries included Xpert MTB/RIF in their national policy stipulating the use of Xpert MTB/RIF as the initial diagnostic test for all people presumed to have TB in 2016, compared to 4/22 (18%) countries in 2015[1,6]. Overall, smear/Xpert ratios decreased in 17/21 (81%) HBCs and increased in four (19%) from 2014 to 2016. The median ratio decreased from 32.6 (IQR: 44.6) in 2014 to 6.0 (IQR: 15.4) in 2016 (Figure 1).

Figure 1 shows thirteen (66%) countries had a smear/Xpert ratio <10, five (19%) countries between 10–50, no countries

[1]No data available from WHO Global TB Report on the use of WRD as an initial diagnostic for all individuals with presumed TB in country algorithms for the year 2014.

Country (WHO classification)	Cartridges Procured # (n)	Modules Operating (n)	Initial Smears ¶ (n)	Smear/ Xpert Cartridge Ratio*	Change in smear/Xpert ratio 2014-2016, %	WRD Algorithm§	Utilization of GeneXpert€, % of full capacity (days of operation/year)
South Africa	2,440,400	3476	0	<0.01∞	-100.0	Yes	40% (365)
Tanzania	97,850	460	14,584	0.2	-98.8	Yes	1% (280)
Ethiopia	153,400	448	1,041,200	6.8	-98.2	No	14% (260)
Kenya	262,650	600	371,467	1.4	-97.0	Yes	56% (146)
Nigeria	306,700	1272	708,695	2.3	-91.7	Yes	13% (240)
Thailand	33,400	140	378,919	11.3	-90.8	No	22% (264)
Myanmar	130,900	300	420,000	3.2	-86.2	No	22% (264)
India	862,870	1256	13049540	14.0	-80.5	Yes	48% (240)
Philippines	283,050	800	1,802,700	6.4	-84.8	No	20% (264)
Mozambique	123,450	288	165,996	1.3	-78.3	Yes	35% (261)
Pakistan	194,600	380	1,402,231	7.2	-76.8	No	28% (300)
Cambodia	55,350	300	305,402	5.5	-73.8	No	15% (240)
Viet Nam	79,000	266	1,540,621	19.5	-68.8	No	19% (252)
Uganda	167,050	150	360,416	2.2	-47.4	Yes	66% (365)
DR Congo	28,350	226	509,711	18.0	-42.4	No	6% (240)
Brazil	247,000	672	1,109,410	4.5	-27.6	Yes	34% (200)
Bangladesh	129,000	204	3,713,376	28.8	-15.3	No	19% (312)
Russian Federation	1,800	NA	5,774,285	3207.9	34.4	Yes	NA (NA)
Zimbabwe	141,650	508	20,1234	1.4	136.8	Yes	14% (264)
Afghanistan	5,750	6	88,1549	153.3	314.4	NA	19% (260)
China	10,000	1200	576,6659	576.7	676.1	No	NA (120)



WHO: World Health Organization; WRD: WHO-recommended rapid diagnostic; NA: not available; #: accumulated procurement in the public sector under concessional prices in 2016 (data from Cepheid received via The Foundation for Innovative New Diagnostics). ¶: for those countries who were not able to stratify total smears for initial diagnosis and treatment monitoring we assumed that, on average, 72% of the total sputum smears were performed for initial diagnosis (the average proportion reported by 12 countries able to stratify smears) [14] ∞ :South Africa reported no longer using smear microscopy for the initial diagnosis of TB. *: 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 of Xpert MTB/RIF cartridges procured were collected for 2016. §: national policy stipulating WRD as the initial diagnostic test for all people presumed to have TB [6] €: Percent difference between utilization at full capacity and actual utilization. Calculations described in manuscript.

Figure 1. Xpert MTB/RIF market penetration in the public sector of 21 high TB burden countries (2014–2016). South Africa decreased its smear/Xpert ratio by 100%, therefore has achieved the highest market penetration of Xpert MTB/RIF in the public sector. Countries are listed in order of greatest percent decrease in smear/Xpert ratio from 2014–2016. Arrows represent percent changes in smear/Xpert ratios 2014–2016. Trends moving closer to 0 (ratio decreasing) signify a greater use of Xpert compared to smear microscopy for the diagnosis of TB. Trends moving away from 0 (ratio increasing) signify a greater use of smear microscopy compared to Xpert for the diagnosis of TB.

between 51–100 and three (14%) countries had a ratio >100, in 2016. Whereas in 2014, five (23%) countries had a ratio <10, 11 (50%) countries between 10–50, three (14%) countries between 51–100 and three (14%) countries had a ratio of >100. South Africa had the largest decrease in smear/Xpert ratio from 2014–2016.

Countries in the African region had a median decline of 34% in the number of initial smears conducted between 2014 and 2016. In South East Asia, Western pacific and the other WHO regions, the median changes in initial smears were -41%, -26% and +2%, respectively. Figure 2 and Figure 3 show the trends of initial smears conducted and Xpert MTB/RIF procurement in each country over the period of 2014–2016, respectively. In 2016, the median GeneXpert utilization was 20%.

Table 1 describes other uses of GeneXpert machines in each HBC. Five (5/21; 24%) countries had procured Xpert Ultra in 2017; three (14%) were utilizing it in the public sector and two (10%) had not yet implemented it. Six (29%) countries have no current plans to procure it in 2018 whereas ten (48%) plan to procure it in 2018. In addition to Xpert MTB/RIF, seven countries (7/19; 37%) were also utilizing tests for other diseases on their NTP-procured GeneXperts in 2017, such as HIV, hepatitis-C virus (HCV), *Chlamydia trachomatis*, and *Neisseria gonorrhoeae*. South Africa was utilizing the previously mentioned tests, as well as *Clostridium difficile*; carbapenem resistance; and influenza. GeneXperts have also been procured by other programmes; 5/15 (33%) countries reported procurement by HIV or HCV programmes in 2016 and/or 2017.

Discussion

Overall, our data shows that high-burden countries have demonstrated a positive trend towards greater use of Xpert MTB/RIF. South Africa had the largest percent decrease in smear/Xpert ratio from 2014–2016, making it the leader in GeneXpert market penetration. This is underscored by the fact that South Africa did not report any smears for initial diagnosis of TB in 2016.

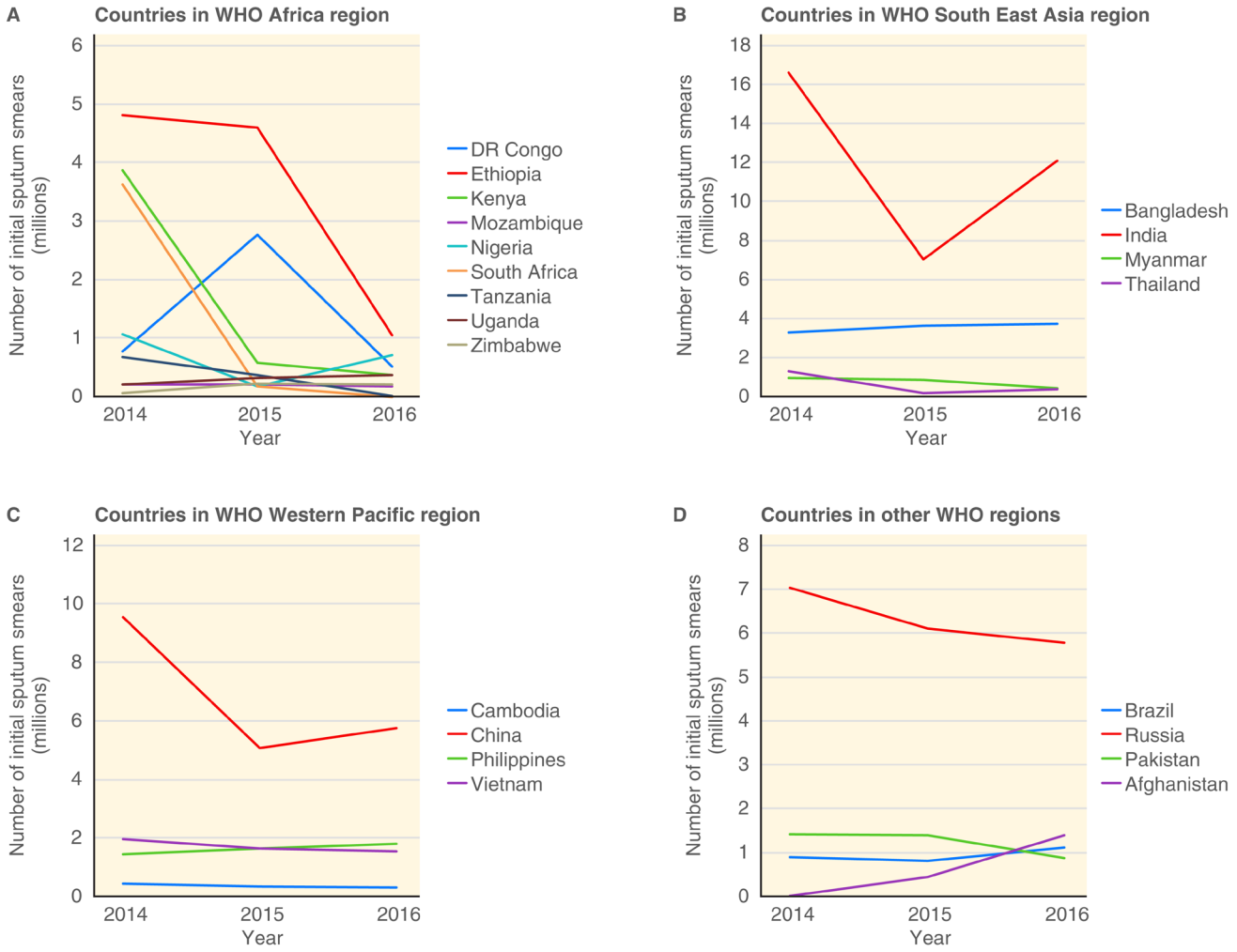


Figure 2. Initial sputum smear microscopy use in World Health Organization (WHO) regions from 2014–2016.

Despite our 3-year trend analysis having shown an increase in the number of countries that included Xpert MTB/RIF in their national policy as the initial diagnostic test for all people presumed to have TB since 2014, only 48% of countries had it included in 2016. More countries are encouraged to adopt this policy to achieve an increase of TB and drug resistant TB (DR-TB) case detection[1]. Xpert MTB/RIF may require high upfront and running costs, however it has been shown in India (a high burden MDR-TB country) that the mean total costs (per MDR case initiated on treatment) are lower when using Xpert MTB/RIF for all presumptive TB patients, compared to solely using it for those at risk of DR-TB[7]. This is particularly relevant for high MDR-TB countries, who represent 17 (77%) of the 22 HBCs.

While most countries showed a positive trend towards greater use of Xpert MTB/RIF, a few showed decreasing Xpert use. A potential explanation for countries with decreasing market penetration trends, (i.e. increasing smear/Xpert ratios), could be the end of Global Fund grants causing a transition to domestic-financing and procurement by NTPs[8]. For example, China's Xpert MTB/RIF procurement decreased considerably in 2016 and the number of initial smears increased, suggesting that other diagnostics tests were being used instead of Xpert MTB/RIF. The Global Fund's substantial co-financing requirements will shift financing and procurement responsibilities towards national programs over the next three years. Close monitoring of the impact on TB diagnostics procurement, utilization, and market penetration will be important to identify and address barriers to access.

Most of the countries in the African region had a decline in the number of initial smears conducted (median= -34%) between 2014 and 2016 (Figure 2), suggesting that Xpert MTB/RIF is replacing smears for the initial diagnosis of TB in most instances. In other regions, there is a slight increase in the use of initial smears (median= +2%). A possible explanation could be the use of GeneXpert in addition to smear for initial diagnosis,

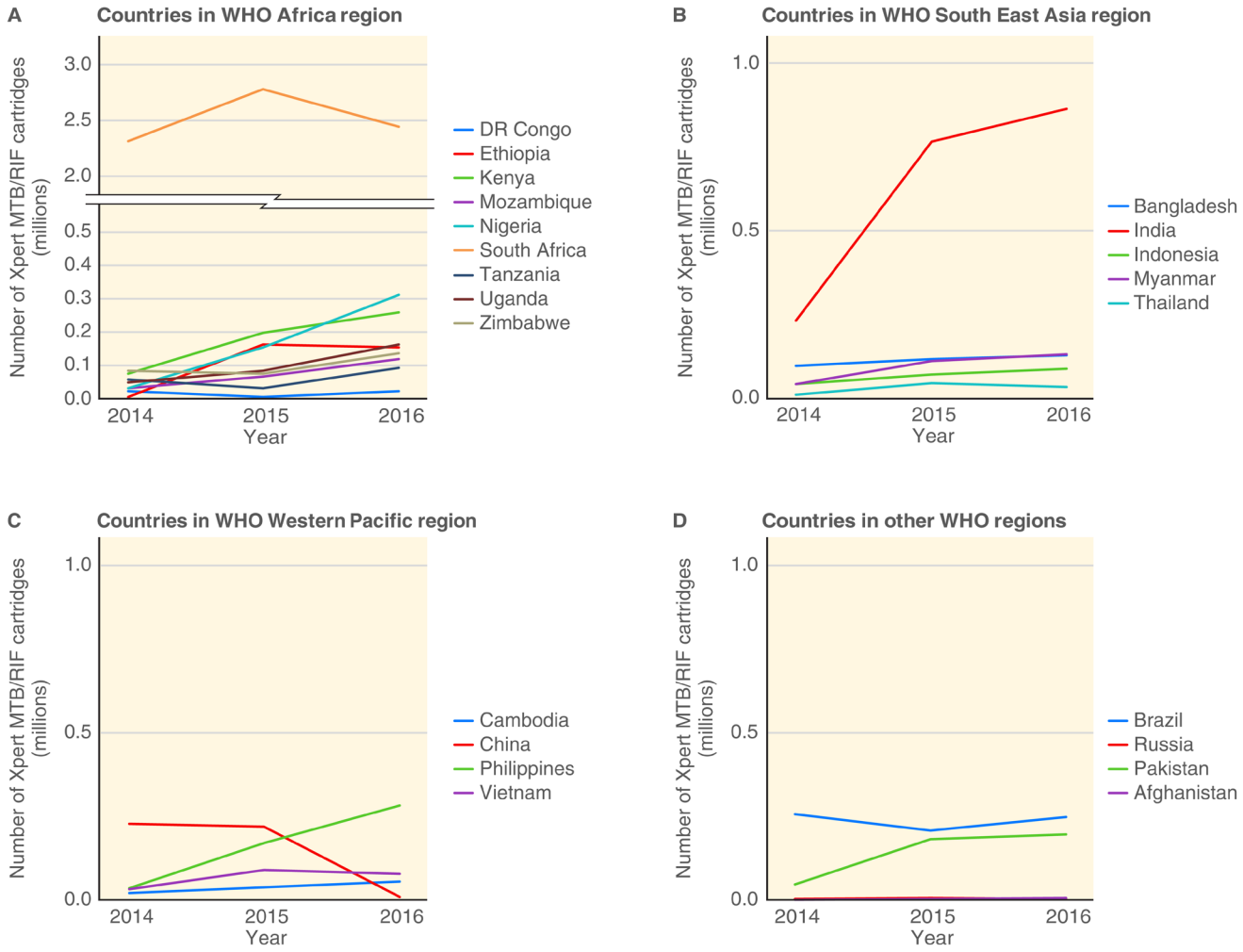


Figure 3. Xpert MTB/RIF cartridge procurement in World Health Organization (WHO) regions from 2014–2016.

or only using it to test specific populations (e.g. those at risk for multi-drug resistant TB (MDR-TB)). Certain countries, such as India and the Democratic Republic of Congo, showed an overall decline in initial smears between 2014 and 2016, however there were large peaks in 2015. This could be due to variations in reporting from year to year.

All countries in our study were underutilizing GeneXpert for TB testing. This is consistent with results from a study conducted in 18 countries where 63% of sites surveyed had access to Xpert MTB/RIF, but only 4% of TB/HIV co-infected patients had been tested for TB using Xpert MTB/RIF. Further, over 50% of the patients that did not receive a TB test at all were treated at facilities where a GeneXpert was available on-site[9].

Full utilization of GeneXpert requires various components such as; familiarization of the technology among health care workers, efficient supply chain, rapid swapping of failed modules, an efficient and wide-reaching sample referral system, and moving away from reliance on empiric treatment, which remain barriers to implementation in certain countries[9,10].

While certain countries in our study were integrating testing services between disease control programmes, our results elucidate the need for more integration amongst vertical disease programs to increase efficient utilization of GeneXpert, which is a multi-disease platform. For example, NTP-procured GeneXpert machines can be utilized to run other tests, such as Xpert HIV-1 viral load (VL)[11]. Zimbabwe has recently shown that integration of the GeneXpert platform for MTB/RIF, HIV-1 VL and HIV-1 qualitative test/Early infant diagnosis (qual/EID) was feasible and improved access to these tests in priority populations[12]. Further, the use of GeneXpert as a multi-disease platform may potentially eliminate redundant purchases of machines thus decreasing equipment costs to health ministries.

Table 1. Other public sector utilization of GeneXpert in 21 high tuberculosis (TB) burden countries (2016–2017).

Country (WHO classification)	Use of NTP GeneXpert for diagnosing other diseases (2017)	Other programs procuring GeneXpert machines (2016, 2017)	Implementation of Xpert Ultra cartridges in the public sector (2017)
South Africa	HCV VL, HIV-1 VL, HPV, NG/CT, C Diff, Carba R, Influenza	HIV	Procured and in use in the public sector
India	No	NA	In discussion*
Tanzania	HCV-VL, HIV-1 VL, HIV-1 qual/EID	No	Procured and in use in the public sector, plan to procure in 2018 (private sector)
Ethiopia	Piloting (HIV-1 qual/EID and HIV-1 VL)	Yes	Plan to procure in 2018
Kenya	No	No	Plan to procure in 2018
Nigeria	HCV-VL, HIV-1 VL, HPV, NG/CT	HIV	Plan to procure in 2018
Thailand	No	No	Do not have definitive plans
Myanmar	No	HIV, HCV	Procured but not yet in use in the public sector#
Philippines	No	No	Do not have definitive plans
Mozambique	No	No	Plan to procure in 2018
Pakistan	HCV VL, HIV-1 VL	No	Procured and in use in the public sector
Cambodia	NA	NA	Plan to procure in 2018
Viet Nam	No	NA	Plan to procure in 2018
Uganda	HIV-VL	NA	Plan to procure in 2018
DR Congo	No	No	Do not have definitive plans
Brazil	No	No	Plan to procure in 2018
Bangladesh	No	No	Do not have definitive plans
Russian Federation	NA	NA	Do not have definitive plans
Zimbabwe	HIV-1 VL, HIV-1 qual/EID	HIV	Procured, but not yet in use in the public sector
Afghanistan	No	No	Plan to procure in 2018
China	NA	NA	Do not have definitive plans

WHO: World Health Organization; NTP: National tuberculosis programme; HCV-VL: Hepatitis-C virus- viral load; HIV-VL: human immunodeficiency virus- viral load; HPV: human papilloma virus; NG/CT: *Neisseria gonorrhoeae* (NG) and *Chlamydia trachomatis* (CT); C Diff: *Clostridium difficile*; Carba R: Carbapenem resistance; Influenza: Detection of Flu A and Flu B with 2009 H1N1 Call Out; HIV-1 qual/EID: human immunodeficiency virus qualitative test/Early infant diagnosis; NA: not available; *India is currently discussing whether Xpert Ultra should be implemented within the public sector; # Myanmar is currently using Xpert Ultra in a prevalence survey.

There are several limitations to our study. First, data from the private sector and data from commercial procurement of Xpert MTB/RIF by public sector entities in certain countries (due to failure to meet concessional pricing conditions) were not included, thus the smear volumes and Xpert procurement are not representative of country totals. However, data shows that Xpert MTB/RIF prices are high in the private sector, and volumes are likely to be low[13]. Due to the Initiative for Promoting affordable and Quality TB Tests (IPAQT) in India, Xpert MTB/RIF is available at lower prices in the private sector[14]. Introducing such initiative in other countries may increase assessibility to Xpert MTB/RIF. Second, cartridge procurement data may not reflect the actual utilisation of Xpert MTB/RIF. Third, to measure the full capacity of utilization for GeneXpert, we used pre-identified assumptions, such as an 8-hour working day. This assumption did not account for the variability in operating hours at different TB laboratories in each country, which could have led to inaccurate estimates. Moreover, we did not account for GeneXperts that may have been used for other diseases. Fourth, it was assumed that two smears were conducted for initial diagnosis of TB in all countries. While this may not be accurate for all countries, this had a limited effect on the trends of market penetration of MTB/RIF in each country over time. Fifth, we did not collect data on financing and procurement efficiency to estimate how these may have impacted utilization. Next, it is possible that survey data was reported differently from one year to the next which could have led to inaccurate estimates of initial smears and thus, smear/Xpert ratios. Next, in 2015 the WHO expanded its high TB

burden list to include an additional ten countries[15]. Our review was unable to analyze results from these countries as our response rate was too low (1/10; 10%). Finally, data availability was limited in some countries (e.g. Tanzania).

Conclusion

Our results show a positive trend for Xpert MTB/RIF market penetration in 21 HBC public sectors, however there remains underutilization of GeneXpert machines, and insufficient use of GeneXpert as a multi-disease platform. There is great scope for countries to improve this and optimize the usage and impact of novel, multi-disease technologies like GeneXpert. HBCs should go beyond specific high-risk groups to a broader use of the technology as a frontline TB test, and use the platform to reach universal drug-susceptibility targets. HBCs should also go beyond using GeneXpert for just TB, and exploit the platform to deliver a variety of tests included in the WHO Essential Diagnostics List.

Data availability

All data presented in this manuscript is available on Open Science Framework (OSF) under the repository "Smear Xpert analysis 2018": https://doi.org/10.17605/osf.io/vsxe8[16].

S1 Raw data contains all responses posed by the questionnaire for 21 HBCs. It also contains Xpert MTB/RIF procurement data which was provided by FIND.

Data are available under the terms of the Creative Commons Zero "No rights reserved" data waiver (CC0 1.0 Public domain dedication).

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Supplementary material

Supplementary File 1: Structured questionnaire.

Click here to access the data.

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15. World Health Organization: **Use of high country burden lists for TB by WHO in the post-2015 era.** Gevena: WHO; 2015.
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16. Pande T: **Smear Xpert analysis 2018.** 2018.
http://www.doi.org/10.17605/osf.io/vsxe8

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Version 1

Reviewer Report 30 August 2018

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✔ **Melissa L. Mugambi**
Department of Global Health, University of Washington, Seattle, WA, USA
Mickey Urdea
Halteres Associates, Emeryville, CA, USA

This is a well written article which is highly relevant to the donor audience and suggests that more work is needed to stimulate demand beyond concessional pricing efforts. It also begs the question – why does it take years before we see the type of scale we want to see with diagnostic devices? What type of business or partnership models can help address the issue of scale? In light of the need to stimulate country demand, it might be helpful for the authors to consider making a bold statement about impact e.g. we estimate that if utilization increased by x% we would expect a y% increase in TB case detection. Stepping beyond a performance assessment and actually stating what closing the gap (increasing market penetration) will do to TB case detection is an important statement that must be made. Similarly, the resource perspective will be helpful as well – what will it cost to close the gap?

The authors raise a key limitation to the study: “it is possible that survey data was reported differently from one year to the next which could have led to inaccurate estimates of initial smears and thus, smear/Xpert ratios.” It is important to note that the quality of the data is probably a big issue and while it cannot feasibly be addressed in this paper, it would be interesting and helpful to explore the validity of this data in more country-specific analyses.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

We have read this submission. We believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 14 Sep 2018

Madhukar Pai, McGill University, Montreal, Canada

Thank you for your comments.

1. While we appreciate this comment, we do not feel we can accurately state what amount of increased market penetration will close the gap in TB case detection. Nor what will it cost to close the gap. The data collected does not allow us to estimate this, since the goal of this study is to assess trends over time.

2. We agree!

Competing Interests: No competing interests were disclosed.

Reviewer Report 20 August 2018

https://doi.org/10.21956/gatesopenres.13923.r26586

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Cesar Ugarte Gil
School of Medicine Alberto Hurtado, Institute of Tropical Medicine Alexander von Humboldt, Cayetano Heredia University (UPCH), Lima, Peru

Interesting manuscript, I have a few comments:

1. Heterogeneity among study sites: Some of the sites (i.e. South Africa) had more experience in Xpert's implementation, and maybe some other sites not. Also, maybe some sites didn't complete the process of implementation. This info can be added in Table 1.
2. Utilization of full capacity: Besides Uganda, all countries are below 50%. What is the reasons/hypothesis behind that?. Also, as a previous reviewer said, the assumption of 8 working

hours can fit in a perfect system, in many of these centers, laboratory technicians are multi-tasking or are not open all day (or didn't have electricity all day). Taking this account can be helpful to see if is a real under-utilization of Xpert.

3. Use of other tests (LAM and LAMP): In the structured questionnaire there are some questions about these tests, is possible to add some info about these answers? The use of these tests can change the screening process. Maybe is not implemented yet, but this can change the Xpert utilization and (maybe) is possible to forecast Xpert use in these settings.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: I have a non-financial competing interest (I collaborate with MP and HS). Also, I'm co-investigator in a TB research project funded by FIND (not related with this study).

Reviewer Expertise: Infectious diseases epidemiology; TB research

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 14 Sep 2018

Madhukar Pai, McGill University, Montreal, Canada

Than you for your comments.

1. Implementation progress of Xpert is represented by the smear/Xpert ratio, which is already included in Table 1. Factors that could have affected implementation in certain countries are included in the text.

2. Addressed this already, based off of Reviewer 1's comments. Included as a limitation.

3. Great point. We decided after designing the questionnaire, however, that this study would focus only on GeneXpert and not include results on TB LAM or LAMP.

Competing Interests: No competing interests were disclosed.

Reviewer Report 08 August 2018

https://doi.org/10.21956/gatesopenres.13923.r26587

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Erica Lessem
Treatment Action Group (TAG) , New York City, NY, USA

This is a very important article and provides useful information about trends in utilization of WHO-endorsed test GeneXpert MTB/RIF at the country level, which can help guide donor policy as well as advocacy for this test and other interventions.

A couple minor questions/suggestions:

- Are authors confident that the smears being reported are only for the initial test (as asked)? I am not sure how countries record those data to know if this would be very reliable, so that could be a potential limitation.
- It is noted that private sector prices are lower in India; I think it would be helpful for less informed readers to briefly explain why (I am assuming this is because of IPAQT)
- Could the authors also suggest what the ideal smear to Xpert ratio for initial test should be in their view? Is it really no smears at all, or are there caveats? This could help contextualize the ranges given in Fig 1.
- Also, if I am reading Fig 3 right, Xpert procurement decreased in South Africa from 2015 to 2016 even though the smear to Xpert ratio has also decreased. Do authors have an explanation for this interesting finding, e.g. does this mean that South Africa has reached saturation and is bending curve downwards, or have they stopped reaching as many people in need of dx?
- I understand given preceding analysis the focus on HBCs as defined by WHO prior to 2015, but I think it could be very interesting to look at the additional HBCs on the 2016-2020 list, even if you won't be able to have the previous data points for historical comparison, it can at least provide a snapshot of where the countries are now and be a baseline for further analyses moving forward.

Great article and very important overall.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: I have a non-financial competing interest in that I collaborate with co-authors Wayne van Gemert and Brenda Waning on various projects. I am Vice Chair of the TB Procurement & Market-Shaping Work Group that Waning chairs and GDF hosts. My organization TAG receives funding (<$200K / year) from the Stop TB Partnership/Global Drug Facility to work on Demand Generation as Part of a Coordinated, Market-Shaping Approach to Procurement of TB Commodities.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 14 Sep 2018

Madhukar Pai, McGill University, Montreal, Canada

Reviewer 2:
Thank you for your comments.

1. Great point, however we feel as if this is covered by the following limitations that were included in the text:
- It is possible that survey data was reported differently from one year to the next which could have led to inaccurate estimates of initial smears and thus, smear/Xpert ratios.
- Data availability was limited in some countries, which could have led to imprecise estimates.

2. This has been added to the text and reference added.

3. This is indicated in the caption of the figure: “Trends moving closer to 0 (ratio decreasing) signify a greater use of Xpert compared to smear microscopy for the diagnosis of TB. Trends moving away from 0 (ratio increasing) signify a greater use of smear microscopy compared to Xpert for the diagnosis of TB".

4. Great point brought up by the reviewer. Authors are unsure of the reasons for decrease, but this could be explored further in the next study.

5. We tried to collect data from additional countries but the response rate was very low (1/10 responded after contacting them a maximum of 3 times), therefore we decided to exclude this data. This information has been added to the text.

Competing Interests: No competing interests were disclosed.

Reviewer Report 08 August 2018

https://doi.org/10.21956/gatesopenres.13923.r26588

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Zibusiso Ndlovu
Southern Africa Medical Unit, Medecins Sans Frontieres (MSF)/Doctors Without Borders, Cape Town, South Africa

Introduction

1. Paragraph 2: First mention of Xpert must be in full (GeneXpert) and the rest could be Xpert
2. Paragraph 2: Put the name '*reagent cartridges*' after Xpert MTB/Rif
3. Paragraph 3: the last sentence of needs paraphrasing, it has the repetitive use of the word '*assess* '. You can use synonyms like: evaluate etc

Methods

1. 3rd paragraph: revise the first sentence and replace 'by' with 'from'=> 'Data on Xpert MTB/Rif cartridge procurement was obtained….**from**'
2. 3rd paragraph: revise the first sentence and add 'TB'. '….and WHO recommended diagnostic algorithms (WRD) for **TB** were obtained from WHO'..
3. Last paragraph: I tend to disagree with the assumption of 'full capacity' utilization Xpert is 16tests per Xpert per day. This is not pragmatic and it is setting the trend high because lab techs multi-task and also, its only feasible 'on average' to conduct 4 tests in the morning, another 4 tests after tea break and another 4 tests after lunch hours….so total possible pragmatically is 12 tests per day.. Your assumption of 16 tests per day, then provides a bias toward a high under-utilization of devices yet the counterfactual is not possible.

Results

1. They do not flow very well from theme-to-theme; you need to work on these.
2. 2nd paragraph: put % next to 5.8million (to show the proportion ordered in HBC vs total ordered)
3. 2nd paragraph: remove the word 'as shown'; and combine the two succeeding sentences. Also, put IQR [x-y] and not mention the words Q1 and Q3 as they make it clumsy; also, remove the % for the countries (17/21 (%)). Also add the median ration of the increases among the 4 countries.
4. Paragraph 4: why do you now have a denominator of 19/19 (100%) yet your survey was to 22 countries? Why not mention the median 'capacity utilization' instead of telling us that 100% were not using to full capacity? These now seem like your own inferences
5. Paragraph 4: (last sentence)=>The statement describing the countries who had recommended and using Xpert as the first diagnostic test, must appear within the first part of your results where you give us a background as to the study countries and who had implemented what etc… currently, your results are not organized.
6. Name of Figure must not be paragraph long.
7. Last paragraph:
   a. Avoid using the word 'running', its not scientific

Discussion

1. Discussion must also flow very well in sync with results chronology. After the small introduction, proceed by discussing why some countries still haven't endorsed Xpert as the first test and how many they are compared to 2014 and rationale.
2. Paragraph 3: revise the 1st sentence and add; '..***number***' of initial smears conducted…. Also, do we have a % of the average decline in the number of SM done vs Xpert?

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 14 Sep 2018

Madhukar Pai, McGill University, Montreal, Canada

Introduction: All comments have been addressed in the revised text.

Methods:
The 2 first points have been addressed in the revised text.
Point 3. This point is well taken. However, this is an assumption and has been acknowledged as a limitation.

Results:
The flow has been revised based on the reviewer's suggestions.
The grammar/sentence changes have been addressed based on reviewer suggestions.
The denominator has become 19 because 2 countries did not respond to this question. These were excluded, and this is explained in the text.
Changed the % under utilizing to median % under utilization.
Name of the figure is short. The description of the figure remains in the caption.

Discussion:

The flow has been revised based on reviewer's suggestions.
Have included the median change in number of initial smears for each region in the results.

Competing Interests: No competing interests were disclosed.