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Detecting tuberculosis: rapid tools but slow progress

K. England,[1] T. Masini,[2] E. Fajardo[1]

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The World Health Organization (WHO) currently recommends Xpert® MTB/RIF as the initial test for all people with presumptive tuberculosis (TB). A number of challenges have been reported, however, in using this technology, particularly in low-resource settings. Here we examine these challenges, and provide our perspective of the barriers to Xpert scale-up as assessed through a survey in 16 TB burden countries in which the Médecins Sans Frontières is present. We observed that the key barriers to scale-up include a lack of policy adoption and implementation of WHO recommendations for the use of Xpert, resulting from high costs, poor sensitisation of clinical staff and a high turnover of trained laboratory staff; insufficient service and maintenance provision provided by the manufacturer; and inadequate resources for sustainability and expansion. Funding is a critical issue as countries begin to transition out of support from the Global Fund. While it is clear that there is still an urgent need for research into and development of a rapid, affordable point-of-care test for TB that is truly adapted for use in low-resource settings, countries in the meantime need to develop functional and sustainable Xpert networks in order to close the existing diagnostic gap.

The World Health Organization (WHO) in 2010 recommended the Xpert® MTB/RIF assay (Cepheid, Sunnyvale, CA, USA) as the initial diagnostic test for all people with presumptive tuberculosis (TB).[1] Xpert provides a rapid method for the diagnosis of TB and rifampicin-resistant TB (RR-TB). Evidence has shown that Xpert can increase the number of bacterial confirmations, reduce the time to treatment initiation and decrease the number of cases lost to follow-up.[2] These benefits make Xpert the best test currently available for the diagnosis of TB, thus driving the WHO recommendation for its role in universal testing as part of the End TB Strategy.[3] In line with these recommendations, nearly all high TB burden countries have expanded their Xpert testing capacity to improve case detection.[4] However, over the past 6 years, the number of diagnosed and reported TB cases globally has remained stagnant at approximately 60%. Only 56% of reported TB cases were bacteriologically confirmed in 2017, and only 30% of new and retreatment cases received a test for RR-TB.[5]

If Xpert is to reach its full potential and diagnose more people with TB and RR-TB, the barriers associated with its scale-up in TB-burden countries needs to be better understood and addressed. Many national TB programmes have struggled to optimise testing and sustain routine operations. Testing errors, instrument failures, reporting delays, insufficient infrastructure and environmental conditions, inappropriate geographical placement of the instruments, poor maintenance support and a high turnover of trained technicians have all been raised as concerns around the sustainability of Xpert for decentralised testing in low-resource settings.[6–8]

This article summarises the key challenges associated with the scale-up of Xpert and compares these with the current realities on the ground, which were assessed through a survey exploring the barriers to the scale-up of testing, carried out between September and December 2017 in 16 TB burden countries in which Médecins Sans Frontière (MSF) was present (Table). We provide a perspective on some of the key challenges that have been reported and on what is required to overcome these barriers. The survey methodology is presented online in Supplementary Data.

KEY CHALLENGES

Policy adoption and implementation

National adoption and implementation of the WHO TB guidelines is the first step if countries are to meet global targets for reducing TB-related morbidity and mortality. The joint MSF and Stop TB Partnership 'Out of Step' (OOS) survey has provided an overview of the level of policy adoption and implementation of WHO TB policies in NTPs of selected countries up to early 2017. According to this investigation, only 52% (15/29) of the surveyed countries had adopted a policy of 'Xpert for all'.[9] Furthermore, only 40% (6/15) of these countries had widely implemented this policy. This shows that even 7 years after the WHO recommendation to use Xpert, the process of updating national documents to reflect this policy, as well as the implementation of this policy at the country level, is severely insufficient.

Following the results of the OOS survey, we explored the reasons for slow implementation of 'Xpert for all'. Comments from several countries revealed three broad themes: cost (reported by five countries), poor sensitisation of clinical staff (reported by four countries) and a high turnover of trained laboratory staff (reported by five countries).

All the countries in our survey are eligible for the High Burden Developing Country (HBDC) Programme offered by Cepheid. All of the countries included in our survey should have access to the reduced cartridge price of US$9.98.[10] While most countries in our survey reported access to this concessional price, additional costs were also reported as a result of the distribution process at country level. Added costs include import

AFFILIATIONS
1 Access Campaign, Médecins Sans Frontières, Geneva, Switzerland
2 Independent Consultant, Camaiore, Italy

CORRESPONDENCE
Kathleen England
Access Campaign
Médecins Sans Frontières
Rue de Lausanne 78
1201, Geneva, Switzerland
e-mail: kathleen.england@geneva.msf.org

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GeneXpert; laboratory; network; expansion; sustainability

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TABLE Selected data reported by 16 countries*

	Service and maintenance										Network funding		
Country	Xpert instruments *n*	With warranty or SLA *n*	Warranty or SLA %	Purchased extended warranty	Module replacement delay under service provision† days *n*	Annual module failure rates‡ %	Surcharge model offered	Expressed interest in surcharge model	ASP in country	Satisfied with overall services	Funding source§	GF and/or other donor support %	Due to transition out of GF support[12]
Armenia	18	13	72	No	—	4	—	—	No	—	Donor	100	Yes
Belarus	30	14	47	No	60	8	No	Yes	Yes	Yes	Both	95	Yes
Brazil	249	41	16	—	7	4	No	Yes	Yes	Yes	Domestic	0	NA
Georgia	38	38	100	Yes	7	5	No	Yes	Yes	Yes	Both	90	No
India¶	1303	—	—	—	—	—	—	—	Yes	—	Both	—	No
Kenya	198	90	45	—	120	4	Yes	NA	Yes	Yes	Donor	100	No
Kyrgyzstan	24	14	58	No	—	21	No	Yes	No	—	Donor	100	No
Malawi	52	51	98	Yes	240	15	Yes	NA	Yes	No	Donor	100	No
Mozambique¶	72	72	100	—	168	—	—	—	Yes	No	Donor	100	No
Russia	221	221	100	No	14	2	No	No	Yes	Yes	Domestic	0	NA
South Africa	325	325	100	No	7	25	Yes	NA	Yes	Moderate	Both	<5	NA
eSwatini (Swaziland)	30	30	100	Yes	365	14	—	—	No	No	Donor	100	No
Tajikistan	15	3	20	No	120	8	No	Yes	No	—	Donor	100	Yes
Ukraine	56	5	9	No	21	5	No	Yes	Yes	Yes	Both	75	No
Viet Nam	172	172	100	No	—	—	—	—	Yes	No	Donor	100	No
Zimbabwe	125	125	100	No	—	12	—	—	Yes	No	Donor	100	No

*Data reported by MSF missions between September 2017 and December 2017.
†Service provision through initial warranty, SLA or extended warranty.
‡Annual rates for the previous year.
§Funding for networks was identified as external, domestic, or both. In most cases, 95% of network interventions (procurement, training, warranties, et cetera) were reported as supported through external funds, primarily by the GF.
¶Survey questionnaire not completed. Data were obtained through desk review and interviews.
SLA = service level agreement; ASP = authorized service provider; GF = Global Fund; — = no information was provided; NA = not applicable; MSF = Médecins Sans Frontières.

tariffs, shipping costs and price hikes imposed by local distributors, increasing the price per cartridge by between 7% and 50%. Even at US$9.98/cartridge, the sheer volumes of tests needed to address all presumptive TB cases makes full implementation of the current WHO recommendations unattainable for most countries. Added costs further reduce affordability and availability and restrict access as tests are reserved for high-risk groups. Furthermore, the private sector is not eligible for concessional pricing, making the cost of cartridges a significant barrier in highly privatised health markets. A study in 2018 noted extremely high cartridge prices in private laboratories, ranging from US$25 (India) to US$235 (Nigeria). The private sector is a major source of health care in one half of the countries with the highest TB burden, where even the poorest patients often seek care from private providers.[11] To procure the volumes required to use Xpert as the primary test for TB, it would benefit governments to implement price controls and regulations to prevent price mark-ups on Xpert technologies in both the public and private sectors.

A number of countries reported poor policy sensitisation as a limitation for policy implementation. Specifically, countries highlighted a lack of knowledge sharing by national-level authorities with peripheral clinical providers regarding updated diagnostic algorithms, as well as the rationale behind current WHO recommendations to prioritise the use of Xpert over smear microscopy. There is a need to provide extensive training on the use of current diagnostic algorithms at all levels of the health care system to support policy uptake. In addition, Xpert is not simply a plug-and-play technology, and requires specific training for laboratory staff to ensure proper use, interpretation of results, troubleshooting and routine maintenance. During initial roll-out of Xpert, Cepheid provided training at the central level upon installation and partners supported 'training of trainers' programmes to build a cadre of qualified experts who could then train peripheral staff. Over time, NTP staff were expected to take over the responsibility to provide refresher training courses. Our survey revealed that refresher training was not consistently provided in all countries, with only 75% (9/12) of countries running refresher training programmes. Continuously available training courses are essential to refresh knowledge and provide technical updates, particularly when there is a high turnover of qualified staff.

Service and maintenance

Cepheid has agreements with local service providers at country level that are intended to assist with procurement and the service and maintenance of Xpert instruments and modules. While a number of studies have reported extensive practical challenges in using Xpert instruments, including high rates of module failure, testing errors and unsuccessful testing rates,[7,8] few studies have examined the level of satisfaction with the service and maintenance provided by Cepheid in overcoming these challenges. This provision is a central component in avoiding long instrument downtimes and in supporting optimal functioning of the instruments.

A number of countries in our survey reported inadequate service provision as one of the longstanding challenges to providing reliable testing services (Table). Although 75% (12/16) of countries had an authorized service provider (ASP) in the country, for

countries with either an ASP or remote services, only 50% (6/12) stated that they were fully satisfied with the services provided. Service provision is based on annual warranty coverage or annual service-level agreements (SLA). Instruments come with a 2-year warranty upon purchase; countries can thereafter choose to purchase extended warranties or annual SLAs. In our survey, 75% (1214/1625) of instruments were covered under a warranty or SLA. However, only three countries had purchased extended warranties. Certain countries had instead negotiated alternative SLAs with the manufacturer. SLAs are typically offered to countries with high testing volumes or extensive networks. Countries reported, however, that even with service provision, there were severe delays for module replacements. Turnaround times for module replacement ranged from 7 days to 1 year, with only 42% (5/12) of countries having modules replaced in <1 month. In addition, reported annual module failure rates ranged from 2% to 25%. Overall, many programmes stated they were losing confidence in the affordability and sustainability of using Xpert due to prolonged instrument downtime, undermining the use of this technology over microscopy. This is consistent with findings reported by Van Deun et al., in which long instrument downtimes were forcing technicians to revert to microscopy, and in some cases, halting TB laboratory work altogether until the problem was resolved.[7]

The model of service provision provided by Cepheid is clearly insufficient, and an alternative model with a more comprehensive service package is needed. Cepheid has recently recognised the need to improve access to services and has expanded the number of service centres globally from four (2015) to 14 (2018) (personal correspondence, P Jacon, Cepheid HBDC Programme).

Despite these efforts, countries continue to report service problems. One alternative under consideration by Cepheid is to provide a comprehensive package under a surcharge model per cartridge. This model includes support for ASP travel to all sites for training, installation, troubleshooting, module replacement and repairs. However, this model is currently available to only a few high-volume countries; three countries in our survey had recently been offered this option, one of which was already enrolled. Among the remaining countries, 86% (6/7) noted interest in this model. The surcharge, however, may vary country-to-country, and it is unclear if volume discount thresholds apply.

It is clear that all countries require an extensive, affordable and reliable service and maintenance provision to overcome the challenges arising from use of Xpert in many settings. Essential elements of any new service model should include on-site support and repairs, prompt module replacements and preventative maintenance provision (Xpert®Check kits). In addition, these services should begin once the instruments have been installed and not on the date of invoice (as currently stands).

Network funding

A major element to achieving the WHO's recommendation for universal testing as part of the End TB Strategy is to secure sustainable funding for Xpert networks. To date, costs relating to the procurement of quality-assured medicines and diagnostics at affordable prices have largely been borne by grants from the Global Fund (GF).[12] Among the countries we surveyed, 88% (14/16) reported a reliance on the GF funding for Xpert networks. Only 44% (7/16) of countries reported having some domestic allocation of funds, with only 19% (3/16) of countries reporting >95% domestic investment. This reveals a significant reliance on GF for the roll-out, sustainability and expansion of Xpert networks. Furthermore, three countries in our survey are due to transition out of GF support by the end of this year.[13] This poses a high risk to the sustainability of existing Xpert networks; one country in our survey stated that while it can currently procure the cartridges at the concessional price of US$9.98, the price they would pay when they transition out of GF support would increase to US$80/cartridge. Another country that domestically funds its Xpert networks reported a price of US$52/cartridge, instead of access to the concessional price available through the GF. Outside of support, countries no longer benefit from the positive coordination role of the GF in pooled procurement and market shaping that makes increased network expansion more affordable and sustainable for countries.

MSF recently called on the GF to urgently carry out risk and readiness assessments for countries expected to increase their co-financing of medical commodities, as well as countries currently undergoing transition. Without this, countries risk falling off a 'cliff' and could 'reverse nearly two decades of progress' against TB.[14] If countries continue to transition out of GF support without appropriate safeguards, NTPs will need to advocate for increased domestic allocations to ensure that Xpert networks remain sufficiently funded and that recent progress and testing momentum are not lost.

CONCLUSIONS

As countries strive to achieve national TB testing targets, it is imperative to have a sustainable and reliable Xpert network that is accessible to test all TB cases as recommended by the WHO. As countries phase out the use of microscopy in favour of developing, maintaining and expanding Xpert networks, they need to ensure that they not only expand their networks to make sure that the network capacity meets national testing demands and targets, but also that their existing instruments are functioning optimally. This challenge is two-fold and will only be made possible through full implementation of WHO policy as a first step, a sufficient service and maintenance provision provided by Cepheid to support optimisation of existing instruments, and sustainable funding for the maintenance and expansion of networks. Ultimately, it is clear that there is still an urgent need for research into and development of a rapid point-of-care test for TB that is truly adapted for use in low-resource settings. In the meantime, it is only through the development of fully functional and sustainable Xpert networks with the capacity to deliver national testing needs that the TB diagnostic gap will begin to close.

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L'Organisation Mondiale de la Santé (OMS) recommande actuellement l'Xpert® MTB/RIF comme test initial pour toutes les personnes suspectes de tuberculose (TB). Le recours à cette technique s'est cependant heurté à un certain nombre de défis, particulièrement dans les contextes de faibles ressources. Nous examinons ici ces défis et proposons notre vision des contraintes à l'expansion comme l'a montré une enquête dans 16 pays très frappés par la TB où Médecins Sans Frontières est présent. Nous affirmons que les entraves majeures à l'expansion incluent un manque d'adoption politique et de mise en œuvre des recommandations de l'OMS relatives à l'utilisation de l'Xpert, résultant des coûts élevés, d'une sensibilisation insuffisante du personnel clinique et d'un taux élevé de renouvellement du personnel de laboratoire formé ; une offre insuffisante de service et de maintenance de la part du fabricant ; et des ressources insuffisantes pour la pérennité et l'expansion. Le financement est un problème crucial à mesure que les pays commencent leur transition vers l'arrêt du soutien du Fonds Mondial. Il est clair qu'il y a toujours un besoin urgent de recherche et de développement d'un test de TB rapide, abordable, réalisable sur place et réellement adapté à une utilisation dans des contextes de faibles ressources. Dans l'intervalle, les pays ont cependant besoin d'élaborer des réseaux d'Xpert fonctionnels et pérennisables de manière à combler le fossé existant en matière de diagnostic.

En la actualidad, la Organización Mundial de la Salud (OMS) recomienda como primer método diagnóstico la prueba Xpert® MTB/RIF en todas las personas con presunción clínica de tuberculosis (TB). Se ha comunicado, no obstante, una serie de dificultades con la utilización de esta técnica sobre todo en entornos con recursos limitados. En el presente estudio se examinan estas dificultades y se ofrece una perspectiva de los obstáculos a la ampliación de escala de la recomendación, a partir de una encuesta realizada en 16 países con carga de morbilidad por TB donde está presente Médicos Sin Fronteras. Los autores afirman que los principales obstáculos a la ampliación de escala son los siguientes: la falta de adopción de políticas en favor de las recomendaciones de la OMS sobre la utilización de la prueba Xpert y el refuerzo de su cumplimiento, debido a los costos altos, la escasa sensibilización del personal médico y una alta rotación del personal de laboratorio capacitado; la insuficiencia de la prestación de servicios y mantenimiento por parte del fabricante; y los recursos insuficientes para la sostenibilidad y la ampliación. El financiamiento constituye un elemento primordial a medida que los países dejan de percibir el apoyo del Fondo Mundial. Es evidente que existe una necesidad urgente de investigación y desarrollo de una prueba en el lugar de la consulta que sea asequible y efectivamente adaptada a los entornos con recursos escasos, pero mientras tanto, los países deben crear redes funcionales y sostenibles de la prueba Xpert a fin de subsanar las deficiencias actuales en el diagnóstico.

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