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Replacing smear microscopy for the diagnosis of tuberculosis: what is the market potential?

To the Editor:

Sputum smear microscopy (SSM) has been the cornerstone of tuberculosis (TB) diagnosis, and is mainly performed in peripheral microscopy centres attached to primary health centres where TB therapy can be administered. Although SSM is inexpensive and easy to perform with a limited infrastructure, the shortcomings are its relatively low sensitivity and its inability to detect drug-resistance. Thus, there is a need for a more sensitive technology that can replace microscopy [1, 2].

Several next-generation molecular diagnostics are under development with the specific intention of use in microscopy centres [3–5]. In a recent survey of 22 high-burden countries (HBCs), we showed that the conditions, equipment and expertise present in microscopy centres are challenging and need to be considered by product developers [6]. While the Xpert MTB/RIF (Cepheid Inc., Sunnyvale, CA, USA) assay is accurate, endorsed by the World Health Organization and is being implemented in many countries, it was not designed for use in peripheral microscopy centres [7, 8]. To assist product developers working on tests for use in microscopy centres, we have outlined the desirable test characteristics [1].

For companies to take on the challenge and invest in new diagnostics, an understanding of the potential market size is paramount [9]. A 2006 global TB diagnostics market analysis predicted that a smear replacement test applied at the level of peripheral clinics and microscopy centres would have a potential market size of 36.6 million tests per year in the 22 HBCs in 2020, assuming it would diagnose pulmonary, extrapulmonary and paediatric TB [10]. However, current and next-generation molecular tests are reliant on sputum specimens and are unlikely to accurately diagnose all forms of TB [5].

To provide a snapshot of the current market, we surveyed experts in each of the 22 TB HBCs, in order to estimate the current SSM market and its potential replacement market for the diagnosis of pulmonary TB. The survey, sent *via* email to staff working in National Tuberculosis Programmes (NTP) (n=17 countries) or TB consultants working closely with NTPs (n=5 countries), included questions on the number of smear microscopy centres, the annual number of smears carried out in the public (NTP) sector (where possible, stratified by initial diagnosis and treatment monitoring), the national recommendation on number of smears, and smear volumes in the private sector. If the annual smear volume of the country seemed unrealistically high or low (>35 or <2 smears per notified TB case, respectively), respondents were contacted again for verification.

Respondents were asked to provide a cost value for one smear in their country. However, this resulted in heterogeneous cost estimates because of variations in how costs were computed. Therefore, we multiplied test volumes by the median unit cost (and interquartile range (IQR)) for one smear obtained from a recent systematic review of SSM from 23 studies in 11 countries [11]. When converted to 2012 US$, the unit cost for a smear was US$1.77 (IQR US$1.28–2.69) and included various components (*e.g.* material, labour, equipment and overheads) although components differed across studies.

We received a response for all 22 HBCs. As shown in table 1, the 22 HBCs performed a total of 77.6 million sputum smears annually at a value of US$137 million in 42 827 microscopy centres. Of these, 61% were performed in the BRICS countries (Brazil, Russian Federation, India, China and South Africa). Most countries (19 out of 22) provided data for 2012, while the rest did so for 2011.

In the majority (13 out of 22) of HBCs, the NTP policy recommended testing three sputum samples for initial diagnosis of pulmonary TB, while the rest had a policy of two smears. 11 (50%) countries disaggregated smear volumes into those performed for initial diagnosis and those for treatment monitoring. On average, 79% of the smears were performed for initial diagnosis (range 65–94%). Since there was not much difference between countries that had a two- or three-smear policy in place, we extrapolated this percentage to all countries.

TABLE 1 The current smear microscopy market and the potential market for a replacement test for initial diagnosis of tuberculosis (TB) in the public sector of the 22 high-burden countries

Country	Notified TB cases in 2012 n[#]	Microscopy centres n	Total microscopy centres %	Total sputum smear volume (millions)	Total sputum smear volume %	Sputum smear market for initial diagnosis[¶]		Replacement test market[+]	
						Smears n (millions)	Estimated (range) expenditure (US$ millions)	Tests n (millions)	Potential market value (US$ millions)
Non-BRICS									
Afghanistan[§]	29 578	710	1.7	0.022	0.0	0.017	0.03 (0.02–0.05)	0.009	0.04
Zimbabwe	38 720	220	0.5	0.064	0.1	0.051	0.09 (0.07–0.14)	0.025	0.13
Cambodia	40 258	214	0.5	0.550	0.7	0.437	0.77 (0.56–1.18)	0.218	1.09
Uganda	47 211	1165	2.7	0.260	0.3	0.206	0.37 (0.26–0.56)	0.103	0.52
Mozambique	50 827	300	0.7	0.248	0.3	0.197	0.35 (0.25–0.53)	0.098	0.49
Thailand	61 208	1081	2.5	1.61	2.1	1.28	2.27 (1.64–3.45)	0.640	3.20
Tanzania	63 892	830	1.9	0.852	1.1	0.677	1.20 (0.87–1.82)	0.338	1.69
Nigeria	97 853	1341	3.1	1.33	1.7	1.06	1.88 (1.36–2.85)	0.530	2.65
Kenya	99 149	1818	4.2	4.86	6.3	3.86	6.83 (4.95–10.40)	1.93	9.64
Vietnam	103 906	818	1.9	2.46	3.2	1.95	3.46 (2.51–5.27)	0.977	4.89
Democratic Republic of Congo	112 499	1522	3.6	0.972	1.3	0.772	1.37 (0.99–2.08)	0.386	1.93
Ethiopia	147 592	2497	5.8	6.04	7.8	4.80	8.51 (6.16–12.94)	2.40	12.0
Burma	148 149	358	0.8	1.17	1.5	0.930	1.65 (1.19–2.51)	0.465	2.33
Bangladesh	173 619	1070	2.5	4.13	5.3	3.28	5.81 (4.21–8.83)	1.64	8.20
Philippines	235 608	2565	6.0	1.81	2.3	1.44	2.54 (1.84–3.87)	0.718	3.59
Pakistan	273 097	1171	2.7	1.79	2.3	1.42	2.52 (1.82–3.83)	0.711	3.55
Indonesia	331 424	5566	13.0	2.04	2.6	1.62	2.88 (2.08–4.38)	0.812	4.06
BRICS countries									
Brazil	82 755	2510	5.9	1.14	1.5	0.905	1.60 (1.16–2.44)	0.453	2.26
Russian Federation	149 921	1031	2.4	8.86	11.4	7.04	12.5 (9.04–19.0)	3.52	17.6
South Africa	349 582	240	0.6	4.57	5.9	3.63	6.43 (4.66–9.77)	1.81	9.07
China	900 678	2800	6.5	12.0	15.5	9.53	16.9 (12.2–25.7)	4.77	23.8
India	1 467 585	13 000	30.4	20.8	26.8	16.6	29.3 (21.3–44.6)	8.28	41.4
Total	**5 005 111**	**42 827**	**100**	**77.6**	**100**	**61.7**	**109 (79.1–166)**	**30.8**	**154**

Countries listed in order of the number of notified TB cases in 2012. BRICS: Brazil, Russian Federation, India, China and South Africa. #: data obtained from [12]. ¶: we assumed for all countries that, on average, 79% of the sputum smears were performed for initial diagnosis (the average proportion reported by 11 countries able to stratify smears for initial diagnosis and those performed for treatment monitoring). The number of initial smears was multiplied by US$1.77 (range US$1.28–2.69); the median unit costs for a smear according to Lu *et al.* [11]. Smear costs included various components (*e.g.* material, labour, equipment and overheads) although the exact components included differed across studies or were not always reported. +: we assumed that a replacement test would only need a single test on one sample (as opposed to an average of two samples for sputum smear microscopy) and multiplied these by US$5, the anticipated costs for a hypothetical replacement test. §: smear volumes were recognised to be under-reported by laboratories.

Using the data above and assumptions, we computed the smear replacement market by: 1) focusing on only initial diagnosis; 2) assuming that only one molecular test is necessary to replace two or three smears; and 3) assuming that the hypothetical unit cost (consumables only) of the replacement test would be US$5.

The annual SSM market size for the initial diagnosis of TB in the 22 HBCs was estimated to consist of 61.7 million smears (79% of 77.6 million) at an expenditure of US$109 million (range based on IQR of smear costs US$79–166 million). After accounting for the assumptions about single replacement tests at a cost of US$5, we estimated the potential market size for a replacement test to be 30.8 million tests, with a potential market value of US$154 million per year.

Our analysis has limitations. We focused on the public sector, while several HBCs (notably India, Pakistan, Bangladesh, Indonesia, Cambodia, Nigeria, Uganda and the Philippines) are known to have a sizable and even dominant private sector [13]. Although countries were asked to provide smear volumes for the private sector, few were able to do so. Therefore, private sector data were not included and the actual market potential may in fact be higher than our estimate. Likewise, by assuming that a smear replacement test would be performed once and would not be used for treatment monitoring or for extrapulmonary TB, we may have underestimated the true potential market. Furthermore, our results relied on the accuracy of existing NTP data which may have missed some smears carried out in the public sector that were not reported to the NTP.

We may have also underestimated the smear market value because we used the same smear cost for all countries while the actual costs varied considerably. In particular, in BRICS, where over half of the smears were performed, the costs for a smear may be higher than our uniform estimate. However, the potential market size may not be fully addressable for a given replacement test. The addressable market will depend on the technology, pricing structures, ability to penetrate the private market, donor subsidies and initiatives, and other competing options, including the market share achieved by the ongoing implementation of Xpert MTB/RIF in some countries.

For some HBCs, our hypothetical price of US$5 for a new molecular test might be too expensive for smear replacement, given limited budgets. For example, if the Xpert MTB/RIF assay (cartridge price of US$9.98) were to be used for all people with presumed TB, the cost will exceed 80% of the total TB spending in countries such as India, Bangladesh, Indonesia and Pakistan [14]. For these countries a new molecular test might be applied as a confirmatory test after a positive triage test. So, the potential market for such a confirmatory test would be lower than a smear replacement test.

In conclusion, we showed that in the 22 HBCs, over 77 million smears are performed annually. Over 60% are carried out in the BRICS, which clearly represent an important market for new technologies. We estimated that a more accurate smear replacement test which would test the same target population in the 22 HBCs would have a market size of at least 30.8 million tests and a potential market value of US$154 million per year. These data should be of value to product developers, donors and investors.

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The estimated market for a sputum smear microscopy replacement test in 22 high-burden countries is $154 million per year http://ow.ly/sTXNc

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