intervention schedules or strategies may be required to maximise the possibility of eradicating bacterial colonisation.

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Colistin inhalation helps prevent recolonisation in CF patients with initial sterile BAL after transplantation http://ow.ly/kRaQg

Hendrik Suhling[1], Jessica Rademacher[1], Mark Greer[1], Axel Haverich[2], Gregor Warnecke[2], Jens Gottlieb[1] and Tobias Welte[1]
[1]Dept of Pulmonary Medicine, Hannover Medical School, Hannover, and [2]Dept of Cardiothoracic, Transplantation and Vascular Surgery, Hannover Medical School, Hannover, Germany.

Correspondence: H. Suhling, Dept of Pulmonary Medicine, Hannover Medical School, Carl-Neuberg Str. 1, 30625 Hannover, Germany. E-mail: suhling.hendrik@mh-hannover.de

Received: Dec 13 2012 | Accepted after revision: March 16 2013

Conflict of Interest: Disclosures can be found alongside the online version of this article at www.erj.ersjournals.com

Acknowledgments: The authors thank Imke Zinowsky and Antje Wollny (Dept of Respiratory Medicine, Hannover Medical School, Hannover, Germany) for data acquisition.

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Eur Respir J 2013; 42: 542–544 | DOI: 10.1183/09031936.00201012 | Copyright ©ERS 2013

Are peripheral microscopy centres ready for next generation molecular tuberculosis diagnostics?

To the Editor:

Sputum smear microscopy is the primary test for tuberculosis (TB) in most high-burden countries. Direct Ziehl–Neelsen (ZN) microscopy is routinely implemented in these countries *via* a vast network of decentralised, peripheral microscopy centres (as opposed to centralised reference laboratories), often located within primary or community health centres. This decentralised approach increases access in primary care settings and may help reduce diagnostic delays [1]. However, microscopy has limitations and novel diagnostics are urgently needed, particularly in settings with high prevalence of drug resistance and HIV [1, 2].

While Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA), a World Health Organization-endorsed test, is already being rolled out in many countries, it is intended for district or sub-district laboratories [3], and not peripheral microscopy centres. In contrast, at least four next-generation nucleic-acid amplification tests (NAATs) are now on the market, with the goal of point-of-care (POC) use in peripheral laboratories [4, 5].

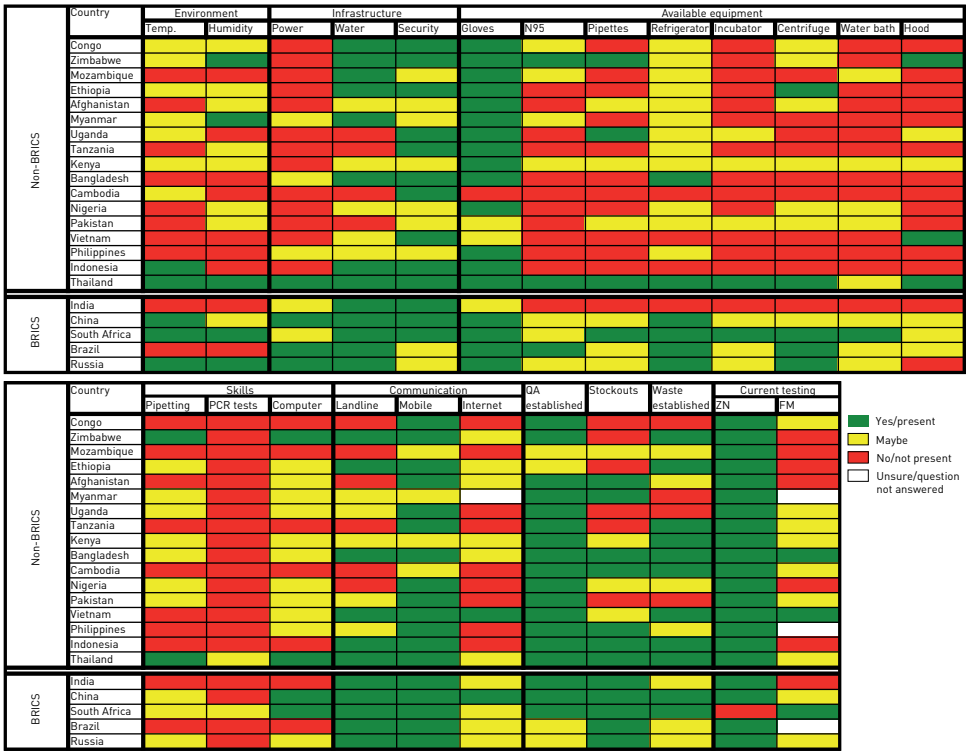

FIGURE 1 Characteristics of peripheral microscopy centres in 22 high-burden countries. Questions related to environmental conditions (Is temperature or humidity not a concern?), infrastructure (Is a stable power supply, clean water supply and room security present?), presence of equipment (gloves, N95 respirator, micropipettes, refrigerator, incubator, centrifuge, hot water bath or biosafety hood) and skills (to operate a micropipette or computer or perform a PCR test) and the presence of means of communication (landline, mobile or internet). Additional questions asked about whether quality assurance (QA) measures and waste management were established or whether stock of testing supplies was always replenished in time. In addition we asked about which diagnostic tests were currently used. Countries are sorted by increasing purchasing power parity. BRICS countries are Brazil, Russia, India, China and South Africa.

Can these so-called ''POC-NAATs'' actually be implemented in peripheral microscopy centres? Is there sufficient expertise (*e.g.* to extract DNA) and biosafety (*e.g.* to process sputum)? Will the necessary infrastructure (*e.g.* stable power supply) be present? Will environmental conditions (*e.g.* high temperature) limit their use?

The introduction of novel diagnostics that aim to replace smear microscopy in peripheral laboratories is more likely to succeed if the new tests are designed with real world conditions in mind. However, there are limited data on landscape of microscopy centres in high-burden countries. We addressed this gap with a survey of 22 high-burden countries. We designed a one-page, 12-question survey. We focused on the most important requirements and considerations for the next generation of TB diagnostics. We included questions about ambient temperature and humidity conditions, safety, infrastructure, availability of equipment and expertise, and communication infrastructure.

We contacted at least three experts in each country. If the responses were discrepant, we attempted to obtain at least one additional response from another expert. All contacts had extensive field experience and were either working for the national TB programme or non-governmental organisations, or were carrying out diagnostics or implementation research in the respective countries. Respondents were instructed to focus on the ''typical'' most peripheral microscopy laboratory in the country.

We were able to obtain at least three responses from 17 of 22 (77%) high-burden countries. For four countries, we received two responses that were consistent and matched well with other countries of comparable purchasing power parity. For one country, we received only one response; however, this response reflected the consensus opinion of several experts within the national TB programme. The answer options were ''yes'', ''no'', ''maybe'' and ''unsure''; ''maybe'' reflecting that some but not all of the microscopy centres had the characteristic in question. If at least two-thirds of the respondents gave the same answer, this answer was chosen as the overall answer; otherwise, the answer was rated as ''maybe''.

Figure 1 presents the results as a color-coded chart. The countries are sorted by increasing purchasing power parity with data for BRICS countries (Brazil, Russia, India, China and South Africa) shown separately at the bottom.

As expected, nearly all microscopy centres were reported to be using conventional ZN microscopy (with established external quality assessment) and more than half also had fluorescence microscopy available in all or at least some centres. Experts from nine countries reported implementation of Xpert MTB/RIF, mostly in the context of demonstration/evaluation projects (at the time of our survey) [6].

Our survey revealed that high indoor temperatures and/or high humidity were perceived as a problem in nearly all countries (17 out of 22; 77%). Only four out of the 22 high-burden countries (18%) reported access to uninterrupted power supply, while a supply of running water was more common (13; 59%).

Equipment for personal protection (*i.e.* N95 respirator) was not available in 12 countries and inconsistently available in seven countries. In contrast, surgical gloves were always available in most countries (18; 82%). Microscopy centres in six countries had refrigerators (27%), and only in five countries (23%) was a centrifuge consistently available. Expertise with non-automated molecular tests was not consistently reported from any country and expertise in using micropipettes was reported in only two countries (10%). Skills in using in a computer were only acknowledged to be always present in four countries (18%).

Interestingly, mobile phones for communication were available in a majority of the centres (82%), with much poorer landline or internet connectivity (only consistently reported for 11 and two countries, respectively). In almost half (45%) of countries, stock-outs of testing supplies were a concern.

When asked about the biggest challenges for implementing molecular assays in these peripheral microscopy centres, the most commonly stated responses were ''lack of stable power supply'', ''harsh weather conditions'' and ''lack of skilled labour''.

Overall, the conditions were much better in BRICS countries compared to the other countries. However, even within the BRICS countries, large variability, in particular in the availability of equipment, was reported, with Indian peripheral microscopy centres being the least equipped.

Our survey highlights scarcity of infrastructure, equipment and skills at the level of peripheral microscopy centres in all high-burden countries, although BRICS countries, as expected, fared better than the others. The results also confirm the known challenges of rough environmental conditions that may impact decentralised scale-up of molecular tests [7].

Our survey was not intended to collect data on every microscopy centre in each country. We acknowledge that there may be large variations across different regions within a country and our data only reflects the ''typical'' or average peripheral microscopy centre. The results also may be overoptimistic, as the mere presence of equipment (*e.g.* centrifuge) does not guarantee its functionality or routine use.

However, our results highlight that unless upgraded and better staffed, existing microscopy centres will find it challenging to implement Xpert MTB/RIF as well as newer NAATs, especially since they require manual sputum processing and DNA extraction [4]. Unanswered questions remain about how newer NAATs will fit with current TB diagnostic algorithms, at which level of care they can be successfully implemented in high-burden countries and how appropriate quality control procedures can be developed and maintained in peripheral laboratories.

Peripheral laboratory strengthening, therefore, should be a priority for high-burden countries. Even if microscopy centres are upgraded, a sustainable system for ensuring biosafety, stock and waste management, quality assurance, and maintenance will need to be developed in many high-burden countries. Fortunately, since external quality assessment and training for smear microscopy is already established, there is much experience that can be leveraged for external quality assessment and proficiency testing for molecular tests.

Our results should also be highly relevant for test developers and diagnostic companies interested in TB diagnostics [8]. There are many barriers to point-of-care testing, and test developers need to align their ideal target product profiles with realistic conditions in which most national TB programmes operate, especially if the goal is same-day diagnosis and treatment at the point of care [9].

On a positive note, our survey suggests new opportunities. The widespread availability of mobile phones may facilitate disease surveillance, supply chain management, and an automated notification of test results to national TB programmes, as well as to providers and patients [10]. In summary, we show the limited available infrastructure and expertise in decentralised microscopy centres. These limitations will need to be addressed by countries and considered by test developers in order for the next generation of molecular diagnostics to succeed.

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The next generation of molecular tests will challenge existing TB infrastructure in high burden countries http://ow.ly/lNGVB

Claudia M. Denkinger[1,2], Ioana Nicolau[2], Andrew Ramsay[3], Pamela Chedore[4] and Madhukar Pai[2,4]
[1]Division of Infectious Disease, Beth Israel Deaconess Medical Center, Boston, MA, USA. [2]McGill International TB Centre and Dept of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, QC, and [4]Respiratory Epidemiology and Clinical Research Unit, Montreal Chest Institute, Montreal, Montreal, QC, Canada.[3]Bute School of Medicine, St Andrews University, Fife, UK.

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

Received: April 16 2013 | Accepted after revision: May 15 2013

Support statement: This work was supported by the Bill and Melinda Gates Foundation (grant OPP1061487) and the Canadian Institutes of Health Research (grants MOP-89918). M. Pai is supported by the European and Developing Countries Clinical Trials Partnership (EDCTP-TBNEAT grant) and the Fonds de recherche du Québec – Santé (FRQS). C.M. Denkinger is supported by a Richard Tomlinson Fellowship at McGill University and a fellowship of the Burroughs-Wellcome Fund from the American Society of Tropical Medicine and Hygiene. The funders had no role in the analysis of data and decision to publish.

Conflict of Interest: Disclosures can be found alongside the online version of this article at www.erj.ersjournals.com

Acknowledgement: We are grateful to all the survey respondents for their time and support.

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Eur Respir J 2013; 42: 544–547 | DOI: 10.1183/09031936.00081113 | Copyright ©ERS 2013

Serum lipids as biomarkers for therapeutic monitoring of latent tuberculosis infection

To the Editor:

The World Health Organization has estimated that more than two billion persons in the world carry latent tuberculosis infection (LTBI). The diagnosis and treatment of LTBI could have an important impact in preventing the development of active tuberculosis (TB), a disease that causes 1.4 million deaths annually [1]. The current standard treatment of LTBI is nine months of isoniazid (INH) [2]. To improve adherence, a shorter regimen of 4 months rifampicin (RIF) is being evaluated in a multicentre randomised trial (CIHR MCT-94831, registered at www.controlled-trials.com/ISRCTN05675547). This ongoing trial offers an opportunity to study potential biomarkers as surrogates of successful prevention of active disease [3].