# Connectivity of diagnostic technologies: improving surveillance and accelerating TB elimination

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## ABSTRACT IN ENGLISH

In regard to tuberculosis (TB) and other major global epidemics, the use of new diagnostic tests is increasing dramatically, including in resource-limited countries. Although there has never been as much digital information generated, this data source has not been exploited to its full potential. In this opinion paper, we discuss lessons learned from the global scale-up of these laboratory devices and the pathway to tapping the potential of laboratory-generated information in the field of TB by using connectivity. Responding to the demand for connectivity, innovative third-party players proposed solutions that have been widely adopted by field users of the Xpert MTB/RIF assay. The experience associated with the utilization of these systems, which facilitate the monitoring of wide laboratory networks, stressed the need for a more global and comprehensive approach to diagnostic connectivity. In addition to facilitating the reporting of test results, the mobility of digital information allows the sharing of information generated in programme settings. These data, when they become easily accessible, can be used to improve patient care, disease surveillance and drug discovery. Therefore they should be considered as a public health good. We list several examples of concrete initiatives that should allow data sources to be combined to improve the understanding of the epidemic, support the operational response, and finally accelerate TB elimination. With the many opportunities that the pooling of data associated with the TB epidemic can provide, pooling of this information at an international level has become an absolute priority.

## Résumé en Français

Dans le domaine de la tuberculose (TB) et d’autres épidémies majeures au niveau international, l’utilisation de nouvelles technologies pour le diagnostic s’est largement répandue, y compris dans les pays à faible ressources. Cependant, malgré la grande quantité de données générées par ces nouveaux outils, cette source d’information reste aujourd’hui largement inexploitée. Dans cet article d’opinion, nous discutons les leçons tirées de l’utilisation de ces nouveaux outils diagnostics et certaines pistes pour mieux mettre à profit, grâce à la connectivité, les informations générées par les laboratoires TB. En réponse à l’absence de solutions permettant cette connectivité, des solutions innovantes ont été proposées par des acteurs tiers et ont été largement adoptées par les utilisateurs du test Xpert MTB/RIF. L’utilisation croissante de ces solutions qui permettent la surveillance de larges réseaux de laboratoires a porté l’attention sur la nécessité de proposer une approche plus globale et intégrée par rapport à la connectivité des laboratoires diagnostiques. Ces solutions facilitent la transmission des résultats, mais permettent également le partage d’informations générées en situation réelle. Ces données, lorsqu’elles deviennent aisément accessibles, peuvent être utilisées pour améliorer la qualité des soins prodigués aux malades, la surveillance des maladies et la découverte de médicaments. Pour ces raisons, elles doivent être considérées comme un bien de santé publique. Nous dressons une liste d’exemples d’initiatives concrètes qui devraient permettre de faciliter le partage de données de laboratoire dans le but de renforcer notre compréhension de l’épidémie, soutenir les réponses opérationnelles, et accélérer l´élimination de la TB. En raison des nombreuses opportunités associées au partage d’information liées à l’épidémie de TB, la centralisation des données au niveau international est devenue une priorité absolue.

## Resumen en español

En el contexto de la tuberculosis (TB), la utilización de nuevas pruebas diagnósticas está aumentando de manera espectacular, especialmente en los países en desarrollo. Pese a que nunca se ha generado tanta cantidad de datos, aún no se aprovechan todas las posibilidades que ofrece esta nueva fuente de información. En el presente artículo de opinión, se examinan las enseñanzas extraídas del uso en todo el mundo de estos nuevos instrumentos diagnósticos y se analiza la hoja de ruta hacia la explotación de las ventajas y el potencial de la conectividad para el diagnóstico de la TB. Respondiendo a la falta de conectividad incorporada a las herramientas de diagnóstico, se han creado soluciones de conectividad, que a su vez han sido adoptadas por usuarios en el terreno con el fin de monitorizar la utilización del test Xpert MTB/RIF. El uso creciente de estas soluciones ha centrado la atención sobre la necesidad de explorar de manera más general y exhaustiva la conectividad destinada al diagnóstico. Además de facilitar a los laboratorios la tarea de comunicar los resultados, la información digital debería favorecer el intercambio y el acopio de la información recogida en el marco programático. Dado que estos datos pueden mejorar la atención al paciente, la vigilancia de enfermedades y el descubrimiento de nuevos medicamentos, es preciso considerarlos como un bien de salud pública. Aquí, enumeramos varios ejemplos de iniciativas concretas que deberían facilitar la combinación de diferentes fuentes de datos para mejorar la vigilancia de la TB y acelerar su eliminación. Habida cuenta de las múltiples soluciones que ofrece, la combinación de datos a escala internacional constituye una prioridad absoluta, pues agilizará el progreso en sectores primordiales como la atención al paciente, la vigilancia epidemiológica y la respuesta operativa.

## Background

In the past decade, the use of new diagnostic tests has increased dramatically in developing countries' laboratories and more recently in decentralised point-of-care facilities. Self-contained molecular diagnostic devices have been successfully deployed to detect tuberculosis (TB) (e.g. GeneXpert [1]) or monitor treatment for HIV (e.g. PIMA [2]) in very basic clinical facilities.

Despite the accumulating evidence that these tools can be successfully used in the most challenging environments[3, 4] and the establishment of distribution and funding channels that should theoretically allow any country to access and scale-up these new technologies, the majority of patients that could benefit from these technical evolutions still do not have access to them. It is clear that the introduction of an improved TB diagnostic is not sufficient for assuring improved outcomes for patients as the details of implementation within existing health-delivery systems have critical influence on impact[5]. We suggest that the introduction of new tools such as GeneXpert offers an important opportunity to better understand, monitor and improve such delivery systems to assure greatest impact. If scale-up of novel diagnostic devices can be accompanied by the simultaneous introduction of up-to-date quality indicators and technical connectivity solutions, the vast amount of data generated by these new generation of automates could actually both simplify and potentiate the global response to the TB epidemic.

On a national and global level, the quantity of information produced following the introduction of new-generation laboratory instruments was not anticipated, thus there were no plans in place for how to manage the information flow or orient it in such a way that it could generate an evolution in the organisation of the epidemic response. In the absence of adequate laboratory information technology infrastructure, complemented with standardised reporting solutions for screening activities and treatment follow-up, many low-resource countries have continued to use slow and error-prone paper-based recording systems. In such systems, editing and transmission of paper reports cause inherent delays and contribute to the cost, complexity and relative inaccuracy of data interpretation.

Diagnostic ehealth solutions have the potential to help overcome some of these problems and maximize patient and public health impact following the introduction of a particular technology. The combination of this unprecedented evolution of the laboratory landscape and the potential of eHealth could be leveraged to generate evolution in national and global health-delivery systems that is needed to achieve TB elimination. Pragmatically, this requires device connectivity, wherein testing data and results are automatically and securely sent to repositories, translated into useful information and channeled to appropriate parties. Although device connectivity within other industries has been commonplace for some time, within the healthcare community it is still considered to be in its infancy [6].

In this paper, we discuss lessons learned from the global scale-up of the first generation of easy-to-connect diagnostic tools [7] and the pathway to tapping the potential of connectivity in the field of TB diagnostics [8].

## Experience from first-generation connected diagnostics: the example of Xpert MTB/RIF

During the last decade, several diagnostic companies, such as Cepheid Inc. (Sunnyvale, USA) and Alere Inc. (Waltham, USA), began developing a new generation of tests—essential to fight diseases of poverty such as TB and HIV—with significant support from public and philanthropic funders including NIH and BMGF.

The Xpert MTB/RIF, run on the GeneXpert platform, was the first truly game-changing test to come out of this work and has since been widely distributed in health facilities with limited human and infrastructure resources. The coverage of GeneXpert varies importantly between countries, with some countries still having only a couple of machines based in reference laboratories, and other countries such as South-Africa which rapidly realized the advantages of implementing this novel platform as a first-line test[9]. In the last five years, more than 13 million Xpert MTB/RIF tests have been procured worldwide. When GeneXpert was rolled out in 2010, the instrument had no built-in connectivity outside basic standards and the TB community did not have the software tools to connect to GeneXpert machines and optimally use the data being generated. As a consequence, valuable information was housed in the hard drives of local computers, was never used to inform surveillance efforts or health care providers, and has largely been lost.

In light of this, national TB programmes called for tools to reduce loss to follow-up and improve device and laboratory management—including a better ability to maintain cartridge supply and local redistribution and to evaluate and fulfill the training needs of device operators and lab technicians. Likewise, TB programmes voiced a need for connectivity systems that could relieve the high overhead costs of data aggregation and analysis that hamstrings the process of collecting raw data and turning it into useful information.

In 2012, responding to this critical gap in the implementation landscape, innovative third-party players developed connectivity solutions. For example, GxAlert (ABT and SystemOne), XpertSMS (Interactive Research and Development and TB REACH) and GenXchange (Université catholique de Louvain and the National TB Program of DRC) were devised to respond to the needs of low-resource countries where often internet is unavailable or unreliable and laboratory information systems or electronic medical records are not widely used. These tools offered immediate solutions and, based on national requests, hundreds of local laboratories have since been interconnected by implementing these systems. The scaling of these connectivity solutions has been taken back by dedicated companies[10, 11].

Cepheid, the manufacturer of GeneXpert, also worked to enable remote monitoring of their devices in response to expressed national needs and requests from the TB community. Like many developers, Cepheid lacked comprehensive information about what use-cases needed to be supported, and for ethical and regulatory reasons prioritized data security and confidentiality. As a result, the company launched an initial software tool that was a step forward but unable to fulfill all programme needs.

In response, a WHO-led alliance of key implementation partners (e.g. USAID, MSF, CHAI and FIND) and donors (e.g. UNITAID and GFATM) was formed to work with Cepheid to ensure secure, open access to critical data and to find a broader, holistic approach to connectivity and data management. An immediate solution was found and both Cepheid and the alliance remain interested in the creation of a non-proprietary, long-term connectivity platform (or a series of integrated and inter-operational platforms). This highlights how the global TB community can collectively define priority needs and work with manufacturers to negotiate and realize solutions for accessing and utilising key data.

Another important lesson from the implementation of first-generation connected diagnostics is the importance of a well-tailored delivery pathway for connectivity software that supports sustainable up-take in country. For instance, Alere, the manufacturer of PIMA, devised a country-based public-private partnership model to ensure appropriate training and support for their connectivity software. Without this support and engagement of key stakeholders, many countries would have struggled to make use of the influx of data. While the tool itself has limited wider applicability because of the proprietary nature of the software, the partnership model offers a valuable example of how non-proprietary, interoperable systems could be disseminated and nurtured in the future.

## Connectivity of diagnostics: a shared responsibility and public health necessity

WHO and research funding agencies have been advocating for, and implementing, data-sharing policies for some time. While these efforts have increased access to synthesized research data, efforts to make national programme data available are in their infancy. The use of new generation diagnostic platforms has triggered thinking about the potential utility of real-time analysis of national data and how diagnostic connectivity could further improve epidemiological surveillance and guide targeted public health responses. Accelerated TB elimination, for example, as called for in the WHO End TB strategy [12], can only be realized if case detection, individual patient management and epidemiological surveillance are intensified simultaneously, and if these efforts are closely monitored and validated. Data generated by Xpert MTB/RIF testing can be used both to improve patient management and treatment efforts, and to provide important population-level information on average infectiousness as a predictor for TB burden[13] and spread of new mutations. This requires optimized programmatic data management, pooling, sharing, analysis and use. Realizing improvements in surveillance and public health demands that information generated by diagnostic technologies in programmatic conditions be easily accessible and usable for national programmes. Ultimately, data access, enabled by diagnostic connectivity, should thus be seen as a public health good. Countries, international organizations, test developers and civil society organizations have a collective responsibility to work together to ensure sustainable use of information and communications technology to improve healthcare. In doing so, important questions regarding ethical obligations, data ownership and stakeholder interests, e.g. market competitiveness, need to be acknowledged and addressed. International collaborative efforts must furthermore address the issue of personal unique identifiers in a context of continuous human migrations and data mobility.

## The way forward: realizing the potential of connected diagnostics

Built-in connectivity has become an evident prerequisite for upcoming diagnostic platforms [14]. Tests that until recently were un-connectable, such as rapid diagnostic tests (e.g. HIV, malaria), can now be connected to digital readers with results collected, stored and transferred (e.g. Fio Corp, Canada).

In the field of TB diagnostics, a wide range of laboratory tests are used in complementarity. This includes rapid diagnostic tests and more conventional approaches such as microscopy, culture, drug susceptibility testing and sequencing [15]. Inter-connecting these diagnostic devices and further integrating this information with clinical indicators is the upcoming challenge for the TB community.

The Connected Diagnostics Initiative (CDx), coordinated by FIND (Geneva, Switzerland), is an example of a potential solution for accelerating connectivity and interoperability of diagnostic devices. CDx is providing an open-source software platform allowing for centralised aggregation of data from diagnostics, regardless of manufacturer. For this new effort to succeed, wide buy-in from implementers, policymakers and developers will be essential. In parallel, FIND is working with WHO towards guidelines for standardised results reporting for diagnostic devices, and assisting developers to be in compliance with these standards. These efforts go hand in hand with further deployment of local laboratory information systems and electronic medical records [16].

Alongside this initiative, various groups are creating global databases with the intention of enhancing research and development applications of data. For instance, genTB (Harvard University) is an open-source platform that allows for the pooling, analysis and visualization of genetic, epidemiological and clinical data. A global partnership, including WHO, CDC, CPATH, Stop TB, NIAID and FIND, has been established to develop a data platform (ReSeqTB) to store, curate and provide access to globally representative TB data that can inform the development of new diagnostics, facilitate clinical decisions and improve surveillance of drug resistance. While the opportunities for sharing information at an international scale must be promoted, countries must be provided with technical solutions that can support them in efficiently managing with whom, and for what purposes, national data are shared, and to ensure that these database efforts ultimately benefit patients.

Consensus is forming around the central role that connected diagnostics and digitization can play in tackling health systems weaknesses and diseases of poverty. However, the global health community must also address complex question of how new tools and practices can be effectively implemented in health systems. Substantial programmatic changes will be required in countries to absorb the innovation of connectivity and capture its benefits. This demands a holistic approach to cultivating effective development and adoption of new diagnostic tools. In this context, laboratory connectivity may serve the need for more efficient post-marketing surveillance of newly rolled-out diagnostics both for national stakeholders and their global partners. As the amount of information collected will rapidly increase beyond our conventional capacities of analysis, the global health community will also need to initiate and intensify innovative collaborations to exploit the data collected, using big data analysis and self-learning algorithms. Managing, visualizing and analysing such big data creates challenges beyond the capacities of standard statistical methods, and thus generates an increasing demand for data science and multidisciplinary efforts.

## Conclusion

Our common goal of TB elimination is not a dream anymore: it is an achievable objective with clear milestones [17]. The elimination effort will require a strengthened collaboration between information technology and big data specialists, social medicine and private companies [6].

In the future, all diagnostic technologies should be inter-connected, allowing data generated by laboratories to merge in a common repository while safeguarding patient confidentiality. The TB community could use such a repository to monitor progress and identify problems and potential solutions, at both patient and global levels. Data pooling will open up opportunities to comprehend the rapid evolution of drug-resistant mutations, which will aid in selecting cost-efficient treatment schemes and improving patient management. With the many solutions it can provide, data pooling at an international level is an absolute priority, as it will accelerate progress in critical sectors including patient care, epidemiological surveillance and operational response. Being an international health emergency, the TB epidemic requires optimal international collaboration and unambiguous political commitment for intensifying data sharing efforts.

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