

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

E. Andre,<sup>\*\*†</sup> C. Isaacs,<sup>§</sup> D. Affolabi,<sup>†#</sup> R. Alagna,<sup>\*\*</sup> D. Brockmann,<sup>†††</sup> B. C. de Jong,<sup>§§</sup>  
E. Cambau,<sup>†††##</sup> G. Churchyard,<sup>\*\*\*</sup> T. Cohen,<sup>†††</sup> M. Delmee,<sup>\*†</sup> J-C. Delvenne,<sup>†††§§§</sup> M. Farhat,<sup>††††</sup>  
A. Habib,<sup>###</sup> P. Holme,<sup>\*\*\*\*</sup> S. Keshavjee,<sup>††††</sup> A. Khan,<sup>††††</sup> P. Lightfoot,<sup>§</sup> D. Moore,<sup>†††††</sup>  
Y. Moreno,<sup>#####</sup> Y. Mundade<sup>†††††</sup> M. Pai,<sup>†††††</sup> S. Patel,<sup>§§§§§</sup> **A. U. Nyaruhirira**,<sup>†††††</sup>  
L. E. C. Rocha,<sup>#####</sup> J. Takle,<sup>††††††</sup> A. Trébuçq,<sup>††††††</sup> J. Creswell,<sup>§§§§§§</sup> C. Boehme<sup>§</sup>

\*Pôle de Microbiologie Médicale, Institut de Recherche Expérimentale et Clinique, Université Catholique de Louvain, Brussels, †Service de Microbiologie, Département de Biologie Clinique, Cliniques Universitaires Saint-Luc, Brussels, Belgium; ‡ European Society for Clinical Microbiology and Infectious Diseases (ESCMID) Study Group for Mycobacterial Infections (ESGMYC), ESCMID, Basel, §Foundation for Innovative New Diagnostics, Geneva, Switzerland; ¶Faculty of Health Sciences, Abomey-Calavi University, Cotonou, #National Tuberculosis Programme, Cotonou, Benin; \*\*TB Supranational Reference Laboratory, Istituto di Ricovero e Cura a Carattere Scientifico San Raffaele Scientific Institute, Milan, Italy; ††Institute for Theoretical Biology, Department of Biology, Humboldt University of Berlin, Berlin, ††Epidemiological Modelling of Infectious Diseases, Robert Koch Institute, Berlin, Germany; §§Unit of Mycobacteriology, Department of Biomedical Sciences, Institute of Tropical Medicine, Belgium; †††Université Paris Diderot, Institut National de la Santé et de la Recherche Médicale, Unité mixte de recherche 1137, Infection, Antimicrobiens, Modélisation, Evolution, Paris, ##Bactériologie, Assistance Publique-Hôpitaux de Paris, Hôpital Lariboisière, Paris, France; \*\*\*Aurum Institute, Johannesburg, South Africa; †††Yale School of Public Health, Yale University, New Haven, Connecticut, USA; ††††Institute of Information and Communication Technologies, Electronics and Applied Mathematics, and §§§Centre for Operations Research and Econometrics, Université Catholique de Louvain, Belgium; †††††Massachusetts General Hospital, Boston, Massachusetts, USA; ###Interactive Health Solutions, Karachi, Pakistan; \*\*\*\*Sungkyunkwan University, Seoul, South Korea; †††††Harvard Medical School Center for Global Health Delivery, Dubai, United Arab Emirates; †††††Interactive Research and Development, Karachi, Pakistan; ††††††TB Centre, London School of Hygiene & Tropical Medicine, London, UK; ††††††Institute for Biocomputation and Physics of Complex Systems (BIFI), and ††††††Department of Theoretical Physics, Faculty of Sciences, University of Zaragoza, Zaragoza, Spain; ††††††UNITAID, Geneva, Switzerland; ††††††McGill International TB Centre & McGill Global Health Programs, McGill University, Montreal, Quebec, Canada; §§§§§University Hospital Southampton NHS Foundation Trust, Southampton, UK; ††††††Management Sciences for Health, Gauteng, South Africa; #####Karolinska Institutet, Stockholm, Sweden; ††††††Université de Namur, Namur, Belgium; †††††††Global Connectivity LLC, Somerville, Massachusetts, USA; †††††††International Union Against Tuberculosis and Lung Disease, France; §§§§§§Stop TB Partnership, Geneva, Switzerland

### SUMMARY

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 have proposed solutions that have been widely adopted by field users of the Xpert® MTB/RIF assay. The experience associated with the utilisation 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. When they become easily accessible, these data can be used to improve patient care, disease surveillance and drug discovery. They should therefore 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.

**KEY WORDS:** laboratory; connectivity; tuberculosis; surveillance; data

Correspondence to: Emmanuel André, Pôle de Microbiologie, Institut de Recherche Expérimentale et Clinique, Université catholique de Louvain, 10 avenue Hippocrate Brussels 1200, Belgium. e-mail: emmanuel.andre@uclouvain.be; emmanuel.andre@outlook.be

Article submitted 26 January 2016. Final version accepted 24 March 2016.

[A version in French of this article is available from the Editorial Office in Paris and from the Union website [www.theunion.org](http://www.theunion.org)]

IN THE PAST DECADE, the use of new diagnostic tests has increased dramatically in the laboratories of developing countries and, more recently, in decentralised point-of-care facilities. Self-contained molecular diagnostic devices have been successfully deployed to detect tuberculosis (TB) (e.g., Xpert<sup>®</sup> MTB/RIF; Cepheid, Sunnyvale, CA, USA<sup>1</sup>) or monitor treatment for the human immunodeficiency virus (HIV) (e.g., Alere Pima<sup>™</sup> CD4, Alere, Waltham, MA, USA<sup>2</sup>) in very basic clinical facilities. Despite the accumulating evidence that these tools can be successfully used in the most challenging environments<sup>3,4</sup> 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 tool is not sufficient to assure improved outcomes for patients, as the details of implementation within existing health delivery systems have a critical influence on impact.<sup>5</sup>

We suggest that the introduction of new tools such as Xpert offers an important opportunity to better understand, monitor and improve such delivery systems to assure greatest impact. If the 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 this new generation of automates could both simplify and potentiate the global response to the TB epidemic.

On a national and global level, as the quantity of information produced following the introduction of new-generation laboratory instruments was not anticipated, no plans were in place on 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 by standardised reporting solutions for screening activities and treatment follow-up, many low-resource countries have continued to use slow, 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 e-health solutions have the potential to help overcome some of these problems and maximise the 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 e-health could be leveraged to generate the revolution in national and global health delivery systems that is needed to achieve TB elimination. Pragmatically, this requires device connectivity, whereby secure testing

data and results are automatically sent to repositories, translated into useful information and channelled to appropriate parties. Although device connectivity within other industries has been routine for some time, within the health care community it is still largely in its infancy.<sup>6</sup>

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

### **EXPERIENCE FROM FIRST-GENERATION CONNECTED DIAGNOSTICS: THE EXAMPLE OF XPERT**

During the last decade, several diagnostic companies, such as Cepheid Inc and Alere Inc, have begun 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 the National Institutes of Health (Bethesda, MD, USA) and the Bill & Melinda Gates Foundation (Seattle, WA, USA).

The Xpert assay, which is run on the GeneXpert platform, was the first truly game-changing test to come out of this research, and it has since been widely distributed in health facilities with limited human and infrastructure resources. The coverage of Xpert varies considerably between countries, with some countries still having only a limited number of machines based in reference laboratories, and others, such as South Africa, that realised the advantages of implementing this novel platform as a first-line test fairly rapidly.<sup>9</sup> In the last 5 years, more than 13 million Xpert 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 use the data being generated to its full capacity. Valuable information housed in the hard drives of local computers was thus never used to inform surveillance efforts or health care providers, and was largely lost.

In the light of this issue, national TB programmes (NTPs) called for tools to reduce loss to follow-up and improve device and laboratory management, including a better ability to maintain cartridge supplies and local redistribution, and evaluate and fulfil the training needs of device operators and laboratory technicians. Likewise, NTPs voiced a need for connectivity systems that could relieve the high overhead costs of data aggregation and analysis, which hamstringing 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. GxAlert

(ABT, Cambridge, MA, USA, and SystmOne, Horsforth, UK), XpertSMS (Interactive Research and Development, Karachi, Pakistan, and TB REACH, Geneva, Switzerland) and GenXchange (Université Catholique de Louvain, Louvain, Belgium, and the NTP, Kinshasa, Democratic Republic of Congo) were devised to respond to the needs of low-resource countries, where internet is often unavailable or unreliable and laboratory information systems or electronic medical records are not widely used. These tools offered immediate solutions and, in response to national requests, hundreds of local laboratories have since become interconnected on implementing these systems. The scaling of these connectivity solutions has been taken back by dedicated companies (Global Connectivity, Somerville, MA, USA. <http://www.globalconnectivity.co/>; and Savics, Brussels, Belgium. <http://www.savics.org>).

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 they prioritised data security and confidentiality. As a result, the company launched an initial software tool that was a step forward but was unable to fulfil all NTP needs.

In response, an alliance of key implementation partners, such as USAID (Washington DC, USA), MSF (Paris, France), Clinton Health Access Initiative (Boston, MA, USA) and Foundation for Innovative New Diagnostics (FIND) (Geneva, Switzerland) and donors, such as UNITAID (Geneva, Switzerland) and the Global Fund (Geneva, Switzerland), was formed, led by the World Health Organization (WHO), to work with Cepheid in ensuring secure, open access to critical data and finding 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 realise 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 uptake in a given country. For example, Alere, the manufacturer of Pima™ CD4, 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**

The WHO and research funding agencies have been advocating for, and implementing, data-sharing policies for some time. While these efforts have increased access to synthesised research data, efforts to make NTP 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,<sup>10</sup> can only be realised 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 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<sup>11</sup> and spread of new mutations. This requires optimised programmatic data management, pooling, sharing, analysis and use. To realise improvements in surveillance and public health demands, the information generated by diagnostic technologies in programme conditions should be easily accessible and usable for national programmes. Ultimately, data access, enabled by diagnostic connectivity, should be seen as a public health good. Countries, international organisations, test developers and civil society organisations have a collective responsibility to work together to ensure sustainable use of information and communications technology to improve health care. In doing so, important questions regarding ethical obligations and data ownership and stakeholder interests, such as 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 migration and data mobility.

### **THE WAY FORWARD: REALISING THE POTENTIAL OF CONNECTED DIAGNOSTICS**

Built-in connectivity has become an evident prerequisite for upcoming diagnostic platforms.<sup>12</sup> Tests that until recently were un-connectable, such as rapid diagnostic tests for, for example, HIV and malaria,

can now be connected to digital readers, with collection of results, storage and transfer (e.g., Fio Corp, Toronto, ON, Canada).

In the field of TB diagnostics, a wide range of complementary laboratory tests are used. This includes rapid diagnostic tests and more conventional approaches such as microscopy, culture, drug susceptibility testing and sequencing.<sup>13</sup> 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, is an example of a potential solution for accelerating the connectivity and interoperability of diagnostic devices. CDx is providing an open-source software platform that allows centralised aggregation of data from diagnostics, regardless of the manufacturer. For this new effort to succeed, wide buy-in from implementers, policy makers and developers will be essential. In parallel, FIND is working with the WHO towards guidelines for standardised result reporting for diagnostic devices and assisting developers to be compliant with these standards. These efforts go hand in hand with further deployment of local laboratory information systems and electronic medical records.<sup>14</sup>

Alongside this initiative, various groups are creating global databases with the intention of enhancing research and development applications for data. For example, genTB (Harvard University, Cambridge, MA, USA) is an open-source platform that allows for the pooling, analysis and visualisation of genetic, epidemiological and clinical data. A global partnership, including the WHO, the US Centers for Disease Control and Prevention (Atlanta, GA, USA), the Center for Policy Analysis on Trade and Health (San Francisco, CA, USA), Stop TB (Geneva, Switzerland), the National Institute of Allergy and Infectious Diseases (Bethesda, MD, USA) 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 opportunities for sharing information at an international scale must be promoted, countries must also 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 digitisation can play in tackling health systems weaknesses and diseases of poverty. However, the global health community must also address the complex question of how new tools and practices can be implemented effectively in health systems. Substantial programmatic changes will be

required in the 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 also serve the need for more efficient post-marketing surveillance of newly rolled out diagnostics, for both 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 collaboration to exploit the data collected using big data analysis and self-learning algorithms. Managing, visualising and analysing 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 longer a dream: it is an achievable objective, with clear milestones.<sup>15,16</sup> The elimination effort will require strengthened collaboration between information technology and big data specialists, social medicine and private companies.<sup>6</sup>

In the future, all diagnostic technologies should be interconnected, allowing data generated by laboratories to be merged 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-effective 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. As an international health emergency, the TB epidemic requires optimal international collaboration and unambiguous political commitment for intensifying data-sharing efforts.

*Conflicts of interest:* none declared.

## References

- 1 Boehme C C, Nabeta P, Hillemann D, et al. Rapid molecular detection of tuberculosis and rifampin resistance. *N Engl J Med* 2010; 363: 1005–1015.
- 2 Scott L E, Campbell J, Westerman L, et al. A meta-analysis of the performance of the Pima CD4 for point of care testing. *BMC Med* 2015; 13: 168.
- 3 Creswell J, Codlin A J, Andre E, et al. Results from early programmatic implementation of Xpert<sup>®</sup> MTB/RIF testing in nine countries. *BMC Infect Dis* 2014; 14: 2.

- 4 Raizada N, Sachdeva K S, Sreenivas A, et al. Feasibility of decentralised deployment of Xpert<sup>®</sup> MTB/RIF test at lower level of health system in India. *PLOS ONE* 2014; 9: e89301.
- 5 Theron G, Zijenah L, Chanda D, et al. Feasibility, accuracy, and clinical effect of point-of-care Xpert<sup>®</sup> MTB/RIF testing for tuberculosis in primary-care settings in Africa: a multicentre, randomised, controlled trial. *Lancet* 2014; 383: 424–435.
- 6 Ohno-Machado L. To share or not to share: that is not the question. *Sci Transl Med* 2012; 4: 165cm15.
- 7 Shinnick T M, Starks A M, Alexander H L, Castro K G. Evaluation of the Cepheid Xpert<sup>®</sup> MTB/RIF assay. *Expert Rev Mol Diagn* 2015; 15: 9–22.
- 8 Theron G, Jenkins H E, Cobelens F, et al. Data for action: collection and use of local data to end tuberculosis. *Lancet* 2015; 386: 2324–2333.
- 9 Meyer-Rath G, Schnippel K, Long L, et al. The impact and cost of scaling up GeneXpert MTB/RIF in South Africa. *PLOS ONE* 2012; 7: e36966.
- 10 Uplekar M, Weil D, Lönnroth K, et al. WHO's new End TB strategy. *Lancet* 2015; 385: 1799–1801.
- 11 Wood E, Kerr T, Marshall B D, et al. Longitudinal community plasma HIV-1 RNA concentrations and incidence of HIV-1 among injecting drug users: prospective cohort study. *BMJ* 2009; 338: b1649.
- 12 Pai M, Schito M. Tuberculosis diagnostics in 2015: landscape, priorities, needs, and prospects. *J Infect Dis* 2015; 211 (Suppl 2): S21–S28.
- 13 Starks A M, Aviles E, Cirillo D M, et al. Collaborative effort for a centralized worldwide tuberculosis relational sequencing data platform. *Clin Infect Dis* 2015; 61 (Suppl 3): S141–S146.
- 14 Fraser H S, Habib A, Goodrich M, et al. E-health systems for management of MDR-TB in resource-poor environments: a decade of experience and recommendations for future work. *Stud Health Technol Inform* 2013; 192: 627–631.
- 15 Lönnroth K, Migliori G B, Abubakar I, et al. Towards tuberculosis elimination: an action framework for low-incidence countries. *Eur Respir J* 2015; 45: 928–952.
- 16 Stop TB Partnership. Global Plan to End TB: the paradigm shift 2016–2020. Geneva, Switzerland: United Nations Office for Project Services, 2016.



## RESUME

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, la majorité de cette source d'information reste aujourd'hui inexploitée. Dans cet article d'opinion, nous discutons les leçons tirées de l'utilisation de ces nouveaux outils diagnostics et la voie pour mieux mettre à profit les informations générées par les laboratoires TB en utilisant leur potentiel de connectivité. 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 permettant 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 devraient 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 devenu une priorité absolue.

## RESUMEN

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.