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PERSPECTIVES

Coronavirus Disease 2019 Diagnosis in Low- and Middle-Income Countries



The Big New Bully Disrupting TB and HIV Diagnostic Services

Alaine Umubyeyi Nyaruhirira,^{*} Jerod N. Scholten,[†] Mustapha Gidado,[†] and Pedro G. Suarez[‡]

From Global Health Systems Innovation,^{*} Management Sciences for Health, Pretoria, South Africa; the KNCV Tuberculosis Foundation,[†] The Hague, the Netherlands; and Global Health Systems Innovation,[‡] Management Sciences for Health, Arlington, Virginia

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Address correspondence to
Alaine Umubyeyi Nyaruhirira,
M.P.H., Ph.D., Management
Sciences for Health, 466 King's
Highway, Lynnwood, Pretoria
0081, South Africa. E-mail:
anyaruhirira@msh.org.

Coronavirus disease 2019 (COVID-19) undermines control of other infectious diseases. Diagnostics are critical in health care. This opinion paper explores approaches for leveraging diagnostics for COVID-19 while retaining diagnostics for other infectious diseases, including tuberculosis (TB) and HIV. The authors reflect on experiences with GeneXpert technology for TB detection and opportunities for integration with other diseases. They also reflect on benefits and risks of integration. Placement of diagnostics in laboratory networks is largely nonintegrated and designated for specific diseases. Restricting the use of diagnostics leaves gaps in detection of TB, HIV, malaria, and COVID-19. Integrated laboratory systems can lead to more efficient testing while increasing access to critical diagnostics. However, the authors have observed that HIV diagnosis within the TB diagnostic network displaced TB diagnosis. Subsequently, COVID-19 disrupted both TB and HIV diagnosis. The World Health Organization recommended rapid molecular diagnostic networks for infectious diseases and there is a need for more investment to achieve diagnostic capacity for TB, HIV, COVID-19, and other emerging infectious diseases. Integrated laboratory systems require mapping laboratory networks, assessing needs for each infectious disease, and identifying resources. Otherwise, diagnostic capacity for one infectious disease may displace another. Further, not all aspects of optimal diagnostic networks fit all infectious diseases, but many efficiencies can be gained where integration is possible. (*J Mol Diagn* 2022, 24: 289–293; <https://doi.org/10.1016/j.jmoldx.2021.12.008>)

The roll-out of new technologies and the substantial growth in political and financial commitment by countries, regions, and bilateral and international donors (such as the Global Fund to Fight AIDS, Tuberculosis and Malaria; President's Emergency Plan for AIDS Relief [PEPFAR]; and US Agency for International Development) and their global partners have facilitated a surge of global progress in health over the past 15 years.¹ Despite major progress in the global HIV and tuberculosis (TB) responses, these diseases continue to represent a public health burden in all regions, with inequitable coverage of diagnosis, prevention, and treatment.²

Globally, an estimated 10 million individuals fell ill with TB in 2019, a number that has been declining very slowly in

recent years; although, in 2019, there was an estimated reduction of 1.2 million TB deaths among HIV-negative individuals.³ Access to TB treatment has grown from 6 million in 2015 to 7.1 million in 2019, with increased access to TB preventive treatment as well, to 4.1 million.⁴ New HIV infections among women aged 15 to 24 years fell by 25% between 2010 and 2018, and since 2010, AIDS-related mortality has declined by 33%.⁵ Other diseases, such as hepatitis C and sexually transmitted diseases, have gained global prominence, with many low- and middle-income

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countries (LMICs) beginning to implement services to reduce morbidity and mortality.

The coronavirus disease 2019 (COVID-19) pandemic has significantly disrupted health services due to cases overburdening the health system or response measures that limit normal health program activities and care-seeking. As of October 14, 2021, there have been 239,007,759 confirmed cases of COVID-19, including 4,871,841 deaths, reported to the World Health Organization (WHO) globally, and 6,471,051,151 vaccine doses have been administered. The pandemic has undermined the progress made in the last decade in part because access to timely diagnostics for TB, HIV, and other opportunistic infections has been compromised; for example, to illustrate a few impacts of COVID-19, TB domestic resources have been diverted to COVID-19 response, affecting also staffing and facilities used to isolate COVID-19 cases. WHO has indicated that TB diagnosis has gone down 21% in 2020 compared with 2019 due to COVID, which translates into one-half million more deaths due to TB. If new strategies are not developed, implemented, and coordinated effectively at the global and national levels, long-term setbacks will result.^{2–6} Effective interventions and services must be targeted to the most vulnerable individuals and populations—for example, pregnant women, young children, individuals living with HIV/AIDS or TB, the poor, and the elderly—while maintaining quality and efficiency in existing health programs.⁶

As countries make progress toward universal health care (UHC), diagnostics are a critical component of health benefits packages because most diseases or conditions cannot be managed without a clear diagnosis and laboratory tests for follow-up. COVID-19 exposes the need for a fundamental shift in service delivery models, including diagnostic integration and involvement of the private sector as highlighted in the last Lancet Commission report^{7,8} (for a supplementary perspective, see <https://www.statnews.com/2019/05/20/diagnostics-universal-health-coverage-succeed>, last accessed December 8, 2020). The pandemic reveals that reality by exacerbating the gaps in detection of TB, HIV, and other opportunistic infections due, on one hand, to lack of laboratory capacity (eg, physical infrastructure and human resources) in some LMICs, even before the pandemic, and on the other hand, to mitigation strategies undertaken to respond to COVID-19.^{7,8} These mitigation steps and shifting of resources have drastically reduced the capacity of health systems in LMICs to respond to other health issues because of overwhelmingly high demand for the care of patients with COVID-19 and interruptions within the supply chain.

Because the diagnostics have been built and funded specifically for certain diseases, the use of new advances that enable technology designed for one disease to detect other diseases is often not permitted. For example, GeneXpert, a technology that revolutionized TB molecular diagnostic testing and has a massive footprint in 145 LMICs, can now be used for HIV (viral load, early infant

diagnosis) and COVID-19 testing through the recent release of the new Xpert Xpress SARS-CoV-2 cartridge (Cepheid, Sunnyvale, CA). However, financial and operational barriers generate concerns about how the utilization of this technology in weak laboratory systems and public health programs will undermine, for example, TB and HIV diagnostic capacity in some countries. Improper integration of technology may lead to suboptimal diagnosis and ultimately greater TB and HIV mortality. The newly introduced diagnostics need to be integrated in a phased, systematic manner, and optimized to meet program needs and targets for both existing diseases and new ones.^{4–8}

Current Situation

Application of nucleic acid amplification tests (NAATs) has revolutionized rapid and accurate diagnostic testing for most pathogens for a decade. Automated batched or modular cartridge-based NAATs offer a combination of excellent sensitivity and specificity and reproducible, accurate test results, with minimal manipulation and decreased risk of cross-contamination, that has made PCR technology an appealing alternative to culture- or immunoassay-based testing for disease diagnosis. Although NAATs are more sensitive than most other tests for TB, culture remains the gold standard. However, culture can take months, whereas NAATs can be performed in less than 2 hours (<http://www.stoptb.org/assets/documents/resources/wd/ERPD%20approved%20TB%20diagnostics%20info%20note.pdf>), last accessed January 25, 2022).^{9–11} The opportunity for decentralization to lower levels of the health system makes NAATs an essential tool to implement the End TB Strategy and realize the UNAIDS 95-95-95 goals.¹²

For the past 10 years, the Xpert assay has represented the first major advance in TB diagnosis, allowing peripheral detection of rifampicin resistance, which enabled detection of drug-resistant TB and exponentially increased the numbers of cases treated. Additionally, the Xpert Ultra test increases the sensitivity of TB diagnosis in children, HIV-infected individuals, and paucibacillary and extrapulmonary TB; and since its endorsement by WHO, most countries have quickly started rolling out Xpert.^{9–11} As of December 31, 2018, 10,562 GeneXpert machines (47,567 modules) had been procured across 136 of the 145 countries eligible for concessional prices (Cepheid, 2018; W. Van Gemert, unpublished data). However, existing GeneXpert technologies typically have low overall utilization, although this is site-dependent in several countries. Countries are not procuring enough cartridges to reach testing targets or fully utilize instruments due to algorithm constraints on implementation, weak specimen referral linkages to testing, and inadequate attention to maintenance and prompt repair.

High-throughput platforms, mostly at centralized levels, have been introduced on a massive scale for HIV early infant diagnosis, drug resistance detection, and viral load

monitoring for treatment response, with funding from the Global Fund, PEPFAR, and other agencies. The volume of viral load tests performed has increased significantly from the 15 million viral load tests conducted in 2017, and the number is projected to double to nearly 30 million by 2022. The UNAIDS 2020 report released during the COVID-19 pandemic showed that only 14 countries have achieved the 90-90-90 HIV treatment targets (90% of individuals living with HIV know their HIV status, of whom 90% are on antiretroviral treatment and of whom 90% are virally suppressed), including Eswatini, which has one of the highest HIV prevalence rates in the world. However, in many parts of the world, COVID-19 is colliding with the ongoing HIV epidemic.^{6–8} A recent WHO HIV guideline recommends point-of-care diagnosis and monitoring as preferred over centralized laboratory testing because they significantly reduce turnaround time and result in saving lives.¹⁰ Further, the WHO Health Assembly recommends integrated services; donors such as the Global Fund may reduce funding and expect further integration.

To control the spread of COVID-19, experts agree that an aggressive strategy of vaccination along with test, trace, and treatment is needed, combined with physical distancing measures and the use of masks. However, SARS-CoV-2 detection in some countries is limited by weak and uncoordinated laboratory systems, as well as insufficient laboratory equipment and test kits for PCR or access to rapid diagnostic tests. This insufficient capacity compels governments, for example, to restrict testing to individuals who meet specific narrow criteria.¹³ Many efforts and partnerships to increase the response to COVID-19 in Africa and around the world have been launched, such as the Access to COVID-19 Tools Accelerator, which is coordinated by the Global Fund, WHO, UNICEF, and the Partnership to Accelerate COVID-19 Testing in Africa. However, after 19 months into the pandemic, lessons and progress in diagnostic pipelines are demonstrating the efficiency of antigen tests. The Global Fund is advocating for using antigen tests (3 USD, rather than GX for COVID-19 at 20 USD), and WHO is updating its antigen rapid diagnostic test guidance as well as preparing interim guidance on Recommendations for National SARS-CoV-2 Testing Strategies and Diagnostic Capacities.

Discussion

This paper aims to identify the best approach to using both existing and new technologies to address the COVID-19 pandemic and coexisting major public health challenges without jeopardizing the gains in diagnostic access for TB, HIV, and other opportunistic infections.

COVID-19 illustrates our common vulnerability to disease across borders, the public–private divide, and the limits of our fragmented approach to health.^{2,11–13} A more coordinated, comprehensive, and integrated decentralization

of services at the community level is urgently needed. In their paper, Pooran et al¹¹ make a case for value for money for point-of-care TB diagnostic services because such services reduce, not only death, but also economic loss in Africa. It also reduces transport costs to have testing performed more locally.

Governments and donors will need to revisit public health programs and systems in line with UHC in LMICs. Doing so will require a paradigm shift, with change management, task shifting, and bold policies. Centralized testing of patients for initial diagnosis should be shifted to the lowest administrative level possible (district), ideally at the point of care. Centralized laboratory staff will continue to have opportunities for leadership of the entire network, for example, quality assurance, introduction of new diagnostics, research, training, and mentoring.

The current diagnostic gaps in the HIV, TB, and COVID-19 response could be greatly mitigated by intensively investing in public health laboratory systems and optimizing use of existing technologies already introduced in many LMICs. However, many of the multiplex technologies are centralized in biosafety level 2 or 3 laboratories, due to high requirements for safety, human skills, resources, and alignment with vertical diagnostic programs.

The US Food and Drug Administration approved Xpert Xpress SARS-CoV-2 on March 21, 2020.^{9,13} The test kit can deliver a COVID-19 diagnosis in 45 minutes. The machine can be placed in a biosafety level 1 or 2 laboratory or in mobile vehicles with similar safety requirements, making it ideal for community testing. This will reduce the costs of referral, from both the patient and health system perspectives. Other affordable point-of-care or near-patient multiplex platforms endorsed by WHO are available, such as TrueNat (Molbio Diagnostics, Goa, India) or TB loop-mediated isothermal amplification assay); and more platforms are in development or in clinical trials that can diagnose and monitor multiple diseases, including drug-resistant malaria [refer to: <https://www.devex.com/news/afterthe-pandemic-how-will-covid-19-transform-global-health-and-development-96936>, last accessed December 8, 2020; <http://www.stoptb.org/assets/documents/covid/Considerations%20for%20selection%20of%20SARS-CoV-2%20diagnostics.pdf>, last accessed December 8, 2020; <https://www.finddx.org/mal-fev/improved-malaria-rdts>, last accessed December 8, 2020].^{14,15}

Multidisease molecular platforms [eg, Abbott's RealTime m2000sp and m-PIMA (Abbott, Abbott Park, IL); Cepheid's GeneXpert GX-4, -16, -48, and -80 modules; Hologic Panther, Roche COBAS AmpliPrep/COBAS TaqMan CAP/CTM 96; Roche cobas 4800/6800/8800 (Roche, Basel, Switzerland); Thermo Fisher's Applied Biosystems 7500 Fast Real-Time PCR system (Thermo Fisher, Waltham, MA); Becton Dickinson's BD MAX (Becton Dickinson, Franklin Lakes, NJ); and genesig Easy qPCR Detection Kit for nCoV-2019 (genesig, Chandler's Ford, UK)]^{6,7,10} have already been introduced for HIV, influenza,

hepatitis, and other diseases in many national reference laboratories and research institutes in LMICs. Additionally, the Food and Drug Administration has authorized—for emergency use—some of the test kits that can be accommodated by some of the platforms listed above for SARS-CoV-2.

Given these developments, the diagnostic pipeline for COVID-19 and other priority diseases is growing. Integrated technologies, such as next-generation sequencing, at peripheral levels might also be used for detection of drug resistance across diseases. Furthermore, treatment monitoring, such as viral load and bacterial load testing, might also be conducted using integrated platforms. Having well-functioning laboratory systems to detect multiple infectious diseases, their drug resistance patterns, and treatment responses at lower levels of the health system would enable a more equitable, human-centered approach, with increased access and decreased turn-around time, ultimately reducing morbidity and mortality from infectious disease, particularly TB and HIV.

Integration of diagnostic networks is at an early stage in LMICs. A few African, Asian, and Latin American countries have piloted diagnostic integration, mainly at selected central and intermediate laboratories; they include Cameroon (HIV and TB), Malawi (HIV and TB), Nigeria (hepatitis C and TB), Zimbabwe (HIV and TB), Brazil, the Caribbean countries, Democratic Republic of Congo, India, and Malaysia.¹¹ Best practices and lessons from these pilots are urgently needed to inform the development and scale-up of an integrated diagnostic laboratory network approach. This network will form the basis for a robust public health laboratory system in each country, with strong international and government collaboration, which will benefit all health programs, including reproductive health, maternal and child health, communicable diseases, emerging diseases, and cancer, in line with UHC.⁷

Several LMICs have already used GeneXpert technology to diagnose both TB and COVID-19,^{8,14,16,17} but such integration has not been uniform across countries, revealing better approaches to follow in the future. The authors believe that no one size fits all, because countries vary in infrastructure, disease burden, and geographic peculiarities. Further, some countries have vector-borne diseases such as malaria and cholera that are relevant only in certain areas of the country. Nonetheless, many common links can be made across most LMICs to integrate their laboratory systems for infectious diseases and create a more resilient response on all tiers of their public health laboratory network, shifted closer and targeted to the communities that need them.

Recommendations

LMICs should take advantage of existing multiplex platforms, such as GeneXpert, high-throughput platform technologies, and laboratory networks, to introduce COVID-19 testing. These networks are already established and working

well to make laboratory diagnostic services available in several countries. By integrating diagnostics for COVID-19 and other infectious diseases into a well-articulated laboratory system, we will gain efficiencies as well as move closer to UHC even during the COVID-19 pandemic. Introducing a vertical COVID-19 diagnostic service model would be expensive and inefficient in reaching the individuals who need the services—and it would not be sustainable.

Integrated, affordable multiplex technologies, particularly at the point of care, local and community levels, have the advantages of avoiding parallel diagnostic systems and duplication of activities such as referral and transport, equipment maintenance, human resource management, quality assurance, supply chain and quantification, and training—and duplication of the costs of those activities. In providing increased capacity and uptake for TB, HIV, COVID-19, and other existing or future opportunistic infections, integrated technologies offer better value for money and sustainability.

Innovative approaches to diagnostic integration can maximize investments while increasing access but require a strategic approach tailored to each country context based on mapping and optimizing the laboratory network, assessing the needs for detection capacity for each disease, and identifying the gaps so resources can be mobilized. Merely having the machines will not translate into great improvements. We must also strengthen:

- Political leadership to remove barriers to diagnostic integration, and roadmaps and strategic plans focused on increasing investment in diagnostic capacity in a holistic, coordinated way, with robust policies;
- Structures for supplies of consumables, maintenance, and sample transportation;
- Coordination and communication among disease control programs, including donors and the private sector;
- Technical assistance to ministries of health, local public health programs and institutions, and the private sector;
- Quality-assured, connected, and sustainable laboratory networks, led by a national public health laboratory or other governance body, to guarantee universal access to prevention, diagnostics, treatment, and care services; and
- Integrated laboratory information systems and dashboards to increase use of data and inform decision-making for patient management, program planning, and service delivery, while ensuring confidentiality.

Conclusion: Looking Ahead

Effective interventions and services will require transforming our way of diagnosing and treating individuals to enable countries to reach the End TB milestones and UNAIDS 95-95-95 goals, even while containing other diseases. If we do not act to mitigate the threat, COVID-19 will

lead to an upsurge in deaths from TB, HIV, and other opportunistic infections. If we take an integrated approach, leveraging the infrastructure and resources we have already invested in and moving swiftly to strengthen the health system as a whole, we can step up the fight against both COVID-19 and other diseases of major public health importance.

The authors call on all ministries of health, donors, implementers, partners, and supported countries to revisit their strategies by looking at all these opportunities. The authors recommend that donors focus investments in COVID-19 testing by taking advantage of existing platforms and infrastructures to maximize service coverage to save lives during the pandemic while serving as a benchmark to gauge progress toward implementing guidelines such as the WHO Essential Diagnostics List and investing in long-term UHC goals. This approach will cost far less than setting up parallel systems or centralizing testing in a few laboratories. This is a time to be bold and act fast.

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Author Contributions

A.U.N. wrote the manuscript; A.U.N., J.N.S., M.G. and P.G.S. wrote, reviewed, edited, and approved the final manuscript equally.

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