

INSIGHTS



The GeneXpert cartridge-based platform is used routinely at the CAPRISA clinic in Durban, South Africa, to rapidly test for tuberculosis and HIV viral load, but it is now also being used to test for COVID-19.

PERSPECTIVES

VIEWPOINT: COVID-19

COVID-19 affects HIV and tuberculosis care

The COVID-19 response should be balanced with the need to manage other diseases

By **Quarraisha Abdool Karim** and **Salim S. Abdool Karim**

Shortly after instituting coronavirus disease 2019 (COVID-19) mitigation measures, such as banning air travel and closing schools, the South African government implemented a national lockdown on 27 March 2020 when there were 402 cases and the number of cases was doubling every 2 days (1). This drastic step, which set out to curb viral transmission by restricting the movement of people and their interactions, has had several unintended consequences for the provision of health care services for other prevalent conditions, in particular the prevention and treatment of tuberculosis (TB) and HIV. Key resources that had been extensively built up over decades for the control of HIV and TB are now being redirected to control COVID-19 in various countries in Africa, particularly South Africa. These include diagnostic platforms, community outreach programs, medical care access, and research infrastructure. However, the COVID-19 response also provides potential opportunities to enhance HIV and TB control.

In Africa, the COVID-19 epidemic is unfolding against a backdrop of the long-standing TB and HIV epidemics. South Africa ranks among the worst-affected countries in the world for both diseases. Despite having just 0.7% of the world's population, South Africa is home to ~20% (7.7 to 7.9 million people) of the global burden of HIV infection (2) and ranks among the worst affected countries in the world for TB, with the fourth highest rate of HIV-TB coinfection (59%) (3). South Africa has made steady progress since 2010 in controlling both diseases. Increased access to antiretroviral drugs for treatment and for prevention of mother-to-child transmission of HIV has resulted in a 33% reduction in AIDS-related deaths between 2010 and 2018 (2). Similarly, the death rate among TB cases has declined from 224 per 100,000 population in 2010 to 110 per 100,000 population in 2018 (3). Have the strategies implemented for COVID-19 mitigation, particularly the lockdown, inadvertently threatened these gains in HIV and TB?

HIV and TB polymerase chain reaction (PCR) tests are key to treatment initiation and monitoring to achieve the United Nations goals for the control of HIV and TB. Disturbingly, these diagnostic tests declined during the lockdown. The 59% drop in the median number of daily GeneXpert TB tests—a cartridge-based PCR test capable of diagnosing TB within 2 hours while simultaneously testing for drug resistance—was

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accompanied by a 33% reduction in new TB diagnoses (4). The restriction of people's movement and curtailment of public transport has led to substantial declines in patient attendance at health care facilities. A survey of 339 individuals in South Africa revealed that 57% were apprehensive about visiting a clinic or hospital during the lockdown, in part because of concerns that they may be exposed to infection by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from COVID-19 patients attending these facilities (5). Delayed HIV and TB testing impedes initiation of appropriate treatment, which increases the risk of new infections and drug resistance (6).

Both TB and HIV diagnostic platforms are important contributors to COVID-19 testing. The GeneXpert point-of-care testing platform, which is widely used in South Africa to diagnose TB, with more than 2 million individuals tested annually (7), is also being used to diagnose COVID-19. Until now, the limited availability of the GeneXpert COVID-19 cartridges has meant that spare capacity is mostly being used with little, if any, displacement of TB testing. Because there was also a decline in CD4⁺ assays (to test for immune status in HIV patients), it indicates decreased demand rather than displacement because this assay is not used for COVID-19. This may change as the demand for COVID-19 point-of-care testing rises and GeneXpert cartridges for COVID-19 become more readily available.

South African clinical laboratories have substantial capacity to perform high-throughput PCR assays for HIV viral load (more than 50,000 tests per day). However, the lack of COVID-19 test kits in South Africa, stemming from the global shortage, has meant that the available spare capacity on these platforms has sufficed for COVID-19 testing. The full potential of this PCR capacity is likely to be called upon when the country needs to expand COVID-19 PCR testing for the expected surge in cases, estimated to exceed 1 million at peak (8). Laboratory capacity for PCR testing developed for HIV and TB is now an essential resource for COVID-19 testing. The use of this capacity for COVID-19 needs to be monitored to identify and address any potential displacement of HIV and TB testing.

South Africa's experience in dealing with substantial HIV and TB epidemics has laid the foundations for the country's rapid,

early community-based response. Both TB and COVID-19 are respiratory infections and can present with similar symptoms. They therefore present substantial infection control challenges, requiring timely and rapid diagnosis. Both diseases can spread more easily in conditions associated with poverty where social distancing is difficult to implement. Well-established community outreach capabilities for contact tracing, established for TB, were deployed to undertake contact tracing and quarantine monitoring for COVID-19.

With the highest HIV burden in the world, South Africa has a highly developed network of health care providers that includes tens of thousands of community health care workers who are trained to interact safely with infectious individuals and have experience in undertaking door-to-door visits in South Africa's most socially vulnerable communi-

"Key resources that had been extensively built up... are now being redirected to control COVID-19..."

ties. About 28,000 HIV community health care workers were deployed for COVID-19 symptom screening and testing referral (HIV outreach was put on hold) in 993 vulnerable, high-density communities, many lacking running water, to identify cases and thus reduce time to diagnosis and hence limit transmission. As clinical cases increased, there were insufficient tests for community-based screening, creating testing backlogs that delayed hospital patient results and led to curtailment of the community program with proposed adjustment to screening and quarantine without testing.

The established community engagement and outreach for HIV, TB, and noncommunicable diseases (such as hypertension and diabetes) provide an opportunity for integrating screening and testing in the long-term COVID-19 response. This approach will play an important role in reaching at-risk populations who do not readily make use of health services to establish a broader program of health promotion, prevention, and early detection. Such integration can be facilitated by the expansion of mobile on-site rapid testing approaches, using newly developed COVID-19 tests (9) and existing tests for HIV and other conditions on readily accessible samples such as saliva and blood from finger pricks. Combining health promotion programs for these diseases will reduce duplication and provide synergistic messaging because social distancing affects not only COVID-19 transmission but also that of TB and other respiratory infections. After the COVID-19 surge, integrated ser-

vices could potentially provide an important approach to balancing ongoing vigilance for COVID-19 with early community-based detection of individuals with HIV and/or TB.

Access to medical care for non-COVID-19 conditions was limited during the lockdown, with health facilities experiencing declines in the number of TB and HIV patients collecting their medication on schedule. The World Health Organization estimates that a 6-month disruption of antiretroviral therapy could lead to more than 500,000 additional deaths from AIDS-related illness in 2021 and a reversal of gains made in the prevention of mother-to-child transmission (10). In South Africa, 1090 TB patients and 10,950 HIV patients in one province have not collected their medications on schedule since the start of the national lockdown (11). A national survey of 19,330 individuals in South Africa found that 13.2% indicated that their medication for chronic disease was inaccessible during the lockdown (12). Furthermore, hospital admissions for HIV and TB declined as a result of hospitals reducing nonurgent admissions

in preparation for a surge of COVID-19 cases and owing to closures to reduce exposure to COVID-19 patients. The potential negative impact on the continuity of care for HIV and TB patients could have substantial repercussions for both treatment and control, including development of drug resistance (6).

The biological and epidemiological interaction of COVID-19, HIV, and TB is not well understood. Patients immunocompromised by HIV or with TB lung disease could be more susceptible to severe COVID-19. However, preliminary results from a study of 12,987 COVID-19 patients in South Africa indicate that HIV and TB have a modest effect on COVID-19 mortality, with 12% and 2% of COVID-19 deaths attributable to HIV and TB, respectively, compared to 52% of COVID-19 deaths attributable to diabetes (13). The small contribution of HIV and TB to COVID-19 mortality is mainly due to these deaths occurring in older people, in whom HIV and active TB are not common. Integrated medical care for these three conditions is important as COVID-19 patients coinfecting with HIV or TB start attending health care services in larger numbers.

South Africa's COVID-19 response, especially the lockdown, has led to substantial economic hardship, particularly among the poor and vulnerable. This has had a disproportionate impact on women, many of whom are self-employed or day laborers without a safety net (14). This may have a longer-term effect on increasing diseases associated with poverty (such as TB) and with gender, such as HIV, for which young women

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bear a disproportionate burden (15). The social determinants of HIV and TB will need to be carefully monitored to assess the impact of COVID-19. The effect of the lockdown on the economy, including declining taxes, is also likely to negatively affect funding for HIV and TB programs, among many others.

New and ongoing research on HIV and TB prevention and treatment have been severely affected by the COVID-19 epidemic. At the initiation of the lockdown in South Africa, the National Health Research Ethics Committee suspended all medical research, including clinical trials. Research progress on these two conditions has also slowed because several of the country's AIDS and TB researchers are redirecting their efforts to COVID-19. However, COVID-19 research efforts have increased collaboration and created new approaches to speed up therapeutic and vaccine development and testing, which will likely have long-term benefits for medical research beyond COVID-19. Several countries in Africa have well-developed HIV and TB clinical trial infrastructure that could contribute to COVID-19 vaccine trials. Past investments in infectious disease training and research have generated handsome returns to the COVID-19 response, highlighting the importance of maintaining these investments in the future. ■

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CORONAVIRUS

Mathematical models to guide pandemic response

Models can be used to learn from the past and prepare for the future

By **C. Jessica E. Metcalf^{1,2}, Dylan H. Morris¹, Sang Woo Park¹**

The ongoing coronavirus disease 2019 (COVID-19) pandemic has put mathematical models in the spotlight. As the theoretical biologist Robert May wrote: "the virtue of a mathematical model...is that it forces clarity and precision upon conjecture, thus enabling meaningful comparison between the consequences of basic assumptions and the empirical facts" (1). On page 413 of this issue, Walker *et al.* (2) use a mathematical model to study the impact and burden of COVID-19 across a wide range of socioeconomic and demographic settings, with a focus on low- and middle-income countries (LMICs). Their analyses show that limited health care capacity in LMICs could counterbalance the benefits of a generally younger population. Unless these countries control the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus causing COVID-19, high disease burdens are likely. This work adds to a growing corpus of disease modeling designed to inform and guide the pandemic response.

Following the emergence of a previously unknown pathogen like SARS-CoV-2, mathematical models can be used to estimate parameters of pathogen spread, explore possible future scenarios, evaluate retrospectively the efficacy of specific interventions, and identify prospective strategies (see the figure). At every stage, communicating the scope of a model's aims and the uncertainty in its outputs is essential to ensure that models effectively inform public health policy.

In early 2020, it was important to assess the global risk posed by SARS-CoV-2 (3). Models provided estimates of R_0 (the average number of new infections caused by each infectious individual when no one in the population is immune) and the infection fatality ratio (IFR), clarifying ambiguities in the latter due to asymptomatic infections and delays between infection and death (4). Models also provided estimates of the incubation period

(the time from infection to symptom onset), allowing public health agencies to decide on 14 days for quarantine of exposed individuals (5). However, this illustrates the need for careful communication: 14-day quarantine and isolation can effectively reduce disease spread on average, but some individuals may spread the disease beyond 14 days.

Building on growing knowledge of mechanisms and parameter estimates allowed researchers to explore possible future scenarios, including worst-case outcomes, and determine the implications for precautionary action (6, 7). The results provided in Walker *et al.* fit within this class of analyses. Of note, the authors do not seek to provide a precise prediction of the epidemic trajectory, but rather to highlight key areas of concern for LMICs and evaluate mitigation measures.

As initial pandemic responses are put in place and data accumulates, the focus shifts to retrospective estimates of the efficacy of particular strategies. Using statistical inference algorithms, researchers can fit core epidemiological models to case data and data on the timing and nature of control interventions. This allows them to account for unknown aspects of underlying transmission dynamics, to tease out the individual effects of interventions, and to quantify the degree of uncertainty in these estimates (8). The amount of mechanistic detail included in such a model depends on its aims. For example, accounting for age-dependent transmission and susceptibility is critical when building models for retrospective estimation of the impact of school closures (9), but that level of detail might be omitted when studying larger-scale interventions, such as contact tracing or bans on travel.

A key challenge of retrospective statistical modeling is that interventions are often entangled with each other, and with other processes. For example, several interventions may be implemented at once, making the individual impact of each intervention on transmission difficult or impossible to estimate. One solution is to compare multiple countries, regions, or municipalities that responded differently or at different times, but this approach is complicated by inevitable differences in their social and eco-

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