EDITORIAL COMMENTARY

Minding the Gap: Specimen Referral Systems for Diagnosis of Infectious Diseases

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(See Viewpoint by Fonjungo et al on pages 796-803.)

With more than 4 million cases of tuberculosis missed every year [1], 6 million human immunodeficiency virus (HIV)–positive Africans lacking access to viral load testing [2], and 47% of all cases in the recent Ebola outbreak never confirmed [3], the gap between patients and high-quality laboratory diagnosis must be considered a major cause of preventable infectious mortality worldwide. Nevertheless, improvement of laboratory referral systems remains low on the global health agenda, often lost as part of broader agendas such as meeting the third Sustainable Development Goal. Stronger laboratories do not primarily benefit a single disease entity and thus remain unsupported by vertical disease programs. But unlike health systems strengthening writ large, improving specimen referral systems for high-quality laboratory diagnosis represents a specific, actionable goal—and one with great potential to improve human health.

In this issue of *Clinical Infectious Diseases*, Fonjungo and colleagues [4] provide a roadmap for strengthening specimen referral systems. These authors highlight 2 models (centralized and decentralized) that have demonstrated effectiveness in high-burden countries and outline a set of critical components that must be considered when establishing a specimen referral network. Importantly, they describe differences between tests that can be conducted at the point of care (POC) and those that require a centralized laboratory. Also, they discuss ways in which emerging technologies—from widely available geographic information systems to unmanned aerial vehicles (drones)—might be used in the context of existing health systems to establish effective and efficient specimen referral systems. Although any such system will need to be adapted to the local context, the authors provide an important first step, illustrating how specimen referral systems can be effectively implemented in resource-limited, high-burden settings. This emphasis on specimen referral is a welcome complement to recent calls for a model list of essential diagnostics [5]—a list that will only be meaningful if specimens can be effectively transported to the laboratories capable of performing those essential tests.

Tuberculosis provides an illustrative example of the importance of specimen referral systems. In settings that lack specimen transport systems, tuberculosis diagnosis must rely on sputum smear microscopy—a test that misses up to half of all tuberculosis cases [6]. For those missed patients, available options include self-transport to a higher level of care (often at a cost of more than a week's salary per trip [7]), empiric treatment (with 6 months of drugs for an unconfirmed diagnosis), and accepting the natural and often fatal consequences of the disease. None of these options is acceptable. While efforts are underway to develop more sensitive diagnostic tests that can be performed at the POC, the cost of decentralization is likely to impede implementation of these tests for decades to come [8]. Furthermore, without a specimen referral system, diagnosis and treatment of drug-resistant tuberculosis are essentially impossible outside of tertiary-level hospitals. As a result, less than 30% of patients with multidrug-resistant tuberculosis ever receive appropriate treatment for their disease [1]. In short, the lack of effective specimen transport systems likely contributes to hundreds of thousands of tuberculosis deaths every year.

The potential impact of an effective specimen referral network on tuberculosis control does not stop with diagnosis of tuberculosis (and drug-resistant tuberculosis). Availability of viral load testing would improve outcomes for people living with HIV, the strongest major risk factor for tuberculosis. Glycated hemoglobin testing would enable diagnosis and treatment of diabetes, which contributes to an equal number of tuberculosis cases globally [9]. Currently, the majority of tuberculosis patients with these comorbid conditions cannot obtain such testing, not because the tests cannot

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be performed but because systems do not exist to get clinical specimens to the laboratories capable of performing them.

This is a problem that can be fixed, and the solution is easier than developing and scaling up multiple POC tests for tuberculosis, HIV viral load, and hemoglobin A1c. For POC tests to be implementable, they must be cheap (when performed at the relatively low volumes typical of many peripheral health centers) and highly durable (as maintenance of any equipment in such centers is exceedingly difficult)—a bar that is very difficult for many assays to attain. By contrast, specimen referral systems can achieve economies of scale by using one set of transport procedures for multiple clinical specimens and integrating multiple health centers into the same network. They are also more reliable, as equipment and expertise are centralized at a single site (the referral laboratory) that is generally located in an urban area where skilled labor and systems for equipment maintenance are more readily available. The success of such systems, where high-level skills and equipment are centralized and linked to peripheral sites via transport networks and distribution chains, is broadly visible in high-burden countries, where one can purchase mobile airtime or a bottle of Coca-Cola™ in even the most remote context. It is also a model widely followed in most low-burden clinical settings, where free-standing peripheral clinics generally do not maintain on-site laboratory capacity but transport specimens to centralized laboratories on a daily basis. The reason such systems have not been implemented for infectious disease control in high-burden settings is not because they do not work, nor because they are infeasible or too expensive. It is primarily because they do not fit

with current funding and organizational streams, which tend to favor solutions that are either disease specific (eg, HIV therapy) or very broad in nature (eg, poverty reduction).

In developing a way forward, we should look to other examples of cross-disease collaboration that have successfully addressed specific, actionable gaps in health systems. One such example is the global immunization response, embodied in the Expanded Programme on Immunization and the Global Vaccine Action Plan 2011–2020 [10]. This effort is credited with preventing more than 2.5 million deaths every year [10] and has succeeded by addressing important cross-cutting challenges such as supply chain maintenance, engagement of peripheral health centers, transportation networks, and distribution of centralized capacity. These are many of the same challenges faced by specimen referral systems. Successful efforts to strengthen immunization systems have been characterized by broad support from many stakeholders and funders, quantitative understanding of the extended health benefits of vaccination, a clear business case for return on investment, and measureable benchmarks for success and accountability. If we are to make serious strides in developing specimen referral systems, we must undertake these same tasks.

In summary, Fonjungo and colleagues have given us a roadmap for the development of specimen referral systems, but it is up to the global infectious disease control community to take the next steps. It is no longer sufficient to understand how specimen referral systems can work, nor to argue in the abstract about why they are important. We must undertake formal studies to quantify the

benefits of specimen referral systems and demonstrate their value for money. And we must find a way to engage a broad spectrum of stakeholders who are willing to be held accountable to measureable benchmarks for success. Until we do so, the gap between the health centers where patients are seen and the laboratories capable of providing those patients effective high-quality diagnosis will continue to consume millions of lives each year.

Note

Potential conflicts of interest. The author certifies no potential conflicts of interest. The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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