Clinical Infectious Diseases

VIEWPOINTS

Combatting Global Infectious Diseases: A Network Effect of Specimen Referral Systems

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The recent Ebola virus outbreak in West Africa clearly demonstrated the critical role of laboratory systems and networks in responding to epidemics. Because of the huge challenges in establishing functional laboratories at all tiers of health systems in developing countries, strengthening specimen referral networks is critical. In this review article, we propose a platform strategy for developing specimen referral networks based on 2 models: centralized and decentralized laboratory specimen referral networks. These models have been shown to be effective in patient management in programs in resource-limited settings. Both models lead to reduced turnaround time and retain flexibility for integrating different specimen types. In Haiti, decentralized specimen referral systems resulted in a 182% increase in patients enrolling in human immunodeficiency virus treatment programs within 6 months. In Uganda, cost savings of up to 62% were observed with a centralized model. A platform strategy will create a network effect that will benefit multiple disease programs.

Keywords. platform strategy; specimen referral; centralized model; decentralized model; innovation.

The recent Ebola virus outbreak in West Africa and the launch of the Global Health Security Agenda clearly highlight the critical role of laboratory systems and networks in disease preparedness and response strategies. Several reports have recommended strengthening national public health capabilities and infrastructure, including disease-surveillance systems and laboratory networks [1, 2]. However, it will be an uphill task to establish functional laboratories at all tiers of the healthcare systems in developing countries. Thus, strengthening specimen referral networks is critical to serve the entire healthcare delivery system and establish preparedness strategies for effective disease control and prevention. For instance, the lack of a specimen referral network in Guinea, Liberia, and Sierra Leone prolonged laboratory confirmation of Ebola cases, for effective control of the epidemic.

Over the past decade, increasing expansion of global health programs to combat existing epidemic, emerging, and infectious disease threats, in addition to the threats posed by increasing noncommunicable diseases, has been the focus of health officials. Key examples include the United States President's Emergency Plan for AIDS Relief (PEPFAR) Blueprint: Creating an AIDS-Free Generation; the Joint United Nations Programme on HIV/AIDS 90-90-90 goals to end the AIDS epidemic as a public health threat by 2030; the World Health Organization international health regulations for strengthening of national disease prevention, surveillance, and response systems; and the US Government Global Health Security Agenda to prevent, detect, and respond to infectious disease outbreaks [3–5]. There have been significant accomplishments with implementation of some of these programs. For instance, in 2003, it was estimated that only 50 000 patients worldwide were receiving human immunodeficiency virus (HIV) antiretroviral therapy (ART) [6]. However, by 2015, 15.8 million individuals had been started on ART in low- and middle-income countries [7]. Despite these accomplishments, significant gaps persist. Only 30% of nations self-reported compliance with international health regulations and 22 million people infected with HIV are unable to access ART [7]. One of the challenges in scaling up some of these interventions has been weak health systems, including fragile laboratory services [8, 9]. Some examples include limited laboratory infrastructure, human resources, sample referral networks, quality management systems, laboratory information systems, and equipment maintenance. Bilateral and multilateral funding support have been used to establish and maintain these laboratory systems for accurate and timely return of laboratory results for use by physicians for patient management [8, 9].

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However, there is still an unmet need for an effective specimen referral system to support increased access to laboratory services for better program coverage.

In this article, we highlight 2 successful models of specimen referral systems (centralized and decentralized models) that have been used to scale up laboratory support for ART in developing countries. In addition, we encourage the need for a platform strategy that is based on innovative approaches to create a network effect for specimen referral for effective and better preparedness to respond to disease control and prevention.

DEFINITION OF A SPECIMEN REFERRAL NETWORK

We define a specimen referral network as a coordinated system that allows a health facility or laboratory lacking capacity to perform test(s) to safely send a patient's specimen to another or higher-level laboratory with capacity to perform the requested test(s). The goal is the safe and efficient handling and treatment of specimens during the process to obtain reliable results without delays to provide optimal care to the patients at the referring facility. The tiered laboratory structure reflects varying complexity of tests performed in each tier, with decreasing test complexities toward the lower tier within a country healthcare structure (Figure 1). Also, specimens can be referred horizontally to a similar testing facility at the same level—for instance, in situations of equipment malfunction or reagent stockout at the referring facility. The tiered laboratory parallels the health services delivery structure to the population with community services and community healthcare workers at the base of the pyramid structure (Figure 1) for outreach and linkages of clients to healthcare facilities.

A PLATFORM STRATEGY

The platform strategy requires that specimen referral systems are designed to serve multiple disease programs (eg, tuberculosis, HIV, polio, malaria). The success of a specimen referral platform strategy is determined by 3 factors:

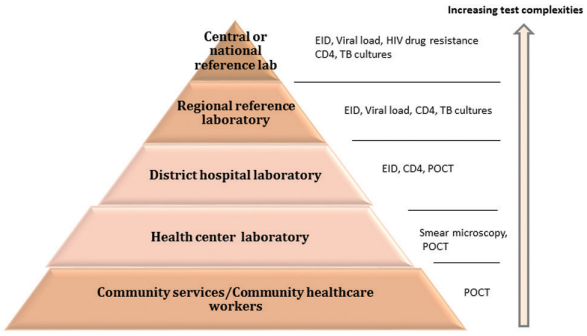

Figure 1. Tiered laboratory structure for providing for HIV and tuberculosis diagnostic services and usually aligned with delivery of healthcare services. Abbreviations: EID, early infant diagnosis; HIV, human immunodeficiency virus; POCT, point-of-care testing (eg, HIV or malaria rapid test); TB, tuberculosis.

1. Linking: how easily each disease program can plug into the platform to share and transact;
2. Magnitude: how well the platform attracts different disease programs; and
3. Flow: how well the platform fosters the exchange and co-creation of value.

Two models have been demonstrated to work well in Ethiopia and Uganda and other countries.

A DECENTRALIZED MODEL: SPECIMEN REFERRAL NETWORK IN ETHIOPIA

During the early 2000s, testing for staging and monitoring of patients on ART was conducted mainly at a private laboratory, the International Clinical Laboratory in Addis Ababa, Ethiopia. Following the development of a national laboratory strategic plan [10], the Ethiopian Public Health Institute (EPHI) was mandated with strengthening public health laboratory systems and decentralized testing for early infant HIV diagnosis (EID), viral load [11], and other major tests to different tiered levels (Figure 1). The strengthening and decentralization of laboratory services paved the way to transfer testing from the private facility to Ministry of Health laboratories within the tiered structure (Figure 2A).

Until 2008, no standard specimen referral network existed with implementing partners transporting specimens/results within the regions they supported [12]. Additionally, laboratory personnel also transported specimens [11]. From 2008, the Ethiopian Postal Services Enterprise (EPSE) was used to courier only dried blood spot (DBS) specimens for EID. Building on this platform in 2010, EPHI and the Centers for Disease Control and Prevention Ethiopia established and successfully piloted in 2 regions (Addis Ababa and Amhara) a specimen referral network for integrated specimen (DBSs, plasma for viral load, sputum for tuberculosis, whole blood for CD4 and hematology, and serum for chemistry for ART monitoring; Figure 2A). Through a PEPFAR–Becton Dickinson public–private partnership [13], EPHI engaged the EPSE to build on the pilot program and establish a specimen referral network for all the regions. The agreement between EPHI and EPSE enabled EPSE to transport DBSs for EID and other specimens (whole blood, serum, and plasma) for CD4 count, hematology, chemistry, and viral load tests. Initially, the referral entailed testing done strictly within regional boundaries. Regions that did not have EID or viral load laboratory capabilities sent DBSs and plasma samples to the national reference laboratory at EPHI in Addis Ababa [11].

Prior to initiating the specimen transport system, EPSE workers were trained on specimen referral and biosafety, and standard transportation containers with packaging were provided. The benefit and impact of the EPSE were consistent schedules for pickup of specimens as well as return of results to facilities using the network.

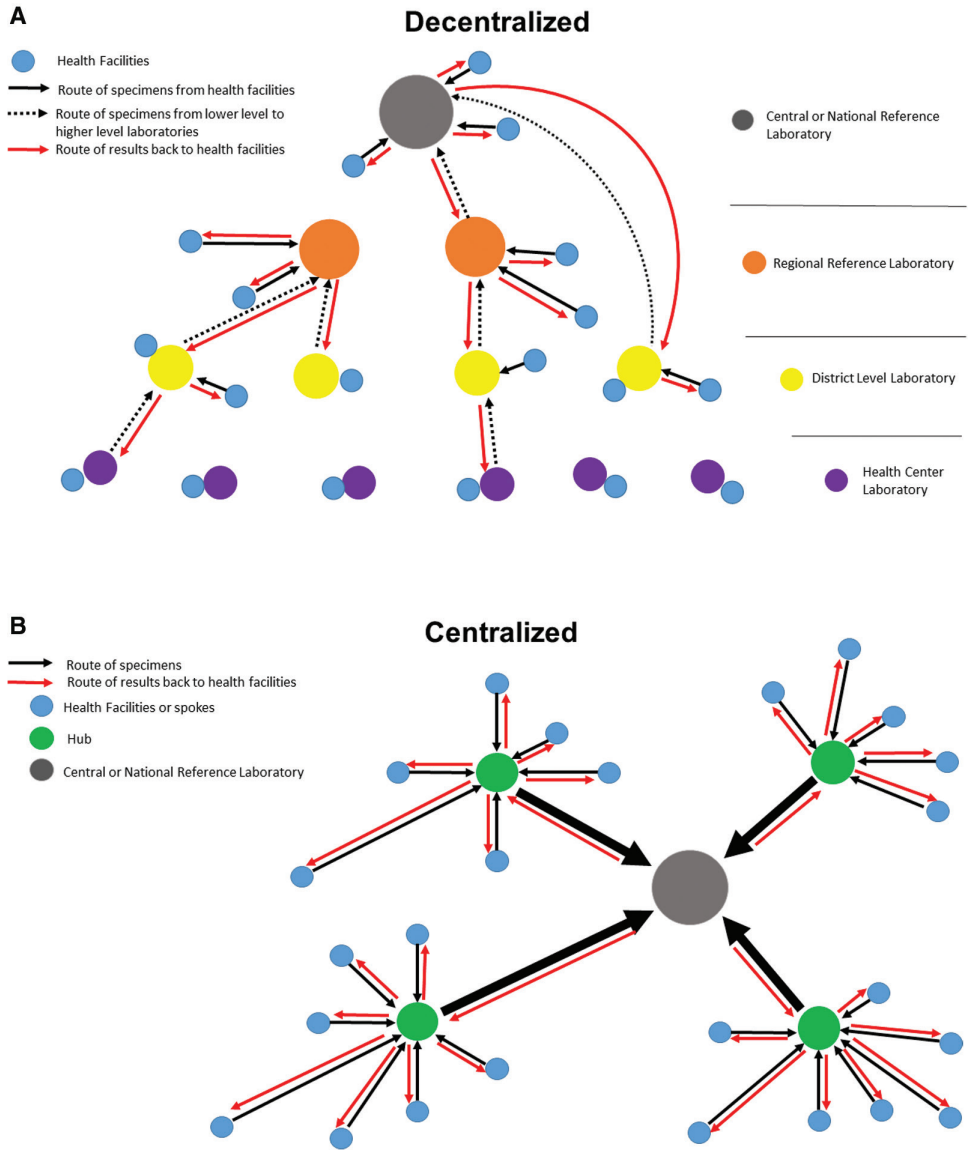

Figure 2. Schematic representation depicting 2 sample referral models for delivery of healthcare services. *A*, Decentralized models showing likely specimen and results routing within the tiered structure and *B*, Centralized model showing the hub-and-spoke routing for specimens and results.

This in turn led to reduction in turnaround time for patient results and improved efficiencies. Later, sample referral sites were mapped using geographic information systems (GIS) software (and linked to a network of testing laboratories), which incorporated supply chain optimization algorithms to develop optimal routes (including beyond regional boundaries) and linking costs to particular variables to determine savings based on various scenarios. This approach reduced the one-way distance from referral sites to testing laboratory from an average of 80 km to 32 km, with a 60% cost savings (personal communication, Jason Williams, December 2014, United States Agency for International Development).

Similarly, a decentralized sample referral system in Haiti increased access to CD4 cell count testing by 315% as well as a 182% increase in patients enrolling in HIV treatment programs within 6 months [14]. Also, in Vietnam, a decentralized network increased access to tuberculosis diagnostic testing by 30% and by 19% the number of new patients starting multidrug-resistant tuberculosis treatment [15, 16].

A CENTRALIZED MODEL: SPECIMEN REFERRAL NETWORK IN UGANDA

Unlike Ethiopia, Uganda laboratory testing evolved from a decentralized to a centralized model system. Initially, there were 8 EID laboratories that received DBSs through ad hoc means, which included the use of couriers for transporting DBSs [17]. With the introduction of a specimen referral network, centralized testing was implemented for EID with a recommendation for all testing performed at the 8 EID laboratories

to be transferred or centralized at the Central Public Health Laboratories (CPHL) in Kampala.

In Uganda, the hub-and-spoke model was established and used for the specimen referral network of DBSs for EID. The hub-and-spoke model is where the "hub" is a central health facility that is identified to serve as a central specimen collection point for specimens coming from multiple referring sites, termed "spokes." From the hub, the specimens are transported to CPHL for testing (Figure 2B). GIS was used to map referring sites or health facilities to hubs. One hub served about 2–40 referring sites within a 30- to 40-km radius, and courier bikers transported samples weekly to the hub [17]. The efficiency of this model was demonstrated with cost reduction of 62%, and turnaround time was reduced from 1–2 months to 5–10 days for EID [17]. Additionally, the turnaround time for tuberculosis testing was reduced from 21 days to 3 days. The success of the hub-and-spoke specimen referral network model made it possible to include other specimen types for CD4, viral load, hematology, chemistry, tuberculosis, and outbreak-related specimens [18, 19].

The centralized model has been replicated in the Caribbean region, which has weak public health infrastructures [14, 20]. The model, whereby specimens were sent directly from clinic sites, has facilitated sample transportation and delivery (for EID, CD4, viral load, and HIV drug resistance testing to support HIV prevention and treatment) to the Ladymeade Reference Unit Laboratory in Barbados for testing and return of results. This initiative has had significant impact on improving quality and access to test results to both adults and infants in the region [20].

CRITICAL ELEMENTS IN ESTABLISHING A SPECIMEN REFERRAL NETWORK AS A PLATFORM

The components to consider when establishing a platform strategy for a specimen referral network are summarized in Table 1. Additionally, there is evidence to show this has worked in some countries with demonstrated impact or outcomes (Table 2).

INTEGRATION AND LEVERAGING EXISTING SPECIMEN REFERRAL SYSTEMS

The need for a reliable specimen referral network cannot be overemphasized, especially with emerging infections and reemerging infections in the era of global health security. Building on an existing network and an integrated approach would allow accommodation of all specimen types that not only strengthens the system for expedited services but is also cost-effective. For example, the Uganda centralized sample network has been reliably and successfully used to support biologic specimen referral and laboratory results reporting within 48 hours of cholera, Ebola virus, and tuberculosis outbreaks in remote areas [18]. The referral network has been used to transport suspected specimens leading to confirmation of West Nile virus, Zika virus, Crimean-Congo hemorrhagic fever virus, hepatitis E virus, and *Neisseria meningitidis* as part of a priority pathogen reporting system. Similarly, in Ethiopia, the decentralized system was used to support other specimen types including hematology, chemistry for HIV, and tuberculosis.

Table 1. Critical Components to Consider When Establishing a Sample Referral Network

Component	Activity
Planning	• Strong leadership from the Ministry of Health for coordination and oversight • Establishment of a functional technical working group, including partners and stakeholders • Mapping of referral sites to testing laboratories • Flexibility for integration, adaptation to innovative technologies and unforeseen outbreaks • Development and dissemination of tools (SOPs, guidelines, and policies)
Human resources	• Identify cadres involved with packaging, transportation, and reception of specimens including drivers, bikers, and community health-care workers
Training	• Guidelines and policies for specimen referral • SOPs, packaging of specimens, and labeling of specimen container • Biosafety for handling of specimens • Documentation of requisition forms and transport logs
Supply chain	• Procurement of standard transportation containers, packaging materials, and storage materials • Procurement of computers, tablets, scanners, real-time temperature monitoring devices (eg, data logger) • Procurement of software, bikes, and personal protective equipment
System for transport	• Identify reliable courier system, vehicles, and bikers
Monitoring and evaluation	• Establish indicators for monitoring specimens (transport time, specimen rejection rate, number of clients seen, etc) • Assess impact on capacity building and sustainability
Partnership	• Engage stakeholders for increased uptake, coverage, implementation, and monitoring and evaluation including public–private partnership
Communication	• Maintain communication between referring sites and testing site(s) to resolve any problem that are identified • Maintain communication strategies for sharing best practices, opportunities, and challenges

Abbreviation: SOP, standard operating procedure.

Table 2. Summary of Interventions and Impact/Outcomes of Sample Referral Models for Patient Management

Country	Source	Sample Referral Model	Program	Intervention	Outcome/Impact
Ethiopia	Kebede et al [12]	Decentralized	HIV, TB	• Efficient mapping of laboratories to sites referring specimens • Training of different cadres (laboratory, postal service personnel) • Provision of standardized packaging and transportation materials	1. Increased access to quality testing with efficient linkages of 554 referral sites to testing laboratories 2. Return of patient results using the specimen referral network 3. Turnaround time for EID results reduced from 7 d to 2 d in Addis Ababa and from 10 d to 5 d in Amhara region 4. Flexible for integrated specimens types for EID, CD4, chemistry, hematology, and TB referral
Uganda	Kiyaga et al [17] Borchert et al [18]	Centralized	HIV, TB, malaria, West Nile virus, Zika virus, Crimean-Congo hemorrhagic fever virus	• Mapping of hub-and-spoke transport system • Training of bike riders	1. Increased access to EID testing with increased volumes by 36.4% and 51.7% per month in Jinja and Kampala, respectively 2. Turnaround time reduced from 1–2 mo to 5–10 d for EID results 3. Turnaround time reduced from 21 d to 3 d for TB results 4. Overall operational cost reduced by 62% (from US$6460 to US$2428) and projected to save US$1.2 million over 4 y 5. Flexible for integrated specimens: EID, CD4, chemistry, hematology, TB, and malaria smear referral
Vietnam	Nguyen G [15, 16]	Decentralized	TB	• Development of SOPs for safe packaging of specimens • Training of facility staff on use of SOPs • Identification and hiring of courier service and transition to postal service • Provision of standard packaging materials for specimens	1. Number of TB specimens examined increased by 30% (from 21 870 to 28 413) and 46% (from 17 160 to 25 097) in Hanoi and Ho Chi Minh City, respectively 2. Number of new patients starting MDR-TB treatment increased by 19% (from 578 to 713) 3. Reduced specimen delivery time from 3 wk to 1 wk 4. Improved safety of referral system
Haiti	Jean Louis et al [14]	Decentralized	HIV	• Establishment of logistic and coordination committee • Mapping of hub-and-spoke transport system for facilities • Improvement of infrastructure at hub and at laboratory • Training of different cadres (laboratory technicians, drivers) • Development of SOPs and provision of standard packaging materials	1. Increased access to quality CD4 testing from 27 sites to 113 sites (315%) 2. Testing volumes for CD4 increased by 76% 3. Number of patients enrolled on ART for new sites joining the specimen referral network increased by 182% within 6 mo
Caribbean region	Alemnji et al [20]	Centralized	HIV, H1N1 influenza	• Planning linking of Caribbean countries to regional reference laboratory in Barbados • Development of SOPs and provision of standard materials for packaging and transportation	1. Enabled initiation of HIV patients on ART treatment 2. Ability to test for H1N1

Abbreviations; ART, antiretroviral therapy; EID, early infant diagnosis; HIV, human immunodeficiency virus; MDR, multidrug resistant; SOP, standard operating procedure; TB, tuberculosis.

COSTING OF A SPECIMEN REFERRAL SYSTEM

Costing of a reliable and sustainable specimen referral network should be evaluated to provide accurate information to health officials for advocacy and appropriate budgeting. Reliable laboratory results depend on how well specimens are collected, processed, packaged, and handled during transportation to the testing laboratory. Costing will depend on whether it is establishing a new specimen referral mechanism or whether it only entails operational cost to support an existing specimen referral system. For the purpose of this article, we focus on costs related to specimen packaging and transportation. Other costs, including accessories for collecting and storing specimens and returning of results, have not been factored into the costing.

The cost to transport a specimen entails both direct and indirect costs. Direct costs include costs for procuring standard transportation containers, materials for labeling and packaging, temperature monitors, communication, personal protective equipment, trainings, transportation (eg, couriers, motorbikes), and monitoring and evaluation of the system for improvement. Indirect costs include benefit for patient retention, rapid clinical decision, salary for staff time at referral sites involved with packaging and labeling of the specimen transportation package, personnel time of those with responsibility for transporting specimens, and time to receive and log in the specimens in the laboratory.

Costs of transporting a specimen also depend on the specimen type and conditions of transportation. For example, tests requiring transporting specimens under cold chain would need ice packs and freezers at referring laboratories to maintain frozen ice packs. Strategies to reduce or save cost should be considered: establishing schedules that enable transportation of multiple specimens and adhering to standard training procedures and conditions for specimen referral to avoid compromising specimen integrity, which can lead to increased specimen rejection rate and requests for re-collection or erroneous results that can compromise or delay patient treatment. In addition, the use of GIS to map specimen referral sites to testing laboratories improves efficiencies and reduces cost. GIS mapping ensures specimen referral based on the shortest possible distances (to testing laboratories) rather than being constrained by regional boundaries.

SPECIMEN REFERRAL NETWORK: NEED FOR INNOVATIVE APPROACHES

One of the remarkable strides during the course of the AIDS epidemic in the past 3 decades has been the rapid advancement in science and technology. Our expanding knowledge in program implementation and innovative approaches has led to hope of an AIDS-free generation [3, 21]. Innovative technology has played an important role in reducing the need for specimen referral networks, so new and validated technologies should be encouraged and rolled out for timely support of programs.

Point-of-Care Technology

Point-of-care testing (POCT) or near-POCT is when portable medical devices or stand-alone lateral flow assay strips are used to test at or near the patient with the goal of obtaining results quickly for immediate use for patient care. Instead of referring specimens or patients, the test is brought closer to the patient. Point-of-care testing has played a significant role in streamlining or eliminating sample referral in certain settings for HIV care, prevention, and treatment. HIV rapid tests have been used to provide timely results for HIV counseling and testing, surveillance, and initiation on treatment compared with the enzyme-linked immunosorbent assay, which requires laboratory facilities [22–24]. Similarly, point-of-care CD4 count following HIV testing enabled patients to be rapidly staged and put on treatment, and reduced pretreatment loss to follow-up [25, 26]. By contrast, if a POCT had been available during the peak of the Ebola virus outbreak, it would have assisted with rapid diagnosis and triaging of positive samples for referral for laboratory confirmation. For high-volume sites, laboratory-based testing with specimen referral is still required for cost-effectiveness.

Specimen Type

The collection and transportation of specimens (whole blood, plasma, serum) from remote areas can be difficult. In some cases, centrifugation as well as cold chain for storage and during transportation of specimens is required (eg, specimens for clinical chemistry analyses). In addition, frequent power outages add to the challenge of maintaining cold chain. Alternative specimen types that have been shown to have comparable results to whole blood, plasma, or serum should be considered where appropriate. For example, DBSs have been evaluated and used for EID [27, 28], viral load [29], and drug resistance [30, 31] testing. Where appropriate, DBS testing offers the advantage of not requiring bulky packaging materials, and can be transported and are stable at room temperature for several weeks when compared to liquid specimens.

Geographic Information Systems

It is important to optimally map and link specimen referral sites to testing laboratories or the hubs, for the hub-and-spoke model, by the shortest feasible distances to reduce time in delivering specimens. Geographic information systems are powerful tools that, when provided with coordinates of testing laboratories and specimen collection facilities, can map testing laboratories to specimen collection sites based on various scenarios such as shortest possible distance and availability of road infrastructure to produce a visual map. These visual maps are helpful for health providers to observe and use for analysis of patterns and relationship for informed program implementation. GISs also incorporate supply chain algorithms to develop optimized routes for cost savings, and were successfully implemented in Ethiopia and Uganda with significant cost efficiencies [17].

Community Healthcare Workers

Exploring new cadres of healthcare workers to support specimen referral network is critical. Outside the tiered laboratory network, community healthcare workers can fill this critical gap through identification of patients in the community and linking them to facilities or collecting their specimens for referral [2]. However, prior to performing this role, the community healthcare workers would need to be trained on safe collection, packaging, and transportation of specimens. Community healthcare workers have played a successful role in delivery of national health services. For example, in Ethiopia, 38 000 health extension workers are bringing basic primary health services to communities and villages [32, 33]. A benefit of the community healthcare worker program is not only their availability but also their acceptability in their communities. This aspect was unfortunately demonstrated during the Ebola virus outbreak in Guinea, where due to cultural differences there was resistance to support from "foreign" health personnel in some communities [34].

Unmanned Aerial Vehicles

Motorbikes and vehicles, including public transportation, have often been used for transport of specimens from referring sites to testing laboratories. However, in topographically challenged environments with limited availability and cost of fuel and hazardous road condition areas, vehicle and motorbike use would be severely restricted, leading to long turnaround times. Unmanned aerial vehicles (UAVs) can overcome some of the challenges and have had wider use in the field of agriculture [35] and are increasingly being used in healthcare. In Papua New Guinea, UAVs have been used to transport tuberculosis specimens in remote areas [36]. Also, UAVs were successfully used to transport specimens for chemistry, hematology, and coagulation tests without affecting the accuracy of the results [37]. The wider use of UAVs is currently limited by uncertain regulatory restrictions, acceptability, biothreats, and safety. There is need for further consultations with appropriate stakeholders together with putting in place proper regulation and monitoring prior to routine use of UAVs.

CONCLUSIONS

A platform strategy for creating specimen referral systems is critical for implementing effective global health programs in resource-limited settings. Successful implementation of either a centralized or decentralized specimen referral platform models in select countries has been shown to improve access to laboratory services and reduced time to patient management. These models can be replicated in other settings and will require careful coordination and planning including situational analysis, adaptation to program context, use of innovative technologies, and involvement of all laboratory stakeholders, including public–private partnerships throughout the entire process to ensure a sustainable specimen referral network for effective disease responses.

Notes

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