Clin Chem Lab Med 2012;50(7):1221–1227 © 2012 by Walter de Gruyter • Berlin • Boston. DOI 10.1515/cclm-2011-0618

Mini Review

Experience of Médecins Sans Frontières in laboratory medicine in resource-limited settings

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Abstract

In medical humanitarian assistance, the diagnosis of diseases plays a crucial role. Laboratory investigations are one of the main diagnostic tools utilized in Médecins Sans Frontières' (MSF) programs. Currently MSF supports and/or operates more than 130 laboratories in approximately 45 countries. The variety of analysis offered depends largely on the context of the program and the availability of context adapted tools and ranges from sophisticated laboratories specializing in tuberculosis culture to small laboratories within a primary health care program or operating as mobile clinics. The largest laboratories in MSF are found in programs with the main objective to diagnose, treat and monitor patients with tuberculosis and/or human immunodeficiency virus. Other MSF programs are either disease-specific (e.g., malaria, Chagas, kala azar or visceral leishmaniasis, sleeping sickness, malnutrition, sexually transmitted infections) or are integrated in primary or secondary health care structures.

Keywords: developing countries; diagnose; laboratory; nongovernmental organization; point-of-care; resource-limited settings.

Introduction

The delivery of laboratory services in resource-limited settings (RLS), especially in sub-Saharan Africa, confronts us with major difficulties (Figure 1B). These challenges include not only the disease burden but also cost, human resource shortages, poor infrastructure, climate, poor education, access to health care and political factors such as migration and instability. Technical solutions have been developed to help overcome some of these challenges, often as a result of collaborative efforts by diagnostic device developers, nongovernmental organizations (NGOs) and the World Health Organization (WHO). In the past, new technologies such as molecular testing was considered too high-tech for RLS but simplified solutions have become more widely available (Table 1).

The WHO's ASSURED criteria outline the ideal characteristics for the design of a diagnostic test for RLS as Affordable, Sensitive, Specific, User-friendly, Rapid and robust, Equipment-free, and Deliverable (ASSURED) to those in need (1). Although originally developed by the WHO's Sexually Transmitted Diseases Diagnostics Initiative (SDI), the ASSURED criteria have been used for other diseases as well, summarizing useful criteria for effective diagnostic tools for diseases faced in RLS.

Equipment manufacturers have the responsibility for making simple, low-cost and robust equipment available to those countries who cannot afford to pay Western prices. This article aims to summarize some of the most important challenges in offering laboratory services in RLS, offer some lessons learned and highlight new technologies which have just emerged or about to be commercialized and were especially developed for use in RLS.

Mortality, disease burden and poverty in resource-limited settings

A few facts shall outline the needs of diagnosis and disease monitoring in RLS: life expectancy in the African region is 54 compared to 75 in the European region (2). In 2004, worldwide 2.6 million deaths occurred in people between the ages of 10 and 24 years; 97% of these occurred in RLS (3).

In 2009, the mortality due to human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) was 177/100,000 in the African region and 10/100,000 in the European region. The tuberculosis (TB) mortality among HIV negatives was 52/100,000 in the African region, 27/100,000 in the south-east Asian region and 7/100,000 in the European region. The mortality due to malaria was 94/100,000 in the African region and 2.9 in the south-east Asian region. The number of physicians per 10,000 is 2.3 in the African region compared to 33.3 in the European region. More than 80% of the world's population live on <$10 (US) per day (4).

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Received September 6, 2011; accepted February 6, 2012; previously published online March 16, 2012

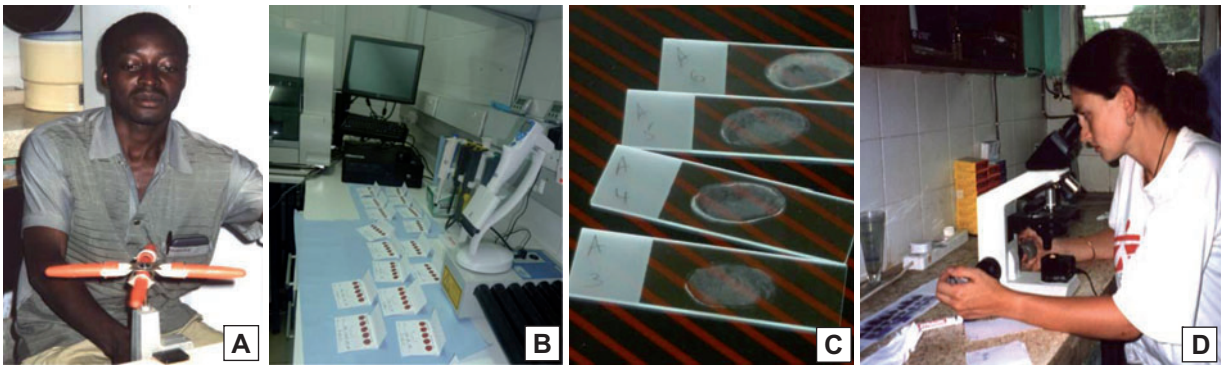

Figure 1 (A) Handcentrifuge, Bundibugyo, Uganda. (B) Dried blood spots for HIV viral load analysis, Thyolo, Malawi. (C) Drying sputum slides for Ziehl-Neelsen stain, Khayelitsha Township, Capetown, South Africa. (D) Microscopy of Giemsa stained thick and thin smears for the diagnosis of malaria, Bundibugyo, Uganda.

HIV diagnosis and monitoring

In 2009, a total of 33.3 million people were living with HIV of which 2.5 million were children under 15 years of age. During the same year 2.6 million were newly infected and 1.8 million died of HIV/AIDS (5).

In RLS HIV in adults is diagnosed with lateral-flow immunoassays (LFIs), mostly in a serial testing approach (6). This approach maybe cost-effective but it has shown that low sensitivity and/or specificity can be encountered (7–11). In various projects MSF decided to confirm testing carried out on LFIs with an indirect solid-phase enzyme immunoassay (EIA), the ImmunoComb® II HIV 1&2 CombFirm (Orgenics, Yavne, Israel). This test separates five antigen specific areas for the gag (group-specific antigens), env (envelope) and pol (polymerase) region of the virus. The 'gag' gene encodes information for the internal structures of the virus, the 'env' gene for different surface proteins and the 'pol' gene encodes for internal proteins, i.e., enzymes taking part in the integration and replication of the virus. The ImmunoComb® II HIV 1&2 CombFirm is interpreted taking separate reactions to each of the five antigen specific areas into account, rather than having two or three antigens combined in one spot or line as classical LFI for HIV screening do. The separation of reactions to the different areas of the virus allows for picking up cross-reactions that are due to one antigen only, which would lead to false positive results when using a typical HIV LFI (9).

Early infant diagnosis (EID) is even more complex as maternal antibodies can be passed to the infant by breast-feeding and cause a positive reaction on tests detecting antibodies. A well working method for EID, the ultrasensitive p24 antigen detection assay, has been developed by Perkin Elmer (Waltham, MA, USA). The test has been evaluated on several occasions and quality of evidence on its accuracy has been considered high by the WHO (12–16). Unfortunately, this test is not commercialized by Perkin Elmer and only available for research purposes as it is not registered as in vitro diagnostic. Discussions with Perkin Elmer have so far been unsuccessful in lobbying for commercialization of this product. The test is relatively simple to perform and could be carried out at a district or reference laboratory and even a protocol for elution from dried blood spots could be developed to ensure access for remote settings as well. The infants of the estimated 1,240,000 HIV positive mothers in need for anti-retroviral for PMTCT would benefit from early infant diagnosis (17).

However, an even more suitable test for remote settings is currently under field validation: a lateral flow assay, with a preparatory heating step to disrupt immune complexes due to maternal antibodies, developed by the Northwestern University (Chicago, IL, USA) (18, 19).

Currently, the most commonly used alternative is the detection of HIV by deoxyribonucleic acid polymerase chain reaction (DNA-PCR) which requires complex analyzers, a well equipped and clean laboratory and excellent trained staff. These are conditions not found in remote and under-resourced settings, thus MSF decided to collect dried blood spots (DBS) which are then eluted at a reference laboratory where the DNA-PCR testing for HIV is carried out. But even when using sensitive DNA-PCR technique we are uncertain whether all early infant infections are detected. If mother and child are taking anti-retroviral therapy for prevention of mother to child transmission (PMTCT) the viral load in the infant may be lower than the detection level of the DNA-PCR and an infection may be missed.

Staging and progression of disease is done using CD4 cell counts and viral load (VL) measurements (Figure 2D). In 2010, the first point-of-care CD4 analyzer, Pima™ CD4 (Alere Inc., Waltham, MA, USA), became commercially available. MSF purchased about 30 machines which are now in use in about 10 countries. Unfortunately, the price of each cartridge is quite high (approx. 6 USD per single use cartridge) and a high error frequency with aborted analysis of up to 14% when used on capillary samples make the device less attractive in RSL as it increases cost further and requires higher educated staff (20). In addition the analyzer cannot measure total lymphocyte counts, thus is not usable for monitoring in children where CD4% are required. However, products under development such as the Daktari™ CD4 Counter (Daktari Diagnostics Inc., Cambridge, MA, USA), the MBio™ Diagnostics CD4 system (MBio Diagnostics, Boulder, CO, USA), Zyomyx CD4

Table 1 Overview of laboratory standard analysis by program type.

Program type	Laboratory analysis
Tuberculosis	Microscopy: Ziehl-Neelsen or Auramine staining
	Xpert®: MTB/RIF
	Culture: MGIT or TLA
HIV	Testing: via lateral flow immunoassays, e.g., Determine®, Uni-Gold®
	Staging: CD4 count and CD4%
	Monitoring HAART: lactate, hemoglobin, ALAT, ASAT, creatinine
Malaria	Microscopy and/or lateral flow immunoassays
	Potentially blood transfusion
Blood transfusion	Blood grouping and cross matching
	Infectious disease screening: HIV, hepatitis B and C, syphilis
Chagas disease	Lateral flow immunoassays
	IHA
	ELISA
Sleeping sickness	CATT
(human African trypanosomiasis)	Microscopy on lymph node aspirates
	mAECT, CTC (also called Woo test)
	Disease staging by examination of CSF
Kala azar (visceral leishmaniasis)	Lateral flow immunoassay: rK 39
	DAT
	Microscopy of lymph node and spleen aspirates
Clinical chemistry	Wet and dry chemistry
Hematology	Microscopy and chamber counts as well as small hematology analyzers
Sexual and reproductive health	Syphilis testing via lateral flow immunoassays
	Urine dipsticks and microscopy
Other disease diagnostics	Brucellosis (by lateral flow immunoassay)
	Dengue (by lateral flow immunoassay)
	Gram staining in bacterial infections
	Meningitis (individual diagnose by gram stain, glucose and protein levels; for outbreak investigation screening with Pastorex®) cholera (screening by lateral flow immunoassay and after confirmation by culture)

ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase; CATT, card agglutination test for trypanosomiasis; CSF, cerebrospinal fluid; CTC, capillary tube centrifugation; ELISA, enzyme-linked immunosorbent assay; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; IHA, indirect hemagglutination; mAECT, mini-anion exchange centrifugation technique; MGIT, mycobacteria growth indicator tube; Pastorex, for the detection of *Neisseria meningitidis* A, B/*Escherichia coli* K1, C, Y/W135, *Haemophilus influenzae* Type b, *Streptococcus pneumoniae, Streptococcus* B.; rK 39, recombinant K39; TLA, thin layer agar; Xpert MTB/Rif, detection method of *Mycobacterium tuberculosis* and resistance to rifampicin.

counter (Zyomyx, Hayward, CA, USA), the CD4 counter developed by the Burnet Institute (Melbourne, Australia) and the CD4 Point-of-Care Technology (BD Biosciences, Franklin Lakes, NJ, USA) may be promising alternatives and will also contribute to a competition on the CD4 point-of-care analyzer market with hopefully the effect of further price reductions to make CD4 cell monitoring widely available (20).

Viral load access is still scarce in MSF programs and is currently not carried out on a routine basis, only targeted, when treatment failure is suspected. For this purpose DBS are collected and sent to an external laboratory for elution and analysis (Figure 1A).

In 2011, MSF implemented one of the few VL platforms in its program in Thyolo, Malawi. The lessons learned are

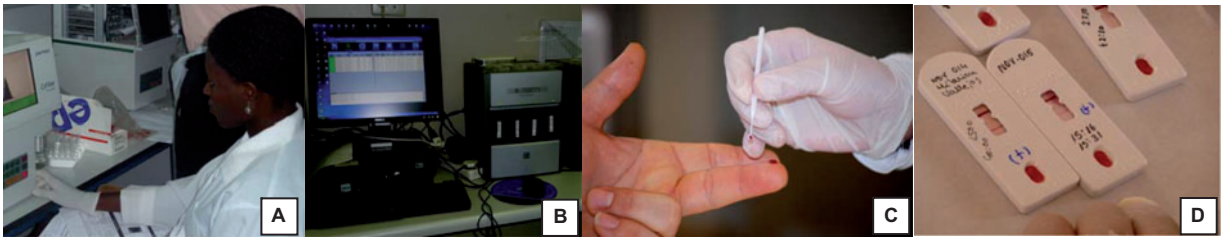

Figure 2 (A) Partec CyFlow analyzer for CD4+ cell counts, Thyolo, Malawi. (B) GeneXpert system for diagnosis of tuberculosis and resistance to rifampicin, Khayelitsha Township, Capetown, South Africa. (C) Blood collection with a microloop for transfer on a rapid diagnostic test. (D) Positive rapid diagnostic tests, Aiquile, Bolivia.

long and include topics like the selection of the platform, additional equipment required, space, construction plans, human resources, standard operating procedures, quality control, equipment maintenance and electricity supply, to just name a few. The use of high-tech methods such as viral load in its current form will always include massive challenges and with upcoming simplified technologies these will be reduced. Promising VL simplified platforms to be commercialized in the coming 1–2 years are the Alere NAT system (Alere Inc., Waltham, MA, USA), the Liat Analyzer (IQuum, Marlborough, MA, USA), SAMBA (Diagnostics for the Real World, Sunnyvale, CA, USA), GeneXpert® System (Cepheid, Sunnyvale, CA, USA) and the rapid RT-PCR testing platform under development by the Northwestern Global Health Foundation (Chicago, IL, USA) and Quidel Cooperation (Santa Clara, CA, USA) (21).

Tuberculosis

In 2009, globally there were an estimated 9.4 million incident TB cases (22). Of these 11%–13% were HIV-positive. Of the TB cases in HIV-positives approximately 80% occurred in the African region (22) (Figure 1C).

In 2009, an estimated 1.3 million TB deaths occurred among HIV-negative cases. In addition, there were an estimated 0.4 million deaths among incident TB cases that were HIV-positive, thus in total, approximately 1.7 million people died of TB in 2009. In 2008, 440,000 cases of multi-drug resistant TB (MDR-TB) were estimated and by July 2010, 58 countries and territories had reported at least one case of extensively drug-resistant TB (XDR-TB) (22). The diagnosis of smear-negative and MDR-TB requires complex culture settings, highly unsuitable, slow and costly for RLS.

The GeneXpert® system (Cepheid, Sunnyvale, CA, USA) and their MTB/Rif assay for the diagnosis of TB and rifampicin resistance was endorsed by the WHO in December 2010 as the initial diagnostic test in settings characterized by high prevalence of multi-drug resistant MDR-TB and HIV (Figure 2C). The GeneXpert system allows a rapid TB diagnosis (turn-around-time <2 h) and includes testing for resistance to rifampicin. The test integrates and automates within one cartridge the three processes required for real-time PCR-based molecular testing of TB: sample preparation, amplification, and detection. Studies have demonstrated good performance of this test on pulmonary samples, with a sensitivity and specificity approaching that of culture, considered the gold standard for TB diagnosis (23). The system also shows favorable results for the diagnosis of some of forms of extrapulmonary TB (24). MSF participated in the multicentric demonstration study of this new technology in Khayelitsha, South Africa, in collaboration with the University of Cape Town and the Foundation for Innovative New Diagnostics (FIND) and has implemented more than 30 analyzers to date. Globally, at the end of April 2011 at least 22 countries were already implementing GeneXpert MTB/RIF and plans were in place to procure instruments and cartridges for 34 countries (25, 26).

Malaria

In 2009, 225 million cases of malaria were estimated and caused an estimated 781,000 deaths, mostly among African children (27). Malaria is responsible for 20% of all childhood deaths. Microscopy is the reference standard for diagnosing malaria but requires considerable training and experience and is time consuming in high case load settings (28, 29) (Figure 1D). Therefore, LFIs, often called rapid diagnostic tests (RDTs), are a commonly used alternative as they are fast and easy to carry out, and provide reliable results (29–33) (Figure 2A, B).

MSF programs commonly use malaria RDTs to diagnose acute malaria infection. Three-line malaria tests *Plasmodium falciparum (P.f.)*/Pan tests are used in MSF programs where both *P.f.* and non-falciparum malaria species (i.e., *Plasmodium ovale, Plasmodium malaria and Plasmodium vivax*) are present and two-line malaria tests, where *P.f.* is dominant. In 2010, MSF procured 6.5 million malaria RDTs.

Case study: sleeping sickness

Sleeping sickness or human African trypanosomiasis (HAT), transmitted by tsetse flies, occurs in 36 sub-Saharan African countries. Affected populations live in remote areas with very limited access to health care which hampers the diagnosis and treatment. During epidemic periods the prevalence can reach up to 50%. The estimated number of actual cases was 30,000 in 2009 (34–36). Most cases were reported in the Democratic Republic of Congo and the Central African Republic where MSF has diagnosis and treatment programs (34–36).

The first stage of the disease, also called the hemolytic phase, is characterized by fever, headaches, joint pain and itching due to the trypanosomes multiplying in the subcuteanous tissue, blood and lymph system.

In the second stage, the neurological stage, the parasite crosses the blood-brain barrier and symptoms like sensory disturbances, confusion, poor coordination changes of behavior and changes in the sleep cycle appear. Without treatment the disease is fatal. Ideally diagnosis is made as early as possible to avoid difficult, risky and complicated treatment of the second stage (37).

The complexity of diagnostic algorithms and protocols faced is exemplified by the testing needs for sleeping sickness (Figure 3) (37, 38). For the diagnosis of HAT, screening is carried out by using the card agglutination test for trypanosomiasis (CATT), followed by confirmation tests detecting the *Trypanosoma* parasites microscopically. Confirmation methods are parasite detection in lymph node aspirates and isolation of parasites from whole blood using capillary tube centrifugation (CTC) technique, also called the Woo test, and/or mini-anion exchange centrifugation technique (mAECT) (39).

For determining HAT disease stage, laboratory investigations are performed on the cerebrospinal fluid (CSF) of patients. White cells (WC/μL) are counted and *Trypanosoma* are detected following centrifugation. In areas of high HAT prevalence (>1%)

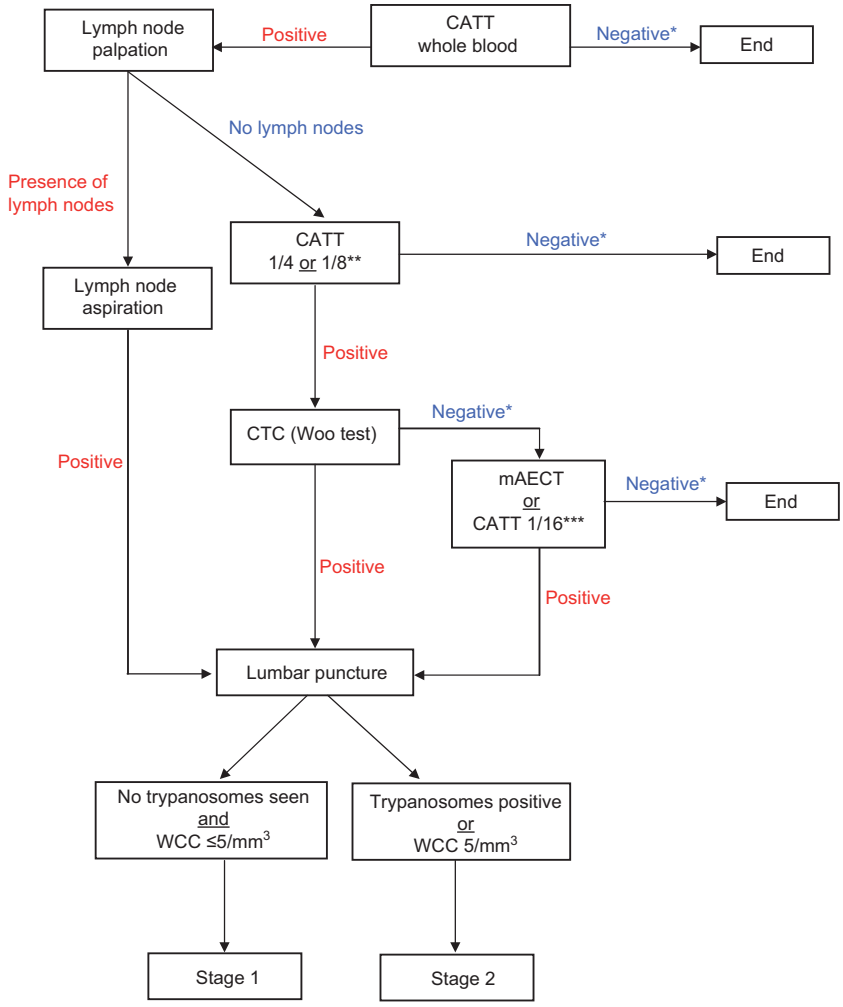

Figure 3 MSF diagnostic algorithm for sleeping sickness (human African trypanosomiasis).
CATT, card agglutination test; CTC, capillary tube centrifugation; mAECT, mini anion exchange centrifugation technique; Stage 1, stage of sleeping sickness without central nervous system involvement and relative simple 1 week treatment with pentamidine; Stage 2, stage of sleeping sickness with central nervous system involvement and complex treatment with high relapse rate and/or use of toxic drugs, e.g., Nifurtimox; WCC, white cell count. *If high clinical suspicion of HAT, move to next step of the diagnostic tree. **If prevalence <1% use cut-off of CATT 1/8. ***Use CATT 1/16 if mAECT not available and prevalence >1%.

where mAECT is not available, treatment can be started on the basis of a CATT positive result in a 1:16 dilution (strong serological suspect), without parasitological confirmation. Disease staging remains, of course, necessary for selecting the appropriate treatment. Besides the complexity of HAT diagnosis and the urgent need for simplified diagnostic tools, one of the main problems regarding HAT diagnosis is access to an uninterrupted supply of diagnostic materials (39).

Clinical chemistry in MSF

Clinical chemistry is mostly used when monitoring treatment side effects, e.g., in HIV or TB treatment programs. For the most part 'wet' semi-automatic photometers such as the Humalyzer 2000 (Human, Wiesbaden, Germany) are used. Programs with low demand prefer opting for 'dry' chemistry due to the maintenance and quality control needs of the analyzer, but the costs of using 'dry' chemistry are high (€1–€2 per test compared with a few cents when using 'wet' methods). In MSF laboratories, the number of tests ordered for 'wet' chemistry analyzers is much higher than for 'dry' analyzers (Figure 4). In 2010, MSF contemplated moving away from 'wet' chemistry systems towards using 'dry' chemistry systems, such as the Reflotron® by Roche. A cost-calculation model showed that using only 'dry' chemistry would mean a cost increase of more than 50 times, which is not financially sustainable.

Quality control

MSF considers quality control (QC) for laboratory testing to be a high priority and has developed a QC protocol for microscopy

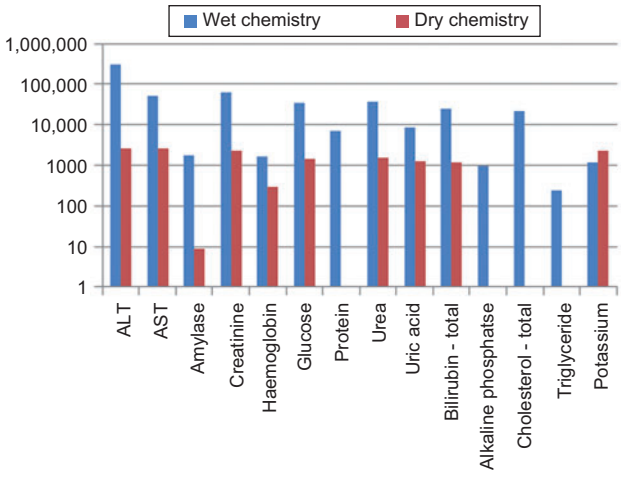

Figure 4 Numbers of 'wet' and 'dry' clinical chemistry tests sent to MSF field programs, 2009.

that is more applicable to RLS than other approaches such as lot quality assurance sampling (LQAS). The MSF QC approach was designed to: (i) allow a small sample size to be feasible across all settings; (ii) enable reliable analysis; (iii) monitor both false-positive and false-negative results; and (iv) be applicable to all microscopy testing (40).

In 2010, MSF enrolled several laboratories in the sub-Saharan region in the international accredited proficiency testing provided by the National Health Laboratory Services (NHLS) and National Institute of Communicable Diseases (NICD) in South Africa. Over time external QC has allowed improvement of performance in the different areas such as malaria, TB microscopy, biochemistry, hematology and CD4 testing.

Conclusions

Access to reliable diagnostic tools in humanitarian settings is a cornerstone of good quality medical humanitarian assistance. MSF's experience in reinforcing laboratory capacity over the last decade has shown that much can be done to improve diagnostic capacity, even in the most remote and unstable settings. However, the scope of the improvements depends largely on the extent to which diagnostic tools are developed with humanitarian settings in mind. Such settings often lack skilled health staff, have limited health budgets, are confronted with a high burden of infectious diseases with most patients accessing care at the primary care level, far from secondary or tertiary hospitals. Unless efforts are made to ensure that advances in diagnostic technology take into account the realities of RLS, they are likely to be irrelevant to the majority of patients who could benefit.

Acknowledgments

The author wishes to thank the MSF Laboratory Working Group. Without their continuous support and dedication, no advance in laboratory diagnosis in MSF would have been possible. Special thanks are extended to Nathan Ford, Oliver Yun, Martina Casenghi, Teri Roberts, Emmanuel Fajardo, Saskia Spijker and Roberto de la Tour for valuable comments and effective assistance during manuscript preparation.

Conflict of interest statement

Author's conflict of interest disclosure: The author stated that there are no conflicts of interest regarding the publication of this article.
Research funding: None declared.
Employment or leadership: None declared.
Honorarium: None declared.

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