



**Joint WHO/FIND meeting on
Diagnostics and Ebola Control**

**Geneva, Switzerland
12 December 2014**

SUMMARY REPORT

This summary of the meeting is provided by the co-hosts of the meeting: the World Health Organization (WHO), represented by Dr Francis Moussy, Focal Point for New Ebola Diagnostics & Diagnostics Innovation, and FIND, represented by Dr Mark Perkins, Chief Scientific Officer.

List of abbreviations

| | |
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| CBC | complete blood count |
| CDC | US Centers for Disease Control and Prevention |
| CDRH | Center for Devices and Radiological Health |
| CT | cycle threshold |
| EDAC | Ebola Diagnostics Access Collaboration |
| EMC | Ebola Medical Centre |
| ETC | Ebola Treatment Centre |
| EVD | Ebola virus disease |
| EQAM | Emergency Quality Assessment Mechanism (WHO) |
| EUA | emergency use authorization |
| FDA | US Food and Drug Administration |
| FIND | Foundation for Innovative New Diagnostics |
| HHS | US Department of Health and Human Services |
| IPC | infection prevention and control |
| IVD | in-vitro diagnostic |
| LFI | lateral flow immunoassays |
| LOD | limit of detection |
| MoH | Ministry of Health |
| MSF | Médecins sans Frontières |
| MTB | mycobacterium tuberculosis |
| NAAT | nucleic acid amplification test |
| NIAID | National Institutes of Allergies and Infectious Diseases (US) |
| NIH | National Institutes of Health (US) |
| PCR | polymerases chain reaction |
| pfu | plaque-forming unit |
| POC | point of care |
| PPE | personal protective equipment |
| RDT | rapid diagnostic test |
| RIF | rifampicin |
| RUO | research-use only |
| TPP | Target Product Profile |
| USAMRIID | US Army Medical Research Institute of Infectious Diseases |
| WHO | World Health Organization |

Welcome

Dr Francis Moussy opened the meeting by welcoming meeting participants.

Opening remarks

Speakers:

Dr Marie-Paule Kieny, Assistant Director-General, Health Systems and Innovation, WHO

Mr Mark Kessel, Chairman, Board of Directors, FIND

Mr Manica Balasegaram, Executive Director, Access Campaign, Médecins Sans Frontières (MSF)

Dr Marie-Paule Kieny (WHO) noted that the Ebola epidemic continues to evolve, providing new challenges for international partners seeking to support Ebola control in affected countries.

Key points of Dr Kieny's presentation included:

- The challenges in Ebola control and the epidemic's impact on health systems given that most deaths in affected countries were non-Ebola deaths in people unable to access disrupted health services. Although the short-term goal in affected countries is clearly fighting the outbreak, the longer-term goal should be to build resilient health systems.
- An update on work to develop Ebola treatment and prevention tools, including planned and on-going blood and plasma, drug, and vaccine trials.
- The critical need for diagnostic tools to guide treatment and control, the continuing relevance of the Target Product Profile (TPP) for Ebola diagnostics, and the support that companies will need with research and development (R&D) and especially test validation.
- The need for advance planning regarding where these new rapid diagnostic tests would be placed, who would use and maintain them, and other implementation issues.

Dr Kieny closed by noting the importance of considering how resources put in place for Ebola could be used for other diseases and the need to plan for the rebuilding of local health systems after the epidemic.

Key points of **Mr Mark Kessel's (FIND)** remarks included: the often-underappreciated economic impact of diagnostics; the urgent need for diagnostics not just for Ebola but for a variety of diseases, such as TB and neglected tropical diseases; the role of diagnostics in achieving global health security; and the need for adequate funding to achieve the development and implementation of the needed assays.

He noted that there is an urgent need to accelerate the Ebola diagnostics development and implementation timeline from years to months, and that the goal should be to plan for a process that would serve not just the present outbreak, but also any future crises.

Dr Manica Balasegaram (MSF) talked about the critical role of diagnostics in the short, medium and long term. He agreed with other panellists: that diagnostics had been lost in the scramble for Ebola control, but that the situation had improved.

Key points of Dr Balasegaram's presentation included:

- the role of diagnostics across all four pillars of outbreak control: prevention, surveillance, detection, and case management;
- how new Ebola diagnostics can open the door for alternative strategies for patient care and disease control for Ebola and other diseases;
- the role of rapid diagnostics for post-outbreak disease surveillance and monitoring;
- the importance of biosafety and compatibility considerations; and
- the issue of handling and management of, and equitable and fair access to, biosamples.

He closed by observing that this Ebola epidemic demonstrated a recurrent problem with the international community scrambling at the last minute to accelerate research in response to an outbreak. He stressed that a more sustainable strategy needed to be put in place.

Objectives of the meeting

Chair

Dr Pierre Rollin, Deputy Branch Chief, Viral Special Pathogens Branch, US Centers for Disease Control and Prevention (CDC)

Dr Rollin began by describing major problems new diagnostics could help address: significant time lags between sample collection and the result being communicated to the patient; biosafety concerns; issues with test sensitivity; the need for simultaneous testing for other causes of fever such as malaria; the need for confirmatory tests; the current requirement for advanced training and biosafety precautions for personnel running tests; and the need for significant laboratory infrastructure.

The speaker outlined the goals of meeting, which included: giving disease control workers, implementing agencies, and donors an overview of emerging diagnostic technologies; discussing how to arrive at long-term solutions to recurrent issues regarding access to patient samples and circulating pathogen sequences; and developing models for sustainable utility for implemented diagnostic systems post-outbreak (to avoid "fantastic equipment becoming a paperweight").

Dr Rollin noted that there is not capacity in the reference laboratories for evaluation of all potential Ebola diagnostic technologies, therefore a process of prioritization is needed. He also pointed out the need for urgency, if new diagnostics are to have a measurable impact on the current outbreak.

Overview of Ebola outbreak: Gaps in control – diagnostics perspectives

Speaker:

Dr Francis Moussy, Focal Point for New Ebola Diagnostics & Diagnostics Innovation, WHO

Dr Moussy presented the Ebola situation report from WHO as of 10 December 2014. He pointed out that the outbreak is far from over and examined the key performance indicators for the three countries with intense transmission: the percentage of districts with the logistical capacity to transport a sample to a laboratory by road within 24 hours of sample collection (100%); the effectiveness of contact tracing (88%); and the percentage of Ebola Treatment Centre (ETC) beds that are operational (55%). There are currently 19 deployed laboratories confirming EVD cases with PCR and three additional laboratories pending.

The speaker then enumerated the major challenges of the current Ebola testing network in the most affected countries:

1. Non-automated PCR methods (including conventional RNA extraction) and systems are being used that require several hours to run, have a high biosafety level requirement, require trained staff, and rely on manual result reporting.
2. There is no standardization of test methods across laboratories.
3. There is a need for ongoing quality assurance of laboratories.
4. There is a growing need for greater geographical distribution or mobility of laboratories to evolve with the epidemic as the epidemic patterns shift from urban to diverse rural settings. Furthermore, most Ebola laboratories do not address the needs of non-Ebola health-care facilities and many non-Ebola clinics are simply not open.

Dr Moussy also presented slides on behalf of Dr Pierre Formenty of the Emerging and Dangerous Pathogens Team at WHO, showing testing volumes for 2014 and projections for 2015. Though testing volumes might be assumed to fall as the epidemic is brought under control, the prediction was made that they would actually increase – most notably in the elimination phase. It was also noted that in order for non-Ebola health-care facilities to re-open and function effectively, there may be a need for integrated testing to rule-out Ebola in routine health-care centres and reassure health-care workers about biosafety. In order to meet these needs, new diagnostics would need to be rapid, simple, and appropriate for local non-Ebola health-care facilities, as outlined in the Ebola technical product profile (TPP) (http://www.who.int/medicines/ebola-treatment/emp_ebola_diagnostics/en/).

The speaker mentioned that WHO has developed an Emergency Quality Assessment Mechanism to guide procurement of Ebola diagnostics, but that there remains a need to facilitate the development, evaluation, and implementation of new tests. He mentioned that implementation faces several challenges: inadequate laboratory infrastructure; lack of trained staff; absent mechanisms for quality-assured electronic data management; lack of equipment maintenance; lack of access to supplies; and most importantly the need to ensure biosafety.

Questions and discussion

In the subsequent discussion, it was noted that the officially registered number of Ebola cases represented a proportion of the total and that informal estimates of actual cases may be two to three times higher based on burial records and reported symptoms of the deceased. Dr Moussy observed that the indicator showing there is 100% coverage of laboratories accessible within 24 hours did not capture the challenges on the ground: problems with phlebotomy and biosafety; transport of samples (sometimes being done by helicopter); sample tracking; and delayed reporting of test results for periods up to several days, even in a major urban centre such as Freetown. He expressed the urgent need not just for more rapid tests, but for a system to facilitate rapid deployment, including the tracking of patients and results.

New Ebola diagnostics pipeline and timeline

Speaker:

Dr Mark Perkins, Chief Scientific Officer, FIND

Dr Perkins began by mentioning that many of the mechanisms that might enable a rapid diagnostic response to epidemics (e.g. an ethical platform for sample and sequence sharing, a rapid and flexible fund to drive R&D for financially unprofitable diagnostic products targeting outbreak diseases, contracted commercial supply of ISO-manufactured primers or other reagents for ubiquitous RT-PCR platforms) have not been resolved in the last 20 years despite multiple significant outbreaks threatening global health security (e.g. Ebola, SARS, MERS, influenza). He described the ideal diagnostic tests for outbreak response as accurate, remotely deployable, mobile enough to move with the epidemic, simple enough to be operated by local health workers, allowing automatic electronic reporting and while-you-wait random access testing, and supporting both outbreak control and routine health care.

He described the potentially significant impact on Ebola control of diagnosing patients closer to the onset of symptoms – interrupting transmission through early detection and isolation – but explained that diagnostic options for Ebola were limited: viral cultures are impractical and immunoresponse is too slow for clinically-meaningful diagnosis, leaving as options antigen detection and molecular detection. He reviewed the various types of immunoassay platforms available and mentioned that though past immunodetection of Ebola antigens during outbreaks was performed by ELISA, most attention now is on lateral flow immunoassays (LFI) developed or under development by companies such as Senova, Corgenix, BTNX, Chembio, Vedalab, and Orasure.

Dr Perkins cautioned that while point-of-care (POC) test methods might seem the obvious solution despite potential compromises in performance, the biosafety precautions necessary to collect clinical samples using current methods keep most imagined testing methods (including simple lateral flow tests) from being easily decentralized to remote areas or primary care settings. Moreover the costs of personal protective equipment (PPE) required for sampling may erode important savings on test costs. More research is needed on expanding options for sample collection, such as an observed self-collected sample in a health-care facility.

Dr Perkins outlined the inherent limitations in the analytic sensitivity of LFIs and wondered if there might still be a role for them even if sensitivity is one or two logs (pfu/ml) lower than that of PCR, especially if such tests become readily available for implementation. He explained that while they are highly sensitive and specific, conventional non-automated RT-PCR tests have several limitations to their use in Ebola-affected countries because of the complexity of operation (and of the RNA extraction process) and the often slow manual relay of results. In this context, he noted the remarkable shift in the diagnostics industry in the past 10 years, particularly with the development of several near-patient molecular testing platforms that automate sample processing, amplification, and result reporting.

Dr Perkins described three automated molecular solutions currently or soon to be available:

1. The BioMérieux (BioFire) FilmArray Panel, originally developed as a research-use only (RUO) product to detect 17 biothreat pathogens (including Ebola), has received an Emergency Use Authorization for Ebola testing from the US FDA. FilmArray panels, which also exist for respiratory infections, blood culture identification, and gastrointestinal infections, are engineered to automate nucleic acid extraction, amplification, and detection all within a pouch on a single instrument. Hands-on time is very brief. The limit of detection for inactivated Ebola in blood is said to be 6×10^5 pfu/ml. He noted that instrumentation and the disposable pouch were currently rather expensive to manufacture.
2. Alere has a portable molecular system called Alere q, which is not engineered for parallel-plex detection like the Biofire assay, but automates sample preparation, amplification, and detection into a cartridge that also can serve as the specimen collection device. An HIV assay has recently been commercialized on this platform. The instrument itself has a small footprint (<8 kg weight), optional battery operation, and robust specifications. The system processes one assay at a time in approximately 45 minutes. The cartridge has a capillary tube which can be applied directly to a patient's finger to take a measured amount of blood and then snapped permanently closed, an important biosafety precaution. The test is engineered for direct data reporting and has connectivity features, allowing information to be uploaded directly to the cloud.
3. The GeneXpert system from Cepheid also automates and integrates all processes for processing, amplification, and detection and has remote monitoring and electronic reporting capability. The system requires a computer, draws enough power such that sustained battery operation is not easily achieved, is modular, and is available in versions processing between 1 and 80 tests at a time (random access, so that no batching is required). There are multiple assays currently available on the GeneXpert system, including the Xpert MTB/RIF test, which is the only widely used molecular test in the public sector of developing countries – now with some 4,000 instruments in use in more than 100 low- and middle-income countries having tested over 8 million individuals suspected to have TB.

Dr Perkins noted that multiple other molecular solutions have been proposed and are under development, including isothermal amplification platforms from companies like Lucigen,

Enviroligix, TwistDx, and Diagnostics for All. These systems benefit from the reduced engineering needs for isothermal assays, but may be susceptible (to the degree that operator skill replaces automation) to human error, especially in multi-step processes. Smaller companies tend to be an ongoing font of innovation, but may have limited experience or capacity for scaled-up manufacture, system implementation and assay distribution, and customer support.

He discussed expected timelines for the development of these diagnostic tools and readiness for trials:

- For lateral-flow assays: several groups have completed development or are at a stage where further progress would require testing against large numbers of clinical samples to help develop evidence for policy.
- For automated PCR assays: the Biofire assay is currently available, the Cepheid assay is expected to be ready to begin trials in January or February 2015, and Alere soon thereafter.

He highlighted the importance of supporting companies developing new assays with diagnostic standards and professional clinical trial capacity. He explained that one of his goals for the meeting is to be able to offer clear advice and procedures for companies to follow rather than having companies all asking advice from multiple international players.

The speaker cautioned that one potential outcome of accelerated development includes the possibility of multiple assays being given a positive emergency assessment by regulatory or other review bodies on the basis of manufacturing quality, but Ebola control programmes and implementing agencies still having no clear idea which test or tests to implement. He also noted that assays used in different places would need to do different things (e.g. triage at transit centres, clearance for non-Ebola-related surgical care, support for community care centres with a smaller number of beds).

Dr Perkins closed by reminding the audience that beyond the question of assay quality, the key question facing those involved in diagnostic deployment is which assay to use, where in the health system, by whom, and for what purpose.

Questions and discussion

Issues touched on in the subsequent discussion included:

- the complexity of coordinating the existing landscape of players;
- validation of lateral-flow assays, the need for live samples to evaluate assay sensitivity, and a proposed plan to provide a set of samples for testing all available assays;
- accounting for protein and RNA mutations in diagnostic tests: while at least two molecular companies have a mitigation strategy in place, mutations detected thus far have had little impact on molecular test performance. It was agreed that ongoing work to detect sequence drift is important, as is a fuller understanding of the potential impact of transcriptional editing on antigenic epitopes. There was some discussion of the utility of multiple targets in molecular assays, not only to ward against loss of a

single target through mutation, but to guard against misinterpreted PCR results when testing individuals vaccinated with a replicating vaccine vector encoding an Ebola sequence;

- the use of different types of samples for diagnosis; e.g. oral versus blood, finger-stick versus venous blood;
- the concern that a negative Ebola test result might not be sufficient to convince people in the primary health-care system that patients did not have Ebola: it was noted that currently, certificates of Ebola-negative status seemed to be enough to access care and were generally well-received in the Ebola affected countries; and
- the industrialization phase of development, manufacturing standards, and the challenges of ongoing quality assurance of new Ebola diagnostics given limited access to large panels of blood for testing antigen detection assays. An example was given of the US CDC's work with the US Food and Drug Administration (FDA) to make panels available for manufacturers to ensure that rapid influenza tests approved 10 years earlier picked up current strains. Companies that ask the US FDA for emergency use authorization are asked to make a validation panel available to their customers.

Update: WHO Emergency Quality Assessment Mechanism of In-Vitro Diagnostics for Ebola Virus Disease

Speaker:

Ms Robyn Meurant, Department of Essential Medicines and Health Products, WHO

Ms Meurant presented the WHO Emergency Quality Assessment Mechanism (EQAM). She began by explaining the initial triaging assessment, which consists of looking at the dossier provided by the manufacturers, firstly, on the evidence of quality manufacturing and capacity for scale-up and, secondly, other data supporting the use of this assay in the current outbreak. As part of this, consideration is given to whether the diagnostic tool is relevant to the published TPP and would be appropriate for use in West African settings. External experts also examine other data provided in the submission, including primarily analytical performance data in this second stage of the assessment process. It is understood that many in-vitro diagnostics (IVDs) may have no or limited clinical performance data. The EQAM then uses external experts and collaborating laboratories for an abbreviated performance evaluation, which includes verification of the limit of detection of the assay and a limited clinical study. There is an anticipated assessment timeframe of less than three months. The final decision to list is made by an internal review committee comprised of WHO experts.

Ms Meurant contrasted EQAM with other assessment mechanisms: it is less comprehensive and shorter than WHO Prequalification and, while many of their requirements align with the US FDA Emergency Use Authorisation (EUA) process, there are differences especially in how they evaluate risk, since the FDA has greater control of performance post approval (as it specifies the end users in the approval). Assays which have received US FDA EUA may have an expedited WHO EQAM process.

Ms Meurant explained that as of 11 December 2014, the WHO EQAM had received 19 applications in response to a call for Expressions of Interest, of which six were RDTs for detection of Ebola antigen, 12 were assays for detection of EVD nucleic acid (RT-PCR tech), and one was “other”.

She briefly reviewed various issues with laboratory evaluation, beginning with the fact that, at the time of the presentation, no readily available commercial assay has received full regulatory approval for use in the field. Many IVDs currently in use have been manufactured and regulated for research use only, with limited data on diagnostic sensitivity and specificity. Furthermore, there are no internationally accepted reference assays or reference preparations and there were limited clinical specimens to constitute evaluation panels. Nucleic acid amplification tests (NAATs) are not appropriate as benchmark assays for antigen detection assays. Additionally, laboratory evaluations need to be conducted at the appropriate biosafety level and the requirement for ethical clearance could be a significant impediment; as of 12 December 2014, the WHO had ethical clearance only for use of leftover specimens from Guinea.

Ms Meurant explained that WHO has developed a laboratory evaluation protocol for the evaluation of NAATs and antigen detection IVDs and identified six potential laboratories for this testing. She cautioned that evaluation would be limited to analytical parameters (limit of detection (LOD) and Prozone effect) and diagnostic sensitivity and specificity.

The final interim step for the WHO EQAM is listing the IVD assays found acceptable as eligible for WHO procurement. Guidance on testing strategies for diagnosis for these assays is yet to be developed. WHO is considering whether Ebola assays found acceptable under EQAM should be part of future full WHO prequalification.

Finally, Ms Meurant outlined the WHO process for post-market surveillance: any complaint reported to the WHO will be followed to ensure the manufacturer undertakes an appropriate investigation. In addition, WHO will work closely with the relevant ministries of health (MoH) to have any complaints they receive resolved in a timely fashion with appropriate remedial actions promptly taken.

Questions and discussion

A question was asked regarding what kind of outreach is being done with existing mobile laboratories in the affected countries to prepare for their role in the evaluation of assays. The answer was that WHO recognized the need to reach out to those laboratories again and would do so through Dr Pierre Formenty.

One participant wondered whether the ELISA assay from 2004 could be used for benchmarking antigen assays. The answer was that it could be considered as a comparator for some of the lateral flow assays, if readily available.

It was noted that there are often problems with consistent manufacturing quality for lateral-flow assays, with the potential for high within-batch and batch-to-batch variation due to the complexity of nitrocellulose.

Access to Ebola virus diagnostic testing: Determinants of late testing and how we can improve it technically and socially

Speaker:

Dr David Brett-Major, Naval Medical Research Center (USA)

Dr David Brett-Major began by outlining the importance of clinical care in outbreak response. Highlights of the presentation included:

- the key clinical issues for Ebola diagnostics: diagnostics drive case disposition (interaction with patient, movement of patient, and reintroduction of patient to community); current diagnostic tests allow for case finding and identification, but they do not substitute for critical clinical laboratory needs;
- the life-cycle of a patient as they approach, receive, and leave care and the various diagnostic needs at each stage;
- the perspective that a clinician must hold not only a patient-centred viewpoint but also a practice-centred viewpoint, weighing personal risk to the doctor with the benefit for the patient and community; and
- the key clinical requirements for diagnostics: that they should be used early and should be rapid, reliable, and distributable.

Dr Brett-Major raised a few questions about ways to:

- test patients non-invasively;
- incorporate diagnostics for endemic pathogens such as malaria, Lassa, and dengue;
- incorporate or advance clinical monitoring alongside the diagnostics; and
- reduce the risks of collection, transportation, and storage of samples from patients.

He discussed existing barriers to effective Ebola testing: patient fear (of testing positive, of isolation, etc.); time requirements (travel, safety precautions, etc.); and problems with scaling up diagnostic care given the increased complexity of scaled-up collection, transport, handling, testing, training and expertise, and the PPE required. Finally, he highlighted that the risk to health-care workers should not be underestimated, because Ebola and fear of the disease have affected the availability of all other forms of health care.

Questions and discussion

A question was asked about the feasibility of performing a clinical differential diagnosis for Ebola in a context where malaria is endemic, in the absence of available laboratory capacity. The answer was that the only option for the clinician is to make a clinical diagnosis, but they might be wrong. Dr Brett-Major explained that a differential diagnosis of malaria versus Ebola is very difficult and pointed out that this question highlighted the demand for good diagnostics.

A question was asked about how Dr Brett-Major would envision the use of quantitative data (e.g. viral load) in diagnostics. The answer was that it would be nice to have this data in order to track and better contextualize patient outcomes, but that absolute quantitative capability is not a requirement for assay implementation.

A comment was made asking those present to consider what would be learned from this epidemic for future epidemics.

A question was asked about the performance of diagnostics given their potential for use in triage in the community and the clinical need to be sure with one test whether the patient has Ebola. The answer was that patients were not coming to clinics, hospitals, or treatment facilities the moment they were sick but were arriving after several days of illness. It was noted, though that catching cases on the second or third day of symptoms would shorten the chain of transmission.

Technical aspects of Ebola virus detection

Speaker:

Dr Jim Strong, Head, Diagnostics and Therapeutics, Public Health Agency of Canada

Dr Jim Strong described the realities of laboratory work in Ebola-affected countries. Key points of his presentation included:

- the conditions under which these new diagnostic tools need to function, including difficult transport conditions and sometimes impromptu locations for laboratory deployment;
- a description of the laboratory set up by the Canadian team, which included the use of a modified class III glove-box and a PCR machine. He noted that the laboratory machines they used were very sensitive to heat and humidity and that, in order to protect the equipment, they used ventilated glove boxes, which included a small anteroom for inactivating the virus (i.e. allows for not having to spray copious bleach around the diagnostics machines); and
- a discussion of the detection limits for EVD; the effectiveness of various types of samples (oral swabs, breast milk, eye swabs, and nose swabs) and comparisons of paired samples; a correlation between high cycle threshold (CT) values and higher survival rates; and a correlation between elapsed outbreak time and decreased viral load.

Dr Strong outlined several lessons learned:

- Women who were pregnant may have viral load at the limit of detection while foetal blood has much higher viral load; the foetus is in effect a “ticking time bomb” of Ebola virus.
- Testing of environmental samples shows the presence of Ebola virus RNA widely distributed within the clinical environment.

- There is a strong belief, based on limited data, that supportive care helps, especially if provided early.
- There is a need for expanding mobile laboratory capacity and enhancing clinical diagnostics for patient management (including, for example, blood chemistries, complete blood count (CBC), blood gases, ultrasound, EKG) in order to implement targeted supportive care.

Regarding the effectiveness of supportive care, Dr Strong mentioned that they were planning to evaluate whether supportive care was helpful before the outbreak became widespread. He noted that some health-care workers were reluctant to provide supportive care because of the increased risk of exposure and lack of evidence as to the impact on patient recovery. His team is hoping to publish results from human and animal studies to show that supportive care is helpful while awaiting confirmation of diagnosis, as well as in the context of appropriate diagnostic management.

Questions and discussion

Issues touched on in the subsequent discussion included:

- what can be learned about the factors that drove people who were sick but not dying to come to care centres when there is not demonstrable evidence that the kind of supportive care being provided saves lives? Dr Strong hypothesized that this was because people were hearing that receiving care was helpful. He also posited that death rates might be declining because contact tracing could be catching cases earlier and that advocacy by people recovered from Ebola is helping to reframe the epidemic for the community.
- a brief discussion about difficulties with the reintegration of survivors: one participant noted that people were more likely to seek testing if they were also able to be treated for other diseases such as malaria. One audience member noted that some patients were self-referring because they didn't want to infect their families, while others were fleeing mobs.
- whether Dr Strong had compared different methods for inactivating the virus. He responded that they had not and that they had used what had been proven to work.
- surprise with the level of agreement between blood samples and oral swabs presented in the slides. Dr Strong hoped to continue studying this effect but they were not getting a lot of paired samples. He noted that agreement between the paired samples was higher if the patient was further along in their disease progression.
- equipment decontamination: the Canadian team's plan was to decontaminate the equipment, although doing so might compromise the circuit boards. It was pointed out that if they waited long enough, the virus would be dead – although PCR testing may continue to identify viral nucleic acids. Decontamination in general was a big issue for use for equipment beyond the current outbreak.

Current issues with lab-based diagnostics and the role of new point-of-care diagnostic tests to support Ebola Treatment Centers

Speaker:

Dr Erwan Piriou, Laboratory Advisor, MSF

Dr Erwan Piriou emphasized the need for more diagnostic testing at point of care (POC) in the current outbreak including: Ebola treatment centres; outreach for active case finding; transit/referral centres; and non-Ebola health-care centres and maternities. Current challenges include data management for all testing and at all levels, delayed patient presentation for diagnosis (average is five to six days after symptom onset), geographic spread of disease and the need to better map the outbreak for decision-making, and the lack of simpler diagnostics that would allow 24/7 testing in deployable laboratories with limited staff.

The speaker described the situation in MSF Ebola Medical Centres (EMC), with many needs covered but diagnostics challenges remaining: a need for more flexible, deployable laboratories and better coverage of the region with EMCs; inconsistencies in CT values and difficulties in gathering comprehensive patient disease and symptom history to complement test findings; sampling methods for infants and children, raising questions on the use of blood versus oral swabs; lack of EVD rapid diagnostic tests for outreach and active case finding; and questions about how best to plan for on-site diagnosis, such as mobile glove-boxes or vans with PCR machines.

He reported that in transit and holding centres, diagnosis is rarely done on site and much time is lost because of logistical issues around sample transport and result reporting, causing substantial treatment delay. Without diagnosis prior to patient transport to an ETC, there is an increased risk of transmission *en route* and limited effectiveness of patient care, as most people arriving by transport are either in advanced stages of the disease or already convalescent.

Dr Piriou explained that the EVD outbreak has crippled basic, non-Ebola-related health care and that the continuing challenge is to triage patients without local testing capacity (which requires near-patient testing technologies and availability of PPE for sampling); this is especially true for patients requiring “wet” care, as in the case of obstetrics or surgery. The lessons learned from MSF workers in the field are: local testing capacity should be increased to diminish time for results from days to hours and active surveillance should be done in outbreak areas when there are no local confirmed cases of Ebola. In response to the challenges of providing basic care in this epidemic, MSF has been forced to shut down some routine health-care activities because they are not feasible.

The difficulties in current EVD algorithms, Piriou argued, are related to the sometimes inconsistent performance of tests and the sample type required. The question with nucleic acid tests versus antigen-based/lateral flow tests was whether to prioritize performance (sensitivity/specificity) or speed in triaging. He noted that data management and connectivity would help diagnosis in EMCs and would enable real time mapping and communication with

partner or government systems; diagnostic manufacturers should keep this in mind and ensure that access to data from their instruments is compatible with that from other systems.

Dr Piriou closed his session by stating that light-footprint, quickly deployable tests would be essential in the future to model, confirm, and contain new outbreaks and epidemics, including among other viral haemorrhagic fevers with similar symptoms.

Questions and discussion

Attendees raised questions and discussed key issues, including:

- whether assay limits of detection should impact how testing is used to inform patient discharge from treatment centres, especially when they are full. During the 2007 epidemic in Uganda, discharging was done based on clinical symptoms, not testing.
- how and whether to try to diagnose asymptomatic patients: testing of such patients is not feasible in outbreak settings, so the patient should be observed; if symptoms develop, the patient can be removed quickly from the community (if rapid testing is available), with little risk of transmission.
- the impact of increased use of vaccines on testing strategies, not only for diagnosis but for future surveillance; for example, post-epidemic use of antibody tests. Piriou clarified the distinction between antibody and glycoprotein, adding that patients would not be tested without signs and symptoms.
- whether the quality of an antigen assay would be measured against PCR CT values, as there is no gold standard, before it goes to the field. Testing should be done with whole blood and not with plasma, if the need for a second round of testing in the field is to be avoided. There is not a CT equivalent that could be used for developing tests, but for a given PCR system, relatively good data exist on the distribution of CT values in newly diagnosed patients (with different lengths of symptomatology), so CT comparators could be used as a surrogate for clinical sensitivity.
- experiences with using different samples (blood, saliva, urine, semen) in recovered patients to confirm cure.

Biosafety considerations for introduction of new Ebola diagnostic tests outside of mobile and designated labs

Speaker: Dr Sébastien Cognat, Team Leader, Laboratory Strengthening and Biorisk Management, WHO

Dr Cognat presented biosafety concerns throughout the cycle of diagnosis, from specimen collection and transport to laboratory testing and waste management. Although handling and storage of Ebola virus is restricted and regulated in many countries, there could be concerns as to expanding specimen banks and in the meantime minimizing biological (and biothreat) risks in unstable countries, in this case in West Africa.

He discussed the necessary precautions for specimen collection, sample packaging and handling in the field, shipping guidelines for 'Category A' infectious substances (such as the Ebola virus),

and laboratory testing of samples. He described the difference between the categories of disease risk group and laboratory biosafety level, noting that these two are not strictly equivalent. Assignment of a sample to a biosafety level is based on a risk assessment taking into consideration the organism, the facilities available, equipment, practices and procedures in use.

Dr Cognat presented the WHO biosafety recommendations for Ebola laboratory diagnostics, noting that other countries' recommendations might be less stringent based on their risk assessment, including available laboratory infrastructure and maintenance.

Regarding the challenges of waste management, he explained the different steps of disposal in EVD diagnostics, including specimen collection and laboratory waste, as well as waste treatment and land disposal, and noted that the WHO book on safe management of wastes from health-care activities¹ should be consulted in case of questions.

Dr Cognat concluded by underscoring the biosafety considerations for the use of diagnostics outside of laboratories and the importance of training clinical and laboratory personnel to prevent transmission in the course of use of any diagnostic test.

Questions and discussion

The subsequent questions and discussion touched on various issues, including:

- the handling of inactivated and active specimens, noting that the earlier the inactivation, the better for the health-care worker or laboratory technician;
- the challenge of storing specimens for further testing or shipping (e.g. freezing of whole blood);
- the logistical challenges with timely inactivation, collection, and labelling of larger quantities of specimens;
- the protective equipment required when inactivating samples (glove-box vs PPE); and
- the need for regular retraining, stocking of supplies, and maintenance of machines.

How improved diagnostics could improve Ebola and general health care delivery in the affected countries

Speaker:

Dr Ahmadou A. Diallo, Chief Research Department, Ministry of Health, Guinea

Dr Diallo presented the state of the Guinean health-care system before the Ebola outbreak in the forested regions around Gueckedou and the impact of the outbreak on its already fragile systems.

His overview included the following key points:

¹ Safe management of wastes from health-care activities. Geneva: World Health Organization, 2014. Available at: http://www.who.int/water_sanitation_health/medicalwaste/wastemanag/en/.

- Guinea has high levels of poverty and low levels of public services;
- national health policies had been aimed at expanding universal coverage, reaching vulnerable patients, and reducing poverty;
- the country is divided into central, regional, and local levels, in which 18 out of 30 prefectures have been affected by the Ebola outbreak;
- the health system structure includes national, regional, and prefectural/local hospitals, with public, parapublic, and private sector actors for general health care; and
- Guinea's key health indicators are the lowest in the region, and national health programmes receive only 2.4% of the National Development Budget.

Key points in the Guinean government's response to the Ebola epidemic included a national response strategy for disease control, case identification, patient care, surveillance and information sharing, and declaring Ebola an outbreak in March 2014.

Dr Diallo described the following obstacles to disease control in Guinea:

- false perceptions about EVD and traditional practices or beliefs that resulted in transmission;
- difficult communication and lack of trust between the people and the government;
- isolated communities and the inability to mobilize local leaders to have communities tested;
- cross-border movement and migration;
- national health programmes that have been burdened and weakened by the epidemic, though there has been little analysis of the effect of EVD on other health programmes;
- difficulties accessing appropriate care, due to the difficulty of differentiating between EVD and other diseases, (e.g. 12.4 % of children under five suffer from diarrhoea and malaria is prevalent);
- lack of properly trained health-care staff;
- the need to increase the allocation of resources in the national budget;
- lack of integrated data between public, private and military sectors; and
- weak partnerships between local, African, and international partners to harmonize efforts.

Through this epidemic, public policy in Guinea has been revised to: increase the coverage and quality of health care; offer more services in non-febrile disease areas; increase collaboration and communication with communities, non-governmental organizations, and media; and strengthen district level health services. The Guinean Ministry of Health now assesses its performance regularly with the goal of being accountable and following up with evaluation to ensure good governance.

Dr Diallo concluded his remarks by noting that despite challenges, control of the EVD epidemic has increased because of political will, engagement of partners to train communities and individuals in good hygiene practices, and results of research into vaccines and treatment possibilities.

Breakout into group discussions

*Of three breakout groups, **Groups 1 and 2** considered implementation planning around emerging tests likely to meet the ideal characteristics in the published TPP (Group 1) or the acceptable characteristics (Group 2). These two groups were instructed as follows: “Assuming the availability of new EVD diagnostic tests that meet the TPP requirements in the next 4-12 months, review their implementation requirements (e.g. biosafety, training, and infrastructure). Consider the level of health care at which these tests should be placed, the workflow, expected number of tests, users, staffing levels, training requirement, social mobilization, and other logistical requirements such as PPE, results reporting, and data management.” **Group 3** was given the following instructions: “Leveraging the attention on new diagnostics that the current Ebola outbreak has generated, list the elements of a laboratory strategy that could strengthen national or regional capacity for ongoing epidemic surveillance and rapid response to future outbreaks.”*

Breakout Group 1 – Meets ideal TPP

Key points of the discussion included:

- where, how, and by whom the test would be used and the training required to properly and safely use it;
- the goal of testing (controlling the disease; eliminating the disease; stopping the epidemic, etc.); and
- the need for symptom-based assays for different diseases (e.g. fever testing for EVD, malaria, typhus, etc.).

There was some discussion around what should happen to patients who tested negative for EVD: on-site testing or treatment for malaria (or other diseases) or referral to the public health system. One suggestion was that Ebola diagnosis could be in effect a fever screening programme, which would serve as pre-triage points accessible within approximately one hour from an outbreak location. Workers at these centres would have PPE and simply need training for test use. This would make an EVD test the entry point into the health-care system, though it would then be a bottleneck for care.

The group noted that an ideal test would perhaps include supervised self-collection of samples, though there remained some concern about asking a possible EVD patient to self-test. The possible social consequences of testing at the village level were noted.

The group agreed that:

- The first sites of use should be Ebola Treatment Centres (ETC) that did not already have laboratories, as well as ETCs that had laboratories that were overwhelmed. To ensure biosafety, staff roles should be specific, including for those who draw blood. The group noted the need for a clear reporting system for results, either an electronic reporting system or through an existing chain of command.

- The second category of locations prioritized for new tests was transit centres where suspected patients are held without treatment or diagnosis, the goal being to replace holding areas with while-you-wait testing to reduce transmission.
- The third priority use is through outreach teams who respond to reports of a suspected EVD case (e.g. among those being actively followed as contacts).
- Finally, a rapid EVD test should be available to test patients needing other types of urgent medical care, especially those with high exposure risk to body fluids (i.e. at maternities or surgical centres).

Breakout Group 2 – Meets acceptable TPP

Key points of discussion included:

- The need for a highly decentralized system with dedicated, well-trained staff: limited training for a simpler test, more training (especially in computer skills) for an automated PCR test. There could be a district coordinator to train and deploy staff and troubleshoot and answer questions. The need for redundancy and replacement parts within the site and district was noted.
- Connectivity: the need for basic cell coverage to upload the data; the question of who would send and receive the data; confidentiality of patient data: even though encrypted data could be identified by a ministry, they could be completely anonymous as well; the issue of connectivity was not important for all participants, with a paper trail viewed as a minimum requirement – more sophisticated technology could pose more problems for users in the field.
- Who would act on the data thus gathered: discussion of problems with result-reporting accuracy and the presence of contradictory data.
- Infrastructure needs on the ground for new products: a generator, especially in non-EVD sites, perhaps accompanying the outbreak team; the need for the team base to have water, power and quality assurance mechanisms.
- The role of effective case management to stop transmission and decentralized monitoring.
- Biosafety issues and training for proper use of PPE and waste management.
- Risks for health-care workers taking samples and rapid response teams. Two to three people would be required for testing, with a subgroup of collected samples used for quality assurance.

The group agreed that:

- Even if portable, platforms meeting TPP acceptable characteristics should be deployed with a district-level supervisor for support. The supervisor should have access to additional technical support by telephone.
- There should be dedicated, trained staff to use even simple molecular platforms.
- Mains or generator power should be backed up with battery and/or solar supply.
- Clinical triage should be based on standardized questions and staff should be trained in the triage algorithms.

- Results data should be communicated electronically with a paper back-up held at the testing site. There should be minimum labelling standards to preserve chain of custody, either through barcodes or pre-printed IDs.
- With full PPE, the glove-box could be eliminated, especially with the use of chlorine. At least two people should conduct testing, with finger-stick testing preferred over venipuncture.
- A national or international monitoring strategy should be in place to ensure that genetic drift is not eroding diagnostic performance.
- Social mobilization would be key to any successful testing strategy.

Breakout Group 3 – Laboratory strategy

Points noted in the discussion included:

- Strengthening laboratory systems should be a key priority. In order to build local capacity, there should be national, inter-country, or regional schools to train laboratory technicians. There is a need for international support to keep capacity in countries. Integrating a research programme into this type of collaboration is useful and will increase access to international funding.
- Laboratories should be polyvalent and not disease specific. Countries need to ensure that a surveillance system is in place, combined with a referral of samples for national or regional laboratory analysis. There must be collaborative agreements in place to cover the sharing of samples. The referral system will enable minimal tests to be conducted at each level of the health system.
- Specimen handling and transportation is an important issue and should be enabled through district or regional cooperation, e.g. hotlines or other mechanisms should be in place for transport of samples to central laboratories, which could report locally and nationally.
- In-country capacity is fragmented among different ministries and each country must have integrated capacity and communication between these sectors to maximize efforts. A centralized health system integrating all sectors would help ensure sustainable success as funding would be given to several different areas dependent on their collaboration.

The group agreed that:

- The international community should leave behind a National Task Force and Rapid Response Team ready to be deployed with rapid testing capacity (potentially multiplex platform or antigen/antibody in the same test) in any future Ebola outbreak.
- This response capacity should be integrated into efforts to strengthen general diagnostic laboratory systems and build human resources.
- Efforts should be made to enhance the capacity to transport outbreak-related samples within the region and abroad, including through shipping agreements and sample inactivation protocols tied to reduced regulatory or other shipping requirements.

Concluding remarks: Roadmap to accelerate R&D: from development to implementation

Speaker: Dr Mark Perkins, Chief Scientific Officer, FIND

Dr Perkins concluded the conference by highlighting that there are always difficulties in implementing any innovation, especially within weak health-care systems. Even so, diagnostics could make an important difference in this epidemic. This meeting has highlighted challenges in using the existing fixed PCR laboratories to provide the kind of rapid time-to-result-reporting required to interrupt disease transmission. Transmission and the generation of new mini-outbreaks will likely continue unless new diagnostics become available soon. There has been much technical progress in this area and new tests will be ready for potential deployment within the coming weeks to months, but implementation strategies and collaborations are key to preparing the field for new tests.

As the global health body with a mandate arising from Member States, Dr Perkins noted that WHO should take the lead on building a roadmap for Ebola diagnostics implementation with support from diverse stakeholders. WHO is making this leadership demonstrable through the formation of the Ebola Diagnostics Access Collaboration (EDAC) to facilitate coordination of partners and abbreviate the development-to-implementation cycle. Through participants in this meeting and members of EDAC working groups, the implementation roadmap will be developed over the coming few months. The role of working groups will be vital in increasing communication, developing strategies, and raising funds to further control the EVD epidemic and support weakened health systems in West Africa.

Appendix 1: List of participants

*Diagnostics and Ebola Control
A joint WHO/FIND meeting
12 December 2014
Geneva, Switzerland*

List of participants

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Appendix 2: Meeting Agenda

Diagnostics and Ebola Control

A joint WHO/FIND meeting

12 December 2014

Geneva, Switzerland

In the absence of a safe and effective vaccine, early diagnosis and isolated care of infected patients is the only available method to halt the Ebola epidemic. A limited number of reference levels are working beyond capacity at present, but diagnostic capability is insufficient - access to testing is significantly limited and <20% of patients get diagnosed in the first 2 days of symptoms. Diagnostics solutions to this problem may feasibly be created, and there are a number of candidate assays and systems. The efficient development of the right tools, speedy information about their performance, and effective implementation in a way that strengthens rather than destabilizes health systems will require a significant degree of coordination between multiple groups: test developers, regulators, virologists, public health experts, national governments, international technical organizations, and donors. This meeting on *Diagnostics and Ebola Control* is intended to inform on coordinating mechanisms that have recently been put into place, and to present a 6 month roadmap to effective use of diagnostic systems to assist in Ebola control. Specifically, the meeting will:

- Familiarize implementing agencies, national policy makers, donors and other interested parties on the landscape of diagnostic needs and opportunities
- Plan how novel diagnostic testing systems will be used in practice to drive decision-making about outbreak management
- Present a 6 month roadmap for improved diagnostic testing and open it for critical discussion
- Examine recent data, and remaining gaps, critical to informing decisions on integrating near-patient testing into control programmes
- Summarize the plans and activities of the Ebola Diagnostics Access Coalition to coordinate the effective development, assessment, and use of new diagnostic solutions.

Agenda

Diagnostics and Ebola Control WHO/FIND 12 December 2014 Geneva, Switzerland

| Time | Topic | |
|-------------|---|--|
| 08.30-09.00 | Coffee - registration | |
| 09.00-09.10 | Welcome | Francis Moussy (WHO) |
| 09.10-09.30 | Opening remarks | Marie-Paule Kieny (WHO) Bruce Aylward (WHO) Mark Kessel (FIND) Manica Balasegaram (MSF) |
| 9.30-9.40 | Objective of the Meeting and Expected Outcomes | Pierre Rollin, US CDC, Chair |
| 9.40-10.20 | Overview of Ebola Outbreak: Gaps in control – diagnostics perspective | Francis Moussy |
| 10.20-11.00 | New Ebola Diagnostics Pipeline and Timeline | Mark Perkins |
| 11.00-11.20 | Break | |
| 11.20-11.30 | Update: WHO EVD Diagnostics Emergency Quality Assessment | Robyn Meurant |
| 11.30-12.00 | Access to EVD diagnostic testing: Determinants of late testing and how we can improve it technically and socially | David-Brett Major |
| 12.00-12.30 | Technical Aspects of Ebola virus detection | Jim Strong |
| 12.30-14.00 | Lunch | |
| 14.00-14.25 | Current issues with laboratory based diagnostics and role of new point of care diagnostic tests to support Ebola Treatment Centers | Erwan Piriou |
| 14.25-14.40 | Biosafety considerations for introduction of new Ebola diagnostic tests outside of mobile and designated labs | Sébastien Cognat |
| 14:40-15:00 | How improved diagnostics could improve Ebola and general health care delivery in the affected countries. Ebola Response -epidemiological capacity (from contact tracing to surveillance) -case management -health-seeking behaviour | Magassouba N’Faly ² |
| 15.00-15.30 | Break | |
| 15.30-15.50 | How improved diagnostics could improve Ebola and general health care delivery in the affected countries Health systems -effects on health care programmes: malaria, TB, HIV, cholera, etc. -infection control gaps in non-Ebola care settings | Ahmadou Diallo |

² Dr Magassouba N’Faly was unable to participate in the meeting and his session was omitted.

| | | |
|-------------|---|---------------------------------|
| 15.50-17.00 | <p>Breakout into Group Discussions:</p> <p>Assuming there will be a new EVD diagnostic test that meets the TPP in the next 4-12 months, the group (<u>Group 1-Meets Ideal TPP, Group 2- Meets Acceptable TPP</u>) will review what needs to be considered now in planning the implementation of these new tests with regards to infection control, training and infrastructure. The group will consider the following: at what level of health care infrastructure these tests should be placed (how decentralized), workflow, expected number of tests, users, staffing levels, training requirement, social mobilization, other logistical requirements such as PPE, tools of communicating results, reporting, data management.</p> <p><u>Group 3:</u> In order to leverage the attention on new diagnostic tests that the current Ebola outbreak has generated, the group will list the elements of a laboratory strategy to strengthen laboratory services and country's responsiveness for future outbreak and surveillance</p> | |
| 17.00-17.30 | Group Presentations (10 minutes each) | |
| 17.30-18.00 | Concluding remarks: Roadmap to accelerate R&D: from development to implementation | Mark Perkins/ Francis Moussy |