Workshop on Quality Assurance of HIV and Hepatitis Testing

Report on an Intercountry Workshop

Kiev, Ukraine, 24–26 September 2003
ABSTRACT

The present intercountry workshop was designed to address quality aspects of laboratory testing for HIV/AIDS and hepatitis viruses. The participants, delegates from Belarus, the Republic of Moldova and Ukraine, were senior professionals involved in laboratory screening, diagnosis and reference testing for bloodborne viruses, and regulatory affairs.

Participants recognized the increasing demand for proficient laboratory services for HIV/AIDS and hepatitis B and C, to ensure the accurate diagnosis of infection and to screen blood donations. Ensuring the safety of blood transfusion depends both on careful donor selection and quality procedures built around the testing, but also collection, storage and use of blood.

Issues like national laboratory organization, relevant regulatory framework, including licensing of kits, evaluation and purchase of diagnostic devices, testing requirements and strategies and laboratory management were presented and discussed.

The need for continuous revision of existing regulatory frameworks in the light of current international practices has been commonly agreed. Member States should support the development of appropriate infrastructure and laboratory networks to sustain implementation of national quality systems for laboratories and blood transfusion services.

Keywords

HIV INFECTIONS – prevention and control – diagnosis
AIDS SERODIAGNOSIS – methods
HEPATITIS B – prevention and control – diagnosis
HEPATITIS C – prevention and control – diagnosis
BLOOD TRANSFUSION – standards
QUALITY CONTROL
LABORATORIES – organization and administration
EUROPE
EUROPE, EASTERN
COMMONWEALTH OF INDEPENDENT STATES

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1. Introduction

The countries of the newly independent states (NIS) are currently experiencing the most rapidly growing HIV epidemic in the world, while the need to readjust to new boundaries and adapt already existing structures to different systems of funding, reporting and control has proved to be a major challenge.

The recent rapid growth of HIV in NIS countries has occurred overwhelmingly through transmission risks associated with sharing paraphernalia used to inject illicit drugs. In some countries of the Region over 90% of HIV cases are estimated to be associated with injecting drug use (IDU), and explosive outbreaks of HIV have been reported among injecting drug users (IDUs) in Belarus, Kazakhstan, the Republic of Moldova, the Russian Federation and Ukraine.

The risk of onward transmission of HIV to non-injecting sexual partners and recipients of blood and other tissues will increase with escalating prevalence in IDUs. Indeed, the very high HIV incidences seen in the IDUs of some NIS countries feed into the population substantial numbers of individuals with the heightened infectivity that is associated with primary infection. Moreover, laboratory detection of HIV infection during the very early phase of infection can prove difficult.

Throughout the world epidemics of HIV in IDUs have been preceded by epidemics of hepatitis B virus (HBV) and hepatitis C virus (HCV). Prevalence of HCV in IDUs has tended to be substantially greater than HIV, reflecting its greater transmissibility through the bloodborne route. Whereas both HBV and HCV are readily transmitted through injecting practices and transfusion/transplantation, HCV is much less frequently transmitted through sexual exposure than either HBV or HIV.

The rapid establishment in eastern Europe of these chronic viral infections presents enormous public health challenges. The infections have a grave impact on the quality and length of life of those infected and, if unchecked, will give rise to escalating healthcare costs and may also lead to a more general economic impact. Bringing the current epidemics under control and minimising further spread into the general population depend on measures such as appropriate laboratory capacity for screening and diagnosis, the provision of safe blood for transfusion and safe injection practices. With respect to sexual transmission of HIV, adoption of less risky sexual behaviour and access to voluntary confidential testing for HIV and rapid diagnosis and treatment of other STIs remain the main lines of defence.

To ensure both safe blood for transfusion and reliable VCT that are cost-effective each process must be carefully controlled from beginning to end. Attention is needed to increase the pool of regular donors, the infrastructure of blood centres needs renewed investment, ad laboratories performing the testing need modern up-to-date equipment, access to accurate screening tests, and continuing professional development of their staff. To achieve this successfully the entire process must be managed and monitored within a total quality management system.
2. Framework of the workshop

The workshop described in this report was planned to address quality and biosafety issues with respect to HIV and hepatitis testing in both VCT and blood screening applications, as well as in confirmatory/reference laboratories.

The workshop was hosted by the Ukrainian Ministry of Health, and was generously accommodated by the Blood Transfusion Station of the Ukraine South-West Railways Company in Kiev. It was attended by selected participants from Belarus, the Republic of Moldova and Ukraine. Additionally, a number of observers from Ukrainian reference and research laboratories, blood banks and professional associations were present.

The workshop activities extended over three days. Presentations, group work sessions and discussions explored issues of laboratory design, staffing and equipment, as well as test kit evaluation and selection, testing algorithms, and process control and evaluation.

The activities of the workshop were facilitated greatly by the interpreters and by the kind hospitality of the staff of the Blood Transfusion Station.

3. Scope and purpose

The main objectives of the workshop were:

1. To upgrade testing performance for HIV and hepatitis B and C and enhance quality approaches in the laboratory through:
   a) good manufacturing practices in the laboratory
   b) quality standards and international requirements
   c) testing performance rating and cost-efficiency
   d) quality of testing strategies and diagnosis algorithm.

2. To improve biosafety procedures in laboratory practice, including:
   a) safety of the personnel
   b) appropriate use of equipment
   c) biological waste disposal.

4. Inaugural session

The workshop was opened in the presence of Dr Ludmila Muharskaia, Head of Disease Prevention Department, Ukraine Ministry of Health, and Dr Olga Stelmah, also from the Ukraine Ministry of Health.

Dr Paraschih, Medical Director of the Ukraine South-West Railways Blood Transfusion Station, where the workshop was being held, also welcomed everybody, and read a letter of greeting from Mr G. M. Kirpa, Minister of Transport of Ukraine and Director-General of
“Ukraliznytsya”. Mr Kirpa expressed his deep appreciation and welcome to the intercountry workshop. He noted the importance of this international forum for specialists in the diagnosis of one of the most severe diseases of the 21st century – HIV/AIDS. He stated that the Blood Transfusion Station of the South-West railways had been chosen as the venue because of its contemporary approach in blood transfusion, and added that it would become a suitable pilot site to implement modern ideas and technologies in screening and diagnosis of HIV infection. He hoped that the workshop, which would focus on best practice, and would be one more step forward in fighting HIV infection. Mr Kirpa’s message closed in wishing participants a fruitful time, and future successes in this honourable and essential work – the fight against disease.

5. Proceedings

5.1 Country reports

5.1.1 Belarus

The delegation from Belarus included the Head of the AIDS Diagnostic Laboratory of the Republic, the Head of the Serologic Infections Diagnostic Laboratory of the Republic Blood Transfusion Station and the Chief Epidemiologist of the Ministry of Health.

In Belarus, laboratories, blood transfusion centres, regional health care facilities, hygiene centres, epidemiological and public health care facilities are established in accordance with the plan approved by the Ministry of Health.

Laboratories are certified by the National Certification Body of the Republic of Belarus (State Committee for Standardization) which checks the compliance of laboratories against certification standards including the ability of a laboratory independently to conduct tests, the technical competence of its staff, and compliance with STB ISO/MEK 17025. Areas which are subject to certification include: serological tests, immunological studies, and molecular biological studies.

In Belarus there are registered societies of epidemiologists and microbiologists which also include laboratory doctors. Recently a society of laboratory doctors has been registered in the country.

Surveillance data on HIV, HBV and HCV are most complete for HIV, showing high rates particularly in IDUs, but also in pregnant women (Table 1).

<table>
<thead>
<tr>
<th>Table 1. Prevalence of markers in Belarus (1987–2003)</th>
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<tbody>
<tr>
<td>HIV</td>
</tr>
<tr>
<td>Blood donors</td>
</tr>
<tr>
<td>Pregnant women</td>
</tr>
<tr>
<td>IDU</td>
</tr>
</tbody>
</table>

HIV test kits must be certified in Belarus. The certification process includes laboratory tests employing standard serum panels from the Tarasevich Institute, Moscow and BBI panels. Only test kits that have been certified may be used for diagnostic purposes. Each manufactured lot is subject to the control by the reference laboratory before it is released for use. The purchase of
test kits and laboratory equipment is conducted through tender by Medteknika taking into account feasibility studies prepared by laboratory specialists.

There are 50 laboratories in Belarus which are engaged in the diagnosis of infectious diseases including HIV and viral hepatitis. The laboratories are tiered as follows: level I – screening laboratories, level II – confirmatory laboratories and level III – reference laboratories.

In accordance with national medical examination rules there are defined populations that are subject to HIV examination. Primary positive samples (repeat blood collection) are sent from screening to confirmatory laboratory and, in case of positive results, forwarded to the reference laboratory for immunoblotting.

HIV negative results are reported to the facility where the blood had been drawn. HIV positive results are reported to the epidemiological department.

External Quality Assessment is conducted through a quarterly distribution of coded samples which, depending on results, allow the assessment of laboratory performance.

5.1.2 The Republic of Moldova

The delegation from the Republic of Moldova included the Head of the AIDS Diagnostic and Reference Laboratory of the Republic Research Centre for Preventive Medicine of the Ministry of Health, the Head of the Blood borne Virus Diagnostic Laboratory of the Republic Blood Transfusion Centre and the Head of Serologic Laboratory of the Republic Dermato-venerological Dispensary.

In the Republic of Moldova, AIDS diagnostic laboratories do not need to be registered since they all function as part of the republican health care system.

The country has a commission for certification of all medical and healthcare facilities, which has been established by the Ministry of Health. In order to be certified, the laboratories that are involved in HIV and hepatitis testing must obtain permission from the Infection Control Commission of the Ministry of Health. Laboratory staff is not subject to special registration since they function in accordance with the duty roster of an institution which is in charge of laboratories performing HIV screening and diagnostic and those that test blood donors.

In the Republic of Moldova there are registered societies of laboratory technicians, immunologists and transfusiologists which are actively functioning. Their goal is to exchange views and information on different medical issues, to arrange conferences, symposia and seminars, to provide inter-laboratory quality control of HIV and hepatitis testing and to implement new methods of research based on the dissemination of the best laboratory practice.

Surveillance data on HIV, HBV and HCV are most complete for HIV, showing high rates particularly in IDUs (Table 2).
Currently only test kits registered in the country have been used for HIV and hepatitis (blood service) testing. For registration of test kits a Drug and Diagnostic Devices Commission has been set up under the Ministry of Health. Test kits for HIV are being evaluated at the AIDS Reference Laboratory of the Republic Research Centre for Preventive Medicine. The manufacturer provides for evaluation 3–5 sets of test kits accompanied by a package of documents containing the description of manufacturing conditions, quality parameters, etc. The use of a single BBI seroconversion panel forms part of the process for registration of test kits. The Commission has power to either register the test kit and define the area of application or to deny registration.

The same regulations apply for test kits for hepatitis. The only difference is that quality control testing is conducted at the Centre of Virology.

The decision to purchase test kits for HIV and hepatitis is made by way of tender and depends on the funds allocated by the Ministry of Health for that purpose.

Primary screening for HIV is conducted by 10 AIDS diagnostic laboratories. If the screening ELISA is reactive, the sample is re-tested (once or twice). If the second ELISA test shows that the sample is HIV reactive, a repeat blood sample is taken. If the repeat result is negative the test result of the initial sample is considered to be negative. If the second blood sample is also reactive both samples are sent to the reference laboratory where additional tests are conducted using other ELISAs and agglutination test kits – provided the test kits are available at the time. If necessary, immunoblotting may be done. If ELISA reactivities are weak the patient will have a repeat examination within 1–3 months.

For hepatitis B and C, donor blood is tested by ELISA at regional laboratories. If the sample is reactive for HBsAg, it is retested twice at the same place. If it is reproducibly reactive in at least one additional test, the blood sample is considered to be positive for HBsAg. In that case a confirmatory neutralization test is done to diagnose hepatitis B in the donor or patient.

If an anti-HCV screening test is reactive the strategy is the similar to that for HBs Ag, however, the confirmatory testing is not done in this situation because of financial constraints.

Panels for internal and external quality control are prepared at the reference laboratory by diluting blood samples with the high titres of anti-HIV, confirmed by immunoblotting, in donor blood serum, negative for HBs Ag, HIV, HCV and syphilis. Similar panels are being developed for HBsAg. Standard panels are not being purchased.

External quality assessment (EQA) is coordinated by the AIDS reference laboratory. The results from testing EQA samples for HIV are rapidly performed, and special meetings are held twice a year for the physicians of regional AIDS laboratories at which EQA results are discussed. There is no participation in international schemes currently.

Table 2. Prevalence of markers in the Republic of Moldova

<table>
<thead>
<tr>
<th></th>
<th>HIV</th>
<th>HBV</th>
<th>HCV</th>
</tr>
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<tbody>
<tr>
<td>Blood donors</td>
<td>0.036% (2003)</td>
<td>4.8–5%</td>
<td>2.0–2.5%</td>
</tr>
<tr>
<td>Pregnant women</td>
<td>Few cases</td>
<td>no data</td>
<td>no data</td>
</tr>
<tr>
<td>IDU</td>
<td>2.27% (2003)</td>
<td>no data</td>
<td>no data</td>
</tr>
<tr>
<td>Male-to-male sex</td>
<td>Rare cases</td>
<td>no data</td>
<td>no data</td>
</tr>
</tbody>
</table>
Confirmed diagnoses of HIV are reported through the Deputy Director-General of the Republic Research Centre for Preventive Medicine for organization of anti-epidemic arrangements. They are also reported to an infectious diseases physician who will perform a clinical assessment, developing a clinical management strategy and making a decision concerning hospitalization into a special AIDS facility where a patient may receive HAART.

5.1.3 Ukraine

The delegation from Ukraine included two senior representatives of the Ministry of Health and other leading specialists in laboratory diagnosis, blood transfusion and epidemiology.

HIV, HBV and HCV infections are established in Ukraine. To ensure the safety of blood transfusion, a number of measures are being taken, including: selection of donors; development of autologous donation; restricting the use of each donation to a single recipient, inactivation procedures for plasma and blood products; six month quarantine of plasma; and restricting the number of transfusions. Additional safety measures include the introduction of mandatory laboratory screening, mostly by EIA, of donated blood for markers of the causative agents of HIV, HBV, HCV and syphilis.

Serological surveys for anti-HIV are conducted within the framework of screening of several population groups (Table 3). The populations screened for anti-HIV are currently defined in the Law of Ukraine, the regulatory instruments providing a framework for voluntary HIV testing, including confidentiality of the testing results.

<table>
<thead>
<tr>
<th>Population groups tested</th>
<th>2001</th>
<th>2002</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Individuals tested</td>
<td>Anti-HIV positive</td>
</tr>
<tr>
<td>Citizens of Ukraine, total</td>
<td>2 145 671</td>
<td>12 713</td>
</tr>
<tr>
<td>Sexual contact with HIV+</td>
<td>4 661</td>
<td>495</td>
</tr>
<tr>
<td>Children of HIV+ mothers</td>
<td>9 646</td>
<td>607</td>
</tr>
<tr>
<td>Injecting drug users</td>
<td>40 674</td>
<td>4 535</td>
</tr>
<tr>
<td>Patients with STDs</td>
<td>88 482</td>
<td>673</td>
</tr>
<tr>
<td>Multiple sex partners</td>
<td>21 425</td>
<td>191</td>
</tr>
<tr>
<td>Donors: blood and tissues</td>
<td>979 319</td>
<td>816</td>
</tr>
<tr>
<td>Pregnant women</td>
<td>599 112</td>
<td>1 325</td>
</tr>
<tr>
<td>Prison inmates</td>
<td>8 508</td>
<td>577</td>
</tr>
<tr>
<td>Clinical indication</td>
<td>129 967</td>
<td>1 747</td>
</tr>
<tr>
<td>Voluntary confidential tests</td>
<td>31 667</td>
<td>875</td>
</tr>
<tr>
<td>Medical contacts</td>
<td>5 370</td>
<td>30</td>
</tr>
<tr>
<td>Other</td>
<td>226 840</td>
<td>842</td>
</tr>
<tr>
<td>Foreigners, total</td>
<td>5 367</td>
<td>30</td>
</tr>
<tr>
<td><strong>Total individuals tested</strong></td>
<td><strong>2 151 038</strong></td>
<td><strong>12 743</strong></td>
</tr>
</tbody>
</table>

Testing is funded by the Government of Ukraine to meet the needs of health care facilities, through the purchase and distribution of test kits to perform screening and confirmatory analysis in the following circumstances: a) donors and pregnant women for anti-HIV 1/2, including
confirmatory tests using immunoblot assay; b) hepatitis B surface antigen (HBsAg); and c) donors for hepatitis C antibodies.

Ukraine is testing all donated blood for HIV, HBV and HCV. Domestic production of EIA test kits has also been established. Initially, anti-HIV testing was performed by the blood transfusion service laboratories, and by those reporting to the Oblast and municipal AIDS Prevention and Control Centres. However, some testing is now performed also by the municipal Sanitary and Epidemiological Stations (SES), and by other healthcare facilities. Facilities for confirmatory testing are available through laboratories reporting to the Regional AIDS Control Centres. They follow a confirmatory algorithm adopted in Ukraine. The algorithm is based on WHO Strategy III. Primary screening for HIV antibodies employs an EIA kits registered in Ukraine, and whose sensitivity and specificity indices comply with WHO recommendations. The strategy uses a combination of EIA test systems which differ in design (direct, indirect, immunometric, competitive) from those used as screening tests (Figure 1).

Fig. 1. Flow chart of testing serum for HIV antibodies (Ukraine)

Primary testing
Blood serum samples tested by the HIV-infection diagnostic laboratories with the use of screening EIA test systems

Stage 1 of confirmatory tests
Regional serum samples delivered to the regional confirmatory laboratories which conduct testing by means of two alternative EIA systems

Stage 2 of confirmatory tests – making the diagnosis of “HIV infection”
A newly drawn serum sample tested with the use of immunoblot or a combination of three alternative EIA test systems

HBV screening continues to be implemented in Ukraine following old directives. This legislation covers HBsAg testing of blood donors, pregnant women, and a broad range of groups at risk of HBV infection. Recent changes in HBV epidemiology in Ukraine indicate the need for revised guidance on screening. The main HBV marker sought is HBsAg, though other markers are employed in clinical work-ups. Confirmation of HBsAg through neutralisation is not routinely practiced due mostly to financial constraints.

HCV screening is mandated only for blood donations, though local decisions have been taken to include other groups. Some infectious diseases hospitals provide testing of in-patients with acute viral hepatitis or chronic liver diseases. A strategy HCV confirmatory testing has not been developed so far. Wider availability of HCV testing and related confirmatory testing is constrained by limited financial resources.

The quality of serological testing for HIV, HBV and HCV is assured through a number of measures. Only those kits officially registered for diagnostic use may be used, which should ensure high sensitivity and specificity. Bulk purchase of registered test kits is done through a tendering process, for which the specifications are drawn up by a group of leading experts, who
also assess the bids. Preference is given to those products with the best performance characteristics, including good performance in clinical trials and independent evaluations such as those done by WHO. Post-market surveillance of devices is conducted by “The Centre of Immunobiological Products” of the Ministry of Health of Ukraine. Additional quality measures include the implementation of “quality control systems” by the majority of diagnostic laboratories and both internal and external quality control of laboratory tests are being established.

5.2 Presentations

5.2.1 Testing requirements

Introduction to quality assurance

An overview was given of the concept and utility of quality management and its implementation in a systematic manner. The five key elements of a quality system, comprising organizational management, standards, training, documentation and assessment, were introduced. Reliably converting an input, such as a blood donation or diagnostic specimen, into a quality output, exemplified by safe blood or a correct diagnosis, may be achieved only by understanding and dissecting all the processes and activities involved. In order to establish a successful quality system both managerial and technical elements must be addressed. The system needs to be developed against a backdrop of recognized guidelines and standards. Mechanisms for evaluation, preventive and corrective action are essential for the desired effect of continuous improvement. Although quality costs, poor quality costs more.

Quality of test kits

WHO has managed evaluations of HIV kits through the WHO Collaborating Centre in Antwerp since 1988. In 1998 a similar arrangement was established for the evaluation of HBsAg and HCV kits at the WHO Collaborating Centre at the United Kingdom Health Protection Agency laboratories in London. In each case a panel of negative and positive specimens has been assembled with broad global representation. Several commercial seroconversion panels are also included for each marker. Specimens are handled to minimize freeze-thaw cycles and are kept frozen in small aliquots to ensure they remain in good condition.

A brief review of recent findings was given, including sensitivity and specificity of 11 HIV rapid test devices (RTDs) and 2 EIAs. Nearly all RTDs achieved >98% sensitivity, several with 100%, and their performance with seroconversion panels generally came close to that of the third generation EIA being used as the reference assay. Their specificity was also good, several attaining 100%, though one achieved only 95.6%. Of seven RTDs challenged with a whole blood panel, three achieved 100% accuracy. For HBsAg 5 of 11 RTDs attained 100% accuracy on the main panel, but sensitivity was generally less than the reference EIA tests on seroconversion panels. Satisfactory results were obtained also with 3 EIAs studied. Of eight anti-HCV RTDs evaluated four achieved 100% sensitivity, and two 100% specificity; one device was <95% sensitive and another was <95% specific. The accuracy of each of five EIAs evaluated was generally good. Performance on seroconversion panels was more variable.

Full details of recent test kit evaluations may be found on the WHO web site at: http://www.who.int/bct/Main_areas_of_work/BTS/HIV_Diagnostics/HIV_Test_Kit_Evaluation.htm#Reports
Selection of test kits
During this session issues relating to the selection of kits were discussed in more detail, as were the theoretical and analytical aspects of the evaluation of test kits. Matters considered ranged from questions of local suitability, through the contrast between evaluation and formal licensing of products, to measures that may be taken at international, national and national levels to ensure the sustained quality of test kits as new lots are prepared and distributed.

Evaluation of test kits is a key first step in ensuring that test kits used in diagnostic or blood screening laboratories are of a high quality. Evaluations must be performed in a quality environment. Particular attention is needed to ensure suitable and fully documented panels of specimens assembled in sufficient numbers for the findings to have statistical validity, and with a view to minimize bias in favour, or against, particular test kits. The panels must be stored in appropriate volumes to minimize freeze-thawing at temperatures of –25°C or colder.

However excellent the performance of a diagnostic test or piece of equipment may prove when examined under ideal evaluation conditions, various other factors must be considered before local selection and use. These include infrastructure (electricity, water, efficient disposal of waste product); technology (kind of tests needed for screening of blood or VCT); turnaround times; training of qualified personnel in the use and maintenance of equipment; documentation of equipment; stock maintenance; security of supply; and preventive maintenance.

Appropriate testing strategies
A defined, consistent and validated testing strategy is essential to reliable diagnosis of HIV, HBV and HCV. WHO has issued revised recommendations for the selection and use of HIV antibody tests. The choice of strategy to be used to provide reliable results in a cost-effective manner needs to be based on the objective of testing and the prevalence of the infection in the target population. Emphasis needs to be placed on selection of the most appropriate test kit, or combination, to suit local conditions. Combinations may include EIAs, RTDs and ‘confirmatory’ tests such as immunoblot.

Diagnostic investigations: case studies
General principles underlying the theory, development and applications of testing strategies were explained. To illustrate an established structured testing strategy in practical use four difficult diagnoses made at the Health Protection Agency’s laboratories in London were described in some detail. The use of anti-HIV EIA kits, p24Ag EIA, Western blot and PCR investigations were discussed. Participants were warned to be wary of weak reactions, even if in several tests, and always to seek a follow-up specimen to confirm initial positive findings and to resolve indeterminate results.

Documentation and standard operating procedures (SOPs)
A comprehensive review of documentation and SOPs was given. Within a quality system documentation is defined as all written instructions, procedures, controls, results and other records involved in providing a service or manufacturing a product. It provides the tools for continuous improvement.

Document control is needed to ensure formal control of authorized documents including their issue, use and review. There is a range of different types of documentation, including: policies; manuals, standard operating procedures, specifications, forms, standards, records and labels.
Documentation may be stratified according to function, with a foundation of records, standards and other supporting procedures.

SOPs are written instructions for stepwise performance of a specific procedure. These should describe the sequence of operation, the method, equipment to be used, cross-referenced SOPs, and details of the records to be kept. Recommendations were given concerning the process of preparing, editing and validating a new SOP, followed by its distribution and associated training and certification of staff to perform that procedure, leading to its implementation.

A mechanism for regular review and archive of previous versions and master copies of all SOPs needs to be established.

**Monitoring of test performance**

Several means of monitoring test kit performance were presented, such as the External Quality Assessment (EQA) schemes and Internal Quality Assurance (IQA) programmes. Checking the performance of new production lots of reagents is also important. However, the above three measures are practiced only intermittently and there is a need to monitor the performance of assay kits on a regular basis. The prescribed use and interpretation of the manufacturer’s internal kit controls, as supplied with the kit, is essential to good laboratory practice. In addition, control specimens that are independent of the manufacturer’s controls provide enhanced and independent evaluation.

Quality Control (QC) Programmes employ standards or QC samples that can be used to monitor the day-to-day or run-to-run performance of an assay, and analysis of the composite and ongoing results. QCs provide assurance that a test is performing appropriately and is producing consistent results. To assure the effectiveness of QCs the results must be reviewed immediately after each run. Testing procedures should be investigated when any variation or potential variation is identified.

The use of external controls, i.e. external to the kit, is imperative because they are the only consistent gauge of assay performance outside the assay itself. An external control may be referred to as a QC Sample. They should be tested on every run in addition to the kit controls. Unlike the kit controls which change with each new lot number, the same lot of QC sample should be used for a length of time, preferably for at least twelve months. This can provide important longitudinal information on assay performance and can be used to monitor lot to lot variation between kits.

When QCs are manufactured “in-house”, at least a year’s supply should be produced and then stored appropriately. The QC sample can also be used in combination with the kit controls to validate runs. In this case a predetermined range, usually chosen on a statistical basis, should be established for the value of the QC sample. The run is valid if results fall within the specified range. Each laboratory should establish their own QC validation range and criteria.

Practical approaches to monitoring and interpreting QC data, including the use of control charts and the application of Westgard rules were described, as well as potential causes and remedial actions for systematic/random variation.
5.2.2 Laboratory management

Biosafety in the laboratory
Many countries have legislation to protect health and ensure safety of workers at the workplace. If biohazards are classified by risk group, laboratory work falls into four categories.

Details on the types of laboratory, their construction and ventilation, laboratory practices and safety equipment needed to perform work at each of the existing four biosafety levels were described. General practices to prevent laboratory-acquired infections were presented, as were specific items of protective equipment including gloves, gowns, safety spectacles, etc. and equipment such as biological safety cabinets.

The appointment of a safety officer and creation of departmental safety committee is needed to keep activities under review and formulate safety policies, consider new activities, undertake internal safety audits, communicate safety information to other members of staff, and draw important safety matters to the attention of senior management.

Further information is available on the WHO web site in the following two documents:
- WHO Laboratory Bio-safety Manual 2nd ed. (revised)
  http://www.who.int/csr/resources/publications/biosafety/Labbiosafety.pdf
- WHO Safety in Health-Care Laboratories

Waste management
The challenges of careful management of laboratory waste, rendering it safe and disposing of it in an environmentally-friendly manner were discussed. As with all other areas of laboratory activity there needs to be a comprehensive system that tackles issues of responsibilities and resources available to manage waste; minimize the quantity and to segregate it into different categories whose disposal will differ; collection, handling, storage before treatment/decontamination, and the specific means of disposal.

In virtually all cases there are likely to be national legal requirements and policies, regulated by a responsible authority. In many legal frameworks the laboratory director will be held accountable if, through their negligence, the laboratory’s waste represents an uncontrolled hazard to their staff, staff of other entities that may be involved in the process of the treatment or disposal of the waste, or to others.

Specific details of approaches to the disposal of bio-hazardous, chemical and radioactive waste were discussed. The use of consistent and clear labelling of different types of waste is a requirement to safe waste management. Training of all staff in the safe disposal of waste is necessary.

Laboratory facilities
Laboratory design, infrastructure and equipment were covered. Laboratories can present different level of hazardous areas that require specific organization and design, to minimize the risk exposure. When refurbishing current facilities several key objectives should be considered, such as environment to suit work requirements, prevailing climactic conditions, running costs and safety.
In view of the pathogenic organisms in the laboratory a prime need is to make the facility safe and secure. In addition to the barrier measures to contain the organism and protect the personnel, tertiary protection that separates the contents of the laboratory from the external environment needs to be considered. Zoning of the entire laboratory facility such that the area around the entrance is safe and the most hazardous work is most distant from the facility entrance is recommended. Ventilation needs to be designed to avoid aerosol spread of pathogens to workers within the facility and also to remove any risk of escape through ventilation and safety cabinet exhausts.

Sufficient and suitable space should be designed for staff, equipment and storage of consumables, chemicals, specimens, records and waste. Equipment and furnishings must be fit for purpose and consideration should be given to their construction materials and position. Plans should consider routes of evacuation in the case of emergencies. Services such as water, drainage, electricity, lighting and gas need to be secure and safe, with good access to emergency shut-off valves. Consideration should be given to the need for emergency provisions.

**Human resources**

Laboratory management should ensure the sufficient numbers of staff with the appropriate education and training to meet the demands of the service. Organization charts that define the functional structure and management of the laboratory need to be prepared and made available. Laboratory’s place in a parent organisation is to be clearly identified as well as the precise lines of responsibility and accountability.

Laboratories should have in place formal procedures to cover all aspects of the management of human resources including recruitment and selection, induction of new staff, records, performance reviews, training and education, grievance and disciplinary procedures. The required tasks of quality manager, training officer and health and safety officer are often filled in all but the largest laboratories by staff in other operational service posts taking on additional responsibilities.

**Equipment maintenance**

The first step to ensure that laboratory performance does not suffer due to equipment failure is to prepare an inventory of equipment critical to the function of the laboratory. To assist, it is advisable to identify the critical processes and activities, including: specimen quality; kit and reagent stability, liquid handling, EIA processing and data handling. Critical equipment will include freezers, refrigerators, cold rooms, centrifuges, micropipettes, EIA plate washers and readers, IT equipment and software, water baths and incubators.

Prevention will minimize the disruption and delay that is usually associated with a breakdown. Consequently, it is advisable to have in place a regular schedule of preventive maintenance tasks defined for each piece of equipment. Their frequency may be advised by the manufacturer, and will probably include daily, weekly and monthly tasks. As with any other task, detailed records must be kept so that the quality system might be audited.

**Procurement of kits and equipment**

Procurement of appropriate kits and equipment needs to be performed on a centralized regular basis, for proper monitoring, cost effectiveness and avoiding delivery gaps.
The World Health Organization has developed a programme of bulk purchase of test kits for HIV diagnosis, recently extended also to hepatitis B and C. This initiative permits economies of scale and very competitive prices for users. It supports procurement for the most cost-effective test kits in the appropriate quantity, using reliable suppliers of high quality products. The supply, shelf life, storage and distribution of the kits are carefully managed and the performance of suppliers is monitored.

For more information you should contact the country WHO Representative or the WHO Regional Office for Europe.

5.3 Visit to blood transfusion station

Thanks to the hospitality of the director of the host blood transfusion station all participants were taken on a tour of the recently refurbished facilities, including the microbiology and blood screening laboratory areas. Staff of the centre was extremely helpful in showing the participants around and responding to the many questions.

5.4 Group work

5.4.1 Determination of quality of reagents and equipment

A short presentation was given on the development and manufacture of quality control specimens.

Issues identified included inadequate financial resources and, in many cases, unsatisfactory facilities and obsolete equipment. Additionally, it was felt that the regulatory framework could be improved. Unified quality control systems (both internal and external) are often lacking, and training and retraining of middle-level personnel is not available. Some deficiencies in the regulatory framework were also identified.

In addition to remedying the matters mentioned above, it was felt that strengthening of state control of test kits being placed on the market is necessary, as well as the use of internal quality controls to monitor assay performance and employment of highly qualified personnel, including technicians for expert servicing of equipment.

5.4.2 Selection of test kits and test strategies

Participants indicated that the WHO guidelines on testing strategies were being followed.

In some cases Strategy 1 was in use for screening blood donations but, in other situations Strategy 2 or 3 was being applied when the donor was being informed of their HIV status. In “diagnostic” investigations Strategy 3 was in use in some settings. Tests for surveillance purposes followed Strategy 2.

There was general agreement that laboratory investigation of children born to HIV-infected mothers was suboptimal, particularly because of inadequate resources for PCR investigation.

Strategies for the investigation of viral hepatitis were poorly developed. For blood donation Strategy 1 alone was applied.
Concern was expressed about the uncertain quality of diagnosis in the countries represented and there was a consensus that: reference panels should be made available to laboratories for experience and training, quality assessment measures such as external performance assessment and quality control monitoring need to be strengthened, and more expert reference laboratories need to be developed and adequately resourced.

6. Recommendations

To participants:

1. All participants should support the implementation of quality systems in their laboratories, through the development and implementation of standard operating procedures (SOP). In addition, existing biosafety practices should be reviewed and upgraded where necessary.

2. Participants should monitor the quality of test kits and testing procedures, which would include introduction of quality control specimens and participation in external quality control and assessment schemes, in laboratories undertaking testing for HIV and viral hepatitis in blood transfusion services, reference centres, clinics, hospitals and other settings.

3. Participants should provide feedback at national level to Ministry of Health and other relevant institutions and professional associations concerning all issues discussed during the workshop.

To Member States:

1. Member States are encouraged to continue to review in the light of current international practice their existing regulatory framework that governs the organization and functioning of laboratories.

2. Member States should support the development of appropriate infrastructure and laboratory networks to sustain implementation of national quality systems for laboratories and blood transfusion services.

3. The availability of an adequate choice of quality reagents for HIV and viral hepatitis screening and confirmatory testing should be strengthened through the full involvement of expert reference and blood screening practitioners in the associated processes of evaluation, registration and procurement.

4. Significant benefit would be derived from appointing and resourcing a national centre to coordinate and support quality assessment initiatives such as external quality assessment and the provision of specimens for quality control monitoring. Such a centre could also be charged with responsibility to advocate best quality practices and provide appropriate training and educational materials.

5. Structured training for all staff is considered a mandatory requirement of the capacity building process.
To WHO:

1. WHO should continue to advocate at the highest level in Member States the importance of quality management systems and biosafety in the laboratory and blood transfusion services.

2. WHO should provide assistance in the development of training programmes at all levels to strengthen the quality of HIV and hepatitis testing and bio-safety procedures in the laboratory. A follow-up technical seminar on testing strategies for HIV and hepatitis in the light of novel technologies should be considered in the near future.

3. WHO should continue to provide technical information and facilitate the provision of reference materials and associated documentation to enable the strengthening of quality systems in blood transfusion services, reference and clinical laboratories performing screening and confirmatory testing for HIV and viral hepatitis.
Annex 1

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