ESSAY ON MICROFLUIDICS POINT OF CARE FOR INFECTIOUS DISEASES

BY

OKON MILDRED

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WHAT IS MICROFLUIDICS

Microfluidics is the word fluidics with the prefix micro- attached to it. Therefore, we’ re looking at the manipulation of fluid at the micro scale, often flowing through channels. It could be referred to flow with a channel dimension less than 1,000 μm . Microfluidics and nanofluidics is a field of science that operates in the micrometer and nanometer scale. A microfluidic– nanofluidic device consists of components such as valves, pumps and mixers for manipulating and transporting the fluid at this scale

Advantages of Microfluidics

A microfluidic device does have a smaller footprint than a huge machine in a lab, but it also uses a lot less fluid too. It is beneficial because it uses less costly chemicals and reagents,lesser waste generation, but it's also attractive due to the physics happening at the micro scale. Matter does behave differently, most evidently in the way liquids flow i.e turbulent and laminar flow.

Application

Because of intensive developments in recent years, the microfluidic system has become a powerful tool for biological analysis. Entire analytic protocols including sample pretreatment, sample/reagent manipulation, separation, reaction, and detection can be integrated into a single chip platform. A lot of demonstrations on the diagnostic applications related to genes, proteins, and cells have been reported because of their advantages associated with miniaturization, automation, sensitivity and specificity. This can be seen in areas like

Biological studies

Microfluidic systems are an ideal platform for biological studies due to their advantages such as low sample requirements, high surface area, and reduced system footprint. The techniques have been used to study cells as well as whole organisms. They have simplified the otherwise laborious tasks such as flow control, stimuli delivery, and animal handling.

Stem cell research

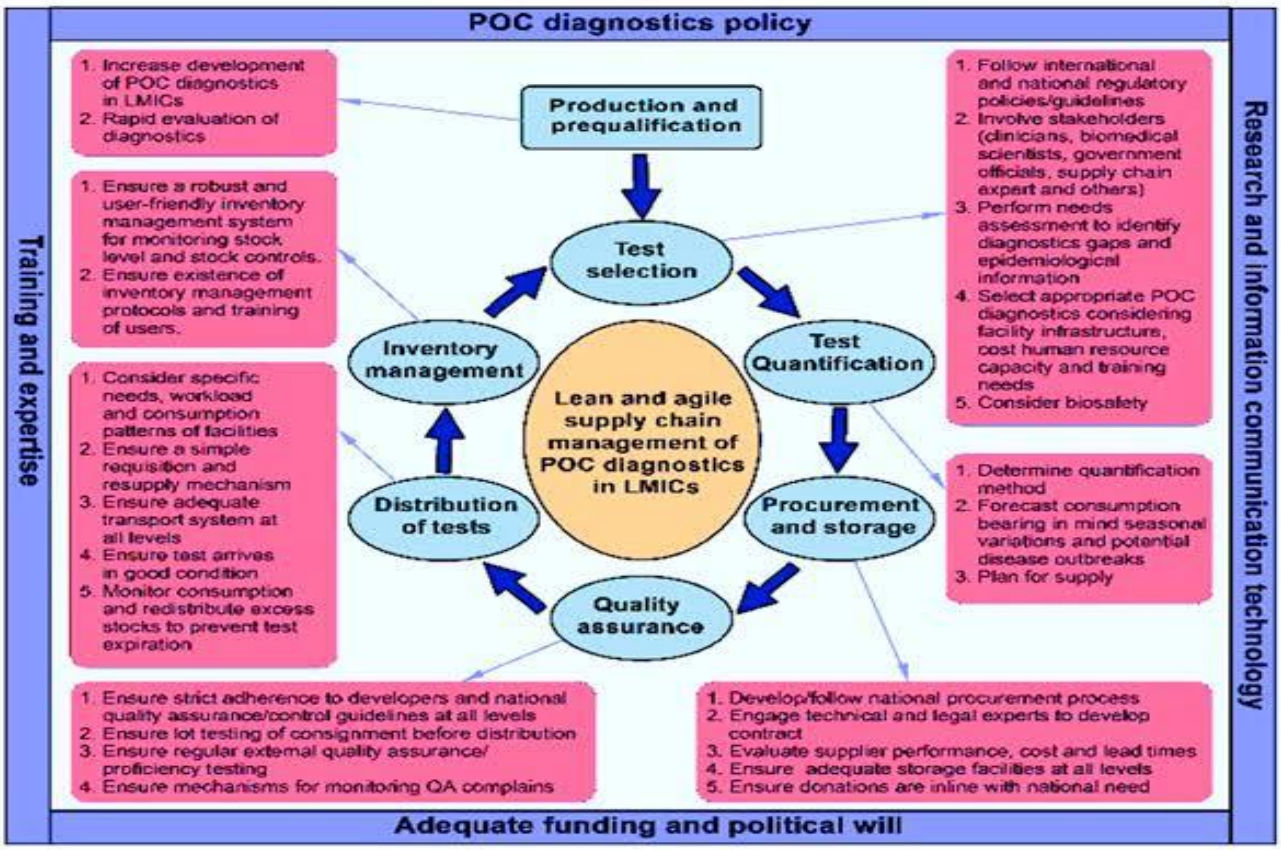
Stem cell research has immensely benefitted from advances in microfluidic technology. Miniaturization has enabled deeper stem cell analyses compared to traditional methods.

Integration of this technology with tools such as fluorescent microscopy offers a more systematic way of studying stem cells and also exhibits promising medical applications.

POINT OF CARE DEVICES ON MICROFLUIDIC PLATFORMS

Point-of-care (POC) diagnostic devices have been predicted to provide a boon in health care especially in the diagnosis and detection of diseases. POC devices have been found to have many advantages like a rapid and precise response, portability, low cost, and non-requirement of specialized equipment. The major objective of a POC diagnostic research is to develop a chip-based, self-containing miniaturized device that can be used to examine different analytes in complex samples. Further, the integration of microfluidics (MF) with advanced biosensor technologies is likely to result in improved POC diagnostics.

Microfluidic pathogen detection chips are an excellent choice in this regard. Mass production of these pathogen diagnostics chips is financially affordable. The chips are highly sensitive and can be designed with the desired level of specificity. They require minimal training and have proven to have a short sample-to-result turnaround. In addition, these portable and handheld chips can be automated without the need for expensive instrumentations.



CLINICAL INTERVENTION FOR INFECTIOUS DISEASES

Many infectious diseases have similar signs and symptoms.The efficient treatment of most diseases requires first that they be accurately diagnosed. Often the diagnosis is made on the basis of clinical symptoms and signs, but the imprecision of this method for many conditions is increasingly recognized. There is an urgent need for new, or improved, sensitive and specific diagnostic tests for many infectious and chronic diseases, that are both simple to use and cheap.

Types of intervention

Interventions can be classified into two broad categories: (1) preventive interventions are those that prevent disease from occurring and thus reduce the incidence (new cases) of disease, and (2) therapeutic interventions are those that treat, mitigate, or postpone the effects of disease, once it is under way, and thus reduce the case fatality rate or reduce the disability or morbidity associated with a disease. Some interventions may have both effects

Preventive interventions

a) Vaccines

Vaccines are administered to individuals, usually before they have encountered the infectious agent against which the vaccine is targeted, in order to protect them when they are naturally exposed to the agent. Many are among the most cost-effective interventions, because, after a single dose or a series of doses of the vaccine, an individual may acquire long-term protection against the agent. Not all vaccines are targeted at persons without previous exposure to the infectious agent.

b) Nutritional interventions

Food and nutrition are major determinants of human health and disease. Particularly in low-income countries and deprived populations in middle-income countries, under-nutrition remains a major cause of disease. Severe malnutrition, such as kwashiorkor or marasmus, is life-threatening, but milder forms of malnutrition are major risk factors that adversely influence the susceptibility to, and the outcome of, many infectious and other diseases, as well as cognitive development. In addition to calorie and protein deficiencies, specific deficiencies in micronutrients, such as iron, folate, zinc, iodine, and vitamin A, may be important determinants of severe diseases.

c) Education and behaviour change

Some interventions directed at preventing disease are based solely upon changing human behaviour (for example, anti-smoking campaigns or campaigns to promote breastfeeding). Nearly all health interventions must have an associated educational component for their effective deployment, but the extent of educational effort required ranges from the provision of simple information.

d)

e) Vector and intermediate host control

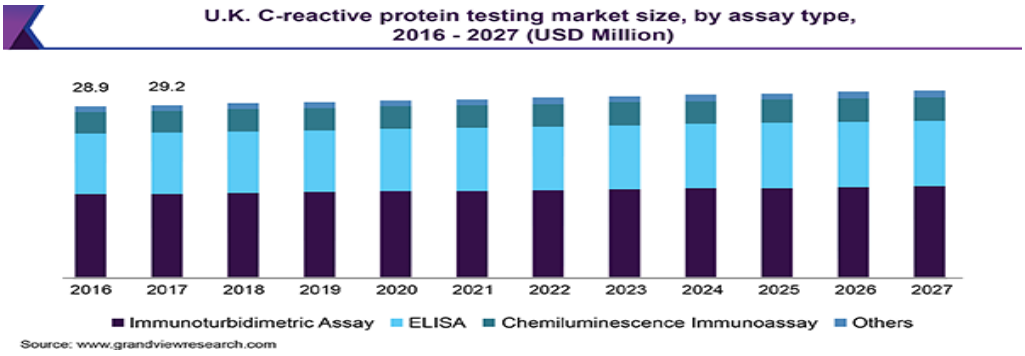
Some major communicable diseases in developing countries depend on vector and intermediate hosts for their transmission. For different infections, the vectors include mosquitoes, tsetse flies,

triatomine bugs, sandflies, ticks, and snails. There are a wide variety of control measures to reduce transmission of these infections through attacking the vectors or the reservoirs of infection. Most interventions require a good understanding of the vector or intermediate host, its life cycle, and the and so on .

Therapeutic interventions

a) Treatment of infectious diseases

The mechanism of action of a drug used for disease control will influence the design of field trials to evaluate its impact. Most drugs employed against infectious disease are used to kill or inhibit the replication or spread of the pathogen in the host. Strategies for disease control that use such agents may involve case detection (which requires an appropriate case definition and a diagnostic method), followed by treatment that is designed to reduce morbidity.



POTENTIAL FOR POINT OF CARE FOR INFECTIOUS DISEASES

Point-of-care tests (POCTs) play an important role in bridging the gap between centralized laboratory diagnostics and peripheral healthcare service providers. Particularly in infectious diseases such as HIV/AIDS and TB where early detection is imperative to improve disease outcome, uptake of an accurate test that is simple, rapid and robust can significantly alter the epidemiology and control of the disease. However, a good POCT can only serve its full potential when adopted in a comprehensive programmatic context linking patients to on-site case management. Immunochromatographic lateral flow devices for detection of antibody or antigen currently dominate available POCTs, and development of such devices has relied on the discovery and optimization of definitive biomarkers suitable for such platforms. In the future, however, there will be an increasing need to develop cost-effective POCTs that address

biomarkers that are well established in laboratory settings but are not currently amenable to point-of-care, such as molecular tests for drug resistance in TB and viral load in HIV and viral hepatitis

Point of Care Testing (POCT) is a testing system that provides beneficial and helpful information for diagnosis and treatment through real-time testing at the bedside. Therefore, POCT has high utility value in the field of infectious diseases as a rapid test that provides, within the consultation hours, useful information for initial treatment. Infectious disease rapid test kits are commercially available for a wide variety of prophlogistic pathogen targets, including bacterial, viral, fungal, protozoal, and other disease agents. One of these kits is immunochromatography assay (ICA), a measuring method used as POCT that is easy to operate, wherein even physicians and nurses can conduct the test.Serodiagnostic method has been adjunctively used in medical practice in Japan for early clinical diagnosis of deep mycosis as a means to determine treatments.

POC TECHNIQUES AND IT' S APPLICATION IN CLINICAL SETTINGS

Point-of-care (POC) tests are laboratory tests designed to be used directly at the site of patient care, which may comprise physicians' offices, outpatient clinics, intensive-care units, emergency rooms, hospital laboratories, and even patients' homes. Such broad availability of diagnostic tests needs systems that are accessible to personnel without specific laboratory medicine training, and allows quicker delivery of results that directly influence the clinical decision. In the last 20 years, the availability and use of POC tests have greatly increased and expanded to all fields of medicine, so that a significant proportion of laboratory testing is currently conducted at the point of care.

POC tests need easily obtained samples such as urine, blood, saliva, or nasopharyngeal swabs. Although the use of these tests does not require laboratory personnel, performance is clearly linked to the experience of the operator

APPLICATIONS

A) Group A Streptococcal Rapid Test

Group A streptococcus is the most frequent aetiology of bacterial pharyngitis, and may cause 5– 10% of pharyngitis cases in adults and up to 30% of pharyngitis cases in paediatric patients. Antibiotic therapy is mainly aimed at preventing acute rheumatic fever and suppurative complications such as peritonsillar abscesses. Although clinical scores have been used to estimate the probability of streptococcal pharyngitis , microbiological assays are needed, as clinical presentation alone does not allow clinicians to reliably discriminate bacterial and viral aetiologies. Throat swab culture on a blood agar plate remains the reference standard. Since the 1980s, several rapid tests targeting the group A carbohydrate antigen of Streptococcus pyogenes have been developed. The first assays using agglutination techniques were replaced by enzyme immunoassays and, more recently, immunochromatographic tests, with a concomitant increase in sensitivity [19] (Table 1). Despite the relative simplicity of these tests, sensitivity has been linked to the experience of the operator [13]. False-negative rapid test results are not systematically explainable by low-level carriage of streptococci [20]. The excellent specificity, commonly higher than 95% [19], allows treatment to be started in the case of a positive test result. Further benefits of immediate-onset antibiotic therapy are an earlier decrease in infectivity and a probable reduction in suppurative complications or at least in their severity [17]. Thus, although the cost of immunochromatography may be slightly higher than that of culture, this POC test is considered to be cost-effective. No further decrease in the acute rheumatic fever rate is expected with rapid tests, as antibiotic therapy may be safely delayed until 9 days after symptom onset [19]. The wide availability of rapid streptococcal tests has led to a substantial reduction in antibiotic prescriptions as compared with the period before their implementation [21], thus potentially contributing to prevention of the emergence of antibiotic resistance. Current recommendations advise confirmation of a negative test result with agar plate cultures, at least for children [17]. The lower frequency of streptococcal pharyngitis and the rarity of acute rheumatic fever in adults may lead to avoid performing culture in this subgroup of patients, at least when the pretest probability of bacterial pharyngitis is low [18]. Not performing cultures implies a loss of follow-up for antibiotic resistance, which is currently not relevant for penicillin, but is an emerging issue for macrolides [22]. Moreover, the aetiological agent of pharyngitis will not be identified if it is a less common agent, such as group B or group G streptococcus.

Pneumococcal Urinary Antigen Test

Community-acquired pneumonia (CAP) is a common disease, and represents the most frequent infectious cause of mortality in industrialized countries. The aetiology of CAP frequently remains undetermined, mainly because of the broad differential diagnosis and the low yield of standard microbiological tests (i.e. sputum examination and culture, and blood cultures). Severe CAP generally justifies a more extensive attempt at aetiological diagnosis [23]. The availability of POC tests may allow clinicians to safely restrict their initial empirical therapy and so help to prevent unnecessary antibiotic use contributing to resistance.

Legionella Urinary Antigen Test

Legionella pneumophila was first recognized in 1976 in the setting of a localized major outbreak. Standard cultures for diagnosis of this fastidious organism usually need 2– 7 days, and seroconversion may take several weeks . Soon after recognition of the organism, diagnostic tests based on specific detection of a lipopolysaccharide portion of Legionella cell wall antigen in urine became available . The broad use of such assays transformed the diagnosis of the disease, allowing rapid detection of the pathogen, as early as 1 day after onset of symptoms. This easier diagnosis may contribute to the observed global increase in the incidence of legionellosis: cases detected by the urinary antigen increased from 15% in 1995 to 33% in 1998, and to more than 90% in 2006

Detection of Group B Streptococci

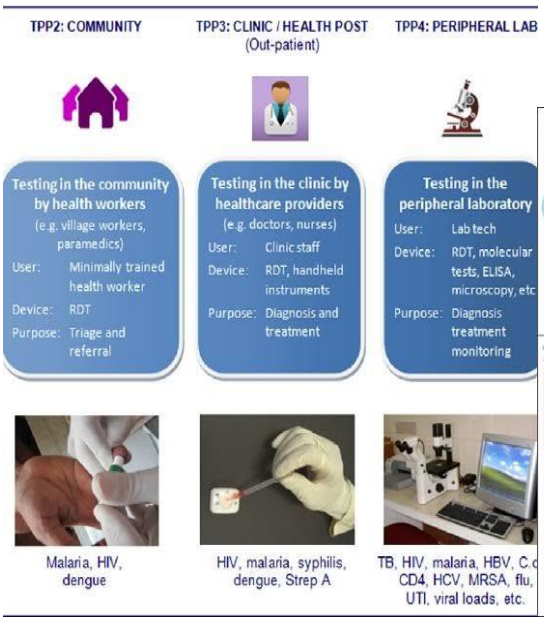
Group B streptococcal (GBS) disease is a leading cause of neonatal morbidity and mortality; rectal and/or vaginal colonization of the mother may lead to vertical transmission of Streptococcus agalactiae to the newborn during labour. Early-onset neonatal disease is efficiently prevented by intrapartum antibiotics. The common use of these new-generation POC tests will not completely replace culture, as antibiotic susceptibility testing will still be needed, at least for patients with severe β-lactam allergy, for whom macrolides and clindamycin represent the best treatment options. Indeed, although group B streptococci are consistently sensitive to penicillin, resistance to these alternative treatments is increasing.

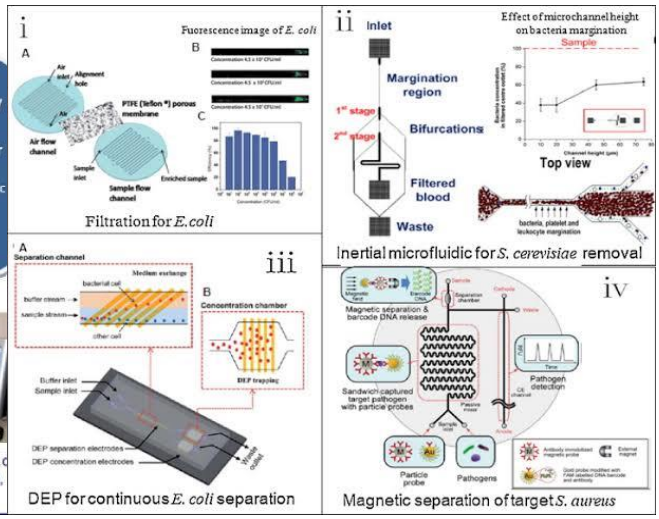
POC Test for Chlamydia trachomatis Infection

C. trachomatis is the most common bacterial sexually transmitted disease worldwide. Most infected patients remain asymptomatic, and high rates of infection have been observed in women from several European settings. Systematic screening programmes or detection based on risk factors may decrease disease transmission and prevent long-term complications, which mainly include pelvic inflammatory disease, subsequent infertility, ectopic pregnancy, and miscarriage. Molecular amplification tests replaced culture of urethral/cervical swabs as the diagnostic reference standard because of their higher sensitivity and better acceptability when performed on urine

Malaria Rapid Tests

Malaria remains a leading cause of death among infectious diseases worldwide, and one of the most severe causes of fever for travellers returning from endemic areas. The clinical presentation is notably protean, and key symptoms such as fever and chills might be missing in a substantial proportion of patients [51]. Thus, about 60% of cases are initially misdiagnosed in North America [52]. Malaria leads to death for about 1% of affected travellers, and many of these fatal evolutions might have been prevented in non-immune subjects, especially if treatment had been promptly initiated [51]. A diagnostic assay is therefore needed in the setting of the broad differential diagnosis and the possibility of co-infections. Careful examination of Giemsa thick blood smears is still considered to be the reference standard for malaria





STRATEGIES OF POC TESTING FOR INFECTIOUS DISEASE

A point-of-care (POC) test is performed at or near the site where a patient initially encounters the health care system, has a rapid turnaround time (approximately 15 min), and provides actionable information that can lead to a change in patient management. Rapid results reduce the need for multiple patient visits, enable timely treatment, and facilitate the containment of infectious disease outbreaks. POC diagnostics also reduce the reliance on presumptive treatment and thereby facilitate antibiotic stewardship

PAST

Perhaps the first large-scale use of the immunoassay for the diagnosis of infectious disease was in a report in 1917 by Dochez and Avery that pneumococcal polysaccharide can be detected by immunoassay of serum and urine from patients with lobar pneumonia. Indeed, the ELISA remains the dominant immunoassay platform technology in the non-POC central laboratory setting. Moreover, with automation, the ELISA technology also enables high-throughput sample processing.

PRESENT

Most POC rapid diagnostics use the LFIA platform. The LFIA platform is extremely versatile. The detection of high-molecular-weight antigens requires an antibody pair where an antibody to one analyte epitope is labeled with a reporter, such as colloidal gold, and a capture antibody to a second epitope on the same analyte is immobilized on the lateral flow strip. In an antigen-capture sandwich format, the intensity of the signal at the test line is proportional to the concentration of the analyte. Sandwich immunoassays are the foundation for POC tests for infectious diseases that detect microbial products in clinical samples, e.g., the group A streptococcal cell wall carbohydrate

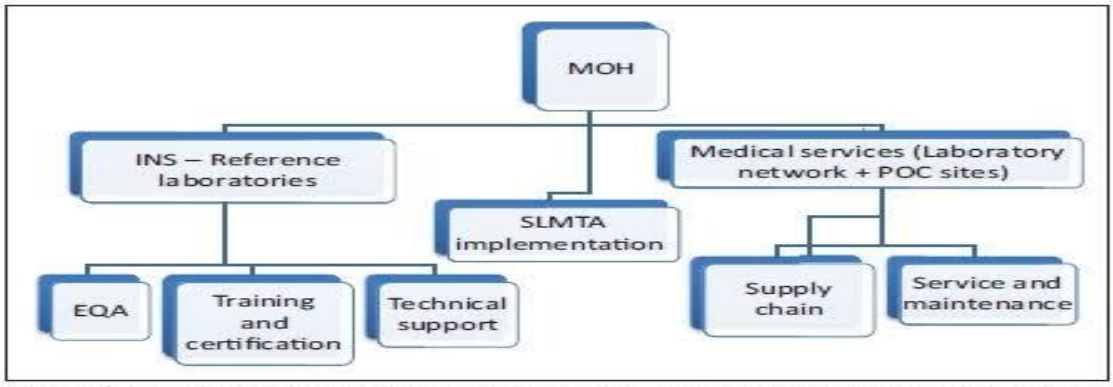
FUTURE

Microfluidics.Microfluidic devices can provide a fully integrated POC device for sample processing, fluid handling, and signal generation. A major goal is a low-cost diagnostic for use in

remote settings. Microfluidics-based devices use channels to transport small amounts of fluid by actuation forces. On-chip immunoassays have many similarities to the standard LFIA, ELISA, or molecular diagnostics platforms; however, the use of microfluidic technologies reduces assay complexity and enables multiplex analysis and high-throughput screening. On-chip nucleic acid analysis is particularly promising because it miniaturizes and integrates the various assay steps, including (i) the lysis or extraction of target cells to yield their genetic contents, (ii) the purification of nucleic acids, (iii) the amplification of nucleic acids, and (iv) on-chip detection of reaction products.

MEDICAL ANALYSIS OF POC TESTING SCHEMES

Diagnostic point-of-care (POC) testing is intended to minimize the time to obtain a test result, thereby allowing clinicians and patients to make an expeditious clinical decision. As POC tests expand into resource-limited settings (RLS), the benefits must outweigh the costs. To optimize POC testing in RLS, diagnostic POC tests need rigorous evaluations focused on relevant clinical outcomes and operational costs, which differ from evaluations of conventional diagnostic tests. Here, we reviewed published studies on POC testing in RLS, and found no clearly defined metric for the clinical utility of POC testing. Therefore, we propose a framework for evaluating POC tests, and suggest and define the term “ test efficacy” to describe a diagnostic test’ s capacity to support a clinical decision within its operational context. We also proposed revised criteria for an ideal diagnostic POC test in resource-limited settings. Through systematic evaluations, comparisons between centralized diagnostic testing and novel POC technologies can be more formalized, and health officials can better determine which POC technologies represent valuable additions to their clinical programs. ACCURACY, COST ANALYSIS AND CLINICAL IMPACT



MOH, Ministry of Health; INS, National Institute of Health; POC, point-of-care; EQA, external quality assessment; SLMTA, Strengthening Laboratory Management Towards Accreditation

FIGURE 1: Governance structure of Mozambique's public laboratory network.

RISK ASSESSMENT IMPACT OF POINT OF CARE TECHNIQUES DURING PANDEMIC OUTBREAK

Prior to any patient interaction, all health care workers (HCWs) have a responsibility to always assess the infectious risk posed to themselves and to other patients, visitors, and HCWs. This risk assessment is based on professional judgement about the clinical situation and up-to-date information on how the specific healthcare organization has designed and implemented engineering and administrative controls, along with the availability and use of Personal Protective Equipment (PPE).

Point of Care Risk Assessment (PCRA) is an activity performed by the HCW before every patient interaction, to:

1. Evaluate the likelihood of exposure to the disease from a specific interaction (e.g., performing/ assisting with aerosol-generating medical procedures, other clinical procedures/ interaction, non-clinical interaction (i.e., admitting, teaching patient/ family), transporting patients, direct face-to-face interaction with patients, etc.), with a specific patient (e.g., infants/ young children, patients not capable of self care/ hand hygiene, have poor-compliance with respiratory hygiene, copious respiratory secretions, frequent cough/ sneeze, early stage of influenza illness, etc.), in a specific environment (e.g., single rooms, shared rooms/ washrooms, hallway, influenza assessment areas, emergency departments, public areas, therapeutic departments, diagnostic imaging departments, housekeeping, etc.), under available conditions (e.g., air exchanges in a large waiting area or in an airborne infection isolation room, patient waiting areas);
2. Choose the appropriate actions/ PPE needed to minimize the risk of patient, HCW/ other staff,

visitor, contractor, etc. exposure to H1N1 2009 /suspect ILI case PCRA is not a new concept, but one that is already performed regularly by professional HCWs many times a day for their safety and the safety of patients and others in the healthcare environment.
For example, when a HCW evaluates a patient and situation to determine the possibility of blood or body fluid exposure or chooses appropriate PPE to care for a patient with an infectious disease, these actions are both activities of a PCRA.

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