

Point of care testing for infectious disease: ownership and quality

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Traditionally, diagnosis of acute infections has been organism-growth based, which makes timely and actionable infection diagnosis a major challenge. In addition, traditional microbial detection methods, including direct microscopy, are not suited for outsourcing to clinical, non-laboratory-educated personnel. Optimal management of patients with known or suspected clinical infections, such as targeted (or no) antimicrobial treatment and correct use of single room contact isolation facilities, requires rapid identification of the causative infectious microorganism. We are now facing a new disruptive paradigm shift in diagnostic microbiology. The availability of small-footprint robust instruments with easy-to-use assay kits allows non-laboratory-trained nurses and physicians to perform high-quality molecular diagnostics in a near-patient setting with results available in <30 minutes. This technology is currently breaking the centralized laboratory monopoly on the delivery of gold-standard clinical microbiology diagnostics. There is clear potential for huge positive impacts on clinical patient management and antibiotic stewardship, especially in settings where access to timely laboratory test results is not possible, but there are also potentially huge risks. Moving diagnostic testing away from the controlled diagnostic laboratory environment will lead to risks such as increased risk of inappropriate use of the diagnostic tests, insufficient training of staff performing the tests, incorrect interpretation of the test results, lack of quality control procedures, failure to capture test results in electronic patient records and compromised local as well as national surveillance. To reap the upside and avoid the downside of point-of-care infectious disease testing, the diagnostic laboratory needs to maintain oversight, and each institution must have a clear strategy for implementation and execution. If we fail, the risks could outweigh the benefits.

Introduction

The mission for clinical microbiology is to provide a definite infectious disease diagnosis in the case of a suspected clinical infection. This includes information that will optimize patient clinical management—such as microbial identification and microbial susceptibility testing—thus enabling necessary escalation or possible de-escalation of antimicrobial therapy, as well as initiation or cessation of infection control measures, such as contact isolation. Impact on clinical patient management requires availability of diagnostic results for the treating physician within a time window in which change of patient management is possible and patient outcome may be altered. Most often, this window will be limited to the first few hours or days of the course of the infection.

As diagnosis of the causative agent(s) of an acute infection has traditionally been organism-growth based, providing an actionable infection diagnosis within this narrow timeframe has been a major challenge, except for specific areas, such as direct microscopy of spinal fluid for diagnosis of bacterial meningitis or direct microscopy of peripheral blood for diagnosis of parasitic infections. In addition, traditional microbial detection methods, including direct microscopy, are so far not fully automated. Therefore, they require highly skilled and educated laboratory personnel and the

methods are not suited for outsourcing to clinical, non-laboratory-educated personnel. The only exception so far has been antigen-detection assays for selected pathogens, such as influenza virus, respiratory syncytial virus or SARS-CoV-2, which are Clinical Laboratory Improvement Amendments (CLIA)-waived and easy to use. However, the clinical utility of these assays is hampered by an unsatisfactory low clinical sensitivity.¹

During the late 1980s and early 1990s, laboratory-developed tests based upon the PCR technology^{2,3} were established for most human infections.^{4,5} Commercially available tests based on PCR or other nucleic acid amplification technologies emerged rapidly^{6,7} and today, lower costs and easy-to-use instrument platforms have allowed almost all microbiology laboratories worldwide to implement 'molecular-based' infection diagnostics.

We are now facing a new disruptive paradigm shift in diagnostic microbiology. The availability of small-footprint robust instruments with easy-to-use assay kits and short turnaround time (TAT) is currently breaking the centralized laboratory monopoly on the delivery of gold-standard clinical microbiology diagnostics.

Definition of point-of-care testing

Infectious disease diagnostic assays performed outside the walls of the central diagnostic laboratory may be positioned in very

different geographic locations and may be executed by clinical healthcare professionals, as well as trained laboratory biotechnicians. To clearly distinguish between assays performed inside the central diagnostic laboratory and those assays performed outside, in the mindset of the clinician as well as the laboratory personnel, several terminologies have been suggested, such as ‘near-patient testing’, ‘point-of-impact testing’, ‘bedside testing’ and ‘point-of-care’ (PoC) testing. One may argue that performing an infectious disease diagnostic test in a biochemistry or pathology laboratory is not outside the central diagnostic laboratory. However, in some parts of the world, especially in parts of Europe, this would be considered as such, because infectious disease diagnostics in Scandinavia, the Netherlands, the UK and Germany, for example, are predominantly performed in specialized clinical microbiology laboratories. One may also argue that performing an infectious disease diagnostic test in a local setting (e.g. the emergency department or in an intensive care unit) may be considered as ‘near-patient setting’ as well as ‘point-of-impact’, but is not quite at the actual ‘point-of-care’ or ‘bedside’ location. We have chosen to use a definition whereby all tests performed outside the walls of the central laboratory—either in an independent specialized clinical microbiology laboratory or a central laboratory comprising clinical microbiology and clinical pathology/clinical biochemistry—are defined as ‘point-of-care’ tests.⁸ This definition is also applied in the Danish National Guidelines for implementation of PoC infectious disease diagnostics.⁹

For the purposes of understanding and successfully addressing the logistic and organizational challenges involved in implementing PoC testing, we suggest the following grading of PoC testing, which is based upon the geographical location as well as the type of healthcare professionals executing the tests.⁸

Point-of-Care Laboratory Grade 1A

In this setting, PoC for infectious disease testing is performed ‘in hospital—in lab’ in a 24/7 laboratory setting staffed with dedicated and trained biotechnicians. This may be considered as a satellite laboratory or as part of the central laboratory and may be operated by trained clinical microbiology technicians but may also be operated by trained biotechnicians from other clinical specialties, such as clinical biochemistry or clinical pathology.

Point-of-Care Laboratory Grade 1B

In this setting, PoC for infectious disease testing is performed ‘in hospital—outside lab’ by local healthcare professionals, e.g. the emergency department, the intensive care unit or any clinical ward. As the healthcare professionals performing the assays in this setting are not dedicated laboratory professionals, but most likely specially trained nurses or nurse assistants, assays must be easy to perform and fail-safe. Thus, assays performed in this and the following (higher-grade) settings should be low complexity and CLIA-waived or similar. The Clinical Laboratory Improvement Amendments of 1988 (CLIA) provides federal standards applicable to all US facilities performing diagnostic testing on human specimens. Waived tests include tests that have been cleared by the FDA for home use.¹⁰

Point-of-Care Laboratory Grade 2A

In this setting, PoC for infectious disease testing is performed ‘outside hospital—in healthcare facility’ by healthcare

professionals—e.g. a general practitioner’s office or laboratory. In this setting, the assays may be performed in the actual office or in a side-room laboratory facility. The healthcare professionals performing the assays will most likely not be professional laboratory workers, but instead may be physicians, nurses or other specially trained staff. Thus, assays performed in this setting should be low complexity, easy to perform and fail-safe.

Point-of-Care Laboratory Grade 2B

In this setting, PoC testing for infectious diseases is performed ‘outside hospital—outside healthcare facility’ by healthcare or other professionals (e.g. use in the field in developing countries or in a military setting). Thus, assays performed in this setting should be of low complexity, easy to perform and fail-safe.

Point-of-Care Laboratory Grade 3

In this setting, PoC for infectious disease testing is performed in a ‘home setting’ by lay users without any formal or informal previous training. Assays performed in this setting must be low complexity, easy to perform and fail-safe.

This grading of PoC tests does not consider TAT, only geographical location. Conventionally, PoC testing is perceived as being ‘rapid’ without a clear definition of the term. All currently available commercial PoC systems meeting the requirements for placement at PoC Grade 1B or higher provide random access and a TAT of 90 minutes or less, with some systems able to provide a test result in 15 minutes or less.^{11,12}

Ownership

Traditionally, the central laboratory providing the diagnostic service has ownership and control over the infectious disease diagnostic platforms/instruments and assays/kits. The type of diagnostics provided—including tests for specific pathogens in specific types of sample material—is generally decided in a collaborative effort between the service provider and the customer (i.e. the clinical healthcare professionals responsible for the clinical patient management). However, the specific choice of platforms, assays and laboratory methods has so far been the responsibility of the central laboratory providing the diagnostic service. When infectious disease diagnostic instruments and assays are implemented for clinical use outside the bounds of the central laboratory, it is crucial that the central laboratory maintains oversight.^{9,13} The actual cost centre and legal ownership of physical instruments and kits may not directly impact the quality of the diagnostic procedure, but the quality of the PoC diagnostic procedure may be compromised if no laboratory expertise is involved in selecting instrument platforms and specific assays and if the end user (e.g. clinical ward) is relying solely on non-peer reviewed manufacturers’ self-declarations. Legal ownership of instruments and kits may be solely in the hands of the end user, but oversight of the implementation process (e.g. choice of instrument/assays, placement, training of testing personnel, verification of the diagnostic test) as well as oversight of the routine use of the PoC test (e.g. test indication, test interpretation, test report, quality control procedures, surveillance) should be the responsibility of the usual service provider of infectious disease diagnostics (i.e. the central

laboratory) in order to maintain a high level of quality. A local PoC steering committee with representatives from the end users as well as the infectious disease diagnostics service provider may facilitate individual business cases and could coordinate institution-wide as well as local implementation of specific PoC tests.

Implementation

In general, molecular-based PoC tests may—and should—provide performance characteristics (i.e. sensitivity, specificity) that equal the performance of gold standard testing in the central laboratory.^{11,14–17} The rationale for moving any diagnostic procedure closer to the patient relies on the clinical and logistic need for faster test results compared with the TAT achievable in the central laboratory. A business case should be established, identifying the derived costs, which are most likely increased, as well as the potential achievable benefits.^{18,19} These potential benefits include proper use of single room contact isolation facilities,²⁰ improved antimicrobial stewardship,^{20,21} reduced length-of-stay/admission rate,²² rapid differential diagnosis²³ and flow between wards. A current example is the possibility of rapidly testing newly admitted patients for SARS-CoV-2 to ensure safety for patients and hospital personnel during the current SARS-CoV-2 pandemic. Once the business case has been approved, the subsequent implementation process should have oversight from the central laboratory.

The implementation process must identify the optimal instrument platform based upon the local current and reasonably foreseeable future needs for rapid PoC identification of specific pathogens (assay menu), the estimated throughput (capacity) and the required TAT. Subsequently, the identified instrument should be placed in a physical location that enables safe performance of the test procedure and addresses issues such as adequate work/bench space, waste facilities and ventilation. Following the installation of the selected instrument(s), the central laboratory should facilitate and oversee training of the clinical healthcare personnel selected to perform the PoC testing. The training must be documented and maintained and must ensure that any assay performed at the PoC setting will be executed at the same quality level as if performed at the central laboratory. Standard operating procedures must be in place and should address test ordering, sampling of the patient, test execution, test interpretation, failed/inconclusive test results, instrument breakdown, instrument service and maintenance, continuous evaluation and documentation of the competence level of the testing personnel, external quality control and ordering and storage of kits and utensils. The installed PoC instrument should be set-up to communicate bidirectionally with the institutional laboratory information system (LIS) in order to avoid patient identification mix-ups and secure data capture to facilitate any local and/or national surveillance of disease incidence (e.g. influenza A or SARS-CoV-2 surveillance). Before initiation of routine use, the central laboratory should facilitate a verification process to ensure that the expected assay performance is met at the local PoC testing site in a ‘live’ setting with testing executed by the intended clinical personnel.

Selection of tests (instruments, menus)

The need for PoC testing is identified in a collaborative effort between the end-users and the service provider of infectious disease

Table 1. Parameters to consider, when selecting a PoC instrument

Which test menu is needed and is it available on the instrument?
How many samples need to be tested in parallel or sequentially every 24 hours?
What is the upper time limit for total assay turnaround time?
Are all tests validated by the vendor and/or may ‘research use only’ or laboratory-developed tests be established and validated locally?
Are validated tests available for all clinically relevant sample materials?
How is verification (or validation) performed for the selected PoC instrument and for each test locally?
Does the PoC instrument have a suitable footprint?
Is the barcode reader stable and able to read all relevant barcodes?
Is the PoC instrument operated by an integrated display or a portable laptop?
Is instrument software user-friendly and robust?
Are pre-test steps, such as sample preparation, easy to perform?
Are test set-up and result read-out easy to perform?
Are the error rate and inhibition rate acceptable?
Is leftover sample material available for further testing?
Can the PoC instrument be connected to the LIS?
Is it possible to access raw data and graphs on the local instrument or by remote connection?
Does the PoC test fit into an overall local testing strategy?

LIS, laboratory information system; PoC, point of care.

diagnostics, thus a mutual business case may be established to warrant the implementation of a PoC instrument. The PoC instrument should be chosen by the service provider of infectious disease diagnostics and should ideally cover the need of the end user, should previously have been validated in industry-independent performance studies and should ensure a quality of testing equal to testing in a central laboratory.

A variety of different parameters should be considered when selecting a PoC instrument (Table 1). Test menus should be selected based on local needs and must reflect local conditions, such as opening hours of the central laboratory, sample logistics, patient population, spread of multiresistant microorganisms in the local geographic area and economy.

For each test, further factors should be considered, such as direct and indirect financial costs, validated types of sample materials and buffer systems, whether a qualitative or quantitative result is needed, whether the test is validated for the intended test population (e.g. children), whether result interpretation and counselling are available to the end-user, whether syndromic testing is needed and whether a screening or a diagnostic test is needed. The latter should reflect the performance characteristics in terms of sensitivity, specificity, accuracy and precision of the selected test.

Other factors may influence the choice of PoC instrument. These may include questions regarding how long clinical sample materials are stable and how they should be kept prior to analysis, how test kits can be stored (e.g. at which temperature and for how long prior to analysis), whether other instrumentation (such as for centrifugation or vortexing) is needed for pre-analytical steps and whether additional testing will be requested on excess sample material—e.g. for influenza subtyping on PoC samples positive for influenza A.

Unfortunately, none of the currently marketed PoC instruments are perfect. Most manufacturers promise a pipeline of new assays but, so far, development times have been longer than expected for a number of assays, such as influenza tests. Furthermore, security of supply during the influenza season may be non-existent; most companies sell more instruments into the market than they are able to supply diagnostic assays for, which has been accentuated by the SARS-CoV-2 pandemic.

Local verification

The service provider of infectious disease diagnostics should be responsible for verification of the test performance before implementation of PoC tests to ensure the quality of the testing. This is especially important if the intention is to deviate from the manufacturer's instructions for use regarding sample material, transport buffer system or patient population to be tested. All PoC instruments and each test should be verified prior to use, even if the test and instrument are used as validated and instructed by the PoC instrument and test provider. No test or instrument should be implemented without a prior validation or verification, because this may lead to erroneous interpretation of test results and, ultimately, erroneous diagnosis and treatment of the patient. IVD and CE-marked tests only need be verified as long as they are used according to the manufacturer's instructions. A laboratory-developed test should be verified for use on the local PoC instrument, but only after a full validation in the central laboratory.

Test indications

Local indications for each test need to be established as part of local guidelines for use.²⁴ Prior to introducing a new test, it may be necessary to establish a business case showing a positive technology assessment, an acceptable cost, expected performance characteristics and a description of benefits for patients, the end users and the community.

In general, the PoC test should perform equally compared with the gold standard of testing in the central laboratory. However, based upon a cost-benefit analysis, it may be desirable to introduce a PoC test even though it does not meet the quality of the gold standard testing. PoC testing may assist in diagnosing, screening and optimizing antibiotic stewardship at the individual patient level. The adoption of a PoC test may improve proper use of side-room contact isolation facilities and reduce hospital admission. Moreover, prudent use of PoC testing may also limit spread of infectious diseases, increase prudent use of antibiotics and limit spread of antibiotic resistance in the community.

Test result reporting (interpretation, LIS, regional/national surveillance)

Results from a PoC instrument should ideally be transferred automatically to the LIS and reported into the electronic patient file. Reported results should be unambiguous, errors should be clearly reported and interpreted, and it should be clear to the end user whether the test has been performed locally on a PoC instrument or at the central laboratory. Local PoC tests are ideally ordered as any other test for microbiological analysis at the central laboratory and a backup system should be in place to identify samples that

have not been analysed on the local PoC instrument—but only sent to the central laboratory—to ensure that all patient samples are tested for the pathogens requested. All results should be reported automatically to any local or national surveillance programme.

Quality control (external programme)

Internal and external quality controls are necessary to ensure the quality of PoC testing. The internal quality controls should be included in the PoC test; they may be a process control or the detection of a sample-specific target to ensure that all steps in the PoC test have been performed correctly. The internal control should always fail if there is sample inhibition and, according to test design, may also fail if insufficient sample material has been used. The results of the internal controls should be reported into the LIS system together with the test results. Local guidelines for use should describe how samples with failed internal quality control are handled and how patient samples are reported if the internal quality control fails.

Participation in external quality control programmes is needed to ensure equal quality compared with the testing in the central laboratory. Participation in external third-party quality control programmes is not needed if a fraction or all PoC samples are reflex tested at the central laboratory. The number and frequency of external quality assurance samples should reflect the clinical importance of a false-positive or a false-negative test result. An individualized quality control plan needs to be established for multiplex assays, as it is not possible to evaluate all targets each time.

Additional quality procedures may be implemented, including a definition of what to do and how to report if the internal run control fails; registration and monitoring of error rates, inhibition rates and positive rates; and registration of maintenance and verifications. The performance of an instrument needs to be verified after any procedure that may have altered software or hardware of the instrument (e.g. service, software updates or repair).

Conclusions

Optimal management of patients with known or suspected clinical infections, such as targeted (or no) antimicrobial treatment and correct use of side-room contact isolation facilities, requires rapid identification of the causative infectious microorganism. Even rapid tests performed in the central diagnostic laboratory will often be unable to provide test results to the treating physician within 6–8 hours due to logistical issues. Obtaining faster results will require moving the diagnostic process closer to the patient. For decades, immunology-based tests, such as lateral flow tests with less than gold-standard performance, have been available for near-patient use, but highly sensitive and highly specific rapid testing has required molecular-based technologies only available in the central diagnostic laboratory. However, new low-complexity, easy-to-use instruments and assay formats are now allowing non-laboratory-trained nurses and physicians to perform high-quality molecular-based diagnostics in a near-patient setting with results available in less than 30 minutes. There is clearly a potential for huge positive impacts on clinical patient management and antibiotic stewardship, but there are also risks. Moving diagnostic

testing away from the controlled diagnostic laboratory environment increases the risk of inappropriate use of the diagnostic tests, incorrect interpretation of the test results, lack of quality control procedures, failure to capture test results in electronic patient records and compromised local and national surveillance. In order to reap the benefits and avoid the disadvantages of PoC infectious disease testing, the diagnostic laboratory needs to maintain oversight and each institution must have a clear strategy for implementation and execution. If we fail, the risks could outweigh the benefits.

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References

- Chartrand C, Tremblay N, Renaud C *et al.* Diagnostic accuracy of rapid antigen detection tests for respiratory syncytial virus infection: systematic review and meta-analysis. *J Clin Microbiol* 2015; **53**: 3738–49.
- Saiki RK, Gelfand DH, Stoffel S *et al.* Primer-directed enzymatic amplification of DNA with a thermostable DNA polymerase. *Science* 1988; **239**: 487–91.
- Saiki RK, Scharf S, Faloona F *et al.* Enzymatic amplification of β -globin genomic sequences and restriction site analysis for diagnosis of sickle cell anemia. *Science* 1985; **230**: 1350–4.
- Smith TF, Wold AD, Epsy MJ. Diagnostic virology—then and now. *Adv Exp Med Biol* 1992; **312**: 191–9.
- Lisby G. Application of nucleic acid amplification in clinical microbiology. *Methods Mol Biol* 1998; **92**: 1–29.
- Wirten M, Larrouy L, Mahjoub N *et al.* Multicenter comparison of the new Cobas 6800 system with Cobas Ampliprep/Cobas TaqMan and Abbott RealTime for the quantification of HIV, HBV and HCV viral load. *J Clin Virol* 2017; **96**: 49–53.
- Cobb B, Simon CO, Stramer SL *et al.* The Cobas[®] 6800/8800 System: a new era of automation in molecular diagnostics. *Expert Rev Mol Diagn* 2017; **17**: 167–80.
- Lisby JG, Schneider UV. Rapid Point-of-Care Assays. In: Bamford DH, Zuckerman M, eds. *Encyclopedia of Virology, Fourth Edition, Volume 5*. Academic Press, 2021; p. 4551.
- Lisby JG, Andersen DT, Chen M *et al.* *Anbefalinger vedrørende implementering og anvendelse af Point-of-Care teknologi til diagnostik af infektionssygdomme*. 2017. <http://dskm.dk/wp-content/uploads/2016/08/POC-Rapport-fra-DSKMs-Udvalg.pdf>.
- CDC. Waived Tests. <https://www.cdc.gov/labquality/waived-tests.html>.
- Tanriverdi S, Chen L, Chen S. A rapid and automated sample-to-result HIV load test for near-patient application. *J Infect Dis* 2010; **201** Suppl 1: S52–8.
- Nie S, Roth RB, Stiles J *et al.* Evaluation of Alere i Influenza A&B for rapid detection of influenza viruses A and B. *J Clin Microbiol* 2014; **52**: 3339–44.
- Dolen V, Bahk K, Carroll KC *et al.* *Changing diagnostic paradigms for microbiology: report on an American Academy of Microbiology Colloquium held in Washington, DC, from 17 to 18 October 2016*. American Society for Microbiology, 2017. <https://www.ncbi.nlm.nih.gov/books/NBK447255/>.
- Jenny SL, Hu Y, Overduin P *et al.* Evaluation of the Xpert Flu A Panel nucleic acid amplification-based point-of-care test for influenza A virus detection and pandemic H1 subtyping. *J Clin Virol* 2010; **49**: 85–9.
- Voermans JJ, Seven-Deniz S, Fraaij PL *et al.* Performance evaluation of a rapid molecular diagnostic, MultiCode based, sample-to-answer assay for the simultaneous detection of Influenza A, B and respiratory syncytial viruses. *J Clin Virol* 2016; **85**: 65–70.
- Cárdenas AM, Edelstein PH, Alby K. Development and optimization of a real-time PCR assay for detection of herpes simplex and varicella-zoster viruses in skin and mucosal lesions by use of the BD Max open system. *J Clin Microbiol* 2014; **52**: 4375–6.
- Woodberry MW, Shankar R, Cent A *et al.* Comparison of the Simplexa FluA/B & RSV direct assay and laboratory-developed real-time PCR assays for detection of respiratory virus. *J Clin Microbiol* 2013; **51**: 3883–5.
- Hansen GT, Moore J, Herding E *et al.* Clinical decision making in the emergency department setting using rapid PCR: results of the CLADE study group. *J Clin Virol* 2018; **102**: 42–9.
- Shengchen D, Gu X, Fan G *et al.* Evaluation of a molecular point-of-care testing for viral and atypical pathogens on intravenous antibiotic duration in hospitalized adults with lower respiratory tract infection: a randomized clinical trial. *Clin Microbiol Infect* 2019; **25**: 1415–21.
- Pedersen CJ, Rogan DT, Yang S *et al.* Using a novel rapid viral test to improve triage of emergency department patients with acute respiratory illness during flu season. *J Clin Virol* 2018; **108**: 72–6.
- Kaku N, Hashiguchi K, Iwanaga Y *et al.* Evaluation of FilmArray respiratory panel multiplex polymerase chain reaction assay for detection of pathogens in adult outpatients with acute respiratory tract infection. *J Infect Chemother* 2018; **24**: 734–8.
- Rahamat-Langendoen J, Groenewoud H, Kuijpers J *et al.* Impact of molecular point-of-care testing on clinical management and in-hospital costs of patients suspected of influenza or RSV infection: a modeling study. *J Med Virol* 2019; **91**: 1408–14.
- Leber AL, Everhart K, Balada-Llasat JM *et al.* Multicenter evaluation of BioFire FilmArray meningitis/encephalitis panel for detection of bacteria, viruses, and yeast in cerebrospinal fluid specimens. *J Clin Microbiol* 2016; **54**: 2251–61.
- Schneider UV, Holm MKA, Bang D *et al.* Point-of-care tests for influenza A and B viruses and RSV in emergency departments—indications, impact on patient management and possible gains by syndromic respiratory testing, Capital Region, Denmark, 2018. *Eurosurveill* 2020; **25**: 1900430.