Best practice guide to point-of-care testing for influenza

IMMUNISATION COALITION

What is a Point-of-Care Test?

A point-of-care testing (POCT) system for influenza diagnosis has the ability to rapidly detect influenza types A and B, with the potential to revolutionise patient outcomes by reducing investigation times, the time to administer appropriate therapies, hospital admissions and the spread of influenza in closed community settings. Such systems are of great benefit in preparing for seasonal epidemics, investigating outbreaks and in preparing for an influenza pandemic.

A POCT can be defined as a medical diagnostic test, performed at the site of patient care, undertaken by healthcare professionals. It is a test to support clinical decision-making, to help the physician to decide upon the best management options, and for which the results can be available in less than 90 minutes.[1]

What types of tests are available?

POCTs have been available since the late 1990s but these first-generation tests had poor specificity and sensitivity and generally depended on immunological detection of viral antigens.

Second-generation nucleic acid amplification tests (NAAT) generally have improved sensitivity, typically in excess of 95%, and rapid test times, from 5 to 90 minutes.[1,3,4,5] They use reverse transcription polymerase chain reaction (RT-PCR) assays or similar technology to detect influenza A and B viruses; however, RT-PCR detection does not necessarily indicate the presence of viable virus, is non-quantitative in these portable systems, and may not necessarily detect novel influenza viruses.

See Table 1.

Rapid NAAT POCTs — potential benefits to the individual

- Initiate antiviral treatment early (antivirals have greatest benefit if initiated within 48 hours)
- Reduce use of unnecessary antibiotics and patient not exposed to unwanted side effects
- Reduce hospital admissions
- Reduce hospital stay
- Reduce ordering of other microbiological tests
- Reduce secondary complications

Rapid NAAT POCTs — potential benefits to the community

If virus is detected and managed early, we can:

- Reduce transmission of the virus (particularly to those most vulnerable e.g. elderly with many co-morbidities)
- Prevent or investigate outbreaks
- Prepare for seasonal epidemics and influenza pandemics
- Reduce use of unnecessary antibiotics so reduce the spread of antibiotic resistance
- Reduce cost in healthcare systems due to more appropriate use of antivirals/antibiotics and reduced use of hospital resources.

When is an influenza test requested?[2]

- When people who are at risk of complications (elderly people and in particular those who are frail) present with respiratory symptoms such as headaches, fever, chills, muscle pain, exhaustion, a stuffy nose, sore throat and a cough
- When influenza has not been reported in the community, to document the presence of influenza in the area and also to diagnose the patient. Other viral (e.g. RSV) or bacterial tests (e.g. Streptococcus A) may be conducted in conjunction
- The person contracts the flu outside of the normal flu season
- Patients likely to be admitted to hospital with respiratory symptoms
- When any patient presents with influenza-like illness (ILI) to determine the appropriate course of treatment.

Factors for successful implementation of POCTs

Robust portable instrumentation is essential and available from several companies for POCT. While the Immunisation Coalition does not endorse any particular device, several groups have described some key factors for the successful implementation of second-generation POCT in hospital settings, which could also be fashioned and applied to other settings.[1,6-9] These include:

- Clear testing policies in place
- Samples to be taken early during hospital admission
- The optimal sample types vary depending on the platform used, however, nose and throat swabs are the most common
- Detailed management algorithms including patient movements
- Linkage to hospital information technology (IT) and surveillance systems; POCT should ideally be reported via hospital Laboratory Information for clinical governance, operational management and surveillance purposes. Holistic integration of influenza POCT results into routine hospital surveillance data is essential to avoid duplication or under-reporting of influenza cases
- The establishment of a POCT co-ordinator and a POCT committee for reporting and audit purposes
- Appropriate record keeping including operator identity
- Regular review of results with particular reference to the patient's history
- Collaboration with an experienced hospital laboratory in a supportive role
- Staff training (including those without a laboratory background) for operating and maintaining the POCT platform
- Equipment maintenance must be regular according to the manufacturer's instructions
- Operator awareness of health and safety issues including the potential hazards associated with the handling and disposal of body fluids, sharps and waste reagents outside of a laboratory setting
- There should be a minimal risk of harm to the patient or operator if performed incorrectly
- Methodologies used should be simple and accurate
- The provision to operators of appropriate training and the use of standard operating procedures (SOPs) as part of an established quality system
- The availability of quality control (QC) reagents to provide assurance that the platform is working correctly
- POCT systems must be registered by the TGA and should ideally be supported by the college of pathology; the regulator may require a post-market surveillance report.

Limitations of POCTs

It should be noted that the gold standard test remains laboratory-based RT-PCR testing for influenza virus (or respiratory viral pathogens). This serves as a comparator for sensitivity and specificity. Furthermore, POCT does not address the public health need for influenza virus isolates, essential for the preparation of vaccine candidates, which are obtained through the collection of respiratory specimens for viral culture. In addition, a positive POCT result for influenza A virus cannot distinguish between influenza A viruses of humans and animals, for instance avian, equine, or swine influenza A viruses. If human infection with a novel influenza A virus is suspected on the basis of recent exposures to poultry, horses or pigs, the WHO reference laboratory should be consulted.[10]

In the future it is expected that other important respiratory targets (such as, parainfluenza, human metapneumovirus, enterovirus, coronavirus, rhinovirus, adenovirus and bocavirus) would be added to POCT platforms, likely in multiplex systems. Some laboratory tests already detect several other pathogens. See Table 2. In Australia, RSV (Respiratory Synctial Virus) has already been added to the platforms of two Nucleic Acid Amplification POCTs for influenza. See Table 1.

Regulatory control of POCTs

Both the EMA and TGA regulate POCT through their guidelines and advice on in-vitro diagnostics,[11] whereas FDA have specific guidelines published in 2017 but most requirements will not fully apply until May 2022.[12] The MHRA have also produced detailed guidance on requirements in the management of POCT devices.[13] In Australia, the TGA regulates the POCTs.

Locations for POCTs

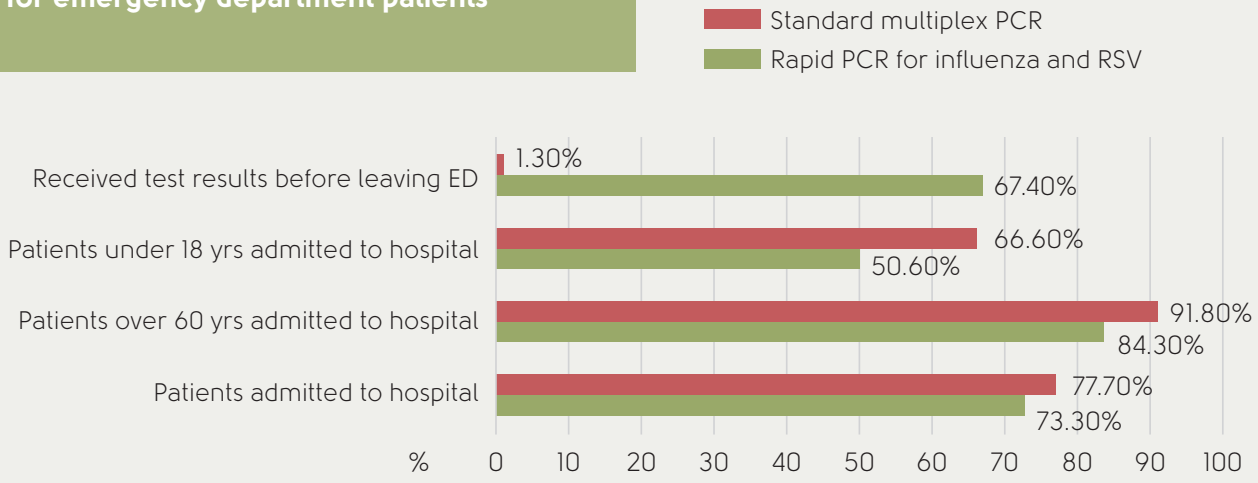
There are a variety of closed settings in which POCT could be regularly used to determine if influenza is the cause of an outbreak. Such settings could include emergency departments, medical admission units, outpatients, hospitals, long-term care facilities, cruise ships, schools, boarding schools, universities, summer camps, the armed services and religious institutions. They can also be used in open venues such as at border control points, medical practices and pharmacies.

Outcomes of POCTs

To date, published studies from the UK, Europe, Australia and the US, where POCTs using RT-PCR have been used in secondary care settings, report different outcomes.[14-18] Nevertheless, as POCT systems improve and experience is gained of their use, they will become invaluable tools for the early diagnosis and control of influenza in the community.

Australian outcome study:

The impact of rapid molecular diagnostic testing for respiratory viruses on outcomes for emergency department patients



A before-and-after study in four metropolitan Emergency Departments (ED) in New South Wales compared standard multiplex PCR during July–December 2016 to rapid PCR during July–December 2017.

Compared with standard PCR testing, rapid PCR was associated with significantly fewer hospital admissions, more rapid test turnaround, more patients receiving test results before leaving the ED and reduced numbers of some other common microbiology tests. It did not significantly affect ED length of stay.[iv]

	Standard (laboratory based) multiplex PCR	Rapid PCR for influenza and RSV
Median turnaround time	26.7 hours	2.4 hours
ED length of stay	6.5 hours	7.4 hours
Blood culture, blood gas, sputum culture and respiratory bacterial and viral serology tests	More than rapid PCR for influenza and RSV	Fewer than standard PCR

iv Nasir Wabe, Ling Li, Robert Lindeman et al The impact of rapid molecular diagnostic testing for respiratory viruses on outcomes for emergency department patients *Med J Aust* 2019; 210 (7): 316-320

Glossary

CLIA Clinical Laboratory Improvement Amendments: regulatory standards that apply to all clinical lab testing performed on humans in US

CLIA waived Tests that are very simple to perform and not requiring scientifically qualified personnel (US)

ED Emergency Department

EMA European Medicines Agency

FDA Food and Drug Administration

ILI Influenza-like illness

IT Information Technology

MHRA Medicines and Healthcare products Regulatory Agency

Multiplex POCT Can test the presence of multiple infectious pathogens within a specimen (such as blood, urine, or sputum)

NAAT Nucleic Acid Amplification Tests

Negative percent agreement The proportion of individuals with the target condition by an imperfect reference standard who test positive

POCT Point-of-Care Testing: A medical diagnostic test, performed at the site of patient care, undertaken by healthcare professionals

Positive percent agreement The proportion of individuals free of the target condition by imperfect reference standard who test negative

QC Quality Control

RSV Respiratory Synctial Virus

RT-PCR Reverse transcription polymerase chain reaction

Sensitivity The percentage of 'true influenza cases' detected by a positive test

Specificity The percentage of 'true non-influenza cases' detected as being negative by a test

SOPs Standard Operating Procedures

TGA Therapeutic Goods Administration

WHO World Health Organisation

References

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https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/846008/Point_of_care_tests_for_influenza_and_other_respiratory_viruses.pdf

2 https://www.labtestsonline.org.au/learning/test-index/flu#thetest

3 https://www.cdc.gov/flu/professionals/diagnosis/overview-testing-methods.htm

4 https://www.ncbi.nlm.nih.gov/pubmed/30602445

5 https://www.alere.com/en/home/product-details/id-now-influenza-ab-2.html

6 www.gov.uk/government/publications/in-vitro-diagnostic-point-of-care-test-devices

7 https://www.cdc.gov/flu/professionals/diagnosis/table-ridt.html

8 https://www.cdc.gov/flu/professionals/diagnosis/rapidlab.htm

9 https://www.asm.org/Articles/2018/October/Bringing-the-Laboratory-Test-to-the-Patient-with-P

10 WHO Collaborating Centre for Reference and Research on Influenza http://www.influenzacentre.org

11 www.ce-mark.com/IVD%20Regulation.pdf

12 https://jcm.asm.org/content/56/10/e00711-18

13 MHRA point of care testing. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/371800/In_vitro_diagnostic_point-of-care_test_devices.pdf

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https://doi.org/10.1111/jpc.13092
https://onlinelibrary.wiley.com/doi/abs/10.1111/jpc.13092

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The Immunisation Coalition is a not for profit advocacy group with a mission to create awareness regarding the importance of immunisation. Immunisation still provides the best protection against infectious diseases. We work with consumers, health professionals and organisations with an interest in immunisation and government health agencies, ensuring that the information provided to consumers through our website and other communication channels is current, easily understood and scientifically informed.

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TABLE 1: RAPID INFLUENZA DETECTION TESTS

Point-of-Care Tests:
Nucleic Acid Amplification Tests (NAATs) available and TGA registered in Australia[i]

All CLIA waived

Name of test	Pathogens detected	Type of test	Accuracy	Hands on time and test run time	Manufacturer	Further information
cobas® Liat® PCR system						
cobas Influenza A/B test	Influenza A/B	Qualitative Multiplex PCR test	Sensitivity Flu A 98.41% Flu B 97.86% RSV 97.81% Specificity Flu A 96.47% Flu B 99.4% RSV 98.42%	Hands on time: ~1 min Run time: Positive and negative results in 20 mins	Roche	• Portable, all in one system (monitor and barcode scanner built in) • Kit storage 2–8°C • User maintenance free • Sample type: nasopharyngeal • Does not require negative confirmation testing
cobas Influenza A/B and RSV test	Influenza A/B RSV					
ID NOW™ Platform						
ID NOW™ Influenza A & B 2	Influenza A/B	Isothermal nucleic acid amplifica-tion (molecular)	Sensitivity: Flu A: 96.3% Flu B: 100% Specificity Flu A: 97.4% Flu B: 97.1%	Hands on time: ~1 min Run time: Positive results in as little as 5 minutes Negative results in 13 minutes	Abbott Rapid Diagnostics	• Portable system (only 3kg) • Kit storage 2–30°C • User maintenance free • Sample Type: influenza A/B assay nasal (nasopharyngeal also compatible); RSV assay Nasopharyngeal
ID NOW™ RSV	RSV					
Xpert® Xpress						
Xpert® Xpress Flu/ RSV	Influenza A/B and RSV	Qualitative Multiplex PCR test	Positive Percent Agreement (PPA) Flu A 98.1% Flu B 100% RSV 98.4% Negative Percent Agreement (NPA) Flu A 98.1% Flu B 99.1% RSV 98.4%	Hands on time: ~1 min Run time: Positive results within 20 minutes Negative results within 30 minutes	Cepheid®	• Portability (~12kg): has carry bag and wheels to help transport • All-in-one integrated touchscreen computer and barcode scanner • Kit storage: room temperature • User maintenance required • Sample type: nasal and nasopharyngeal • Does not require negative confirmation testing

i The Immunisation Coalition does not endorse any particular device

TABLE 2: RAPID INFLUENZA DETECTION TESTS

Laboratory Tests[ii]
Nucleic Acid Amplification tests (NAATs) available in Australia[iii]

Name of test	Pathogens detected	Turnaround time	Manufacturer
QIAstat-Dx Respiratory Panel to be installed on QIAstat Analyser	22 bacteria and viruses (or their subtypes) Influenza A Influenza A subtype H1/N1 2009 Influenza A subtype H1 Influenza A subtype H3 Influenza B Coronavirus 229E Coronavirus HKU1 Coronavirus NL63 Coronavirus OC43 Parainfluenza virus 1 Parainfluenza virus 2 Parainfluenza virus 3 Parainfluenza virus 4 RSV A/B human Metapneumovirus A/B Adenovirus Bocavirus Rhinovirus/Enterovirus Mycoplasma pneumoniae Legionella pneumophila Bordetella pertussis	60-70 mins for over 20 pathogens	Qiagen
Liaison MDX Simplexa Flu A/B and RSV Simplexa Influenza A (H1N1)	Influenza A Influenza B RSV	60 mins	Diasorin
Biofire FilmArray	Respiratory panel for 20 pathogens Adenovirus Coronavirus 229E Coronavirus HKU1 Coronavirus OC43 Coronavirus NL63 Human Metapneumovirus Human Rhinovirus/Enterovirus Influenza A Influenza A/H1 Influenza A/H1-2009 Influenza A/H3 Influenza B Parainfluenza 1 Parainfluenza 2 Parainfluenza 3 Parainfluenza 4 RSV *Bordetella pertussis* *Chlamydophila pneumoniae* *Mycoplasma pneumoniae*	60 mins	BioMerieux
BD Max Bench top analyser Certest FluA/FluB/ RSV kit	Flu A Flu B RSV	2 hours	Becton Dickinson

ii Not an exhaustive list, there may be other NAAT laboratory tests not listed
iii The Immunisation Coalition does not endorse any particular device