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Point-of-Care Testing for Influenza



Image courtesy of Roche Diagnostics.

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Summary

- The cobas Liat System is a rapid, reverse transcription (RT)-polymerase chain reaction (PCR) point-of-care test that may be as effective as gold standard (lab-based) methods for diagnosing influenza A and influenza B.
- Rapid RT-PCR tests for influenza may be better at detecting the presence or absence of influenza than other types of rapid influenza detection tests.
- There is limited evidence comparing the cobas Liat System with other rapid influenza detection tests.
- Canadian pricing for the cobas Liat System is not available.
- There is limited evidence for using rapid RT-PCR tests outside a laboratory setting.

Background

Influenza is a highly contagious respiratory infection caused, in most cases, by the influenza A or influenza B viruses.¹ Influenza is spread from infected people to others through respiratory secretions that contain the virus, most commonly through coughing and sneezing.²

The symptoms and severity of influenza vary greatly, with some patients showing no signs of illness and others requiring hospitalization.¹ Usually, though, influenza symptoms include the quick onset of fever, cough, and muscle aches that are sometimes accompanied by headache, chills, fatigue, loss of appetite, sore throat, and stuffy or runny nose.¹

Once a person is infected, the influenza virus incubates for one to four days before it begins spreading (shedding) to others.² Virus shedding starts about 24 hours before symptoms

begin.² It peaks during the first 24 to 72 hours of illness before declining over the next few days, although this period is often longer in immunocompromised adults and in children.²

Preventive measures — for example, handwashing and an annual influenza vaccination — are the most effective way to stop its spread.¹ Diagnosing influenza infections through clinical assessment or diagnostic tests may also help to determine when to use isolation and personal protective equipment precautions, and if and how to treat the patient.²⁻⁴

Because of the considerable time, equipment, and facilities required to test for influenza using conventional methods such as the reverse transcription-polymerase chain reaction (RT-PCR) technique — a nucleic acid amplification method that detects the virus's ribonucleic acid (RNA) — a market has emerged for quick (results in less than 30 minutes) point-of-care tests. Many of these rapid tests use viral antigen detection with antibodies

to determine the presence of influenza infection, but this rapid testing method is not as sensitive as RT-PCR and negative results cannot rule out influenza infection and should not be used to withhold appropriate treatment.⁵ Now, newer rapid RT-PCR tests, which aim to address some the limitations of existing tests, are becoming available. One of these tests is the cobas Liat System.

A nasopharyngeal (NP) swab is used to collect a respiratory secretion sample from patients with suspected influenza.⁸ The sample is then transferred by pipette into the single-use assay tube and loaded into the analyzer, where it is compressed at different points and times, releasing reagents and moving the sample from one segment of the tube to another.⁸ The presence or absence of influenza A and influenza B is determined using an established nucleic acid assay that detects viral RNA, using RT-PCR. Results are reported in approximately 20 minutes.⁸

Tests for Influenza

The influenza tests compared in this report can be broadly characterized by the target they are trying to detect and the setting for their intended use.

Laboratory-Based Tests

- Viral culture (results can take 1 to 14 days)
- Conventional RT-PCR tests (results available in a few hours)
- Commercial RT-PCR test kits (results available in a few hours)

Point-of-Care Tests

- Rapid RT-PCR that can be used at the point of care (results in less than 30 minutes)
- Rapid antigen tests that can be used at the point of care (results in less than 30 minutes)

The Technology

The cobas Liat System (Roche Diagnostics, Laval, Quebec) is a rapid, point-of-care, RT-PCR test device that can be used to diagnose influenza infection. The system consists of a small, bench-top analyzer and a pencil-sized assay tube.⁶ It was originally developed by iQuum, and acquired by Roche in 2014.⁷

Who Might Benefit?

An estimated 10% to 20% of Canadians become infected with influenza each year, leading to about 12,000 hospitalizations and 3,500 deaths.¹ The burden of influenza varies by year and region. Reported hospitalizations and deaths represent only a portion of all actual cases.^{1,9,10}

The US Centers for Disease Control and Prevention (CDC) suggests that rapid diagnosis of influenza may help clinicians decide whether to prescribe antiviral therapy to patients and could also help to determine the cause of respiratory outbreaks in institutions, particularly in settings such as nursing homes, hospitals, or schools.⁵

Availability

The cobas Liat System is not currently available in Canada; however, the manufacturer plans to submit a Class III medical device licence application to Health Canada in the fall of 2016 (Michele D'Elia, Director, Medical Affairs, Roche Diagnostics, Laval, QC: personal communication, 2016 Apr 29).

In the US, the cobas Liat Analyzer and Influenza A/B Assay received 510(k) (substantially equivalent to existing tests) clearance as a Class II medical device from the FDA in 2011¹¹ prior to being acquired by Roche in early 2014.^{7,12} In 2015, the cobas Liat System was a Clinical Laboratory Improvement Amendment (CLIA) waived by the FDA as a moderate complexity test for use outside traditional laboratory facilities.¹³

The cobas Liat System has CE marking that allows it to be marketed in Europe.¹²

How Much Does It Cost?

Canadian pricing for the cobas Liat System is not yet available.

A 2015 poster presentation reported a cost of US\$25,000 for the cobas Liat Analyzer and a cost per test (including reagents, instruments, and labour) of US\$100.¹⁴

Current Practice

In Canada, most cases of influenza do not require professional medical care and patients are usually asked to stay home to rest, manage symptoms, and avoid contact with others.¹ People at higher risk of complications — such as pregnant women, infants, the elderly, and people with cancer, diabetes, or other immune system diseases — may become very ill with influenza and their treatment may include antiviral medications.¹

Generally, however, influenza will resolve in 7 to 10 days, and clinicians seeing sick patients can use the encounter as an opportunity for education about when to seek treatment and how to prevent the spread of influenza through proper handwashing, and sneeze and cough etiquette.¹

Diagnosing Influenza

Accurate and early diagnosis of influenza — and, more specifically, the particular strain of influenza — is important when considering treatment with antiviral medications, and for preventing and controlling outbreaks in hospitals and long-term care facilities.^{3,4} Canadian guidelines recommend using laboratory-based RT-PCR assays, with samples collected by nasopharyngeal swab when diagnosis is important.⁴ However, in many cases, clinicians diagnose influenza through a combination of physical examination and knowledge of local influenza patterns, although a recent study in US emergency departments raises questions about the accuracy of such diagnoses.^{2,15} Research from Public Health Ontario¹⁶ and guidance from the US CDC⁵ also suggest a role for influenza testing during outbreaks.

It is important to note, however, that while diagnosing influenza may be helpful for guiding treatment, and that Canadian guidelines recommend treating some people with antiviral medications, there are questions about whether antivirals reduce the duration of influenza symptoms or reduce complications, and if these medications increase other adverse events.^{2-4,17}

Laboratory-Based Tests

Both conventional RT-PCR tests and commercial RT-PCR test kits, as well as viral culture, are accepted as standards for diagnosing influenza and are conducted inside approved laboratory facilities.⁵

Viral culture, through either traditional or shell virus culture methods, identifies influenza infection by taking a sample from a person with an influenza-like illness (ILI), growing the viruses in mammalian cells or chicken embryos, and staining the cells with virus-specific antigens or antibodies that are then visualized using methods such as immunofluorescence.¹⁸ Traditional methods can take 3 to 10 days for results, whereas shell virus culture takes about 1 to 3 days.^{5,18}

For laboratory-based RT-PCR, influenza virus RNA is extracted from patient samples and amplified before being coupled to fluorescent labels that identify specific sequences of influenza virus RNA.¹⁸ This method of virus detection is more sensitive than other tests (including viral culture) and can be completed within a few hours.^{5,18}

The Evidence

We found seven studies evaluating the cobas Liat System's ability to detect influenza A and influenza B.^{8,14,19-23} Four of these studies were available only as a conference abstract or poster presentation.^{14,21-23} Two studies were funded by the manufacturer,^{8,23} one was independently initiated,¹⁹ and four did not state a source of funding.^{14,20-22} The studies included a mixture of fresh, prospectively analyzed samples, and frozen, retrospectively analyzed samples. All seven studies compared the cobas Liat System to commercial RT-PCR test kits or conventional laboratory RT-PCR tests, and two studies^{8,23} also compared the cobas Liat System to viral culture. One study included a comparison to a rapid antigen test²³ and one study compared the cobas Liat System to another rapid RT-PCR test, the Alere i (see [Concurrent Developments](#) for more information about the Alere i).¹⁹ An additional study begun by the previous manufacturer of the cobas Liat System was also identified, but data from this study have not been published.²⁴

Test Performance

The performance of diagnostic tests is determined by comparing the test of interest with a reference standard of testing, which is considered to most accurately detect the true presence or absence of disease. To do this, samples are collected prospectively from patients with symptoms that suggest the disease of interest may be present. Samples are then run independently on both tests, with the results of the test of interest compared with the results of the reference standard to determine how well the new test performed. The ability of a diagnostic test to correctly identify patients with a disease is called sensitivity. Specificity, on the other hand, is the ability of a diagnostic test to correctly identify a patient as not having the disease.²⁵

The performance of the cobas Liat System, compared with several laboratory-based RT-PCR tests, viral culture, one rapid antigen test, and one rapid RT-PCR test, is summarized in [Table 1](#).

Comparison With Laboratory-Based RT-PCR

Seven studies^{3,8,14,19,20,22,23} evaluated the sensitivity and specificity of the cobas Liat System and found it to be comparable to laboratory-based RT-PCR tests.

A manufacturer-funded study of 842 nasopharyngeal samples collected prospectively from patients presenting with possible influenza in nine physicians' offices and three emergency rooms in the US found the cobas Liat System had a sensitivity and specificity — compared with the Prodesse ProFlu+ assay (a commercial RT-PCR test kit) — of 96.9% and 98.9%, respectively, for influenza A.⁸ For influenza B, sensitivity was 95.5% and specificity was 99.2%.⁸ A second US study, of 197 samples, of which 121 were known to be positive for influenza A or influenza B, and only 123 of which were collected by nasopharyngeal swab, found the sensitivity and specificity of the cobas Liat System compared with the Simplexa Flu A/B & RSV Direct assay (a commercial RT-PCR test kit) to be 99.2% and 100%, respectively, for influenza A and 100% and 100% for influenza B.²⁰ However, the test performance may be higher because samples with known disease status were used. A 2016 investigator-initiated study of 129 known frozen samples collected from US outpatient and in-patient sites found the cobas Liat System had a sensitivity of 100% for both

influenza A and influenza B when compared with the FilmArray Respiratory Panel (a commercial RT-PCR kit).¹⁹ Specificity for influenza A and influenza B was also 100%.¹⁹ Two additional studies,^{14,22} reported as poster presentations, also compared the cobas Liat System with commercial RT-PCR test kits and found sensitivities of 95% to 96.6% and specificities of 99% for influenza A and influenza B combined. However, one poster²² did not describe the test performance methodology, and sensitivity and specificity was not reported as a primary outcome; and the second poster¹⁴ used known retrospective samples and did not use a true reference standard for comparison.

Roth et al.²¹ found high agreement (100% for influenza A and 95% for influenza B) between the cobas Liat System and a conventional RT-PCR test, when the viral load (the amount of influenza virus present) in the samples was high. In samples with lower viral load, agreement between the two tests dropped to 50% for influenza A and 83% for influenza B.

A 2015 manufacturer-funded poster presentation²³ found high positive (100% for both influenza A and influenza B) and negative agreement (97.1% and 99.4% for influenza A and influenza B, respectively) between the cobas Liat System and an unnamed laboratory-based RT-PCR test when comparing 179 retrospectively collected frozen samples.

Comparison With Rapid RT-PCR Tests

A 2016 investigator-initiated study compared the cobas Liat System with the Alere i Influenza A & B (a rapid RT-PCR test).¹⁹ Using the same 129 known frozen samples from US outpatient and in-patient sites, the authors found the cobas Liat had a sensitivity of 100% for influenza A compared with 71.3% for the Alere i when results from the two tests were compared to the FilmArray Respiratory Panel (a commercial RT-PCR test kit). The authors concluded that cobas Liat detected significantly more positive samples than the Alere i, although the performance of the Alere i test may have been affected by samples with low viral count. For influenza B, the cobas Liat System had a sensitivity of 100%, and the Alere i had a sensitivity of 93.8% although the difference was not statistically significant. The specificity of both tests for influenza A and influenza B was 100%.

Comparison With Rapid Antigen Tests

A 2015 manufacturer-funded poster presentation²³ evaluating the performance of the cobas Liat System to viral culture also compared Quidel QuickVue Influenza A+B Test (a rapid antigen test) with viral culture using the same 435 prospectively collected samples. The authors found the cobas Liat System had higher sensitivity (100% for both influenza A and influenza B) compared with the QuickVue test (26.5% and 76.7% for influenza A and influenza B, respectively).

Safety

None of the studies reported any direct safety issues with the use of the cobas Liat System.

In its licensing decision for the cobas Liat System, the FDA noted that the performance characteristics of the test are based on specific strains of influenza circulating at the time of licensing.¹¹ Test performance may vary, depending on the strain(s) of influenza circulating during any given influenza season.

The FDA approval also noted that negative test results do not preclude influenza and positive results do not rule out other types of respiratory infection.¹¹

A 2016 study of the performance of the cobas Liat System noted that coinfection with other respiratory viruses was found in 13.6% of influenza A samples and 6.3% of influenza B samples.¹⁹ The authors noted that these coinfections would not have been identified if the cobas Liat were used as the primary test for influenza.

Limitations of Current Research

Only one study compares the cobas Liat System with another rapid RT-PCR test¹⁹ and only one study²³ compares the cobas Liat System to an existing rapid antigen test. This makes it difficult to place the performance of the cobas Liat System within the current spectrum of available point-of-care influenza tests.

Although the time required to collect and run a test is often reported as less than 20 minutes, only one study¹⁹ specifically addresses this claim, making it difficult to know how the cobas Liat System compares with existing tests.

The use of known samples in some studies may increase the reported performance of the cobas Liat System.

More research conducted by non-laboratory personnel in point-of-care situations is also needed to better understand the performance of rapid RT-PCR tests in these settings.¹⁹

Other Considerations

A 2016 conference abstract, funded by the manufacturer, presented a US budget impact model based on data from 100,000 risk-stratified patients and concluded that the cobas Liat System may:

- increase the appropriate use of antivirals and antibiotic medications
- reduce use of hospital resources
- reduce the cost of patient management.²⁶

However, further validation of the model using real-world data is needed.²⁶

A 2015 conference abstract by authors at the Hospital of the University of Pennsylvania assessed the cobas Liat System against a conventional RT-PCR test. It found that the cobas Liat System would increase the costs of performing influenza testing in its facility, but the time savings (from eight hours to 40 minutes) may reduce other health care costs.²¹

A 2016 comparison of the cobas Liat System with the Alere i Influenza A & B noted that the cobas Liat System required fewer steps and less hands-on time (about one minute) to perform than Alere i (about six minutes).¹⁹

Concurrent Developments

Other Rapid RT-PCR Tests for Influenza

Like the cobas Liat System, the Alere i Influenza A & B test (Alere Scarborough, Inc., Scarborough, Maine, US) is a rapid RT-PCR test designed to detect and differentiate between influenza A and influenza B infections.²⁷ Using isothermal nucleic acid amplification with primers and fluorescent probes, the Alere i Influenza A & B test amplifies RNA targets from influenza A and B viruses.²⁷ The test unit is designed for use

outside traditional laboratory sites; results are available in about 15 minutes.²⁷

In Canada, the Alere i Influenza A & B is licensed by Health Canada as a Class III medical device.²⁸ It is also 510(k) cleared and CLIA-waived by the US FDA.^{29,30}

We found 15 studies (including three conference abstracts) comparing the Alere i Influenza A & B test with other methods of diagnosing influenza.^{19,27,31-43} One conference abstract⁴² was subsequently reported in full.⁴¹ The results of these studies are summarized in [Table 2](#). One study comparing the Alere i Influenza A & B test with the cobas Liat Influenza A/B test was found and is discussed [previously in this report](#).¹⁹

The sensitivity and specificity of the Alere i Influenza A & B assay varies from 65.96% to 93.8% for sensitivity and 59.1% to 100% for specificity for influenza A virus, and 53.33% to 100% for sensitivity and 53.6% to 100% for specificity for influenza B virus, when compared with laboratory-based RT-PCR and viral culture standards.^{19,31,32,39-41,43} Reasons for this variation include the reference standard to which the Alere i was compared, the method by which samples were collected and transported, and the use of fresh versus frozen samples.

When compared with rapid antigen tests, the performance of the Alere i Influenza A & B assay also varied. Although the Alere i test was generally found to have a higher sensitivity than rapid antigen tests, a lower specificity was reported for the influenza B virus in one case.^{33-35,38}

Rapid Antigen Tests

Many rapid antigen tests designed to quickly detect influenza infection using viral antibodies are available in Canada. These include QuickVue Influenza A+B (Quidel Corporation, San Diego, California, US) (Class III),^{44,45} FebriDx (Rapid Pathogen Screening, Inc., Sarasota, Florida, US) (Class III),⁴⁶⁻⁴⁸ BD Veritor System (Becton Dickinson and Company, Sparks, Maryland, US) (Class III),^{49,50} and RAMP Flu A + B (Response Biomedical Corp., Vancouver, British Columbia) (Class II).^{51,52} Like rapid RT-PCR tests, these rapid antigen tests typically provide results in less than 30 minutes.⁵ Rapid antigen tests work by detecting the presence or absence of viral nucleoprotein antigens in respiratory samples using different types of immunoassays

and many can be used outside a lab setting without the need for a separate analyzer.^{5,18}

As highlighted in a 2014 study of 20 rapid antigen tests available in Japan, the sensitivity of rapid antigen tests to detect seasonal influenza varies depending on the strains of influenza circulating at any given time, and the test used.⁵³

A 2012 collaboration between the US CDC and the Medical College of Wisconsin examined 11 rapid antigen tests and further emphasized the variability of test performance and the need to collect samples for testing at a time when viral load is expected to be highest (i.e., within 24 to 72 hours of the onset of symptoms).⁵⁴

A 2012 meta-analysis of the performance of rapid antigen tests to detect a variety of influenza strains compared with viral culture and laboratory-based RT-PCR tests found 159 studies evaluating 26 commercially available rapid antigen tests.⁵⁵ The authors concluded that the specificity of rapid antigen tests was more consistent between tests (ranging between 50.5% and 100%, and only 17 of 159 studies falling below 85%) than sensitivity (ranging between 4.4% and 100%). After pooling results, the sensitivity of the rapid antigen tests was 62.3% and the specificity was 98.2%.⁵⁵ The authors also found that, whereas no one test performed better than another, there was a lack of comparison between tests in most studies and that rapid antigen tests, despite their limitations, help address a need at the point of care where waiting for viral culture or laboratory-based RT-PCR test results may not be feasible.⁵⁵

A 2012 meta-analysis of the performance of rapid antigen tests to detect the 2009 pandemic H1N1 influenza virus found that the specificity of different rapid antigen tests showed less variability (ranging between 80% and 100%) than sensitivity (ranging between 11% and 88%) and concluded that, whereas rapid antigen tests may be useful in that they provide immediate results, until sensitivity is improved, laboratory-based RT-PCR tests remain the most effective method for detecting this particular strain of influenza.⁵⁶

A 2016 Rapid Response from CADTH found that one rapid antigen test (QuickVue) could be a useful tool for diagnosis and triage, but that its low sensitivity would require that negative test results be confirmed using an laboratory-based RT-PCR test.⁵⁷

Implementing Point-of-Care Influenza Tests

A 2015 poster presentation describes the impact of using the cobas Liat System on patient care in a US emergency department.²² The authors found emergency department physicians who used the test changed patient management in 70 of 105 cases (67%). Patient management changes included the addition or cancellation of antiviral or antibiotic treatments in 80% of patients, and the revision of admission and discharge orders in 18% of patients.

A 2014 Cochrane review on the use of rapid viral testing in children presenting to the emergency department with acute respiratory infection found testing resulted in lower rates of chest X-ray utilization but had no effect on length of stay, or use of blood or urine tests.⁵⁸

A retrospective study of 4.9 million visits to US emergency departments found that, when influenza was diagnosed with a rapid antigen test, patients received fewer additional tests and were more likely to receive antiviral medications than when influenza was diagnosed without a rapid antigen test.⁵⁹

Diagnosing Influenza in Community Pharmacies

One suggested use of point-of-care influenza testing is to make the tests available to the public in community pharmacies.⁶⁰⁻⁶³ Proponents of pharmacist-administered influenza testing believe there may be value in providing these tests outside traditional health care settings. This is because the knowledge and skills of pharmacists may help with a more appropriate use of antiviral medications, and the convenient location and hours of operation of pharmacies may be a better option for many patients.⁶¹⁻⁶³

A small 2016 pilot study of a partnership between physicians' offices and 55 community pharmacies in the US to provide influenza testing (using rapid antigen testing) and treatment found the partnership was successful in providing antivirals to low-risk patients, without the need for a visit to a physician's office.⁶² The authors also concluded that this type of collaboration between physicians and pharmacists could

reduce the number of patients who seek care from a physician when they only require symptom relief.⁶²

In Canada, Shoppers Drug Mart locations in Alberta, British Columbia, and Ontario piloted a pharmacist-led screening program for patients with ILI from December 2014 to April 2015 (Karen Sullivan, Director of Pharmacy and Professional Affairs, Shoppers Drug Mart, Calgary, AB: personal communication, 2016 Jul 17).^{60,64} Run in 150 locations, the pilot program was intended to evaluate the impact, value, feasibility, and interest in an in-pharmacy screening program led by pharmacists (Karen Sullivan: personal communication, 2016 Jun).⁶⁰ Patients were required to pay \$25 for the test (using the BD Veritor System, a rapid antigen test). Two hundred and eighteen patients agreed to be tested for influenza and approximately 30% tested positive. Those who tested positive were, depending on the scope of practice of pharmacists in their province, offered antiviral therapy on-site, or referred to a physician's office with a recommendation for antiviral therapy, as appropriate (Karen Sullivan: personal communication, 2016 Jun).⁶⁰ Overall, the pilot program was found to be feasible and of interest to patients, and the investigators felt that in-pharmacy testing could play a role in assisting with the appropriate prescription and use of antiviral medications.

However, a 2016 Rapid Response by CADTH found no published evidence on the clinical effectiveness of point-of-care testing for infectious diseases by pharmacists.⁵⁷

We did not find any studies that assessed the use of rapid RT-PCR tests, such as the cobas Liat System or Alere i, in pharmacies.

Appropriate Use of Antimicrobials

Using rapid and point-of-care influenza tests may help clinicians more appropriately prescribe antibiotics and antiviral medications.^{58,59,65,66}

Two small 2014 studies examined the effect of positive point-of-care test results on physician-prescribing of antibiotics.^{65,66} Both concluded that point-of-care tests may help reduce the use of antibiotics. Similarly, the retrospective analysis of 4.9 million US emergency department visits found patients received fewer antibiotics if they tested positive

for influenza by rapid antigen testing.⁵⁹ However, in its 2014 systematic review of rapid viral testing of children presenting to the emergency department with acute respiratory infection, the Cochrane Collaboration found no evidence to support the use of routine rapid testing to reduce antibiotic use in children.⁵⁸

Cost-Effectiveness

A 2015 cost-effectiveness model from Quebec found that using a rapid influenza test to guide antiviral treatment could be more effective and less expensive than treatment guided by clinical diagnostic criteria alone, estimating that, when applied to the population of Quebec, such a test could save up to 154 lives per year and cost \$605,840 less than treatment based on clinical diagnostic criteria alone.⁶⁷

Two additional cost-effectiveness studies — one from Spain⁶⁸ and one from the US⁶⁹ — both published in 2015 also found rapid antigen tests may offer cost savings through more timely diagnosis, reduced costs of laboratory materials, and reduced use of antibiotics — although these results may depend on whether the rapid antigen tests are used in an in-patient or outpatient setting.

Final Remarks

The cobas Liat System is one of a new kind of rapid RT-PCR test for influenza that may provide greater diagnostic performance than existing rapid antigen tests and other rapid RT-PCR tests.

The available evidence on current rapid antigen tests suggests that these kinds of tests may reduce health care costs and improve patient care through a more appropriate use of antibiotic and antiviral medications. These tests may also improve access to testing outside of traditional laboratory settings. However, further studies and Canadian cost-effectiveness studies of the cobas Liat System are needed to determine how this test may affect patient care and health care costs.

Methods

A peer-reviewed literature search was conducted using the following bibliographic databases: MEDLINE, PubMed, Embase, and the Cochrane Library. Grey literature was identified by searching relevant sections of the Grey Matters checklist (www.cadth.ca/grey-matters). No methodological filters were applied. The search was limited to English-language documents published between January 1, 2011 and April 19, 2016. Regular alerts were established to update the search until September 6, 2016.

Table 1: Performance and Test Characteristics of the cobas Liat Influenza System

| Study | Design | Reference Standard | Sensitivity (%) | Specificity (%) | Other Outcomes | Notes |
|-----------------------------------|--|---|---|---|--|--|
| Nolte et al. (2016) ¹⁹ | 129 known frozen respiratory samples (126 NP samples) collected from outpatient settings and in-patient settings for routine testing. Samples were frozen and retested concurrently using both the cobas Liat System and the Alere i (rapid RT-PCR test) | FilmArray Respiratory Panel (commercial RT-PCR) | <i>cobas Liat</i> Influenza A: 100 Influenza B: 100 <i>Alere i</i> Influenza A: 71.3 Influenza B: 93.8 | <i>cobas Liat</i> Influenza A: 100 Influenza B: 100 <i>Alere i</i> Influenza A: 100 Influenza B: 100 | The cobas Liat was found to detect statistically significantly more positive samples of influenza A. There was no significant difference in the tests' ability to detect positive samples of influenza B. | Investigator-initiated. Performance of Alere i may be affected by samples with low viral count. |
| Chen et al. (2015) ⁸ | 842 NP samples collected from physician offices and emergency rooms from patients presenting with ILI | Prodesse ProFlu+ assay (commercial RT-PCR); viral culture | <i>Prodesse</i> Influenza A (n = 841): 96.9 Influenza B: 95.5 <i>Viral Culture</i> Influenza A (n = 784): 97.5 Influenza B (n = 784): 96.7 | <i>Prodesse</i> Influenza A (n=841): 98.9 Influenza B: 99.2 <i>Viral Culture</i> Influenza A (n = 784): 97.9 Influenza B (n = 784): 97.9 | Comparison of performance in 60 fresh versus 60 frozen samples was also conducted; 600 additional retrospectively collected frozen samples were also examined. | Industry-funded. |

| Study | Design | Reference Standard | Sensitivity (%) | Specificity (%) | Other Outcomes | Notes |
|---------------------------------------|--|---|--|---|--|--|
| Binnicker et al. (2015) ²⁰ | 121 known frozen positive samples; 76 prospectively collected samples tested by reference standard, then refrigerated and stored for no more than 48 hours | Simplexa Flu A/B & RSV Direct assay (commercial RT-PCR) | Includes both retrospective and prospective samples Influenza A: 99.2 Influenza B: 100 | Includes both retrospective and prospective samples Influenza A: 100 Influenza B: 100 | | Only 123/197 samples were collected using NP swabs as recommended by the manufacturer; no funding source declared. |
| Roth et al. (2015) ²¹ | 104 known positive and negative samples | Conventional RT-PCR | NA | NA | Agreement between tests was measured and was greater (near 100%) in samples with presumed high viral load. | Conference abstract; no funding source declared. |
| Hansen et al. (2015) ²² | 289 prospectively collected samples from patients with suspected influenza presenting at a single US emergency department | GenMark Respiratory Viral Panel (commercial RT-PCR) | 96.6 | 99.0 | Impact of cobas Liat testing on change in management of suspected influenza patients. | Poster presentation; test performance was not the primary outcome of the study; no funding source declared. |

| Study | Design | Reference Standard | Sensitivity (%) | Specificity (%) | Other Outcomes | Notes |
|---------------------------------------|--|---|---|--|--|---|
| Nattanmai et al. (2015) ¹⁴ | Retrospective analysis of 275 consecutive NP specimens originally received by laboratory for respiratory infection analysis and tested by one of three methods. Frozen sample were analyzed by cobas Liat | FilmArray Respiratory Panel (commercial RT-PCR); Prodesse ProFlu or Prodesse FAST (commercial RT-PCR) | 95 | 99 | Test costs (see How much does it cost?) and limit of detection. | Poster presentation; No true comparison to a reference standard (samples were considered positive if they tested positive by two of three methods); no funding source declared. |
| Chen et al. (2015) ²³ | 435 prospectively collected NP samples from patients presenting with ILI at multiple US sites comparing both the cobas Liat and Quidel QuickVue Influenza A+B (rapid antigen test) tests with viral culture; 179 retrospective frozen samples comparing the cobas Liat with RT-PCR | Viral culture for prospective samples; unnamed RT-PCR sequencing for retrospective samples | <i>cobas Liat</i> Influenza A: 100 Influenza B: 100 <i>Quidel QuickVue</i> Influenza A: 26.5 Influenza B: 76.7 | <i>cobas Liat</i> Influenza A: 96.8 Influenza B: 94.1 <i>Quidel QuickVue</i> Influenza A: 100 Influenza B: 97.5 | Agreement between cobas Liat and PCR for frozen samples was: Influenza A: Positive agreement, 100; Negative agreement, 97.1 Influenza B: Positive agreement, 100; Negative agreement, 99.4 | Manufacturer-funded; poster presentation. |

NA = not applicable; NP = nasopharyngeal; ILI = influenza-like illness; RIDT = rapid influenza diagnostic test; RT-PCR = reverse transcription polymerase chain reaction.

Table 2: Test Characteristics of the Alere i Influenza A & B

| Study | Design | Reference Standard | Sensitivity (%) | Specificity (%) | Other Outcomes | Notes |
|--|---|---|--|--|--|-----------------------|
| Nguyen Van et al. (2016) ³² | 96 patients (86 adults and 10 children) presenting with ILI during the 2014-2015 French flu season | XpertFlu RSV (commercial RT-PCR test) | Influenza A: 93.8 Influenza B: 100 | Influenza A: 100 Influenza B: 100 | PPV Influenza A NPV Influenza A PPV Influenza B NPV Influenza B | Independently funded. |
| Chiarella et al. (2016) ³¹ | 119 samples (99 adults and 20 children); 46 samples collected prospectively from patients presenting with ILI, then refrigerated and tested; remaining 73 known frozen samples tested retrospectively | <i>Commercial RT-PCR</i> Roche rRT-PCR (n = 46); CLART PneumoVir DNA assay (n = 82); 9 samples tested using both <i>Rapid Antigen Test</i> Alere Binax Now | Influenza A: 65.96 Influenza B: 53.33 | Influenza A: 98.51 Influenza B: 95.96 | Agreement with Alere BinaxNow (a rapid antigen detection test) was low. | Independently funded. |
| Berry et al. (2015) ³³ | Sample collected prospectively from patients, then tested on-site (for the BD Veritor) and frozen and tested off-site using Alere i | BD Veritor (rapid antigen test) | NA | NA | Agreement between tests: Influenza A: 85.7% Influenza B: 100% | Conference abstract. |

| Study | Design | Reference Standard | Sensitivity (%) | Specificity (%) | Other Outcomes | Notes |
|---|---|--|--|--|---|--|
| Chapin & Flores-Cortez (2015) ²⁷ | 278 frozen samples previously tested for influenza | XpertFlu A/B assay (commercial RT-PCR) | Influenza A: 93.8 Influenza B: 91.8 | Influenza A: 62.5 Influenza B: 53.6 | | Industry-funded. Use of known samples (many of which were positive) affects results. |
| Hazelton et al. (2015) ³⁴ | 201 samples from adults 16 years and older presenting with ILI in Australia. Samples shipped to lab for testing but refrigerated, not frozen | Conventional RT-PCR | Influenza A: 77.8 Influenza B: 75.0 | Influenza A: 100 Influenza B: 99.0 | When compared with two rapid antigen tests, there was no significant difference in the agreement between the three tests for influenza A, but some false-positives for influenza B. | Test kits provided by industry; sensitivity may be have been affected by splitting samples for testing, lack of pediatric samples, and not asking about symptom onset. |
| Hurtado et al. (2015) ³⁷ | 98 prospectively collected samples (40 female; 58 male; 46 children) and shipped to a lab for testing. All samples were refrigerated or frozen and testing took place within 72 hours | Conventional RT-PCR | Not reported | Not reported | PPA influenza A: 93.8%; PPA influenza B: 94.1% NPA influenza A: 100%; NPA influenza B: 100% | Industry-funded. Higher reported rate of invalid tests than other studies. |

| Study | Design | Reference Standard | Sensitivity (%) | Specificity (%) | Other Outcomes | Notes |
|--|--|--|--|--|---|--|
| Busson et al. (2015) ³⁸ | 258 samples from 169 children and 84 adults (118 male; 135 female) collected using NP swabs (n = 169), NP aspirates (n = 102), and bronchoalveolar lavage (n = 2) | Sofia Influenza A+B (rapid antigen test); conventional PCR | Influenza A: 91.38 Influenza B: 54.55 | Influenza A: 97.61 Influenza B: 98.83 | Assessed impact of test and found it helped avoid 10.71% of hospitalizations, 46.42% of antibiotic prescriptions, and 42.86% of additional examinations. Also helped determine when to isolate patients and when to prescribe antivirals. | Conference poster presentation; no funding source declared. |
| Jokela et al. (2015) ³⁵ | 112 samples from 8 children and 104 adults collected prospectively (65 samples analyzed within 24 hours, remaining frozen and tested later); 28 known frozen influenza B samples | XpertFlu (commercial RT-PCR); conventional RT-PCR | Influenza A: 80.0 Influenza B: 98.9 | Influenza A: 93.3 Influenza B: N/A | Samples also tested using the mariPOC (antigen detection test), which was found to have a sensitivity of 53.1% for influenza A. | Testing kits provided by manufacturer; freeze-thaw cycles may have affected results. |
| Beckmann and Hirsch (2015) ³⁶ | 436 consecutively collected NP swabs from patients with ILI (178 female and 258 males, 275 pediatric and 161 adults). Samples collected over the course of 2 influenza seasons; 13 additional frozen samples | RespiFinder 22 (commercial RT-PCR) | Influenza A: 82.3 Influenza B: 99.7 | NA | 211 samples also tested using Sofia Influenza A+B and Alere BinaxNow; sensitivity of Alere i reported to be much higher than other tests. | No funding declared. |

| Study | Design | Reference Standard | Sensitivity (%) | Specificity (%) | Other Outcomes | Notes |
|------------------------------------|---|---|--|--|--|---|
| Riazzo et al. (2015) ⁴³ | 70 frozen samples with known influenza status (24, influenza A; 25 influenza B) detected by in-house RT-PCR or SD Bioline Influenza Antigen tests (RIDT). Thawed samples retested for influenza and compared with conventional RT-PCR | Conventional RT-PCR | <p><i>Alere i</i> Influenza A: 59.1 Influenza B: 83.3</p> <p><i>SD Bioline (RIDT)</i> Influenza A: 22.7 Influenza B: 45.8</p> <p><i>Simplexa Flu A&B</i> (commercial RT-PCR) Influenza A: 100 Influenza B: 100</p> | 100 for all tests. | | No funding declared. |
| Nie et al. (2014) ⁴¹ | 360 frozen specimens: 193 female, 167 male; 69 children, 291 adults; 40 influenza A-1, 40 influenza A-3, 37 influenza A unknown, 41 influenza B, and 202 negative specimens (60 of which were positive for other viruses) | FilmArray Respiratory Panel (commercial RT-PCR) | Influenza A: 73.2 Influenza B: 97.4 | Influenza A: 100 Influenza B: 100 | | Industry-funded; samples with unknown strain of influenza had lowest sensitivity. |
| Bell et al. (2014) ⁴⁰ | 545 samples collected prospectively from patients presenting with fever within last 72 hours additional flu-like symptom (465 children, 80 adults) | Viral culture | Influenza A: 97.8 Influenza B: 91.8 | Influenza A: 85.6 Influenza B: 96.3 | Discordant results also compared with another molecular test. Specificity was higher in this comparison. | Industry-funded; samples collected from external nares, which is not the standard for collection. |

| Study | Design | Reference Standard | Sensitivity (%) | Specificity (%) | Other Outcomes | Notes |
|---|--|--|--|--|----------------|------------------|
| Bell and Selvarangan (2014) ³⁹ | 236 frozen samples collected from children; 158 mid-turbinate swabs, 78 NP swabs/aspirates. Samples had previously been tested by RIDT or RT-PCR | Viral culture; Prodesse ProFlu (commercial RT-PCR) | <i>Viral Culture</i> Influenza A: 93.3 Influenza B: 100 <i>Prodesse ProFlu</i> Influenza A: 88.8 Influenza B: 100 | <i>Viral Culture</i> Influenza A: 94.5 Influenza B: 100 <i>Prodesse ProFlu</i> Influenza A: 98.3 Influenza B: 100 | | Industry-funded. |

NA = not applicable; NP = nasopharyngeal; ILI = influenza-like illness; NPA = negative predictive agreement; NPV = negative predictive value; PCR = polymerase chain reaction; PPA = positive predictive agreement; PPV = positive predictive value; RIDT = rapid influenza diagnostic test; RT-PCR = reverse transcription-polymerase chain reaction.

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