The Enigma ML FluAB-RSV assay: a fully automated molecular test for the rapid detection of influenza A, B and respiratory syncytial viruses in respiratory specimens

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The Enigma® ML FluAB-RSV assay (Enigma Diagnostics, Porton Down, Salisbury, UK) is a CE-IVD marked multiplex molecular panel for the detection of influenza A, B and respiratory syncytial viruses in nasopharyngeal swabs. The assay runs on the fully automated Enigma ML platform without further specimen manipulation and provides a sample-to-answer result within 95 min. The reported sensitivity and specificity for influenza A are 100% (95% CI: 98.2–100) and 98.3% (95% CI: 95.5–99.4), respectively, for influenza B are 100% (95% CI: 98.2–100) and 98.7% (95% CI: 96–99.6), respectively, and for respiratory syncytial virus are 100% (95% CI: 98.2–100) and 99.4% (95% CI: 97.2–99.9), respectively.

KEYWORDS: automation • influenza A • influenza B • multiplex PCR • point of care • rapid diagnosis • respiratory infection • RSV

Community-associated respiratory tract infections are a common cause of acute illness in both adults and children, leading to high rates of hospitalizations and lost working days. Upper respiratory tract infections are predominantly caused by viruses, such as rhinovirus, adenovirus and respiratory syncytial virus (RSV), whereas lower respiratory tract infections are frequently caused by bacteria, such as Streptococcus pneumoniae, Haemophilus influenzae, as well as a broad range of viruses including RSV and influenza. Globally, lower respiratory tract infections are the fourth leading cause of death. Influenza and RSV accounted for 507,900 and 253,500 deaths, respectively, in 2010 [1].

During the past few years, an increasing number of rapid diagnostic tests have become available to diagnose bacterial and viral causes of respiratory tract infections [2]. However, despite significant advances in diagnostic techniques, the majority of patients with suspected infections are still managed with empirical antimicrobials rather than more appropriate, directed therapy informed by the identification of the infecting agent [3]. This overuse of antibiotics in both the community and the hospital setting is considered a significant driver for selecting resistance, hence the wider adoption of rapid tests at the point of decision making has the potential to reduce inappropriate treatment dramatically.

Influenza and RSV are two common viral causes of respiratory infections of global significance. They usually present as self-limited, uncomplicated upper respiratory tract infections characterized by an acute febrile illness, or are asymptomatic. Nonspecific symptoms...
may include headache, fever, myalgia, conjunctivitis, rhinorhoea, pharyngitis, dyspnoea, nonproductive cough, wheeze and nasal congestion. In some patients, particularly children aged <2 years and those with underlying immunosuppression, influenza and RSV may spread to the lower airways causing pneumonia and pneumonitis [45]. Infection in these high-risk patient groups is associated with more severe infection, often requiring hospitalization and excess mortality.

The clinical diagnosis of influenza and RSV is especially problematic during periods of endemic prevalence because other respiratory viruses (e.g., adenovirus, parainfluenza viruses and picornaviruses) also circulate during the same period. Some bacterial infections (e.g., *Chlamydia, Legionella* and *Mycoplasma*) may also present with similar nonspecific symptoms, and clinical features are a very poor predictor of infectious etiology [67].

A study of 3744 patients derived from clinical trials of zanamavir showed that a combination of fever and cough had the best sensitivities of 64% and a specificity of 67% for detecting influenza [8]. A further study in 706 children found that fever was the only sign that independently predicted influenza infection [9]. Thus, clinical findings may help to identify patients with influenza like illness but are poor predictors for confirming or excluding the diagnosis of influenza [10]. Furthermore, mixed infections with two or more respiratory pathogens are not uncommon, occurring in 10–40% of cases and which further complicates both clinical and laboratory diagnosis [11,12].

### Respiratory syncytial virus

RSV is an enveloped, single-stranded sRNA virus of the family Paramyxoviridae family [13]. There is an increased incidence in the winter months in temperate climates; this seasonality follows closely that of influenza viruses [14,15].

RSV most commonly affects children and the elderly [16] and has an incubation period of 2 to 8 days [16]. In the USA, RSV is the most common cause of hospitalization in infants [17]. Almost all children are affected by the age of 2 years; however, immunity is incomplete and reinfections are common. Primarily RSV has traditionally been considered a pediatric infection, and its burden on adults is probably under-recognized.

Transmission is by direct contact with either respiratory droplets or the hands of healthcare workers where it can survive for several hours, and several nosocomial outbreaks have been described [17–21]. In transplant patients and young children, infection with RSV can cause serious complications with mortality rates as high as 70–100% [22,23]. Because of these poor outcomes, most centers will delay stem cell transplant until the patient clears the infection.

### Influenza viruses

Influenza is an enveloped, single-stranded RNA virus of the family Orthomyxoviridae. Influenza A is the most common, and it is further subtyped according to the sequence of two glycoproteins: hemagglutinin (H) and neuraminidase (N). Influenza B is less common, but it still causes significant numbers of infection. Influenza C is rare and not usually included in diagnostic assays [5].

In temperate climates, flu causes seasonal infections in the colder winter months. Infection is highly contagious and spread from person to person by droplet infection through sneezing, coughing and by touching inanimate surfaces [24].

Approximately 20% of all children and 5% of all adults globally have symptomatic influenza infection each year [5]. The incubation period is between 1 and 4 days [4]. Each annual flu season is normally associated with a major influenza subtype, which changes from year to year. Influenza is one of the most changeable and mutable viruses affecting humans because of the low fidelity of the viral RNA replicase enzyme and the segmented RNA genome [25]. Influenza A has the ability to undergo antigenic shift causing unpredictable pandemics.

Antiviral drugs, such as oseltamivir and zanamivir, reduce the duration and frequency of symptoms, hospitalizations and complications, such as otitis media, bronchitis and pneumonia, if administered within 48 h and may also reduce mortality in certain populations [26–31]. In addition, using either drug as prophylaxis reduces the risk of developing symptomatic influenza in vulnerable household and hospital contacts.

#### Conventional testing for influenza & RSV

Accurate diagnosis is essential for the clinical management of the infected patient and of vulnerable healthcare and household contacts because antiviral prophylaxis may be offered to these individuals. The narrow time period available to offer these treatments requires a rapid diagnostic turnaround time, which is a challenge for current conventional testing techniques. Confirmatory laboratory results may influence a range of clinical management decisions including the institution or withholding of antivirals and antibiotics, whether to admit or discharge the patient, and the institution or withholding of infection control precautions. Empirical treatment and presumptive isolation prior to laboratory diagnosis are wasteful of resources and could be contributing to the emergence of resistance. Thus, there is a clinical need for rapid, accurate diagnostics, which could have a real role in helping to prevent indiscriminate and inappropriate use of these agents.

Conventional methods used to diagnose influenza and RSV include culture, direct fluorescent antibody assays and serology. Each of these methods has its disadvantages; slower culture growth, takes 7–14 days, meaning that the result is of little relevance to clinical treatment decisions and infection control interventions [32,33]. In addition, culture requires specialized laboratory facilities and expertise and is reliant on the subjective determination of cytopathic effect. Although highly specific, the direct fluorescent antibody tests are relatively complex, requiring significant expertise and reagents with a turnaround time of 2–4 h. Similarly, serology can offer only a retrospective diagnosis limiting the impact on patient care because antibody titers peak at 4–7 weeks after infection. This technique is most usefully used for conducting seroepidemiological studies [34].

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Rapid influenza tests

The two main bottlenecks for conventional laboratory-based testing are usually sample transportation from the patient to the centralized laboratory and the requirement for testing in batches. Rapid antigen tests were introduced to alleviate these delays and move the test closer to the patient [35].

These rapid tests and simple to use tests are enzyme and optical immunoassays for virus antigen. They generally provide results in 15–30 min, and there are a number of commercially available tests for both influenza and RSV [34,36–39], some of which are Committee for Laboratory Improvement Act waived or moderately complex tests.

Although these tests are usually fairly inexpensive (US$ 15–20) [40], they are variable in terms of diagnostic accuracy with reported sensitivities ranging from 10 to 80% [41–44]. In a pooled analysis of 159 studies of rapid influenza tests, sensitivity was reported at 62.3% (95% CI: 57.9–66.6%) with a range between 4.4 and 100% and specificity 98.2 (95% CI: 97.5–98.7) with a range between 50.5 and 100% [45]. The early reports of low sensitivity led to the recommendation that negative test results could not be used to rule out infection confidently and that negative samples should be further tested with more sensitive assays [46,47]. In addition, positive samples also require further testing for subtyping.

Despite this, the high specificities and positive predictive values (PPVs) during peak respiratory virus season allow faster diagnosis and treatment decisions and allow improved patient care by limiting additional and often unnecessary diagnostic tests in these patients. Pediatric studies, in particular, have demonstrated the reduced use of antibiotics and more appropriate use of antivirals after introducing influenza rapid testing [48–52].

Molecular methods

The first description of reverse transcription PCR for the detection of influenza was in 1991 and since then molecular diagnostics have been increasingly developed by Pillet et al. [53–55]. These have replaced traditional viral culture as the preferred diagnostic technique because of problems with turnaround time (usually 3 to 14 days) and reduced sensitivity of other methods [34,56]. In periods of outbreaks, these assays are very useful for testing large amounts of samples in a relatively short time.

Despite significantly quicker turnaround times, most of the molecular assays for detection of influenza and other respiratory viruses must be performed by specialist personnel in a centralized laboratory setting. Most samples will be tested in batches, and there may be significant sample transportation time to include.

Recently, there has been a trend to automation and miniaturization and molecular assays, and there are now several commercially available tests that might be suited to deployment in settings other than centralized laboratories. Committee for Laboratory Improvement Act waived or moderately complex tests can be performed by appropriately trained laboratory assistants or similar healthcare workers on instruments located outside of the centralized laboratory. Examples of this might be rapid response or satellite laboratories, where results can be used to make critical patient management decisions.

Current commercially available assays include the AlereTM influenza A&B assay [57,58], the Enigma ML FluAB-RSV Assay (Enigma Diagnostics, Salisbury, UK), the FilmArray® (BioFire Diagnostics, Inc., Salt Lake City, UT, USA) [59–61], the LiatTM influenza A/B Assay (Roche, Basel, Switzerland), the SimplexaTM Flu A/B & RSV Direct assay (Focus Diagnostics, Cypress CA, USA) [62–64], the Verigene® Respiratory Virus Plus test (Nanosphere, Inc., Northbrook, IL, USA) [61,63,65], and the Xpert® Flu assay (Cepheid, Sunnyvale, CA, USA) [66–68]. These assays range from being able to detect one or two targets (Liat and Alere-i) to a multiplex panel of over 20 pathogens including atypical bacteria (FilmArray) and have turnaround times of 15 (Alere-i) to 155 min (Vertigene). Relative performance characteristics of these assays are summarized in Table 1.

<table>
<thead>
<tr>
<th>Table 1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Enigma ML FluAB-RSV assay</strong></td>
</tr>
<tr>
<td><strong>Diagnostic Profile</strong></td>
</tr>
<tr>
<td><strong>Methods</strong></td>
</tr>
<tr>
<td><strong>Rapid influenza tests</strong></td>
</tr>
<tr>
<td><strong>Molecular methods</strong></td>
</tr>
</tbody>
</table>

There are multiple laboratory-based diagnostic accuracy studies comparing the performance of several of these assays. These appear to give favorable results, particularly when compared with the rapid enzyme immunoassays [57–68]. However, there are few reports in the literature of examples where these systems have been placed in a near-patient setting. Notable exceptions are a set of two small studies conducted in Japan using the Verigene Respiratory Virus Panel [52,69]. These evaluated the clinical use of this assay in the pediatric outpatient setting and in adult inpatients presenting with influenza like illness, where the assay was performed by non–laboratory-based physicians. The assay was able to facilitate better triage into isolation rooms. A further study evaluated the FilmArray Respiratory Panel when placed in a core laboratory of a regional children’s hospital, this allowed the mean turnaround time to be reduced from 7 to 1.6 h when compared with a direct fluorescence assay performed in a centralized laboratory [70].

Modeling of the use of a rapid influenza PCR in the emergency department has suggested that the economic benefit depends on the prevalence of the disease [71]. At a prevalence of 3 to 7%, it is cost–effective to use a rapid PCR; however, at a prevalence >7%, it is more cost–effective to treat all patients with antivirals. This study assumed a cost of US$ 53 per rapid PCR test, which included labor; clearly, the cost–effectiveness of a less expensive test may dominate. In addition, the model did not consider the often considerable burden of presumptively isolating and using personal protective equipment for patients with a presumptive diagnosis of influenza.

Like many other point-of-care tests that might be used to improve infection prevention and control, there is often a lack of good clinical outcomes data to support their widespread adoption [35]. Although many of these tests might be suited for the use outside of a laboratory setting, their use requires significant training for staff with no molecular biology or even laboratory experience. The use of these tests requires adherence to specific protocols that could potential cause disruption in the
<table>
<thead>
<tr>
<th>Table 1. Relative performance characteristics of several commercially available, rapid, multiplex molecular assays for the detection of influenza, RSV and other respiratory viruses.</th>
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<tr>
<td><strong>Assay name and manufacturer</strong></td>
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<tr>
<td>----------------------------------</td>
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<tr>
<td>Alere™ I Influenza A&amp;B</td>
</tr>
<tr>
<td>Enigma™ ML FluAB-RSV, Enigma Diagnostics, Salisbury, UK</td>
</tr>
<tr>
<td>FilmArray® Respiratory Panel, BioFire Diagnostics Inc. (now BioMerieux), Salt Lake City, UT, USA</td>
</tr>
<tr>
<td>LiaT™ Influenza A/B Assay, IQuum Inc. Marlborough, MA, USA (now Roche)</td>
</tr>
<tr>
<td>Simplexa™ Flu A/B RSV Direct assay, Focus Diagnostics, Cypress CA, USA</td>
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</table>

†As stated in manufacturer’s package insert. 
CLIA: Committee for Laboratory Improvement Act; NA: Nasal aspirate; NPS: Nasopharyngeal swab; NS: Nasal swab; NW: Nasal wash; RSV: Respiratory syncytial virus; RT-PCR: Reverse transcriptase polymerase chain reaction.

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clinical workflow and increase demands on already busy clinical personnel. There is a need to study the practicalities of using these tests in a near-patient setting and which look at ease of use, patient and staff acceptability, clinical outcomes and cost–effectiveness.

### The Enigma® ML (mini-laboratory) platform

The Enigma ML is a CE-IVD marked, fully integrated and automated molecular testing platform using real-time PCR to produce rapid results in approximately 90 min. It uses single-use disposable cartridges that can be stored at ambient temperature. These are self-contained units containing all reagents necessary for sample extraction, amplification and detection. All assay reagents are retained within the cartridge, minimizing the risk of cross-contamination or human error. The Enigma ML system was designed for ease of use targeting non-laboratory personnel in a point-of-care or near-patient setting.

The system requires less than 2 min of hands on time. Once the patients details have been entered and the cartridge has been loaded, the user can walk away, leaving the instrument to complete testing. A built-in barcode reader facilitates transfer of operator, patient and cartridge/assay identification.

The platform is scalable with each module operating independently; this allows a menu of assays to be run at the same time. This obviates the need for batch testing, allowing true random access and providing clinical results on demand. The instrument has a footprint of 35 × 31 cm for a single module option up to 35 × 94 cm for a six-module option, weighing between 20 and 76 kg. The instrument does not require an external computer because it is controlled by a built-in touch screen color display. Figure 1 shows the platform in a single module configuration.

### The Enigma ML FluAB-RSV assay

The Enigma ML influenza A/B & RSV A/B assay has CE-IVD designation and is available in all European countries, where CE marking is recognized and there are plans to seek FDA approval in the near future. The assay is based on a magnetic bead sample purification and concentration combined with a fluorogenic reverse transcriptase PCR. Cartridges are foil sealed in blisters for stability and are supplied with a sample collection kit. The nasopharyngeal swab is collected and placed in the sample collection tube, which is then loaded into the cartridge and placed in the ML. As the sample tube is pushed forward, the foil cap is pierced allowing the contents to flow into the cartridge sample well. The sample pipettor transfers and mixes sample into the freeze-dried internal process control (bacteriophage MS2). This validates that both sample preparation and PCR amplification have occurred efficiently. Any failure to detect MS2 indicates that the test has failed. This mixture is then transferred to the lysis well, which contains a guanidine salt. Nucleic acids are released by the combination of chemical and thermal cell lysis. A magnetic wand is used first to transfer magnetic beads, mix the sample and keep the beads suspended. The beads bind the released nucleic acids, which are captured...
by the wand and transferred to wash wells. Two sequential wash steps are used in this process to remove inhibitory substances before transferring to the elution well where the sample is mixed. After the magnetic beads have been removed, the sample is mixed with the freeze-dried PCR reagents containing fluorescently labeled primers and probes and transferred to the Electrically Conducting Polymer capillary. This is overlayed with mineral oil and a stopper seals the capillary before PCR, which prevents cross-contamination. Figure 2 shows a visual representation of the Enigma ML disposable cartridge.

Primers and probes have been designed for the qualitative detection of influenza A (matrix gene), influenza B (non-structural gene), RSV (fusion gene) together with the previously described internal process control. Primers are used to generate pathogen-specific cDNA for signal detection using one-step reverse transcriptase PCR. Hybridization probes are then used to differentiate between target nucleic acid through dual-hybridization and fluorescent resonant energy transfer. Fluorescent resonant energy transfer allows for a single excitation source, which ‘excites’ the donor fluorophore, this then transfers its energy to an ‘acceptor’ fluorophore when stably positioned in close proximity. The acceptor then emits energy as light at a longer fluorescent wavelength, which is detected in specific channels. The light source and fluorophores that are chosen to ensure only target-specific sequences are detected by the binding of both probes. The amount of acceptor fluorescence is proportional to the amount of PCR product present, which allows for amplification detection.

The ability of ML for high resolution melt enables in silico design of probes, which have specific melting temperatures at which they denature from the amplicon, thereby reducing fluorescence. This allows for differentiation of bound probes, allowing identification of target nucleic acids across the four signaling channels on the ML. These temperature-dependant specific responses are detected and measured by the Enigma ML optics, and an automated algorithmic process reports the presence or absence of each target. Finally, the cartridge is ejected and disposed of as clinical waste.

Performance characteristics in experimental & clinical studies
There are no published data on the clinical performance of the Enigma assay. However, performance data are available from the package insert [72]. The analytical sensitivity claimed by Enigma is 0.2–5 TCID50/ml for influenza A,
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Table 2. Performance characteristics of the Enigma ML FluAB/RSV assay using the Luminex xTAG RVP as gold standard comparator.

<table>
<thead>
<tr>
<th>Test</th>
<th>True positive (n)</th>
<th>True negative (n)</th>
<th>False positive (n)</th>
<th>False negative (n)</th>
<th>Sensitivity (%) (95% CI)</th>
<th>Specificity (%) (95% CI)</th>
<th>Positive predictive value (%) (95% CI)</th>
<th>Negative predictive value (%) (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>Influenza A</td>
<td>25</td>
<td>176</td>
<td>3</td>
<td>0</td>
<td>100 (98.2–100)</td>
<td>98.3 (95.5–99.4)</td>
<td>89.3 (84.3–92.8)</td>
<td>100 (98.2–100)</td>
</tr>
<tr>
<td>Influenza B</td>
<td>53</td>
<td>149</td>
<td>2</td>
<td>0</td>
<td>100 (98.2–100)</td>
<td>98.7 (96–99.6)</td>
<td>96.4 (92.8–98.2)</td>
<td>100 (98.2–100)</td>
</tr>
<tr>
<td>RSV</td>
<td>24</td>
<td>179</td>
<td>1</td>
<td>0</td>
<td>100 (98.2–100)</td>
<td>99.4 (97.2–99.9)</td>
<td>96 (92.4–100)</td>
<td>100 (98.2–100)</td>
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</table>

RSV: Respiratory syncytial virus; RVP: Respiratory viral panel.

0.1–0.5 TCID50/ml for influenza B and 0.06–2.5 TCID50/ml for RSV.

A study was performed using clinical samples obtained in Uganda during the 2013 Southern Hemisphere influenza season. Samples were collected from both adults and children before shipping on dry ice to Enigma Diagnostics for testing. A total of 204 nasopharyngeal swabs derived from patients showing symptoms of influenza-like illness were tested using both the Enigma ML and the Luminex Respiratory Viral Panel FAST version 2 CE-IVD system (Luminex Corp., Austin, TX, USA). Samples were split and tested in parallel, using the xTAG Respiratory Viral Panel as gold standard. For influenza A the sensitivity, specificity, PPV and negative predictive value (NPV) were 100% (95% CI: 98.2–100), 98.3% (95% CI: 95.5–99.4), 89.3% (95% CI: 84.3–92.8) and 100% (95% CI: 98.2–100), respectively. There were three false-positives and no false-negatives. For influenza B, the sensitivity, specificity, PPV and NPV were 100% (95% CI: 98.2–100), 98.7% (95% CI: 96–99.6), 96.4% (95% CI: 92.8–98.2) and 100% (95% CI: 98.2–100), respectively. There were two false-positives and no false-negatives. For RSV, the sensitivity, specificity, PPV and NPV were 100% (95% CI: 98.2–100), 99.4% (95% CI: 97.2–99.9), 96.4% (95% CI: 92.4–100) and 100% (95% CI: 98.2–100), respectively. There was one false-positive and no false-negatives. Table 2 summarizes the performance characteristics for the three targets.

Future developments on the Enigma ML system

Currently, the FluAB-RSV assay is the only available test for the EnigmaML platform; however, Enigma are in late stage development of tests for a multiplexed Respiratory Virus Panel (influenza A and B, RSV, parainfluenza and rhinovirus) and multidrug resistant tuberculosis, which will detect all rifampicin and isoniazid resistant variants directly from sputum, reflecting their initial focus on respiratory infections. In the longer term, Enigma are developing multiplexed tests for sexually transmitted infections (chlamydia gonorrhoea and syphilis), bacterial pneumonia (covering community and ventilator-associated infection), detection of carbapenem-resistant organisms from rectal swabs and a test for bacteremia directly from blood samples.

Conclusion

The Enigma ML FluAB-RSV assay is a new CE-IVD marked assay with encouragingly high sensitivity and specificity. It is rapid, providing a qualitative result in 95 min and allows for operation by nonlaboratory trained personnel. It is thus well suited to deployment in a near-patient setting and is capable of testing up to 30 samples during an 8-h shift. Because of the nonspecific symptoms of respiratory infections, the ability to rule in or out a particular organism rapidly could improve patient pathways and reduce inappropriate prescribing and infection control interventions. The platform and planned menu of assays may be an attractive option for rapid diagnosis in the near-patient setting, as well as centralized laboratories that do not have the expertise or resources to develop their own molecular panels.

Expert commentary

Enigma ML FluAB-RSV assay is a fully automated and integrated test that has the potential to reduce laboratory turnaround times significantly by overcoming delays in sample transportation and batching. The system has the advantage of being able to be run by nonspecifically trained operators close to the frontline.

There are limited clinical data available on this system, and its adoption will depend on results of independently conducted investigations that verify its performance; ideally, these would include more than just diagnostic accuracy data. An assessment of ease of use and clinical use are important factors for healthcare organization to consider before committing to a particular assay.

Five-year view

Fully automated PCR and other molecular tests show great promise in offering sensitive and rapid results that are operator friendly and simple to use. Most are moderate complexity meaning that in North America at least this limits the
opportunity for placement in point of care settings, such as emergency departments. However, these are the exact environments where such tests can realize their full potential.

Technological advances will allow increasingly multiplexed assays to be introduced during the next 5 years, permitting whole body system-based syndromic diagnosis of disease, which will enhance epidemiological surveillance. This approach may also be suitable for other areas, such as gastrointestinal infection and meningitis.

Currently available molecular panels are very diverse ranging from the very fast (15 min) detection of one or two targets to a slower but much broader simultaneous diagnosis of a range of both bacterial and viral pathogens. The turnaround time requirement will likely affect the environment in which such a system is placed.

These assays should offer benefits to individual patients in both the hospital and the community setting, as well as enhancing epidemiological surveillance and public health. However, the additional cost and lack of clinical outcomes and cost-effectiveness data will be the major barriers to widespread adoption.

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No writing assistance was utilized in the production of this manuscript.

Key issues
- Influenza and respiratory syncytial virus (RSV) are pathogens of global importance with the potential to cause large outbreaks in the community and hospital setting.
- Diagnosis based on clinical signs and symptoms alone is unreliable because the features of infection are poorly discriminating. Diagnostic tests are required to confirm the presence of infection.
- Rapid influenza antigen tests are poorly sensitive and thus cannot be relied on to exclude infection.
- There are a number of commercially available molecular assays that are able to detect influenza and RSV from clinical specimens, many of which are suited to a rapid testing laboratory.
- The Enigma® ML FluAB-RSV assay is one such commercially available test, providing a result in 95 min. There are limited data on its performance but early reports suggest high sensitivity and specificity.
- There is a need to study the clinical use of these assays, which include data on patient outcomes and cost-effectiveness.

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• of interest
** of considerable interest
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Enigma ML FluAB-RSV assay

Diagnosis Profile

**A Cochrane Intervention Review of 20 oseltamivir and 26 zanamivir trials. The duration of influenza-like illness symptoms was found to be shortened by less than 1 day.**


72. Enigma. Enigma ML FluAB-RSV package insert. Enigma ML