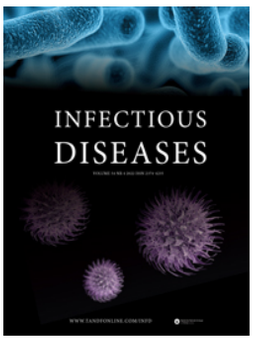

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ORIGINAL ARTICLE

Comparison of rapid molecular testing methods for detecting respiratory viruses in emergency care: a prospective study

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ABSTRACT

Background: Respiratory tract infections (RTIs) caused by contagious viruses are common among patients presenting to the emergency department (ED). Early detection of these viruses can help prevent nosocomial transmission.

Aim: To investigate the efficacy of three rapid molecular methods, namely FilmArray® Pneumonia Panel plus (FAP plus), ID NOW™ Influenza A and B 2 (ID NOW2) point-of-care test, and an in-house real-time polymerase chain reaction (RT-PCR) test, to identify patients with viral RTIs requiring isolation in an emergency setting.

Methods: We included a FilmArray® Pneumonia Panel plus in the initial workup of patients with suspected RTIs during a flu season. The RT-PCR and the influenza point-of-care test were performed as part of routine diagnostics, on demand from the treating physicians. We compared viral detections and compared time to positive test results for each method.

Findings: The FAP plus significantly reduced the turnaround time and was able to identify 95% patients with potential contagious viral RTI. Routine diagnostics ordered by the treating physician had a turnaround time of a median 22 h and detected 87% of patients with potential contagious viral RTI. In patients that had all three tests, the ID NOW2 detected 62% of patients with influenza.

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Conclusions: The FAP plus was able to rapidly and reliably identify patients with potential contagious viral RTIs; its use was feasible in the ED setting. Failing to test patients with viral RTI and using tests with long turnaround time may lead to nosocomial transmission of viral infections and adverse patient outcomes.

KEYWORDS
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Introduction

Respiratory tract infections (RTIs) are among the most common complaints of patients presenting to the emergency department (ED) during flu season [1]. The United States Centres for Disease Control and Prevention recommend using droplet precautions when caring for patients with influenza virus infections and contact precautions when caring for those with parainfluenza virus, rhinovirus, respiratory syncytial virus (RSV) or human metapneumovirus (hMPV) infections. Cases of nosocomial transmission of these viruses have been reported [2–7]. Contact precautions include housing patients in a single-patient room and wearing of gown and gloves for healthcare personnel caring for patients in potentially contaminated areas in the patient's environment. Droplet precautions include similar measures but also require healthcare personnel to wear a mask for close contact with an infectious patient. Most EDs lack the space to isolate all patients with respiratory tract symptoms; standard operating procedures require patients to remain in crowded waiting rooms until patient rooms become available. Such space limitations and overcrowding facilitate nosocomial transmission of infections [8]. Early identification of patients with communicable RTIs is thus an important preventive measure. In fact, in the initial days of the severe acute respiratory syndrome coronavirus-2 (SARS CoV-2) outbreak, hospital-associated transmission was the suspected mechanism for the disease spreading in a large proportion of patients [9].

Nucleic acid amplification tests are commonly used methods of testing for the presence of respiratory viruses. Although these tests can be highly sensitive and specific, their observed sensitivity and specificity depend on the kind of respiratory specimen and the specific testing method used, and false negatives are possible depending on testing method and time since symptom onset. Nucleic acid amplification tests can be performed with different kinds of respiratory samples, including those obtained through swabs, brush, aspiration and wash/lavage. Samples can be taken from the upper respiratory tract, including the anterior and posterior nasopharynx, oropharynx and nares, or the lower respiratory tract, including sputum, tracheal aspirates or bronchoalveolar lavage. Different sampling methods and assays have been associated with different diagnostic sensitivity [10–12]. RT-PCR is considered a gold standard for diagnosis of respiratory viruses [13]. However, a gold standard for diagnostic testing has not been established, and studies have suggested that respiratory viruses may progress from the upper respiratory tract to the lower airways with the duration of the disease [14,15].

The Biofire® Pneumonia FilmArray® panel (FAP plus) tests for 18 bacteria, seven antibiotic resistance markers and nine viruses that cause pneumonia and other lower RTIs. Previous studies have focussed on detection of bacteria [16–18]. We aimed to assess the feasibility of the BioFire® FilmArray® Pneumonia Plus Panel (Biomérieux, Marcy l'Etoile, France), in detecting respiratory viruses in an ED setting. We hypothesized that, compared with other types of tests, FAP plus may provide a more rapid and reliable microbiological diagnosis and thus optimize the use of isolation procedures. To the best of our knowledge, this is the first study to test the efficacy of the FAP plus in identifying respiratory viruses in ED patients suspected of having RTIs that according to guidelines should be handled with contact or droplet precautions among those presenting at the ED with symptoms of RTI.

Methods

This investigation was a sub-study nested within a feasibility study conducted prior to an ongoing randomized controlled trial on community-acquired pneumonia. The feasibility study was a prospective cohort study of patients with community-acquired pneumonia admitted to the ED. The sub-analysis was done on patients with one or more positive test for a respiratory virus that according to guidelines, should be handled with

increased infection control measures. The study was approved by the Regional Committee for Medical and Health Research Ethics in Norway (Ethics approval: REK 31935 and NCT 04660084), and the data collection was conducted in accordance with the Declaration of Helsinki's principles of Good Clinical Practice. Written consent was obtained from all participants or their legal guardians or next of kin at the time of recruitment.

The study was conducted at the Haukeland University Hospital in Bergen, Norway, between 2 December 2019 and 17 February 2020. Only adult patients who were admitted to the ED with clinical signs of lower RTI were eligible for inclusion in this study. Patients were enrolled on weekdays between 08:00 a.m. and 09:00 p.m. Most patients were enrolled in the ED shortly after admission. To compensate for the restricted study operating hours, some cases were included at the wards up to a maximum of 24 h after admission. Patients were excluded from this study if they met any of the following criteria: diagnosis of cystic fibrosis or severe bronchiectasis, hospitalization within 14 d prior to admission, requiring a palliative approach (defined as life expectancy $<$ 2 weeks), or unwillingness or lack of capacity to provide a lower respiratory tract sample.

Patients' baseline characteristics were collected during a structured interview. Patients' symptoms and findings from clinical examinations were recorded, as was the time of microbiological sampling and reporting of results. Data were stored in an electronic case report form provided by VieDocTM (Viedoc Technologies, Uppsala, Sweden).

We included a FAP plus test in the initial workup of patients with suspected RTIs during a flu season. The RT-PCR and ID NOW2 were performed as part of routine diagnostics on request from the treating physicians. Saline-induced sputum was collected for all patients. For patients unable to produce a sputum sample, endotracheal aspiration was performed. Saline-induced sputum or endotracheal aspirates were analysed on the FAP plus. The time used to obtain a sputum sample was recorded in 10-min intervals by the study staff. Except for the FAP plus, the choice of running other microbiologic tests was at the discretion of the treating physician. In addition to culture-based microbiological diagnostics, the clinicians could use The ID NOW™ Influenza A and B 2 tests provided by ID NOW Influenza A and B 2 (Lake Forest, IL) and an in-house nucleic acid amplification-test, using real-time PCR. We recorded the time for presentation in the ED, time for microbiologic sampling and the time when the test results were available for the clinician. The time from presentation in the ED to the time when the test results were available for the clinician for microbiological tests was compared with Student's paired t-test.

FAP plus is a closed system that performs nucleic acid extraction, nested multiplex PCR analysis, and the endpoint melting curve analysis, using FilmArray 1.5 and 2.0 and torch instruments. The assay tests for 15 typical bacterial pathogens (11 Gram-negative and 4 Gram-positive species), three atypical bacterial pathogens, nine viral pathogens and seven antibiotic resistance genes. Results for typical bacteria are reported in a semi-quantitative format. The viral pathogens included in our current analysis were adenovirus, hMPV, human rhinovirus/enterovirus, influenza A, influenza B, parainfluenza virus, RSV and coronavirus. The assay was performed according to the manufacturer's instructions. According to the manufacturer, the test is valid for induced and expectorated sputum, endotracheal aspirates and bronchoalveolar lavage samples [19].

The ID NOW™ Influenza A and B 2 (Abbott Scarborough Diagnostics, Lake Forest, IL; 'ID NOW2') uses isothermal nucleic acid amplification technology that is based on the nicking enzyme amplification reaction method used for the detection and differentiation of influenza A and B viruses. The test targets the polymerase basic gene-2 and polymerase acidic gene to differentiate between influenza A and B viruses, providing results within 15 min. The assay was performed according to the manufacturer's instructions. The test is validated for nasal swabs only [20].

The in-house PCR provides results for *Bordetella pertussis*, *Bordetella parapertussis*, *Mycoplasma pneumonia*, *Chlamydia pneumonia*, influenza A and B, human parainfluenza viruses 1, 2 and 3, RSV, hMPV and rhinovirus. The test has been validated for samples obtained with nasopharyngeal swabs, throat swabs, sputum, bronchoalveolar lavage and bronchoscopic protected specimen brushes. In this study, only nasopharyngeal swabs and throat swabs were analysed in the in-house PCR.

The ID NOW2 test was available in the ED, allowing for a short delay between collecting samples and receiving results; meanwhile, other tests were performed off site, requiring transport to another building or a laboratory further afield. In addition, as the microbiology laboratory does not operate overnight, samples collected late in the day or at night were analysed the following day. FAP plus required approximately 70 min to complete. As the testing capacity at our FilmArray platform was limited, results could be delayed when there was

large number of samples. The in-house RT-PCR machine was operated twice per day during the flu season.

For the purpose of this study, influenza viruses, parainfluenza virus, rhinovirus, RSV or hMPV or a combination of these viruses were considered as agents for a contagious viral RTI requiring isolation.

Analysis

We compared the sensitivity of virus detection among the test strategies. Detection rates were calculated using viral detections from all three tests. To represent real-life test performance, we did an intention-to-diagnose analysis for all patients, comparing detected respiratory viruses in tests ordered by the treating physician with the viruses detected by all three tests. To test the performance of each test, we separately analysed data from patients who had undergone all three tests. We also compared the time from collection of respiratory samples to result for each method. For each method, we calculated the time from presentation in the ED to the detection of a potential contagious respiratory virus. We also estimated the time to appropriate isolation associated with different testing strategies, including combinations of tests. The time for delay of isolation using FA plus in addition to standard diagnostics was compared using the Mann–Whitney U-test for continuous data using SPSS (IBM Corp., Armonk, NY).

Results

This study included a total of 104 patients. Among them, 55 patients provided respiratory tract samples that tested positive for either influenza, parainfluenza, rhinovirus, RSV, hMPV or a combination of these viruses in one or more of the tests used in the study. These patients were included in further analyses. The median time from presentation in the ED to inclusion was 0.98 h (interquartile range 0.4–2.9 h). In accordance with the study design, all 55 patients (100%) received the FAP plus test. The median time to perform saline induce sputum was between 10 and 20 min (exact time was not recorded). A total of 49 (89.1%) patients received an in-house PCR test (based on throat swabs, nasopharyngeal swabs or both), and 48 (87.3%) patients received the ID NOW2 test. Forty-two patients received all three tests, and a separate analysis was performed for these patients (see Figure 1).

The patients' baseline characteristics are presented in Table 1. Influenza virus A was the most frequent finding in this study and was present in 29 of 55 (52%) patients, followed by hMPV, which was present in 16 (29%) patients. Two (4%) patients tested positive for multiple viruses.

Table 1. Baseline characteristics for the 55 patients included in the study.

	Median	Range		Count	(%)
Age (years)	73.0	18–96	Females	30	55
NEWS	3.0	0–9	Current smokers	17	31
qSOFA	1.0	0–2	Former smokers	15	27
SOFA	2.0	1–5	Chronic lung disease	20	36
CRB65	1.0	0–2	Hypertension	25	45
CURB65	1.0	0–3	Coronary artery disease	7	13
PSI	86.5	18–154	Chronic kidney disease	9	16
LOS (days)	3.9	0.04–8.2	Diabetes mellitus	9	16
–	–	–	Cancer	3	5

NEWS: National Early Warning Score; qSOFA: quick Sepsis-related Organ Failure Assessment; CRB65: CRB-65-score for Pneumonia Severity; CURB65: CURB-65 Score for Pneumonia Severity; SOFA: Sepsis-related Organ Failure Assessment; PSI: Pneumonia Severity Index for CAP; LOS: length of stay

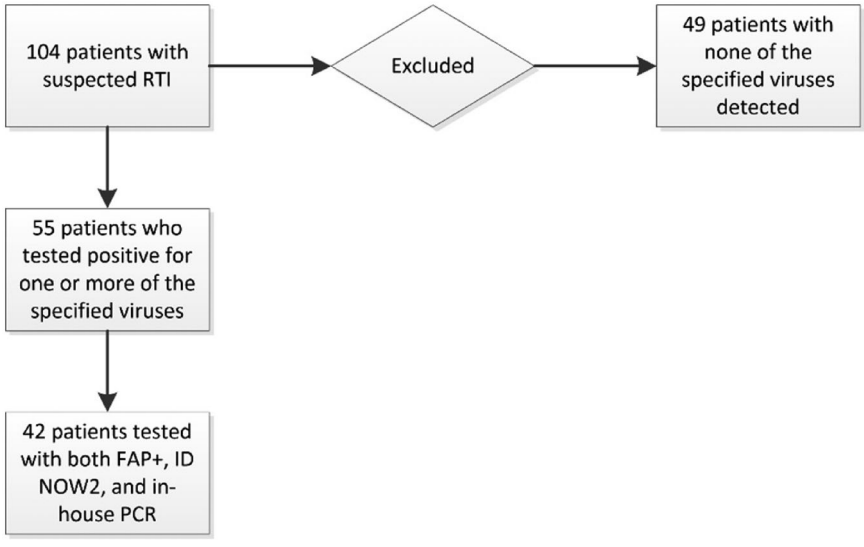

Figure 1. Study population and enrolment.

Table 2. Detected adenovirus, human metapneumovirus, human rhinovirus/enterovirus, influenza A, influenza B, parainfluenza virus, respiratory syncytial virus in patients with complete test sets and sensitivity when compared to all methods.

Virus	Total count	FAP plus (%)	In-house PCR (%)	ID NOW2
Influenza	21	21 (100)	19 (91)	13 (62%)
Respiratory syncytial virus	5	5 (100)	5 (100)	NA
Human metapneumovirus	13	10 (77)	11 (85)	NA
Rhinovirus	2	2 (100)	1 (50)	NA
Parainfluenza	1	1 (100)	1 (100)	NA
Total	42	39 (93)	37 (88)	–

Viral detections

Systematic use of the FAP plus resulted in detection of 54 of 57 (95%) viruses, identifying 52 of the 55 (95%) patients with contagious viral RTI. The intention-to-diagnose analysis revealed that 49 of 57 (86%) viruses were detected by routine diagnostics (RT-PCR and ID NOW2) during the study period, identifying 48 of 55 (87%) patients with potential contagious viral RTI. The in-house RT-PCR test detected 44 of 57 (77%) viruses, identifying 45 of 55 (82%) patients with potential contagious viral RTI. Only 17 (59%) of the 29 patients with influenza, or 30% of the patients with potential contagious RTI, were detected by the ID NOW2 test in the ED.

All three tests, i.e. both ID NOW2, in-house PCR and the FAP plus, were performed in 42 (76.4%) patients. Data from these patients were analysed separately. Table 2 presents the microbiological findings. The FAP plus had a 100% detection rate for all viruses of interest, except hMPV. The in-house RT-PCR detected 37 of 42 viruses (88%). The ID NOW2 detected influenza A in only 64% of patients which was confirmed by at least one other test. A single patient tested positive for influenza B *via* ID NOW2 while other analyses for influenza B were negative. The same patient tested positive for human rhinovirus/enterovirus using the FAP plus, leading to a conclusion that the ID NOW2 result was likely a false positive.

Time to positive test result

Overall, the median time from test initiation to result for the ID NOW2, the FAP plus, and the RT-PCR test was 0.25 (range not recorded), 2.6 (range 1.4–17.6) h and 23.0 (range 7.6–49.8) h, respectively. For the cases with influenza virus infection ($n = 29$), it was 0.25, 2.6 (range 1.4–17.6) h and 22 (range 13.1–45.8) h, respectively. The median time from presentation in the ED to test result for the ID NOW2, the FAP plus and the RT-PCR was 0.6 (range 0.25–3.1) h, 4.9 (range 2.6–26.6) h and 25.2 (range 9.4–50.4) h, respectively.

We calculated the time from ED presentation to identification of isolation needs given different testing strategies. When using a combination of all three tests, the median time from testing to a positive result was 2.4 (range 0.25–27.9) h for patients with any virus and 1.8 (range 0.25–17.6) h for patients with influenza. Corresponding numbers when using our standard diagnostics (a combination of the ID NOW2 and in-house PCR) were 21.5 (range 0.25–49.8) h for all viruses and 6.7 (range 0.25–43.9) h for influenza. If using a combination of the FAP plus and the in-house PCR, time to a positive test result would have been 2.7 (range 1.4–25.0) h and 2.6 (range 1.4–17.6) h, respectively. Adding FAP plus to the standard diagnostics significantly reduced the time to a positive test result ($p < .001$).

Discussion

In this study, addition of the FAP plus was associated with a shorter time than standard diagnostics to detection of respiratory virus that according to guidelines should be handled with increased infection control measures. It also had a high sensitivity. There is a growing body of evidence that a rapid diagnosis of viral RTI improves patient management and clinical outcomes, reduces the rate of hospital admissions, improves the ED triage time, optimizes the duration of isolation and total hospitalization, and supports effective use of ancillary laboratory procedures, including imaging-based and antimicrobial tests. Infection prevention and control is a critical and integral part of clinical management of patients, now more than ever in light of the ongoing pandemic [21]. Knowledge of characteristics of diagnostics tests, including sensitivity, is important to understand how to best apply these tests for patient care and disease surveillance. In our study, we have studied the detection of respiratory viruses, but in a clinical setting, a negative test result with a highly sensitive test can be equally important for optimal patient handling [22–24]. Thus, the introduction of the FAP plus in an emergency care setting may help reduce the risk of nosocomial spread of communicable RTIs by rapid, reliable identification of isolation needs.

At our hospital, we have used different approaches for determining the need for isolation among patients with suspected contagious RTI. One of these approaches involves isolating all patients, while awaiting the confirmation of a contagious RTI by the in-house RT-PCR

test. Another approach involves performing a rapid influenza test and isolating only those patients whose test results are positive. The latter approach was used during the study period. An ideal test for identification of patients with respiratory viruses that according to guidelines should be handled with contact or droplet precautions in the ED should have a high sensitivity and a short turnaround time. The FAP plus has a relatively short turnaround time; however, in practice, this time may be extended due to the limited laboratory capacity. This delay may be reduced to a minimum if platform capacity is adequate and transportation to the test-facility optimized. In addition to the turnaround time in the laboratory, the time from ED presentation to the test result is available for the treating clinician is dependent on the time from patient arrival to testing, the sampling time and time for transportation to the laboratory. Although we used saline-induced sputum for the FAP plus, the time from presentation in the ED to test result was significantly shorter with this test when compared to our standard diagnostics.

The ID NOW2 has a short turnaround time; however, it can only test for influenza virus, and differentiate between influenza virus A and B. According to Abbot, the test has a sensitivity of 96.3 and 100% and a specificity of 97.4 and 97.1 for Influenza A and B, respectively, when compared to PCR [25]. In other studies, the test has shown mixed results [26–28]. The test seems to perform better when performed off site by trained laboratory personnel [29,30]. In this study, the ID NOW2 was associated with poor detection rate when compared to the other tests for influenza, suggesting that relying solely on this test may increase the risk of nosocomial transmission of influenza. This low sensitivity may be due to several factors. First, the test has been validated only for samples obtained through nasal swabs; in some patients, the viral load may be higher in other parts of the respiratory tract [15]. Second, the test was performed by the ED staff rather than by trained laboratory personnel. The ID NOW2 is designed to be placed in EDs and other point-of-care locations [25]. Consequently, its real-life sensitivity may be lower than that achieved in controlled settings, as reported by the manufacturer.

In this study, we have used different sampling materials for the different diagnostic assays. Most previous studies have found nasopharyngeal swabs to be the most sensitive sampling method of detecting viruses in the respiratory tract [10,12]. However, few studies have compared the sensitivity of tests performed using samples from the upper *vs*. lower part of the respiratory tract for detection of respiratory viruses. In a study by Jeong et al., the overall infection detection rate in adult patients was 68% for sputum compared to 53% for nasopharyngeal swabs using multiplex RT-PCR [31]. This finding is consistent with that of a separate study, in which sputum samples were associated with a higher diagnostic yield than were nose and throat swabs obtained from adult patients and analysed using RT-PCR [14].

Most previous studies that compared different respiratory specimen collection methods focussed only on their use in the detection of the influenza virus [10,11,32]. However, the most suitable respiratory specimen may vary between viruses [12]. During the SARS CoV-2 outbreak, samples obtained from the lower airways have been associated with sensitivity higher than that associated with samples obtained from the upper respiratory tract [33]. Influenza, RSV, and hMPV infection may manifest as lower RTIs; in fact, false-negative results from tests based on samples obtained from the upper airway have been reported [15]. A recent review recommends that lower respiratory tract samples be collected from patients supported by mechanical ventilation, as the viral load is typically higher and the shedding process is longer in this region than are those observed in the upper airways [34]. Although sputum samples may be more sensitive than nasopharyngeal swabs for the detection of respiratory viral detection, the use of sputum samples is limited by the fact that some patients with RTIs, for example, older adults may not produce sputum [35]. In this study, we used saline-induced sputum; this approach tends to be time consuming and may be challenging in the ED setting, but in our study, most of the patients were able to produce a sputum specimen in less than 20 min. However, other validated point-of-care tests based on samples obtained through throat swabs and nasopharyngeal swabs are commercially available and may be suitable in cases where lower respiratory tract samples are difficult to obtain[17,36].

The intention-to-diagnose analysis has revealed that physicians did not suspect communicable viral RTIs in some of the patients. This shows that routine testing for respiratory viruses may be warranted in all patients presenting with symptoms consistent with an RTI. This approach may be particularly relevant in the context of the ongoing outbreak of the SARS CoV-2. As the in-house PCR test has a long turnaround time, relying on it may lead to the overuse of resources, including isolation rooms and treatment equipment, which in turn may drive up the cost of care, increase staff workload and

delay treatment [37]. A previous study has found that isolated patients are twice as likely to experience an adverse event and seven times more likely to experience a preventable adverse event than those who are not isolated [38]. These findings suggest that unnecessary isolation should be prevented.

This study has some limitations. First, the sample size was small; however, our findings were consistent with those of previous studies showing that analysis of lower respiratory tract samples detects more pathogens than swabs from upper airways. Second, we have compared the diagnostic sensitivity of samples obtained from different parts of the respiratory tract and analysed using different testing methods. In a future study, we intend to compare the diagnostic sensitivity of different sampling methods, using the same method to analyse all samples. Quantitative RT-PCR data would have been useful to help address the question of active replication in the lower airways *vs.* low residual levels of RNA from a prior infection. However, provided that all patients in this study had symptoms of RTI, a positive detection is more likely to be clinically relevant than if asymptomatic patients were tested. Finally, this study was performed before the SARS CoV-2 was epidemic in Norway. The pandemic, however, has changed the flow of patients through the ED. Early identification of contagious RTIs is paramount to patient safety and more important now than ever. A point-of-care rapid diagnostic test for RTIs should include tests for SARS CoV-2.

Conclusion

A short turnaround time of microbiologic tests and high diagnostic sensitivity are important to ensure effective use of isolation procedures in the ED. Using the FAP plus may provide relatively quick results and reliably identify patients with potential communicable RTIs; moreover, collecting saline-induced sputum samples from patients with suspected RTI is feasible in the ED setting. In adult patients presenting with RTI, systematic testing with samples collected from the lower respiratory tract were associated with detection rates of respiratory viruses that were higher than when testing only patients where the clinician suspected viral RTI.

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Disclosure statement

None declared.

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