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Original Article

Evaluation of FilmArray respiratory panel multiplex polymerase chain reaction assay for detection of pathogens in adult outpatients with acute respiratory tract infection

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ABSTRACT

Although viruses are the major pathogen that causes upper respiratory tract infection (URTI) and acute bronchitis, antibiotics have been prescribed. This was a prospective observational study in influenza epidemics that enrolled adult outpatients who visited a hospital with respiratory tract infection symptoms. In this study, we evaluated the usefulness of FilmArray respiratory panel (RP). Fifty patients were enrolled. FilmArray RP detected the pathogens in 28 patients. The common pathogens were *influenza virus* (n = 14), *respiratory syncytial virus* (n = 6), and *human rhinovirus* (n = 6). Of the 14 patients with *influenza virus*, 6 were negative for the antigen test. The physicians diagnosed and treated the patients without the result of FilmArray in this study. Of the patients with positive FilmArray RP, 9 were treated with antibiotics; however, bacteria were detected in only 3 patients. By implementing FilmArray RP, URTI and acute bronchitis would be precisely diagnosed, and inappropriate use of antibiotics can be reduced.

1. Introduction

Acute respiratory tract infection (ARTI) is one of the major infectious diseases that may occur at any age and accounts for 3.5 million deaths worldwide [1]. ARTIs are classified as acute upper respiratory tract infection (URTI), acute bronchitis, or pneumonia. Diagnosis of ARTI except pneumonia is largely based on clinical signs and symptoms, because viruses, the most commonly causative pathogens of URTI and acute bronchitis, are difficult to detect. However, antibiotics have been prescribed in many patients with URTI or acute bronchitis [2–4]. Inappropriate prescription of antibiotics promotes antibiotic resistance. Therefore, these viruses should be detected.

These viruses could be detected using rapid antigen determination tests; however, their sensitivity was relatively low, e.g., the pooled sensitivity of influenza antigen test in adults and children with influenza-like illness was 62.3% [5]. To improve the sensitivity in detecting the viruses, the nucleic acid amplification test (NAAT) can be used. The NAAT has been developed for various viruses [6] and could detect multiple targets [7]. Despite these advantages, the use of NAAT has been infrequent because of its complicated procedures and difficulty in performing at community hospitals.

In the past few years, several fully automated platforms for NAAT were developed. These platforms can be performed simply, provide rapid results, and are used as an assay for multiple organisms from a single sample. In this study, one of the fully automated platforms, the FilmArray® Respiratory panel (RP), was evaluated. FilmArray® RP targets 20 pathogens, including 17 viruses and subtypes and 3 bacteria, and is performed in approximately 1 h turn-around-time in adult outpatients with ARTI.

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2. Material and methods

2.1. Study design

A prospective observational study was conducted between January 15 and April 5, 2016, in Nagasaki University Hospital and Nagasaki Genbaku Hospital. We enrolled adult outpatients who visited the Department of Respiratory Medicine and the Japanese Red Cross Nagasaki Genbaku Hospital with respiratory tract infection symptoms such as cough, sputum, sore throat, nasal mucus, headache, dyspnea, or hypoxemia. Based on the physician's discretion, chest X-ray and microorganism tests, such as gram stain, culture, and influenza antigen test, were performed at the Japanese Red Cross Nagasaki Genbaku Hospital. Informed consent and nasopharyngeal swabs for FilmArray RP were obtained from all patients. The FilmArray RP analysis was performed at Nagasaki University Hospital; however, the results were not reported to the physicians.

2.2. Diagnostic criteria

The physicians determined the clinical diagnosis without the FilmArray RP results. Patients with abnormal shadow in the chest X-ray were diagnosed with pneumonia. The classification of URTI and acute bronchitis were determined based on the clinical history and findings of the two physicians, who are certified board members of the Japanese Respiratory Society.

2.3. Influenza antigen test

Influenza antigen test was performed at the Japanese Red Cross Nagasaki Genbaku Hospital. In most cases, BD Veritor System™ for rapid detection of Flu A + B (Becton, Dickinson and Company, New Jersey, USA) was performed as recommended by the manufacturer. ImmunoAce Flu (TAUNS Laboratories, Inc., Sizuoka, Japan) was performed as recommended by the manufacturer for some patients who visited the hospital after consultation hours.

2.4. FilmArray RP

FilmArray RP was supplied by the SYSMEX bioMérieux Co., Ltd. (Tokyo, Japan). It includes assays that detect *Adenovirus*; *Coronavirus* (229E, HKU1, OC43 and NL63); *Human metapneumovirus*; *Human rhinovirus*; *enterovirus*; Influenza A with specific detection of subtypes H1, H1-2009, and H3; Influenza B, Parainfluenza types 1 to 4; *Respiratory syncytial virus*; *Chlamydophila pneumoniae*; *Mycoplasma pneumoniae*; and *Bordetella pertussis*. Testing was performed at Nagasaki University Hospital as recommended by the manufacturer.

2.5. Quantitative reverse transcriptase polymerase transcription assay (qRT-PCR)

In two samples, FilmArray RP detected only one gene (FluA-pan2), and their results were “equivocal.” In these samples, further genetic analysis using the qRT-PCR was performed as previously reported [8], because there was a possibility of a false positive or negative for *Influenza virus* A. A one-step qRT-PCR was performed using LightCycler 480 RNA Master Hydroas [8]. RT-PCR was performed at 63 °C for 3 min and 95 °C for 30 s, followed by 45 cycles at 95 °C for 10 s and 58 °C for 30 s. Standard curves were drawn from serial dilutions of viral RNA standards.

2.6. Ethics

This study was approved by the ethics committee of Nagasaki University Hospital (approval number, 15122108) and the Japanese Red Cross Nagasaki Genbaku Hospital (approval number, 413). This study was registered at UMIN-CTR (reference number: UMIN000026464).

2.7. Statistical analysis

A statistical software package (StatMate V; ATMS Co., Ltd., Tokyo, Japan) was used for all the statistical comparisons, which were all two-tailed unpaired and tests of significance. The statistical significant α-level was set as ≤ 0.05. The chi-square or Fisher's exact test was used to compare categorical variables.

3. Results

3.1. Patient characteristics

During the study period, a total of 50 patients (22 men and 28 women) with respiratory tract symptoms were evaluated. Patient characteristics were shown in Table 1. The mean, maximum, and minimum age of the patients were 63.1 ± 20.0, 89, and 24 years, respectively. Among the study patients, 29 (58%) had underlying diseases: bronchial asthma (10, 20%); COPD (5, 10%); hypertension (4, 8%); Bronchiectasis (3, 6%); Diabetes mellitus (3, 6%); other respiratory diseases (4, 8%); and other diseases (3, 6%). Common symptoms were fever (74%), cough (74%), sputum (48%), and nasal mucus (46%). In 23 patients (46%), abnormal respiratory sounds were auscultated. The most common microbiology test in patients was influenza antigen test (41, 82%). The positive rate of the influenza antigen test was 22.0% (n = 9). Sputum culture was conducted in 18 patients; 12 of them had positive results. The most common bacteria isolated was *Haemophilus influenzae*, which was detected in seven patients.

Table 1
Patient characteristics.

Age	63.1 ± 20.0	
Sex (male/female)	22/28	
Clinical symptoms	50	(100%)
Fever	37	(74%)
Cough	37	(74%)
Sputum	24	(48%)
Nasal mucus	23	(46%)
Sore throat	16	(32%)
Dyspnea	15	(30%)
Headache	12	(24%)
Hypoxemia	10	(20%)
Abnormal respiratory sounds	23	(46%)
Coarse crackles	14	
Wheezes	8	
Decreased breath sounds	2	
Chest X-ray	26	(52%)
Abnormal shadow	21	
Microbiology test		
Influenza antigen test	41	(82%)
positive	9	
Pneumococcal urinary antigen test	25	(50%)
positive	2	
Legionella urinary antigen test	24	(48%)
positive	0	
Sputum culture	18	(36%)
Positive	12	
Haemophilus influenzae	7	
Staphylococcus aureus	2	
Escherichia coli	2	
Others	5	

3.2. Clinical diagnosis and treatment

The clinical diagnosis and treatment were determined by the physicians without the FilmArray RP results. A total of 20, 8, and 22 patients had URTI, acute bronchitis, and pneumonia, respectively (Table 2). One patient with pneumonia was diagnosed with interstitial pneumonia. The treatments used for the patients were also shown in Table 2. A total of 27 and 10 patients were treated with antibiotics and anti-influenza agents, respectively. Two patients were treated with both antibiotics and anti-influenza agents.

3.3. Pathogens detected using FlimArray RP

FilmArray RP detected the pathogens in 28 patients (56%), namely, *Influenza virus* (n = 14, 28%), *Respiratory syncytial virus* (n = 6, 12%), and *Human Rhinovirus* (n = 6, 12%) (Table 3). Two viruses were detected in two patients: *Influenza virus* and *Respiratory syncytial* virus and *Influenza virus* and *Human rhinovirus*. When the FilmArray RP results were arranged in time series (Fig. 1), *Respiratory syncytial virus*, *Human rhinovirus*, and *Coronavirus* were observed during the influenza epidemics (from January 17 to February 27).

The FilmArray RP results were equivocal in two samples with *Influenza virus*. These samples were investigated using qRT-PCR [8], and *Influenza virus* A subtype H1 was detected in both samples. In the 14 patients positive for *Influenza virus* in the FilmArray RP, six were negative during the influenza antigen test. Of the six patients, two were clinically diagnosed with influenza and treated with anti-influenza agents.

3.4. Relationship between diagnosis and FilmArray RP

Fig. 2 shows the relationship between the clinical diagnosis and FilmArray RP. In patients with URTI (n = 20), 85% were positive in the FilmArray RP and the most common pathogen was *influenza virus* (Fig. 2A). In patients with acute bronchitis (n = 8), *Influenza virus* (n = 1), *Respiratory syncytial virus* (n = 1), *Human rhinovirus* (n = 1), and *Human metapneumovirus* (n = 2) were detected (Fig. 2B). In patients with pneumonia (n = 22), 73% were negative in the FilmArray RP (Fig. 2C). Patients with URTI were significantly higher than those with pneumonia (85% versus 27%, $P < 0.001$).

Nine of the patients who were positive in the FilmArray RP (21.4%) were treated with antibiotics. Of the nine patients, sputum culture and bacteria were conducted and detected in six and three patients, respectively.

4. Discussion

In this study, FilmArray RP detected the pathogens in 56% of all adult outpatients. The detection rate increased to 85% when limited to the patients with URTI. In the previous study on FilmArray RP, Genmark eSensor RVP, Luminex xTAG RVP v1, and Luminex Fast Multiplex Assays, the consensus positive rate of pathogens in patients with URTI was 80.5% [9]. However, the detection rate decreased to 27% when limited to patients with pneumonia in this study. Therefore, FilmArray RP was recommended for patients with URTI, but not for those with pneumonia. However, the performance of FilmArray RP in patients with pneumonia could be improved using lower respiratory specimens, such as bronchoalveolar lavage fluids [10–12].

Influenza virus is the most common pathogen detected in the FilmArray RP. In 14 patients with *Influenza virus* in the FilmArray RP, six (42.9%) were negative in the influenza antigen test. The sensitivity of influenza antigen test was reported as 62.3% [5]. Additionally, in the study comparing the FilmArray RP and conventional culture, the former identified *Influenza viruses* in all 24 influenza culture-positive cases, with a predictive value of 100% [13]. Accordingly, the result of influenza antigen test in the six patients might be false-negative. A multiplex PCR or loop-mediated isothermal amplification was performed to compensate for the low sensitivity of the influenza antigen test. However, conventional NAAT have not been commonly used as point of care testing (POCT) because their procedures are complicated and included manual operation. FilmArray RP is a fully automated platform for NAAT and reports a result within an hour. FilmArray RP requires only 2 min hands-on time, while in-house real-time PCR requires 200 min [14]. The mean turnaround time of FilmArray was 2.1 h as compared with the in-house real-time PCR with a mean of 26.5 h ($P < 0.001$) [15]. In the previous comparative study on FilmArray RP and in-house real-time PCR, after conducting the FilmArray, the mean time to the test result was significantly shorter and the percentage of patients with a result in the emergency department was greater than those before implementation [16]. Therefore, with its high sensitivity, simplicity, and rapidity, FilmArray RP can be used as a POCT in patients with URTI. If FilmArray RP was used as a routine

Table 2
Clinical diagnosis and treatment.

Clinical diagnosis		Treatment			
		Antibiotics		Anti-influenza agents	
URTI	(n = 20)	1	(5.0%)	8	(40.0%)
Acute bronchitis	(n = 8)	5	(62.5%)	1	(12.5%)
Pneumonia	(n = 22)	21	(95.5%)	1	(4.5%)

URTI, acute upper respiratory tract infection.

Table 3
Results of FilmArray.

***Influenza virus* A**	14	(28%)
A H1-2009	11	
No subtype	1	
Equivocal	2	
Respiratory syncytial virus	6	(12%)
Human Rhinovirus	6	(12%)
Coronavirus	2	(4%)
229E	2	
Human Metapneumovirus	2	(4%)
Negative	22	(44%)

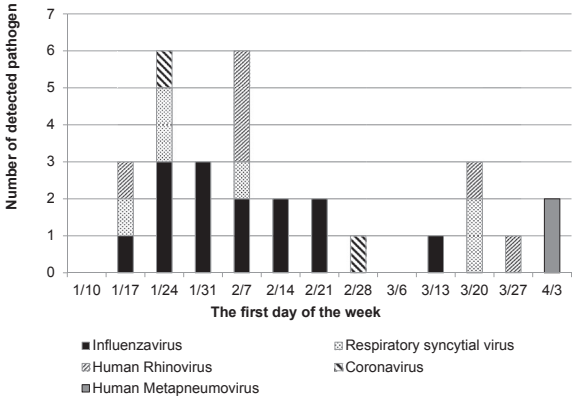

Fig. 1. Time-Series data of FilmArray RP. A prospective observational study was conducted between January 15 and April 5, 2016. During the influenza epidemics, *respiratory syncytial virus, human rhinovirus*, and *coronavirus* were detected.

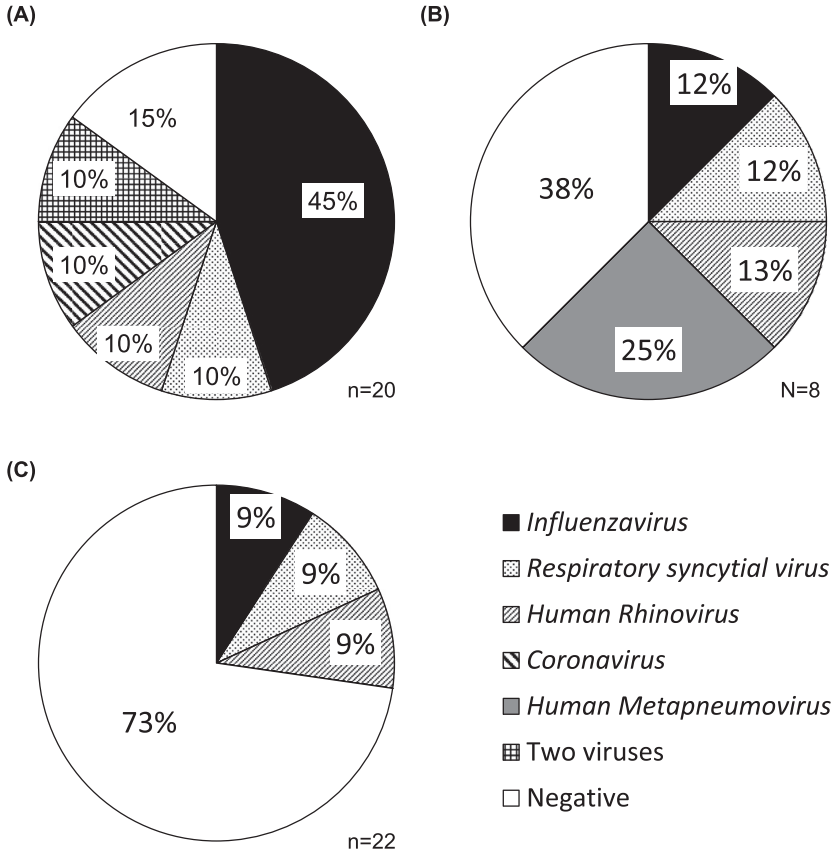

Fig. 2. FilmArray RP results in each clinical diagnosis. The clinical diagnosis was determined by the physicians without the FilmArray RP results. (A) In patients with acute upper respiratory tract infection, the most common pathogen was *influenza virus*. In two patients, two pathogens were detected: *influenza virus* and *respiratory syncytial* virus and *influenza virus* and *human Rhinovirus*. (B) In patients with acute bronchitis, *influenza virus* (n = 1), *respiratory syncytial virus* (n = 2), and *human metapneumovirus* (n = 2) were detected in the FilmArray RP. (C) In patients with pneumonia, 73% were negative in the FilmArray RP.

test, we could diagnose the illness of four patients, who were negative for influenza antigen test and not treated with anti-influenza agents, as influenza.

Verigene and GeneXpert were other fully automated platforms to detect respiratory pathogens aside from the FilmArray; however, they could only detect fewer pathogens. The comparative study on FilmArray RP and Verigene RV + reported that the sensitivity and specificity of FilmArray RP was equivalent to Verigene RV+ [17]; however, another study reported that the sensitivity of FilmArray RP in detecting *Influenza virus* was higher than that of Verigene [18]. A comparative study on FilmArray RP and GeneXpert (Xpert Flu) for the detection of *Influenza virus* reported that the positive predictive value for FilmArray RP was almost the same as that of Xpert Flu (FilmArray RP, 98.3% and Xpert Flu, 100%, respectively) [19]. Furthermore, a previous study on FilmArray RP and GeneXpert (Xpert Flu/RSV XC) for the detection of *Influenza virus* and *Respiratory syncytial virus* reported that the sensitivity and specificity of FilmArray RP were equivalent to those of the Xpert Flu/RSV XC) [20]. Since this study revealed that many viruses caused ARTI even in influenza epidemics, FilmArray might be more useful than Verigene and GeneXpert for the detection of pathogens.

We detected *Influenza virus*, *Coronavirus*, *Human metapneumovirus*, *Human rhinovirus*, and *Respiratory syncytial virus*; however, no antimicrobial agents were available for these pathogens, except for *Influenza virus*. However, these pathogens should be detected. In this study, nine patients positive in the FilmArray RP were treated with antibiotics, and only three patients were positive during the sputum culture among them. From these results, prescribing antibiotics for six patients might be inappropriate. The inappropriate use of antibiotics has become a global concern, because it led to the emergence of multidrug-resistant pathogens. Although viruses are the most common causative pathogens for ARTI, antibiotics have been commonly prescribed in many patients with URTI or acute bronchitis [2–4]. A previous study reported that the mean duration of antibiotic use was significantly shorter after implementation of FilmArray than that before the implementation [16]. Furthermore, the combination of FilmArray RP and serum procalcitonin showed the potential to improve the prescription of antibiotics [15]. In this study, FilmArray RP results were not reported to the physicians, and its use as a routine test may reduce the inappropriate use of antibiotics.

This study has some limitations. First, the samples were obtained from one community-hospital in Nagasaki, and this may limit the generalizability of the findings. Second, the samples were obtained only in influenza epidemics. The epidemiology of the pathogens detected by FilmArray RP might depend on the season. Third, the actual impact of FilmArray RP on ARTI diagnosis was not determined, because the results and pre- and post-implementation of FilmArray RP were not reported to the physicians. Finally, in qRT-PCR analysis, we could detect only H1 but could not detect 2009 pandemic. We could not verify whether the one gene (Flu-pan2) detected by FilmArray RP in two “equivocal” samples were true positive.

5. Conclusions

This study showed the significance of FilmArray RP in patients with ARTI. By implementing this kind of fully automated platforms for NAAT, illnesses can be precisely diagnosed, and inappropriate use of antibiotics can be reduced.

Declaration of interest

This study was funded by the SYSMEX bioMérieux Co., Ltd. (Tokyo, Japan).

Authorship statement

All authors meet the ICMJE authorship criteria.

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