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Clinical Effectiveness of Respiratory Virus Detection by FilmArray Method in Children Admitted with Respiratory Infection

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Abstract

Purpose: Respiratory virus infection is a common cause of hospitalization in children. Rapid testing for respiratory viruses, such as the FilmArray method, can be clinically useful. However, insufficient evidence exists to support its use in standard clinical care. *Methods:* We retrospectively analyzed data from children under 18 years old who received the multiplex real-time polymerase chain reaction array (multiplex RT-PCR) method in 2017 and by FilmArray respiratory panel (FilmArray RP) in 2018. *Results:* Between January 2017 and December 2018, we reviewed data from 1,480 hospitalized children. The number of children with virus detection in respiratory viral PCR was 523 in the multiplex RT-PCR method and 419 in the FilmArray method. Seasonal virus outbreak patterns were similar to those of the Korea Centers for Disease Control and Prevention in both groups. There was no difference between the 2 groups in the mean length of hospital stay. The time from admission to isolation by influenza infection was significantly shorter in the FilmArray group than in the multiplex RT-PCR group among patients who were not diagnosed with influenza infection by rapid antigen test at the time of admission. *Conclusion:* The use of the FilmArray method for respiratory viruses did not diminish the length of hospital stay. However, the FilmArray method may quickly detect the prevalence of respiratory infection and aid in clinical treatment. In addition, it was related to a reduced time from admission to isolation by influenza infection in hospitalized children who were not identified with influenza infection by rapid antigen test at the time of admission.

Keywords

Respiratory tract infections
Viruses
Multiplex polymerase chain reaction
Real-time polymerase chain reaction
Child

1. Introduction

Acute respiratory tract infections are the first leading cause of death in children under 5 years of age after the neonatal period worldwide [1], and are a common cause of hospital visits and hospitalization in children, causing a socioeconomic burden on healthcare services [2,3]. Respiratory viruses are the most common causative agents, and the symptoms of respiratory tract infections vary from fever, cough, and dyspnea. In recent years, it has been reported that the type of respiratory virus cannot be accurately predicted by clinical symptoms in pediatric respiratory infections [4,5]. Therefore, molecular diagnostic tests for respiratory viruses are important because clinical symptoms alone cannot differentiate respiratory virus infections.

Many countries around the world report the seasonal prevalence of acute respiratory viruses in their respective countries, and in Korea, the Korea Centers for Disease Control and Prevention (KCDC) reports the prevalence of respiratory viruses weekly in the Annals of Infectious Disease Surveillance through respiratory virus surveillance [6]. Identifying and analyzing the seasonal prevalence of respiratory viruses is important for timely infection control, administration of antiviral drugs, and prediction of the course of disease. Rapid and accurate diagnosis of respiratory virus infections using respiratory virus polymerase chain reaction (PCR) testing in hospitalized children can help isolate patients at high risk of transmission and analyze seasonal trends.

To date, multiplexed real-time PCR (multiplexed RT-PCR) has been used in clinical practice for respiratory virus testing, with the recent introduction of FilmArray, a point-of-care testing (POCT) system. Multiplex RT-PCR is a test using real-time one-step reverse transcription polymerase chain reaction (RT-PCR). In contrast, FilmArray is a point-of-care diagnostic test that introduces a rapid molecular testing platform for respiratory viruses without sample preparation such as centrifugation. It is a single-use, hermetically sealed, automated system in which all the chemistry required to isolate, amplify, and detect nucleic acids from multiple respiratory pathogens is performed in a single pouch, and is known to be able to detect multiple pathogens in a single test in less time than conventional multiplex RT-PCR methods [7].

Currently, several studies have been conducted on the clinical effects of using FilmArray in patients with respiratory tract infections, such as length of stay and antibiotic use [8-10]. A randomized controlled trial in the UK showed that the application of FilmArray in adult patients with acute respiratory tract infections was clinically beneficial in terms of shorter hospital stays and reduced antibiotic use [8], and a retrospective study in the US showed the same clinical findings [9]. On the other hand, a retrospective study in Germany showed that the use of FilmArray had no significant effect on antibiotic therapy, duration, and length of hospital stay [10]. However, there is still a lack of clinical studies comparing FilmArray and Multiplex RT-PCR in Korea.

In this study, we aimed to determine the seasonal prevalence trends of viruses using the FilmArray method compared with the multiplex RT-PCR method in children hospitalized with respiratory tract infection symptoms and diagnosed with lower respiratory tract viral diseases and to investigate the clinical effectiveness of the FilmArray method.

2. Subjects and methods

2.1. Study

This study was a retrospective study conducted through a clinical data warehouse (CDW) on patients under the age of 18 who were admitted to a tertiary care hospital in Seoul from 1 January 2017 to 31 December 2018 and were entered with lower respiratory tract disease (ICD code: J00-J99) and had a respiratory virus PCR test performed. Our hospital has been conducting tests for children admitted since 2017, using either multiplex RT-PCR or FilmArray, depending on the clinician's judgment. The respiratory virus PCR test was performed on children with respiratory symptoms according to a standardized procedure, and a nasopharyngeal swab was collected by a clinician. The

samples were analyzed in our Diagnostic Laboratory using a respiratory PCR panel.

Children who were assigned a diagnosis code for lower respiratory tract disease and underwent respiratory virus PCR testing (multiplex RT-PCR or Film Array) were time-stratified using a clinical data warehouse (CDW). The data of 879 patients who underwent multiplex RT-PCR from 1 January to 31 December 2017 and 583 patients who underwent FilmArray from 1 January to 31 December 2018 were identified. After excluding 349 patients in the multiplex RT-PCR group and 159 patients in the FilmArray group who reported negative pathogens and 7 patients in the multiplex RT-PCR group and 5 patients in the FilmArray group who lacked height and weight data, clinical features were retrospectively analyzed in only those patients who were confirmed positive for respiratory viruses. This study was approved by the Institutional Review Board of Kangdong Sacred Heart Hospital, Hallym University (approval number: 2020-03-008).

2.2. Respiratory virus testing methods

The time and cost of each PCR test and the respiratory virus panel included were as follows.

Multiplex RT-PCR (Allplex TM Respiratory Panel 1, 2, 3, Seegene, Seoul, Korea) was performed according to the manufacturer's recommended method. The time required is about 1 hour for pretreatment and 3 hours for RT-PCR, for a total of 4 hours, but the test can be performed when a certain number of specimens are collected, so the time from specimen receipt to result is more than 6 hours. The respiratory virus panel includes 19 species: influenza A/H1, A/H1pdm 09, A/H3, and B viruses, respiratory syncytial viruses (RSV A and B), and human metapneumoviruses, parainfluenza virus 1, 2, 3, 4, adenovirus, coronavirus 229E, NL63, OC43, enterovirus, rhinovirus A/B/C, and bocavirus.

The FilmArray (BioFire, Salt Lake City, UT, USA) requires approximately 1 hour for the pouch containing the nasopharyngeal smear specimen to be inserted into the device and for the results to be returned, but in practice, the time from receipt of the specimen to reporting of the results in the Department of Diagnostic Laboratory Medicine was approximately 2–3 hours. FilmArray is a nested multiplexed PCR method, which means that the FilmArray respiratory panel pouch is inserted into one machine and analyzed by an automated machine, and the results are obtained through the process of nucleic acid purification, reverse transcription and 1st stage multiplex PCR, 2nd stage PCR, and DNA melting analysis. The panel includes three bacteria (*Bordetella pertussis*, *Chlamydophila pneumoniae*, and *Mycoplasma pneumonia*) and 17 viruses, with the respiratory virus panel including adenovirus, coronavirus 229E, HKU1, NL63, and OC43, human metapneumovirus, parainfluenza virus 1, 2, 3, 4, influenza A, A/H1, A/H1-2009, A/H3, B virus, rhinovirus/enterovirus, and respiratory syncytial virus.

2.3. Viral data analysis

When comparing the multiplex RT-PCR and FilmArray groups, viruses were analyzed regardless of their subtypes. Unlike FilmArray, rhinovirus and enterovirus were separated in multiplex RT-PCR, so they were combined into one item, rhinovirus/enterovirus. Also, bocavirus was not included in the FilmArray panel, so it was excluded from the analysis. The length of stay was analyzed as the difference between the discharge date and the admission date. At our hospital, influenza rapid antigen tests were performed in the outpatient department or emergency department at the time of admission, and if the test was positive for influenza virus, the child was admitted to an isolation room, and if the test was negative, the child was admitted to a multi-bedded room, and all of these children were further confirmed by FilmArray or multiplex RT-PCR regardless of the rapid antigen test result. The time from admission to isolation was analyzed using the difference between the time of admission to the multi-bedded room and the time of admission to the isolation room, and the time of admission to the isolation room. The time from admission to isolation was treated as 0 hours for patients

whose initial rapid antigen test was positive and who started isolation from the time of admission.

To examine the annual detection rate and seasonal prevalence distribution of respiratory viruses in Korea, we used information from the KCDC's infectious disease portal on acute respiratory tract infectious disease surveillance [11]. The KCDC reports the number of hospitalized patients (including both adults and children) by virus on an annual and weekly basis by aggregating data on patients hospitalized with acute respiratory tract infections who were diagnosed with positive pathogen tests. The respiratory viruses reported are adenovirus, bocavirus, parainfluenza virus, RSV, rhinovirus, human metapneumovirus, and coronavirus. As bocavirus is absent from the FilmArray panel and rhinovirus and enterovirus cannot be detected separately, bocavirus and rhinovirus were excluded from the KCDC statistics in the seasonal prevalence analysis. For the analysis, the respiratory viruses detected by the multiplex RT-PCR group in 2017 and the FilmArray group in 2018 were organized by month, and the statistical data of KCDC respiratory viral infections were organized by month of the year to compare the distribution by year. At this time, the number of hospitalized patients with influenza virus infection was not provided in the KCDC's acute respiratory infection statistics, so the graph of respiratory virus detection rate for each month of the year was compiled by excluding the influenza virus. The seasonal distribution of the influenza virus was compared with the seasonal trends of influenza virus isolation status (number of positive cases) and number of physician patients reported by KCDC in its annual infectious disease surveillance annals, as well as the monthly detection rate of influenza virus by respiratory virus PCR test.

2.4. Statistical analysis

Statistical analyses were performed using IBM SPSS ver. 18.0 (IBM Co., Armonk, NY, USA). Continuous data were expressed as mean and standard deviation, and statistical significance between the two groups was analyzed by Student *t*-test. Categorical data were compared between the two groups using the chi-squared test and expressed as *n* (%). Statistical significance was determined when the *P* value was less than 0.05.

3. Results

3.1. Characteristics of the study population

The number of children with virus detected by respiratory virus PCR testing was 523 (59.2%) in the multiplex RT-PCR group and 419 (70.1%) in the FilmArray group. The mean age was 2.0 ± 2.5 years in the multiplex RT-PCR arm and 2.3 ± 2.5 years in the FilmArray arm, with no statistically significant difference between the two groups. In terms of gender, boys were slightly more common than girls (56.2% in the multiplex RT-PCR group and 51.3% in the FilmArray group), but there was no statistically significant difference between the groups, nor was there a difference in height or weight between the two groups (**Table 1**).

Table 1. Characteristics of subjects studied

Characteristic	Multiplex RT-PCR	FilmArray	*P*-value*
Overall collective	872	578	
Positive result	523 (60.0)	419 (72.5)	0.000†
Age (yr)	2.0 ± 2.5	2.3 ± 2.5	0.068
Male sex	294 (56.2)	215 (51.3)	0.134†
Height (cm)	88.3 ± 19.9	90.2 ± 22.2	0.154
Weight (kg)	13.5 ± 7.9	14.7 ± 9.3	0.030
Length of hospital stay (day)	4.7 ± 1.4	4.6 ± 1.5	0.466

Values are presented as numbers (%) or mean ± standard deviation. Abbreviation: RT-PCR, real-time polymerase chain reaction.*Student *t*-test. †Chi-squared test.

3.2. Annual virus-specific detection rates

In 2017, the detection rates of human metapneumovirus, coronavirus, and parainfluenza virus were 5.2%, 0.4%, and 12.6%, respectively, in the multiplex RT-PCR group. RSV and adenovirus were 21.6% and 14.9%, respectively, and rhinovirus/enterovirus and influenza virus were 10.1% and 11.7%, respectively. In 2018, the detection rates for human metapneumovirus and coronavirus were 13.0% and 9.3%, respectively, and for parainfluenza virus, RSV, and adenovirus were 14.8%, 26.0%, and 15.5%, respectively, in the FilmArray group. Rhinovirus/enterovirus had the highest detection rate of 39.4%, while influenza virus had the lowest detection rate of 6.4% (**Table 2**). According to the data from KCDC, the distribution of respiratory viruses detected in hospitalized patients during 2017 was RSV (25.0%), parainfluenza virus (13.3%), adenovirus (11.2%), human metapneumovirus (7.2%), and coronavirus (6.5%). The highest proportion of viruses in the multiplex RT-PCR group at the study hospital was RSV (21.6%), followed by adenovirus (14.9%), parainfluenza virus (12.6%), human metapneumovirus (5.2%), and the lowest proportion was coronavirus (0.4%) (**Figure 1A**). In the 2018 KCDC data, RSV (55.2%), human metapneumovirus (13.8%), parainfluenza virus (10.9%), adenovirus (6.9%), and coronavirus (5.6%).In the FilmArray group of this study, the highest positive rate was RSV (26.0%), followed by adenovirus (15.5%), parainfluenza virus (14.7%), human metapneumovirus (13.3%), and the lowest positive rate was coronavirus (9.3%) (**Figure 1B**).

3.3. Monthly virus detection rate

According to KCDC's 2017 data, human metapneumovirus was detected most frequently in March (27.1%) and April (23.3%), while coronavirus prevalence was highest in January (18.4%), followed by February (11.2%) and December (12.2%). Parainfluenza virus had a high prevalence in May (32.7%) and June (31.7%), while RSV had the highest detection in November (51.1%) and December (52.8%), with high detection in January (37.2%) and February (20.6%). Adenovirus had a slightly higher prevalence in May (16.4%) and June (19.0%), but was consistently detected throughout the year (**Figure 2A**). In our multiplex RT-PCR group, human metapneumovirus had higher positivity rates in March (17.8%) and April (16.6%), coronavirus in December (3.6%), and parainfluenza virus in May (30.7%) and June (32.5%). RSV had high positivity rates in January (44.8%), October (56.6%), and November (67.2%), while adenovirus showed some variation, with high positivity rates from March (28.5%) to June (25%). Influenza virus peaked in January (37.9%) and February (25%) in 2017 and remained detectable until May, before reemerging in December (40.0%) (**Figure 2B**).

In the 2018 KCDC results, human metapneumovirus had a high prevalence in April (26.7%), coronavirus in January (25%), and parainfluenza virus in June (31.2%). The prevalence

Table 2. Distribution of detected viruses by the test method

Virus	Multiplex RT-PCR† (*n* = 523)	FilmArray‡ (*n* = 419)	*P*-value*
Human metapneumovirus	27 (5.2)	56 (13.0)	0.000
Coronavirus	2 (0.4)	39 (9.3)	0.000
Parainfluenza virus	66 (12.6)	62 (14.8)	0.332
RSV	113 (21.6)	109 (26.0)	0.113
Adenovirus	78 (14.9)	65 (15.5)	0.799
Rhino/enterovirus	53 (10.1)	165 (39.4)	0.000
Influenza virus	61 (11.7)	27 (6.4)	0.006

Values are presented as numbers (%). Abbreviations: RT-PCR, real-time polymerase chain reaction; RSV, respiratory syncytial virus. *Chi-squared test. †Patients tested Multiplex RT-PCR from 1 January 2017 to 31 December 2017. ‡Patients tested FilmArray from 1 January 2018 to 31 December 2018.

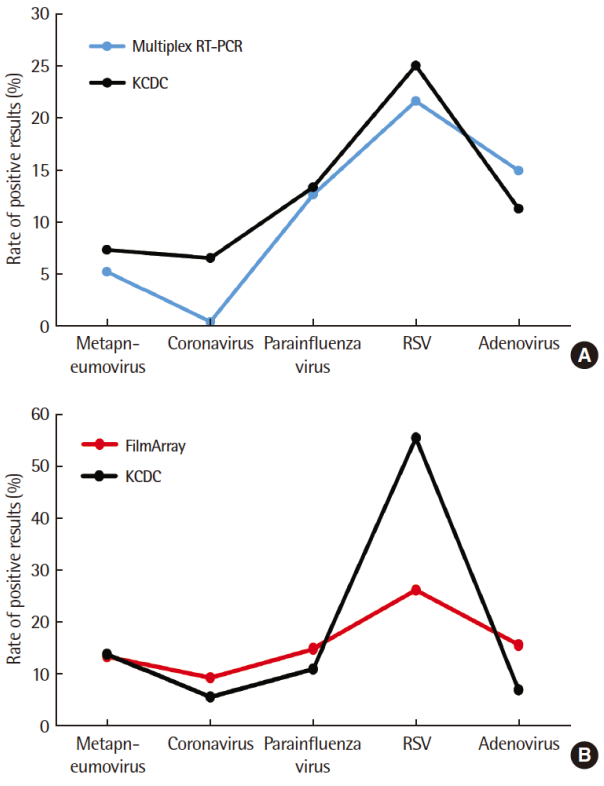

Figure 1. Patients tested for viruses and rate of detection. (A) Comparison of multiplex RT-PCR group and KCDC data in 2017. (B) Comparison of FilmArray group and KCDC data in 2018. Abbreviations: RT-PCR, real-time polymerase chain reaction; KCDC, Korea Centers for Disease Control and Prevention; RSV, respiratory syncytial virus.

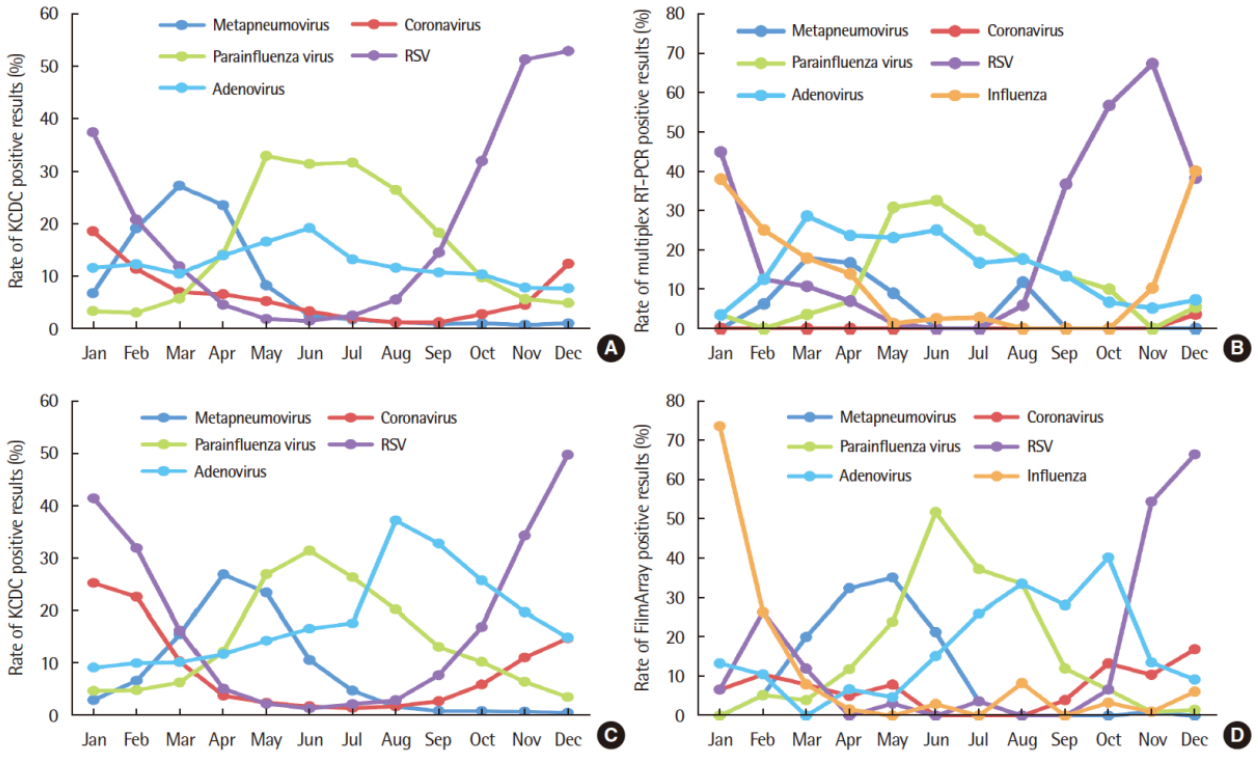

Figure 2. Pathogens detected, according to month. (A) The monthly incidence rate of respiratory viruses except the influenza virus was investigated by KCDC in 2017, and (B) respiratory viruses including the influenza virus detected by multiplex RT-PCR. (C) The monthly incidence rate of respiratory viruses except the influenza virus investigated by KCDC in 2018, and (D) respiratory viruses including influenza virus by FilmArray. Abbreviations: KCDC, Korea Centers for Disease Control and Prevention; RT-PCR, real-time polymerase chain reaction; RSV, respiratory syncytial virus.

of RSV peaked in January (41.2%) and December (49.5%), while adenovirus had a high prevalence in August (37.0%) and September (32.6%) (**Figure 2C**). Analysis of our FilmArray population showed that human metapneumovirus had high positivity rates in April (32.2%) and May (34.9%), coronavirus had high detection rates in February (10.5%) and December (16.9%), and parainfluenza virus in June (51.5%). RSV had a high positive rate in February (26.3%), November (54.1%), and December (66.1%), and adenovirus had a consistently high positive rate in August (33.3%) and September (28%), with the highest positive rate in October (40.0%). Influenza virus showed an epidemic pattern until April with a high detection rate in January (73.3%) and February (26.3%) in 2018, and then again in November (1.04%) and December (6.15%) in 2018 (**Figure 2D**).

3.4. Clinical characteristics

The mean length of hospital stay of the children was analyzed as 4.7 ± 1.4 days in the multiplex RT-PCR group and 4.6 ± 1.5 days in the FilmArray group, with no significant difference between the two groups (**Table 1**).

In the analysis of the use of isolation rooms for children infected with the influenza virus, out of a total of 88 children admitted with influenza virus infection, 61 were confirmed by multiplex RT-PCR and 27 by FilmArray. The mean time from admission to isolation was 13.5 ± 22.9 hours in the multiplex RT-PCR group and 3.0 ± 5.7 hours in the FilmArray group, a significant difference between the two groups (**Table 3**).

4. Discussion

This study retrospectively compared clinical characteristics such as length of stay, seasonal virus detection rates, and time spent in isolation after admission between different groups of children hospitalized with lower respiratory tract infections, including those who were detected by multiplex RT-PCR in 2017 and those who tested positive for respiratory viruses by FilmArray in 2018. Multiplex RT-PCR, which has traditionally been used to detect respiratory viruses, is inexpensive ($85,950 for an institution) and can detect multiple respiratory viral pathogens by single-channel multiplexing using real-time PCR. However, it is a labor-intensive method that requires considerable operator involvement to prepare for pretreatment and real-time one-step RT-PCR and to perform data analysis, and requires more than four hours of turnaround time. FilmArray is more expensive than multiplex RT-PCR at $264,420 for an investigator's institution, but it includes three bacteria in the assay, and the POCT system requires less manual work than multiplex RT-PCR to analyze samples and generate results, providing a faster turnaround time of one hour. Therefore, if the clinical utility of the FilmArray is proven, it is expected to be highly practical in medical settings. However, there are few studies on the clinical utility of FilmArray compared to conventional multiplex RT-PCR in Korean respiratory patients. Lee *et al.* compared the accuracy of the Allplex respiratory Panel and FilmArray methods in 426 specimens in Korea, but they did not analyze

Table 3. The duration from admission to isolation by influenza infection

	Multiplex RT-PCR† (*n* = 61)	FilmArray‡ (*n* = 27)	*P*-value*
Time to isolation (hr)	13.5 ± 22.9	3.0 ± 5.7	0.022

Values are presented as mean ± standard deviation. Abbreviation: RT-PCR, real-time polymerase chain reaction. *n* = positive result of influenza A/B. *Student *t*-test. †Patients tested Multiplex RT-PCR from 1 January 2017 to 31 December 2017. ‡Patients tested FilmArray from 1 January 2018 to 31 December 2018.

clinical characteristics such as age, gender, and financial resources of the test population [12].

The number of children with virus detected by respiratory virus PCR was 523 (60%) in the multiplex RT-PCR group and 419 (72.5%) in the FilmArray group, with a higher positivity rate in the FilmArray group, which is consistent with other studies [8,13]. The higher positive rate of respiratory viruses in the FilmArray method can be supported by previous studies showing that the FilmArray method has higher sensitivity and specificity than the conventional multiplexed PCR method [14,15]. In our hospital, patients are tested by choosing between multiplex RT-PCR and FilmArray at the time of admission, and the opinions of parents and medical staff influence the choice of test. Therefore, in addition to selective bias due to the choice of test based on length of CDW, there may also be selective bias due to clinicians encouraging caregivers of patients with clear and severe symptoms to choose FilmArray, which is more expensive than multiplex RT-PCR but provides faster test results, and this bias may have led to a higher positive rate for FilmArray.In this study, the mean age of the two groups tested by multiplex RT-PCR and FilmArray was approximately 2 years and did not differ. The distribution of respiratory virus detections was dominated by RSV, with the exception of rhinovirus/enterovirus. These results are consistent with other previous studies [16,17]. In a retrospective study conducted in Korea, parainfluenza virus, adenovirus, human metapneumovirus, and coronavirus accounted for 25% of the pathogens detected by respiratory virus RT-PCR in nasopharyngeal secretions [18]. This is consistent with similar studies of pediatric lower respiratory tract infections where these pathogens accounted for 25%–40% of the pathogens detected [16,17,19]. The proportion of rhinoviruses/enteroviruses was significantly higher in both groups, especially in the FilmArray group. This is consistent with the results of a study that showed a significantly higher proportion of rhinoviruses in children hospitalized with respiratory symptoms [18]. However, due to the characteristics of FilmArray, which cannot detect rhinoviruses and enteroviruses separately, rhinoviruses and enteroviruses were combined in the comparison with the multiplex RT-PCR group in this study, so interpretation should be cautious, and future comparative studies considering only rhinoviruses should be conducted. Compared to the data from KCDC, RSV was the most common respiratory virus detected by both multiplex RT-PCR and FilmArray, and coronavirus was the least common respiratory virus. These findings are consistent with those of domestic epidemiological studies in children [20,21]. However, when comparing the KCDC data, multiplex RT-PCR, and FilmArray groups by year, the positivity rates for RSV and coronavirus, as well as parainfluenza virus, adenovirus, and human metapneumovirus, were similar, but not exactly in the same order. In addition, there were respiratory viruses with significant differences in detection rates, such as coronavirus, which was the lowest detected in all groups, but the difference was 6.5% in KCDC statistics in 2017 and 0.4% in the multiplex RT-PCR group, and RSV, which was the highest detected in all groups in 2018, but the difference was 55.2% in KCDC statistics and 26% in FilmArray group. Adenovirus was also detected differently in 2018, with 15.5% in the KCDC and 6.9% in the FilmArray group. We believe this is due to a significant difference in the number of hospitalizations due to these viruses between the study sites and the KCDC data. The total number of patients hospitalized with coronavirus in 2017 was 3,763 according to KCDC statistics, while the number detected by multiplex RT-PCR in this study was 2. The data in this study is too small to interpret this result with caution. In addition, this study analyzed the data without considering the subtypes of each respiratory virus, and the coronaviruses detected by multiplex RT-PCR in 2017 included only the subtypes 229E, NL63, and OC43. However, the KCDC statistics do not specify the type of test used to detect respiratory viruses, and it is likely that each laboratory used a variety of testing techniques to detect the virus,

including multiplex RT-PCR, FilmArray, and viral culture. Therefore, it is possible that each test detected a different subtype of coronavirus and detected more. In addition, the most likely reason for this difference in detection rate is that the KCDC data includes adult patients with acute respiratory infections, not just children, so it is not possible to accurately determine the respiratory virus detection rate for children.

The monthly respiratory virus detection rate was similar to that of KCDC in both groups, which suggests that many respiratory viruses are seasonal. In 2017, multiplex RT-PCR data from both KCDC and the researchers' hospitals showed that human metapneumovirus was prevalent in spring (March–April), coronavirus in winter (December), and parainfluenza virus in early summer (May–June). RSV showed an epidemic pattern from late autumn to winter (January, November–December). In 2018, both the KCDC and researcher hospitals' FilmArray groups showed similar seasonal trends. These trends are consistent with the results of a 10-year epidemiological survey of respiratory viruses in Korean children [13]. However, adenovirus showed a slight difference in the monthly detection rate trends of multiplex RT-PCR at the investigator's hospital compared to the prevalence rate surveyed by the KCDC in 2017, which may be due to the fact that the KCDC data included both children and adults, and further analysis is needed to consider the difference with the prevalence of adenovirus in adults. In addition, the KCDC results were based on the number of cases reported by each sentinel surveillance center that tested positive for respiratory viruses and lacked statistics on the types and methods of PCR used for detection, thereby limiting the analysis.

In addition, the influenza virus epidemic in the multiplex RT-PCR group showed an epidemic that ended from January to May 2017 and reemerged in December 2017, while the FilmArray group showed an epidemic that ended from January to April 2018 and reemerged in November 2018. These results are consistent with the KCDC's report in the Annals of Infectious Disease Surveillance that since 2016, influenza epidemics have started in December, peaked in January, and lasted until May and June. Influenza viruses have different epidemic periods depending on the subtype, and according to the KCDC's 2017 influenza virus isolation status, influenza A (H3N2) peaked in weeks 1–9 and 48–52 in 2017, influenza A (H1N1) pdm09 peaked in weeks 49–52, and influenza B peaked in weeks 11–20, while in 2018, influenza A (H3N2) peaked in weeks 1–13, influenza A (H1N1) pdm09 peaked in weeks 1–14, and influenza B peaked in weeks 43–52 [22,23]. Although it is important to analyze the timing of epidemics by subtype, the lack of data on seasonal epidemics by subtype is a limitation of this study because the viruses were not divided into subtypes in this study.

Predicting the timing of an epidemic by detecting respiratory viruses is likely to reduce antibiotic overuse and improve parental satisfaction with empirical diagnosis in clinical practice, and FilmArray is likely to be as effective as conventional multiplex RT-PCR or KCDC's epidemiological investigation.

In this study, the mean length of hospital stay was not statistically different between the FilmArray and multiplex RT-PCR groups. A retrospective study of children aged 16 years and younger in Germany found that the choice of PCR did not affect the length of stay [10], and a study of children presenting to emergency departments in Belgium also found no effect on the length of stay [24]. Studies in adults have reported a significant reduction in the length of stay [8,9], and a randomized study in Argentina of children and adults reported a reduction in the length of stay, but the number of patients admitted was too small to be significant [25]. We believe that the lack of effect of rapid viral detection using FilmArray in children on hospital length of stay is due to the fact that the decision to discharge a patient is not based on a positive viral result, but on a comprehensive assessment of the patient's clinical presentation, blood tests such as general hematology, C-reactive protein (CRP),

erythrocyte sedimentation rate, and procalcitonin, and imaging findings. This may be explained by the aforementioned German retrospective study, which found that clinical indicators such as CRP, previous antibiotic use, and age had a greater impact on hospital length of stay than virus detection using FilmArray [10].

Influenza virus detection was significantly higher in the multiplex RT-PCR group compared to the FilmArray group. This result contradicts other studies that have shown a higher detection rate of influenza virus in the FilmArray group [8]. In the investigator's hospital, when patients with suspected influenza are admitted, a rapid antigen test is performed first, followed by either FilmArray or multiplex RT-PCR on the ward for confirmation. Interpretation of the detection rate should be done with caution, as the cost of FilmArray may have led to economic selection by caregivers. In addition, according to the annual influenza pseudo-patient incidence rate in the 2018 KCDC Infectious Disease Surveillance Yearbook, the rate was 8.9 per 1,000 outpatients in the 2016–2017 season and 6.6 per 1,000 outpatients in the 2017–2018 season, so it can be assumed that influenza was more prevalent in 2017, which may explain the higher detection rate of influenza virus by multiplex RT-PCR method.

Influenza can be treated with antiviral drugs (oseltamivir, peramivir) within 48 hours of the onset of clinical symptoms such as fever to shorten the course of the disease and reduce complications [26-28]. Therefore, it is important to diagnose influenza quickly, and in this study, the time from admission to the isolation of the influenza virus by respiratory virus PCR was significantly shorter in the FilmArray group, with a mean of 3.0 ± 5.7 hours, which is the same result as many studies [8,13]. These results can be interpreted as, first, the difference in the time required for the PCR test itself, which was more than 1 hour for FilmArray and more than 4 hours for multiplex RT-PCR, and second, FilmArray is a one-machine-per-sample system in terms of material consumption and cost, while the conventional multiplex RT-PCR method is a one-machine-per-multiple-sample system in terms of material consumption and test cost, which may have taken more time in the actual clinical environment. In the case of our clinic, multiplex RT-PCR is performed after more than 30 samples are collected, and the test is performed once a day if the samples are received by 8:00 a.m. In the case of FilmArray, PCR can be run directly in a single pouch after sample collection. Future studies that measure turnaround time after excluding these differences in the laboratory environment will provide more accurate results. We believe that the use of FilmArray in children with false-negative results due to the failure of rapid antigen tests to detect influenza, followed by positive confirmation and rapid isolation, can help prevent nosocomial transmission and lead to early initiation of antiviral medication, which can help treat influenza infection.

Limitations of this study include that it was a retrospective, non-randomized, single-center study with a limited sample size, which may not be representative of all children in Korea. In addition, the fact that multiplex RT-PCR and FilmArray were not performed simultaneously on the same specimen, and the analysis was performed on different methods at different times, suggests that there may be a selection bias, and we believe that future studies should perform both tests simultaneously on the same specimen or conduct a randomized study to obtain more accurate results. The difference in cost between the two tests may have been caused confounding by socioeconomic factors. The comparison of respiratory virus positivity rates between the two tests is not accurate because of the slightly different patterns of virus prevalence from year to year, and it would be necessary to conduct a study comparing the two tests at the same time. Finally, due to the characteristics of FilmArray, it was not possible to detect rhinovirus and enterovirus separately, so it was not possible to analyze the exact detection rate and monthly prevalence of rhinovirus, which is known to be highly detected in children with lower respiratory tract infections.

This study is the first comparative analysis of the clinical impact of FilmArray in children hospitalized with lower respiratory tract infections in Korea. The monthly positive rate of respiratory viruses followed a similar pattern to the seasonal prevalence of respiratory viruses reported by the KCDC in Korea, suggesting that FilmArray can be used to quickly detect outbreaks of certain diseases. Furthermore, the use of FilmArray for respiratory virus detection did not reduce the length of hospital stay, but it was significantly associated with a reduction in the time between influenza diagnosis and isolation through confirmation of influenza on admission. These findings may support the clinical utility of FilmArray in the diagnosis of pediatric respiratory disease in the future. Further research is needed to determine the impact of FilmArray implementation on clinical treatments such as antibiotics, steroids, and antivirals.

Disclosure statement

The authors declare no conflict of interest.

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