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Original Article

The impact analysis of a multiplex PCR respiratory panel for hospitalized pediatric respiratory infections in Japan☆

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ABSTRACT

Background: Rapid molecular diagnosis of infections has contributed to timely treatments and antimicrobial stewardship. However, the benefit and cost-effectiveness vary in each country or community because they have different standard practices and health care systems. In Japan, rapid antigen tests (RATs) have been frequently used for pediatric respiratory infections. We investigated the impact and cost-effectiveness of a multiplex PCR (mPCR) respiratory panel for pediatric respiratory infections in a Japanese community hospital.

Methods: We replaced RATs with an mPCR respiratory panel (FilmArray®) for admitted pediatric respiratory infections on March 26, 2018. We compared the days of antimicrobial therapy (DOT) and length of stay (LOS) during the mPCR period (March 2018 to April 2019) with those of the RAT period (March 2012 to March 2018).

Results: During the RAT and mPCR periods, 1132 and 149 patients were analyzed. The DOT/case was 12.82 vs 8.56 ($p < 0.001$), and the LOS was 8.18 vs 6.83 days ($p = 0.032$) in the RAT and mPCR groups, respectively. The total costs during admissions were \258,824 ($2331.7) and \243,841 ($2196.8)/case, respectively. Pathogen detection rates were 30.2% vs 87.2% ($p < 0.001$).

Conclusion: Compared to conventional RATs, the mPCR test contributed to a reduction in the DOT and LOS in a Japanese community hospital for admission-requiring pediatric respiratory infections. However, a proper stewardship program is essential to further reduce the unnecessary usage of antimicrobials.

1. Background

Respiratory infections cause a significant burden on the health of children worldwide [1–3]. While children with respiratory tract infections caused by bacterial pathogens may benefit from antimicrobials, antimicrobial use for viral respiratory infection is not indicated and has led to the subsequent emergence of antimicrobial-resistant microorganisms [4–7]. Although viral infections account for the majority of pediatric respiratory infections, antimicrobials are often prescribed for these cases [8,9]. Previous surveys pointed out that the overprescription of oral cephalosporins and macrolides, which are usually prescribed for pediatric respiratory tract infections, is a serious issue in Japan [10,11].

Rapid molecular diagnosis of infections has contributed to timely treatments and antimicrobial stewardship. The FilmArray® respiratory panel, a multiplex PCR (mPCR) test for respiratory infections, diagnoses 17 types of viruses and 3 types of bacteria with approximately 2 min of preparation time and a 60-min turnaround time. The FilmArray® has high sensitivity and specificity with the overall accuracy of 84.4–100% sensitivity and 89.1–100% specificity. The mPCR for respiratory infections has been shown to be effective in reducing antimicrobial prescription and the length of stay (LOS) in the USA and European countries, while other studies concluded that the effects of mPCR on reducing the prescription of antimicrobials and LOS were controversial [12–15]. For example, Rogers BB et al. reported that the mPCR respiratory panel test led to a

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reduced duration of antimicrobial use ($p = 0.003$) and reduced LOS ($p = 0.03$) [12]. Lee BR et al. also showed that the rapid turnaround of the mPCR respiratory panel resulted in the decreased use of antimicrobials, including broad-spectrum antimicrobials [14]. However, these studies compared the mPCR test with viral respiratory panels or batched PCR tests. The benefit and cost-effectiveness of new tests vary in each country or community because they have different standard practices and health care systems. In Japan, rapid antigen tests (RATs) are widely used for pediatric respiratory infections instead of respiratory viral panels. Thus, unlike other countries, we need to compare the mPCR respiratory panel test with the RAT in terms of its impact and cost. Therefore, we investigated the impact and cost of the mPCR respiratory panel for pediatric respiratory infections in Japan.

2. Materials and methods

2.1. Design and setting

This was a retrospective study (Pre-post study). We replaced rapid antigen tests with the mPCR respiratory panel (FilmArray®; Biofire, Utah, USA) as a microbiological diagnostic test for pediatric respiratory infections admitted since March 26, 2018. The RAT period in the study was from March 1, 2012, to March 25, 2018, while the mPCR period was from March 26, 2018, to April 10, 2019. In the mPCR period, if clinicians decided that a child needed to be admitted after history taking and physical exam, they ordered the mPCR test instead of the RATs. The nasopharyngeal swab samples were collected for the mPCR test. The exclusion criteria were *Streptococcus* pharyngitis because cases with *Streptococcus* pharyngitis were treated with beta-lactams for 10 day throughout the study period, and including these cases might have had significant effects on the primary outcome. Patients whose primary clinical diagnoses were not respiratory infections and who had already been treated with antimicrobials for some other reasons before the onset of respiratory symptoms were also excluded. Because the mPCR test was only available on weekdays from 8:30 to 17:15 in the mPCR period, patients who were hospitalized on weekends or during the night were excluded throughout the study period to exclude a selection bias. The RATs for influenza, human metapneumovirus, respiratory syncytial virus, adenovirus, Group A *Streptococcus* (Tauns, Laboratories, Inc., Shizuoka, Japan) and *Mycoplasma pneumoniae* (Mizuho Medi, Co., Ltd, Saga Japan) were available. No antimicrobial stewardship program (ASP) was implemented throughout the study period.

Primary outcomes were days of antimicrobial therapy (DOT)/case and LOS. Secondary outcomes were net cost, pathogen detection rate and treatment failure. The treatment failure is defined as the need of re-treatment of any antimicrobials within 14 days after the completion of the first antimicrobial course. The net cost in the study included hospitalization cost, social cost and test costs for the RATs or mPCR test. The hospitalization cost was calculated according to the Diagnosis Procedure Combination system (DPC system; Japanese medical reimbursement system based on LOS and clinical diagnosis). For the medical cost, outpatient and antimicrobial costs were not included because these are not reimbursed in the DPC system. The social cost by parental work absence was calculated by the time for a family member to take care of their hospitalized children because our pediatric ward required one family member to accompany their child throughout the hospitalization. The time of parental absence from work to care for their hospitalized children was converted to money by multiplying the average daily wage in Japan [16]. The test costs for RAT and mPCR were calculated by reference to the applicable company websites or direct inquiry to the applicable companies [17]. The cost of the mPCR test included both the reagent cost and the device cost. The device cost per test was estimated according to the device cost in the mPCR period divided by the number of the mPCR tests performed in the mPCR period. The Japanese yen (JPY) was converted to the United States Dollar (USD) at a rate of \111 JPY per $1 USD.

All statistical analyses were performed using StataCorp (2015, *Stata Statistical Software: Release 14*, College Station, TX: StataCorp LP) and Microsoft Excel 2016 (Redmond, WA, USA). The study was approved by the Institutional Review Board of Nara Prefecture General Medical Center, Nara, Japan, with a waiver of written informed consent.

3. Results

During the RAT and mPCR periods, 1132 and 149 patients were analyzed. The backgrounds of the two groups are presented in Table 1. During the mPCR period, 210 mPCR tests were performed. Among these 210 patients, 21 cases were discharged upon receipt of the mPCR results. Among the 189 hospitalized patients, the primary diagnoses of 38 cases were not respiratory infections, and 2 patients had prophylactic antimicrobials for other reasons. Therefore, 149 patients were finally analyzed in the mPCR group (Fig. 1). The primary and secondary outcomes are shown in Table 2.

The DOT/case was 12.82 vs 8.56 ($p < 0.001$), and the LOS was 8.18 vs 6.83 days ($p = 0.032$) in the RAT and mPCR groups. The total costs during admissions in the RAT and mPCR groups were \258,824 ($2331.7) and \243,841 ($2196.8)/case, respectively. The hospitalization costs were \157,776 ($1421.4) and \142,811 ($1286.6). The social costs were \96,683 ($871.0) and \80,708 ($727.1). The test costs were \4365 ($39.3) and \20,323 ($183.1)/case, respectively.

Microbiological detection rates were 30.2% vs 87.2% ($p < 0.001$). More than one pathogen was detected in 27 patients (18.1%) in the mPCR group. The detected pathogens are presented in Fig. 2.

Table 1
Background.

	Rapid Antigen Test group (N = 1132)	mPCR Group (N = 149)	p-value
Age (year)	3.33 ± 3.53	2.23 ± 2.36	<0.001
Sex (male)	55.0%	59.1%	0.344
WBC count (/μl)	10,962 ± 5625	10,612 ± 5071	0.731
CRP (mg/dl)	2.75 ± 3.63	2.65 ± 3.13	0.974
Clinical diagnosis			
Pneumonia	36.8%	35.6%	0.775
Bronchitis/bronchiolitis	41.3%	47.0%	0.185
URI	17.2%	12.1%	0.116
Asthma	4.3%	2.6%	0.325
Others	0.3%	2.7%	<0.001

The values are shown as the average value ± standard deviation.
CRP; C-reactive protein, URI; upper respiratory tract infection (including tonsillitis and sinusitis), WBC; white blood cell.

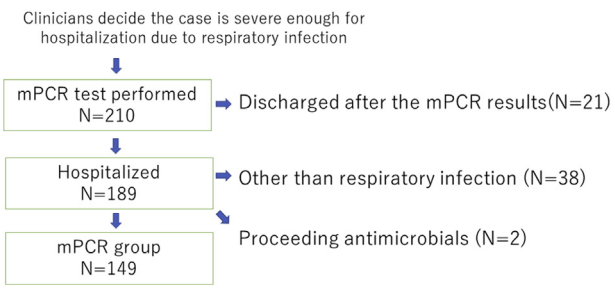

Fig. 1. mPCR group chart.

Table 2
Outcomes.

	Rapid Antigen Test Group (N = 1132)	mPCR Group (N = 149)	p-value
DOT/case	12.82 ± 9.62	8.56 ± 5.13	<0.001
LOS (days)	8.18 ± 9.78	6.83 ± 2.03	0.032
Total cost (JPY)	\258,824	\243,841	
Hospitalization cost	\157,776	\142,811	
Social cost	\96,683	\80,708	
Cost of the tests	\4365	\20,323	
Pathogen detection	30.2%	87.2%	<0.001
Treatment failure	2.6%	2.0%	0.661

The values are shown as the average value ± standard deviation.
The cost of the mPCR test was calculated according to the reagent cost and device cost per test.
The device cost per test was estimated according to the device cost in the study period divided by the number of tests performed in the study period.
DOT; days of therapy, DPC; diagnosis procedure combination, JPY; Japanese yen, LOS; length of stay.

Treatment failure rates were not significantly different between the two groups (2.6% vs 2.1%, p = 0.661).

The DOT per category of antimicrobial between the two groups is presented in Fig. 3. DOT reductions in cephalosporins (5.35 ± 4.47 vs 4.24 ± 2.44; p < 0.001), macrolides (6.43 ± 6.81 vs 3.42 ± 4.73; p < 0.001), and tetracyclines (0.52 ± 2.00 vs 0.11 ± 0.75; p < 0.001) were observed in the mPCR group compared to the RAT group, the DOT of penicillins was slightly increased (0.31 ± 1.64 vs 0.77 ± 1.82; p < 0.001).

4. Discussion

Our study highlights that compared to RATs, the mPCR respiratory panel could reduce DOT and LOS for pediatric respiratory infections, although LOS was longer than has been reported in other developed countries partly because of the difference in the health care system [12–15]. In addition, the DOT/case was also high because of the lack of an ASP. Introducing an appropriate ASP to further reduce antimicrobial usage is necessary. The distinguishing feature of our study is the comparison of the mPCR test with RATs, instead of a viral respiratory panel or batched PCR tests, which have been compared in other previous studies. Approximately 10% of cases who had mPCR tests were not admitted, even though the pediatrician judged that they should be admitted at the time of the presentation. This means that the mPCR test may have reduced

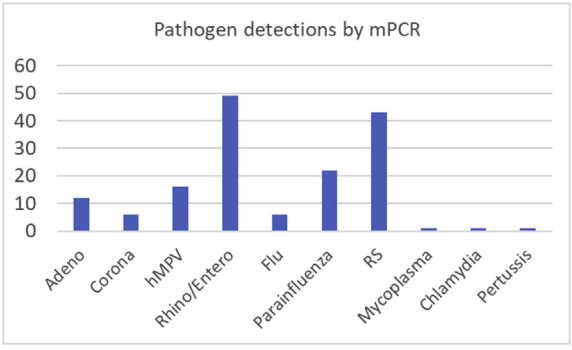

Fig. 2. The number of pathogen detections by mPCR. Adeno; Adenovirus, Corona; Coronavirus HKU1, NL63, 229E or OC43, hMPV; human metapneumovirus, Rhino/Entero; Rhinovirus or Enterovirus, Flu; Influenza virus A, A H1, A H3, A H1-2009 or B, RS; Respiratory syncytial virus, Para; Parainfluenza virus 1, 2, 3 or 4, Mycoplasma; *Mycoplasma Pneumoniae*, Chlamydia; *Chlamydia Pneumoniae*, Pertussis; *Bordetella pertussis*.

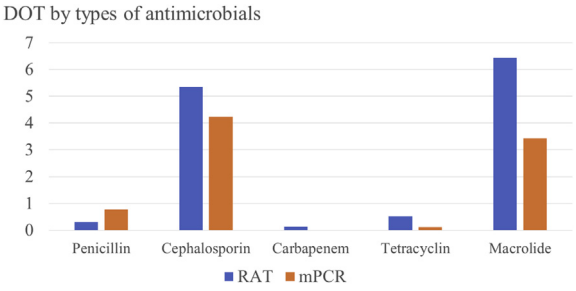

Fig. 3. DOT by type of antimicrobial.

admissions, and this effect would further increase the cost-effectiveness of mPCR.

The Japanese Ministry of Health, Labour and Welfare (MHLW) announced the National Action Plan on Antimicrobial Resistance 2016–2020 with a goal of a 33% reduction of total antimicrobial prescription in 2020 compared to 2013 [18]. The Japanese MHLW also started an additive reimbursement system for the support of antimicrobial stewardship in hospitals where the stewardship criteria have been met since 2018 [19]. In addition, another additive reimbursement system to support not using antimicrobials for pediatric upper respiratory tract infections was also started in 2018 [19]. This means that the nation places a high value on reducing the prevalence of antimicrobial-resistant microorganisms. Unfortunately, the goals have yet to be adequately achieved, although these strategies have significantly affected physicians' antimicrobial prescription behavior [20]. Therefore, the rapid mPCR test can be a powerful tool to further reduce unnecessary antimicrobial usage and help achieve this reduction goal.

Previous studies reported that certain respiratory pathogens, such as Adenovirus, Coronavirus, Enterovirus and Rhinovirus, were present in asymptomatic patients [21–25]. Therefore, it is unlikely that all pathogens detected in our study were directly associated with respiratory infections. Because this study did not compare the pathogen detection rates between symptomatic and asymptomatic patients, it is difficult to investigate how much these viruses were related to the respiratory symptoms. Therefore, further studies on the topic are warranted. In addition, we need to be cautious about the possibility of missing non-infectious diseases by over-detecting colonized or insignificant pathogens. Over-relying on the result of the mPCR test without considering the patient's clinical information can be misleading.

There are some limitations of this study. First, there may be a selection bias in the mPCR group. Because only one mPCR respiratory panel device was available during the mPCR period in our study, we could not perform more than one mPCR test concurrently. Therefore, if more than one patient with respiratory infections was admitted, only the patient with the most severe symptoms received the mPCR test, while other patients were admitted without having the mPCR test, which could explain why the mPCR group was younger than the RAT group. However, we believe that this selection bias does not negate the impact and cost-effectiveness of the study in a Japanese hospital; rather, the real impact of the mPCR test could be larger than that shown in our study. Second, a proper ASP is crucial for the mPCR test to have the greatest impact in each situation. Ideally, the impact of mPCR should be measured in a situation where appropriate and thorough ASP has been implemented in both study periods. The management of antimicrobial treatment for respiratory infections varies widely among health care facilities. Therefore, the cost-effectiveness of a new diagnostic test can differ in each situation. In other words, our study reveals that the mPCR alone could help reduce the unnecessary use of antimicrobials;

however, only performing the mPCR is not sufficient for appropriate antimicrobial use, and implementation of an ASP is mandatory in a facility where the mPCR will be used.

For the effective use of the promising mPCR test in Japan, we propose some important points. First, the mPCR should be coupled with another additive reimbursement system for hospitals to be motivated to further improve antimicrobial stewardship. For example, the government should set a goal of average DOT or LOS for respiratory infections in hospitals where the mPCR respiratory panels are introduced. If the hospitals achieve the goal, they can receive additive reimbursement as appropriate stewardship implementations. Second, we need to prevent abuse of the mPCR test. Patients who are unlikely to receive any benefits from the test or any changes in their clinical management should not receive the test.

In our study, we revealed that the mPCR respiratory panel is a powerful tool to reduce DOT and LOS; however, we also learned that simply introducing the test to Japan is not enough to maximize its effects. Appropriate support from ASPs in each hospital and the national health care system are mandatory to achieve appropriate antimicrobial prescription and maximize cost-effectiveness.

5. Conclusion

Our study is the first to evaluate the impact and cost of the mPCR respiratory panel in Japan. Compared with conventional the RATs, the mPCR has contributed to the reduction in DOT and LOS in a Japanese community hospital for admission-requiring pediatric respiratory infections. However, a proper ASP is necessary and essential to further reduce unnecessary antimicrobial usage.

Declaration of interest

The research was funded by BioMérieux/Biofire for reagents and a device of the FilmArray® respiratory panel test.

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