INTRODUCTION

Bacterial meningitis is a life-threatening condition that requires urgent treatment, whereas viral meningitis is usually self-limiting. Although bacterial meningitis is very rare relative to viral meningitis, partly because of vaccines such as the pneumococcal conjugate vaccine (PCV) and the Haemophilus influenzae type B (Hib) vaccine, many children with meningitis are hospitalized and treated with antimicrobials anyway because of the severity of bacterial meningitis, lack of accurate and timely pathogen diagnosis, and lack of evidence that they can be safely managed without antimicrobials (1). Therefore, the use of rapid molecular diagnostic techniques, such as a multiplex polymerase chain reaction (mPCR) to determine the causative agent of meningitis, could make a significant contribution to more appropriate and timely treatment without the need for hospital stays or use of antimicrobials. For example, obtaining timely results to ascertain enterovirus or parechovirus infection can contribute to a reduction in both the time spent in hospital and use of antimicrobial treatment (2). Another study revealed that the use of mPCR tests also led to a reduction in the duration of antimicrobial treatment (3). To reduce length of hospital stay and unnecessary antimicrobial use in cases of viral meningitis in Japan, epidemiological and clinical data for central nervous infections are needed. Here, we report on the epidemiology and economic burden of central nervous system infections and a simulation of the cost-benefit analysis of the FilmArray® Meningitis/Encephalitis (FAME) test for possible clinical use in Japan. We performed FAME tests on samples from 27 patients with pleocytosis aged between 0 and 20 years seen in six community hospitals in Nara and Osaka prefectures. All clinical management procedures were performed without knowledge of the mPCR test results. We analyzed the clinical data and calculated the required reduction in average length of stay for the FAME test to be cost-beneficial. Among the 27 cases, the FAME test revealed causal pathogens in 13 cases (48.1%). The average medical and social costs per case were ¥299,118 ($2,719.2) and ¥171,768 ($1,561.5), respectively. The minimal needed reduction in average length of stay for the FAME test to be cost-beneficial was 0.32–0.86 days per meningitis case. The result can be informative for evaluating the cost-effectiveness of the clinical use of the FAME test in Japan.

SUMMARY: To investigate the clinical use of multiplex polymerase chain reaction (mPCR) in Japan, epidemiological and clinical data for central nervous infections are needed. Here, we report on the epidemiology and economic burden of central nervous system infections and a simulation of the cost-benefit analysis of the FilmArray® Meningitis/Encephalitis (FAME) test for possible clinical use in Japan. We performed FAME tests on samples from 27 patients with pleocytosis aged between 0 and 20 years seen in six community hospitals in Nara and Osaka prefectures. All clinical management procedures were performed without knowledge of the mPCR test results. We analyzed the clinical data and calculated the required reduction in average length of stay for the FAME test to be cost-beneficial. Among the 27 cases, the FAME test revealed causal pathogens in 13 cases (48.1%). The average medical and social costs per case were ¥299,118 ($2,719.2) and ¥171,768 ($1,561.5), respectively. The minimal needed reduction in average length of stay for the FAME test to be cost-beneficial was 0.32–0.86 days per meningitis case. The result can be informative for evaluating the cost-effectiveness of the clinical use of the FAME test in Japan.

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Tables 1. Organisms tested by FilmArray® Meningitis/Encephalitis panel

| Organism                          |
|----------------------------------|
| **Bacteria**                     |
| _Escherichia coli K1_             |
| _Haemophilus influenzae_          |
| _Listeria monocytogenes_          |
| _Neisseria meningitidis_          |
| _Streptococcus agalactiae_        |
| _Streptococcus pneumoniae_        |
| **Virus**                         |
| Cytomegalovirus                   |
| Enterovirus                       |
| Herpes simplex virus 1            |
| Herpes simplex virus 2            |
| Human herpesvirus 6               |
| Human parechovirus                |
| Varicella zoster virus            |
| **Yeast**                         |
| _Cryptococcus neoformans/gattii_  |

and economic effectiveness of using FAME panels for pediatric meningitis (2,3,5). However, the diagnostic environment, including the availability of other rapid molecular tests and the type of support offered by the local health care system, such as reimbursement and length of stay, vary considerably by country and region. Before considering the introduction of new tests to Japan, more data on the epidemiology and disease burden of CNS infections in the post-vaccine era are needed to analyze the cost-effectiveness of these tests. To investigate its possible cost-effectiveness in pediatric CNS infection cases, we retrospectively used the FAME panel assay for pediatric CNS infection cases and performed a simulated cost-benefit analysis for Japan.

MATERIALS AND METHODS

Design and Setting: We performed the FAME panel assay on CSF samples from patients aged between 0 and 20 years who were diagnosed with CNS infection with pleocytosis in six community hospitals in Nara and Osaka prefectures between September 2017 and May 2019. The cut-off for pleocytosis was a CSF white blood cell (WBC) count >22 cells/µl at <1 month of age, >15 cells/µl at 1–2 months of age, or >5 cells/µl at ≥2 months of age (based on values obtained from a previous study) (6). Exclusion criteria were patients who had received neurosurgery, patients without pleocytosis, and patients whose parents did not give consent. Both consent and assent forms were obtained for all eligible participants prior to lumbar puncture. All clinical management was performed without medical staff being aware of the results of the mPCR tests. No hospitals included in the study had any in-house rapid PCR testing facilities. Some hospitals could send samples to a regional public health institute; however, it took approximately 2 to 3 months for clinicians to obtain the results. Tests performed in regional institutes included viral culture and PCR tests, including testing for mumps (Japan is currently experiencing a mumps epidemic due to the lack of routine vaccination for this disease). Approval from the Institutional Review Boards of all six hospitals was obtained before beginning the registration of participants.

Next, we investigated the epidemiology and disease burden of the participants. We reviewed the participants’ clinical data. We also looked at the diagnostic rate of microorganisms using mPCR compared with that when using conventional tests (culture, antigen and antibody tests, and batched PCR tests). We then performed a cost-benefit analysis to evaluate the possible cost-effectiveness of the FAME panel assay for future clinical use in Japan.

Cost-benefit analysis: We evaluated the economic burden of the study participants. The estimation of economic burden was based on calculating both medical and social costs. If a patient was managed only as an outpatient, we calculated the medical cost based on the patient’s electronic medical record. If a patient was hospitalized, we calculated the hospitalization cost according to the Diagnosis Procedure Combination system (DPC system, a Japanese medical reimbursement system based on length of stay and clinical diagnosis). The social cost, defined as parental absence from work, was calculated by the time needed for family members to take care of their hospitalized children because most pediatric wards in Japan require that one family member accompanies their child throughout hospitalization. The time of parental absence from work to take care of their hospitalized children was converted to a monetary value by multiplying the time spent by the average daily wage in Japan (7). For the medical cost in hospitalized cases, outpatient and antimicrobial costs were not included because they are not reimbursed in the DPC system. Japanese yen (JPY) was converted into US dollars (USD) at a rate of 110 JPY per 1 USD.

A cost-benefit ratio (the proportion of the total cost potentially saved by the test to the incremental cost of the test) from a payer’s (governmental) perspective was used as a simulation of the future cost-effectiveness. If the ratio is higher than 1.0, the test is considered cost-beneficial. In this study, the cost-benefit ratio was calculated as follows:

\[ \text{Cost-benefit ratio} = \frac{\text{cost potentially saved by the test}}{\text{incremental cost of the test per meningitis case}} \]

Using the average medical and social costs per one day hospital stay among participants, the cost potentially saved by the test was calculated as follows:

\[ \text{Cost potentially saved by the test} = \text{potential reduction in length of stay because of the test (days)} \times \text{average total cost (medical and social costs) per day per case} \]

The required reduction in average length of stay per meningitis case for the FAME test to be cost-beneficial was then calculated. Because the governmental reimbursement of the FAME test has not yet been established, the cost for the respiratory panel was referred to as the incremental cost per FAME test.
RESULTS

A total of 27 patients were included over the course of the study period. The participants’ backgrounds, clinical courses, and economic burdens are shown in Table 2. The median age of the participants was 6.0 (0.0–14.7) years, and the length of stay was 13.0 (7.0–37.8) days. All participants were managed as inpatients. Of the 27 patients, 23 (85.2%) received a clinical diagnosis of meningitis, 2 (7.4%) had encephalitis, and 2 (7.4%) had acute flaccid paralysis (AFP). In terms of clinical outcomes, all but two of the patients with CNS infection experienced a complete recovery from their symptoms, while one patient with encephalitis and one with AFP experienced minor neurological sequelae. Antimicrobials were administered to 22 patients (median days of therapy: 7.3 [4.1–17.8] days) and antivirals were administered to 12 patients (median days of therapy: 8.7 [3.7–13.5] days).

The pathogens identified using conventional tests and the FAME panel tests are shown in Table 3. The FAME panel test identified pathogens from 13 cases (48.1%) among the 27 patients (enteroviruses in 10 patients, varicella-zoster virus [VZV] in two patients, and Listeria monocytogenes in one patient). A discrepancy in results occurred in one case (FAME, VZV; conventional PCR, human herpesvirus [HHV] 6B). This discrepancy did not affect our cost-benefit calculations. Fifteen CSF samples were sent to regional public health institutes for conventional testing. No in-house or rapid PCR tests, except for the FAME panel assay, were performed in any of the hospitals throughout the study period. Of the 23 meningitis cases, only one was bacterial meningitis. This was a one-year-old girl who presented with fever and lethargy. The patient was first empirically treated with meropenem and cefotaxime. The following day, her CSF culture sample grew Listeria monocytogenes. Therefore, the antimicrobial treatment was switched to ampicillin. Although her fever persisted for weeks, she was discharged without any neurological complications following antimicrobial treatment.

Of the 27 CNS infection cases, the average medical and social costs per case were ¥299,118 ($2,719.2) and ¥171,768 ($1,561.5), respectively. Among the 23 meningitis patients, the average medical and social costs per case were ¥245,994 ($2,236.3) and ¥161,270 ($1,466.1), and the average total cost per one day hospital stay was ¥29,831 ($271.2). The minimal needed reduction in average length of stay for the FAME test to be cost-beneficial was 0.32–0.86 days per meningitis case.

DISCUSSION

Our study found that the FAME panel could identify the pathogens in approximately 50% of children with CNS infection. Compared with previous studies in other countries, our study revealed that children with

| Background | N = 27 |
|------------|--------|
| Age (year) | 6.0 (0.0–14.7) |
| Sex, male (%) | 74.1% |
| Clinical diagnosis | |
| Meningitis | 23 (85.2%) |
| Encephalitis | 2 (7.4%) |
| Acute flaccid paralysis | 2 (7.4%) |
| Blood | |
| WBC (/μl) | 10,000 (5,540–17,428) |
| CRP (mg/dl) | 0.26 (0.02–3.33) |
| Procalcitonin (ng/ml) | 0.18 (0.11–0.55) |
| CSF | |
| WBC (/μl) | 133 (26–397) |
| Poly (/μl) | 36 (6–152) |
| Protein (mg/dl) | 61.0 (22.2–132.8) |
| CSF/blood glucose ratio | 0.56 (0.43–0.73) |
| Clinical outcomes | |
| Complete resolution | 25 (92.6%) |
| Minor neurological sequelae | 2 (7.4%) |
| Major neurological sequelae | 0 (0.0%) |
| Death | 0 (0.0%) |
| Antimicrobials used | 22 (81.5%) |
| Days of antimicrobial therapy / case (days) | 7.3 (4.1–17.8) |
| Antivirals used | 12 (44.4%) |
| Days of antiviral therapy / case (days) | 8.7 (3.7–13.5) |
| Hospitalization rate | 27 (100%) |
| Length of stay (days) | 13.0 (7.0–37.8) |
| Medical cost / case | ¥253,210 (139,110–518,890) |
| Social cost / case | ¥153,566 (82,690–446,523) |

The values are exhibited as the median value (10th percentile-90th percentile).

CRP, c-reactive protein; CSF, cerebrospinal fluid; Poly, polymorphonuclear leukocyte; WBC, white blood cell.

| Identified pathogens | Conventional test | mPCR test |
|---------------------|-------------------|-----------|
| Detection of any pathogen | 7 (25.9%) | 13 (48.1%) |
| Enterovirus | 4 (14.8%) | 10 (37.0%) |
| VZV | 0 (0.0%) | 2 (7.4%) |
| HHV 6 | 1 (3.7%) | 0 (0.0%) |
| Mumps | 1 (3.7%) | 0 (0.0%) |
| Listeria monocytogenes | 1 (3.7%) | 1 (3.7%) |

VZV, varicella-zoster virus; HHV, human herpesvirus.
CNS infections in Japan received longer treatment with antimicrobials and had greater length of stay (1–3). This may be due to the paucity of commercially available rapid PCR tests in Japan and the differences in healthcare systems. Therefore, the effect of the FAME panel assay may be much greater in Japan if it is accepted for commercial use. The simulation of the cost-benefit analysis highlighted that a 0.32–0.86-day reduction in length of stay would be required for the FAME test to be cost-beneficial. The Japanese Ministry of Health has recently begun a nationwide antimicrobial stewardship plan (10). As part of this stewardship plan, it is recommended that the treatment of viral infections with antimicrobials should be avoided. The FAME panel may potentially help the stewardship program by also promoting testing for viral CNS infections. We did not consider the antimicrobial cost in our cost-beneficial analysis because all participants were hospitalized in our study, and the antimicrobial cost is not reimbursed in Japan.

Our study revealed one case of bacterial meningitis both when using the FAME panel test and conventional testing (CSF culture). In cases of bacterial meningitis, the rapid identification of causal pathogens is crucial for timely treatment using appropriate antimicrobials. Although bacterial meningitis is becoming rarer in Japan due to high coverage rates having been achieved for both the PCV (96.6% for the 1st dose at 6 months in 2016) and the Hib vaccine (97.9% for the 1st dose at 6 months in 2016) (11), any delay in the accurate diagnosis of bacterial pathogens can have a devastating influence on a patient’s outcome. In our study, the cost reduction or health benefit of rapid treatment from timely identification of causal pathogens was not considered, which could make the FAME test more cost-effective.

Our study has several limitations. First, the sample size of the study was small. Therefore, it may be difficult to generalize the findings of the study or to suggest that the study reflects the national average regarding the epidemiology and economic burden of pediatric CNS infections. However, we believe that our study is important for the nation when considering the introduction of this new rapid molecular test for CNS infections. Second, this study included only participants who had pleocytosis; many studies, however, have shown that a significant number of patients with CNS infections do not have pleocytosis, especially neonates and young infants (12–14). Therefore, we would have missed CNS infections that were not associated with pleocytosis. There is no consensus as to whether universal or selective mPCR testing for CNS infections is more cost-effective once the mPCR test has been approved for commercial use. Although our data cannot be used to develop a universal mPCR test strategy, this study may provide important basic data for the future analysis of selective mPCR testing because clinicians may be more likely to perform mPCR tests for CNS infections with pleocytosis. Third, our study retrospectively performed the FAME test, and the results were not shared with healthcare providers. Thus, we can only speculate how case management may have changed if these results were available to clinicians. Therefore, further studies based on more comprehensive data are warranted.

In conclusion, the study provided the required reduction in length of stay once the FAME test was introduced and reimbursed in the Japanese health care system. The result can be informative for evaluating the cost-effectiveness of clinical use of the FAME test in Japan.

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REFERENCES

1. Blaschke AJ, Holmberg KM, Daly JA, et al. Retrospective evaluation of infants aged 1 to 60 days with residual cerebrospinal fluid (CSF) tested using the filmarray meningitis/encephalitis (ME) panel. J Clin Microbiol. 2018;56: e00277-18.
2. Chakrabarti P, Warren C, Vincent L, et al. Outcome of routine cerebrospinal fluid screening for enterovirus and human parvovirus infection among infants with sepsis-like illness or meningitis in Cornwall, UK. Eur J Pediatr. 2018;177:1523-9.
3. Eichinger A, Hagen A, Meyer-Bühl M, et al. Clinical benefits of introducing real-time multiplex PCR for cerebrospinal fluid as routine diagnostic at a tertiary care pediatric center. Infection. 2019;47:51-8.
4. Tansari GS, Chapin KC. Diagnostic test accuracy of the BioFire® FilmArray® meningitis/encephalitis panel: a systematic review and meta-analysis. Clin Microbiol Infect. 2020;26:281-90.
5. Duff S, Hashburn R, Gincocchio CC, et al. Economic analysis of rapid multiplex polymerase chain reaction testing for meningitis/encephalitis in pediatric patients. Future Microbiol. 2018;13:617-29.
6. Bonadio WA, Stanko L, Bruce R, et al. Reference values of normal cerebrospinal fluid composition in infants ages 0 to 8 weeks. Pediatr Infect Dis J. 1992; 11: 589-91.
7. Japanese Ministry of Health, Labour and Welfare. Monthly labour survey, e-stat annual survey, 2017. Tokyo: Japanese Ministry of Health, Labour and Welfare; 2017. Available at <https://www.e-stat.go.jp/>. Accessed July 10, 2020.
8. Kitano T, Nishikawa H, Suzuki R, et al. The impact analysis of a multiplex PCR respiratory panel for hospitalized pediatric respiratory infections in Japan. J Infect Chemother. 2020;26:82-5.
9. Japanese Ministry of Health, Labour and Welfare. Reimbursement of clinical test, 2019 November. Available at <https://www.mhlw.go.jp/content/12404000/000558331.pdf>. Accessed July 18, 2020. Japanese.
10. Japanese Ministry of Health, Labour and Welfare, Tokyo. National Action Plan on Antimicrobial Resistance 2016-2020. Available at <https://www.mhlw.go.jp/file/06-Seisakujouhou/1090000-Kenkoukyoku/0000120769.pdf>. Accessed Apr 30, 2019. Japanese.
11. National Institute of Infectious Diseases. Vaccine coverage rate surveillance 2016. Available at <https://www.nih.go.jp/niiid/images/vaccine/cum-vaccine-coverage/cum-vaccine-coverage_28.pdf>. Accessed July 10, 2020. Japanese.
12. Song JY, Nam SO, Kim YA, et al. Cerebrospinal fluid non-pleocytosis in pediatric enteroviral meningitis: large-scale review. Pediatr Int. 2018;60:855-61.
13. Tan NWH, Lee EY, Khoo GMC, et al. Cerebrospinal fluid white cell count: discriminatory or otherwise for enteroviral meningitis in infants and young children? J Neurovirol. 2016;22:213-7.
14. Yun KW, Choi EH, Cheon DS, et al. Enteroviral meningitis without pleocytosis in children. Arch Dis Child. 2012;97:874-8.