MICROBIOLOGY SOCIETY

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A retrospective study examining the clinical significance of testing respiratory panels in children who presented to a tertiary hospital in 2019

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Abstract

Background. Respiratory tract infections are a leading cause of hospital visits in the paediatric population and carry significant associated morbidity and mortality in this population. The introduction of respiratory panel testing has been said to guide clinicians in the overall management of patients.

Methods. We conducted a retrospective study examining all respiratory panels carried out in our hospital during 2019 on paediatric patients. Patients included were those who had symptoms indicative of respiratory infections who presented acutely, including those with chronic respiratory conditions. A total of 188 respiratory panel results were obtained along with collected patient data. These were analysed using SPSS V. 25.0 to get the below mentioned results.

Results. The majority (76.6%) of patients were less than 3 years with 59% of total population being males. The majority (80.9%) had mild clinical severity score. The most common pathogen that was detected on the respiratory panel was *Enterovirus Human Rhinovirus* spp, followed by the *influenza* viruses. Only four cases were positive for bacterial pathogens (two *Mycoplasma pneumoniae*, one *Bordetella pertussis* and one *Chlamydia pneumoniae*), which accounts for 2.1% of all panels analysed. The significance of respiratory panels in influencing treatment were analysed in the forms of change of management plans before and after results of respiratory panels. This was observed in 14.4% of patients who were not on any empiric medication and then based on panel results were started on medications, as well as 11.7% who were on medications already, and the medications were altered based on the result of the panel (Chi square *P*=0.057). This was mainly seen with cases of *influenza A H1N1* patients and to a lesser extent, *Mycoplasma pneumonia*.

Conclusion. The use of respiratory panels in our hospital had little impact on patient care and management. The main organisms that influenced clinician decision in treatment were *influenza A* viruses and bacterial organisms (*Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and *Bordetella pertussis*). Other than that, the use of clinical judgement proved more beneficial. We recommend use of specific testing for these organisms rather than the whole panel as case to case bases, which would be more cost-effective and consistent with patient management.

INTRODUCTION

Acute respiratory tract infections (RTI) are considered the leading cause of hospital visits and contribute to a significant morbidity and mortality worldwide. In the paediatric population, particularly those under the age of 5 years, RTI are the second leading cause of death. The aetiology in the majority of cases is of viral origin, while there are still cases of primary as well as secondary bacterial infections [1, 2].

Until recently, conventional tests such as cultures of nasopharyngeal aspirates, throat swabs, serological titres, and antigen detection by immunofluorescence assays were considered the gold standard for the diagnosis of the aetiology of RTIs. These

tests are labour intensive, offer a limited range of detection and have a long turnaround time [1, 3]. The recent development of molecular testing allowed rapid detection of multiple microbes with a higher yield of viruses and bacteria in the clinical setting [1].

In our study, we look into the clinical significance of molecular testing by respiratory panels and its correlation with clinical course for children who visited the paediatric emergency, paediatric inpatients ward, and the PICU of King Hamad University Hospital.

The FilmArray Respiratory Panel (RP) is a fully automated multiplex PCR device which allows simultaneous qualitative detection of 19 pathogens in its current version. The process is rapid (about 65 min between hand and instrument time), 61% sensitive and 91% specific and is not affected by prior antibiotic use [2].

In contrast, conventional methods like immunofluorescence assays and immunochromatographic antigen testing have a limited range of detection and lack sensitivity as they depend on viral titre, patient's age and time of sampling in relation to symptoms. Based on a literature review, most studies found that respiratory panels are superior, while other methods are time consuming, labour exhaustive, and rely on technical expertise in interpretation of cell cultures [1, 2, 4].

METHODS

To establish the clinical significance of carrying out respiratory panel testing in children, we conducted a retrospective observational study. All FilmArray respiratory panels ordered in our hospital for children younger than 14 years of age were collected and analysed. All patients were consented on admission for the use of their demographic and clinical information for research purposes while maintaining confidentiality.

Criteria to be included in the study were: at least one symptom of upper or lower respiratory tract infection (fever, cough, dyspnoea, tachypnea, etc.), symptom onset for less than 2 weeks, patients who suffer from chronic respiratory illness who present acutely, and patients who demonstrated radiological findings. A total number of 188 respiratory panels that met the inclusion criteria were found during the target duration of the study (11 months between February 2019 and December 2019).

Electronic medical records were accessed to obtain demographic data, clinical features, laboratory tests, imaging results and information on the patient's hospital course. The collected data was recorded on a Microsoft Excel sheet. The data analysis was done by using SPSS version 25.0. Descriptive statistics was used to compute the frequencies and percentages of the categorical variables. Mean, standard deviations, median and range were described for the continuous variables. Chi-square test was used to compare significant differences between two groups with categorical data. Significant differences between non-normally distributed continuous variables were computed using Mann-Whitney tests. All statistical analyses were two-tailed, and a *P* value<0.05 was considered statistically significant.

Nasopharyngeal samples were collected by the standard technique as per the instructions of the manufacturer and immediately transported in a viral transport medium. A minimum sample volume of 300 micromol was required. The sample was processed in the hospital's microbiology laboratory and tested as soon as possible where each pouch of the reagent was analysed separately.

The panel used was the BioFire FilmArray Respiratory panel (R). This panel targets detection of 22 pathogens through isolating available nucleic material on the nasopharyngeal sample and runs a multiplex Polymerase Chain Reaction (PCR), followed by a single-plex reaction. Then this is analysed by an automated system and interpreted to reflect the presence of absence of each of the target pathogens. The manufacturer claims a 97.1% sensitivity and 99.3% specificity of this system.

RESULTS

Patient characteristics

Table 1 describes both the demographic and clinical features of the studied patients. The majority (76.6%) of our patient population are toddlers and infants, with just above half (59%) of them being males. With regards to the clinical characteristics, 40.5% of the patients admitted had premorbid medical conditions detailed in the table, 14.4% were asthmatics. The commonest admission diagnosis was upper respiratory tract infection (35.1%) followed by bronchiolitis (12.2%). The clinical severity score that was used to stratify the admissions showed that 80.9% were classified as mild severity illnesses [5]. Only 2.6% needed mechanical ventilation, and 22% needed non-invasive ventilation.

Aetiology

Table 2 and Fig. 1 reveal the spectrum of respiratory pathogens. The most commonly detected pathogen is *Human Rhinovirus* (25.5%) followed by the *influenza* viruses (16.5%). We had one case of *Bordetella pertussis*, one case of *Chlamydia pneumoniae* and two cases of *Mycoplasma pneumoniae*. There were also co-infections described in Table 2.

Table 1. Describing patients demographic and clinical characteristics (*n*=188)

Median age (months)	19 months
	Frequency (%)
Age distribution	
Neonate (<28 days)	10 (5.3%)
Infant (29 days −12 months)	54 (28.7%)
Toddler (12 months – 3 years)	80 (42.6%)
Pre-school (3 years – 5 years)	13 (6.9%)
School age (5 years – 10 years)	30 (16.0%)
Adolescent (10 years −14 years)	1 (0.5%)
Gender	
Male	111 (59.0%)
Female	77 (41.0%)
Need for admission	
Yes	166 (88.2%)
No	22 (11.7%)
Coexisting comorbidity	
Cardiology/cardiovascular	4 (2.1%)
Endocrine related	2 (1.1%)
Gastric/metabolic	8 (4.3%)
Neurological related	17 (9.0%)
Respiratory (asthma)	27 (14.4%)
Others (genetic, premature, ENT, etc.)	18 (9.6%)
Admission diagnosis	
URTI*	66 (35.1%)
Bronchiolitis	23 (12.2%)
Asthma	15 (8.0%)
Pneumonia	14 (7.44%)
Febrile seizure	13 (6.91%)
Gastritis/gastroenteritis	13 (6.9%)
Sepsis†	10 (5.3%)
Croup	5 (2.7%)
Others	29 (15.4%)
Severity score‡	
Mild	152 (80.9%)
Moderate	34 (18.1%)
Severe	2 (1.1%)
PICU§	
Yes	22 (11.7%)
No	163 (86.7%)
Duration of hospital days‖	
0	22 (11.7%)
1–2 days	58 (30.2%)
3–7 days	81 (43.1%)
>7 days	27 (14.4%)
NIV¶	
Yes	43 (22.9%)
No	145 (77.1%)
Mechanical ventilation**	
Yes	5 (2.6%)
No	182 (96.8%)

*Upper respiratory tract infection.
†Patients with positive blood cultures on admission correlating with their clinical presentation (i.e. not contaminant) are designated as sepsis
‡The Clinical Respiratory Score was used to stratify patients according to six parameters (respiratory rate, auscultation, use of accessory muscles, mental status, room air SpO_2 and colour).
Each parameter has minimum score of 0 and maximum of 2. Total score reflect severity as follow: Mild is (<3), Moderate (4-7) and Severe (8-12). [5].
§Paediatric Intensive Care Unit.
‖Duration is counted from initial presentation to hospital until discharge.
¶Non-invasive ventilation.
**Patients who require intubation and use of mechanical ventilation during admission.

Table 2. Pathogen patterns detected by a Respiratory Panel: describing the frequencies of detected bacteria as well as frequencies of viral co-infections

Bacteria	Frequency
Bordetella pertussis	1
Chlamydia pneumoniae	1
Mycoplasma pneumoniae	2
Co-infections	
Adenovirus +Human Coronavirus	1
Adenovirus +Human Coronavirus +Influenza	1
Adenovirus +Human Metapneumovirus	1
Adenovirus +Human Rhinovirus	4
Adenovirus +Human Rhinovirus +Chlamydia Pneumoniae.	2
Influenza+Human Rhinovirus	2
Influenza+Human Rhinovirus	3
Human Coronavirus +Adenovirus	1
Human Coronavirus +Human Rhinovirus	3
Human Coronavirus +Influenza	2
Human Coronavirus +Human Rhinovirus	2
Human Metapneumovirus +Human Rhinovirus	1
Human Metapneumovirus +Human Rhinovirus +Influenza	1
Human Rhinovirus +Bordetella pertussis	1
Human Rhinovirus +Human Metapneumovirus	3
Mycoplasma pneumoniae +Human Rhinovirus	1
Parainfleuza +Human Rhinovirus	4
Respiratory syncytial Virus +Human Rhinovirus	2
Respiratory syncytial Virus +Adenovirus	3

Hospital admission rate and length of hospital stay

In total, 88.2% of children in whom a respiratory pathogen was detected by the respiratory panel actually required admission. Out of those, 22 patients (11.7%) required PICU care. The average hospital stay of the studied population was 3–7 days and a total number of 88 patients stayed for this duration.

Age related distribution of respiratory pathogens

Fig. 2 illustrates the commonest pathogens among each age group. As one can see, in infants and toddlers there were 41 cases of *Human Rhinovirus*. Among the neonatal group there were three cases of *influenza A* viruses, while the school aged children had 11 cases of the same pathogen.

Other diagnostic investigations

With regards to ancillary tests, we evaluated an inflammatory marker (C reactive protein), haematological indices, microbiology investigations like blood culture and throat swab, as well as a chest X-rays. These were some of the remarkable observations:

(A) *CRP*: Of the samples processed, worthy of note, were the cases of adenovirus and *Human Rhinovirus* which had a CRP of more than 50.
(B) *White blood cells (WBC):* Mostly were within normal range, however, (nine cases) 4% showed low WBC counts, while again, *Adenonvirus* and *Human Rhinovirus* cases had a predilection to be high.
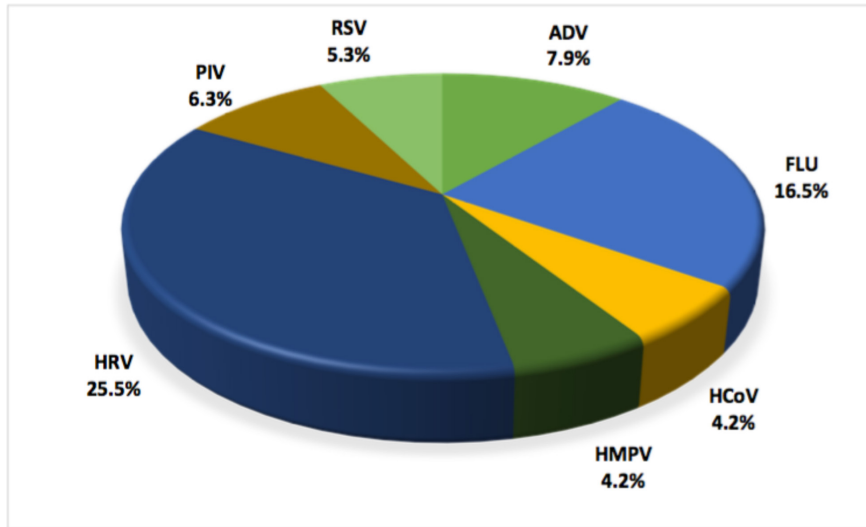
Fig. 1. Types of respiratory pathogen. A pie chart listing the proportions in percentages of the different viruses detected by respiratory panels from a total of 188 samples. HRV: Human Rhinovirus, FLU: Influenza Virus (inclusive of all strains A, B, C and D), ADV: Adenovirus, PIV: Parainfluenza Virus, RSV: Respiratory Syncytial Virus, HMPV: Human Metapneumovirus, HCoV: Human Corona Virus.

(C) *Blood culture:* Blood culture was done for nearly (87) 56.3% of cases. There was no growth in 77 (40.9%) cases. In patients who had positive blood cultures (ten cases) the microorganism in the respiratory panel was mostly human rhinovirus (seven cases).

(D) *Throat swabs* were done for 31 patients and were negative.

(E) *Chest X-ray*: Chest X-ray was not done for 65 (34.5%) patients. In those who underwent a chest X-ray examination, 80 (42.5%) had normal findings. Viruses that had significant chest X-ray findings included *Human Rhinovirus* and *Adenovirus* (six and four cases respectively) in the form of consolidation. Another significant finding was lung collapse with two cases of *Respiratory syncytial virus* and one case of *Human Rhinovirus*.
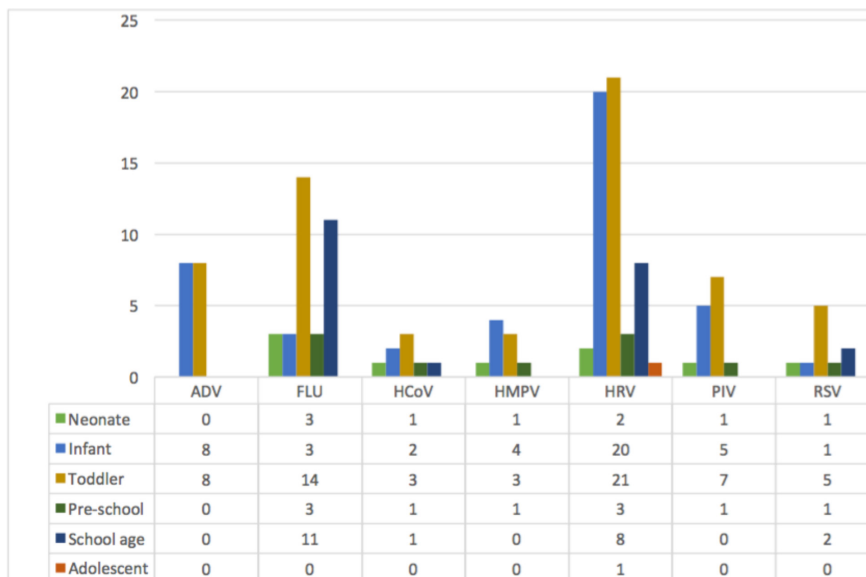

	ADV	FLU	HCoV	HMPV	HRV	PIV	RSV
Neonate	0	3	1	1	2	1	1
Infant	8	3	2	4	20	5	1
Toddler	8	14	3	3	21	7	5
Pre-school	0	3	1	1	3	1	1
School age	0	11	1	0	8	0	2
Adolescent	0	0	0	0	1	0	0

Fig. 2. Respiratory infection virus's (individual) distribution in the age groups (Counts). Stacked bar charts describing the frequencies of each virus among the different paediatric age groups. ADV: Adenovirus, FLU: Influenza Virus (inclusive of all strains A, B, C and D), HCoV: Human Corona Virus, HMPV: Human Metapneumovirus, HRV: Human Rhinovirus, PIV: Parainfluenza Virus, RSV: Respiratory syncytial Virus.

Table 3. Change in antimicrobials. Describes the frequencies of cases where empiric antibiotics were initiated by physicians and whether they were changed or not after the release of respiratory panel

Empirical medication (before test)	Change in medication after respiratory panel test	
	Yes	No
Yes	22 (11.7%)	43 (22.9%)
No	27 (14.4%)	96 (51.1%)
Chi square *P*=0.057		

Medical management before and after release of the respiratory panel report

Empiric antimicrobials

The use of empiric antimicrobials was uncommon in the reviewed cases. In total, 65 cases (34.6%) were started on empiric antibiotics and two cases (1.1%) only were started on empiric antivirals based on clinical picture and history.

Regarding the two cases where empiric antivirals were prescribed, the first one was a case of atypical febrile seizures where acyclovir was prescribed for the possible diagnosis of encephalitis and was later stopped. The other case was a child who came with an upper respiratory infection and had contact with cases who tested positive for *influenza A H1N1*. Therefore from the start they were started on ostelamivir and the respiratory panel was positively confirmed *influenza A H1N1*.

Changes in the medical management after the respiratory panel report

Respiratory panel results had an insignificant impact on prescribing medications. We found 27 (14.4%) patients who were not on any medications, were started on medication after the results of panel were known. In total, 22 (11.7%) patients who were initially on empirical medications received altered medications based on the results of the panel.

There were two cases with non-URTI diagnosis where medical management was started based on the result of the respiratory panel. One was a case of febrile seizures in which ostelamivir was prescribed after the release of the respiratory panel result which was positive for *influenza A H1N1*. There was one child who was started on acyclovir after the respiratory panel result (*Enterovirus Human Rhinovirus*), but that was because he progressed into a clinical picture of Acute Demyelinating Encephalomyelitis (ADEM).

In the cases where medical management was changed after the release of the respiratory panel results the indications were clinical. It was either that the patient looked septic, had a moderate to high severity index of respiratory distress, had abnormal chest X-ray findings like consolidation or lung collapse, or had a significantly high CRP in the context of a sick child. There were only five cases of bacteria detected in the panel where we prescribed either azithromycin, clarithromycin or clindamycin after knowing the pathogen, for example *Mycoplasma pneumoniae; Bordetella pertussis* and *Chlamydia pneumoniae*.

In the 96 cases where no empiric antibiotics were started and there were no changes in the medical management after the release of respiratory panels, the detection of the potentially responsible pathogen was mostly utilized in counselling patient families about the aetiology. It was also used in cohorting patients with regards to isolation measurements. However, in these 96 cases the standard management of the admission diagnosis was done without the influence of respiratory panel results on the clinical decisions of the medical team.

One of the reasons behind the fact the respiratory panels did not influence the management strategy is because there are already fixed clinical practice protocols for the management of admitting diagnosis in the different department sections where the respiratory panels were obtained. Clinicians followed these protocols of management as standard of care and respiratory panels results did not impact the clinical course apart from counselling and infection control measures. In the 23 cases described meticulously in appendix (available in the online version of this article) one we can clearly see the clinical events that happened in the patients course and influenced the physicians' clinical decisions after the release of respiratory panels.

Table 3 shows the pattern of change in the prescription of antimicrobials. For more detail, please refer to Appendix one.

DISCUSSION

This report demonstrates that requesting respiratory panels does not significantly affect the medical management of children who present with fever or symptoms of upper and lower airway disease. In this analysis we evaluate the distribution of respiratory pathogens, which appears to be mostly heterogeneous, with the largest percentage of cases being attributed to *Human Rhinovirus* followed by *influenza* viruses. However, as we predicted, the result of the respiratory panel has guided physicians to the prescription of ostelamivir in viral cases where indicated. It does not appear that the results of respiratory panels decreased the prescription of complimentary studies, nor did it affect the length of hospital stay.

Current knowledge shows that acute respiratory infections are a significant cause of mortality and morbidity in children worldwide but especially in developing countries. According to WHO statistics Acute Respiratory Infections (ARI) contribute to 50% of mortality in children under 5 years of age [6]. Additionally, ARIs have a major impact on medical services consumption and emergency visits. They are associated with excessive antimicrobial prescription, hospitalizations, and a burden on work and school commitments [1–3].

It is consistent within various studies that viruses are the commonest cause of ARIs in children followed by bacteria, yet most of ARIs are managed initially by over-prescribing antibiotics, which mostly is ineffective against the responsible pathogen. Although there is conflicting data on the most common viruses that cause ARIs, the most frequently reported viruses are *Human rhinovirus*, *influenza* viruses, *Respiratory syncytial virus, Parainfluenza* virus, *Adenovirus, Human Metapneumovirus, Human Coronavirus* [5–8].

Nonetheless, atypical pathogens are a serious cause of ARIs in children. One of the commonest atypical pathogens is *Mycoplasma pneumoniae*. Early detection of such pathogens is helpful for proper prescription of antimicrobial while preventing overuse and abuse of medications. More importantly, rapid diagnosis is essential for proper cohorting of cases and preventing the spread of contagious pathogens like *Bordetella pertussis* and *influenza* viruses [9].

While multiplex PCR testing is emerging to replace traditional testing, distinguishing colonizing pathogens from causative ones is not feasible. Additionally, in critically ill children, positive results do not necessarily exclude other pathogens as bacterial co-infection can occur [10, 11]. An appropriate approach is to comprehensively consider clinical assessment as well as the results of blood and radiology investigation and make management decisions in the clinical context of each individualized child.

Considering that FilmArray respiratory panels are relatively new, published data is scarce in literature. The majority of studies looked only on the prevalence of microorganisms and rapid detection of FilmArray. Very few studies examined the clinical significance of these investigations in the medical practice and are almost all related to adults [12]. There were a number of paediatric research projects that we were able to identify. The study conducted by Echavarria *et al.* [1] was one of the biggest randomized controlled trials that proved that RPs had a better clinical impact with regards to prescription of ostelamivir and antibiotics as well as reduction in requesting other investigations. Likewise, Chiu *et al.* [8] revealed that respiratory panels are more superior in relation to better diagnosis, improved patient's outcomes and lesser abuse of antimicrobials.

This study has significant implications to our medical practice, especially after discovering through our literature review that there are few studies conducted in the paediatric population. Clearly in our population, RP testing did not affect medical management in a significant way, which means that routine testing from the emergency, inpatient ward and outpatient clinics is not always indicated. FilmArray respiratory panels can help in the targeted use of ostelamivir, but testing is available for specific influenza viruses which, although less sensitive, is much less expensive than FilmArrays. Cost-effectiveness is an integral part of management decisions. Respiratory panels are expensive, as the cost of the reagent and the consumables is 240$ USD and 40$ respectively per patient [3]. This should be weighed against the fact that, as per our data analysis, respiratory panels did not appear to affect the length of hospital stay nor did it lessen the prescription of antibiotics and ancillary testing. Physicians have used clinical judgement in assessing the holistic picture of each clinical case while making medical management decisions, which is in fact the approach that most published literature advocate for.

A few aspects in this study could be improved. To start with, it is a single centre study which may not be truly representative of the paediatric population of Bahrain and did not allow sufficient power to show statistically significant results. Secondly, this was a retrospective study therefore it wasn't possible to compare the results of the FilmArrays to gold standard tests like cultures or serology testing. We would hope to achieve this a future prospective study.

CONCLUSION

Although respiratory panel testing can be quite useful and may help guide physicians in managing patients, yet this should always be in accordance with utilizing the clinical judgement of the treating team and clinical picture of the patient. Moreover, the cost-effectiveness of this tool and whether all elements of the panel are worth obtaining is yet to be determined.

We recommend a large multi-centre study to assess the cost-effectiveness of respiratory panels and to determine the clinical relevance of testing for each of these organisms keeping in mind the patients' condition, as well as the necessity of looking for them in the clinical setting.

Conflicts of interest
The authors declare that there are no conflicts of interest.

Ethical statement
This study received ethical approval by the Institutional Review Board of King Hamad University Hospital. Consent to participation in research was obtained from all parents or legal guardians on presentation to the hospital.

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