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Impact of multiplex molecular assay turn-around-time on antibiotic utilization and clinical management of hospitalized children with acute respiratory tract infections

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ABSTRACT

Background: Empiric antibiotic treatment is common among children with acute respiratory tract infections (ARTI), despite infections being predominately viral. The use of molecular respiratory panel assays has become increasingly common for medical care of patients with ARTIs.

Study design: This was a 6-year retrospective, single-centered study of pediatric inpatients who tested positive for an ARTI respiratory pathogen. We examined the relationship between clinical outcomes and whether the patient was tested using the Luminex Respiratory Viral Panel ([RVP]; in-use: Dec. 2009 – Jul. 2012) or Biofire Respiratory Pathogen Panel ([RP]; in-use Aug. 2012 – Jun. 2016). The prevalence and duration of pre-test empiric antibiotics, post-test oseltamivir administration to influenza patients, chest x-rays and length of stay between the two assays was compared.

Results: A total of 5142 patients (1264 RVP; 3878 RP) were included. The median laboratory turn-around-time for RP was significantly shorter than RVP (1.4 vs. 27.1 h, respectively; $p < .001$). Patients tested with RP were less likely to receive empiric antibiotics (OR: 0.45; $p < .001$; 95% CI: 0.39, 0.52) and had a shorter duration of empiric broad-spectrum antibiotics (6.4 h vs. 32.9 h; $p < .001$) compared to RVP patients. RP influenza patients had increased oseltamivir use post- test compared to RVP influenza patients (OR: 13.56; $p < .001$; 95% CI: 7.29, 25.20).

Conclusions: Rapid molecular testing positively impacts patient management of ARTIs. Adopting assays with a shorter turn-around-time improves decision making by decreasing empirical antibiotic use and duration, decreasing chest x-rays, increasing timely oseltamivir administration, and reducing length of stay.

1. Background

Acute respiratory tract infections (ARTI) —including the common cold, otitis media, pharyngitis, acute bronchiolitis, and pneumonia—are the most common diagnoses among patients seeking medical care in the US, and account for the majority of all antibiotic prescriptions [1,2]. Donnelly et al. estimated that each year there are 43 million emergency department (ED) visits for patients < 5 years of age with a diagnosis of ARTI (rate: 354 per 1000 ED visits). [3]. Antimicrobials are not indicated for the common cold, bronchitis/bronchiolitis and the vast majority of pharyngitis cases, and specific criteria exists to target appropriate antibiotic use for otitis media, sinusitis and streptococcal pharyngitis. Yet, antibiotic prescribing is very common among children with ARTI, for bronchitis (71%), sinusitis (89%), and acute otitis media (86%) [4]. A study evaluating bronchiolitis management before and after the 2006 AAP guidelines found a significant reduction in RSV testing ($p < .001$) and decreased corticosteroids and bronchodilators use ($p < .001$) [5]. However, the trend in antibiotic use did not change ($p = .07$) in the post-AAP guideline period further highlighting the significant problem of overuse of antibiotics for ARTI.

While the use of stringent diagnostic criteria to confirm the diagnosis of ARTI is key in optimizing antibiotic prescribing, empiric treatment for ARTI remains common because viral symptoms are often clinically similar and difficult to distinguish from those caused by bacteria. Therefore, laboratory testing that provides accurate and prompt detection of pathogens associated with respiratory infections is

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important for proper patient care management. Molecular respiratory panel (MRP) assays are becoming increasingly popular due to their ability to detect multiple pathogens with high sensitivity and specificity and documented cost savings [6–8]. While research has demonstrated that MRPs may have a positive impact on patient outcomes such as decreasing empiric antibiotic exposures, length of hospital stay (LOS), and improving timely oseltamivir treatment for influenza patients [9–14], there is a dearth of information on whether this clinical impact is conditional on the turn-around-time (TAT) of the MRP assay.

Both xTAG Respiratory Viral Panel (RVP) and Biofire Respiratory Panel (RP) are FDA-cleared MRP assays that can detect 12 and 20 respiratory pathogens, respectively. The objective of this study was to compare the impact of RVP and RP on clinical outcomes for patients that were admitted in our hospital from 2009 to 2016. We hypothesized that the rapid detection of respiratory pathogens by RP compared to RVP would be positively associated with changes in antibiotic treatment, initiation of oseltamivir and LOS on pediatric patients < 18 years old.

2. Methods

2.1. Study sample

We performed a retrospective cohort study of pediatric patients who were admitted to our 354-bed free-standing children's hospital between December 2009– June 2016 and who tested positive for at least one of the respiratory pathogens on either the RVP (Luminex Inc., Texas) or RP (Biofire LLC, Idaho) MRP assay. Data were abstracted from the electronic medical record for patients where the RVP or RP assay occurred either while admitted as an inpatient or during the ED encounter. For patients initially seen at the ED and subsequently admitted, all medical services were considered one clinical episode. Patients were excluded for all who were either 1) undergoing immune suppressive therapy; 2) were admitted to the NICU; 3) had a LOS greater than 7 days; or 4) RVP or RP assay was not ordered within the first 48 h of hospitalization. This study was reviewed and approved by the Children's Mercy Hospital Institutional Review Board.

2.2. Molecular-multiplex assays

In our hospital the RVP assay was introduced in December 2009 and was replaced by the RP assay in August 2012. Patients' respiratory samples were tested by either the RVP or RP based on test in use date. At our institution RVP tests were run in batch mode once daily, 7 days a week, whereas RP tests were run as the samples arrived (24/7) in the clinical lab.

2.3. Study outcomes

The primary outcome of this study was appropriate antimicrobial therapy. Binary treatment indicators were based on antimicrobial use during a 48-hour period both before and after the MRP assay results were reported in the laboratory information system (Fig. 1), including: 1) use of empiric systemic antibiotic treatment between time of admission and result availability and 2) administering oseltamivir to influenza positive patients during the 48 h following result availability. The prevalence of narrow- and broad-spectrum empiric antibiotic treatment was also calculated, including the duration of empiric therapy, which was defined as the time difference, in hours, between the first and last antibiotic administration. We considered penicillin, ampicillin and clindamycin as narrow-spectrum antibiotics; all other antibiotics were considered broad-spectrum. We also evaluated use of chest radiographs within the first 48 h of admission and LOS (in hours) as secondary outcomes. Lastly, we calculated the turn-around-time ([TAT]; i.e., time from when the clinical laboratory received the specimen to when the test was completed and results reported in the laboratory information system) for each specimen tested.

2.4. Clinical predictors

We dichotomized our study time period into either RVP patients or RP patients. The patient's age at the time of admission was categorized into either < 90 days (infant sepsis work-up), 3–24 months (upper age range from 2015 AAP guideline on bronchiolitis management [15]) or 2 years and older. A mutually exclusive pathogen indicator was created based on the organism(s) detected in the RVP/RP assay (rhinovirus/enterovirus, influenza virus, respiratory syncytial virus (RSV), adenovirus, human metapneumovirus, parainfluenza, co-detection [2+ viruses], or bacterial pathogen). For example, a patient who was positive for RSV only was categorized as 'RSV' whereas a patient who tested positive for both RSV and rhinovirus/enterovirus was categorized as 'co-detection'. Any patient with a bacterial pathogen, regardless of concurrent viral infection, was categorized as 'bacterial pathogen'. In order to further depict clinical presentation and medical decision making, we included the location where the MRP assay was ordered (PICU, ED, medical/surgical, or other) and the calendar quarter.

2.5. Data analysis

The frequency distribution of our categorical outcomes was calculated for both RVP/RP time periods, with Pearson's chi-square used to compare proportions. Hospital LOS and TAT were treated as continuous outcomes with the Mann-Whitney *U* test used to compare distributions. Multivariable logistic models were used for each of our categorical outcomes to examine the relationship with RVP/RP time period, after adjusting to medical service, patient age, pathogen, and seasonality. All analysis were completed using SAS (SAS 9.4; SAS Institute, Cary, NC).

3. Results

A total of 12,803 patients in whom either one of the MRP assays (Luminex RVP or Biofire RP) was obtained during the study time period were initially identified. We excluded 5129 (40.1%) patients who tested negative for any pathogens since the focus of the current study was to describe the impact of rapid detection of respiratory pathogens in management of hospitalized patients. We further excluded 349 (2.7%) who were admitted to either the NICU or hematology/oncology ward, 456 (3.6%) who did not have the RVP/RP ordered within the first 48 h of admission, 708 (5.5%) who had a LOS > 7 days, 1007 (7.9%) who were seen in the ED but were not admitted to the hospital, and 12 (.09%) who were ≥18 years old at the time of the admission. Our final study group included 5142 patients

A total of 1264 (24.6%) patients were tested with the RVP assay (Table 1). Those patients who were ≥2 years old represented the largest age group in our analysis (n = 2246; 43.7%). Nearly half of our patients tested positive for rhinovirus/enterovirus only whereas 110 (2.1%) patients were positive for ≥1 bacterial organisms.

The frequency distribution of respiratory pathogens between the two RP/RVP time periods were comparable (Fig. 2), with the exception of influenza (RVP: 119 [9.4%] vs. RP: 157 [4.1%]; $p < .001$) and human metapneumovirus (RVP: 139 [11.0%] vs. RP: 301 [7.8%]; $p < .001$), which suggests reasonable stability in the epidemiology of respiratory pathogens during our study time period.

Patients who were tested with RP were significantly less likely to receive any empiric antibiotic therapy prior to results from the MRP assay reported in the laboratory information system when compared to RVP patients (32.0% vs. 51.1%; $p < .001$ [Table 2]). After adjusting for patient age, organism, location, and seasonality, RP patients continued to be less likely to have empiric therapy (odds ratio [OR]: 0.45; 95% confidence interval [CI]: 0.39, 0.52). When considering just those patients who had > 1 empiric antibiotic administration, RP patients had a significantly shorter median duration of broad-spectrum (6.4 h vs. 32.9 h; $p < .001$) and narrow-spectrum therapy (9.1 h vs. 31.4 h; $p < .001$) compared to RVP patients.

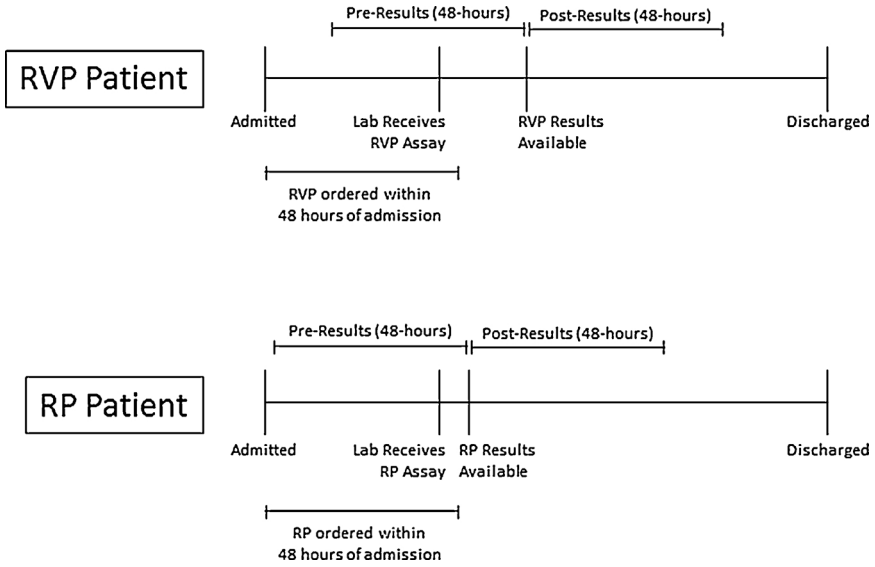

Fig. 1. Timing of Antibiotic Treatment Categories Relative to MRP Assay.

Table 1
Demographic and Clinical Characteristics of ARTI Patients with Respiratory Pathogen Detection.

		No. (%) of Tested (N = 5142)
MRP Assay		
	Luminex	1264 (24.6%)
	Biofire	3878 (75.4%)
Age at Admission		
	< 90 days	819 (15.9%)
	3-24 months	2077 (40.4%)
	2+ years	2246 (43.7%)
Organism		
	Any Bacterial Organism [a]	110 (2.1%)
	Rhino/Entero	2518 (49.0%)
	Influenza	237 (4.6%)
	RSV	706 (13.7%)
	Metapneumo	344 (6.7%)
	Coronavirus	134 (2.6%)
	Parainfluenza	322 (6.3%)
	Adenovirus	191 (3.7%)
	Viral Co-detection	580 (11.3%)
Location of MRP Order		
	PICU	151 (2.9%)
	ED	1439 (28.0%)
	Med/Surg	3301 (64.2%)
	Other/Unknown	251 (4.9%)
Calendar Quarter of Order		
	Q1	1840 (35.8%)
	Q2	1193 (23.2%)
	Q3	1027 (20.0%)
	Q4	1082 (21.0%)

[a] Includes *M. pneumoniae*, *C. pneumoniae*, and*B. pertussis*.

RP influenza patients were more likely to receive oseltamivir during the 48 h after result availability when compared to RVP influenza patients (79.0% vs. 19.3%; $p < .001$). After adjusting for patient age, order location, and calendar quarter, RP patients were more likely to receive post-MRP oseltamivir (OR: 13.56; 95% CI: 7.29, 25.20) when compared to RVP patients. Nearly 50% of RP influenza patients received oseltamivir within 6 h following the results (Fig. 3), whereas less than 10% of RVP patients received a dose during that same time period.

The median LOS for RP patients (49.0 h) was significantly shorter when compared with RVP patients (54.3 h; $p < .001$). In addition, the median TAT for patients tested with the RP assay (1.4 h) was significantly shorter compared to the RVP (27.1 h; $p < .001$).

Empiric antibiotics were more likely for patients who had detection of a bacterial organism (67.3%), influenza (43.9%), RSV (45.8%), and parainfluenza (45.3%) relative to patients with rhinovirus/enterovirus (30.9%) [Table 3]. After adjusting for MRP assay, patient age, order location, and calendar quarter, an increased likelihood of empiric antibiotics was observed for patients with a bacterial organism (OR: 5.50; 95% CI: 3.63, 8.35) and parainfluenza (OR: 1.75; 95% CI: 1.37, 2.24).

4. Discussion

Utilizing MRP assays may increase the likelihood of optimal treatment of viral ARTI [9–12]. However, since some of these studies have been restricted to adult patients [11], examined clinical impact for influenza patients only [12] or only included data from peak respiratory seasons [9,10] more studies are needed to provide a comprehensive assessment of the clinical impact for pediatric ARTI patients. Our study included 5142 pediatric patients with positive respiratory pathogens that were collected over 6 years. We observed that relying on rapid diagnostic testing for ARTI cases may have a direct impact for the patient management, including reducing unnecessary antibiotic and radiation exposure, and reducing LOS.

Despite ARTIs being predominately viral in nature, empiric antibiotic treatment for ARTI remains prevalent. Kronman et al. found that antibiotics were frequently prescribed for bronchitis, sinusitis, and acute otitis media patients. [4] Byington et al. examined patients who received a direct fluorescent assay for respiratory pathogens and found that only 12.8% of patients who also received bacterial cultures tested positive for a bacterial infections [16]. We propose that use of MRP assays significantly improves diagnostic yield and accurately identifies viral etiology in majority of patients (~60%; internal data monitoring over past 5 years), providing clinicians added confidence in antibiotic treatment decisions. Our findings provide much needed data to federal programs and insurance agencies that question the value of MRP assays in management of ARTI patients [17]. We feel our study contributes to existing evidence [18] on how rapid molecular diagnostics may further optimize appropriate care and management of ARTI patients.

Our study found that patients tested with RP, which had a shorter TAT, were less likely to receive empiric antibiotics. We hypothesized that having a shorter TAT may influence the clinician's decision making to delay empiric antibiotic therapy knowing that assay results would be available within a few hours. A study among patients who tested positive using a rapid influenza test found that when the clinician was aware of the results they were significantly less likely to prescribe antibiotics (7.3% vs. 24.5%) and more likely to give an antiviral

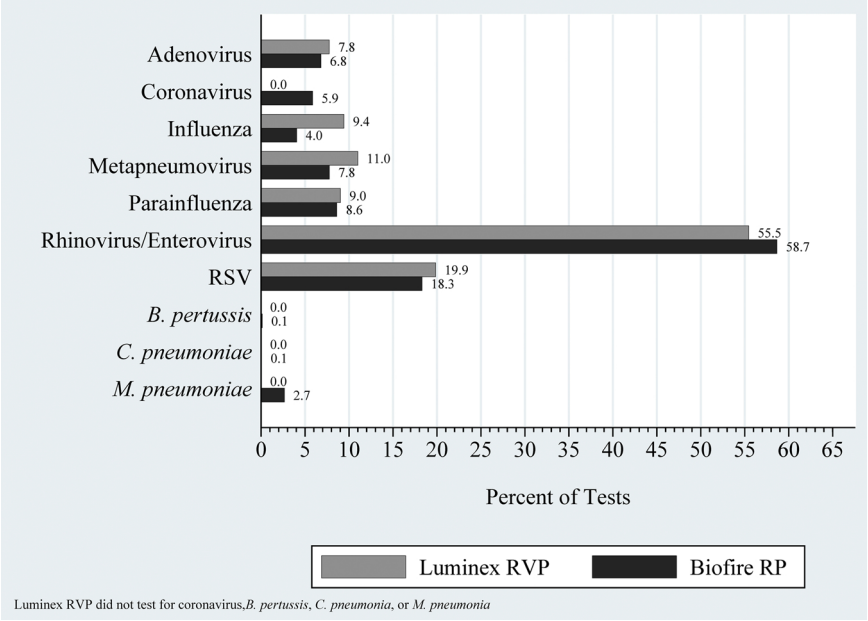

Fig. 2. Distribution of Respiratory Pathogens, by Study Time Period.

Table 2
Comparison of Medication Administrations, Chest X-rays, Turn-around-Time, and LOS by MRP Assay Type.

	Unadjusted			Adjusted [b]	
	Luminex	Biofire	p-value [a]	OR (95% CI)	p-value
Empiric antibiotics – no. (%)	646 (51.1%)	1239 (32.0%)	< .001	0.45 (0.39, 0.52)	< .001
Empiric broad-spectrum	447 (35.4%)	829 (21.4%)	< .001	0.50 (0.43, 0.58)	< .001
Broad-spectrum duration (hours) [c] – median [IQR]	32.9 [22.9, 45.8]	6.4 [1.9, 13.2]	< .001	—	—
Empiric narrow-spectrum – no. (%)	382 (30.2%)	625 (16.1%)	< .001	0.44 (0.38, 0.52)	< .001
Narrow-spectrum duration (hours) [c]– median [IQR]	31.4 [18.1, 43.4]	9.1 [6.1, 16.3]	< .001	—	—
Oseltamivir post-test [d] – no. (%)	23 (19.3%)	124 (79.0%)	< .001	13.56 (7.29, 25.20)	< .001
Chest x-rays within 48 hours of admission	803 (63.5%)	2245 (57.9%)	< .001	0.71 (0.62, 0.82)	< .001
Length of stay (hours) – median [IQR]	54.3 [38.6, 89.0]	49.0 [32.2, 78.9]	< .001	—	—
Turn-around-time (hours)	27.1 [24.7, 50.3]	1.4 [1.2, 1.7]	< .001	—	—

Abbreviation: IQR, inter-quartile range; OR, odds ratio; CI, confidence interval.
[a] Based on Fisher's Exact test for categorical and Kruskal-Wallis test for continuous.
[b] Odds relative to Luminex after adjusting for patient age, organism, location, and calendar quarter.
[c] Among patients with more than one empiric antibiotic administration.
[d] Among patients positive for influenza.

prescription (18.8% vs. 6.7%) relative to when the clinician was unaware the patient was positive for influenza. [13] In our study, patients with RP test results available approximately 26 h faster than RVP were less likely to have empiric antibiotic therapy (32.0% vs. 51.1%) as well as a significantly shorter duration of empiric broad-spectrum (6.4 vs. 32.9 h) and narrow-spectrum therapy (9.1 vs. 31.4 h).

According to CDC guidelines, anti-influenza therapy is recommended for patients < 2 years with signs and symptoms of flu-like illness. [19] In addition, multiple observational studies have demonstrated that receipt of oseltamivir significantly improves patient outcomes for patients with influenza [20–25], although clinical improvement is more likely if oseltamivir is initiated shortly after symptom onset [22,21–25]. A prospective study of ICU influenza patients compared early treatment vs. late treatment oseltamivir administration and found that early treatment had shorter ICU LOS (18.4 vs. 22.7 days), shorter hospital LOS (27.2 vs. 34.0 days), and decreased likelihood of mortality (21.5% vs. 34.3%) [24]. In our study, nearly 80% of RP influenza patients received oseltamivir within 48 h of result availability, compared with 19.3% for RVP influenza patients. Utilization of tests with shorter TAT may ensure that optimal treatment for influenza infections is given.

Determination of cost effectiveness is important when hospitals decide on adopting rapid diagnostic testing. An increasing number of studies have concluded that rapid diagnostics that test for ARTI viruses provide a cost savings. [6,7] In our study, RP patients had decreased empirical antibiotic use, decreased likelihood of chest x-rays, and shorter LOS which could translate into decreased hospital cost. Further cost effectiveness research is needed that also considers the cost of the rapid test for all patients, not just those who test positive.

There were limitations with this study. We excluded patients seen in the either the NICU or hematology/oncology ward as well as patients who had a LOS > 7 days. However, we purposely excluded these patients in an attempt to have a sample of otherwise healthy children. Second, this was a single-center study at a freestanding pediatric hospital, therefore our results may not generalize to all centers that provide care for ARTI. Third, we did not examine concurrent bacterial infections, which could partly explain empiric antibiotic treatment. Since the prevalence of concurrent bacterial infection is unlikely to be influenced by the assay type (i.e., RVP/RP), we would argue the potential of this biasing our results is minimal. We observed less human metapneumovirus and influenza cases during the RP phase which may have influenced treatment strategies, especially oseltamivir use. Patients tested

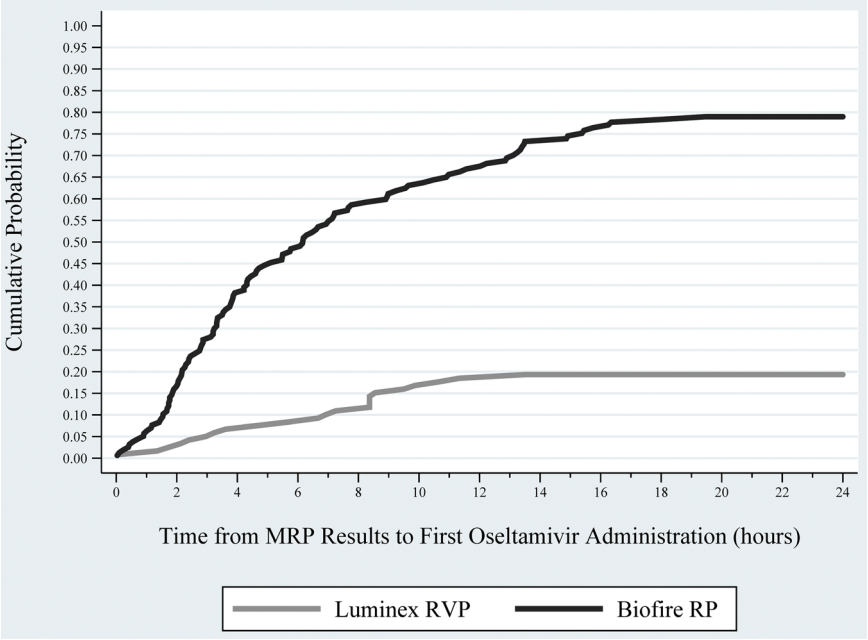

Fig. 3. Probability of Oseltamivir Initiation Among Confirmed Influenza Patients, by Study Time Period.

Table 3
Prevalence of Empiric Antibiotic Administration by Respiratory Organism.

	Unadjusted			Adjusted [a]	
	Received – no. (%)	OR (95% CI)	p-value	OR (95% CI)	p-value
Any Bacterial Organism [b]	74 (67.3%)	4.59 (3.05, 6.89)	< .001	5.50 (3.63, 8.35)	< .001
Rhino/Entero	779 (30.9%)	-ref-	—	-ref-	—
Influenza	104 (43.9%)	1.75 (1.33, 2.29)	< .001	1.42 (1.07, 1.89)	0.015
RSV	323 (45.8%)	1.88 (1.59, 2.23)	< .001	1.62 (1.34, 1.97)	< .001
Metapneumo	154 (44.8%)	1.81 (1.44, 2.27)	< .001	1.60 (1.25, 2.04)	< .001
Parainfluenza	146 (45.3%)	1.85 (1.46, 2.34)	< .001	1.75 (1.37, 2.24)	< .001
Adenovirus	56 (29.3%)	0.93 (0.67, 1.28)	0.641	0.84 (0.60, 1.17)	0.307
Coronavirus	43 (32.1%)	1.05 (0.73, 1.53)	0.779	1.08 (0.73, 1.60)	0.688
Viral Co-detection	206 (35.5%)	1.23 (1.02, 1.49)	0.033	1.15 (0.94, 1.41)	0.179

Abbreviation: OR, odds ratio; CI, confidence interval.
[a] Odds after adjusting for MRP assay, patient age, nurse unit, and calendar quarter.
[b] Includes*M. pneumoniae*, *C. pneumoniae*, and*B. pertussis*.

but never admitted were excluded, thus our inpatient sample may represent patients with more severe ARTI symptoms. Lastly, we did exclude patients who tested negative, thus our study does not provide a complete representation of ARTI patients but rather addresses the importance of rapid respiratory pathogen detection on management of hospitalized patients. We intend to conduct future research on MRP assays that includes both negative and positive patients.

This study demonstrates that adopting MRP assays with a shorter TAT can have a significant improvement for pediatric inpatients with viral ARTI, including decreased exposure to empirical antibiotics, decreased exposure to chest x-rays, increased optimization of timely oseltamivir administration, and shorter LOS. By providing respiratory pathogen results in a timely manner, rapid diagnostics have the ability to help guide clinicians on judicious antibiotic use for ARTI patients.

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None.

Conflict of interest

None.

Author contributions statement

Brian Lee: Conception, Methodology, Formal Analysis, Writing – Original Draft, Writing – Review & Editing, Visualization. **Ferdaus Hassan:** Conception, Methodology, Writing – Original Draft, Writing – Review & Editing. **Mary Anne Jackson:** Conception, Writing – Review & Editing. **Rangaraj Selvarangan:** Conception, Methodology, Writing – Review & Editing, Visualization.

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