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Clinical impact of rapid molecular detection of respiratory pathogens in patients with acute respiratory infection

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A R T I C L E I N F O

Keywords:
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A B S T R A C T

Background: Acute respiratory infections (ARI) are a leading cause of morbidity and mortality worldwide. There is a need to demonstrate the clinical impact of using the new, rapid and sensitive molecular assays in prospectively designed studies.
Objectives: To study the impact on medical management of a rapid molecular assay in patients with respiratory infections.
Study design: A prospective, randomized, non-blinded study was performed in patients presenting to the Emergency Department during two respiratory seasons (2016–2017). Diagnosis was performed by FilmArray Respiratory Panel (FilmArray-RP) or by immunofluorescence assay (IFA).
Results: A total of 432 patients (156 children and 276 adults) were analyzed. Diagnosis with FilmArray-RP was associated with significant changes in medical management including withholding antibiotic prescriptions (OR:15.52, 95%CI:1.99–120.83 in adults and OR:12.23, 95%CI:1.56–96.09 in children), and reduction in complementary studies in children (OR:9.64, 95%CI:2.13–43.63) compared to IFA. Decrease in oseltamivir prescriptions was significantly higher in adults in the FilmArray-RP group ($p = 0.042$; OR:1.19, 95%CI:0.51-2.79) compared to adults managed with IFA. Diagnostic yield was significantly higher by FilmArray-RP (81%) than by IFA (31%)($p < 0.001$). The median time from sample collection to reporting was 1 h 52 min by FilmArray-RP and 26 h by IFA ($p < 0.001$).
Conclusions: The high respiratory viruses' detection rate and availability of results within two hours when using FilmArray-RP were associated with decreases in antibiotic prescriptions and complementary studies and more accurate use of oseltamivir.

1. Background

Acute respiratory infections (ARI) are a leading cause of morbidity and mortality worldwide. Although usually more severe in children, the elderly and immunocompromised patients, all populations and age groups are susceptible. These infections have a significant impact on medical office and emergency department (ED) visits, antimicrobial prescriptions, hospitalizations and lost time from work and school.

The most frequent agents responsible for ARI are respiratory viruses followed by bacteria [1,2]. Empiric treatment with antibiotics is frequently initiated even when viral infection is a strong possibility, leading to unnecessary antibiotic use [3,4].

Direct diagnosis of respiratory viruses by antigen detection using immunofluorescence assays (IFA), is still used but is typically limited to eight viruses (adenovirus [AdV], influenza A [FluA], influenza B [FluB], parainfluenza [PIV] 1–3, human metapneumovirus [HMPV] and respiratory syncytial virus [RSV]) and may lack sensitivity depending on the viral titer, patient´s age and time of testing in relation to the onset of

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symptoms [5]. Molecular methods increase viral detection due to a greater analytic sensitivity compared to conventional methods such as antigen detection and/or viral culture. Additional increased yield results from the detection of respiratory viruses that are not effectively detected by conventional methods, including rhinoviruses and coronaviruses.

In children with ARI, viral positivity rates range from 40 to 45% by IFA to 67–88% by molecular methods [6–9]. Viral positivity rates are lower in adults and can vary from 14 to 29% by IFA [10] to 66% by molecular methods [11].

New multiplex molecular systems using closed test formats have significantly decreased processing times. The FilmArray® Respiratory Panel (FilmArray-RP) (BioFire/bioMérieux, Salt Lake City, UT) can detect 20 pathogens within two hours [9]. There is a need to demonstrate the clinical impact of using these new, rapid, sensitive molecular assays in prospectively designed studies [12].

1.1. Objectives

The aim of this study was to determine if timely etiological diagnosis could have an impact on medical management in relation to antibiotic and antiviral prescription, and use of complementary studies, when patients were tested by either FimArray-RP or IFA. In addition, the diagnostic yield, admission rate and length of stay (LOS) in hospitalized patients, were compared between both diagnostic methods.

2. Study design

We performed a prospective, randomized, non-blinded study in children and adults with acute lower respiratory infection (ALRI) who attended the ED at Centro de Educación Médica e Investigaciones Clínicas (CEMIC) University Hospital, Buenos Aires, Argentina over two respiratory seasons (April-November 2016 and April-October 2017). Inclusion criteria were: age 2 months – 6 years of age (children) or greater than 18 years (adults), with signs/symptoms of ALRI with onset within the preceding 7 days, and signed informed consent.

Exclusion criteria were: congenital cardiac disease, neurological or genetic disorders, cancer, HIV, immunosuppression or solid organ or hematopoietic stem cell transplantation.

This study was approved by the CEMIC Institutional Review Board (N°0962).

ALRI was defined as presence of at least two of the following signs or symptoms: fever/history of fever, cough, tachypnea, wheezing, difficulty breathing, diffuse or focal signs at auscultation or presumptive diagnosis of bronchiolitis, influenza-like illness (ILI), bronchitis, laryngotracheitis or pneumonia.

A change in medical management was defined as any change between the initial intention to treat with antibiotics or oseltamivir and/or to order complementary studies and the final decision- after test results were available.

2.1. Procedure and randomization

While evaluating the patient, the attending physician invited the patient to participate in the study. After acceptance, the doctor documented demographic data, signs/symptoms, presumptive clinical diagnosis and medical management plan (planned antibiotic and antiviral prescriptions and complementary studies) on a standardized form. At that moment, the physician obtained a nasopharyngeal swab (Puritan, USA) that was placed in 3 mL viral transport media. The physician called the laboratory for study randomization (FilmArray-RP or IFA) that was assigned by a computer generated allocation. Subjects were recruited Monday through Friday from 8 a.m. to 7 pm. From April to May 2016 the randomization ratio was 1:1. From July to November 2016, this ratio could not be maintained because of staffing constraints. Thus, samples received from 10 a.m. to 5 pm were processed by FilmArray-RP while samples received outside that period were processed by IFA. In 2017, randomization ratio returned to 1:1.

Samples assigned to the FilmArray-RP group were retrieved from the ED by a member of the research team and immediately processed upon arrival in the virology laboratory, while samples that were assigned to the IFA group were transported to the general laboratory and subsequently to the virology laboratory by routine processes.

2.2. Laboratory diagnosis

The FilmArray-RP detects 17 viruses (RSV, FluA H1, H1-2009, H3, FluB, AdV, PIV 1–4, RV/EV, HMPV, HCoV OC43, 229E, NL63, HKU1), and 3 atypical bacteria (*Bordetella pertussis*, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae*). Samples were tested according to the manufacturer´s instructions. Addition of rehydration buffer and sample to the RP-FilmArray pouch was performed in a biological safety cabinet and the pouch was then inserted into the FilmArray instrument (version 1.5) (BioFire/bioMérieux). Test time was approximately 65 min. The IFA was an indirect immunofluorescence assay with specific monoclonal antibodies for RSV, FluA, FluB, PIV 1–3 and AdV (Millipore/Chemicon, Temecula, CA) that takes a minimum of 3 h to perform. Samples were batched and the assay was performed once per day, with results reported by 4:00 pm each day. IFA is used as standard of care in children at our institution.

2.3. Results reporting and information in hospitalized patients

Results of the FilmArray-RP or IFA were reported by telephone to the physician who initially saw the patient, as soon as they were available and results were also uploaded into the laboratory system. At that moment, the physician was questioned by a member of the study team about any changes in medical management (antibiotic or antiviral therapy or complementary studies) between the original plan previously documented on the standardized form and the final management plan with the reported test results. In patients who required hospitalization, information about LOS, oxygen therapy, ICU stay or mortality was obtained from medical records.

2.4. Complementary studies

Complementary studies included chest x-ray, computerized tomography scan, complete blood count, urinary antigen for *Streptococcus pneumoniae* or *Legionella pneumoniae* and bacterial cultures of blood, urine or sputum.

2.5. Power and sample size calculations

To identify a two-fold difference in medical change with a 95% confidence and a power of 80%, the minimum sample size required was 200 in the FimArray-RP group and 100 in the IFA group.

2.6. Statistical analysis

Demographic, clinical characteristics and changes in medical management between patients tested by FilmArray-RP or IFA were compared using Chi-square or Fisher´s exact test for categorical variables and Mann-Whitney-Wilcoxon test for numeric variables. Multivariate analyses using logistic regression models were adjusted for age (months for children and years for adults), sex, and randomization using STATA 14 (Stata Corp, College Station, TX, USA). Associations were measured by estimating the odds ratios (OR) and associated 95% confidence intervals (CI). P values < 0.05 were considered statistically significant.

Table 1
Demographic and clinical characteristics of children and adults with lower ARI according to diagnostic method.

	Children							Adults							
	Total		FilmArray-RP		IFA		p	Total		FilmArray-RP		IFA		p
	(n = 156)		(n = 113)		(n = 43)		value	(n = 276)		(n = 176)		(n = 100)		value
	n	(%)	n	(%)	n	(%)		n	(%)	n	(%)	n	(%)	
Demographic characteristics														
Age[a], Median (IQR)	9 (3.5–21.5)		9 (3–17)		15 (5–31)		0.117	43 (34–63)		46 (35–68)		41 (33–53)		0.009
Sex (male)	100	(64.1)	73	(64.6)	27	(62.8)	0.833	113	(40.9)	73	(41.5)	40	(40.0)	0.810
Vaccines up-to-date	133	(85.8)	96	(85.7)	37	(86.1)	0.958	NA		NA		NA		
Influenza vaccine [b]	37	(55.2)	29	(56.9)	8	(50.0)	0.775	42	(51.9)	32	(58.2)	10	(40.0)	0.102
Presumptive Diagnosis														
Bronchiolitis	76	(48.7)	55	(48.6)	21	(48.8)	0,985	NA		NA		NA		
Bronchitis	13	(8.3)	9	(7.9)	4	(9.3)	0.754	55	(19.9)	36	(20.5)	19	(19.0)	0.771
Influenza-like illness	60	(38.4)	44	(38.9)	16	(37.2)	0.843	144	(52.2)	83	(47.2)	61	(61.0)	0.027
Laryngotracheitis	NA		NA		NA			16	(5.8)	10	(5.7)	6	(6.0)	0.922
Pneumonia	7	(4.5)	5	(4.4)	2	(4.6)	0.999	62	(22.5)	48	(27.3)	14	(14.0)	0.011
Hospitalization	29	(18.6)	20	(17.7)	9	(20.9)	0.643	34	(12.3)	24	(13.6)	10	(10.0)	0.377

[a]Age given in months for children and years for adults. [b] Influenza vaccine was analyzed in children (n = 67) ages 6 months - 2 years old, and adults (n = 81) > 65 years of age, and pregnant women. FilmArray-RP: BioFire FilmArray respiratory panel, IFA: immunofluorescence assay, n = number, IQR: interquartile range, NA: not applicable.

3. Results

3.1. Population characteristics

From April-November 2016 and April-October 2017, 442 patients were enrolled in the study. Ten of these patients (2%) were not included (3 had inadequate samples, 3 declined participation, 2 consented but the test was not performed, and 2 had incomplete forms). Thus 432 patients (156 children and 276 adults) were enrolled and included in the analysis. Demographic, epidemiological and clinical characteristics were similar between the two groups (Table 1). For children, the median age was 9 months, 64% were male, and 86% were up to date with mandatory vaccines. For adults, the median age was 43 years, 41% were male and 24% were older than 65 years.

The lack of 1:1 ratio randomization during the second portion of 2016 resulted in a higher number of patients being enrolled in the FilmArray-RP group: 289 were tested by FilmArray-RP and 143 by IFA.

3.1.1. Etiology

The diagnostic yield was significantly higher for FilmArray-RP than for IFA ($p < 0.001$). Using FilmArray-RP, a respiratory pathogen was detected in 93% of children (99% viruses and 1% *M. pneumoniae*) and in 74% of adults (100% viruses). In contrast, when using IFA, a respiratory virus was detected in 49% of children and in 23% of adults. Respiratory pathogen distribution in children and adults for the IFA or FilmArray-RP diagnostic group is shown in Fig. 1. The percentage of viral coinfections with FilmArray-RP was 31% in children and 7% in adults. IFA did not detect any coinfections.

3.1.2. Test turnaround time

The median transport time from sample collection at ED to arrival at the laboratory was 15 min (IQR 10–25) for the FilmArray-RP samples and 120 min (IQR 42–930) for IFA samples ($p < 0.001$). The median time from sample collection to results reported to the attending physician (turnaround time [TAT]) was 1h 52 min (IQR 1h 38min-2h 30min) for the FilmArray-RP group and 26 h 40 min (IQR 20 hours–48 hours) for the IFA group ($p < 0.001$).

3.2. Changes in medical management

Overall, a change in medical management was four times more frequent in the FilmArray-RP group than the IFA group. Specifically, the odds ratio for changing was 8 times higher in children (OR = 8.07 CI95% 3.03–21.47) ($p < 0.001$) and more than 2 times higher in adults (OR = 2.67 CI95% 1.32–5.40) (p = 0.006) (Table 2). In children, the changes were associated with decreases in antibiotics and complementary studies. In adults, they were associated with decreases in antibiotics and oseltamivir prescriptions.

Univariate and multivariate analysis of the period with a 1:1 randomization ratio and without 1:1 randomization ratio (second portion of 2016) showed the same trend for the changes in medical management (Suppl. Table 1a and b).

3.2.1. Antibiotics

A significant change between the initial treatment plan and the final plan in relation to antibiotic prescriptions was observed more frequently in children (23%) and adults (14%) in the FilmArray-RP group versus the IFA group (2% and 1%, respectively) (p = 0.001 for both children and adults). The odds ratios for these changes were: 12.23 (CI95% 1.56–96.09; p = 0.017) for children and 15.52 (CI95% 1.99–120.83; p = 0.009) for adults (Table 2). Most changes in antibiotic management consisted of deciding not to treat with antibiotics in cases with viruses detected by the diagnostic test. The greatest change was observed in adult patients with bronchitis (31% in the FilmArray-RP group versus 0% in the IFA group; p = 0.005) (OR 9.27 CI95% 1.12–419.18, p = 0.019) and in adult patients with ILI (11% in the FilmArray-RP group versus 2% in the IFA group; p = 0.014) (Supplemental Table2).

In the whole population, antibiotics were withheld in 52 patients (31%) out of 167 patients who empirically were prescribed antibiotics.

In contrast, changes in plans consisting of a decision to initiate treatment with antibiotics when diagnostic test results were available occurred in 5 patients: 3 children (2 tested by FilmArray-RP-one positive for *Mycoplasma pneumoniae* and the other Filmarray-RP negative-; the third patient tested by IFA with negative result) and 2 adults (both tested negative by FilmArray-RP).

3.2.2. Neuraminidase inhibitors

In adults, a change from an initial intention to treat with oseltamivir and the final decision to not treat occurred in 12% of FluA/B negative adults tested by FilmArray-RP versus 9% of FluA/B negative tested by IFA (p = 0.042). On the other hand, changes consisting of a decision to treat with oseltamivir made when the diagnostic test result was available were observed in FluA/B positive adults tested by FilmArray-RP

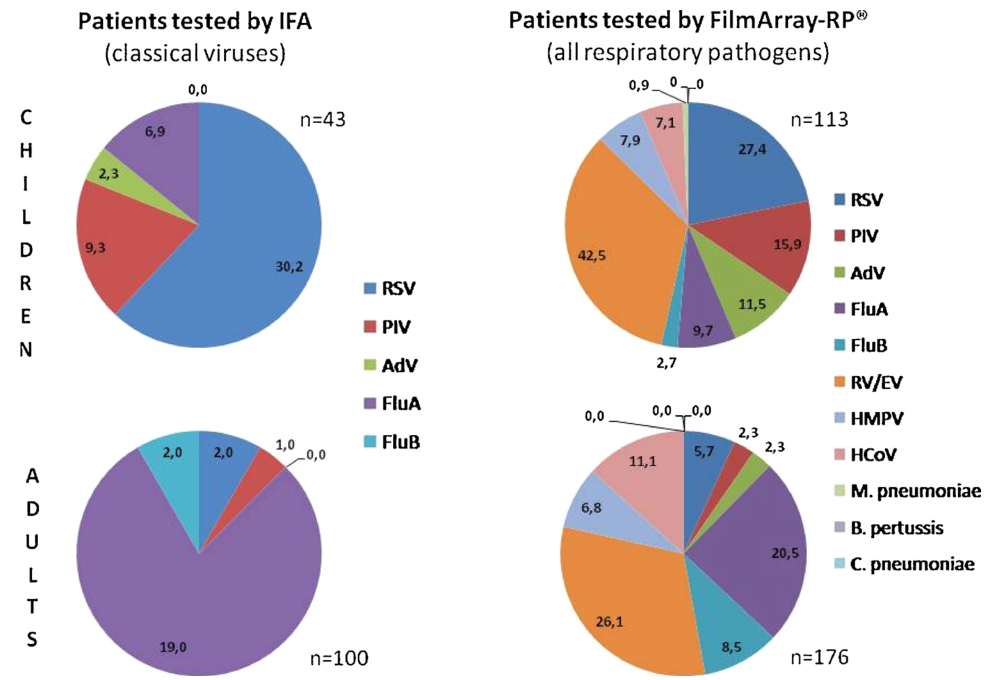

Fig. 1. Distribution of positive results by age and diagnostic method.

Table 2
Changes in medical management in children and adults by diagnostic method.

	Univariate Analysis					Multivariate Analysis[a]		Multivariate Analysis[b]	
	FilmArray-RP		IFA		p	OR (CI95%)	p	OR (CI95%)	p
	n	(%)	n	(%)					
Children	**113**		**43**						
Total n of children with a medical change	**62**	**(54.8)**	**6**	**(13.9)**	**< 0.001**	**7.77 (3.02–20.03)**	**< 0.001**	**8.07 (3.03–21.47)**	**< 0.001**
Decrease in antibiotic prescriptions	26	(23.0)	1	(2.3)	**0.001**	**13.17 (1.71–101.01)**	**0.013**	**12.23 (1.56–96.09)**	**0.017**
Increase in antibiotic prescriptions	2	(1.8)	1	(2.3)	0.697				
Decrease in oseltamivir prescriptions	2	(1.8)	1	(2.3)	0.621				
Increase in oseltamivir prescriptions	2	(1.8)	1	(2.3)	0.621				
Decrease in complementary studies	29	(25.7)	2	(4.7)	**0.001**	**6.84 (1.53–30.49)**	**0.012**	**9.64 (2.13–43.63)**	**0.003**
Increase in complementary studies	6	(5.1)	0	(0.0)	0.087				
Adults	**176**		**100**						
Total n of adults with a medical change	**55**	**(31.3)**	**14**	**(14.0)**	**0.001**	**2.60 (1.35–5.01)**	**0.004**	**2.67 (1.32–5.40)**	**0.006**
Decrease in antibiotic prescriptions	24	(13.6)	1	(1.0)	**0.001**	**15.90 (2.10–119.96)**	**0.007**	**15.52 (1.99–120.83)**	**0.009**
Increase in antibiotic prescriptions	2	(1.1)	1	(1.0)	0.657				
Decrease in oseltamivir prescriptions	21	(11.9)	9	(9.0)	**0.042**	1.19 (0.51–2.79)	0.683		
Increase in oseltamivir prescriptions	12	(6.8)	3	(3.0)	0.091				
Decrease in complementary studies	1	(0.6)	0	(0.0)	0.594				
Increase in complementary studies	0	(0.0)	1	(1.0)	0.364				
Total n patients with a medical change	**117**	**(40.5)**	**20**	**(14.0)**	**< 0.001**	**4.21 (2.48–7.16)**	**< 0.001**	**4.35 (2.49–7.60)**	**< 0.001**

FilmArray-RP: BioFire FilmArray respiratory panel, IFA: immunofluorescence assay, OR: odds ratio, CI: confidence interval, n = number, p values < 0.05 in bold.
[a] Logistic regression model adjusted for sex and age.
[b] Logistic regression model adjusted for sex, age and randomization.

(6.8%) and by IFA (3%)(p = 0.091).

Of 66 adults who empirically were prescribed with oseltamivir, 21 (32%) were withheld in the FilmArray-RP group and 9 (14%) in the IFA group.

In children, oseltamivir usage was very low and no significant changes in treatment with the drug were observed between the two study groups.

3.2.3. Other diagnostic studies

In children, significant changes consisting of a decrease in complementary studies was observed in the FilmArray-RP group (25.7%) versus the IFA group (4.7%)(p = 0.001) with an OR = 9.64 (95%CI 2.13–43.63)(p = 0.003). This change was associated with a reduction in ordering of chest X-rays (59%) and in blood cell counts (41%). Of 100 patients who empirically had complementary studies ordered, 29% were withheld in the FilmArray-RP group. In adults, there was no change in ordering of complementary studies in either diagnostic group.

3.3. Hospital admission rate and length of stay (LOS)

Among children with ALRI attending the ED, 29/156 (18.6%) required hospitalization. The hospitalization rate was lower in children tested by FilmArray-RP (17.7%) than by IFA (20.9%) but the difference was not statistically significant (p = 0.643). The median LOS (measured in days) was lower in the FilmArray-RP group (3 days [IQR 2–3]) compared to the IFA group (5 days [IQR 2–8]) although this difference was also not statistically significant (p = 0.218). No children died.

Among adults with ALRI attending the ED, 34/276 (12%) required hospitalization. Hospitalization rates were 13.6% in the FilmArray-RP group and 10% in the IFA group (p = 0.377). The median LOS was lower for the FilmArray-RP group (4 days [IQR 2–8] than the IFA group (10 days [IQR 2–13]) although the difference was not statistically significant (p = 0.382). Six adults died during the hospital stay, 3 were older than 96 years old.

4. Discussion

This study demonstrated that significant changes in medical management occurred in both children and adults when the results of a multiplex molecular respiratory panel were rapidly available to physicians in the ED compared to patient management using conventional testing (IFA). These changes included a decrease in antibiotic prescriptions in children and adults, more accurate oseltamivir treatment in adults (treatment in influenza positive patients and no treatment in influenza-negative patients) and a decrease in complementary studies in children.

Decreasing antibiotic prescription has an impact not only on avoiding collateral effects [13] but also in contributing to public health efforts to combat increasing antibiotic resistance. Antibiotic overprescribing is a particular problem in primary care, where viruses cause most of the respiratory infections [4]. Despite the fact that children and adults were managed by different attending physicians using different treatment protocols, our study demonstrated a change around 14–23% in decreasing antibiotic prescriptions in the ED when the FilmArray-RP results were provided within two hours.

Studies evaluating the impact of respiratory virus diagnosis in relation to antibiotic use are mostly retrospectively and have shown controversial results for several reasons. Use of a conventional real-time PCR assay showed little impact on antibiotic use most likely because test results were available only after 12–36 hours [14]. A retrospective study using the FilmArray-RP in older adult outpatients showed a decrease in antibiotics only in influenza-positive patients [15]. Other study showed that rapid diagnostic tests for influenza permitted a decrease in antibiotics when patients were influenza-positive [16].

Recently, the first prospective randomized study in adults comparing FilmArray-RP to conventional PCR assays (or no testing at all) was published from the U.K. Although no reduction in antibiotic prescriptions was observed, a decrease in antibiotic doses (single dose or brief courses-less than 48 h) occurred in patients tested by FilmArray-RP [17]. This was probably due to the fact that patients were immediately started on antibiotics even before test results were available. In our study, we were able to demonstrate a change in medical management in relation to a reduction in antibiotic prescriptions in patients tested by FilmArray-RP. This change was observed not only in influenza- positive patients but also in those positive for other respiratory viruses. The greatest change was observed in patients with bronchitis and ILI, while the smallest decrease was observed in patients with presumptive pneumonia in whom a positive viral diagnosis could not rule out a potential co-existing bacterial infection. Brendish et al, also showed little change in antibiotic use in patients with pneumonia tested by FilmArray-RP. They demonstrated that the greatest impact on antibiotic decrease was in patients with asthma and acute exacerbation of chronic obstructive pulmonary disease [17].

In relation to oseltamivir usage, Chu et al. showed that the implementation of rapid influenza PCR testing was associated with a decrease in unnecessary antiviral use among adult inpatients who tested negative for influenza [18]. In our study, we demonstrated a significant decrease in oseltamivir prescriptions in adults when they were influenza-negative by FilmArray-RP. On the other hand, an increase in oseltamivir use was observed in patients who tested influenza- positive permitting initiation of appropriate antiviral treatment within the time frame required for therapeutic efficacy.

Minimizing radiation exposure in children has become an increasing priority among pediatricians [19]. In our study, a significant decrease in complementary studies in children, mostly chest X-rays, occurred when the diagnosis was available in a timely manner, avoiding unnecessary irradiation. Reduction in radiographs has also been observed when studying the impact of rapid diagnosis of influenza in the pediatric ED [20].

Our study found trends toward reduced LOS in the FilmArray-RP group when compared to the IFA group (mean of 3 days vs 5 days for children and 3 days vs 7.5 days for adults). These results were not statistically significant, probably due to the low number of patients who required hospitalization in this study. Brendish et al. found a shorter mean LOS in patients tested by FilmArray-RP. Furthermore, patients with a positive FilmArray-RP had the shortest length of stay [17]. A one-day LOS reduction for adults with respiratory infection represents a minimum mean cost saving of approximately 530 $US/day which is consistent with our previous study on respiratory infections and associated costs performed in children [21].

We found FilmArray-RP had a very high yield in both children (92%) and adults (71%). IFA, although less sensitive and limited to eight viruses, provided adequate detection for RSV, FluA and PIV 1–3 in children. In contrast, the detection rate for the classical viruses was lower in adults, probably because of the lower viral load in the respiratory secretions of adults [22].

The rapidity in test result availability to physicians in this study was a key factor for determining changes in medical practice. Performing this study in routine clinical practice with less assurance of rapid turnaround time (TAT) may not have had the same impact on patient management and antimicrobial prescriptions. A very recent prospective study failed to achieve the optimum TAT due to a delay in the specimen processing [23]. Other strengths of this study are that it included both children and adults, and that enrollment took place during two respiratory seasons. The study demonstrated a change in medical management in decreasing antibiotics prescriptions in both populations.

This study has limitations. It was a single center study and was not sufficiently powered to show a statistically significant drop in LOS. Another limitation is that we could not maintain the intended 1:1 randomized enrollment during the second portion of 2016. However, we believe that the non-random allocation of patients during this period did not influence clinical behavior. Logistic regression did not show a statistically significant effect of study period on outcome.

In summary, in this prospective study of ALRI in immunocompetent patients who presented to the ED, the use of a rapid multiplex PCR respiratory panel (FilmArray-RP) was associated with significant changes in medical management. The short TAT from sample collection to reported results gave physicians the option to adjust empirical decisions and change medical management during the ED consultation, leading to decreased antibiotic prescriptions and complementary studies and permitting a more targeted use of oseltamivir.

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Competing interest

ME has received speaker's fee from BioMérieux. The other authors report no conflict of interest.

Author contribution

Marcela Echavarria: Conceptualization, Methodology, Investigation, Data curation, Writing original Draft, Review & Editing, Supervision, Project Administration; Débora N. Marcone: Formal analysis, Investigation, Data curation, Writing original Draft, Review & Editing; Marcia Querci: Resources, Writing Review & Editing; Alejandro Seoane: Investigation, Writing Review & Editing; Martin Ypas: Investigation, Writing Review & Editing; Cristina Videla: Resources, Writing Review & Editing; Candelaria O'Farrell: Investigation, Writing Review & Editing; Santiago Vidaurreta: Resources, Writing Review & Editing; Jorge Ekstrom: Resources, Writing Review & Editing; Guadalupe Carballal: Conceptualization, Writing original Draft, Review & Editing.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:10.1016/j.jcv.2018.09.009.

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