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Contribution of the FilmArray Respiratory Panel in the management of adult and pediatric patients attending the emergency room during 2015–2016 influenza epidemics: An interventional study

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ABSTRACT

Aim: To evaluate the contribution of a multiplex PCR for respiratory viruses on antibiotic and antiviral prescription, ancillary test prescription, admission and length of stay of patients.
Methods: Two hundred ninety-one adult and pediatric patients visiting the emergency department during the 2015–2016 influenza epidemic were prospectively included and immediately tested 24/7 using the FilmArray Respiratory Panel. The results were communicated to the practitioner in charge as soon as they became available. Clinical and biological data were gathered and analyzed.
Findings: Results from the FilmArray Respiratory Panel do not appear to impact admission or antibiotic prescription, with the exception of a lower admission rate for children who tested positive for influenza B. Parameters that account for the clinical decisions evaluated are CRP level, white blood cell count, suspected or proven bacterial infection and, for adult patients only, signs of respiratory distress. Length of stay is also not significantly different between patients with a positive and a negative result. A rapid influenza test result permits a more appropriate prescription of oseltamivir.

Introduction

Multiplex molecular techniques for respiratory virus detection have already shown benefits in terms of sensitivity gained and a greater range of detected pathogens in comparison to conventional techniques. Recent progress has made it possible to shorten turnaround time (TAT) and to allow delivery of results in a timely manner, especially in comparison to cell culture and direct fluorescence assays (DFA) (Hodinka and Kaiser, 2013; Xu et al., 2013; Zumla et al., 2014). However, molecular techniques have not clearly shown cost-effectiveness. Studies report conflicting results, possibly due to differences in study design. What seems to be agreed upon is that results of molecular tests should be delivered rapidly in the course of patient management. The availability of results in the emergency room (ER) would most likely help avoid antibiotic use and ancillary test prescription, improve antiviral prescription and shorten length of stay in the ward by facilitating discharge of patients or cohorting of hospitalized patients, namely for influenza viruses (Xu et al., 2013; Rappo et al., 2016; Busson et al., 2017). Selecting the population for which the test should be applied also seems of great importance to increase cost-effectiveness (Boeckh, 2008; Vallières and Renaud, 2013). To shed some light on this important issue, we report the results of a prospective interventional study including selected adult and pediatric patients visiting the emergency departments of the tertiary care

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hospital Saint-Pierre in Brussels during the 2015–2016 influenza epidemic. All patients were immediately tested 24/7 with the same standard of care, the FilmArray (FA) Respiratory Panel (bioMérieux, Marcy L'Etoile, France). The evaluated outcomes were antibiotic and antiviral prescriptions, admission, length of stay of hospitalized patients, prescription of ancillary tests and patient isolation.

Materials and methods

Population and inclusion criteria

The study took place from the 1st of February (week 5) to the 15th of March (week 11) 2016 in Saint-Pierre University Hospital, a 626-bed tertiary care hospital in Brussels. The 2015–2016 influenza season in Belgium was moderate and lasted from week 4 to week 13. More than 90% of influenza A isolates collected in Belgium were A(H1N1)pdm2009. Regarding influenza B, circulating strains were almost exclusively from the Victoria lineage, according to the Belgian Public Health Institute (2016). Adults and children visiting the emergency room and presenting with upper or lower respiratory symptoms were prospectively included if either they were expected to be hospitalized or if they had any of the following conditions: chronic respiratory diseases (such as cystic fibrosis, asthma or chronic obstructive pulmonary disease), sickle-cell disease, asplenia, neuromuscular diseases, severe neurological impairments, hereditary metabolic disorders including diabetes, congenital or acquired immunosuppression, heart defects, chronic nephropathies, chronic liver diseases and pregnancy. Children under 3 months of age with a fever without focus (FWF) were also included.

Study workflow

Upon inclusion, patients had a respiratory sample collected, usually nasopharyngeal aspirates (NPA) for children <2 years and nasopharyngeal swabs (NPS) (flocked swab + UTM 3 mL, Copan, Brescia, Italy) for older children and adults. The samples were sent to the microbiology laboratory accompanied by a form on which the practitioner noted his intention concerning the management of the patient (hospitalization, isolation, prescription of antibiotics, antiviral treatment and ancillary tests). Samples were immediately analyzed with the FilmArray Respiratory Panel 24/7. The results were communicated as soon as they were available to the practitioner in charge of the patient. Data were collected concerning the changes in the management of the patient for the parameters noted on the form previously sent to the lab with the sample. Other parameters were collected from patients' files.

FilmArray Respiratory Panel

FilmArray Respiratory Panel v1.7 is a fully automated multiplexed PCR technique with short hands-on time (<5 min). It detects 14 viral targets: adenovirus, coronaviruses (OC43, NL63, 229E, HKU1), influenza A (with distinction between H1, H1-pdm2009 and H3), influenza B, human metapneumovirus, parainfluenza 1–4, human rhinovirus/enterovirus (without distinction between the two), respiratory syncytial virus (RSV), and 3 bacterial targets; *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae* and *Bordetella pertussis*. Tests are performed, one at a time, on an analyzer (FilmArray 2.0 system) in approximately one hour. Before testing, NPA were diluted with 3 mL viral transport medium composed of veal infusion broth (Difco, Becton Dickinson, Sparks, MD, USA) supplemented with bovine albumin (Sigma-Aldrich, St. Louis, MO, USA). Testing was performed using 300 μL of diluted sample.

Statistical analysis

Continuous variables were compared between groups with Student's t-test and nominal variables with Pearson's chi-squared test. Correction for age was performed using binary logistic regression where age was significantly different between compared groups. The software used were IBM-SPSS v24.0 and NCSS v10. For adults, statistical analyses for viruses were only performed on the 3 most prevalent viruses, namely, influenza A, influenza B and rhino/enteroviruses. The p-Value was considered significant if <0.05.

Results

A total of 299 samples from 291 patients were analyzed; 149 samples were obtained from 142 children (<15 years old), 62 females and 80 males (mean age: 1.8 years old; median age: 7 months), and 150 samples were obtained from 149 adults (≥15 years old), 73 females and 76 males (mean age: 53 years old; median age: 52.1). The characteristics of the population are detailed in Table 1. Samples were composed of 93 NPA and 206 NPS. Detected pathogens are listed in Table 2. One hundred and twenty-five out of the 149 samples from children (83.9%) and 85 out of the 150 samples from adults (56.7%) were positive according to FA. Mean turnaround time for delivering the result was 1.8 h.

Results for the pediatric population

Hospitalization

Of the 149 visits to the pediatric ER, 45 were discharged. Hospitalized children (104) were significantly younger than nonhospitalized children (1.4 vs 2.7 years; $p = 0.019$). Due to a significant difference in median age in the different groups, a correction for age was performed using binary logistic regression in order to mitigate the influence of age, if any, on the calculations. Results of the statistical analyses are in Table 3. Significant p-Values are noted in bold characters. Results at the limit of significance are underlined.

To focus on the most critical population, patients who were not hospitalized after examination and for whom no intention of hospitalization was reported on the form attached to the sample were excluded from the analysis. The remaining subset (n = 125) was split up into patients effectively hospitalized (n = 104) and those discharged from ER after examination (n = 21). The above-mentioned parameters were then compared between the two groups to determine which could have been utilized in the decision to discharge or admit. The mean age was significantly lower for hospitalized patients (1.4 vs 2.8 years; $p = 0.032$); a correction for age was performed (Table 3).

Table 1
Characteristics of enrolled patients. Mths = months, NA = not applicable, y = years.

	Children	Adults
Age (mean/median)	1.8 y/7 mths	53 y/52.1 y
Gender (male/female)	80 (56.3%)/62 (43.7%)	76 (51%)/73 (49%)
Number of samples/patients	149/142	150/149
Chronic respiratory disease	14 (9.9%)	60 (40.3%)
Heart defect	3 (2.1%)	39 (26.2%)
Sickle-cell disease	6 (4.2%)	3 (2%)
Neuromuscular disease/severe neurological affection	10 (7%)	9 (6%)
Immunosuppression	2 (1.4%)	22 (14.8%)
Chronic nephropathy	5 (3.5%)	0 (0%)
Diabetes	0 (0%)	31 (20.8%)
Pregnancy	0 (0%)	11 (7.4%)
<3 months old	55 (38.7%)	NA

Table 2
Detected pathogens; total number of positive samples and number of samples with co-detection. RSV = respiratory syncytial virus.

	Children		Adults		Total	
	Detected	Co-detected	Detected	Co-detected	Detected	Co-detected
Rhino/enterovirus	56 (28.4%)	33/56 (58.9%)	13 (13.1%)	5/13 (38.5%)	69 (23.3%)	38/69 (55.1%)
Influenza A	25 (12.7%)	12/25 (48%)	30 (30.3%)	0/30 (0%)	55 (18.6%)	12/55 (21.8%)
Influenza B	30 (15.2%)	16/30 (53.3%)	23 (23.2%)	6/23 (26.1%)	53 (18%)	22/53 (41.5%)
Adenovirus	21 (10.7%)	17/21 (80.9%)	6 (6.1%)	3/6 (50%)	27 (9.1%)	20/27 (74.1%)
RSV	10 (5.1%)	8/10 (80%)	5 (5%)	0/5 (0%)	15 (5.1%)	8/15 (53.3%)
Metapneumovirus	10 (5.1%)	4/10 (40%)	5 (5%)	0/5 (0%)	15 (5.1%)	4/15 (26.7%)
Coronavirus HKU1	17 (8.6%)	15/17 (88.2%)	7 (7.1%)	0/7 (0%)	24 (8.1%)	15/24 (62.5)
Coronavirus OC43	6 (3%)	3/6 (50%)	5 (5%)	1/5 (20%)	11 (3.7%)	4/11 (36.4%)
Coronavirus NL63	8 (4.1%)	4/8 (50%)	1 (1%)	0/1 (0%)	9 (3%)	4/9 (44.4%)
Coronavirus 229E	0	0	1 (1%)	0/1 (0%)	1 (0.3%)	0/1 (0%)
Parainfluenza	7 (3.6%)	6/7 (85.7%)	1 (1%)	1/1 (100%)	8 (2.7%)	7/8 (87.5%)
M. pneumoniae	3 (1.5%)	2/3 (66.7%)	1 (1%)	0/1 (0%)	4 (1.3%)	2/4 (50%)
C. pneumoniae	4 (2%)	4/4 (100%)	1 (1%)	0/1 (0%)	5 (1.7%)	4/5 (80%)
B. pertussis	0	0	0	0	0	0
Total	197	124/197 (62.9%)	99	16/99 (16.2%)	296	140/296 (47.3%)

When data were available, length of stay of hospitalized children was compared between the group of patients with a positive FA result (n = 82) and the group with a negative result (n = 19). The hypothesis was that having a positive result early in the course of patient management could shorten length of stay. The mean age of the two groups was not significantly different (1 year for the group with a positive result vs 1.8 years for the group with a negative result; p = 0.323). The mean length of stay was not significantly different between the two groups (3.9 days for the group with a positive FA result vs 5.2 days for the group with a negative FA result; p = 0.286).

Antibiotic prescription

The same above-mentioned parameters were compared between groups of children receiving antibiotics (n = 72) and those not receiving antibiotics (n = 77).

Patients for whom there was no intention of antibiotic prescription and who did not receive antibiotics after availability of test results were excluded. The remaining subset was separated into two groups depending on whether the patients indeed received antibiotics (n = 66) or not (n = 13). The same parameters as above were compared between the two groups (Table 3).

Patient isolation

The patient isolation policy regarding children implies that every child with a suspected or confirmed infectious disease, respiratory or not, should be isolated. As all included children were suspected of having an infectious disease, a positive FA result did not change the decision to isolate patients. Moreover, isolation was not avoided based on negative results as a negative FA result does not rule out every infectious cause. On the 24 children with a negative FA result, 12 patients had a fever of undetermined origin, 2 patients had a urinary tract infection, one patient had measles, one patient had scarlet fever, one patient had rotavirus infection, one patient had a bacterial bronchopneumonia, one patient had a cutaneous infection and 5 patients had a diagnosis of a non-infectious disease. Some of these conditions require isolation and it is usually maintained until confirmation is obtained that it is no longer necessary.

Results for adults

Hospitalization

When comparing the groups of hospitalized patients (n = 93) and discharged patients (n = 57), mean age was significantly higher for hospitalized patients. A correction for age was performed and statistical analyses results are in Table 4. Significant p-Values are in bold characters and p-Values at the limit of significance are underlined.

Again, the subset of patients for whom hospitalization was not intended and not instituted after test results were received was excluded to focus on the most critical population. The remaining subset (n = 106) was then split up into the group of patients who were indeed hospitalized (n = 93) and those who were discharged from the ER (n = 13). The groups were significantly different in age, as hospitalized patients were older (60.4 vs 36.8 years; $p < 0.001$) and a correction for age was performed for statistical analyses (Table 4).

When data were available, length of stay of hospitalized patients was compared between the group with a positive FilmArrray result (n = 49) and the group with a negative result (n = 43). As the mean age was different between the two groups (55.8 years for the group with a positive result vs 65.7 years for the group with a negative result; p = 0.010), a correction for age was applied. Even though the length of stay was longer when the FA result was negative (15.7 vs 9.3 days), the apparent difference was at the limit of significance after correction for age (p = 0.056).

Antibiotic prescription

The group of patients receiving antibiotics (n = 70) was compared to the group that did not receive antibiotics (n = 80). As patients receiving antibiotics were significantly older (61 vs 46.2 years; $p < 0.001$), a correction for age was applied.

The group of patients with no intention for antibiotic treatment and who did not receive antibiotics after results were received was then excluded from the analysis. The remaining subset was split up into the group of patients receiving antibiotics (n = 57) and those who did not (n = 21). As patients receiving antibiotics were significantly older (60.2 vs 44.4 years; p = 0.001), a correction for age was applied (Table 4).

Patient isolation

Local isolation procedures for respiratory pathogens in adults recommend isolation of patients infected with viruses, atypical bacteria (*M. pneumoniae* and *C. pneumoniae*), *Bordetella pertussis* or *Mycobacterium tuberculosis* complex. If we consider isolation

Table 3
Statistical analysis of clinical and biological parameters for hospitalization and antibiotic prescription for children. Selected population for hospitalization excludes the patients for whom hospitalization was not intended and not instituted after test results were received. Selected population for antibiotics prescription excludes the patients for whom antibiotics prescription was not intended and not prescribed after test results were received.

Children	All children			Selected population			All children			Selected population		
	Hospitalized	Discharged	p-Value after correction for age	Hospitalized	Discharged	p-Value after correction for age	Antibiotics	No antibiotics	p-Value	Antibiotics	No antibiotics	p-Value
N°	104	45		104	21		72	77		66	13	
Age (years)	1.4	2.7	NA	1.4	2.8	NA	1.71	1.88	0.725	1.6	1.4	0.745
Gender (F/M)	51/53	16/29	0.217	51/53	10/11	0.843	40/32	27/50	**0.014**	38/28	4/9	0.127
CRP (mg/L)	29.5	14	**0.004**	29.5	15.8	**0.024**	34.7	16.1	**0.007**	36.1	7.6	<**0.001**
WBC count (.10^3/μL)	12.5	10.6	0.141	12.5	10.1	0.144	13.3	10.6	**0.004**	13.4	5.3	<**0.001**
Chronic respiratory disease	7.6%	20%	0.085	7.6%	9.5%	0.842	11.1%	11.7%	1.000	9%	15.4%	0.612
SpO2 in ambient air (%)	97.6	98.5	0.344	97.6	98.4	0.590	96.6	98.9	**0.017**	97.4	98.4	0.466
O2 supplementation	17.3%	0%	0.998	17.3%	0%	0.998	19.4%	9.1%	0.098	16.7%	0%	0.195
Positive FilmArray RP	80.8%	91.1%	0.053	80.8%	100%	0.997	84.7%	83.1%	0.827	83.3%	100%	0.195
Mean detected pathogens	1.3	1.4	0.225	1.3	1.6	0.069	1.4	1.3	0.421	1.4	1.4	0.985
Influenza A	20.2%	8.9%	0.126	20.2%	14.3%	0.593	16.7%	16.9%	1.000	18.2%	38.5%	0.139
Influenza B	12.5%	56.7%	**0.001**	12.5%	38.1%	**0.012**	18.1%	22.1%	0.683	18.2%	30.8%	0.449
Adenovirus	14.4%	13.3%	0.935	14.4%	14.3%	0.976	16.7%	11.7%	0.481	18.2%	0%	0.199
Metapneumovirus	8.6%	2.2%	0.252	8.6%	4.8%	0.685	4.2%	9.1%	0.330	4.5%	0%	1.000
Parainfluenza	4.8%	4.4%	0.720	4.8%	4.8%	0.717	5.6%	2.6%	0.430	6%	7.7%	1.000
Rhino/enterovirus	37.5%	37.7%	0.580	37.5%	47.6%	0.207	40.3%	33.8%	0.497	39.4%	30.8%	0.756
RSV	6.7%	6.6%	0.891	6.7%	9.5%	0.545	8.3%	5.2%	0.523	7.6%	0%	0.584
Coronavirus HKU1	11.5%	11.1%	0.813	11.5%	14.3%	0.537	13.9%	9.1%	0.443	13.6%	15.4%	1.000
Coronavirus NL63	4.8%	6.6%	0.427	4.8%	4.8%	0.847	2.8%	7.8%	0.278	3%	7.7%	0.421
Coronavirus OC43	2.9%	6.7%	0.466	2.9%	4.8%	0.686	4.2%	3.9%	1.000	3%	7.7%	0.421
Chlamydophila pneumoniae	1.9%	4.4%	0.558	1.9%	4.8%	0.614	2.8%	2.6%	1.000	1.5%	0%	1.000
Mycoplasma pneumoniae	1.9%	2.2%	0.999	1.9%	0%	0.999	2.8%	1.3%	0.610	6%	0%	1.000
Lumbar puncture	21.1%	0%	0.998	21.1%	0%	0.998	27.8%	2.6%	<**0.001**	27.3%	7.7%	0.171
Urinalysis	67.3%	19.5%	**0.004**	67.3%	28.6%	**0.004**	57%	59.7%	0.742	57.6%	61.5%	1.000
Blood culture	84.6%	60%	**0.005**	84.6%	76.2%	0.637	84.7%	70.1%	0.050	87.9%	84.6%	1.000
Bacterial respiratory infection	15.4%	15.6%	0.749	15.4%	14.3%	0.947	27.8%	3.9%	<**0.001**	28.8%	0%	**0.031**
Urinary tract infection	7.7%	0%	0.999	7.7%	0%	0.999	11.1%	0%	**0.002**	12.1%	0%	0.340
Otitis media	3.8%	4.4%	0.812	3.8%	9.2%	0.254	4.2%	3.9%	1.000	4.5%	0%	1.000
Antibiotics	56.7%	28.9%	**0.002**	56.7%	28.6%	**0.039**	NA	NA	NA	NA	NA	NA

Table 4
Statistical analysis of clinical and biological parameters for hospitalization and antibiotic prescription for adults. Selected population for hospitalization excludes the patients for whom hospitalization was not intended and not instituted after test results were received. Selected population for antibiotics prescription excludes the patients for whom antibiotics prescription was not intended and not prescribed after test results were received.

Adults	All adults			Selected population			All adults			Selected population		
	Hospitalized	Discharged	p-Value after correction for age	Hospitalized	Discharged	p-Value after correction for age	Antibiotics	No antibiotics	p-Value after correction for age	Antibiotics	No antibiotics	p-Value after correction for age
N°	93	57		93	13		70	80		57	21	
Age (years)	60.4	41.1		60.4	36.8		61	46.2		60.2	44.4	
Gender (F/M)	43/50	30/27	0.654	43/50	6/7	0.460	30/40	43/37	0.591	26/31	13/8	0.288
CRP (mg/L)	73.9	44	**0.039**	73.9	26.3	0.066	97	31.4	**<0.001**	94.9	29.4	**0.015**
WBC count ($.10^3/\mu L$)	11.2	8	**0.005**	11.2	7.3	**0.028**	11.4	8.8	**0.014**	11.5	9.5	0.224
Chronic respiratory disease	49.5%	24.6%	0.114	49.5%	23.1%	0.542	48.6%	32.5%	0.403	54.4%	38.1%	0.653
Heart insufficiency	36.6%	8.8%	0.051	36.6%	7.7%	0.260	32.9%	20%	0.988	29.8%	28.6%	0.284
Immunosuppression	14%	15.8%	0.728	14%	15.4%	0.808	15.7%	13.7%	0.345	17.5%	9.5%	0.293
Diabetes	29%	7%	0.088	29%	0%	**<0.001**	25.7%	16.3%	0.953	22.8%	33.3%	**0.025**
SpO2 in ambient air (%)	90.7	97.5	**0.009**	90.7	97.5	**0.006**	90.7	95.8	0.055	89.9	93.3	**0.005**
O2 supplementation	51.6%	1.8%	**<0.001**	51.6%	0%	**<0.001**	50%	17.5%	**0.005**	54.4%	28.6%	0.370
Positive FilmArray RP	52.7%	73.7%	0.682	52.7%	69.2%	0.708	50%	70%	0.380	47.4%	71.42	0.350
Influenza A	15%	28%	0.480	15%	30.8%	0.584	15.7%	23.7%	0.818	15.8%	28.6%	0.615
Influenza B	9.7%	24.6%	0.148	9.7%	15.4%	0.875	4.3%	25%	**0.005**	5.3%	14.3%	0.200
Rhino/enterovirus	9.7%	7%	**0.046**	9.7%	7.7%	0.167	10%	7.5%	0.095	8.8%	4.8%	0.283
Urinalysis	50.5%	31.6%	**0.018**	50.5%	38.5%	**<0.001**	51.4%	36.2%	0.071	52.6%	23.8%	**0.024**
Blood culture	82.8%	50.9%	**<0.001**	82.8%	12.5%	**<0.001**	87.1%	56.3%	**<0.001**	89.5%	66.7%	0.123
Bacterial respiratory infection	46.2%	7%	**0.001**	46.2%	0%	**<0.001**	57.1%	8.8%	**<0.001**	52.6%	14.3%	**0.024**
Urinary tract infection	5.4%	1.8%	**<0.001**	5.4%	0%	**<0.001**	5.7%	2.5%	0.280	5.3%	4.8%	0.687
Antibiotics	66.7%	14%	**<0.001**	66.7%	7.7%	**0.009**	NA	NA	NA	NA	NA	NA

Table 5
Prescription of oseltamivir for adults and children depending on the FilmArray result and medical indication.

	Oseltamivir	Children	Adults	Total
Influenza negative	Indicated and avoided	23 (15.4%)	86 (57.3%)	109 (36.5%)
	Not indicated	74 (49.7%)	11 (7.3%)	85 (28.4%)
Influenza positive	Instituted after result	9 (6%)	31 (20.7%)	40 (13.4%)
	Already instituted	0 (0%)	7 (4.7%)	7 (2.3%)
	Symptoms >48 h	1 (0.7%)	6 (4%)	7 (2.3%)
	Not indicated	42 (28.2%)	9 (6%)	51 (17.1%)
		149	150	299

procedures were adequately applied for the 93 hospitalized adults, 37 were appropriately placed in isolation after the FA result was delivered, 6 patients for whom isolations were initially planned were not isolated based on the results, 7 patients for whom isolation was already planned were properly isolated, and 34 patients for whom isolation was not planned were appropriately not isolated after the results were received. Data concerning isolation intentions were missing for 9 patients.

Oseltamivir prescription

In our institution, oseltamivir is prescribed to influenza positive patients presenting symptoms since less than 48 h and either having one or more of the co-morbidities mentioned in the inclusion criteria, or, regardless of co-morbidities, to children born prematurely until they are aged of 6 months, to hospitalized adults and to pregnant women. The impact of positive FA results for influenza A and B viruses on the prescription of oseltamivir is reported in Table 5. Oseltamivir was instituted in 40/105 (38.1%) of patients after a positive influenza test result; it was indicated, had the influenza test been positive, yet avoided in 109/194 (56.2%) of patients after a negative influenza test result. The total estimated avoided financial waste was 3 000 euros (3 545 US dollars).

Prescription of ancillary tests

For children, the subset of patients for whom a lumbar puncture (LP) was intended prior to reception of results was split into those who underwent the test (n = 22) and those who did not (n = 8). The two groups were then compared. A significant difference was only observed concerning the prescription of antibiotics, where children who underwent LP more often had antibiotics prescribed (82% vs 0%; $p < 0.001$). No significant difference was observed for other parameters, notably including those who had a positive FA result; indeed, all patients who did not undergo LP had a positive FA result vs 77.3% of those that did undergo LP ($p = 0.287$). For adult patients, no statistical analysis could be performed because there were only two intended LPs, one of which was not performed.

Of the 299 emergency room tests ordered, avoidance of ancillary tests other than LP was minimal; 8 urinalysis of 160 intended, 1 blood culture of 222 intended and 3 chest radiographs of 197 intended were also avoided. To evaluate the impact on ancillary test prescription for patients admitted after the ER, we listed the number of blood samples, urinalysis, blood cultures, respiratory samples, other microbiological samples (other than urinalysis, blood cultures and respiratory samples), chest radiographs and ancillary tests other than aforementioned per 1000 days of hospitalization when data were available. We then compared the numbers between patients with positive and negative FA results. For adults, the only significant differences

were that patients with a positive FA result (n = 48) had more blood samples (507 per 1000 day of hospitalization vs 381; p = 0.012) and more blood cultures taken (144 vs 61.8; p = 0.033) in comparison to patients with a negative FA result (n = 43). The proportion of patients in intensive care was not significantly different between the two groups (25% vs 25.6%; p = 0.867). For children, patients with a positive FA result (n = 79) had less blood samples (108.4 per 1000 days of hospitalization vs 265.4), less blood cultures (7.4 vs 44.7; p = 0.015) and less other microbiological samples taken (39.9 vs 111.7: p = 0.029) in comparison to patients with a negative FA result (n = 19). The 5 children admitted in intensive care from the ER were excluded from this analysis as they were transferred to another hospital and that access to clinical data was not available.

Discussion

Multiplex molecular techniques for detection of respiratory viruses allow the delivery of test results in a timely manner; however, these techniques have not yet clearly shown their cost-effectiveness. We report here the results of a prospective interventional study including selected adult and pediatric patients attending the emergency room in a tertiary care hospital during the 2015–2016 influenza epidemic. The goal was to analyze whether FA results influenced patient management in terms of antibiotic or antiviral prescription, ancillary test prescription, admission, length of stay and isolation.

We found that parameters significantly associated with hospitalization and antibiotic prescription were mainly high white blood cell count or CRP level, having blood cultures or urinalysis performed in search of a bacterial infection or having a diagnosis of such an infection. Signs of respiratory distress were also associated with hospitalization and antibiotic prescription for adults but not for children. This difference could be explained by the fact that respiratory distress in adults occurred mainly in patients with decompensated chronic obstructive pulmonary disease, which is often caused by an infection. For children, respiratory distress was mainly encountered during bronchiolitis or decompensated asthma; these conditions do not systematically imply antibiotic prescription or hospitalization if the symptoms improve following aerosol treatment in the emergency room. A correction for age had to be applied for children concerning admission and for adults concerning admission and antibiotics prescription. This finding indicates that younger age for children is associated with a higher admission rate and older age for adults with higher admission rates and antibiotic prescriptions. This can be explained as children <1 month of age attending the emergency room are consistently hospitalized according to the local management algorithm. They represented 15 of the 149 included children (10%). However, hospitalized patients are still significantly younger than nonhospitalized ones even after removing the subset of patients aged <1 month from the calculation (1.6 years old vs 2.8; p = 0.032).

Statistical analyses comparing hospitalization status and prescription of antibiotics showed no significant difference between patients with a positive FA result and patients with a negative result. This could be explained by the fact that virology results are not crucial in management algorithms. Indeed, guidelines regarding patients' management with community-acquired pneumonia state that the detection of a virus in a respiratory sample makes a bacterial infection less likely, provided there are no other clinical, biologic or radiographic signs of such an infection (Bradley et al., 2011; Woodhead et al., 2011). When antibiotic prescription is necessary in our institution, it relies on the association of intravenous ampicillin and cefotaxime for children <3 months old. For children >3 months old, cefotaxime alone is prescribed for systemic infections or cefuroxime for respiratory infections. For adults, respiratory infections are treated with cefuroxime or amoxicillin/clavulanic acid. The administration can be intravenous or oral depending on the severity of the symptoms. Antibiotics are maintained at least 48 h for hospitalized patients and reevaluated based on the evolution of the symptoms and the results of the microbiological and blood analysis. The impact of the FA result on antibiotic discontinuation for hospitalized patients would need further evaluation. Keske et al. (2018) observed that in addition to providing a rapid molecular test result, offering training sessions for physicians about the diagnosis and the management of respiratory tract infections could decrease antibiotic use, at least for children. Other studies did not find a difference in antibiotic use when testing adult or pediatric patients with molecular techniques (Hernes et al., 2014; Rogers et al., 2015; Andrews et al., 2017; Semret et al., 2017; Trabattoni et al., 2018); however, some pediatric studies report a shorter antimicrobial treatment duration (Rogers et al., 2015; Schulert et al., 2013). In these studies, the results of molecular tests were not delivered in a timely manner, which can explain the lack of impact on the initial prescription of antimicrobial treatment even though there was an impact on the duration. Duration of antimicrobial treatment was not recorded in our study.

Children discharged from the hospital significantly more often had a positive FA result for influenza B than children admitted to the hospital. The only significant difference was that children with a positive influenza B result less often had urinalysis performed than children with a negative influenza B result (33.3% vs 64.7%; p = 0.004), meaning they were possibly less suspected of having a urinary tract infection. Some studies also report a trend toward a lower rate of admission of adult patients when the influenza test is positive with a molecular technique in comparison to conventional methods (Rappo et al., 2016; Trabattoni et al., 2018).

The contribution of the FA result to patient isolation depends on management algorithms. As previously described, FA results had no impact on the isolation of children, as all children with a proven or suspected contagious infectious process are to be kept in isolation. Nevertheless, rapid delivery of the FA result allowed better management of hospitalized children by cohorting, as individual rooms are not available for every patient. The delay in the emergency room before admission was not recorded but was shortened according to the pediatricians involved in this study. For adults, screening patients with a molecular technique having a broad panel of detected pathogens triggers more isolations and avoids few. This approach, albeit expensive, permits better application of isolation procedures and likely diminishes nosocomial spread of respiratory viral pathogens, which has been shown to be an underappreciated cause of morbidity and mortality in hospitalized patients (Gilca et al., 2014; Chow and Mermel, 2017).

More appropriate prescription of oseltamivir was already reported by other authors (Xu et al., 2013; Mitchell et al., 2018). In our study, oseltamivir could be confidently avoided in cases in which FA was negative for influenza, resulting in savings of approximately 3000 euros. The result was also communicated before oseltamivir was prescribed in 40 cases, reminding its institution. However, the total expense for the utilization of FA tests was approximately 40 000 euros. The use of a sensitive and specific molecular technique targeting only influenza A and B might be a more cost-effective option in adult populations (Trabattoni et al., 2018; You et al., 2017). Moreover, the detection of viruses other than influenza seems to have a low impact on hospitalized adult patients' management (Semret et al., 2017). Techniques detecting a broader panel of pathogens might be more suitable for immunosuppressed patients, notably hematopoietic stem cell transplant recipients, for whom viruses other than influenza should be treated (Boeckh, 2008; Semret et al., 2017).

Concerning the sparing of ancillary tests in the ER, it was minimal. This could be explained since ER management involves empiric testing in order not to delay the triage. We would expect that a positive FA result could explain clinical symptoms of the patients and thus limit further investigations. For adult patients admitted after the ER, we paradoxically observed more blood samples and blood cultures taken for patients with a positive FA result. For children, it was the opposite; we observed less blood samples, blood cultures and other microbiological samples taken in the group with a positive FA result. A hypothesis would be that admitted adults with a viral infection are more likely to already have complications from the infection. For children, the respiratory viruses might more probably be responsible for the clinical symptoms and complications requiring further analysis could be less frequent. However, these findings would require further evaluation in order to appreciate all possible confounding parameters.

Few studies evaluating the cost-effectiveness of multiplex molecular techniques for respiratory viruses delivered test results in a time frame comparable to our study; three were identified in the last 10 years. Firstly, a study from Rappo et al. (2016) found lower antimicrobial use, fewer chest radiographs ordered and a shorter length of stay for patients positive for influenza according to FA in comparison to conventional methods. This difference was significant, regardless of the virus, after correction for age, immunosuppression status and asthma and intensive care unit admission, reflecting the importance of the target population for the tests. However, Rappo et al. studied the management of adult patients during two consecutive winter seasons. This type of design notably adds bias to the interpretation of the data due to difference in circulating viruses and to possible change in management algorithms between two seasons. Secondly, a study from Trabattoni et al. (2018) evaluating adult patients visiting the ER and tested with a rapid molecular technique for influenza in comparison to conventional methods also reported fewer radiographs and biological tests ordered, fewer admissions and shorter length of stay in the emergency room in the group tested by the molecular technique. However, the group tested with conventional methods was older and showed more comorbidities. Thirdly, Echavarría et al. (2018) prospectively studied children and adults visiting the emergency room with acute respiratory tract infection and compared patients tested with immunofluorescent assay to those tested with FA. They demonstrated a decrease in antibiotic prescription for adults and children, a decrease in antiviral prescription for adults and a decrease in ancillary test prescription for children in the FA group. The advantages of our evaluation in comparison to other studies are prospective design, inclusion of selected children and adults visiting the emergency department during the same epidemic season, use of the same standard of care for every patient and delivery of test results while patients were still in the emergency department. In the majority of studies, only test results were taken into consideration, and confounding factors might have been missed, while in our study, clinical parameters were also taken into account during analysis.

Conclusion

Providing a rapid molecular result with the FilmArray Respiratory Panel does not seem to impact hospitalization decisions, length of stay and initial antibiotic and ancillary tests prescription for selected children and adult patients visiting the emergency room of our hospital. Other parameters appeared more consistently to account for hospitalization decisions and antibiotic prescriptions, such as CRP levels, white blood cell count, suspected or proven bacterial infection and, for adult patients only, signs of respiratory distress. For children, younger age is also associated with a higher admission rate, but this could be explained by local management algorithms. For adult patients, older age is associated with higher admission and antibiotic prescription rates. One exception is having an influenza B-positive result, leading to a significantly higher rate of discharge for children, suggesting that use of a sensitive molecular technique targeting only influenza A and B could be more cost-effective in our setting. The positive impact of the use of the FilmArray Respiratory Panel might be more important in high-risk populations, such as immunosuppressed patients, for whom more than just influenza viruses are to be treated, which would possibly avoid detrimental outcomes. Training sessions for physicians about the diagnosis and management of respiratory tract infections could improve the impact.

Benefits resulting from the use of FA, in addition to a more adequate prescription of oseltamivir, are hard to appraise, making cost-benefit calculations difficult. Such benefits are mainly a faster and better implementation of isolation algorithms for hospitalized patients, probably resulting in a decrease in nosocomial infections. These points, as well as the contribution of molecular test results on the avoidance of ancillary tests and on the discontinuation of antibiotics once patients are hospitalized, need to be further evaluated.

Conflict of interests

None declared

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Ethical approval

This study was approved by the ethics committee of University Hospital Saint Pierre (Brussels) with the reference AK/15-10-109/4563Bis.

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