

Prognosis of hospitalized children under 2 years of age with co-detection of influenza A and respiratory syncytial virus at the healthcare facility

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Abstract

Objectives: the aim of this study is to evaluate the impact of co-detection of Flu A and RSV using rapid immunochromatographic tests at the point of care, in pediatric patients under 2 years of age in a general hospital.

Methods: a retrospective cohort study was conducted to analyze clinical outcomes in hospitalized infants with viral respiratory disease with positive results of rapid immunochromatographic test for RSV and/or Flu-A, from 2013 to 2018. A logistic regression model was adjusted to analyze predictors of orotracheal intubation during hospitalization.

Results: we analyzed 220 cases: RSV (192), Flu-A (9), co-detection (19). Lethality rate was 1.8% (2 cases), and 88% (194) were under 1 year of age. Mean time of hospitalizations was higher in patients with co-detection. Variables significantly associated with orotracheal intubation were: younger age in months, comorbidities, RSV and Flu-A co-detection, and bacterial pneumonia during hospitalization.

Conclusions: RSV and Flu-A co-detection was associated with the least favorable clinical prognoses in this study. Rapid test diagnosis may provide important information at the point of care, because molecular panels are not widely accessible in general hospitals. Rapid diagnosis allows timely evaluation and treatment.

Key words Respiratory syncytial virus, Influenza virus, Point of care testing, Prognosis



Introduction

Respiratory syncytial virus (RSV) and influenza (Flu) virus contribute substantially to the overall burden of severe respiratory tract infection in children. Of all respiratory viruses, RSV is estimated to be the main cause of hospitalizations for children under 2 years of age worldwide, and the first year of life is the period with the highest risk of infection.¹⁻³ Both RSV and Flu viruses have seasonal incidence patterns, although there are annual variations in the number of cases and in fatality rates.^{4,5} The burden of morbidity and mortality caused by these respiratory viral infections in children has been reported in several studies in Brazil and other parts of the world.^{1,5,6}

A rapid diagnosis is necessary to determine antiviral therapy early (especially for Influenza) and to apply hospital infection control measures.⁷ Molecular information from viral panels using reverse transcriptase polymerase chain reaction (RT-PCR) is sensitive and facilitates accurate diagnosis, but this technology is expensive and not available in most health services, especially public hospitals.⁸ In addition, with the exception of rapid molecular assays tests, the results can take a few days, especially if the sample is sent to public health reference laboratories, delaying the treatment decision and implementation. In contrast, immunochromatographic tests, such as a rapid influenza diagnostic test (RIDT), although less sensitive, can be performed at bedside and provide valuable information in a few minutes.⁹ Rapid tests are also important to reduce antibiotic use, and can identify viral co-infection,⁹ particularly relevant in the context of the SARS CoV-2 epidemic.

Viral co-detection has been reported in the literature frequently; however, the clinical and prognostic impact, particularly in children, is still controversial.¹⁰⁻¹³ It is more common in children under one year of age, probably due to delay in the development of upper respiratory viral clearance capacity and an immature immune system, but it is unclear whether such cases involve co-infection or only co-detection.⁷

The aim of this study is to evaluate the association between co-detection of FluA virus and RSV on the prognosis and clinical outcomes of children diagnosed by rapid tests performed at the point of care.

Methods

This is a retrospective cohort study to evaluate clinical outcomes in children <2 years old, hospitalized

from 2013 to 2018 with respiratory viral infection with a positive rapid test for FluA, RSV or both in the pediatric department of the Pontifical Catholic University of Campinas Hospital (PUC-Campinas - Portuguese) in the city of Campinas (approximately 1.2 million inhabitants), São Paulo State. It is a 325-bed university hospital with an 8-bed pediatric ICU and 16-bed neonatal intensive care unit. The hospital receives referrals from primary care and other health services in the municipality and the metropolitan region, especially from low-income areas.

Severe acute respiratory syndrome (SARS) is defined as any patient with symptoms of fever, even if referred, accompanied by cough or sore throat and with dyspnea or O₂ saturation <95% or respiratory distress. Observing the biosecurity measures, every child with SARS and hospitalization criteria, underwent RSV and Flu rapid immunochromatographic test (RICT) for qualitative detection of RSV fusion protein, and Flu A/B antigen. One sample of nasal secretion aspirate was collected using a disposable plastic collector bottle with vacuum control for each test, according to Ministry of Health protocols of influenza surveillance. RICT was performed just after sample collection. RICT use is routinely performed in our service, and this practice brings security to medical assistance in the point of care, facing the high cost of molecular testing, and lack of availability in our public health service.

We used two rapid tests (RT): an in vitro immunochromatographic assay for detection Flu virus and an assay for the detection of RSV fusion protein antigen, both using Alere® technology, United Kingdom, Scotland.

We analyzed retrospectively all medical records of patients under 2 years of age with a respiratory condition requiring hospitalization and who underwent rapid test from a sample of nasopharyngeal aspirate or swab with positive results for RSV and/or Flu-A. Patients with negative results for both tests were excluded. This age group was chosen because it represents the majority of severe cases of viral respiratory conditions.^{3,12}

The following study variables were recorded: age in months, length of hospital stay, signs and symptoms at admission, comorbidities, prematurity, diagnosis of bacterial pneumonia during hospitalization, orotracheal intubation (occurrence and time of intubation), positive rapid test for RSV only, FluA only, or both, ICU admission, and clinical outcome (death or discharge). The diagnosis of bacterial pneumonia was defined in children with SARS, radiological infiltration, and introduction of antimicrobials by the pediatrician.

Temporal distribution of cases according to dates and length (in days) of hospitalization were analyzed. The proportions of categorical variables were compared using Pearson's chi-square test, and variables with continuous data were analyzed via ANOVA or Kruskal-Wallis test when variance was not homogeneous. Orotracheal intubation (OTI) was considered a categorical parameter of infection severity (yes/no). To assess association between the study variables and the outcome (OTI) an initial logistic regression model included all the variables that presented an association at a level of $p < 0.20$ in the univariate analysis. Then, a multiple logistic regression model was adjusted and those variables that presented a p value lower than 0.05 remained in the final model.

We used Excel 2013 for database construction and time series graph; SPSS v. 21 was used for the statistical analysis.

The study was approved by the Research Ethics Committee, *Pontifícia Universidade Católica de Campinas* (recommendation process number: 2.727.512).

Results

The lethality rate of the study population ($n = 220$) was 1.8% ($n = 4$): two premature children under 6 months, one child had fatal Flu A infection complicated by chronic neuropathy with O_2 dependence who underwent gastrostomy and tracheostomy, and the last child without comorbidities with bronchiolitis associated bacterial lung infection. Two children were not included in the analysis due to transfer to other services.

Table 1 shows the demographic, epidemiological, and clinical variables according to positive RT results for RSV-only, FluA only, and RSV+FluA, comparing the proportion between groups of test results. No children tested positive for FluB. RT identified 192 (87.3%) RSV-only infections and 19 (8.6%) co-detections.

Although we include children < 2 years old, 194 (88.2%) were younger than 1 year and 160 (72.7%) were younger than 6 months. Twenty-nine (13.2%) patients were premature, and of these, only 3 (10.3%) were classified as "very preterm" according to the World Health Organization (28–30 weeks of pregnancy); there were no cases of extreme prematurity. Only 29 (13.2%) patients had no associated clinical conditions (congenital heart disease, Down syndrome, congenital gastrointestinal malformations, renal failure, or bronchopulmonary dysplasia). Length of hospital stay was longer and OTI was

more frequent among those with viral co-detection at the time of admission. We observed a lower frequency of intubated children among those with RSV infection only.

Fever was more common among those with positive rapid tests for Flu-A and co-infection with both viruses (FluA and RSV) compared with RSV only. Children with RSV+FluA co-detection had a longer hospitalization (Figure 1) and more frequently underwent orotracheal intubation, the intubation time was similar among children who underwent this procedure (Table 1).

Variables associated with OTI, as a measure of severity, and poor clinical outcome were: younger age in months, comorbidities, viral co-detection (FluA and RSV), and diagnosis of bacterial pneumonia during hospitalization (Table 2). Detection of isolated Flu-A was not associated with OTI in the univariate or multivariate analysis. Of the 33 cases of pneumonia, we found 9 isolated microorganisms in 8 patients: *Moraxella catarrhalis*, *Haemophilus influenzae*, *Enterobacter cloacae*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Streptococcus pneumoniae*.

We also observed a clear seasonality of hospitalizations with marked peaks in April through June, which are months of greater circulation of the RSV and Flu viruses, respectively (Figure 2).

Discussion

In this study, we evaluated the records of 220 patients with confirmed FluA and/or RSV who were < 2 years of age on admission, during a 6-year period. RSV had a higher incidence in this study (87.3%) than Flu viruses (4.1%).^{3-5,14} Higher incidence of RSV occurs even at peak periods of Flu virus circulation,¹¹ especially in children < 2 years of age who are more frequently hospitalized for respiratory conditions.^{3,12}

The most severe symptoms, signaled by indication for OTI, were detected in younger children, with comorbidities, with a diagnosis of bacterial pneumonia and those with viral co-detection. The role of comorbidities and bacterial pneumonia aggravating viral respiratory conditions is well described in the literature.^{1,14-17} Particularly influenza infection has been associated with secondary bacterial infection in up to 65% of cases in a previous meta-analysis.¹⁶

Although the number of cases of influenza was small in our point-of-care study, co-detection was associated with the poorest prognosis, suggested by a higher risk of OTI, ICU admission, and longer hospital stay. Studies evaluating viral co-detection

Table 1

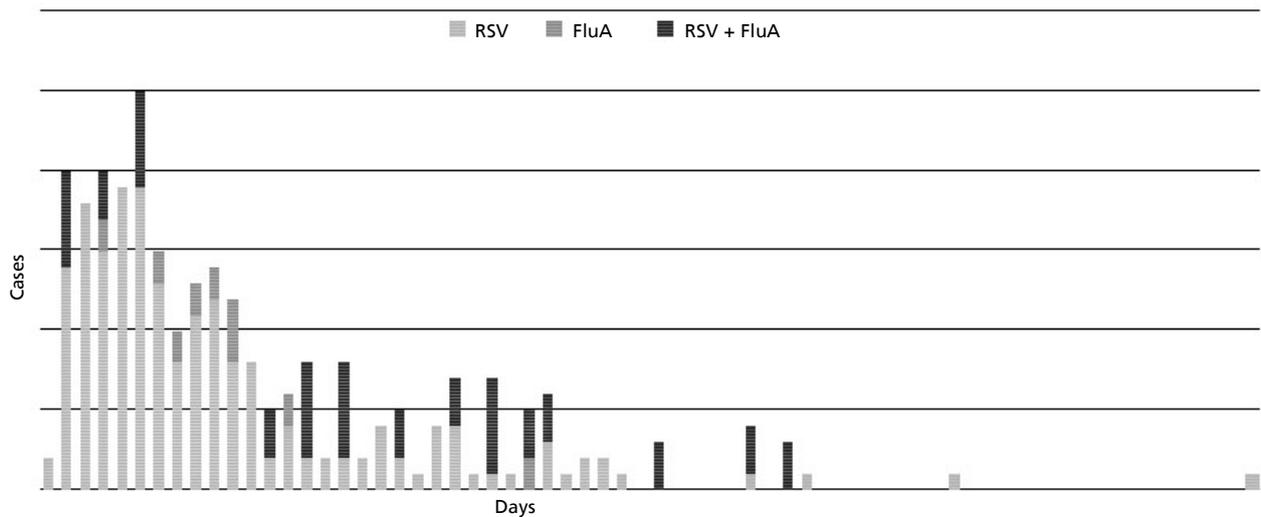
Clinical variables associated with RSV and influenza detection in children < 2 years hospitalized at PUC-Campinas Hospital, 2013 to 2018.

Variables	RSV		FluA		RSV+FluA		Total		p
	n	%	n	%	n	%	n	%	
Age									0.01
< 6 months	145	75.5	2	22.2	13	68.4	160	72.7	
6 to 1 year	26	13.5	4	44.4	4	21.1	34	15.5	
1 to 2 years	21	11.4	3	33.3	2	10.5	26	11.8	
Prematurity	21	23.1	3	33.3	5	26.3	29	13.2	
Comorbidities**	24	12.7	0	-	5	26.3	29	13.2	0.05
Bacterial Pneumonia	24	12.5	2	22.2	7	36.8	33	15.0	0.15
Symptoms / Signs									
Fever	127	66.2	9	100.0	17	89.5	153	68.6	0.01
Cough	177	84.3	8	88.9	17	89.5	202	91.8	0.91
Wheezing	185	88.1	3	33.3	16	84.2	189	85.9	<0.01
Cyanosis	36	18.8	0	-	7	36.8	43	19.3	0.03
Whoop.Cough Synd.	6	3.1	1	11.1	0	-	7	3.1	0.29
Outcome									
Hospital (days) \bar{X} (SD)	9.2 (9.4)		10.2 (6.6)		17.9 (11.9)		10.0 (9.8)		<0.01 †
Oxygen therapy	191	99.5	3	33.3	19	100.0	214	96.8	<0.01
ICU***	57	29.7	2	22.2	15	79.0	74	33.6	<0.01
OTI****	50	26.0	6	66.7	14	73.7	70	31.8	<0.01
OTI (days) \bar{X} (SD)	2.4 (9.2)		8,7 (5.2)		13.1 (5.2)		3.9 (7.4)		0.16 ‡
Total	192	87.3	9	4.1	19	8.6	220	100.0	

* Pearson chi-square test; **Comorbidity= congenital heart disease; Down syndrome, other GIT congenital malformation, renal failure, bronchopulmonary dysplasia; RSV= respiratory syncytial virus; FluA= influenza A; ***ICU= Intensive Care Unit; ****OTI= orotracheal intubation; † p value of ANOVA test; ‡ Kruskal-Wallis test (variance not homogeneous).

Figure 1

Length of hospitalization (days) of children under 2 years old according to the results of rapid tests RSV, Influenza A and both, PUC-Campinas Hospital, 2013 to 2018.



RSV= respiratory syncytial virus; FluA= influenza A.

Table 2

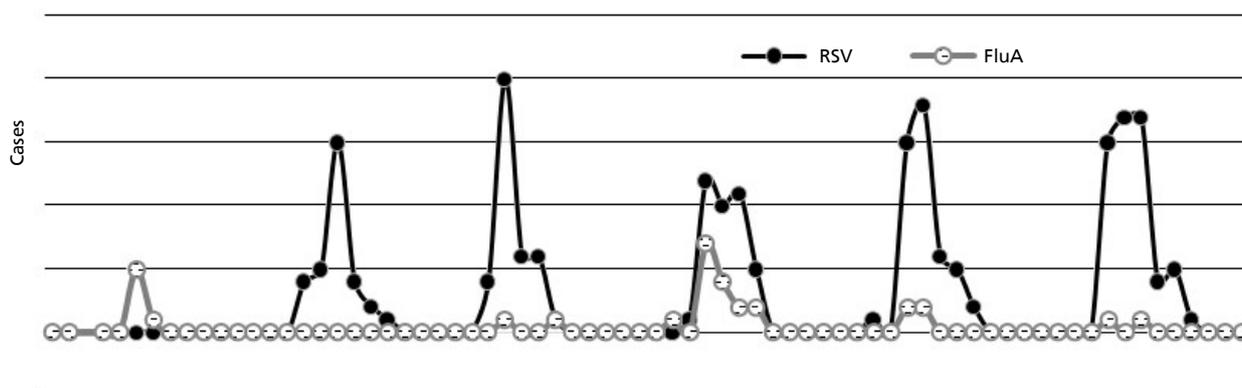
Factors associated with orotracheal intubation (OTI) in children <2 years hospitalized for respiratory viral infection, obtained in a univariate and multiple logistic regression model, PUC-Campinas Hospital, Brazil 2013-2018.

Variable	OTI		OR crude (CI95%)	OR adjusted (IC95%)
	n	%		
Age in months			0.94 (0.88-0.99)	0.89 (0.82-0.98)
RT+ * Only RSV	64	34.7	0.12 (0.42- 0.32)	-
RT+ Only Influenza A	6	66.7	3.05 (0.74-12.5)	-
RT+ FluA+RSV	17	89.0	15.0 (3.4-66.9)	14.3 (3.0-68.2)
Comorbidity**	17	58.6	1.9 (0.9-4.5)	2.7 (1.02-7.11)
Prematurity (< 37 weeks)	16	55.2	1.3 (0.5-2.9)	-
Associated bacterial pneumonia	25	75.8	5.9 (2.5-13.8)	4.78 (1.83-12.55)

*RT= Rapid Test; **Comorbidity: congenital heart disease, Down syndrome, other GIT congenital malformations, renal failure, bronchopulmonary dysplasia; RSV= respiratory syncytial virus; FluA= influenza A.

Figure 2

Temporal distribution of hospitalization of children < 2 years old with viral respiratory infection, PUC-Campinas Hospital, 2013 to 2018.



RSV= respiratory syncytial virus; FluA= influenza A.

are heterogeneous, analyzing different viral combinations, age groups, and outcomes.^{3,12,15,18-23} Although still controversial, our results corroborate findings from several studies that correlate viral co-detection with higher risk of hospitalization.^{20,21}

Diagnostic methods today are extremely sensitive, particularly molecular RT-PCR viral tests with approximately 99% sensitivity. However, this technology is not accessible in primary care and general hospital settings, and in most cases does not allow real-time diagnosis, because technical expertise is required.^{8,9} Conversely, rapid immunochromatographic antigen detection tests, despite lower sensitivity (Flu, 77%–80%; RSV, 50%–94%), have high specificity (>95%),^{8,22-25} and can be an important

tool for point-of-care diagnosis. In addition, there is evidence of increased sensitivity of testing in young children due to high viral excretion.²⁵

Rapid immunochromatographic antigen detection tests allow immediate decision making regarding the introduction of antiviral treatments, improving the effectiveness of infection prevention and control measures, and reducing hospital admission rates.²⁶ A randomized trial performed in pediatric patients showed that RIDTs result in fewer antibiotic prescriptions and fewer unnecessary investigations, such as blood cultures, and X-rays.²⁷

With the increase in the use of multiplex RT-PCR, high co-detection rates of different viruses are identified, ranging from 18% to 40%.^{11,28}

Nevertheless, there is evidence that the seasonality of a virus can interfere competitively with the incidence of other viruses.²⁷ In our study, we detected (4.1% influenza and 8.6% influenza plus RSV), which can be considered low, given the active circulation of these viruses in the fall and winter seasons^{21,28} (Figure 1). In another study, detection rates for both viruses (RSV and influenza) in hospitalized children were $\geq 8.6\%$ among children < 1 year of age.²⁰

This study has some limitations, such as the retrospective design, the use of rapid diagnostic tests with a lower sensitivity in contrast to RT-PCR, and inclusion of tests only for RSV and influenza, despite other relevant virus as metapneumovirus, adenovirus, and rhinovirus. Moreover, the study of cases from a specific clinical referral service does not allow for analysis of risk factors related to all cases of viral respiratory infection in the community. On the other hand, these tests are potentially accessible in the routine employed in most emergency pediatric care services.

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Author's contribution

Mendes ET: Laboratory and clinical data collection, conception, article writing, literature review. Paranhos HL: Data collection, conception, article writing. Santos ICM and Souza LB: Data collection, literature review. Aquino JLB, Merhi VAL and Lima MPJS: Data interpretation and manuscript review. Silva RV: Laboratory and clinical data collection, discussion and review of results. All authors approved the final version of the article.

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