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Brief Report

Prevalence of co-infection between respiratory syncytial virus and influenza in children

Sarah D. Meskill [a,*], Paula A. Revell [c], Lakshmi Chandramohan [d], Andrea T. Cruz [a,b]

[a] Sections of Emergency Medicine, Department of Pediatrics, Baylor College of Medicine, Houston, TX, USA
[b] Sections of Infectious Diseases, Department of Pediatrics, Baylor College of Medicine, Houston, TX, USA
[c] Department of Pathology, Baylor College of Medicine, Houston, TX, USA
[d] Biopharma Division, NeoGenomics Laboratories, 2575 West Bellfort St, Houston 77054 United States

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ABSTRACT

Background: Respiratory syncytial virus (RSV) and influenza have varying degree of seasonal overlap.
Objective: To determine the prevalence of co-infection of RSV and influenza compared to the prevalence of those infections independently when both are in season.
Methods: This was a retrospective cross-sectional study of children evaluated between July 2010 and June 2013 for viral respiratory infection using multiplex PCR. Seasonality was defined retrospectively as weeks when >2% of the total annual positive tests were obtained and was calculated for influenza A, influenza B, and RSV independently. Periods of overlapping seasonality of RSV and influenza A and RSV and influenza B were identified. The expected incidences of co-infection were modeled as the product of the incidences of the individual viruses.
Results: 13,664 specimens were sent for PCR during the study period. Over all 3 seasons, RSV overlapped with influenza A and B for 22 and 18 weeks, respectively; in 2011–12, RSV overlapped with neither influenza A nor B. Based on modeling, there were 6–7 fold fewer cases of RSV/influenza co-infection observed than expected: RSV/influenza A 77 vs. 12, ($p \leq 0.001$; RSV/influenza B 76 vs. 11 ($p \leq 0.001$).
Conclusions: The observed incidence of co-infectivity of RSV and influenza was significantly less than the expected incidence even when both were co-circulating. In light of these data, it may be reasonable to forgo rapid influenza testing or empiric antiviral treatment for children whom rapid RSV testing is positive and who are at low risk of influenza-related complications, especially in times of antiviral therapy shortages.

1. Introduction

1.1. Background

Respiratory syncytial virus (RSV) and influenza are two viruses that disproportionately affect children. Each year, there are various degrees of overlap of the two viral seasons, primarily associated with the less predictable nature of influenza. However, this variation is also geographic: winter viral seasons are longer and tend to have more overlap closer to the equator [1]. *In vitro* studies suggest RSV and influenza might share the same ecologic niche. The growth of RSV is blocked by competitive infection with influenza in a susceptible cell population [2]. Epidemiologic data show that when rates of infection with RSV are high, influenza infections are low; the converse is also true [3].

1.2. Importance

Emergency medicine providers are challenged during respiratory viral seasons to distinguish between RSV and influenza in children who have similar clinical presentations. Rapid RSV testing is more sensitive than rapid influenza testing [4]. Furthermore, there are no effective empiric outpatient treatments for RSV as opposed to neuraminidase inhibitor therapy for early influenza. Therefore, if there is niche competition of RSV and influenza at a host level, a positive RSV test could support not treating the otherwise well-appearing child empirically for influenza when both are in season.

1.3. Goal of this investigation

We sought to compare the observed incidence of the co-infection of RSV and influenza to the expected incidence of co-infection when both viruses are circulating in the community.

* Corresponding author at: 6621 Fannin Street, Suite A2210, Houston, TX 77030, USA.
E-mail addresses: sdmeskil@texaschildrens.org, meskill@bcm.edu (S.D. Meskill).

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2. Materials and methods

2.1. Study design and setting

This was a retrospective cross-sectional study of a consecutive series of patients in whom respiratory samples were obtained for virologic testing at a quaternary care children's hospital emergency center in Houston, Texas, between July 5, 2010 and June 30, 2013 as identified through virology laboratory records.

2.2. Selection of participants

All specimens in pediatric patients (≤18-years-old) submitted for viral PCR testing were included and the frequency of observed and expected co-infections was calculated during time periods when both RSV and influenza were prevalent in the community.

2.3. Methods and measurements

The PCR used was a multiplex real-time PCR assay (Prodesse; Hologic Gen-Probe, Inc.; Waukesha, WI). This assay identifies influenza A/B and RSV. This commercially available assay has a reported sensitivity/specificity of 100/92.6% for influenza A, 97.8/98.6% for influenza B, and 89.5/94.9% for RSV [5]. This assay is a single test in which all three viruses are tested for on the same sample and the exact same reaction. Performance was validated using the ABI 7500 Real Time PCR System (Applied Biosciences; Carlsbad, CA) and the QIAsymphony extraction platform (QIAGEN; Germantown, MD). The PCR assay was available 6 days/week. PCR specimens were stored at 2–8 °C in M4-RT viral transport media for up to 72 h before processing. Sources of specimens included nasal wash, nasopharyngeal swab, broncheoalveolar lavage, and tracheal aspirate.

Trained laboratory personnel performed PCR according to either manufacturer instructions or institutional protocols. Respiratory testing at the institution was performed algorithmically. All rapid tests had PCR performed. However, not all specimens submitted for PCR had a corresponding rapid viral test. If a rapid test was positive for influenza A, the specimen was sub-typed using molecular methods. If a specimen tested positive for Flu A, Flu B, or RSV by PCR, only the flu A results were subtyped and no other testing was performed. PCR was run with positive and negative controls. Institutional review board approval was obtained prior to study initiation.

Seasonality for RSV and influenza were determined using the Centers for Disease Control [6] definition for influenza epidemic: when percentage of cases occurring in two consecutive weeks comprised ≥2% of the annual case burden. Given geographic differences in viral seasonality, local data were used to identify the shoulders of RSV and influenza seasons.

2.4. Outcome

The outcome was a comparison of the actual incidence of co-infection of RSV and influenza A or RSV and influenza B to the expected incidence of co-infection.

2.5. Analysis

Weeks when RSV was co-circulating with influenza A and influenza B were identified. Expected incidence was calculated as the product of the incidences of the individual viruses during the weeks of seasonal co-circulation: Number of expected patients (expected incidence) = [(# of RSV positive patients / total # patients tested while both in season) * (# of influenza A positive patients / total # patients tested while both in season)] * (total # patients tested while both in season) Comparisons between RSV and influenza co-infections were analyzed by percentages and chi-square using Stata 11 (Stata, Inc.; College Station, TX).

3. Results

3.1. Characteristics of the study population

During the three-year study period, 13,664 specimens were submitted for PCR. Of these samples, 3954 (28.9%) tested positive for either influenza A (377, 2.8%), influenza B (582, 4.3%), or RSV (3018 specimens, 22.1%). The demographics of the study population are summarized (Table 1).

3.2. Main results

Using multiplex PCR, the annual burden of influenza A, influenza B, and RSV was determined separately from the 13,664 specimens received. After calculating viral incidence by week, the week when ≥2% of the annual burden was identified and considered as the beginning of the viral season for each virus. The season ended when the weekly incidence dropped below 2%. From these identified seasons, the weeks when both influenza A and RSV co-circulated in season and when influenza B and RSV co-circulated in season were stratified for analysis [Fig. 1].

Twenty-two weeks of overlap between influenza A and RSV and 18 between influenza B and RSV occurred between 2010 and 2013. In 2011–2012, RSV did not overlap with either influenza A or influenza B (Tables 2a, 2b). Given the prevalence of influenza A and RSV, we expected to see 77 co-infections between these two viruses when both were circulating in the community. Instead, we observed only 12 co-infections [odds ratio 0.15 [95% confidence interval (CI): 0.08–0.28]]. For influenza B and RSV, 76 co-infections were expected when both were circulating in the community. Instead, only 11 co-infections were observed [Odds ratio: 0.14, CI: 0.07–0.26]. Overall, observed co-infections between RSV and either influenza A or B were over 6 times less likely than expected.

In total over the three years examined, only 15 patients tested positive with RSV and influenza A and only 15 patients tested positive for RSV and influenza B. The demographics of those patients are summarized (Table 3). Of the three patients that tested positive for RSV and influenza A outside of the overlapping seasons, all were >2 years of age. One patient was during a one week resurgence in RSV at the end of the '10–'11 season. The other two were during the '11–'12 season when there was no overlap. Of the four patients that tested positive for RSV and influenza B outside of the overlapping seasons, all were >2 years of age and three of them were during the '11–'12 season where there was no overlap. While many clinical factors are unable to be gathered from the source information, analysis of all specimens

Table 1
Information on the study population and specimens.

Variable	Subcategory	# (% of total specimens)
Age	<1 month	1005 (7.4%)
	1–<6 months	3021 (22.1%)
	6–<12 months	1719 (12.6%)
	1–<5 years	4473 (32.7%)
	5–<10 years	1870 (13.7%)
	≥10 years	1576 (11.5%)
RSV positivity	2010–2011	888 (20.2%)
	2011–2012	967 (23.1%)
	2012–2013	1163 (22.9%)
Influenza A positivity	2010–2011	177 (4.0%)
	2011–2012	38 (0.9%)
	2012–2013	162 (3.2%)
Influenza B positivity	2010–2011	175 (4.0%)
	2011–2012	155 (3.7%)
	2012–2013	252 (5.0%)

RSV: respiratory syncytial virus.
In 2010–2011 (7/5/10 to 7/3/11) 4393 total specimens were submitted for PCR.
In 2011–2012 (7/4/11 to 7/1/12) 4188 total specimens were submitted for PCR.
In 2012–2013 (7/2/12 to 6/30/13) 5083 total specimens were submitted for PCR.