



EDITORIAL

## Respiratory viral coinfection and clinical disease severity<sup>☆,☆☆</sup>

### Coinfecção viral respiratória e gravidade da doença clínica

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Even though the pandemic caused by Influenza A(H1N1)pdm09 (pH1N1) infection has been extensively investigated, there are few studies that have examined the impact of viral coinfection on disease severity, and they have yielded conflicting results. In this issue of the *Jornal de Pediatria*, Scotta et al.<sup>1</sup> report on a retrospective study of 120 Brazilian children hospitalized with pH1N1 infection, which found respiratory viral coinfection to be a risk factor for respiratory failure. Consistent with this finding, Torres et al. observed that viral coinfection with respiratory syncytial virus (RSV) was associated with increased mortality in a multivariable analysis of 142 children admitted for intensive care during the first pandemic wave in Argentina.<sup>2</sup> In contrast, viral coinfection was infrequent and had little impact on morbidity and mortality in a sample consisting mostly of adult patients (79.3%) admitted to an intensive care unit (ICU) in Australia.<sup>3</sup> In a large study of children and adults conducted in North West England, coinfection with RSV or adenovirus was associated with increased risk of admission to the general ward, while influenza B increased risk of admission to ICU; however, in multivariable logistic regression models, these increases in risk were not

statistically significant.<sup>4</sup> In the same study, coinfection with seasonal influenza A and influenza B viruses was associated with a significant increase in risk of ICU admission or death. Rhedin et al. observed no correlation between detection of additional viruses and disease severity in Swedish children hospitalized with pH1N1 infection.<sup>5</sup> Similarly, studies with limited sample sizes in Spain<sup>6</sup> and Brazil<sup>7</sup> found no association between respiratory viral coinfection and severity of pH1N1 infection. Meanwhile, in a study sample that included 96 (42.0%) children, Esper et al. found that rhinovirus coinfection had little impact on severity of influenza disease; in fact, such patients had a lower median clinical severity score, while the opposite was observed for non-rhinovirus coinfection.<sup>8</sup>

Similar to studies of pH1N1 infection, reports focusing on the relative importance of mixed viral respiratory infections generally have resulted in equally divergent findings. Some studies documented increased severity<sup>9–11</sup> of respiratory illness in children infected with two or more viruses compared to those with single virus infections, while some observed the opposite.<sup>12–14</sup> Other studies found no association of respiratory coinfections with illness severity.<sup>15–17</sup> These discrepant findings may be explained by several factors. They include differences in the population studied (variation in age ranges, breadth of illness severity, and proportions of subjects with comorbid conditions), geographical and seasonal differences regarding circulating respiratory viruses, method of viral detection (traditional methods, such as culture and direct immunofluorescence, *versus* molecular assays), and composition and performance characteristics of

DOI of original article:

<http://dx.doi.org/10.1016/j.jpmed.2013.01.010>

<sup>☆</sup> Please cite this article as: Tran D. Respiratory viral coinfection and clinical disease severity. *J Pediatr (Rio J)*. 2013;89:421–3.

<sup>☆☆</sup> See paper by Scotta M.C. et al. in pages 444–9.

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the molecular respiratory panels. The mechanisms driving disease virulence in coinfections are not clearly understood. Some authors have proposed three major groups of virus-virus interactions to explain potential mechanistic models of disease: (1) direct interactions of viral genes or gene products, (2) indirect interactions resulting from alterations in the host environment, and (3) immunological interactions.<sup>18</sup> In this context, it would not be surprising for different pathogenic mechanisms to be triggered by different viruses that mutually potentiate or mitigate each other's effects; thus, certain pairings of viruses may be more clinically relevant than others. Furthermore, the simultaneous detection of multiple viruses does not necessarily implicate pathogenic effect at the time of detection, especially when molecular methods are used. In some instances, detection of two viruses may represent an acute infection in the presence of viral persistence from a recent infection.<sup>19</sup>

The potential confounding influence of concurrent bacterial infections is another important factor that may have contributed to the conflicting results in studies examining the role of respiratory viral coinfection in the determination of disease severity due to respiratory infections, including influenza. Influenza and other respiratory viral infections are known to predispose to secondary bacterial pulmonary infection.<sup>20</sup> Bacterial coinfection complicates at least 2.5% of influenza cases in older individuals and those with predisposing conditions.<sup>20</sup> In a series of 838 critically ill children with pH1N1 infection, 22% had clinical evidence of bacterial coinfection along with positive bacterial cultures.<sup>21</sup> Thus, failure to account for the influence of bacterial coinfection may bias results. For example, a recent study by Chorazy et al.<sup>13</sup> of 346 archived respiratory specimens from children treated for acute respiratory illness at the University of Iowa Hospitals and Clinics found that children with viral coinfections were less likely than those with single virus infections to require intensive care in unadjusted analysis.<sup>13</sup> However, the authors observed that children with virus-bacteria coinfections were more likely to require ICU admission than those with single virus infections, even after controlling for potential confounders; they also found that virus-bacteria coinfections represented a greater proportion of virus-positive specimens than virus-virus-bacteria coinfections. Once children with virus-bacteria coinfections were excluded from the analysis, the observed odds ratio moved toward the null, suggesting that the observed association of virus-virus coinfection with better outcome can be partly explained by virus-bacteria coinfection. Besides the study by Chorazy et al.,<sup>13</sup> a minority of the studies cited in the present editorial either considered or adjusted for bacterial coinfection, or a proxy thereof, as a potential confounder in the analysis.<sup>5,11,12,17</sup> Even when such adjustments are performed, residual confounding by undetected bacterial coinfections may remain, as exemplified by Scotta et al.<sup>1</sup> in this issue of the *Jornal de Pediatria*. The authors had stipulated bacterial co-detection (defined as a positive culture for a possible pathogen in respiratory secretions, blood, or other sterile specimens) as one of the independent variables to be examined, but presented no bacterial co-detection data, presumably due to the lack of microbiologically-confirmed bacterial infection in the study cohort.

The increasing use of molecular respiratory viral panels in clinical settings underscores the importance of a fuller understanding of the impact of viral coinfection on disease severity. Future prospective longitudinal studies that include serial respiratory tract sampling, not only for virus detection but also for mechanistic experiments, will be paramount to the understanding of the clinical significance of polymicrobial acute respiratory infections, as well as viral pathogenesis. Implementation of multiplex quantitative polymerase chain reaction assays into the study design may also be a worthwhile goal, as is the precise and comprehensive identification of bacterial coinfection.

## Conflicts of interest

The author declares no conflicts of interest.

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