Current Infectious Disease Reports (2020) 22: 3
https://doi.org/10.1007/s11908-020-0711-8

PEDIATRIC INFECTIOUS DISEASES (I BROOK, SECTION EDITOR)

Respiratory Virus Co-infection in Acute Respiratory Infections in Children

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Published online: 24 January 2020

Abstract

Purpose of Review This investigation aims to understand the role and burden of viral co-infections for acute respiratory illnesses in children. Co-infection can be either viral-viral or viral-bacterial and with new technology there is more information on the role they play on the health of children.

Recent Findings With the proliferation of multiplex PCR for rapid diagnosis of multiple viruses as well as innovations on identification of bacterial infections, research has been attempting to discover how these co-infections affect each other and the host. Studies are aiming to discern if the epidemiology of viruses seen at a population level is related to the interaction between different viruses on a host level. Studies are also attempting to discover the burden of morbidity and mortality of these viral-viral co-infections on the pediatric population. It is also becoming important to understand the interplay of certain viruses with specific bacteria and understanding the impact of viral-bacterial co-infections.

Summary RSV continues to contribute to a large burden of disease for pediatric patients with acute respiratory illnesses. However, recent literature suggests that viral-viral co-infections do not add to this burden and might, in some cases, be protective of severe disease. Viral-bacterial co-infections, on the other hand, are most likely adding to the burden of morbidity in pediatric patients because of the synergistic way they can infect the nasopharyngeal space. Future research needs to focus on confirming these conclusions as it could affect hospital cohorting, role of molecular testing, and therapeutic interventions.

Keywords Viral co-infections · Pediatric respiratory illness · RSV · PCR, viral interactions

Introduction

Acute respiratory illnesses are the most common cause of under-5-year-old mortality worldwide [1]. In particular, pneumonia is responsible for approximately 1.4–1.8 million fatal cases in children under age five globally [2]. Beyond the mortality burden, there is significant morbidity with symptomatic viral infections estimated at more than five episodes per year in children under age three [3]. While single viral infections are relatively straightforward, there is interest in understanding the role of dual respiratory infections in pediatric patients. Dual infections could either be viral-viral or viral-bacterial as the human respiratory tract is a reservoir for many organisms.

This article is part of the Topical Collection on *Pediatric Infectious Diseases*

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Identification of Viral Pathogens

Molecular diagnostics have increased the ability to diagnose causative agents in patients with respiratory illnesses. Real-time polymerase chain reaction (RT-PCR) allows for the detection of multiple viruses at once and is found to be more reliable and expedient than viral culture [4]. Furthermore, newer methods, such as multiplex PCR and next-generation sequencing are producing more accurate and quicker results towards identifying these organisms [5]. Given this ability, studies have attempted to discern if the positive test for pathogen is actually causative or if it is asymptomatic shedding leading to a positive test result.

One study evaluated adult visitors to a tourist attraction taking clinical history of symptoms as well as testing PCR

for common respiratory illnesses [6]. Of those participants who tested negative for respiratory viral infections, 81.9–99.6% reported to be asymptomatic depending on the definition applied. Only 6.2% of patients tested positive for a respiratory virus. Of these positive results, up to 48.1% were considered symptomatic.

Another study focused on respiratory viral infection positivity specifically in the pediatric population [7]. Testing children biweekly whether symptomatic or not, 56% of symptomatic episodes had detection of a viral pathogen compared to 40% of asymptomatic episodes. The younger the patient, the less likely a pathogen positive episode was asymptomatic ($p = 0.01$); in addition, multiple pathogens were found in significantly less asymptomatic episodes ($p = 0.02$). Further studies attempted to discern which viruses were more likely to cause symptoms. One study in children under age 5 years old found that respiratory syncytial virus (RSV), human metapneumovirus (HMPV), and parainfluenza viruses (PIV) were more likely to be causative of disease [8]. Another study still found high rates of asymptomatic shedding of RSV and PIV with more than half of positive tests associated with an asymptomatic patient [9]. However, within these data, younger patients were associated with higher rates of positive test results correlating with a symptomatic event demonstrating the importance of age in clinical manifestation of viral infections.

Important Viruses in Co-infection

RSV is responsible for an extremely high burden of disease in children. Infection with RSV is one of the leading causes of death in children under 1 year of age worldwide, second only to malaria [10]. In a surveillance of acute respiratory infections in children under age 5, RSV was responsible for 20% of annual hospitalizations, 18% of emergency department visits, and 15% of office visits [11]. In an evaluation of children under 18 years old admitted to the hospital with a diagnosis of pneumonia, the most common cause of infection, whether bacterial or viral, was RSV quickly followed by rhinovirus [12]. Rhinovirus is the most common cause of respiratory viral illness during all seasons except winter when RSV is predominant [13]. Rhinovirus is second only to RSV in causing bronchiolitis in hospitalized patients [14]. Unfortunately, the true burden of rhinovirus is under-reported as many studies do not include this virus in there molecular diagnostic testing as the rates of asymptomatic shedding are quite high and it is difficult to differentiate shedding from actual cause of disease [13].

While some studies do have RSV and rhinovirus as the leading cause of pneumonia in children, another important common viral contributor is influenza [15]. Influenza and its complications are the leading cause of morbidity and mortality [15]. Despite antiviral medications and vaccines, it is estimated by the World Health Organization (WHO) that the annual influenza epidemics cause 3 to 5 million severe infections and 250,000–500,000 deaths each year in developed countries and 300,000 hospitalizations and 35,000 deaths in the USA [16, 17]. Influenza has recently been recognized as having a higher burden of disease than previously thought because of poor recognition and diagnosis even with molecular testing [18]. Although vaccination against influenza decreases the risk of infection, now with less vaccination we are witnessing less herd immunity and those more vulnerable are becoming severely ill [19]. In my practice, I've witnessed a 2-month-old infant—too young for the Influenza vaccine and caregivers opted out of the influenza vaccination for themselves—develop respiratory failure requiring endotracheal intubation due to influenza A epiglottitis [20].

Human metapneumovirus (HMPV) also causes acute respiratory infections globally. HMPV has been shown to cause high hospitalization rates of 1 per 1000 in children 5 years old or younger, with an estimated 20,000 hospitalizations annually which is similar to the rates seen with influenza [21]. Outpatient visits were estimated at one million clinic visits and 263,000 emergency department visits annually in the same population [21]. Admitted pediatric patients with HMPV were more likely than those without the infection to require supplemental oxygen and had longer intensive care stays [21].

Pathophysiology of Viral-Viral Co-infection

At the host level, the outcome of dual infection is commonly viral interference, such as when one virus competitively inhibits the replication of another virus, but it can also enhance replication in some cases [22]. It is postulated that the sequence of infections, the time interval between viral exposure, and the route of infection affect the pathogenicity of the co-infection [22]. One example of this used mice models. When the mice cell models that were infected with rhinovirus were then infected with influenza A virus 2 days later, there was an attenuated response to the influenza infection with less severe manifestation of disease [23]. This demonstrates that the preceding infection altered the host response and the timing and order of infection of the host are crucial in outward disease manifestation.

Co-infections can also alter the epidemiology of viral infections. For example, rhinovirus is a rapidly replicating virus and can interfere with the replication of other viruses while PIV is an extremely slow replicator and its replication can be interrupted by the presence of other viruses [22]. Viral loads can be compared among patients with one or multiple infections. One study found that viral loads were consistently high regardless of co-infection status (such as RSV, influenza A, and HMPV) but others had viral load vary based on co-infection status (such as PIV1 and adenovirus) [24]. Of these

viruses, influenza A is least likely to be identified in co-infected patients. In mathematical modeling, the idea of resource competition can explain viral loads as the faster-replicating viruses overcome slower replicating viruses by leaving no resources [25]. In this model, influenza A replicates faster than RSV and therefore keeps the RSV viral load below detection level.

Epidemiology of Viral-Viral Co-infections

The pathophysiology behind dual viral infections can explain some of the epidemiology of viral-viral co-infections seen at the population level. Given the high rates of RSV and rhinovirus infections, it makes sense that they are the most commonly identified viruses in co-infected patients across multiple studies [14, 49–55]. However, one study did conclude that the odds of rhinovirus detection were lower when RSV was present and the odds of rhinovirus were significantly higher in those patients who received RSV immunoprophylaxis [56]. This indicates that despite the high prevalence of co-infection with these viruses, there is still viral interference occurring.

There is also evidence of viral competition when it comes to RSV and influenza. In terms of viral competition, when RSV infection rates are high, influenza rates of infection are low and the converse is true [57]. In addition, when both viruses are circulating in a small population the rates of co-infection of RSV and influenza are over 6 times less than expected [58]. On review of influenza interactions with other viral pathogens, there is evidence of competitive interference with RSV, rhinovirus, other influenza strains, and HMPV virus by evaluating population incidence and co-infection detection [59].

Burden of Disease from Viral-Viral Co-infection

Multiple studies have attempted to evaluate the clinical importance of viral co-infections. It would seem intuitive to think that having more than one virus causing disease in a person would lead to more severe symptoms and sequelae. One study did support this conclusion. In it the authors looked at all pediatric patients who had a respiratory viral panel sent, they found an unadjusted increase in the risk of moderate-severe illness, non-invasive ventilation, ECMO, and death in co-infected patients however in the adjusted analysis only the risk moderate-severe disease continued to be increased [60].

Some studies found certain clinical outcomes to be at increased risk but not a persistence of high risk in all outcomes. One study evaluated patients under 12 months in France and found that viral co-infections were 2.7 times more likely to be in the PICU however once in the PICU there was no difference in length of stay, duration of mechanical ventilation, duration of supplemental oxygen [52]. Another study supported this finding by evaluating children in the PICU retrospectively comparing one virus vs co-infected viral status and found that the co-infected patients had longer average length of stay in the PICU and longer time of intubation [61]. However, there was no difference in rates of needing high-flow nasal cannula, mechanical ventilation, or having cardiovascular dysfunction. It is possible that the prolonged intubation times could be because patients who were co-infected with viruses had higher odds of bacterial co-infection.

There are some studies that also found increased risk of clinical outcomes but these actually were based on specific viral combinations. One study found that specifically influenza viral co-infection with another influenza strain significantly increased the risk of ICU admission or death but this did not carry through to any other co-infected status [62]. Another study did a multicenter evaluation of bronchiolitis over 3 years and found longer length of stay in those with RSV/RV co-infection but no proof that these patients were sicker (as in no difference in ICU admission or support with CPAP or mechanical ventilation) [14]. Another study also found an increase in length of stay and oxygen use in those patients with specifically RSV/RV co-infected status [63].

There are a few studies that found no difference in clinical outcomes on co-infected patients. The study looking at tourists did not find any association between viral co-infections and the likelihood of being symptomatic or presenting with more severe symptoms [9]. Another one looking at hospitalized pediatric patients found no increased risk of ICU admissions in those with multiple viruses identified [64].

Beyond no difference in clinical outcomes, quite a few found less severity in those patients with multiple viral infections. One study found age to be important in understanding the risk of severe disease. In this study, they evaluated children with bronchiolitis in the Netherlands and found those patients with dual infection had no difference in severity under 3 months of age but significantly less severe disease in patients over 3 months [65]. Another study in the Netherlands looking at pediatric patients had shorter mean length of stay and no difference in oxygen supply needs or intensive care (ICU) admission [53]. Another found that viral co-infected patients were significantly less likely on the inpatient ward (OR 0.55), ICU stay (OR 0.32), require oxygen supplementation (OR 0.55), or have length of stay greater than 3 days (OR 0.32) [24]. One study was actually able to see a linear response to length of stay with a shorter length of stay the more viruses detected when evaluating all pediatric patients with hospitalized respiratory infections [66].

The best evaluation of the literature on viral co-infections and clinical severity is going to be in systematic reviews. There are three looking at viral co-infections that warrant discussion. Scotta et al. [67•] did a large systematic review of respiratory viral co-infections with illness severity in children with over 17,000 patients in the combined evaluation. In this review, viral co-

infections did not influence risks of all outcomes assessed: mean length of stay, length of supplemental oxygen, need for hospitalization, need for intensive care admission, mechanical ventilation, or death. They also looked at sub-analyses of specific viral combinations and did not see any influence on outcomes. Lim et al. [68] did a systemic review for children under age 5 years with respiratory illness and found insufficient evidence to suggest a difference in any clinical outcome based on co-infected status. In a very small subset of patients, they found a suggestion that children without co-morbidities actually did worse when only a single virus was identified. Goka et al. [55] did a systemic review of patients of all ages with respiratory illnesses and found that studies that recruited young children were more likely to report high rates of co-infection and that there were inconclusive results on risk of hospitalization or ICU admission.

Pathophysiology of Viral-Bacterial Co-infection

To cause respiratory illnesses, bacterial pathogens first need to colonize the nasopharyngeal space [26]. Organisms achieve this colonization via positive and/or negative associations: positive association exists through mutualism, symbiosis or helping to evade the host's immune system; negative association exists through ammensalism, predation, or the host immune system disproportionally affecting one organism over the other [26]. Overall, there are multiple mechanisms, for viruses and bacteria, to aid in the success of invasion and colonization of the human body.

Mechanisms of Viral Influences on Bacterial Invasion and Colonization

1) Viral pre-disposition to bacterial adherence: alteration of the host's respiratory epithelium causes viruses to increase the susceptibility of bacterial colonization during a simultaneous infection and after full recovery of a viral illness [26, 27]. Examples include: Influenza and *Streptococcus pneumoniae* and adenovirus and *Streptococcus pneumoniae* [26, 28].
2) Disruption of the epithelium barrier: viruses can intracellularly disarrange cellular processes or destroy infected cells through metabolic exhaustion or lysis [26]. The destruction of cells leads to the denuding of the epithelial layer, exposing the basement membrane; therefore, causing introduction of bacterial organisms [29, 30]. Examples of this mechanism are *S. pneumoniae* binding to fibronectin after the denudation of the epithelium layer, and *Staphylococcus aeurus* and *Morexella catarrhalis* binding to extracellular matrix protein after destruction to the epithelium [31–33]. Loss of the epithelium integrity and promotion of bacterial translocation are also seen in rhinovirus-induced paracellular migration of *Haemophilus influenzae* [34].
3) Upregulation of adhesion proteins: viral infected cells may decrease the innate immune response by altering the expression of antimicrobial peptides (defensins), which are secreted in the respiratory mucosa [35]. During viral infections, there are cascades of pro-inflammatory responses leading to the upregulation of adhesion proteins found on epithelial cells, which leads to the cellular invasion of pathogenic organisms [26]. For example, RSV and parainfluenza viruses upregulate intracellular and outer membranes proteins such as intracellular adhesion molecule 1 (ICAM-1), P5-homologous fimbriae (P5 fimbriae), carcinoembryonic adhesion molecule-1 (CEACAM-1), and platelet-activating factor receptor (PAFr) [36, 37]. With the expression of these proteins, several bacterial organisms, *S. pneumoniae and H. influenzae,* are able to adhere to these molecules leading to invasion of the host's cells [36, 37].
4) Production of viral factors: production of viral components such as neuramindase (NA), a glycoprotein produced by influenza and parainfluenza, and protein-G—expressed on RSV cells—destroy the integrity of infected cells. This destruction exposes bacterial receptors and aids in bacterial co-infections [38–41].
5) Dysfunction of immune system components: respiratory viruses may affect the immune system by impairing neutrophil function, decreasing oxidative burst, and enhancing neutrophil apoptosis, thus increasing the susceptibility to bacterial superinfection [42, 43]. Also, viruses can predispose to bacteria superinfection by rendering natural killer (NK) cells recruitment and activation ineffective, which is seen with influenza and *S. pneumoniae* [44]. Viruses also alter monocyte function, decrease production and activity of cytokines, and prevent appropriate immune response routing, leading to enhanced bacterial colonization and increasing risk for mortality [45–48].

Epidemiology of Viral-Bacterial Co-infection

Because of the interaction between viruses and bacteria, there are many known specific virus-bacteria relationships (Table 1). For example, influenza interacts with both *Streptococcus pneumoniae* and *Staphylococcus aureus*. The most common bacteria found in viral, secondary bacterial infections is *S. pneumoniae* [15]. *S. pneumoniae* has over 97 distinct serotypes and is a common cause of acute otitis media (AOM), pneumonia, sepsis, and bacterial meningitis [85–87]. One of the most common complications of influenza infection is AOM from either *S. pneumonia* or *S. aureus* [15, 88]. Since influenza is one of the common viral contributors to pneumonia, it also increases the rates of bacterial pneumonia from *S. pneumoniae* and *S. aureus*. This is because influenza with both of these bacteria has synergistic relationships using the

Table 1 Viral and bacterial co-infections and associated complications

Virus	Bacteria	Co-infection complication
Influenza	*S. pneumoniae*	CAP, AOM, acute and chronic rhinosinusitis [15], invasive pneumococcal disease[a] [69]
	S. aureus	Necrotizing pneumonia, CAP [70], bacteremia [71] chronic sinusitis [72]
	Haemophilus influenza	AOM, exacerbation of COPD, sinusitis [73], bronchial necrosis, bronchitis [74]
Rhinovirus	*S. pneumoniae*	Acute and chronic rhinosinusitis [2] CAP [75], AOM [76], invasive pneumococcal disease[a] [77]
	S. aureus	Chronic rhinosinusitis [78]
	H. influenza	AOM [79], Acute and chronic rhinosinusitis [2], exacerbation of COPD [80]
	Moraxella catarrhalis	AOM [76]
RSV	*S. pneumoniae*	AOM [81], CAP [75], invasive pneumococcal disease[a] [77]
	S. aureus	CAP, LRTI [70]
	H. influenza	AOM [81], CAP, LRTI [82]
	M. catarrhalis	AOM [81], CAP, LRTI [82]
	Pseudomonas aeruginosa	Cystic fibrosis exacerbation [83]
Human metapneumovirus	*S. pneumoniae*	Pneumonia [46]
Parainfluenza	*S. pneumoniae*	AOM, acute rhinosinuisitis [78]

[a] Invasive pneumococcal disease: pneumococcus is isolated from a sterile site, i.e., sepsis, meningitis [84]

CAP community acquired pneumonia, *AOM* acute otitis media, *COPD* chronic obstructive pulmonary disease, *LRTI* lower respiratory tract infection

mechanisms listed above [15, 26]. In addition, the bacteria increase influenza's infectivity by activating hemagglutinin on the membrane, thus neutralizing antibodies and allowing more virions to be replicated inside the host cell [15, 89]. Table 1 reviews the most common viral-bacterial co-infections and their associated complications.

There are also reports of preceding bacterial infections leading to increase viral susceptibilities [26]. For example, *S. pneumoniae* and HMPV have a unidirectional synergistic relationship where *S. pneumoniae* predisposes children less than 2 years old to HMPV infections [90]. Similarly, *H. influenza* stimulates adhesion proteins on human epithelial cells, creating an entry point for rhinovirus [91]. Rhinovirus also has a bi-directional relationship with *S. aureus*: rhinovirus aids in the bacterial adhesion and engulfment into the epithelium cell and *S. aureus* promotes the replication of rhinovirus [70]. Rhinovirus can actually increase the nasal load of *S. aureus* by 39% over baseline [70].

Burden of Disease from Viral-Bacterial Co-infection

The evaluation of viral-bacterial co-infection on disease severity is an advancing field however no study reports a decrease in severity with viral-bacterial co-infection. One study [92] evaluated children presenting with bronchiolitis using nasal swabs to identify a plethora of viruses in addition to *S. pneumoniae*, *M. catarrhalis*, and *H. influenza*e. In this study, RSV and *S. pneumoniae* co-detection was significantly associated with severe disease in the regression analysis. In a cohort study of children admitted with acute respiratory disease, bacterial superinfections were significantly associated with higher illness severity scores (OR = 2.12), more severe respiratory distress (OR = 4.4), required more respiratory support (OR 3.4), and have longer hospital length of stay [93]. It is encouraging to note that the children who received the pneumococcal vaccine had lower illness severity, less respiratory distress, required less respiratory support, and had less admissions to the PICU [93].

In a review of the clinical significance of viral-bacterial co-infections in pediatric patients [94•], 16 studies were found to evaluate clinical severity in this co-infected group. Only four of these studies did not observe increased clinical severity, such as more frequent and longer PICU admissions or longer ventilation requirements.

It is also important to place this discussion in a historical context and discuss the Influenza A pandemic of 1918. This pandemic had a mortality rate of 40–50 million people worldwide [15]. It is now known that secondary bacterial pneumonia caused the majority of the deaths during this time [95]. This further underscores that the viral infection alone was not as detrimental as the viral-bacterial co-infection.

Conclusion

There is still a lot to learn about pediatric respiratory illness co-infections, as the interplay is intricate and not fully understood. Looking at viral-viral co-infections, it seems that ultimately RSV seems to be the major decider of severity of infection whether or not the child has one or multiple viruses identified [96]. This information could influence the role of molecular testing in routine hospitalized patients. Viral-bacterial co-infections, on the other hand, usually lead to more severe diseases. Overall, being able to better understand coinfection relationships can aid in the development of therapeutic methods as well as potentially affect the role of molecular testing.

Compliance with Ethical Standards

Conflict of Interest All authors declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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