**Temporal association between rhinovirus activity and *Kingella kingae* osteoarticular infections**

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**Short title:** Rhinovirus and *Kingella kingae*: a temporal association

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**Abbreviations:**

HRV: human rhinovirus

*K. kingae: Kingella kingae*

OAI: osteoarticular infections

PCR: polymerase chain reaction

RSV: respiratory syncytial virus

**Abstract**

**Objective** To determine whether the seasonal distribution of *Kingella kingae* osteoarticular infections (OAI) is similar to those of frequent respiratory viruses.

**Study design** From October 2009 to September 2016, we extracted the results of *K. kingae* specific real-time polymerase chain reactions performed in bone or joint samples in patients from 2 pediatric tertiary care centers in Paris; we used data of respiratory virus detection from the RENAL network with the coordination of the National Influenza Center of France. Spearman’s rank correlation was used to assess a correlation between weekly distributions, a p<0.05 denoted a significant correlation.

**Results** During the 7-year period, 322 children were diagnosed with *K. kingae* OAI, while 317 were *K. kingae* negative. We observed high activity for both *K. kingae* OAI and human rhinovirus (HRV) during the fall (98 [30.4%] and 2,401 [39.1%] cases, respectively) and low activity during summer (59 [18.3%] and 681 [11.1%] cases, respectively). Their weekly distributions were significantly correlated (r= 0.30, p= 0.03). In contrast, no significant correlation was found between the weekly distribution of *K. kingae* OAI and other respiratory viruses (r= -0.17 [p= 0.34], r= -0.13 [p= 0.34], and r= -0.22 [p= 0.11] compared to respiratory syncytial virus, influenza virus, and metapneumovirus, respectively).

**Conclusion** A temporal association was significantly observed between HRV circulation and *K. kingae* OAI, strengthening the hypothesis of the role of viral infections in the pathophysiology of *K. kingae* OAI. More than influenza or respiratory syncytial viruses, the role of HRV appears interesting to explore.

**Introduction**

*Kingella kingae* is an oropharyngeal commensal agent of toddlers but is also recognized as the primary cause of osteoarticular infections (OAI) in children in several countries, especially in the 6-23 months group of age. 1–5

Some evidence suggests that *K. kingae* colonizes the oropharynx before penetrating the bloodstream and invading distant organs, such as joint and bone. 6 However, variation in *K. kingae* carriage rate has not been shown to explain variations in incidence of invasive disease. 7 Several factors have been suggested to be involved in the pathophysiology of *K. kingae* invasive infections, such as age-related immunity 8,9, antibiotic exposure 1,7, and intrinsic virulence factors such as hemolytic RTX toxin 10, type IV pili 11, or polysaccharide capsule 12, or even some major *K. kingae* clones 13 but further evidence is needed. Recent studies have linked concomitant viral infections, such as primary herpetic stomatitis 14, varicella zoster virus infection 14,15, hand-foot-mouth disease/herpangina 16,17, human rhinovirus 18, and, more rarely, influenza virus 19, to *K. kingae* invasive infections. As the peak of incidence of herpetic and many respiratory viral infections coincides with the age of *K. kingae* carriage and invasive infections, it seems plausible that damage to the mucosal layer caused by a viral disease facilitates the entry of *K. kingae* organisms in the bloodstream. 1 Of interest, in a recent longitudinal study, 90.5% of patients presenting with a *K. kingae* OAI carried a virus in their oropharynx versus 37.5% of children with a non-*K. kingae* OAI (p=0.008). 20 Human rhinovirus (HRV) appeared as the most frequently virus identified 20, especially during winter whereas a low HRV activity was recorded, suggesting that some respiratory viruses, such as HRV, might be specifically associated with *K. kingae* infections.

In order to highlight this possible relationship between such respiratory viruses and *K. kingae* invasive infections, we aimed to compare the weekly distribution of *K. kingae* OAI in our cohort with the weekly circulation of the main respiratory viruses during the same period and in the same region.

**Materials and Methods**

**Study population and data sources**

We extracted the *K. kingae* OAI cases occurring in 2 major pediatric tertiary care centers in Paris (Robert-Debré and Armand-Trousseau Hospitals) from October 2009 (week 40) to September 2016 (week 39), using the microbiology laboratory register of the Robert-Debré Hospital.

A confirmed *K. kingae* OAI case was defined by a positive *K. kingae* specific real-time polymerase chain reaction (PCR) targeting the *cpn*60 gene, as previously described, 4 in joint fluid, bone samples or synovial biopsy. As the specific *K. kingae* real-time PCR was systematically performed in children aged from 6 to 48 months with a suspicion of OAI, negative results were used to determine the weekly percentage of *K. kingae* cases.

**Respiratory virus Diagnosis**

We collected the data of respiratory viral activity during the same period (from October 2009 to September 2016), in the Parisian region (Ile-de-France), using the data collected of the National Influenza Centre (NIC), based in Paris through the RENAL (Réseau National des Laboratoires) Network for hospitalized patients (children and adults). Age of patients was not available. The laboratory diagnosis of viruses used real-time reverse transcription PCR assays for detection of the viruses.

These results are integrated on a secured on-line software (Voozanno “RENOG”, version 2009).

Thus, the numbers of positive and negative samples were collected for each week during the same 7-year-period for the most frequent respiratory viruses: influenza virus, respiratory syncytial virus (RSV), HRV and metapneumovirus.

**Statistical Analysis**

Continuous variables were compared by Mann-Whitney U test and categorical variables were compared by Fisher’s exact test or Chi-square.

As few cases of *K. kingae* OAI are identified each week, time series analysis or repeated measures analysis of variance could not be performed. Thus, we pooled the numbers of positive and negative cases for each week of the 7-year-period, and then we calculated the weekly-pooled percentages of *K. kingae* OAI. A similar method was used for the viral samples. Most years had 52 weeks; the 53-week years in the range 2009-2016 were 2009 and 2015. For both, we distributed the low number of cases collected during the 53rd week between the 1st and the 52nd weeks.

Correlations between the weekly-pooled positive percentage of *K. kingae* OAI and that of each respiratory virus were explored by Spearman’s rank correlation. All statistical tests were 2-tailed with the significance level set at 5%. The analyses were conducted using R statistical package 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria).

**Ethics**

This study was declared to the French National Commission of Data Processing Files and Individual Liberties and was approved by the Institutional Review Board (IRB n°: 1997747v0).

**Results**

**Characteristics of the study group**

During the 7-year period, 322 children were diagnosed with *K. kingae* OAI, while 317 children presented a negative *K. kingae* PCR in bone or joint samples. A median of 48 *K. kingae* OAI was observed per year (range, 39-55 cases) when full years were assessed (2010-2015 period), with no significant difference in the percentage of positive results between years (median 49.6%, [range, 45.6-58.2%], p=0.66). The median age in the *K. kingae* group was 15.7 months (interquartile range: 12.1-21.9 months), and most of cases occurred in children aged from 7 to 12 months and from 13 to 24 months (n= 93 [29%] and n= 161 [50%], respectively) (Figure 1). In the non-*K. kingae* OAI group, the median age was 22.6 months (interquartile range: 14.7-33.2 months).

**Seasonal distribution of *K. kingae* OAI**

The weekly-pooled distribution of *K. kingae* OAI observed from October 2009 to September 2016 is depicted in Figure 2.

*K. kingae* OAI occurred all along the years, however a seasonal variation was observed, with a higher activity during the fall (98 cases [30.4%] between the 38th and the 50th weeks) than during summer (59 cases [18.3%] between the 25th and the 37th weeks) (medians 8 versus 4 cases per week, respectively; p=0.04). Two peaks were observed in May (18 cases during the 20th week) and September (15 cases during the 40th week); 88 cases (27.3%) were observed in spring (between the 12th and the 24th weeks) and 77 cases (23.9%) in winter (between the 51st and the 11th weeks).

**Respiratory viruses circulation**

The weekly-pooled percentages of positive samples for four major respiratory viruses (i.e. RSV, influenza, metapneumovirus and HRV) are depicted in Figure 3. The year-by-year results are available in online Figures 4, 5 and 6.

RSV, influenza virus and human metapneumovirus presented distinctive and variable winter peaks. Firstly, RSV exhibited the most pronounced seasonality, with peak activity at the year-end (7,748 cases [68.9%] between the 39th and the 52nd weeks), and lowest activity in mid-year (April-June). Then, most cases of influenza occurred in winter (7,773 cases [70.9%] between the 51st and the 11th weeks), whereas metapneumovirus was detected at the highest rate between November and February, with 1,146 cases (66.2%) between the 44th and the 9th weeks. In contrast, although HRV was observed all along the year, we identified periods of high HRV activity during the fall (2,401 cases [39.1%] between the 38th and the 50th weeks) with a peak in September (40th week), while a lower HRV activity period was observed during summer (681 cases [11.1%] between the 25th and the 37th weeks) (medians 181 versus 49 cases per week, respectively; p<0.001).

**Temporal association between respiratory viruses and *K. kingae* OAI**

Interestingly, we observed a similar seasonal distribution between *K. kingae* OAI and HRV infection with a higher activity during the fall and spring than during summer and winter (Figure 3). To go further, we estimated the Spearman’s rank correlation in order to confirm such a temporal association. We compared the weekly-pooled positive percentage of *K. kingae* samples to those of viral samples, and observed a significant correlation between *K. kingae* OAI and HRV weekly distributions (r= 0.30, p= 0.03) (Figure 3). This correlation appeared even stronger during the fall (r= 0.69 [p< 0.01]). In contrast, there were no significant correlations between *K. kingae* OAI and other respiratory viruses (r= -0.13 [p= 0.36], r= -0.17 [p= 0.34], r= - 0.13 [p= 0.34], and r= -0.22 [p= 0.11] compared with any virus, RSV, influenza virus, and metapneumovirus, respectively). Of note, during winter when the prevalence of influenza is strong, no significant correlation was found between influenza and *K. kingae* OAI (r=-0.26 [p= 0.38]), while during the fall, when RSV detection is gradually increasing, a significant negative correlation was observed with *K. kingae* OAI, which are progressively decreasing (r= -0.62, p=0.02).

**Discussion**

To our knowledge, we present the first large-scale epidemiological study comparing the seasonal distribution of *K. kingae* OAI and respiratory viruses using the results of a 7-year-period in Ile-de-France.

In the largest cohort reported to date, we confirmed that *K. kingae* OAI occurred in young children with almost 80% aged of 6-24 months. Moreover, we observed that *K. kingae* OAI occurred all along the year, with a significant seasonal variation, with peaks in May and September, in accordance with previous studies. 7,21,22

Furthermore, we highlighted for the first time that the weekly distributions of the *K. kingae* OAI and HRV circulation were significantly correlated. This temporal association extends related findings from other recent studies. A higher percentage of respiratory virus oropharyngeal carriage was previously reported in *K. kingae* OAI than in non-*K. kingae* OAI cases, with HRV being highly represented. 20 Of interest, in this previous study, HRV was the leading identified virus even during winter despite its low concomitant circulation, 20 that may suggest a specific relationship between HRV and *K. kingae* andmay explain, at least partially, the discrepancy observed between high *K. kingae* OAI prevalence and low HRV activity at the end of winter (from week 6 to 11) (Figure 3). The upper respiratory tract hosts a vast range of commensals and potential pathogenic bacteria, which form a complex microbial community, but also several viruses that may be present asymptomatically in the naso- or oropharynx. The viral-bacterial interaction is now well recognized as an important factor in the pathogenesis of bacterial diseases. 23 Viral presence may render the epithelium more susceptible to bacterial colonization. 24,25 The most well-known interaction is the synergism between influenza virus and *S. pneumoniae* 26,27; infuenza virus predisposing to pneumococcus adherence, invasion and induction of the disease. Other interactions between viral and bacterial species have been described, between influenza virus and *Staphylococcus aureus* 28, RSV and *S. pneumoniae* 29, for instance. Moreover, recent studies suggest that HRV infection may be a contributor in the development of pneumococcal invasive infections in the population of young children. 30,31 HRV has been temporally associated with pneumococcal invasive infections in children. 30 Furthermore, HRV has been found to stimulate bacterial adherence to airway epithelial cells by increasing platelet-activating factor receptor expression, the activation of NF-**B and promoter-specific transcription factor 1. 31 Overall, these findings suggest that HRV may be specifically associated with *K. kingae* OAI. This might be strengthened by the fact that no temporal association was observed with influenza virus or RSV.

Finally, outbreaks of invasive *K. kingae* infections were described among day-care center attendees in Israel, France and USA. 32 In two clusters, hand, foot, and mouth disease related to coxsackievirus, were identified. 16,17 More epidemiological studies are needed to confirm our results and to explore the influence of other viruses, especially coxsackievirus, to the seasonal evolution of *K. kingae* OAI.

This study is subject to some limitations. First, as the number of *K. kingae* OAI in a given year was relatively low, a statistical correlation test was performed, as previously described. 30 Then, it would be necessary to set up a larger study aiming to perform time series analysis. However, we can be confident in our results, since the respiratory viruses’ circulation appeared similar over the years (Figures 4, 5, 6; online), except during the H1N1 pandemic (between the 40th and 50th week in 2009, Figure 5; online). Of interest, no significant correlation was observed between *K. kingae* OAI and influenza weekly distributions during the pandemic (r= -0.003 [p= 0.97]). Second, our study was based in a single geographic region (Ile-de-France) and thus our findings may not be generalizable. We can not exclude that the increase of *K. kingae* OAI and HRV in September could be related to the onset of the scholar year, since crowding may facilitate their person-to-person transmission among young daycare center attendees with poor hygienic habits. Nevertheless, we found that *K. kingae* OAI epidemiological results were similar to those described in other countries. 7,21,22 Similarly, HRV has a worldwide distribution with a well-established seasonal pattern. 33 HRV infections were reported in Europe and in USA with a peak of incidence during the early fall (September), and a smaller spring peak. 30,34–37 Finally, we compared data from children (*K. kingae* OAI group) with data from both children and adults (respiratory viruses). However, among adults, HRV carriage rates are considerably lower than those among children. 33, 38-42

**Conclusion**

This large epidemiological study highlighted a correlated weekly distribution between HRV circulation and *K. kingae* OAI. Exploring the role of HRV, more than that of influenza virus or RSV, appears interesting to better understand the pathophysiology of *K. kingae* OAI. Further epidemiological, clinical or experimental studies could establish a causal relationship in order to confirm and explore this hypothesis.

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**Legends to Figures**

**Figure 1.** Distribution by age group (in months) of the 322 cases of *Kingella kingae* osteo-articular infections diagnosed from October 2009 to September 2016

**Figure 2**. Distribution of the weekly-pooled number of *Kingella kingae* osteo-articular infections observed from October 2009 to September 2016.

**Figure 3.** Distribution of the weekly-pooled percentage of *Kingella kingae* positive osteo-articular samples (bars) compared to those of viral samples (lines): human rhinovirus (HRV), influenza virus, respiratory syncytial virus (RSV), and metapneumovirus in Ile-de-France from October 2009 to September 2016. A statistically significant correlation was observed between *Kingella kingae* OAIand HRV weekly distribution, using the Spearman’s rank correlation test (r=0.30, p=0.03).

**Figure 4; online.** Weekly percentage of human rhinovirus (HRV) positive respiratory samples. Each color represents one year, black line represents the pooled results.

**Figure 5; online.** Weekly percentage of influenza virus positive respiratory samples. Each color represents one year, black line represents the pooled results.

**Figure 6; online.**  Weekly percentage of respiratory syncytial virus (RSV) positive respiratory samples. Each color represents one year, black line represents the pooled results.