



HAL
open science

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

Nina Droz, Vincent Enouf, Philippe Bidet, Damir Mohamed, Sylvie Behillil,
Anne-Laure Simon, Manon Bachy, Marion Caseris, Stéphane Bonacorsi,
Romain Basmaci

► To cite this version:

Nina Droz, Vincent Enouf, Philippe Bidet, Damir Mohamed, Sylvie Behillil, et al.. Temporal association between rhinovirus activity and *Kingella kingae* osteoarticular infections: Rhinovirus and *Kingella kingae*: a temporal association. *The Journal of Pediatrics*, 2018, 192, pp.234-239. 10.1016/j.jpeds.2017.09.052 . inserm-02129829

HAL Id: inserm-02129829

<https://inserm.hal.science/inserm-02129829>

Submitted on 15 May 2019

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

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

Nina Droz, Vincent Enouf, Philippe Bidet, Damir Mohamed, Sylvie Behillil,
Anne-Laure Simon, Manon Bachy, Marion Caseris, Stéphane Bonacorsi,
Romain Basmaci

► **To cite this version:**

Nina Droz, Vincent Enouf, Philippe Bidet, Damir Mohamed, Sylvie Behillil, et al.. Temporal association between rhinovirus activity and *Kingella kingae* osteoarticular infections. *Journal of Pediatrics*, Elsevier, 2018. inserm-02129829

HAL Id: inserm-02129829

<https://www.hal.inserm.fr/inserm-02129829>

Submitted on 15 May 2019

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

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

Nina Droz¹, MD, Vincent Enouf², PhD, Philippe Bidet^{3,4}, MD, PhD, Damir Mohamed^{5,6}, MSc, Sylvie Behillil², PharmD, Anne-Laure Simon⁷, MD, Manon Bachy⁸, MD, PhD, Marion Caseris⁹, MD, Stéphane Bonacorsi^{3,4}, MD, PhD, Romain Basmaci^{1,4}, MD, PhD

Affiliations:

¹Service de Pédiatrie-Urgences, Hôpital Louis-Mourier, AP-HP, F-92700 Colombes, France;

²Unité de Génétique Moléculaire des Virus à ARN, UMR 3569 CNRS, Université Paris Diderot-Paris 7, Sorbonne Paris Cité, Centre National de Référence des Virus Influenzae, Institut Pasteur, F-75015 Paris, France;

³Service de Microbiologie, Hôpital Robert-Debré, AP-HP, Centre National de Référence associé *Escherichia coli*, F-75019 Paris, France;

⁴IAME, UMR 1137, INSERM, Université Paris Diderot, Sorbonne Paris Cité, F-75018 Paris, France;

⁵Unité d' Epidémiologie Clinique, Hôpital Robert Debré, AP-HP, F-75019, Paris, France;

⁶Inserm, CIC-EC 1426, F-75019 Paris, France;

⁷Service de Chirurgie Orthopédique Pédiatrique, Hôpital Robert-Debré, AP-HP, Paris, France;

⁸Service de Chirurgie Orthopédique et Réparatrice de l'Enfant, Hôpital Armand Trousseau, APHP, Université Pierre et Marie Curie Paris 6, 26 avenue du Dr Arnold Netter, F-75571 Paris Cedex 12, France;

⁹Service de Pédiatrie Générale, Equipe Opérationnelle d'Infectiologie, Hôpital Robert-Debré, AP-HP, F-75019 Paris, France

Funding Source: No external funding for this manuscript.

Potential Conflict of Interest: The authors have indicated they have no potential conflicts of interest to disclose.

Key words: bone and joint infections, respiratory viruses, seasonal distribution, viral-bacterial interaction, children

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

Corresponding author. Romain Basmaci, Service de Pédiatrie-Urgences, Hôpital Louis Mourier, 178 rue des Renouillers 92700 Colombes, romain.basmaci@aphp.fr, tel: +33 (0)1.47.60.63.58, fax: +33 (0)1.47.60.63.76

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 toxin¹⁰, type IV pili¹¹, or polysaccharide capsule¹², or even some major *K. kingae* clones¹³ but further evidence is needed. Recent studies have linked concomitant viral infections, such as primary herpetic stomatitis¹⁴, varicella zoster virus infection^{14,15}, hand-foot-mouth disease/herpangina^{16,17}, human rhinovirus¹⁸, and, more rarely, influenza virus¹⁹, 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 identified²⁰, 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 *cpn60* 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* and may 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 asymptotically 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}; influenza 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- κ 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.

Acknowledgements

We gratefully acknowledge the hospital laboratories from the RENAL network in the Ile-de-France region for contributing their data to the NIC. [Dr E. Gault (Hôpital Universitaire Ambroise Paré); Dr P. Deny (Hôpital Universitaire Avicenne); Pr J.C. Lucet (Hôpital Universitaire Bichat); Pr P. Nordmann (Hôpital Universitaire Bicêtre); Pr J.M. Pawlotsky (Hôpital Universitaire Henri Mondor); Dr S. Marque-Juillet (Centre Hospitalier de Versailles); Dr M. Leruez-Ville (Hôpital Universitaire Necker); Pr Afonso-Roque (Hôpital Universitaire Paul Brousse); Dr D. Boutolleau (Hôpital Universitaire Pitié Salpêtrière); Pr E. Bingen (Hôpital Universitaire Robert Debré); Dr J. Le Goff (Hôpital Universitaire Saint-Louis); Pr F. Rozenberg (Hôpital Universitaire Cochin); Dr A. Schnuriger (Hôpital Universitaire Trousseau); Dr M. Thibault (Centre hospitalier de Pontoise); Dr V. Serazin (Centre Hospitalier Intercommunal de Poissy); Dr Farfour (Hôpital Foch)].

References:

1. Yagupsky P. *Kingella kingae*: Carriage, Transmission, and Disease. Clin Microbiol Rev 2015;28:54-79.
2. Al-Qwbani M, Jiang N, Yu B. *Kingella kingae*–Associated Pediatric Osteoarticular Infections: An Overview of 566 Reported Cases. Clin Pediatr 2016;55:1328–1337.
3. Haldar M, Butler M, Quinn CD, Stratton CW, Tang YW, Burnham CA. Evaluation of a real-time PCR assay for simultaneous detection of *Kingella kingae* and *Staphylococcus aureus* from synovial fluid in suspected septic arthritis. Ann Lab Med 2014;34:313–316.
4. Ilharreborde B, Bidet P, Lorrot M, Even J, Mariani-Kurkdjian P, Liguori S, et al. New real-time PCR-based method for *Kingella kingae* detection: application to samples collected from 89 children with acute arthritis. J Clin Microbiol 2009;47:1837–1841.

5. Ceroni D, Cherkaoui A, Ferey S, Kaelin A, Schrenzel J. *Kingella kingae* osteoarticular infections in young children: clinical features and contribution of a new specific real-time PCR assay to the diagnosis. *J Pediatr Orthop* 2010;30:301–304.
6. Yagupsky P, Porat N, Pinco E. Pharyngeal colonization by *Kingella kingae* in children with invasive disease. *Pediatr Infect Dis J* 2009;28:155–157.
7. de la Llana RA, Dubois-Ferriere V, Maggio A, Cherkaoui A, Manzano S, Renzi G, et al. Oropharyngeal *Kingella kingae* carriage in children: characteristics and correlation with osteoarticular infections. *Pediatr Res* 2015;78:574–579.
8. Slonim A, Steiner M, Yagupsky P. Immune response to invasive *Kingella kingae* infections, age-related incidence of disease, and levels of antibody to outer-membrane proteins. *Clin Infect Dis* 2003;37:521–527.
9. Amit U, Dagan R, Yagupsky P. Prevalence of pharyngeal carriage of *Kingella kingae* in young children and risk factors for colonization. *Pediatr Infect Dis J* 2013;32:191–193.
10. Kehl-Fie TE, Geme JWS. Identification and characterization of an RTX toxin in the emerging pathogen *Kingella kingae*. *J Bacteriol* 2007;189:430–436.
11. Kehl-Fie TE, Miller SE, Geme JWS. *Kingella kingae* expresses type IV pili that mediate adherence to respiratory epithelial and synovial cells. *J Bacteriol* 2008;190:7157–7163.
12. Porsch EA, Kehl-Fie TE, Geme JWS. Modulation of *Kingella kingae* adherence to human epithelial cells by type IV pili, capsule, and a novel trimeric autotransporter. *MBio* 2012;3:e00372–12.
13. Amit U, Porat N, Basmaci R, Bidet P, Bonacorsi S, Dagan R, et al. Genotyping of invasive *Kingella kingae* isolates reveals predominant clones and association with specific clinical syndromes. *Clin Infect Dis* 2012;55:1074–1079.
14. Amir J, Yagupsky P. Invasive *Kingella kingae* infection associated with stomatitis in children. *Pediatr Infect Dis J* 1998;17:757–758.

15. Kampouroglou G, Schaller D, Salvo D, Ceroni D. Subacute osteomyelitis by *Kingella kingae* in a 5-year-old boy after chickenpox infection. *Minerva Pediatr* 2016;68:314-315.
16. El Houmami N, Minodier P, Dubourg G, Martin-Laval A, Lafont E, Jouve JL, et al. An outbreak of *Kingella kingae* infections associated with hand, foot and mouth disease/herpangina virus outbreak in Marseille, France, 2013. *Pediatr Infect Dis J* 2015;34:246–250.
17. El Houmami N, Cointat V, Mirand A, Fouilloux V, Bzdrenga J, Bakour S, et al. An Outbreak of *Kingella Kingae* Infections Complicating a Severe Hand, Foot, And Mouth Disease Outbreak in Nice, France, 2016. *Pediatr Infect Dis J* 2017;36:530–532.
18. Basmaci R, Ilharreborde B, Doit C, Presedo A, Lorrot M, Alison M, et al. Two atypical cases of *Kingella kingae* invasive infection with concomitant human rhinovirus infection. *J Clin Microbiol* 2013;5:3137–3139.
19. Le Bourgeois F, Germanaud D, Bendavid M, Bonnefoy R, Desnous B, Beyler C, et al. *Kingella kingae* Sequence Type 25 Causing Endocarditis with Multiple and Severe Cerebral Complications. *J Pediatr* 2016;169:326–326.
20. Basmaci R, Bonacorsi S, Ilharreborde B, Doit C, Lorrot M, Kahil M, et al. High respiratory virus oropharyngeal carriage rate during *Kingella kingae* osteoarticular infections in children. *Future Microbiol* 2015;10:9–14.
21. Yagupsky P, Peled N, Katz O. Epidemiological features of invasive *Kingella kingae* infections and respiratory carriage of the organism. *J Clin Microbiol* 2002;40:4180–4184.
22. Dubnov-Raz G, Ephros M, Garty BZ, Schlesinger Y, Maayan-Metzger A, Hasson J, et al. Invasive pediatric *Kingella kingae* infections: a nationwide collaborative study. *Pediatr Infect Dis J* 2010;29:639–643.
23. Bosch AA, Biesbroek G, Trzcinski K, Sanders EA, Bogaert D. Viral and bacterial interactions in the upper respiratory tract. *PLoS Pathog* 2013;9:e1003057.

24. Bogaert D, de Groot R, Hermans PWM. *Streptococcus pneumoniae* colonisation: the key to pneumococcal disease. *Lancet Infect Dis* 2004;4:144–154.
25. Peltola VT, McCullers JA. Respiratory viruses predisposing to bacterial infections: role of neuraminidase. *Pediatr Infect Dis J* 2004;23:87–97.
26. McCullers JA. Insights into the interaction between influenza virus and *pneumococcus*. *Clin Microbiol Rev* 2006;19:571–582.
27. Morens DM, Taubenberger JK, Fauci AS. Predominant role of bacterial pneumonia as a cause of death in pandemic influenza: implications for pandemic influenza preparedness. *J Infect Dis* 2008;198:962–970.
28. Iverson AR, Boyd KL, McAuley JL, Plano LR, Hart ME, McCullers JA. Influenza virus primes mice for pneumonia from *Staphylococcus aureus*. *J Infect Dis* 2011;203:880–888.
29. Smith CM, Sandrini S, Datta S, Freestone P, Shafeeq S, Radhakrishnan P, et al. Respiratory syncytial virus increases the virulence of *Streptococcus pneumoniae* by binding to penicillin binding protein 1a. A new paradigm in respiratory infection. *Am J Respir Crit Care Med* 2014;190:196–207.
30. Peltola V, Heikkinen T, Ruuskanen O, Jartti T, Hovi T, Kilpi T, et al. Temporal association between rhinovirus circulation in the community and invasive pneumococcal disease in children. *Pediatr Infect Dis J* 2011;30:456–461.
31. Ishizuka S, Yamaya M, Suzuki T, Takahashi H, Ida S, Sasaki T, et al. Effects of rhinovirus infection on the adherence of *Streptococcus pneumoniae* to cultured human airway epithelial cells. *J Infect Dis* 2003;188:1928–1939.
32. El Houmami N, Minodier P, Dubourg G, Mirand A, Jouve JL, Basmaci R, et al. Patterns of *Kingella kingae* disease outbreaks. *Pediatr Infect Dis J* 2016;35:340–346.
33. Jacobs SE, Lamson DM, George KS, Walsh TJ. Human rhinoviruses. *Clin Microbiol Rev* 2013;26:135–162.

34. Brittain-Long R, Andersson LM, Olofsson S, Lindh M, Westin J. Seasonal variations of 15 respiratory agents illustrated by the application of a multiplex polymerase chain reaction assay. *Scand J Infect Dis* 2012;44:9–17.
35. Pierangeli A, Ciccozzi M, Chiavelli S, Concato C, Giovanetti M, Cella E, et al. Molecular epidemiology and genetic diversity of human rhinovirus affecting hospitalized children in Rome. *Med Microbiol Immunol* 2013;202:303–311.
36. Brownlee JW, Turner RB. New developments in the epidemiology and clinical spectrum of rhinovirus infections. *Curr Opin Pediatr* 2008;20:67–71.
37. Gwaltney Jr JM, Hendley JO, Simon G, Jordan Jr WS. Rhinovirus infections in an industrial population: the occurrence of illness. *N Engl J Med* 1966;275:1261–1268.
38. Peltola V, Waris M, Österback R, Susi P, Ruuskanen O, Hyypiä T. Rhinovirus transmission within families with children: incidence of symptomatic and asymptomatic infections. *J Infect Dis* 2008;197:382–389.
39. Vesa S, Kleemola M, Blomqvist S, Takala A, Kilpi T, Hovi T. Epidemiology of documented viral respiratory infections and acute otitis media in a cohort of children followed from two to twenty-four months of age. *Pediatr Infect Dis J* 2001;20:574-581
40. Advani S, Sengupta A, Forman M, Valsamakis A, Milstone AM. Detecting respiratory viruses in asymptomatic children. *Pediatr Infect Dis J* 2012;31: 1221-1226
41. Self WH, Williams DJ, Zhu Y, Ampofo K, Pavia AT, Chappell JD, et al. Respiratory viral detection in children and adults: comparing asymptomatic controls and patients with community-acquired pneumonia. *J Infect Dis* 2016;213:584-91
42. Graat JM, Schouten EG, Heijnen M-LA, Kok FJ, Pallast EG, de Greeff SC, et al. A prospective, community-based study on virologic assessment among elderly people with and without symptoms of acute respiratory infection. *J Clin Epidemiol* 2003;56:1218–1223.

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* OAI and 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.

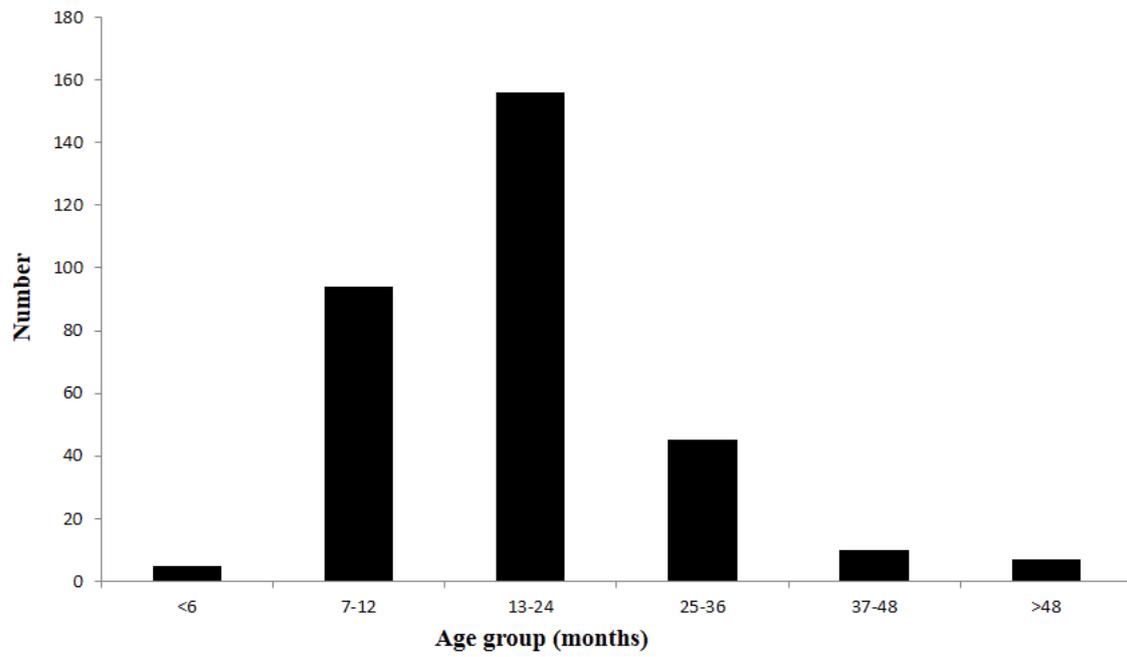


Fig1

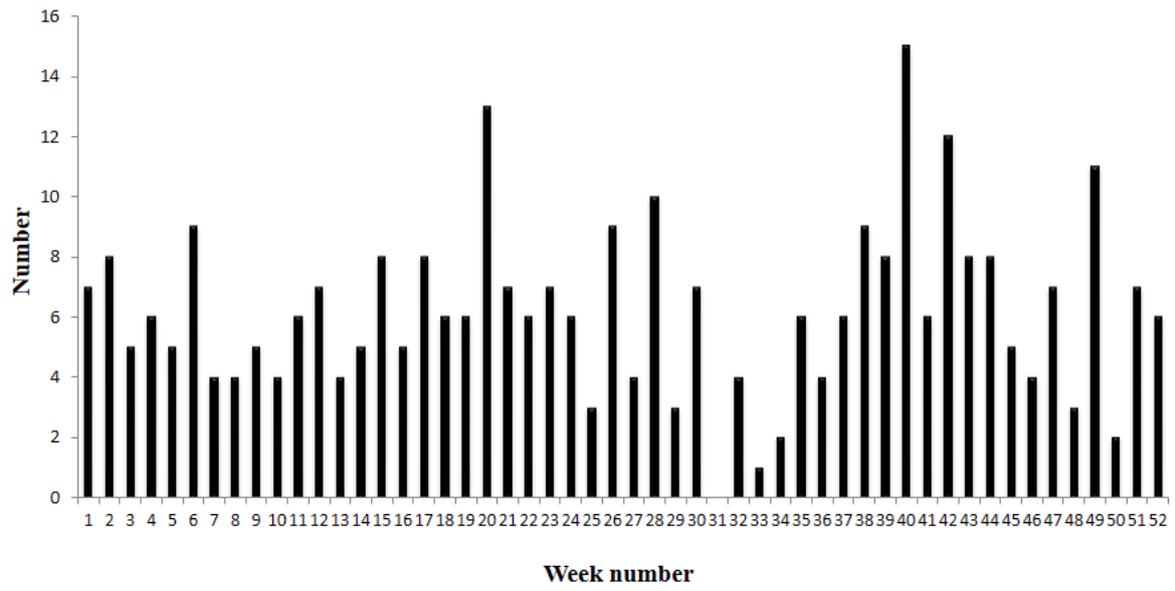


Fig2

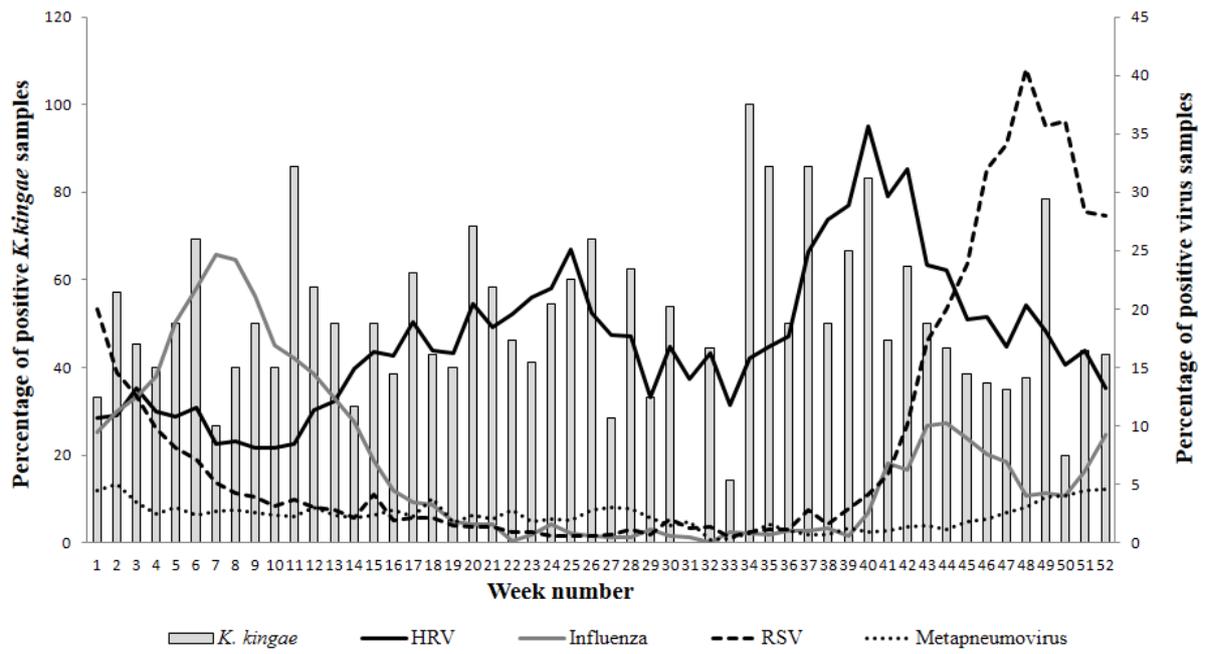


Fig3

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

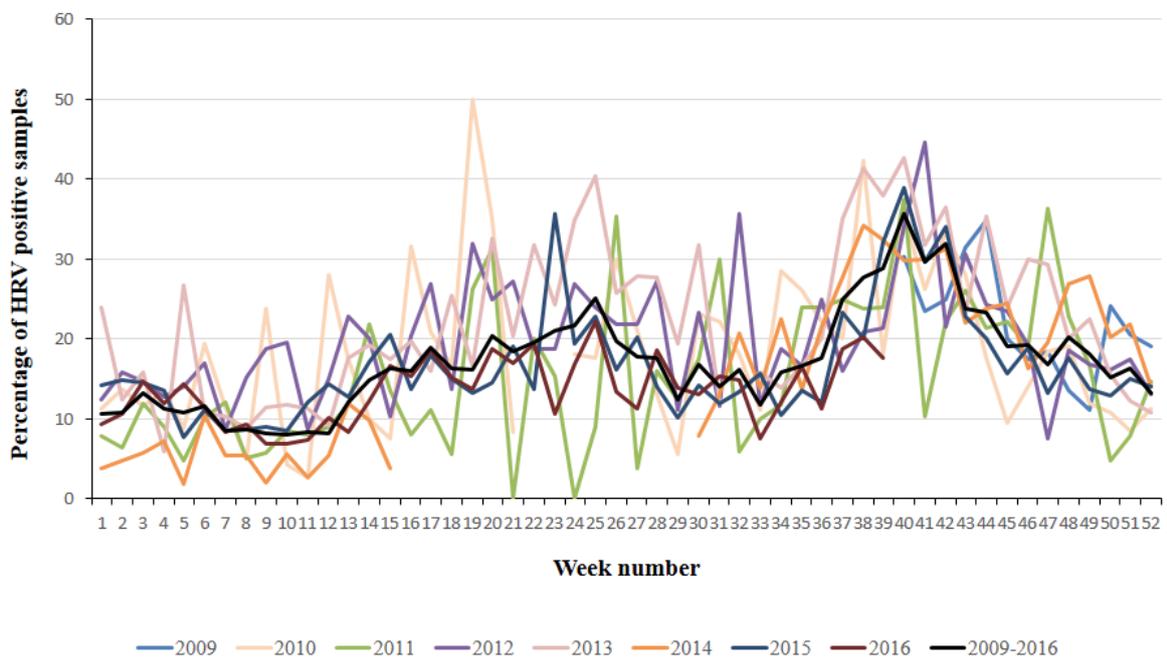


Figure 6; online. Weekly percentage of respiratory syncytial virus positive samples. Each color represents one year, black line represents the pooled results.

