

# Association between oropharyngeal carriage of *Kingella kingae* and osteoarticular infection in young children: a case–control study

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## ABSTRACT

**BACKGROUND:** *Kingella kingae* has been increasingly identified in patients with osteoarticular infections. Our main objective was to evaluate the association between carriage of *K. kingae* in the oropharynx of preschool children and osteoarticular infections.

**METHODS:** We conducted this prospective case–control study in 2 tertiary care pediatric hospitals (Canada and Switzerland) between 2014 and 2016. Potential cases were children aged 6 to 48 months with a presumptive diagnosis of osteoarticular infection according to the treating emergency physician. Confirmed cases

were those with diagnosis of osteomyelitis or septic arthritis proven by positive findings on technetium-labelled bone scan or magnetic resonance imaging or identification of a microorganism in joint aspirate or blood. For each case, we recruited 4 age-matched controls from among children presenting to the same emergency department for trauma. The independent variable was presence of oropharyngeal *K. kingae* DNA identified by a specific polymerase chain reaction assay. We determined the association between oropharyngeal carriage of *K. kingae* and definitive osteoarticular infection.

**RESULTS:** The parents of 77 children admitted for suspected osteoarticular infection and 286 controls were invited to participate and provided informed consent. We identified *K. kingae* in the oropharynx of 46 (71%) of 65 confirmed cases and 17 (6%) of 286 controls; these results yielded an odds ratio of 38.3 (95% confidence interval 18.5–79.1).

**INTERPRETATION:** Detection of oropharyngeal *K. kingae* was strongly associated with osteoarticular infection among children presenting with symptoms suggestive of such infection.

**A**cute osteoarticular infection is an important problem in the pediatric population, potentially threatening both life and limb.<sup>1,2</sup> Historically, such infections have largely been attributed to *Staphylococcus aureus*, *Streptococcus pyogenes* and *Haemophilus influenzae* type b,<sup>3,4</sup> but most series have reported a high proportion (23% to 70%) of culture-negative infections.<sup>4–6</sup> Recent European studies reported substantial proportions of cases with *K. kingae* infection, ranging from 15% to 75%.<sup>7–9</sup> Although these high proportions may be related to increasing prevalence of the pathogen, they are more likely related to improvements in detection techniques, including a *K. kingae*-specific polymerase chain reaction (PCR) assay.<sup>10,11</sup>

Diagnosing *K. kingae* infections of the bones and joints is difficult for 2 reasons. First, the clinical presentation is often subtle, and the results of paraclinical investigations may remain within

normal ranges.<sup>7,12</sup> Second, *K. kingae* is a fastidious microorganism that is difficult to grow on solid media,<sup>13</sup> which may explain the high proportion of negative culture results for joint aspirates from children with symptoms highly suggestive of infection.

The pathogenesis of osteoarticular infection related to *K. kingae* remains unclear, but there is evidence that the bacterium initially colonizes the oropharynx before penetrating the bloodstream and invading distant organs.<sup>14</sup> Recent studies from Europe and Israel have suggested a strong association between oropharyngeal carriage of *K. kingae* and the risk of osteoarticular infection in young children.<sup>14–16</sup> However, this relation has never been shown in North America.

In this multicentre study, we sought to evaluate the association between osteoarticular infection and detection of oropharyngeal *K. kingae* by PCR in young children.

## Methods

### Study design

This prospective, multicentre case-control study involved a convenience sample of children visiting 2 tertiary care pediatric hospitals. We recruited participants at the emergency departments of Geneva University Hospitals (Geneva, Switzerland) and the Centre hospitalier universitaire Sainte-Justine (Montréal) between August 2014 and June 2016. Both sites are university-affiliated hospitals, and the annual emergency department census is about 30 000 and 80 000, respectively. We chose these sites because 1 member of the study team (S.M.) has worked at both locations, both sites have good clinical research infrastructure, and there was previous collaboration on another study.<sup>17</sup>

### Study population

We recruited 2 populations of participants, aged 6 to 48 months: cases and controls. Potential cases were children with clinical suspicion of osteoarticular infection, according to the treating physician. These children presented to the emergency department for joint pain, limp or decreased limb movement without trauma, with or without fever. After identifying a potential case, the treating physician contacted a research assistant, who invited the family to participate in the study.

To identify definitive cases, 2 of the investigators (J.G., C.R.) reviewed the medical charts of all recruited potential cases at the end of the study. They were blinded to the oropharyngeal swab results and to each other's reviews assessing the probability of osteoarticular infection. The assessors classified each of these cases as impossible, possible, highly probable or confirmed. Children with a classification of "impossible" had another confirmed diagnosis (e.g., leukemia or fracture). Those with a classification of "possible" had abnormal findings on analysis of joint aspirate, but no growth of microorganisms. Those with a classification of "highly probable" had positive findings on technetium-labelled bone scanning or magnetic resonance imaging, but no growth of microorganisms. Children with a classification of "confirmed" had suspicious imaging findings and identification of a microorganism in the joint aspirate or blood. For purposes of the analysis, children with classification of "highly probable" or "confirmed" were considered to represent definitive cases.

The control group consisted of a convenience sample of children visiting the same emergency departments for benign trauma, matched for age (within 3 mo). The charts for all of these children were reviewed to ensure that osteoarticular infection did not develop during the week following recruitment.

### Exposure

The primary independent variable of interest was the presence of *K. kingae*, as detected by PCR from an oropharyngeal swab sample, as described below.

All participants underwent clinical and paraclinical evaluations at the discretion of the treating physician. In all cases, these evaluations included blood sampling (for complete blood count, erythrocyte sedimentation rate, C-reactive protein and culture) and various imaging investigations, depending on the clinical presentation and the treating physician.

After a parent provided written informed consent, an oropharyngeal sample was obtained using a dry swab (ESwab Liquid Amies nylon flocked applicator, Copan Diagnostics) for PCR identification of *K. kingae*. For patients with suspected septic arthritis, a joint aspirate was obtained for analysis and culture, including Gram staining and PCR assay specific to *K. kingae*. Aerobic blood culture and synovial fluid culture (using blood bottles and plates) were performed according to standard protocols to identify the most common aerobic bacteria. For a few patients with suspected bone infection, a bone aspirate was obtained for analysis and culture, including Gram staining and PCR testing for *K. kingae*.

All oropharyngeal samples from the Montréal site were kept frozen at -20°C until batch shipment of 25 samples to the central laboratory in Geneva, Switzerland. Samples from Geneva were analyzed in the 24–48 hours after recruitment. The oropharyngeal samples were analyzed with a real-time PCR assay designed to detect 2 gene targets from the *K. kingae* RTX toxin locus, *rtxA* and *rtxB*.<sup>18</sup> To evaluate the analytical sensitivity of these assays, we used a range of serially diluted *K. kingae* genomic DNA. The assay exhibited a sensitivity of 30 colony-forming units, which is 10 times more sensitive than a previously published semi-nested, broad-range assay for the 16S rRNA gene, as described previously.<sup>18</sup> DNA was extracted with a MagNAPure LC instrument using the MagNAPure LC DNA isolation kit II (Roche Molecular Biochemicals) according to the manufacturer's instructions. TaqMan Universal PCR Master Mix reagent with AmpErase UNG (uracil *N*-glycosylase; Applied Biosystems) was used, with 5 µL of input DNA and nuclease-free water (Promega). Each PCR analysis was performed in duplicate, with blinding as to the type of participant (case or control). A PCR-positive sample collected from a culture-proven *K. kingae* sample was used as a positive control.

For each participant, a standardized chart review form was completed by a research assistant, with baseline demographic characteristics, information about the disease and results of paraclinical investigations. For all participants, the treating physicians and research personnel were blinded to the results of oropharyngeal swab testing.

### Statistical analysis

Baseline demographic characteristics and types of infection were described for both the hospitals and the types of participants. The primary analysis included definitive cases and controls, to measure the association between oropharyngeal carriage of *K. kingae* and osteoarticular infection. We constructed a 2 × 2 table showing the numbers of positive oropharyngeal samples for cases and controls and then calculated odds ratios (ORs). We calculated 95% confidence intervals (CIs) for all measurements.

Previous studies suggested that the prevalence of *K. kingae* was as high as 75% among young children with osteoarticular infection<sup>15</sup> and was 5% to 10% among controls.<sup>13,19,20</sup> We estimated that recruitment of 32 cases would yield 90% power to identify a difference of 25% in the prevalence of *K. kingae* between the 2 groups, with an  $\alpha$  value of 0.05. Therefore, we recruited 4 controls for each case.

### Ethics approval

The study was approved by the research ethics boards of the Centre hospitalier universitaire Sainte-Justine and the Geneva University Hospitals. For inclusion in the study, each child's legal guard-

ian had to provide written informed consent. Assent from the children was deemed unnecessary because of their young age.

## Results

From August 2014 to June 2016, the parents of 77 children admitted for suspected osteoarticular infection and of 286 controls were invited to participate and provided written informed consent to be included in the study (Figure 1). Of the 77 potential cases, 69 had a definitive diagnosis of osteoarticular infection, according to the 2 chart reviewers (100% agreement between reviewers). Four cases were excluded because no oropharyngeal sample was obtained. As a result, 65 definitive cases and 286 controls were included in the final analysis.

Table 1 describes the baseline demographic characteristics of the study participants. The 2 sites recruited similar numbers of participants. Median age and sex were similar for the cases from the 2 hospitals and the control group. Blood culture results were available for 62 (95%) of the participants with confirmed osteoarticular infection.

In 34 cases, *K. kingae* infection was identified in the joint or bone aspirate (4 by culture and 30 by PCR), and in 8 cases, another microorganism was identified in the blood ( $n = 2$ ), in a joint ( $n = 5$ ) or both ( $n = 1$ ). After *K. kingae*, the most common bacterial species was *S. aureus* (4 cases); 2 cases had *S. pyogenes*, 1 case had *Salmonella*

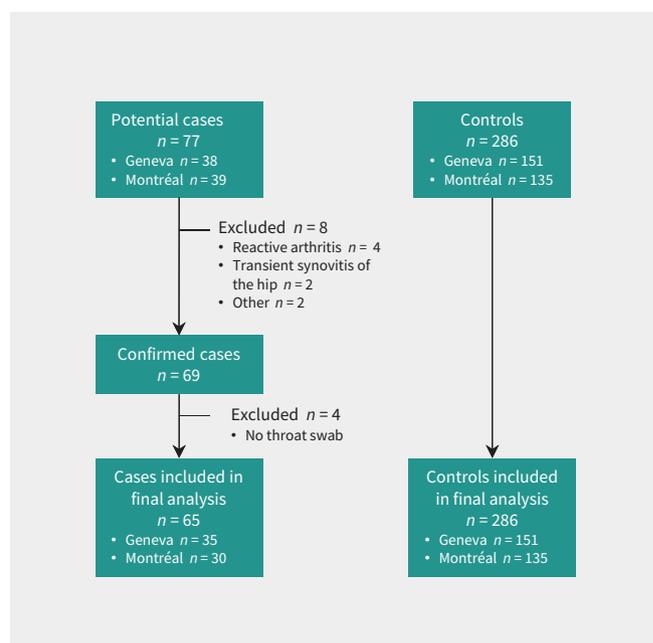


Figure 1: Flow chart for cases and controls included in a study of the association between oropharyngeal carriage of *Kingella kingae* and osteoarticular infection.

Table 1: Baseline characteristics of the participants

Characteristic	Group; no. (%) of participants*		
	Potential cases n = 77	Included cases n = 65	Controls n = 286
Site			
Geneva	38 (49)	35 (54)	151 (53)
Montréal	39 (51)	30 (46)	135 (47)
Age, mo, median (IQR)	19 (14–26)	19 (14–25)	21 (15–28)
Sex, male	44 (57)	37 (57)	144 (50)
Duration of symptoms, d, median (IQR)	4 (2–7)	4 (2–7)	NA
Fever present	46 (60)	39 (60)	NA
Final diagnosis			
Osteoarticular infection			
Bone	27 (35)	23 (35)	NA
Joint	37 (48)	33 (51)	NA
Mixed	13 (17)	9 (14)	NA
Laceration	NA	NA	16 (6)
Soft-tissue injury	NA	NA	56 (20)
Fracture	NA	NA	58 (20)
Pulled elbow	NA	NA	60 (21)
Head injury	NA	NA	51 (18)
Other	NA	NA	45 (16)
Total blood leukocytes, $\times 10^9/L$ , median (IQR)	13 (10–16)	13 (11–16)	NA
C-reactive protein, nmol/L, median (IQR)	25 (13–59)	24 (14–56)	NA

Note: IQR = interquartile range, NA = not applicable.  
\*Except where indicated otherwise.

**Table 2: Presence of oropharyngeal *Kingella kingae***

Pharyngeal PCR result	Culture result; no. of cases					Total
	Total no.	<i>K. kingae</i>	Other bacteria*	No bacteria identified	Controls	
<i>K. kingae</i> present	46	31	1	14	17	63
<i>K. kingae</i> absent	19	3	7	9	269	288
Total	65	34	8	23	286	351

Note: PCR = polymerase chain reaction.  
\*In 4 cases, *Staphylococcus aureus* was identified; in 4 cases, other bacterial species were identified.

*typhi*, and 1 case had *Escherichia coli*. The proportion of cases with *K. kingae* infection was similar at the 2 sites: 17 (49%) of 35 cases in Geneva and 17 (57%) of 30 cases in Montréal. The proportion of cases with another bacterium was also similar for both sites (5 [14%] in Geneva and 3 [10%] in Montréal). In the remaining 23 cases, no bacteria were identified in blood, bone or joint, including the 13 cases for which no culture of joint or bone aspirate was performed; of these 23 cases, oropharyngeal *K. kingae* was identified in 14.

The PCR assays detected *K. kingae* in the oropharyngeal samples of 46 of the 65 cases (71%, 95% CI 59%–80%) (Table 2). This proportion increased to 31 of the 34 cases with proven osteoarticular infection caused by *K. kingae* (91%, 95% CI 77%–97%). Among the 8 patients with growth of another bacterial species, oropharyngeal *K. kingae* was identified in only 1 patient. *Kingella kingae* was identified in 17 of the 286 controls (6%, 95% CI 4%–9%). The OR for the association between oropharyngeal carriage of *K. kingae* and the risk of osteoarticular infection was 38.3 (95% CI 18.5–79.1).

The presence of oropharyngeal *K. kingae* was strongly associated with proven osteoarticular infection by *K. kingae* (OR 158, 95% CI 44–568). A subanalysis identified a higher prevalence of oropharyngeal carriage of *K. kingae* among the controls at the Geneva site (14/151 [9%]) than among controls at the Montréal site (3/135 [2%]), a difference of 7 percentage points (95% CI 1.5–13 percentage points). However, this difference had no effect on the association between oropharyngeal carriage of *K. kingae* and risk of osteoarticular infection at each site: for Geneva, OR 33 (95% CI 12–86), and for Montréal, OR 76 (95% CI 19–297). Finally, 31 of the 34 cases with *K. kingae* infection involved children younger than 23 months.

## Interpretation

Using a highly sensitive PCR-based assay designed to detect 2 gene targets from *K. kingae* DNA, the current study showed that oropharyngeal carriage of this bacterial species was strongly associated with osteoarticular infection among young children presenting with symptoms suggestive of this diagnosis.

The association between oropharyngeal carriage of *K. kingae* and osteoarticular infection was first reported in a case series documenting 3 children with invasive *K. kingae* infection in Israel, published in 2009.<sup>14</sup> A subsequent prospective study, published in 2013, found that *K. kingae* was the causative agent for osteoarticular infection in 75% of 40 Swiss children aged 6 to 48 months.<sup>15</sup> More important, the

oropharyngeal swabs from all 30 of the *K. kingae* cases yielded positive results. Finally, a French study published in 2012 similarly reported positive throat culture results for *K. kingae* for 8 of 12 children with confirmed *K. kingae* joint infection.<sup>16</sup>

Although determining the frequency of pathogens was not an objective of this study, the most common pathogen responsible for osteoarticular infection among young children in our study was *K. kingae*. It was present in 17 of the 30 cases in Montréal, while another pathogen was identified in only 3 other cases. Overall, *K. kingae* represented 85% of the Montréal cases in which bacteria were identified. Previous studies conducted in North America<sup>21–23</sup> have suggested a lower prevalence of *K. kingae*, leading to the belief that *K. kingae* is a European problem that is not present in North America.

Recent review articles have generally suggested *S. aureus* as the most common pathogen for osteoarticular infection.<sup>1,24</sup> Studies conducted in California,<sup>21</sup> Tennessee<sup>22</sup> and Texas<sup>23</sup> have reported *S. aureus* as the most common pathogen of osteoarticular infection in children, with proportions ranging from 40% to 85%. However, in contrast to those earlier studies, we used a highly sensitive technique to identify *K. kingae* in the joint aspirate samples. In addition, we primarily identified *K. kingae* in children younger than 23 months. It is possible that the younger age of our study population accounts for the difference in reported pathogens, relative to earlier studies.

The strong association between oropharyngeal carriage of *K. kingae* and osteoarticular infection has several clinical implications. First, given the important OR value, detection of *K. kingae* in the oropharynx might be useful to confirm a potential diagnosis of osteoarticular infection. Second, oropharyngeal swabbing could be useful to suggest the pathogen in many young children with suspected bone infections, from whom bone aspirate is more complicated to obtain and for whom blood culture frequently yields negative results.<sup>23</sup> In this clinical situation, detection of oropharyngeal *K. kingae* could help to establish the presumptive causative microorganism. This approach was suggested in a recent study reporting *K. kingae* infection in 10 children with culture-negative spondylodiskitis.<sup>25</sup> However, this possibility must be considered with caution because our study reported oropharyngeal *K. kingae* in 1 of 8 children with osteoarticular infection and presence of another bacterial species. Identification of oropharyngeal *K. kingae* may help to guide antibiotic treatment, given that resistance to  $\beta$ -lactams and high-level resistance to clindamycin have been reported for *K. kingae*. In the current study, 14 of the 23 cases in which no pathogen was identified by culture had oropharyn-

geal *K. kingae* identified by PCR. It could be inferred that this was the pathogen causing the osteoarticular infection. PCR-based assays could also reduce the time for bacterial identification from days to hours, relative to current culture standards.<sup>26</sup>

## Limitations

This study had limitations, many inherent to the case-control design. We attempted to mitigate selection bias by conducting case determination and identifying oropharyngeal *K. kingae* in a blinded fashion. Also, all potential cases were reviewed by 2 co-investigators, who were blinded to the oropharyngeal results in determining the diagnosis. Despite involvement of 2 centres, the sample size was small. Although the magnitude of the association between oropharyngeal carriage of *K. kingae* and osteoarticular infection was large, the prevalence of oropharyngeal carriage should be validated in multiple North American cities. Finally, the delay and conditions of transport from Canada to Switzerland for the oropharyngeal swabs may have reduced the ability of swab testing to identify *K. kingae*. However, the observed association was similar at the 2 sites.

## Conclusion

This study showed a strong association between oropharyngeal *K. kingae* detected by PCR and osteoarticular infection among preschool children presenting with symptoms suggestive of this diagnosis. In light of these results, investigation for oropharyngeal *K. kingae* by a PCR assay should be considered for children with clinical suspicion of osteoarticular infection. Identification of the pathogen in the oropharynx should orient the presumptive diagnosis toward this pathogen. The prevalence and natural evolution of oropharyngeal carriage of *K. kingae* among healthy children should be evaluated by means of multicentre studies.

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