**COMMENTARY**

**Kingella kingae**: From carriage to infection

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In a linked research paper,1 Gravel and colleagues evaluated the association between carriage of *Kingella kingae* in the oropharynx of preschool children and osteoarticular infections in a prospective case–control study in two countries. *Kingella kingae* is difficult to isolate in bone and joint samples, and blood cultures are frequently sterile. The oropharynx is considered to be the portal of entry for invasive *K. kingae* infections; therefore, assessing oropharyngeal carriage of *K. kingae* during osteoarticular infection could be of interest for microbiological diagnosis. However, because healthy young children may be oropharyngeal carriers of *K. kingae*, interpreting positive culture or polymerase chain reaction (PCR) results is tricky. Evidence suggests that oropharyngeal carriage of *K. kingae* is a prerequisite for developing an invasive *K. kingae* infection; however, the pathophysiological mechanism of infection is not yet clearly understood.

For two decades, *K. kingae* has been increasingly shown to be associated with osteoarticular infection in young children, and it is now recognized as the leading pathogen of this type of infection in children younger than four years of age, accounting for as many as 80% of microbiologically confirmed cases in Israel2 and France,3 but also in Switzerland,1 Spain4 and now in Montréal.1 Between 1968 and 2000, about 120 cases of invasive *K. kingae* infections were reported, yet a recent review found 566 cases of osteoarticular infection involving the organism in the English-language literature between 2000 and 2014.5 This highlights improved detection of *K. kingae* owing to molecular techniques, as well as awareness of clinicians and microbiologists, more than a real “emergence” of the pathogen. In the 1990s, improvement in culture methods allowed for increased detection of *K. kingae* in synovial fluid. Furthermore, in a recent review, molecular methods such as 16S rRNA gene PCR,6 followed by *K. kingae*-specific real-time PCR targeting either the *cpn60* housekeeping gene7 or the *rtxA/rtxB* hemolysin genes1 showed a sensitivity of 99.5% (387/389 cases) for detecting *K. kingae* in children with osteoarticular infection. However, a sensitivity of 24.9% (68/273 cases) was observed with culture methods.7 Observational studies and reviews reported that most children with osteoarticular infection caused by *K. kingae* presented with limited clinical and biological inflammatory responses.2,8 However, whether clinical and biological features can discriminate between septic arthritis resulting from *K. kingae* and other pathogens remains unclear.2

**KEY POINTS**

- *Kingella kingae* is the leading pathogen associated with osteoarticular infection in young children in several countries.
- Carriage of *K. kingae* is common in the oropharynx of young children, reaching 10% prevalence in 12- to 24-month-old children; current evidence suggests capacity for transmission and dissemination.
- The pharynx is considered to be the portal of entry for invasive disease, and several virulence factors and environmental factors may play a role in the pathophysiology.
- Detection of *K. kingae* in the oropharynx may be useful for the diagnosis of osteoarticular infections, but additional data are needed to interpret positive results with confidence.

Worth bearing in mind, however, is that *K. kingae* is commonly found in the oropharynx of young children without evidence of invasive infection. A recent review found rates of carriage of *K. kingae* to be similar among children in Israel and Switzerland.2 *K. kingae* was not isolated before the age of six months, and the colonization rate was low at six months (1.5%), increased in 12-month-old children, remained relatively stable between 12 and 24 months of age (10%), and decreased at 30 months (5%).2 Additional data are now available from Montréal and New Zealand.1,7 Data from longitudinal studies suggest that colonization with *K. kingae* is a dynamic process; some children carry a given strain intermittently or continuously for up to eight months and others acquire and carry sequentially diverse strains.2 Simultaneous carriage of multiple strains appears to be uncommon. A close genetic association was observed between the strains isolated among siblings and in neighbourhoods, indicating transmission and dissemination of the clones, which could explain why attending a day-care centre represents an independent risk factor for carriage of *K. kingae*.2

Experimental and observational studies, as well as epidemiologic data, suggest that the oropharynx is the portal of entry for *K. kingae*. Indeed, identical genotypes were identified between the strains isolated in the oropharynx and joint fluid in cases of osteoarticular infection caused by *K. kingae*.6 Different virulence factors are well identified, such as a hemolytic RTX toxin, responsible for a wide-spectrum cytotoxic effect, especially against macrophages.
leukocytes, synoviocytes and respiratory epithelial cells; a type IV pilus, which plays a role in pathogen adherence to respiratory and synovial epithelia; and a polysaccharide capsule, four types of which were recently described globally, with types a and b representing more than 95% of the invasive isolates. In the largest international collection of *K. kingae* strains published to date, some major and international clones (sequence-type complexes 6, 14, 23, 25 and 35) were associated with specific clinical syndromes, but others appeared to be associated with carriage in Israel.

Bacterial characteristics and virulence factors cannot, however, fully explain the pathophysiology of invasive *K. kingae* infections. Indeed, the seasonal distribution of *K. kingae* invasive infections (which peak during the fall) and carriage (no substantial seasonality) appeared to be unrelated in different epidemiologic studies. No difference in the oropharyngeal bacterial load was shown between carriers and patients with osteoarticular infection, and the risk of a healthy carrier developing osteoarticular infection caused by *K. kingae* was assessed to be lower than 1% per year. Thus, it has been suggested that co-factors such as viral infections play a role in the *K. kingae* pathophysiology. Invasive *K. kingae* infections are frequently observed to precede or coexist with viral infections, and a recent prospective observational study showed that at least one respiratory virus was identified in the oropharynx of 90.5% of children with osteoarticular infection caused by *K. kingae* with human rhinovirus being predominant. Host susceptibility is likely to explain certain severe disease presentations. However, to the best of our knowledge, most children studied have not shown any underlying condition and, to date, no immune deficiency has been associated with *K. kingae* infections in the pediatric population; this is in contrast to what has been observed with severe *K. kingae* infections in adults.

The findings of the linked study show a strong association between detection of oropharyngeal *K. kingae* and osteoarticular infection, with an odds ratio of 38.3 (95% confidence interval 18.5–79.1). However, with a carriage rate among healthy children as high as 10% in some countries, relying on oropharyngeal detection as a proxy for diagnosis in the case of a joint infection would result in a high false-positive diagnosis. Additional data, such as genotyping, capsule typing or specific viral detection, would improve the performance of oropharyngeal screening.

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