**OBJECTIVES:** In this study, we aimed to contrast the bacteriologic epidemiology of osteoarticular infections (OAIs) between 2 patient groups in successive 10-year periods, before and after the extensive use of nucleic acid amplification assays in the diagnostic process.

**METHODS:** Epidemiologic data and bacteriologic etiologies of all children presenting with OAIs on admission to our institution over 20 years (1997–2016) were assessed retrospectively. The population was divided into 2 cohorts, using the standardized use of polymerase chain reaction as the cutoff point (2007). The conventional cohort included children with OAIs mainly investigated by using classic cultures, whereas the molecular cohort referred to patients also investigated by using molecular assays.

**RESULTS:** *Kingella kingae* was the most frequently isolated pathogen, responsible for 51% of OAIs, whereas other classic pathogens were responsible for 39.7% of cases in the molecular cohort. A statistically significant increase in the mean incidence of OAIs was observed, as was a decrease in the mean age at diagnosis after 2007. After 2007, the pathogen remained unidentified in 21.6% of OAIs in our pediatric population.

**CONCLUSIONS:** Extensive use of nucleic acid amplification assays improved the detection of fastidious pathogens and has increased the observed incidence of OAI, especially in children aged between 6 and 48 months. We propose the incorporation of polymerase chain reaction assays into modern diagnostic algorithms for OAIs to better identify the bacteriologic etiology of OAIs.

**WHAT'S KNOWN ON THIS SUBJECT:** *Staphylococcus aureus* is still currently considered the most common cause of osteoarticular infections across all pediatric age groups, accounting for 25% to 90% of all infections.

**WHAT THIS STUDY ADDS:** In this study, we provide further robust evidence that *Kingella kingae* has become the predominant causative pathogen of osteoarticular infections among the pediatric populations in European countries, especially among children aged between 6 and 48 months old.
Osteoarticular infections (OAIs) are serious, with potentially severe consequences for bone development and function. Identification of the causative organism is required to confirm the diagnosis and tailor the antibiotic therapy and thus optimize outcomes. Until recently, Staphylococcus aureus was considered the most common microorganism regardless of age. An understanding of the microbiologic causes of OAIs has evolved significantly in recent years, and the clinical and paraclinical findings of OAIs are currently considered to be closely correlated to children’s ages and the pathogens responsible. Indeed, it is now recognized that the pathogens responsible for pediatric OAIs depend on the child’s age, comorbidities, immune and vaccination statuses, socioeconomic conditions, changes in patterns of immunomodulating diseases, and the emergence of resistant bacteria. The BACTEC blood culture system, which enhances the rate of successful cultivation of Kingella kingae, and the use of molecular methods have increased the ability of detection of OAIs. In the current study, therefore, we aimed to assess the changing epidemiology of OAIs (in a single health district over 2 distinct successive periods) by using nucleic acid amplification assays (NAAAs) as the diagnostic test. We particularly looked at incidences, patient ages, types of OAI, and their bacteriologic etiology.

METHODS

After approval by the Children’s Hospital Ethics Review Committee (Children Ethics 14-102R), we retrospectively reviewed the medical charts of all the children aged from 0 to 15 years old who had been admitted to our institution between January 1997 and December 2016 for a suspected OAI. Our 111-bed tertiary pediatric hospital serves the city of Geneva and surrounding areas; it is the only facility providing 460 000 local inhabitants with inpatient and specialized medical services for pediatric OAIs. The cantonal population office’s annual statistical charts were used for epidemiologic analysis. Two distinct 10-year periods were defined: 1997 to 2006 and 2007 to 2016. January 2007 was chosen as the study’s midpoint because this was the time when our institution began to use large-scale polymerase chain reaction (PCR) assays, especially a real-time PCR assay specific to K. kingae.

Children’s risks of bone or joint infection were estimated by using criteria established by Morrey. The current study included cases of OAI confirmed by positive imaging studies (plain radiography, 99mTC bone scanning, MRI) and pathogen isolation in blood cultures and/or bone and/or joint fluid. Highly probable cases of OAI were analyzed for K. kingae by using imaging studies, clinical and laboratory data, and positive PCR assays on oropharyngeal swab specimens. Study exclusion criteria included chronic osteomyelitis or infections subsequent to an open fracture or surgery.

Microbiologic Methods

Blood cultures have been used systematically to isolate the microorganisms responsible for OAI. The blood culture media used in the current study were BACTEC 9000 (before 2009) and the BD BACTEC FX automated blood culture system (as of 2009). Joint fluid or bone aspirate samples were sent to the laboratory for Gram staining, cell count and immediate inoculation onto Columbia blood agar (incubated under anaerobic conditions), chocolate agar (incubated in a CO₂-enriched atmosphere), and brain–heart broth. These media were incubated for 10 days. Two PCR assays were also used for bacterial identification when standard culture results were negative. Initial aliquots (100–200 µL) were stored at −80°C until processing for DNA extraction. A universal, broad-range amplification of the 16S ribosomal RNA gene was performed using BAK11w, BAK2, and BAK533r primers for the detection of gram-negative bacteria at concentrations of 10²CFU per PCR (Eurogentec, Seraing, Belgium). From 2007, our institution also used a real-time PCR assay targeting the K. kingae gene’s RTX toxin. This assay was designed to detect 2 independent gene targets from the K. kingae RTX toxin locus, namely rtxA and rtxB. This PCR assay for detecting K. kingae was also used to analyze other biological samples, such as synovial fluid, bone or discal biopsy specimens, or even peripheral blood. Since September 2009, our institution has also been conducting oropharyngeal swab PCR for children aged from 6 months to 4 years. It has been demonstrated that this simple technique for detecting K. kingae RTX toxin genes in the oropharynx provides strong evidence that this microorganism is responsible for OAI or even stronger evidence that it is not.

Data Analyzed

Two cohorts were defined; the patient populations admitted from 1997 to 2006 and from 2007 to 2016 were labeled conventional and molecular, respectively. Multiple data fields were recorded for each cohort: sex, age at admission, type of OAI, location of infection, and the results of the bacteriologic investigations. Findings were then interpreted for the entire population together and with the consideration of children's
ages. Three patient categories were defined as follows: (1) a young infants group including infants <6 months old because this corresponds with the end of maternally derived immunity, (2) an older infants and toddlers group comprising children from 6 to 48 months old because *K. kingae* is recognized as primarily affecting children of this age, and (3) a juveniles and teenagers group including children older than 4 but younger than 16 years old.

### Statistical Analyses

Student *t* test results are presented as mean (SD), and χ² test results are presented as *n* (percentage). Differences between groups were considered to be significant at *P* < .05. Ten-year periods were used for the comparison of annual incidences.

### RESULTS

The study included 369 children, all of whom were admitted for an OAI (212 boys, 157 girls) during the 20 years considered, with ages ranging from 15 days to 15.7 years old. Patients involved were identified from a mean community population of 72 095 (SD 3129) children <16 years old. Thus, the average annual incidence of OAI during the 20 years studied was 25.5 new cases per 100 000 children per year. Four patients (3.1%) were younger than 6 months old, 60 (46.9%) were aged between 6 and 48 months old, and the remaining 65 (50%) were >4 years old. Overall, we recorded 52 cases of acute hematogenous osteomyelitis, 50 cases of septic arthritis, 10 cases of primary spine infections (spondylodiscitis or vertebral osteomyelitis), 9 cases of sacroiliitis, 5 cases of concomitant septic arthritis with osteomyelitis, 1 case of dactylitis with septic tenosynovitis, and 1 case of pyomyositis.

Pathogens were recovered from blood cultures in 27 (26.2%) of the 103 examinations performed. Standard isolation methods identified pathogens in 68 (59.1%) of the 115 bone biopsy specimen, joint fluid, or disk sample examinations conducted. The detection and identification of 2 additional cases of OAI due to *Borrelia burgdorferi* were made possible by using joint fluid serology. Identification of the microorganism was possible in 76 cases (59.4%), although in 13 cases, no bone biopsy, joint arthrocentesis, or disk aspiration biopsy was performed. The most commonly identified causative pathogens of OAI were cocc Gram-positive bacteria (59 cases, 45.7%), that is, methicillin-sensitive *S. aureus* (42 cases, 57.9%), *Streptococcus pyogenes* (11 cases, 14.5%), and *Streptococcus pneumoniae* (6 cases, 7.9%). Another germ was found in 13.2% of cases, whereas no germ was detected in 50 cases (40.6%) (Table 1). Only 1 infection due to *K. kingae* was recorded during this period.

### Molecular Period (2007–2016)

During this period, 241 children were admitted for an OAI (136 boys, 105 girls), with ages ranging from 15 days to 15.7 years old (mean: 51 ± 53.3 months). Patients were identified from a mean community population of 73 700 children (SD 1320) <16 years old. Thus, the average annual incidence of OAI during the second 10 years studied was 32.7 new cases per 100 000 children per year. Thirteen patients were <6 months old, 154 were aged between 6 and 48 months old, and the remaining 74 were >4 years old.

We recorded 89 cases of septic arthritis, 72 cases of acute hematogenous osteomyelitis, 29 cases of concomitant septic arthritis with osteomyelitis, 25 cases of primary subacute infections (osteomyelitis or osteoarthritis), 25 cases of primary spine infections (spondylodiscitis or vertebral osteomyelitis), 6 cases of sacroiliitis, 9 cases of septic tenosynovitis, 2 cases of septic chondritis, and 4 cases of pyomyositis. Three cases involved concomitant lesions (ie, osteomyelitis and pyomyositis, osteomyelitis and tenosynovitis).

Identification of the microorganism was possible in 151 patients (62.7%), either from blood (cultures or PCR) or in operative samples (cultures or PCR), and 31 patients (12.9%) had

### Table 1

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<tbody>
<tr>
<td>Age at diagnosis in mo, mean (SD)</td>
<td>72.2 (57.4)</td>
<td>51.0 (53.3)</td>
<td>&lt;.001&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.385</td>
<td>9.1 to 33.2</td>
</tr>
<tr>
<td>Mean annual incidence rate (SD) per 100 000 per y</td>
<td>18.3 (3.6)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>32.7 (5.4)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt;.001&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3.317</td>
<td>−18.7 to −10.0</td>
</tr>
</tbody>
</table>

*Student t* tests were used for results presented as mean (SD). Differences between groups were considered significant at *P* < .05. The effect size (ES) index is also provided. Negative values of the 95% confidence interval (CI) imply inferior annual incidence in the conventional period (1997–2006), comparing to the molecular period (2007–2016).

<sup>a</sup> *n* = 10 per group (number of years) for annual incidence comparison.

<sup>b</sup> *P* < .05 significant difference between groups.
positive blood culture results and positive operative samples. Pathogens were recovered from blood cultures in 40 (20.8%) of 192 examinations performed. In 11 additional cases, PCR assays were conducted after negative blood culture results, and microorganisms were identified in 8 of them (4.5%, all *K. kingae*). Pathogen identification in bone specimen, joint fluid, or discal biopsy specimens was possible in 60 (30.3%) of the 198 standard isolation experiments performed and in 83 additional cases when using PCR assays.

In 40 cases (16.6%), a bone aspirate or biopsy, joint arthrocentesis, or a disc aspiration biopsy was not performed. Of these, 25 cases were considered highly likely to be *K. kingae* infections because the patients were aged from 6 to 48 months old and presented positive osteoarticular symptomatology and positive oropharyngeal swab PCR. The most commonly identified causative pathogens of OAI were *K. kingae* (77 cases, 32%), far ahead of methicillin-sensitive *S. aureus* (50 cases, 20.7%), *S. pyogenes* (8 cases, 3.2%), and *S. pneumoniae* (2 cases, 0.8%). Other microorganisms were found in 21 cases (8.7%), whereas no microorganism could be identified in 52 cases (21.5%) (Table 2). When only considering the results of the 151 bacteriologically confirmed cases, *K. kingae* was responsible for 51% of OAI, and pyogenic bacteria were responsible for 39.7% of cases.

**DISCUSSION**

Since the 2000s, the increasing use of NAAAs in the diagnostic process for OAI significantly raised the ability of detection of fastidious pathogens and has changed contemporary bacteriologic epidemiology and the incidence of pediatric OAI. The current study revealed a statistically significant 79% rise in the mean annual incidence of OAI when we compared molecular versus conventional groups (Table 1). In recent literature, researchers have estimated incidences of OAI at <15 per 100 000 population (incidences of osteomyelitis ranging from 1 to 13 and joint infections from 1 to 4 per 100 000 population). However, the current study’s reported incidence of 32.7 cases per 100 000 children per year seems, instead, to confirm the conclusions of earlier studies in which researchers had reported significant increases in OAI rates.23–25,31

Analyzing the results by age group showed that the older infants and toddlers group was responsible for most of the statistically significant increase in the mean annual incidence; 2.4 times more cases were observed in the molecular decade than in the conventional decade group (Table 1). As shown in Table 2, a great increase was also observed for the young infants group between the 2 decades, but it was not statistically significant. On the other hand, as for juveniles and teenagers, the annual incidence remained almost unchanged during the conventional and molecular periods. The differences in the incidence of OAI between these 3 age groups can be explained by the distinct immune status of such age group. In young infants, defense against invasive infection is provided by vertically acquired immunity. Longitudinal investigations have shown low immunoglobulin G levels for 6-month-old children until their age of 18 months. Later on, immunoglobulin G levels are rising because of actively acquired immunity. Longitudinal investigations have shown low immunoglobulin G levels for 6-month-old children until their age of 18 months. Later on, immunoglobulin G levels are rising because of actively acquired immunity. Immunoglobulin A antibodies (found in breast milk and transferred to the infant’s gut) are almost undetectable at 2 months and then slowly increase from 4 to 7 months old, provided that the child is breastfed. Thus, this relatively deficient immunologic coverage exposes children aged 6 to 48 months to invasive infections, such as OAI. Furthermore, they risk greater exposure because of viral respiratory infections from social contacts, and these may damage upper respiratory surfaces and facilitate bloodstream invasions by the pathogens subsequently responsible for OAI.

In the current study, *K. kingae* was responsible for 51% of confirmed OAI in Geneva’s pediatric population, with the older infants and toddlers subgroup being responsible for that pathogen’s overall predominance (*P* < .001).

This provides evidence that *K. kingae* may have become the dominant pathogen of OAI in pediatric populations in other European countries, as well. To the best of our knowledge, only 1 other study, albeit with a shorter, 2-year follow-up, has presented *K. kingae* as the leading cause of OAI in children of all ages.32 The number of cases of OAI associated with *K. kingae* has increased markedly since the 1980s, and most current studies seem to demonstrate that *K. kingae* is the major bacterial cause of OAI in children from 6 to 48 months old (30%–93.8% of all culture-positive OAI).4,8,13–18 *K. kingae* OAI are characterized by mild-to-moderate clinical and biological inflammatory responses, which may explain why 20% to 70% of OAI had negative results from culture tests before the use of PCR assays, despite the collection of blood, joint fluid, and bone for standard cultures.1,34 Hence, the revealed modifications in microbial epidemiology of OAI in the pediatric Geneva population can be attributed to the spreading use of molecular diagnostic methods.11

The current study’s results do not corroborate those of previous publications, however, which still define *S. aureus* as the most common cause of OAI in pediatric age groups, accounting for 25% to 90% of all OAI.5,24,27,33,35–37 No confirmed Methicillin-resistant Staphylococcus aureus (MRSA) OAI were observed.
in the current study, which is in accordance with other European epidemiologic studies. Since 2000, OAIIs caused by MRSA have become an increasingly common problem, especially in the United States, where community-acquired (CA) MRSA has been reported to be the causative agent of 30% of pediatric OAIIs. However, we do not consider the emergence of CA MRSA can explain the difference in the bacteriologic epidemiology of OAIIs noted between these studies and ours. Most of these studies did not use PCR assays, and there were many cases with unidentified pathogens, ranging from 44% to 55%. Thus, one could assume that many cases without an identifiable microorganism were OAIIs attributable to *K. kingae*. Finally, because of the incidence of MRSA infections in the United States, we can hypothesize that *K. kingae* may be less predominant there than in Europe.

Nevertheless, the fact that no microorganisms were detected in 21.6% (52 out of 241) of the molecular period’s OAIIs remains a problem, despite the broad use of NAAAs for this group; most of those cases (38 out of 52) were in the 6 to 48 months age group. One possible explanation could be the lack of sensitivity of the real-time PCR assay used in the current study because it targeted the RTX locus. El Houmami et al recently reported the design of a novel real-time PCR assay targeting *K. kingae*’s malate dehydrogenase (mdh) enzyme; this was developed with no nucleotide mismatches between DNA sequences of primers and probes and with 18 variants of the *K. kingae* mdh gene. Their new, highly sensitive and highly specific real-time PCR assay targeting *K. kingae*’s mdh gene detected 7 new OAIIs caused by *K. kingae* that had previously been found negative using previously negative using a specific real-time PCR test targeting its groEL gene and the RTX locus of *K. kingae*. Moreover, part of the 21.6% of cases of suspected OAIIs may have been caused by unidentified pathogens for which no specific probe is currently available. The newly

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**TABLE 2 Etiology of Bacterial OAI by Age Groups in the Conventional and Molecular Diagnostic Decades**

<table>
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<tbody>
<tr>
<td></td>
<td><em>n</em> = 4</td>
<td><em>n</em> = 13</td>
<td><em>P</em></td>
</tr>
<tr>
<td><strong>No cases, germs, (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>K. kingae</em></td>
<td>0 (0)</td>
<td>1 (9)</td>
<td>&gt;999</td>
</tr>
<tr>
<td>Suspected <em>K. kingae</em></td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>&gt;999</td>
</tr>
<tr>
<td>Pyogenic bacteria</td>
<td>2 (50)</td>
<td>5 (58)</td>
<td>&gt;999</td>
</tr>
<tr>
<td>Others</td>
<td>1 (25)</td>
<td>5 (58)</td>
<td>&gt;999</td>
</tr>
<tr>
<td>No pathogen</td>
<td>1 (25)</td>
<td>2 (15)</td>
<td>&gt;999</td>
</tr>
<tr>
<td><strong>6–48 mo</strong></td>
<td><em>n</em> = 60</td>
<td><em>n</em> = 154</td>
<td></td>
</tr>
<tr>
<td>Annual incidence rate, mean (SD)</td>
<td>31.5 (13.7)b</td>
<td>77.2 (14.0)b</td>
<td>&lt;.001c</td>
</tr>
<tr>
<td>No cases, germs, (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>K. kingae</em></td>
<td>1 (2)</td>
<td>79 (51)</td>
<td>&lt;.001c</td>
</tr>
<tr>
<td>Suspected <em>K. kingae</em></td>
<td>0 (0)</td>
<td>25 (16)</td>
<td>&gt;999</td>
</tr>
<tr>
<td>Pyogenic bacteria</td>
<td>16 (27)</td>
<td>6 (4)</td>
<td>&lt;.001c</td>
</tr>
<tr>
<td>Others</td>
<td>10 (18)</td>
<td>6 (4)</td>
<td>&gt;999</td>
</tr>
<tr>
<td>No pathogen</td>
<td>33 (55)</td>
<td>38 (25)</td>
<td>&lt;.001c</td>
</tr>
<tr>
<td><strong>&gt;4 y</strong></td>
<td><em>n</em> = 65</td>
<td><em>n</em> = 74</td>
<td></td>
</tr>
<tr>
<td>Annual incidence rate, mean (SD)</td>
<td>13.8 (4.0)b</td>
<td>15.0 (4.8)b</td>
<td>.549</td>
</tr>
<tr>
<td>No cases, germs, (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>K. kingae</em></td>
<td>0 (0)</td>
<td>3 (4)</td>
<td>&gt;999</td>
</tr>
<tr>
<td>Suspected <em>K. kingae</em></td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>&gt;999</td>
</tr>
<tr>
<td>Pyogenic bacteria</td>
<td>41 (63)</td>
<td>49 (68)</td>
<td>&gt;999</td>
</tr>
<tr>
<td>Others</td>
<td>8 (12)</td>
<td>10 (14)</td>
<td>&gt;999</td>
</tr>
<tr>
<td>No pathogen</td>
<td>16 (25)</td>
<td>12 (16)</td>
<td>&gt;999</td>
</tr>
</tbody>
</table>

---

Student *t* tests were used when results are presented as mean (SD), and *χ*² tests were used when they are presented as % differences between groups were considered significant at *P* < .05. The effect size (ES) index is also provided. CI, confidence interval; —, not applicable.

a Pyogenic bacteria: *S. aureus*, *Streptococcus agalactiae*, *S. pneumoniae*, *S. pyogenes*.

b *n* = 10 per group (number of years) for annual incidence comparison.

c *P* < .05 significant difference between groups.
described species, Kingella negevensis, is particularly interesting.42–44 Closely related to K kingae, it has been isolated in both Israel and Switzerland from the oropharynxes of healthy children and seems to validate the hypothesis that part of the suspected OAI may have been caused by pathogens for which no specific probe was available.42,43 K negevensis’ DNA was also detected in an infant’s hip joint fluid, indicating that this pathogen may also now be considered as responsible for OAIs in young infants.44–46 Furthermore, although a rare occurrence in pediatric patients, some OAIs diagnosed as septic arthritis or septic osteomyelitis may have been the early manifestations of rheumatoid disease or related conditions or may even have been caused by viral pathogens.

The current study has the limitations of being retrospective and including children from a single medical center. As stated above, in Europe, OAIs resulting from CA MRSA remain relatively uncommon, confirming the different bacteriologic epidemiology of OAIs between countries. Our current findings may be neither generalizable nor applicable to other populations. They do reveal an interesting observation in our tertiary institution, and we recommend that further investigations use worldwide prospective studies to confirm whether K kingae is the current main pathogen for OAIs in pediatric populations. Additionally, other fastidious microorganisms involved in OAIs have yet to be recognized as pathogens, and further efforts should be made to develop new techniques to identify them, focusing on the age group from 6 to 48 months old because most OAIs of unknown etiology appear in this age group.

**ABBREVIATIONS**

CA: community-acquired  
mdh: malate dehydrogenase  
MRSA: Methicillin-resistant Staphylococcus aureus  
NAAA: nucleic acid amplification assay  
OAI: osteoarticular infection  
PCR: polymerase chain reaction

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Kingella kingae and Osteoarticular Infections
Eleftheria Samara, Vasiliki Spyropoulou, Anne Tabard-Fougère, Laura Merlini, Raimonda Valaikaite, Amira Dhouib, Sergio Manzano, Céline Juchler, Romain Dayer and Dimitri Ceroni
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