

# Outbreak of Osteomyelitis/Septic Arthritis Caused by *Kingella kingae* Among Child Care Center Attendees

Karen M. Kiang, MD\*§; Folashade Ogunmodede, MBBS, MPH\*; Billie A. Juni, MS‡; David J. Boxrud, MS‡; Anita Glennen, BS‡; Joanne M. Bartkus, PhD‡; Elizabeth A. Cebelinski, BS‡; Kathleen Harriman, PhD, MPH, RN\*; Steven Koop, MD||; Ralph Faville, MD||; Richard Danila, PhD, MPH\*; and Ruth Lynfield, MD\*

**ABSTRACT.** *Objective.* *Kingella kingae* often colonizes the oropharyngeal and respiratory tracts of children but infrequently causes invasive disease. In mid-October 2003, 2 confirmed and 1 probable case of *K kingae* osteomyelitis/septic arthritis occurred among children in the same 16- to 24-month-old toddler classroom of a child care center. The objective of this study was to investigate the epidemiology of *K kingae* colonization and invasive disease among child care attendees.

*Methods.* Staff at the center were interviewed, and a site visit was performed. Oropharyngeal cultures were obtained from the staff and children aged 0 to 5 years to assess the prevalence of *Kingella* colonization. Bacterial isolates were subtyped by pulsed-field gel electrophoresis (PFGE), and DNA sequencing of the 16S rRNA gene was performed. A telephone survey inquiring about potential risk factors and the general health of each child was also conducted. All children and staff in the affected toddler classroom were given rifampin prophylaxis and recultured 10 to 14 days later. For epidemiologic and microbiologic comparison, oropharyngeal cultures were obtained from a cohort of children at a control child care center with similar demographics and were analyzed using the same laboratory methods. The main outcome measures were prevalence and risk factors for colonization and invasive disease and comparison of bacterial isolates by molecular subtyping and DNA sequencing.

*Results.* The 2 confirmed case patients required hospitalization, surgical debridement, and intravenous antibiotic therapy. The probable case patient was initially misdiagnosed; MRI 16 days later revealed evidence of ankle osteomyelitis. The site visit revealed no obvious outbreak source. Of 122 children in the center, 115 (94%) were cultured. Fifteen (13%) were colonized with *K kingae*, with the highest prevalence in the affected toddler classroom (9 [45%] of 20 children; all case patients tested negative but had received antibiotics). Six colonized children were distributed among the older classrooms; 2 were siblings of colonized toddlers. No staff ( $n = 28$ ) or children aged <16 months were colonized. Isolates from

the 2 confirmed case patients and from the colonized children had an indistinguishable PFGE pattern. No risk factors for invasive disease or colonization were identified from the telephone survey. Of the 9 colonized toddlers who took rifampin, 3 (33%) remained positive on reculture; an additional toddler, initially negative, was positive on reculture. The children of the control child care center demonstrated a similar degree and distribution of *K kingae* colonization; of 118 potential subjects, 45 (38%) underwent oropharyngeal culture, and 7 (16%) were colonized with *K kingae*. The highest prevalence again occurred in the toddler classrooms. All 7 isolates from the control facility had an indistinguishable PFGE pattern; this pattern differed from the PFGE pattern observed from the outbreak center isolates. 16S rRNA gene sequencing demonstrated that the outbreak *K kingae* strain exhibited >98% homology to the ATCC-type strain, although several sequence deviations were present. Sequencing of the control center strain demonstrated more homology to the outbreak center strain than to the ATCC-type strain.

*Conclusions.* This is the first reported outbreak of invasive *K kingae* disease. The high prevalence in the affected toddler class and the matching PFGE pattern are consistent with child-to-child transmission within the child care center. Rifampin was modestly effective in eliminating carriage. DNA sequence analysis suggests that there may be considerable variability within the species *K kingae* and that different *K kingae* strains may demonstrate varying degrees of pathogenicity. *Pediatrics* 2005;116:e206–e213. URL: [www.pediatrics.org/cgi/doi/10.1542/peds.2004-2051](http://www.pediatrics.org/cgi/doi/10.1542/peds.2004-2051); *Kingella kingae*, *osteomyelitis*, *septic arthritis*.

ABBREVIATIONS. MDH, Minnesota Department of Health; PHL, Public Health Lab; PFGE, pulsed field gel electrophoresis; rRNA, ribosomal RNA; MIC, minimum inhibitory concentration; WBC, white blood cell; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

From the \*Acute Disease Investigation and Control Section and the ‡Public Health Laboratory, Minnesota Department of Health, Minneapolis, Minnesota; §Epidemic Intelligence Service, Epidemiology Program Office, Centers for Disease Control and Prevention, Atlanta, Georgia; and ||Gillette Children's Hospital, St Paul, Minnesota.

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Address correspondence to Ruth Lynfield, MD, Section of Acute Disease Investigation and Control, Minnesota Department of Health, 717 Delaware St, SE, Minneapolis, MN 55414. E-mail: [ruth.lynfield@health.state.mn.us](mailto:ruth.lynfield@health.state.mn.us)  
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Although *Staphylococcus aureus* and *Streptococcus pyogenes* account for >60% of culture-confirmed pediatric skeletal infections,<sup>1–4</sup> *Kingella kingae* is becoming increasingly recognized as another important cause.<sup>5–16</sup> *K kingae* is a fastidious Gram-negative coccobacillus that was first described in the 1960s as a species of *Moraxella*. It was later reclassified into its own genus, *Kingella*.<sup>5,8,9</sup> *K kingae* is a known oropharyngeal colonizer and occasionally causes invasive disease in young, healthy

children, primarily osteomyelitis and septic arthritis, bacteremia, and endocarditis.<sup>5–25</sup>

The documented occurrence of invasive disease that is caused by *K kingae* is uncommon, although infections that are caused by this organism are likely underdiagnosed. Only sporadic, nonepidemiologically linked cases have been reported to date. In 2003, we investigated an outbreak of skeletal infections caused by *K kingae* among children in a child care center. This article details our investigation and represents the first reported outbreak of *K kingae* invasive disease.

## METHODS

### Background

In October 2003, the Minnesota Department of Health (MDH) was notified of 3 (2 culture-confirmed, 1 probable) cases of skeletal infection caused by *K kingae* among children who attended the same toddler classroom of a child care center. All presented within the same week with fever and limp. The 2 culture-confirmed case patients had been hospitalized at the same medical center, where the epidemiologic link between the cases was established.

### Epidemiologic Investigation

The parents of the 3 case patients were interviewed regarding their child's clinical course, and their child's medical records were reviewed. Child care center staff were interviewed, and a site visit was performed to elicit detailed information about the number and age distribution of the attendees, classroom organization, staffing, daily schedules and operations, physical layout of the building, and routine sanitation practices. Attendance rosters were obtained, and absentee, illness, and biting records were reviewed.

A cohort study was conducted to determine potential risk factors for illness or colonization. Parents were interviewed by telephone regarding their child's recent illness history; recent antibiotic use, breastfeeding, bite, and dental history; and history of exposure to household tobacco smoke and animals. Immunization records were obtained from each child's physician.

Invasive disease cases were compared with asymptomatic colonized children in their classroom. Colonized children were compared with noncolonized children within the toddler 1 classroom and within the entire center. Bivariate analyses were performed on dichotomous variables using the  $\chi^2$  test. Student *t* tests were used for comparisons involving continuous variables. Statistical analyses were performed using SAS version 8.2 (SAS Institute Inc, Cary, NC).

All clinical and reference laboratories in Minnesota and border areas of adjoining states were queried electronically for information regarding all *K kingae* culture-positive specimens identified from January 1, 2003, to the time of the outbreak and for cases of culture-negative joint fluid or bone specimens in children aged  $\leq 5$  years. Telephone calls were placed to parents of all children who attended the toddler 1 class during the year preceding the outbreak to ascertain additional cases of skeletal infections.

### Laboratory Methods

The *K kingae* isolates from the 2 case patients were sent to the MDH Public Health Laboratory (PHL) for confirmation, pulsed-field gel electrophoresis (PFGE) subtyping, antimicrobial susceptibility testing, and DNA sequencing. To determine the prevalence of *K kingae* colonization, we obtained oropharyngeal cultures on the staff and children from the infant, toddler, and preschool classrooms after parental informed consent was obtained. Swabs were brought in transport medium (liquid Stuart medium; Fisherbrand Transport Swabs, Houston, TX) to the MDH PHL and cultured within 4 hours. Swabs were plated onto 1 plate each of trypticase-soy agar with 5% sheep blood with and without 2  $\mu\text{g}/\text{mL}$  vancomycin. Vancomycin was used to suppress the growth of other oropharyngeal bacteria.<sup>26</sup> Culture plates were incubated at 37°C in CO<sub>2</sub> and observed after 48 hours of incubation. Cultures were screened visually for colonies compatible with *K kingae*. Suspect colonies were isolated, and conventional metabolic and morphologic tests were performed for identification.

PFGE was performed using a modified PulseNet protocol.<sup>27</sup> Modifications included no proteinase K in plug preparation, *Eag1* used as the restriction endonuclease, the initial switch time of 2.2 seconds, and final switch time of 37.3 seconds. PFGE patterns were compared visually and using BioNumerics Software (Applied Maths, Kortrijk, Belgium) with the Dice coefficient. Strains with indistinguishable PFGE patterns were considered to be the same subtype.

National Committee for Clinical Laboratory Standards antimicrobial susceptibility breakpoints are not established for *K kingae*. Three specific antimicrobials (rifampin, penicillin, and azithromycin) were evaluated. Susceptibility testing was performed on the 2 confirmed case patients' isolates by 2 methods: (1) microdilution panel that contained Mueller-Hinton broth with 5% lysed horse blood and (2) Etest on Mueller-Hinton agar with 5% sheep blood. Incubation in ambient air for 24 hours was satisfactory for most isolates. Because the 2 methods produced similar results, the Etest method was performed on all subsequent child care isolates.

For genetic sequencing, genomic DNA was extracted using a routine method. A 1500 base pair fragment of the 16S ribosomal RNA (rRNA) gene was amplified from extracted DNA by polymerase chain reaction using primers rD1 and rP1.<sup>28</sup> Amplification products were purified and sequenced on a Beckman CEQ 8000 automated DNA sequencer using Beckman DTCs reagents (Beckman Coulter, Fullerton, CA). DNA sequences were edited and analyzed using Sequencher (Gene Codes, Ann Arbor, MI) and Vector NTI Suite (InforMax, Bethesda, MD), respectively. Obtained sequences were compared with archived sequences for strain identification by conducting searches of rDNA databases.

### Intervention

Preliminary antimicrobial susceptibility testing performed on the 2 confirmed case patients' isolates demonstrated a rifampin minimum inhibitory concentration (MIC) of 0.064  $\mu\text{g}/\text{mL}$ . Considering the high illness rate within the toddler 1 classroom and the concern that this *K kingae* isolate might be a more virulent strain than those previously seen, we recommended that all children and staff in the classroom be administered a short prophylactic course of rifampin (2 mg/kg per dose up to 600 mg per dose for adults, twice daily for 2 days) immediately after undergoing oropharyngeal swabbing. Each parent and staff member was contacted, and recommendations for prophylaxis were discussed. They were recultured 10 to 14 days after completion of rifampin. In addition, the staff performed a thorough cleaning and disinfection of the facility classrooms, surfaces, and toys.

### *K kingae* Colonization Prevalence Study of a Control Child Care Center

To assess the prevalence and colonizing strains of *K kingae* in a child care center without invasive disease, we obtained oropharyngeal cultures on children from a second large suburban child care center from the same commercial chain and with similar demographics to the outbreak facility. Children in the toddler and preschool classrooms were eligible to participate, and informed consent was obtained from their parents. Swabs were analyzed using the same laboratory methods as above. Colonized children did not receive treatment.

## RESULTS

### Case Reports

Case patient 1 was a 21-month-old boy who had a history of prematurity (32 weeks' gestation) and presented in mid-October with 6 days of progressive limp and fever of 103°F (39.4°C). His white blood cell (WBC) count and erythrocyte sedimentation rate (ESR) were normal. A right hip radiograph showed an abnormality in the proximal femur, which was diagnosed as a possible fracture. His limp deteriorated to a crawl, and he underwent surgery 7 days after initial presentation. He received a diagnosis of femoral neck osteomyelitis and hip septic arthritis, which required extensive surgical debridement. At the time of surgery, his WBC count and ESR were

slightly elevated (17 200 cells per mm<sup>3</sup> and 51 mm/hour, respectively), and his C-reactive protein (CRP) was normal (<0.5 mg/dL). Gram stain of bone exudate showed many WBCs but no organisms. Synovial swab and bone exudate cultures became positive for a Gram-negative organism after 3 days of incubation; *K kingae* was identified after 5 days of incubation. He was initially treated with intravenous cefazolin and switched to intravenous piperacillin/tazobactam when a Gram-negative organism was recovered. On discharge, he was treated with piperacillin/tazobactam for 3 more weeks, then changed to oral amoxicillin/clavulanic acid for the final 2 weeks of treatment.

Case patient 2 was a healthy 20-month-old girl who had finished a 14-day course of amoxicillin/clavulanic acid for otitis media in early October. In mid-October, she presented with irritability, refusal to bear weight on her right foot, and a warm right ankle. In the following 4 days, she developed a fever to 101.6°F (38.7°C), and her right ankle became swollen and red. An MRI revealed fluid in her ankle joint. She had a normal WBC count and slightly elevated ESR (7700 cells per mm<sup>3</sup> and 38 mm/hour, respectively). She underwent surgical drainage for ankle and subtalar septic arthritis. Gram stain of synovial fluid was negative, but *K kingae* was identified from culture after 4 to 5 days of incubation. She was initially treated with intravenous cefazolin and switched to piperacillin/tazobactam when a Gram-negative organism was identified. Maintaining intravenous access was difficult, so she was discharged on oral amoxicillin/clavulanic acid for 4 weeks.

Case patient 3 was a healthy 17-month-old boy who presented to the emergency department in mid-October with irritability, a limp for 2 days, refusal to bear weight on his right leg, and a temperature of 102°F (38.9°C). His right ankle was moderately warm and swollen on physical examination. His ankle radiographs were normal. His WBC count was normal (12 500 cells per mm<sup>3</sup>), and CRP was slightly elevated (1.27 mg/dL). He received a diagnosis of reactive synovitis and otitis media, was given a 7-day course of oral amoxicillin, and was discharged from the emergency room. Although his clinical picture improved, he continued to limp after foot manipulation; MRI of his right ankle 16 days later revealed evidence of distal tibial osteomyelitis. He was treated

conservatively with serial examinations and radiographic studies without additional antibiotics. No specimens were obtained for culture.

All 3 case patients had upper respiratory infection symptoms preceding or concurrent with their skeletal infections. A singular aphthous ulcer was noted at the time of case patient 3's illness and a few weeks before case patient 2's illness; widespread stomatitis, a condition documented in other cases of *K kingae* invasive disease, was not present.

### Child Care Center Investigation

The child care center was a 170-child facility in suburban Minneapolis. Classrooms were organized by ascending age (Table 1). All 3 initial case patients attended the toddler 1 classroom. Two to 3 staff members were assigned to each classroom, with minimal crossover of staff between classrooms. The toddler 1 and 2 classrooms were combined during the early mornings and late afternoons, and the children interacted daily on the outside playground. Otherwise, all children played in their specific classrooms, which were divided by physical barriers (walls or sliding glass doors). No unusual practices, behaviors, or obvious sources were identified to explain this cluster of illnesses.

We obtained oropharyngeal cultures from 115 (94%) of 122 children and 28 (97%) of 29 staff from the infant, toddler, and preschool classrooms. Fifteen (13%) children were colonized with *K kingae* (Table 1). The highest prevalence occurred in the affected (toddler 1) classroom, where 9 (45%) of 20 tested positive. The 3 case patients tested negative, but all had recently received antibiotics. The remaining 6 colonized children were distributed among 3 classrooms of older children (Table 1); 2 were siblings of colonized children in the toddler 1 classroom. In addition, a child in preschool 3 was colonized with a *Kingella* species with biochemical characteristics that did not correspond to a described *Kingella* species. No staff or children aged <16 months (*n* = 14) were colonized.

The *K kingae* isolates from the case patients and the colonized children had an indistinguishable PFGE pattern. The *Kingella* species isolate from the preschool 3 child, as well as 3 clinical isolates from unrelated sources and 2 control isolates, showed dif-

**TABLE 1.** Outbreak Child Care Center: Baseline Characteristics, Parental Interview Rate, and Prevalence of *K kingae* Oropharyngeal Colonization According to Classroom

Classroom	Age, mo	Classroom Size, <i>N</i> (122 Eligible for Interview/Culture)	Interviewed, <i>n</i> (%)	Cultured, <i>n</i> (%)	Colonized, <i>n</i> (%)
Infant	<16	16	11 (69)	14 (88)	0
Toddler 1	16–24	21	20 (95)	20 (95)	9 (45)
Toddler 2	25–32	17	16 (94)	17 (100)	2 (12)
Preschool 1	33–35	19	16 (84)	16 (84)	2 (13)
Preschool 2	36–47	19	17 (89)	18 (95)	2 (11)
Preschool 3	48–59	30	28 (93)	30 (100)	0*
School age	>60	48	—	—	—
Total		170	108 (89)	115 (94)	15 (13)

\* One child was colonized with a *Kingella* species with biochemical characteristics that did not correspond to a described *Kingella* species.

ferent PFGE patterns with different degrees of genetic variability (Fig 1).

Antimicrobial susceptibility testing by Etest of the outbreak isolates (isolates from the case patients and colonized children with an indistinguishable PFGE pattern) demonstrated a MIC range of 0.064 to 0.125  $\mu\text{g}/\text{mL}$  to rifampin, a MIC range of 0.023 to 0.047  $\mu\text{g}/\text{mL}$  to penicillin, and MICs of  $\leq 0.032$   $\mu\text{g}/\text{mL}$  to azithromycin. DNA sequencing of the 16S rRNA gene demonstrated that the outbreak strain exhibited  $>98\%$  homology to the ATCC-type strain. The DNA sequences of the first 500 base pairs were nearly 100% homologous; the sequence differences between the 2 strains occurred among the remaining 1000 base pairs (Fig 2).<sup>29,30</sup> A search of the RIDOM 16S rRNA database showed no close relative of the *Kingella* species identified in the preschool 3 child.<sup>31</sup>

Parents or guardians of 108 (89%) children completed the telephone questionnaire (Table 1). No statistically significant risk factors for invasive disease or for colonization were identified within either the toddler 1 class or the center as a whole (Table 2).

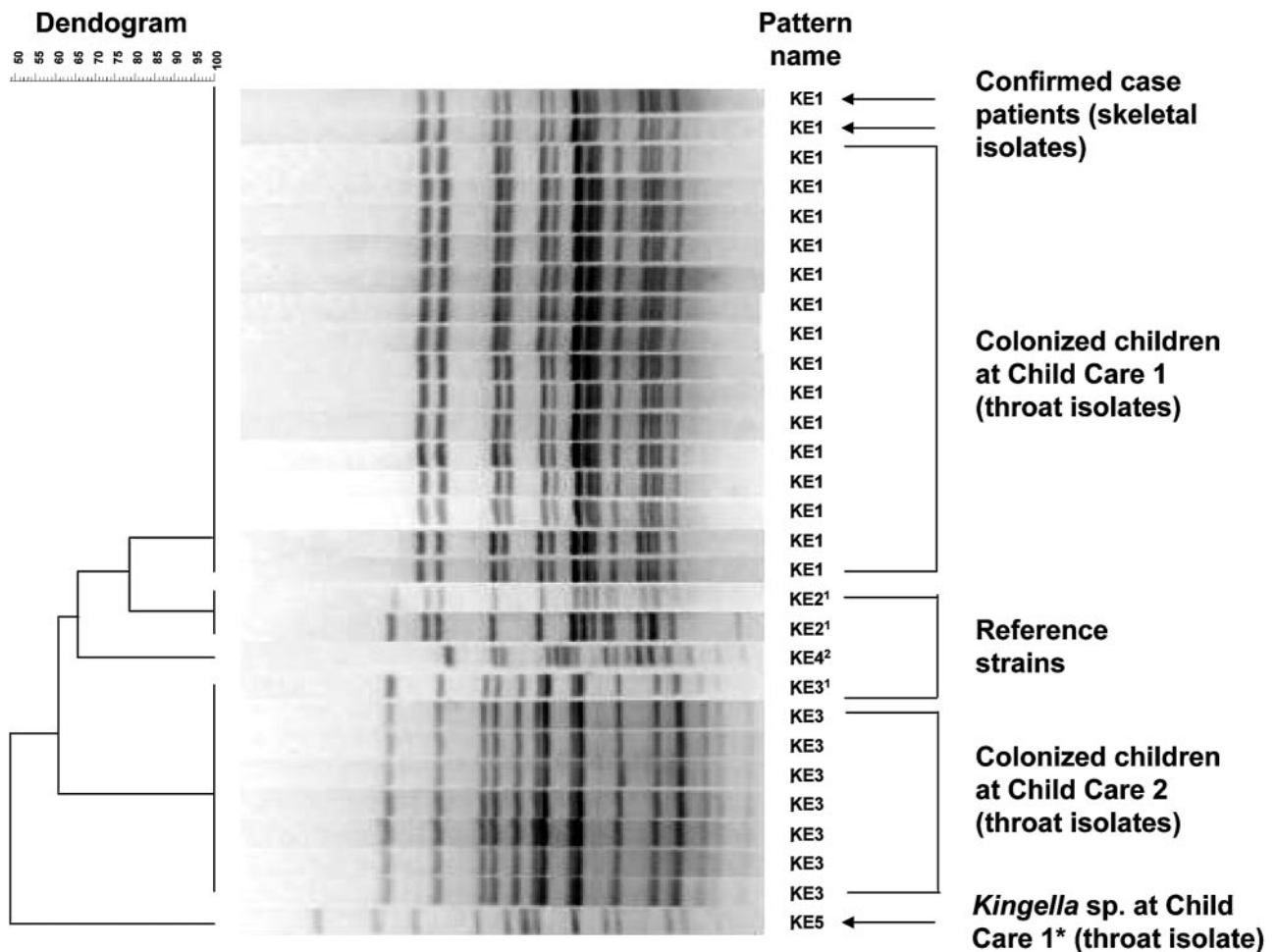
### Toddler 1 Postrifampin Cultures

Every toddler 1 child and staff member received rifampin prophylaxis. Of the 9 originally colonized

toddler 1 children, 3 (33.3%) remained positive for *K kingae* on reculture 10 to 14 days later. An additional toddler, who was initially negative on the first culture, was positive for *K kingae* on reculture. None of the staff members was positive. The bacterial isolates from these repeat swabs ( $n = 4$ ) were indistinguishable from the initial isolates by PFGE analysis and antimicrobial susceptibility results.

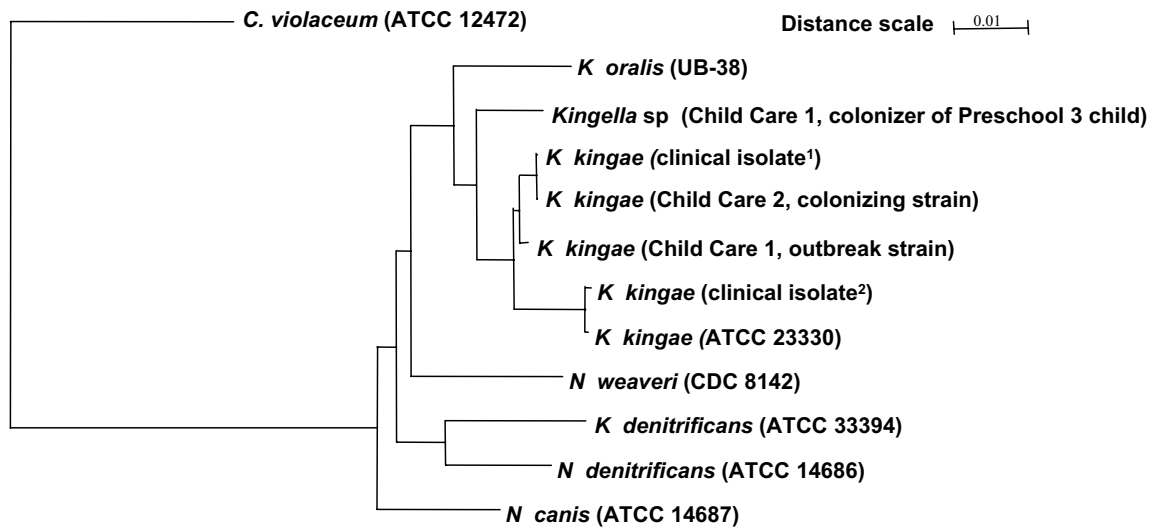
### Laboratory Query and Historical Look-Back

All laboratories ( $n = 116$ ) responded to our request for information. In total, 1 clinical laboratory in the Minneapolis area reported 2 specimens that were culture positive for *K kingae* during January to November 2003. Both specimens were taken from adult outpatients. Two cases of culture-negative joint infection in young children were reported, but most laboratories could not provide this information because of limitations in their computer systems. The look-back of all children who were enrolled in the toddler 1 classroom during the 12 months preceding the outbreak revealed 2 additional children with culture-negative joint infections (November 2002 and March 2003, respectively), both requiring hospitalization.



**Fig 1.** PFGE results of *K kingae* isolates from the confirmed case patients and colonized children of the outbreak child care center and colonized children from the control child care center. *EagI* was the restriction enzyme used in the analysis. Child care 1 is the outbreak child care center; child care 2 is the control child care center. \**Kingella* species isolate with biochemical characteristics that did not correspond to a described *Kingella* species. Reference *K kingae* isolates: <sup>1</sup>clinical isolates from unrelated sources; <sup>2</sup>ATCC 23330.

A.



B.

	113	253	274	598	990	1002	1026	1120
Child Care 1	A	C	T	C	TCTTC	GGAAGA	A	T
Clinical isolate <sup>2</sup>	A	T	T	C	GAGAG	ACTCIT	G	A
ATCC 23330	A	C	T	C	GAGAG	ACTCIT	G	A
Clinical isolate <sup>1</sup>	G	C	C	T	TCTTC	GGAAGA	A	A
Child Care 2	G	C	C	T	TCTTC	GGAAGA	A	A

Fig 2. DNA sequence analysis of the 16S rRNA gene of the *Kingella* species isolates. A, Phylogenetic tree of *Kingella* isolates showing sequence homologies. Data analysis was performed using PHYLIP<sup>29</sup> software interfaced through the Ribosomal Database Project (RDP).<sup>30</sup> A distance matrix was calculated by the Kimura 2-parameter method, and the phylogenetic tree was cast using the neighbor joining method. The tree includes partial 16S rDNA sequence data from study isolates of *K kingae* as well as sequences from other related *Kingella* and *Neisseria* species sequences present in the RDP database. The 16S sequence from *C violaceum* was used to root the tree. B, Sequence differences between strains of *K kingae*. Child care 1 is the outbreak child care center; child care 2 is the control child care center. The GenBank accession numbers for isolates sequenced at MDH PHL are AY551999 (*K kingae* ATCC 23330), AY551996 (child care 1, outbreak strain), AY628416 (child care 2, colonizing strain), AY551997<sup>2</sup> and AY551998<sup>1</sup> (clinical isolates), AY644511 (*Kingella* species, child care 1, colonizing strain of preschool 3 child). Clinical isolates from unrelated sources: <sup>1</sup>PFGE pattern KE3 on Fig 1; <sup>2</sup>PFGE pattern KE2 on Fig 1.

TABLE 2. Characteristics and Risk Factors of Ill, Colonized, and Noncolonized Children

	Ill, <i>n</i> (%) ( <i>N</i> = 3)	Colonized in Toddler 1, <i>n</i> (%) ( <i>N</i> = 10)	Noncolonized in Toddler 1, <i>n</i> (%) ( <i>N</i> = 7)	Colonized in Center, <i>n</i> (%) ( <i>N</i> = 16)	Noncolonized in Center, <i>n</i> (%) ( <i>N</i> = 95)*
Antibiotics within 3 mo	2 (67)	3 (30)	2 (29)	4 (25)	25/87 (29)
URI symptoms within 3 mo	3 (100)	9 (90)	6 (86)	14 (88)	79/88 (90)
Median (mean) number of ear infections	3.0 (2.3)	2.5 (5.1)	4.0 (4.3)	2.0 (4.9)	3.0 (4.7)
Chronic medical condition†	2 (67)	3 (30)	2 (29)	6 (38)	27/87 (31)
Invasive bacterial infection in past‡	0	0	0	0	7/87 (8)
Hospitalizations for any illness in past	2 (67)	1 (10)	0	2 (13)	7/86 (8)
Breastfed	3 (100)	6 (60)	4 (57)	12 (75)	57/86 (66)
Smoker in house	1 (33)	3 (30)	1 (14)	4 (25)	21/87 (24)
Pets in house	2 (67)	6 (60)	4 (57)	9 (56)	43/87 (49)
Any PCV-7 vaccine	3 (100)	10 (100)	6 (86)	16 (100)	74/93 (80)
Completed PCV-7 vaccine series	3 (100)	8 (80)	4 (57)	11 (69)	59/93 (63)
<i>H influenzae</i> vaccine	3 (100)	10 (100)	7 (100)	16 (100)	88/92 (96)

PCV-7 indicates Pneumococcal conjugate vaccine-7.

\* Percentages are based on the number of patients for whom information was available; some parents did not recall the information.

† Chronic medical condition; includes chronic otitis media, allergies, and chronic sinusitis.

‡ Invasive bacterial infection; includes pneumonia, meningitis, and bacteremia.

### *K kingae* Colonization Prevalence Study of a Control Child Care Center

Of 118 children who were enrolled in the toddler and preschool classes of the control child care center,

45 (38%) underwent oropharyngeal culture and 7 (16%) were colonized with *K kingae* (Table 3). The highest prevalence occurred in the toddler 1 classroom, followed by the toddler 2 classroom. All 7 *K*

**TABLE 3.** Control Child Care Center: Prevalence of *K kingae* Oropharyngeal Colonization According to Classroom

Classroom	Age, mo	Class Size, N	Cultured, n (%)	Colonized, n (%)
Toddler 1	15–20	15	4 (27)	3 (75)
Toddler 2	20–29	14	8 (57)	2 (25)
Preschool 1	29–36	18	6 (33)	1 (17)
Preschool 2	36–48	24	8 (33)	1 (13)
Preschool 3	42–54	18	10 (56)	0
Preschool 4	48–60	29	9 (31)	0
Total		118	45 (38)	7 (16)

*kingae* isolates from the control facility had an indistinguishable PFGE pattern; this pattern was different from the PFGE pattern observed from the outbreak center's isolates (Fig 1). DNA sequencing of the 16S rRNA gene demonstrated that the control center's strain was more homologous to the outbreak center's strain than to the ATCC-type strain. Like the outbreak strain, the sequence variations occurred primarily in the final 1000 base pairs of the gene (Fig 2).

### DISCUSSION

This article describes the first reported outbreak of invasive *K kingae* disease. The high incidence of colonization and invasive disease in the affected toddler 1 classroom and the indistinguishable PFGE pattern of the isolates within the outbreak child care center are consistent with child-to-child transmission, which may include direct person-to-person and/or fomite transmission.

Invasive infections in young children are frequently caused by pathogens that are carried asymptotically in the oropharynx, such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis*; *K kingae* seems to behave similarly. Although *K kingae* is a common colonizer, it is identified only occasionally as a cause of invasive disease, primarily osteomyelitis or acute monoarticular septic arthritis (65–75% of cases) in young children, bacteremia (20–30% of cases) in infants 6 to 12 months of age, and endocarditis in all ages, especially in those with preexisting structural defects.<sup>5–25</sup> Diskitis, laryngotracheobronchitis, meningitis, and endophthalmitis also have been documented.<sup>5–13,19–25</sup> The vast majority of children who develop invasive disease are previously healthy.<sup>8–11,13</sup> Approximately 90% of patients with invasive *K kingae* disease are  $\leq 4$  years of age, with most cases occurring between 6 months and 2 years of age.<sup>5,3–16,21–25</sup>

Those with *K kingae* skeletal infection present with low-grade fever and seem mildly toxic, as was the case with the 3 children reported here. WBC counts are variable, with most presenting with counts of 10 000 to 15 000 cells per mm<sup>3</sup>. Almost all present with elevated inflammatory markers (ESR and CRP),<sup>5,8,9,11–13,15,20–22</sup> although these were only modestly elevated in our case patients. This contrasts markedly with those who present with skeletal infections caused by more common pathogens such as *S aureus* or *S pyogenes*, who usually present acutely with high fever, more notable clinical findings, and much higher inflammatory markers. *K kingae* invasive disease is frequently associated with concomitant or antecedent upper respiratory illness (present

in all 3 case patients here)<sup>5,8–13,15,22,24,25</sup> or stomatitis (singular aphthous ulcers were noted in 2 of the 3 case patients);<sup>19,20</sup> disrupted respiratory or buccal mucosa is hypothesized to facilitate bacterial invasion and hematogenous dissemination.

Patient case series and in vitro studies have shown that infections are readily treatable with a wide variety of antimicrobial agents.<sup>5,8–10,15,16,18,22,24,32,33</sup> Our *K kingae* isolates were found to have low MICs for penicillin as well as rifampin and azithromycin. The length of antimicrobial treatment for skeletal infections caused by *K kingae* has not been standardized.

The presence of *K kingae* is difficult to detect if clinical suspicion is not immediately present. Fewer than 15% of *K kingae*-positive clinical specimens reveal organisms on Gram stain.<sup>5–10,12,13,15,16,19,21,24</sup> Lack of experience with *K kingae* can also lead to the organism's being misidentified as *Moraxella*, *Haemophilus*, or hemolytic streptococcus (as a result of incomplete decolorization on Gram stain) or dismissed as a contaminant.<sup>5,8,9,11,26,34</sup> Recovery of the organism may be difficult on routine bacterial culture because of its fastidious nature and low concentration in clinical specimens. Growth on conventional culture is rarely seen before 4 days, and laboratories may need to hold cultures up to 7 to 10 days for primary isolation. If *K kingae* is suspected, then communication between clinicians and laboratorians is essential, because laboratories usually discard culture plates after 48 to 72 hours. The disease of the case patients described here was diagnosed because the clinician had suspected an atypical organism and asked the laboratory to hold the culture plates longer.

Multiple studies have shown that inoculating synovial fluid or bony exudates directly into blood culture bottles with a continuous monitoring system substantially increases the rate of recovery of *K kingae*<sup>5,8,9,13,14,16,19,21–24,34–38</sup> and other pathogens<sup>39–43</sup> from culture compared with direct plating of specimens on solid media and that multiple systems (eg, BACTEC or BacT/Alert blood culture bottle systems, Isolator 1.5 Microbial Tubes system) are effective. These studies have shown that 84% to 91% of cases of *K kingae* septic arthritis would have been missed if only conventional culture technique were used without an accompanying blood culture bottle method.<sup>13,21,24,38</sup> Moreover, isolates can be detected earlier, usually after 1 to 3 days of incubation, using the blood culture bottle system.<sup>8,16,20,22,34,35</sup> At present, this method is not used routinely in clinical laboratories because of limited specimen volume, reluctance to use blood culture bottles for a non-Food and

Drug Administration–approved indication, and, frequently, lack of awareness.<sup>44</sup>

The cause of osteoarticular infections is frequently not identified (ie, culture negative). That our look-back revealed 2 additional cases of culture-negative septic arthritis in the same toddler classroom in the previous year is notable. Current studies estimate that no causative organism is found in 40% to 70% of pediatric septic arthritis or osteomyelitis cases<sup>6,44–47</sup> and that *K kingae* may account for up to 50% of undiagnosed septic arthritis cases in children <2 years of age.<sup>5–7,19,21,22,24,34</sup> Widespread immunization against *H influenzae* and *S pneumoniae* (which may create a wider niche for oropharyngeal colonization by *K kingae*), improved clinician awareness, and enhanced laboratory capabilities to identify and isolate this organism may be responsible for the increase in invasive *K kingae* infections reported in recent years.<sup>5–11,22,47</sup>

Limited data are available about the epidemiology or transmission of *K kingae*. Because it is an oropharyngeal colonizer, *K kingae* is most likely transmitted through respiratory secretions, saliva, and potentially oral contact with contaminated fomites. Infection shows a seasonal distribution, with most cases occurring in the autumn and winter months.<sup>9,10,16,24,25</sup> In southern Israel, the annual incidence of invasive infections is estimated to be 17.8 to 27.4 cases per 100 000 in children <2 years of age.<sup>21,24,48</sup>

The age and equal gender distribution of colonization parallels that of invasive disease.<sup>25,47</sup> During an 11-month study of children aged 6 to 42 months at an Israeli child care center,<sup>47,49</sup> the monthly prevalence of *K kingae* colonization ranged from 6% to 35%, with 73% of children being colonized at some point during the study period; no invasive disease was observed.<sup>47</sup> Subtyping demonstrated that they were colonized with 2 dominant subtypes, which clustered temporally and lasted for weeks to months.<sup>49</sup> Isolates from a cohort of randomly selected children were also subtyped and showed substantially more subtype variability than seen among isolates from the child care center.<sup>49</sup> These studies indicate person-to-person transmission occurring within the facility, with children being a reservoir for the pathogen. Our investigation is consistent with these previous studies.

The incidence of invasive disease was exceptionally high among the children of our affected child care center. No risk factors for either invasive disease or for colonization were identified, perhaps because the small number of children who were ill or colonized limited the power to detect small differences in responses between groups.

Although no treatment is currently recommended to eliminate the carriage state, the high rate of invasive disease in the toddler 1 classroom warranted an attempt at antibiotic prophylaxis. Prophylactic rifampin (same as the *N meningitidis* prophylactic dosing) was moderately successful (67%) in eliminating *K kingae* colonization.

Although the outbreak and control isolates were identified as *K kingae* using biochemical methods, DNA sequence analyses of the 16S rRNA genes dem-

onstrated several sequence deviations from the ATCC-type strain. As shown in Fig 2, these child care strains may represent distinct sequevars of *K kingae*. Furthermore, our investigation suggests that different *K kingae* strains may demonstrate varying degrees of pathogenicity and that our outbreak isolate may have been a more virulent strain. Additional evaluation is needed.

We believe that *K kingae* is an appreciably underdiagnosed cause of pediatric skeletal infections and that it may become an increasingly important pathogen as conjugate vaccination in children for other respiratory pathogens curb their colonization of the oropharynx. Heightened clinician awareness, enhanced laboratory protocols, and communication between clinicians and laboratorians will be critical to achieve a fuller understanding of the true burden of pediatric skeletal infections caused by *K kingae*.

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