Outbreaks of *Kingella kingae* Infections in Daycare Facilities

[Announcer] This program is presented by the Centers for Disease Control and Prevention.

During the past 3 decades, Western countries have reported a rising number of mothers entering the workforce and, consequently, a growing number of children receiving care outside the home. This trend has substantial public health consequences because the incidence of infectious diseases in general, and of those caused by respiratory pathogens in particular, has substantially increased among daycare center attendees. These organisms are usually spread within daycare centers by child-to-child transmission; they colonize the upper respiratory tract surfaces, from which they can disseminate to other attendees. From the upper airways, pathogens may invade adjacent structures, such as the lungs, middle ear, or nasal sinuses, and may penetrate into the bloodstream, causing invasive diseases. Most bacterial pathogens responsible for such infections are enclosed by polysaccharide capsules that protect them from phagocytosis and complement-mediated killing, ensuring their persistence on the respiratory mucosa and survival in the bloodstream and deep body tissues. Maturation of the T-cell independent arm of the immune system in humans is delayed until the age of 2 to 4 years; thus, young children are prone to colonization and infection by encapsulated bacteria.

Besides the microorganisms' virulence and the hosts' age-related immunologic immaturity, many other factors contribute to the enhanced colonization, transmission, and illness rates observed among children in daycare centers, including the number of children present, the degree of crowding, efficacy of ventilation, time spent in daycare, length of time from enrollment, frequency of enrollment, age group mixing, and occurrence of seasonal viral infections. Because of age stratification, child-care groups comprise attendees of approximately the same age who have similar degrees of immunologic immaturity and susceptibility to infectious agents. This epidemiologic setting substantially differs from that of large families in that the latter include children of different ages and therefore, at any given time, only a fraction of siblings belong to the age group at enhanced risk for bacterial colonization and invasion, which limits the chances to acquire and transmit the organism. In daycare centers, respiratory organisms spread easily through large droplet transmission among young children with poor hygienic habits who share toys contaminated with respiratory secretions or saliva. Under these circumstances, introduction of a virulent bacterium in a crowded daycare facility attended by immunologically naïve children may result in prompt dissemination of the organism and initiate outbreaks of disease.

Because of the improved culture methods and sensitive nucleic acid amplification assays developed in recent years, *Kingella kingae*, a gram-negative coccobacillus of the *Neisseriaceae* family, is increasingly recognized as an invasive pathogen of early childhood. The organism is a frequent source of childhood bacteremia and the most common agent of skeletal system infections in children 6 months to 3 years of age; it is also a cause of bacterial endocarditis in children and adults. Because of the fastidious nature of *Kingella kingae*, many illnesses caused by this organism are probably overlooked. Although most cases of invasive *Kingella kingae* infections are sporadic, clusters of invasive disease have been detected among attendees of daycare centers in Israel, Europe, and the United States.

Kingella kingae tends to retain crystal violet dye and, therefore, it may appear to be gram-positive, and laboratories unfamiliar with its cultural and staining features may misidentify the bacterium altogether or dismiss invasive isolates as culture contaminants. Identification of *Kingella kingae*, however, is not difficult, and many commercial instruments and technologies correctly identify the organism.

Most young children in whom an invasive *Kingella kingae* disease developed have been otherwise healthy. In contrast, children older than 4 years of age and adults who become infected frequently have underlying conditions, such as congenital heart diseases, chronic renal failure, or a variety of primary immunodeficiencies.

The prevalence rate in healthy children during the second year of life ranges between 10 percent and 12 percent, which coincides with the peak attack rate of invasive infections. The colonization rate drops substantially in older children and adults. Pharyngeal carriage of *Kingella kingae* and occurrence of disease before a child is 6 months of age are exceptions, indicating that maternal immunity and limited social contact provide protection.

In an 11–month longitudinal study, 35 of 48 daycare center attendees carried the organism at least once and an average of 27.5 percent of the children were colonized at any given time. Molecular typing of isolates from asymptomatic colonized attendees showed genotypic similarities, indicating person-to-person transmission of the organism in the facility. Two *Kingella* strains represented 28 percent and 46 percent of all isolates, demonstrating that some strains are particularly successful in colonizing mucosa. Children harbored the same strain continuously or intermittently for weeks or months, and then it was replaced by a new strain, showing that carriage is a dynamic process in which there is frequent turnover of colonizing organisms, as observed for other respiratory pathogens. Despite the high prevalence of the organism in the daycare center, an invasive *Kingella kingae* infection did *not* develop in any of the attendees in the course of the follow-up period.

The link between out-of-home child care and *Kingella kingae* carriage was recently confirmed in a study conducted among 1,277 children younger than 5 years of age who were referred to a pediatric emergency department. Daycare attendance was strongly associated with *Kingella kingae* carriage after controlling for other factors. Surveillance studies not only have shown that *Kingella kingae* organisms colonizing attendees of a given daycare center are frequently identical, but have also demonstrated that carried strains differ between facilities located close together, indicating that each daycare center is like an independent epidemiologic unit.

Considering these findings, it is not surprising that clusters of proven and presumptive cases of invasive *Kingella kingae* disease have been detected in daycare centers in France, the United States, and Israel.

Three of the 6 *Kingella kingae* illness outbreaks in daycare centers reported during 2003 to 2013 were detected in Israel, a small country with a population of 8 million inhabitants. Although Israel's relatively high annual birthrate compared with Western countries, and the widespread and early daycare center attendance could partially account for this observation, it seems plausible that similar events occur worldwide but are frequently overlooked.

The epidemiologic investigation of these outbreaks revealed that the *Kingella kingae* colonization rate among asymptomatic attendees to the daycare centers where clinical cases were detected was unusually high and all pharyngeal isolates detected in the classrooms where disease occurred were genotypically identical and indistinguishable from the patients' clinical isolates. The age of the colonized or infected daycare center attendees coincided with the age of increased susceptibility to *Kingella kingae* carriage and disease; the organism was detected in the pharyngeal culture of only1 of the caregivers, supporting the hypothesis that healthy adults rarely carry *Kingella kingae.*

Despite a background carriage rate as high as 5 percent to 12 percent, the incidence of invasive *Kingella kingae* infections reported in Israel was 9.4 per 100,000 children younger than 5 years of age, and the calculated annual risk of developing *Kingella kingae* osteomyelitis or septic arthritis for young carriers in Switzerland was less than 1 percent. When data from the 6 clusters of invasive disease detected in daycare centers are pooled, a documented or presumptive *Kingella kingae* infection developed in 1 in 7 classmates within a 1-month period, indicating that the outbreak strains combined enhanced colonization fitness, high transmissibility, and remarkable virulence.

To prevent further cases of disease and eradicate the invasive strain, prophylactic antibacterial drugs have been administered to children attending the facilities where clusters of *Kingella kingae* were detected. Rifampin was chosen because *Kingella kingae* is especially susceptible to that antibacterial drug. Rifampin is secreted in saliva and reaches high concentrations in the upper respiratory mucosa and has shown efficacy in the eradication of colonization by *Neisseria meningitidis* and *Haemophilus influenzae* type b, and in disease prevention in daycare centers. However, because only partial success was achieved with this drug in the Minnesota cluster, high-dose amoxicillin was added to the regimen in 2 more recent outbreaks. Following administration of antibacterial drugs, a respiratory carriage of the organism decreased, but complete eradication occurred only in the Durham, North Carolina daycare center, and new colonization of several attendees by the original strain was later observed. Persistence of the organism in the facility was not caused by bacterial resistance to the administered antibacterial drugs, however. Similar observations have been made in outbreaks in daycare centers caused by *Haemophilus influenzae* type b and pneumococci. Poor compliance or failure to administer prophylactic antibacterial drugs to family contacts could have resulted in incomplete suppression of the reservoir and recurrent dissemination of the strain in the facility.

Because antibacterial drugs have been relatively ineffective in eradicating *Kingella kingae* carriage, the need for antibacterial drug prophylaxis in the setting of a cluster of invasive disease is being disputed. Notably, however, after administration of antibacterial drugs to the asymptomatic children, no further cases of disease were detected in the affected daycare centers, even when a few children continue to carry the invasive strain. Reducing the bacterial density among colonized children by antibacterial drug administration or an effective immune response induced by prolonged mucosal carriage may have been sufficient to prevent new cases of infection. Improved hygiene and institution of other infection control measures could also have limited further transmission of the organism.

In recent years, clusters of invasive *Kingella kingae* infections among attendees of daycare centers have been reported, although because of the low rate of testing for this pathogen, many events are probably overlooked. Detection of these events requires a high level of suspicion, use of sensitive culture techniques and nucleic acid amplification tests, and familiarity of the clinical microbiology laboratory with the identification of this elusive pathogen. The same improved detection methods should be employed for the thorough investigation of these clusters, and recovered *Kingella kingae* isolates should be genotyped and compared.

Many issues remain unsettled, including whether antibacterial drugs should be administered prophylactically to daycare center contacts of an index case-patient, to young siblings of clinical case-patients, and to carriers, or whether antibacterial drugs should be offered to confirmed carriers only, or limited to children with disease. If administration of antibacterial drug prophylaxis is decided on, the preferred drug regimen will have to be determined. Whether an epidemiologic investigation should be carried out in daycare centers after detection of a single case of disease also remains to be determined.

I'm Dr. Mike Miller and I've been reading an abridged version of the article, Outbreaks of *Kingella kingae* Infections in Daycare Facilities. You can read the entire article in the May 2014 issue of *Emerging Infectious Diseases* or online at cdc.gov/eid.

If you'd like to comment on this podcast, send an email to eideditor@cdc.gov.

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