Viral mumps: Increasing occurrences in the vaccinated population

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Before the introduction of the vaccine, mumps was the most common salivary gland disease and was one of the most common infectious diseases in children globally. Following the introduction of the mumps vaccine in 1967, the disease was almost nonexistent in the United States and was only found to occur in nonvaccinated patients, and even then, it did not present in epidemic portions because of the extent of vaccination in the population at large. Beginning in the early 2000s, viral mumps began to present itself in vaccinated populations, and currently, outbreaks are continuing to increase in number. This article presents information on the various outbreaks, a review of the virus and the disease, including symptoms and comorbidities, and new recommendations for management. Dental practitioners should be aware of the increasing incidence and prevalence of this disease, be able to recognize it, and make appropriate referrals for management. (Oral Surg Oral Med Oral Pathol Oral Radiol 2019;128:386−392)

Before the introduction of the vaccine, mumps was the most common salivary gland disease and was one of the most common infectious diseases in children globally. Following the introduction of the mumps vaccine in 1967, the disease was almost nonexistent in the United States and was only found to occur in nonvaccinated patients, and even then, it did not present in epidemic portions because of the extent of vaccination in the population at large. Beginning in the early 2000s, the mumps began to present itself in vaccinated populations, and mump outbreaks are continuing to increase in number. This article presents information on the various outbreaks, a review of the virus and the disease, including symptoms and comorbidities, and new recommendations for management. Patients with swelling of the parotid gland typically present to the dental office, so the dental practitioner should be aware of the increasing prevalence of this disease, be able to recognize it, and make appropriate referrals.

Mumps is generally caused by paramyxovirus, although it can also, rarely, be caused by other viruses (Table I). Paramyxovirus was first discovered in 1934 by Johnson and Goodpasture; these authors were able to filter out a virus from 4 patients and then inoculated rhesus monkeys, which then developed an acute, nonsuppurative parotitis analogous to mumps.[1]

It is difficult to accurately ascertain the incidence of mumps before 1967 because of unreported occurrences and the lack of published data. A prospective study in Hillsborough County Florida by the Hillsborough County Health Department, the Florida State Division of Health, and the National Communicable Disease Center (the precursor organization of the Centers for Disease Control and Prevention [CDC]), found an incidence of 2000 cases per 100,000 population (which was 10 times the number of reported cases at this time).[2] The number of cases in the United States Army reported from 1942 to 1945 was 100,616, with a rate of 3.95% per 1000 Figure 1.[3] The same article included a statement that mumps outbreaks were typically occurring in prisons, orphanages, boarding schools, and military garrisons and on ships. Similarly, recent outbreaks have been observed in schools, summer camps, and college campuses, where individuals are in close contact with infected individuals for prolonged periods.

OUTBREAKS IN THE VACCINATED POPULATION

In 2005, 31 cases of mumps were reported at a summer camp in Sullivan County, New York. Twelve of these cases occurred among camp attendees, who were U.S. residents age 10 to 15 years and had all received 2 doses of the measles−mumps−rubella (MMR) vaccine. The remaining 19 cases were found among camp staff from the United Kingdom, Germany, the United States, and Australia. Of the affected staff, 4 had received 2 doses of the mumps vaccine.[4]

In March 2006, a second outbreak, numbering 219 cases, was identified across several college campuses in Iowa.[5] By April, mumps had spread to 6 neighboring states, resulting in a total of 515 identified cases.[5] By May, 2597 cases had been reported across the country. Additional smaller outbreaks were noted later that year

Statement of Clinical Relevance

There are increased outbreaks of mumps in both the vaccinated and the unvaccinated populations. Mumps is commonly misdiagnosed as an obstructive salivary gland disorder. Because of the increase in occurrence, the dental practitioner should be aware of the disease.

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Received for publication Jun 10, 2019; accepted for publication Jun 23, 2019.

2212-4403/$-see front matter
https://doi.org/10.1016/j.oooo.2019.06.012

Table I. Viruses associated with epidemic viral parotitis (mumps)

Paramyxovirus
Epstein-Barr virus (EBV)
Cytomegalovirus (CMV)
Human herpes simplex virus (HHSV-8)
Hepatitis C virus (HCV)
Human papillomavirus (HPV)
Cocksackievirus
Influenza virus
Echovirus

in Colorado, Minnesota, and Mississippi.[6] In total, 6584 cases were reported to the CDC in 2006. This was the highest number since 1986, when the CDC Advisory Committee on Immunization Practices had updated its guidelines to include a second dose of the MMR vaccine.[7]

Another outbreak that occurred in 2009 through 2010 predominantly affected the Orthodox Jewish community in the New York metropolitan area. The index case in this outbreak was an 11-year-old boy who had recently traveled to the United Kingdom, where a mumps outbreak had occurred. The boy attended an Orthodox Jewish all-male summer camp in Sullivan County, New York, attended by approximately 400 boys from multiple Orthodox Jewish communities from across the Greater New York City area. Following the end of the summer camp, attendees and staff returned home to their respective communities, where the virus continued to spread. Initial outbreaks were reported in the Orthodox Jewish communities of Brooklyn, New York, and Rockland County, New York. From infected persons in Brooklyn, the virus was transmitted to the Orthodox Jewish communities in Orange County (New York) and Ocean County (New Jersey). Of the 3502 reported cases, 3405 (97%) occurred within the Orthodox Jewish community.[8] The extent of the outbreak prompted re-examination of the existing vaccination guidelines. A study by Ogbuanu et al. reported administration of a third dose of MMR vaccine to students, age 11 to 17 years, in 3 Orthodox Jewish schools. The results demonstrated a 96% reduction in incidence in this population.[9] Within the same time frame, an outbreak of 505 cases was reported in Guam, prompting a similar study on the need for a third MMR vaccine.[10]

In the 2014−2015 season, a small but highly publicized outbreak occurred in the National Hockey League. Although details are limited to those in news reports and press releases, affected teams included the Anaheim Ducks, St. Louis Blues, Minnesota Wild, Pittsburgh Penguins, New York Rangers, and New Jersey Devils. In total, 23 players and 2 linemen are believed to have been infected. The outbreak resulted in missed games by multiple starting players and officiating staff across the league.[11] In 2015−2016, additional outbreaks occurred across 2 college campuses: 317 cases at the University of Illinois (Urbana-Champaign, IL) and 259 at the University of Iowa (Des Moines, IA).[12] In August 2016 to July 2017, the Arkansas Health Department reported 2951 cases within that state.[13] The outbreak first spread among Marshallese school children in northwest Arkansas, where this ethnic group is most prominently present Figure 1.[13]

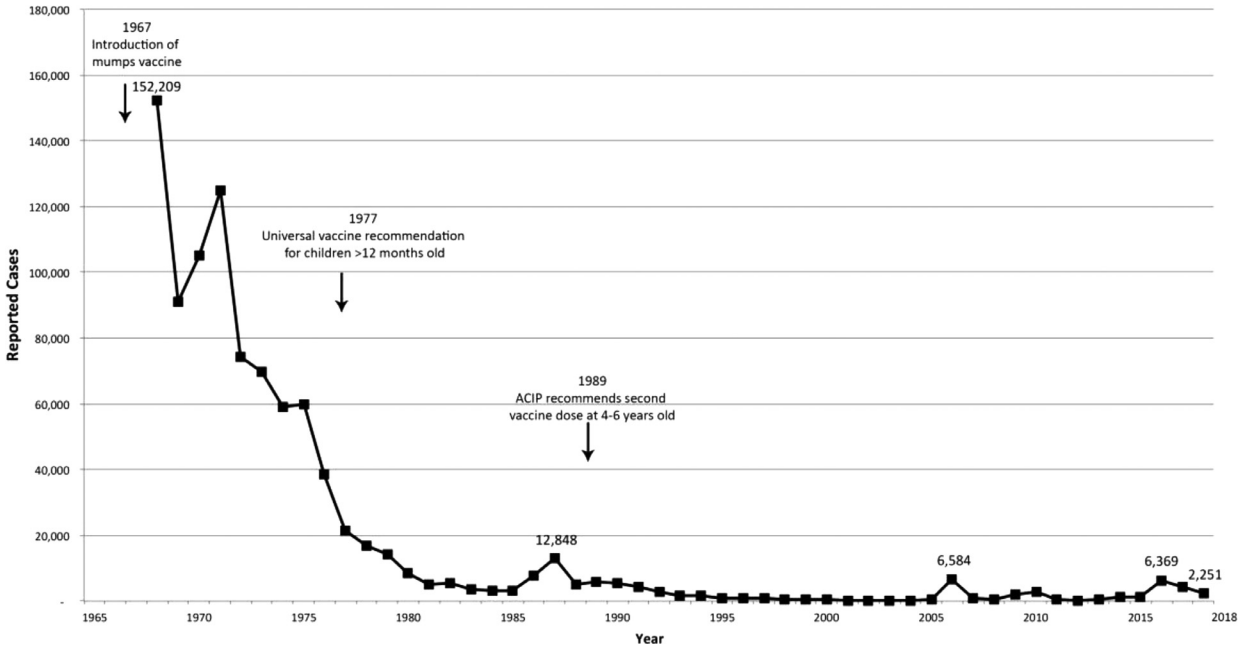

Figure 1. Annual reported cases of mumps in the United States (1968-2018), from CDC data.

PATHOGENESIS

The mumps virus is a single-stranded RNA virus consisting of 15385 nucleotides. The genome codes for 8 proteins: fusion protein (F), nucleocapsid protein (NP), phosphoprotein (P), matrix protein (M), L protein, hemagglutinin−neuraminidase protein (HN), and small hydrophobic protein (SH).[14] The World Health Organization recognizes 12 genotypes of the virus based on sequence variations in SH and HN. Despite genotypic variances, the virus is serologically monotypic.[14] Genotyping has been utilized in tracking the distribution and transmission patterns of the virus. In the United States, genotypes C, D, G, K, and H have been detected in circulating wild-type strains. Genotype A, has been historically found within the United States. However, it has not been identified in the country since 1991.[15]

CLINICAL PRESENTATION AND MEDICAL MANAGEMENT

Symptoms present approximately 2 to 4 weeks after the initial exposure to the virus. Differentiation of mumps from other salivary gland diseases can sometimes be difficult because of the similarity of the parotitis symptoms to obstructive salivary gland disorders. A suspicion of a diagnosis of mumps is the presence of prodromal symptoms. Prodromal symptom are flu-like and nonspecific and include low-grade fever, malaise, anorexia, and headaches. The parotitis occurs approximately 2 to 4 days after the prodromal period. Patients who present with new-onset parotitis should be asked during history taking about their present illness and whether they have experienced these flu-like symptoms. When parotitis occurs, the onset of the swelling is generally asymmetric but progresses after 1 to 2 days to involve the contralateral gland in 75% of cases; this is different from obstructive parotitis, which is typically unilateral and differs from an acute bacterial infection in that it is nonsuppurative in nature.

Peak pain and swelling occur on days 2 and 3 after the onset of mumps, and patients may present with fever. Tenderness of the gland will correlate to the degree of edema. Trismus, edema of the Stensen papilla, and pain with salivation without purulence are frequently observed. Parotid enlargement may obscure the mandibular angle, and superolateral lifting of the ear can be observed. These changes are best appreciated by viewing the patient from behind. Concomitant involvement of the submental and submandibular glands has been reported in 10% of cases. Following peak swelling, parotid symptoms typically resolve within 1 week.[16]

The virus is known to cause epididymo-orchitis in 20% to 30% of postpubertal males. This effect can occur before, during, and after parotitis or even in the absence of parotitis. Symptoms manifest as fever, chills, headache, vomiting, and testicular pain. Of those affected, 17% experience bilateral involvement.[16] Testicular atrophy occurs in 50% of cases and may result in subfertility.[17] There is lack of evidence for infertility as a possible sequelae of mumps orchitis.[18] Studies examining mumps orchitis as a predisposing factor for testicular malignancies have reported conflicting results. In postpubertal females, the reported incidence of oophoritis is 5%, with similar concerns regarding infertility.[19] Current data show that vaccinated patients have a significantly lower rate of comorbidities compared with the historically unvaccinated population.[20] In a study of 4 patients with bilateral mumps orchitis, each patient was administered subcutaneous interferon-α_2 B for 7 days. All 4 patients experienced resolution of acute orchitis within 4 days, and normospermia was found to have returned at the 6-month follow-up.[15]

Other common clinical manifestations of the disease include cerebrospinal fluid pleocytosis (51% of cases), meningitis, mild renal impairment, and electrocardiographic abnormalities. Temporary deafness, pancreatitis, and arthritis have been reported.[16]

DIFFERENTIAL DIAGNOSIS

Episodic mumps presentation is similar to that of other forms of parotitis. The suspicion of mumps over other conditions should be based on the following: exposure to mumps, with a consideration weighted secondary to the patient's vaccination status; unilateral parotid swelling that progresses to bilateral swelling within 2 to 3 days; and flu-like symptoms 2 to 3 days before parotitis. Other conditions that can also be considered in a differential diagnosis are discussed below.

The most common cause of swelling of the parotid gland is occlusion of the salivary flow by a mucous plug or sialolith. Formation of salivary calculi is a chronic process facilitated by xerostomia, salivary stasis, and variations in ductal anatomy. Patients will complain of rapid-onset edema associated with eating which typically resolves in 2 to 3 hours. Mucous plugs, particularly in the parotid, are the most common cause of salivary obstruction. In recurring swellings, sialoliths and strictures should also be considered. Diagnosis of sialoliths are confirmed by utilizing either sialography, computed tomography, computed tomography sialography, or ultrasonography.[21] Sialography can aid in evaluating areas of ductal stricture and dilation, particularly in cases of radiolucent or incomplete obstruction.[22] In some instances, particularly in chronic obstructions, the affected gland can then develop acute suppurative sialadenitis.

Acute suppurative sialadenitis is a bacterial infection of the salivary gland attributed to retrograde infection caused by oral flora. Similar to mumps, these infections present with edema, fever, and tenderness of the affected gland. However, unlike mumps, the infection occurs unilaterally. As the name *acute suppurative sialadenitis* implies, purulence will be evident upon milking of the

duct, which is not seen in cases of mumps. Periglandular abscess formation can occur, requiring surgical drainage. Leukocytosis is expected in bacterial sialadenitis, whereas it is uncommon in mumps. The common causative organisms include *Staphylococcus aureus* and anaerobic gram-negative bacilli. Predisposing factors include tortuous ductal anatomy, immunodeficiency, and cachexia in severe systemic disease. Acute bacterial sialadenitis is treated with a combination of antibiotics, aggressive rehydration, and dietary sialagogues. In pediatric populations, bacterial parotitis can present as a sequela of sepsis via hematogenous spread to the parotid lymph nodes.[21,23]

Juvenile recurrent parotitis is an idiopathic inflammatory condition that presents with fever, malaise, and painful swelling of the gland in pediatric populations. After the introduction of the mumps vaccine, it is now the leading cause of parotitis in children. While the disease is in its active phase, patients report on average 3 to 4 attacks per year. Both unilateral involvement and bilateral involvement have been reported, and symptoms are self-limiting. Sialography demonstrates lymphocytic infiltration and intraglandular cystic dilations, called *sialactases*.[24] Juvenile recurrent parotitis differs from the mumps in that the former is recurrent. Although its pathophysiology is poorly understood, some authors believe that the etiology is related to congenital malformation of the duct. The duct demonstrates an avascular appearance on sialendoscopic examination.[25]

Other reported, but far less common, viral etiologies of bilateral parotitis include influenza A, human herpes virus-6B, Epstein-Barr virus, and, less commonly, herpes simples virus-1 and -2, parainfluenza virus-2 and -3, and adenovirus.[26,27] In addition to serology and culture, clinical findings, such as concurrent upper respiratory infection or vesicular lesions, may lead one to suspect non−mumps-related viral infections. Lymphoepithelial cysts of the parotid, which often present bilaterally, are a classic hallmark of HIV infection.[28,29] In a study of 200 patients with HIV infection, the reported incidence of ultrasonography-detected lymphoepithelial cysts was 42%.[30]

Bilateral noninflammatory and nonneoplastic salivary gland enlargement, known as *sialosis*, may present in patients with xerostomia and other conditions, including diabetes, alcoholism, and Sjögren syndrome. Unlike mumps, sialosis is chronic and rarely painful.[21]

Malignancies may present with pain or facial nerve palsy. Bilateral involvement and constitutional symptoms can occur in lymphomas and metastatic disease. Benign salivary neoplasms, which are painless and unilateral, share few clinical characteristics of a mumps infection. Diagnostic imaging and biopsy are recommended in the presence of any suspicion of a neoplastic process.[21]

THE VACCINE

The live attenuated Jeryl Lynn strain vaccine (MUMPSVAX Merck & Co., Inc., Whitehouse Station, NJ) was developed in 1967 by Maurice Hilleman and is still being used today in the United States. Later developments of the measles and rubella vaccines led to the release of the combined MMR vaccine in 1971. In 1977, the Advisory Committee on Immunization Practices issued a universal recommendation to all children older than 12 months of age. The recommendation for 2-dose MMR vaccination was introduced in 1989 after multiple measles outbreaks occurred in the 1980s. These guidelines recommended routine administration of the vaccine at 12 to 15 months and a second dose at age 4 to 6 years. The guidelines were further expanded in 2006 in response to outbreaks in college campuses in 2006. The updated guidelines recommend that in an outbreak, a second dose of mumps vaccine be given to children age 1 to 4 years and to adults who had received 1 previous dose. The documented requirement for adequate vaccination was changed from 1 dose to 2 doses. For health care workers, persons born before 1957 and without documented immunity are recommended to receive 1 dose, whereas those born in or after 1957 are recommended to receive 2 doses. A third dose is now recommended in populations where an outbreak is occurring.[20] In one study, epidemiologic data from the 2004−2015 Scottish mumps outbreaks were used to create a mathematical model to simulate the effects of a third vaccine dose. The study found that a third dose would decrease outbreak intensity by two-thirds and reduce the frequency as well. However, it would fail to eliminate outbreaks altogether, even at a theoretical immunity duration of 80 years.[31] Aseptic meningitis has been reported with the Urabe AM9 strain (0.3% incidence), although studies on the Jeryl Lynn strain have not shown such an association.[32,33] Use of the vaccine is contraindicated in pregnancy, immunosuppression, immunodeficiency, advanced malignancy, or severe febrile illness.[34] The only reported case of serious complication associated with the MMR vaccine is a fatal case of measles pneumonitis in a 21-year-old man with poorly controlled HIV infection. A retrospective cohort study examining the effect of the MMR vaccine on patients with well-controlled HIV (mean CD4 count: 540 cells/μL) showed no statistically significant changes to the CD4 count at the 2-year follow-up. Limited data from the study also suggest a reduced immunogenic response to a second mumps vaccine in individuals with HIV infection.[35]

TRANSMISSION

The virus is spread through direct contact with infected individuals via respiratory droplets and saliva. Studies on mumps transmission have found that saliva swabs can contain the virus up to 7 days before and 5 days after the onset of parotitis.[36] The CDC National Immunization Surveys have indicated that at the time of the 2006 outbreaks,

the 2-dose vaccination rate in adolescents was 87%.[37] A study of this outbreak found that among those infected, 25% had received 1 dose and 63% had received 2 doses.[38]

As recent reports have shown, outbreaks are known to develop in such settings as schools and college campuses. Prolonged face-to-face speaking and reduced interpersonal space have been suggested as environmental risk factors for transmission of infection that may overwhelm even twice-immunized individuals.[39]

LABORATORY DETECTION AND THEORIES OF VACCINE FAILURE

In an acute mumps infection, anti-NP antibody levels will increase sharply within days and decline over months. Anti-HN antibodies increase at a slower rate, peaking at 2 to 4 weeks after infection. Levels of anti-HN also decline more slowly and can remain detectable for years. Relative levels of these 2 antibodies can give useful information about when an individual was infected.[14] Immunoglobulin M (IgM) is detectible in the acute phases of the infection and is used in serologic diagnosis. However, the likelihood of false-negative results increases with the number of prior vaccinations. Detection of IgG is indicative of prior exposure, but not necessarily immunity.[40]

Vaccine failures can occur through antigenic variation, primary failure, and secondary failure. Antigenic variation between the vaccine and wild-type strains can cause the immune system to produce antibodies specific to the vaccine genotype, rather than to the circulating strain. However, studies have shown that the mumps virus is less affected by this phenomenon compared with other viruses.[41,42] Primary failure occurs when the host does not respond to an initial dose, causing the vaccine to be clinically ineffective. Despite the reported seroconversion rates of 95%, the reported rates of vaccine effectiveness range from 62% to 91% for the Jeryl-Lynn strain.[43]

Currently, there is no serologic testing or titer level that is predictive of immunity.[44] Of note, Hilleman's original studies on the Jeryl Lynn vaccine reported 97% effectiveness rates.[45] A 2018 review by Ramanathan et al.[46] suggested that the prevalence of the circulating wild-type mumps virus in the historical population may have been a confounding factor in early studies on effectiveness rates. Prior exposure to the wild-type virus is thought to boost the immune response and, thus, cause overestimation of the clinical effectiveness rate of the vaccine.[46] In secondary failures, or waning immunity, the body successfully mounts a response to the initial vaccine, but the effectiveness of B-cell memory is believed to decrease over time. Although many studies have suggested waning immunity as the primary contributor to recent outbreaks, the mechanism remains unknown.[27,42] A retrospective study of the 2006 outbreak by Cortese et al. found a 2.4 odds ratio for mumps infection when the second MMR dose was received 10 years ago or earlier, suggesting that waning immunity over time may explain the resurgence.[47] This concurs with the findings of earlier titer studies that suggested vaccine failure occurring 7 to 10.5 years after vaccination.[48] The mechanisms behind waning immunity are largely unknown and remain an active area of research. Enzyme-linked immunosorbent assay testing of mumps-specific IgG avidity has been used to distinguish between failures of primary and secondary mumps vaccines. IgG avidity measures the ability of a patient's mumps-specific IgG to bind to a standardized commercial mumps antigen. Maturation of IgG from low avidity to high avidity occurs after initial exposure to the virus, whether wild-type or vaccine.[49-51]

Similar IgG avidity testing is used for different viruses across the field of immunology. The labels "low" and "high" avidity indicate an arbitrarily defined threshold of the avidity index (AI), which varies among viruses. Of note, the AI of the mumps virus is much lower compared with measles virus, rubella virus, human papillomavirus, and cytomegalovirus.[49,52] Some authors have suggested that lower AI may correlate to higher rate of vaccine failures.[52] However, the clinical picture of vaccine failure is complex, and the ability to establish causal relationships between avidity and immunologic mechanisms is limited. Avidity studies are subject to variations in laboratory methodology and study design. To date, these studies have not been conducted on U.S. populations in which largescale outbreaks have occurred.

REPORTING

Mumps is on the national list of reportable diseases, and thus, mandatory reporting by health care providers is required, including personal identifying information for purposes of immediate disease control. Reporting may be received by state and local health agencies, which compile the required data for the CDC. Isolation of infected individuals, with standard and droplet precautions, are recommended for 5 days after the onset of clinical symptoms.[53]

CONCLUSIONS

Mumps has now started to occur even in vaccinated populations. Although there is no firm evidence to ascertain why these outbreaks are happening, it should be noted that the affected individuals are typically in their 20s, and this has led to the notion that the vaccine's effect begins to wane in 7 to 10 years after administration. If a patient presents with what appears to be mumps, health care providers should report their findings to the state or local health department or to the CDC directly.

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