MAJOR ARTICLE

Viruses Detected Among Sporadic Cases of Parotitis, United States, 2009–2011

Albert E. Barskey,[1,a] Phalasy Juieng,[2] Brett L. Whitaker,[1] Dean D. Erdman,[1] M. Steven Oberste,[1] Shur-Wern Wang Chern,[1] D. Scott Schmid,[1] Kay W. Radford,[1] Rebecca J. McNall,[1] Paul A. Rota,[1] Carole J. Hickman,[1] William J. Bellini,[1] and Gregory S. Wallace[1]

[1]Division of Viral Diseases, National Center for Immunization and Respiratory Diseases and [2]Division of Scientific Resources, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia

Background. Sporadic cases of parotitis are generally assumed to be mumps, which often requires a resource-intensive public health response. This project surveyed the frequency of viruses detected among such cases.

Methods. During 2009–2011, 8 jurisdictions throughout the United States investigated sporadic cases of parotitis. Epidemiologic information, serum, and buccal and oropharyngeal swabs were collected. Polymerase chain reaction methods were used to detect a panel of viruses. Anti–mumps virus immunoglobulin M (IgM) antibodies were detected using a variety of methods.

Results. Of 101 specimens, 38 were positive for a single virus: Epstein-Barr virus (23), human herpesvirus (HHV)-6B (10), human parainfluenza virus (HPIV)-2 (3), HPIV-3 (1), and human bocavirus (1). Mumps virus, enteroviruses (including human parechovirus), HHV-6A, HPIV-1, and adenoviruses were not detected. Early specimen collection did not improve viral detection rate. Mumps IgM was detected in 17% of available specimens. Patients in whom a virus was detected were younger, but no difference was seen by sex or vaccination profile. No seasonal patterns were identified.

Conclusions. Considering the timing of specimen collection, serology results, patient vaccination status, and time of year may be helpful in assessing the likelihood that a sporadic case of parotitis without laboratory confirmation is mumps.

Keywords. mumps; parotitis; diagnostics.

Mumps is an acute, viral illness whose classic symptom is parotitis, or swelling of the parotid salivary glands. During mumps virus infection, the occurrence of unilateral or bilateral parotitis is often preceded by nonspecific prodromal symptoms, such as fever, headache, malaise, and anorexia. Although other causes of parotitis exist, mumps is the only known cause of epidemic parotitis in humans. However, up to 30% of mumps virus infections can be asymptomatic or present with only nonspecific respiratory symptoms, making the recognition and clinical diagnosis of mumps difficult [1].

Laboratory methods used to confirm mumps include detection of anti–mumps virus immunoglobulin M (IgM) antibodies, demonstration of a mumps virus–specific antibody response (either a 4-fold increase in immunoglobulin G [IgG] titer as measured by quantitative assays or a seroconversion from negative to positive using a standard serologic assay of paired acute and convalescent serum specimens), detection of mumps virus RNA using conventional or real-time reverse transcription polymerase chain reaction (RT-PCR), or isolation of mumps virus in cell culture [2]. However, reinfection with mumps virus has been well documented [3–6], and people who have a prior immune history—either through vaccination or natural infection—may not mount an IgM response, may not have a 4-fold rise in IgG titer, or may already be positive for IgG on the initial blood draw, and may have a viral load below the

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[a]Present affiliation: Division of HIV/AIDS Prevention, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention, Atlanta, Georgia.

Correspondence: Albert E. Barskey, MPH, Centers for Disease Control and Prevention, 1600 Clifton Rd NE, MS E-47, Atlanta, GA 30333 (abarskey@cdc.gov).

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level of assay detection [6]. Thus, a negative laboratory test result cannot exclude mumps etiology.

Due to a successful immunization program in the United States, mumps is a well-controlled disease in this country, with approximately 300 cases reported annually [7]. The identification of cases of mumps is important in the initiation of control measures to prevent the spread of the disease among persons who do not have presumptive evidence of immunity. When a case of mumps is reported to local health agencies, public health personnel routinely obtain patient specimens, assess the vaccination status of the case patient and his or her contacts, and, if appropriate, recommend and enforce measures to control further disease transmission. Follow-up for even a single case of suspected mumps can be time-consuming and costly for state and local health department staff.

The foundation for mumps surveillance is its status as a nationally notifiable condition— that is, laboratories and healthcare providers in all 50 states are required to report confirmed and probable cases of mumps to local public health authorities who, in turn, report them to the Centers for Disease Control and Prevention (CDC) via state health departments [8]. This reporting alerts the CDC to increases in disease incidence, to clusters of disease, and to disease trends, all of which guide the public health response. However, accurate reporting relies on accurate clinical and laboratory assessment, and as described above, this can be challenging with mumps.

Following the 2006 US mumps outbreak [9], several state health departments anecdotally reported increased numbers of sporadic cases of parotitis (ie, suspect mumps cases) without geographic or social connections to one another. Although mumps virus is the only agent known to cause epidemic parotitis, sporadic cases have been associated with other viral pathogens, such as adenoviruses, enteroviruses (EVs; including coxsackieviruses and echoviruses), Epstein-Barr virus (EBV), human herpesviruses (HHVs) 6A and 6B, influenza viruses A and B, human parainfluenza viruses (HPIVs) 1–3, and parvovirus B-19 [10–14]. Although laboratory diagnostics for mumps have improved greatly since the 2006 outbreak, especially those for viral detection [15], a negative laboratory test result for mumps, especially a serological test result, cannot rule out the disease. Because of this, and because testing for alternative causes of parotitis is not routinely performed, the etiologic cause of a sporadic case of parotitis in a vaccinated individual with negative laboratory test results for mumps is often undetermined, but assumed to be mumps. This places a large burden on state health agencies because all suspected cases of mumps must be investigated.

This enhanced surveillance project attempted to characterize the profile of viruses associated with sporadic cases of parotitis, as well as one virus (human bocavirus [HBoV]) whose possible association with parotitis had not been previously studied, in an effort to better assess the likelihood of such cases being mumps in the absence of confirmatory test results.

METHODS

Patient Selection

The jurisdictions of Arizona, California, Kansas, Michigan, North Carolina, Philadelphia, Tennessee, and Washington State identified sporadic cases of parotitis during 2009–2011. Cases of parotitis were investigated according to routine procedures established for investigating a case of mumps. Information was collected, including parotitis onset date, patient date of birth, sex, mumps vaccination history, and exposure history. Blood specimens, buccal swabs, and oropharyngeal swabs were requested. A case was considered sporadic, and therefore appropriate for this project, if the patient was not epidemiologically linked to a laboratory-confirmed case of mumps and not epidemiologically linked to ≥2 other cases of parotitis.

This project was determined to be surveillance and not research by the CDC's institutional review board liaison.

Laboratory Methods

Nucleic Acid Extractions

At the CDC, the Roche MagNA Pure LC automated nucleic acid extraction system was used with the Roche MagNA Pure LC Total Nucleic Acid Extraction Kit (Roche Diagnostics) according to the manufacturer's instructions to extract the total nucleic acid from each specimen. All extracts were tested for the human RNase P gene to assess the presence of PCR inhibitors and as a measure of specimen quality.

Mumps Virus

Real-time RT-PCR (rRT-PCR) was used to screen specimens for mumps virus (MuV) using primers targeting the N (nucleoprotein) gene. A sample was considered positive by rRT-PCR if the cycle threshold (Ct) value for the N gene was <40 [15].

Human Herpesviruses 6A and 6B

Conventional PCR was used to screen specimens for the presence of HHV-6. Primers targeted a short region of the major transactivating protein gene that included a short insertion/deletion that permitted the discrimination of HHV-6A from HHV-6B [16]. HHV-6A and HHV-6B discrimination was made by gel electrophoresis with the amplicon displaying the correct product size band at 325 bp or 553 bp, respectively.

Epstein-Barr Virus

Real-time fluorescence resonance energy transfer PCR was used to screen specimens for the presence of EBV. Primers targeted the BamHI repeat region of EBV (CDC, unpublished methods).

Enteroviruses and Human Parechoviruses

Specimens were screened for the presence of EV using rRT-PCR targeting the 5′-nontranslated region (NTR) [17]. Human parechoviruses (HPeVs) were detected and identified by analogous methods using rRT-PCR targeting the HPeV 5′-NTR [18]. For both EV and HPeV, a sample was considered positive if the Ct was <45.

Adenoviruses

A real-time PCR assay was used to test specimens for adenovirus (AdV) using primers described previously [19]. A sample was considered positive if the Ct was <45.

Human Parainfluenza Viruses 1–3

Specimens were tested for HPIV-1–3 using rRT-PCR assays as previously described [20]. A sample was considered positive if the Ct was <45.

Human Bocavirus

Real-time PCR was used to screen specimens for HBoV. A sample was considered positive if the Ct was <45. A positive test result for both HBoV NS1 and NP-1 gene targets or for a single gene target confirmed from a second extraction from a new sample aliquot was considered definitive evidence of HBoV infection [21].

Mumps IgM Antibody

Serum specimens were tested for mumps IgM at commercial, public health, and CDC laboratories using a variety of methods including immunofluorescence assays (IFAs) and indirect and capture enzyme immunoassays (EIAs).

Statistical Methods

Proportions were compared using the Fisher exact test. Medians were compared using the Wilcoxon rank-sum test. The χ^2 independence test was used to assess associations. Binomial confidence intervals were constructed using exact methods. Analyses were performed using SAS software, version 9.3.

RESULTS

Viruses Detected

Mumps virus was not detected in any specimen from a patient without a known exposure to mumps. Of the 101 specimens meeting inclusion criteria and tested for the full panel of 11 viruses, 38 (38%) were positive for a single virus: 23 EBV, 10 HHV-6B, 3 HPIV-2, 1 HPIV-3, and 1 HBoV. No specimen was positive for >1 virus. MuV, EV, HPeV, HHV-6A, HPIV-1, and AdV were not detected.

Timing of Swab Collection

Most (60/101 [59%]) swab specimens were collected within 2 days of parotitis onset (Figure 1). A virus was detected in 42% (25/60) of specimens collected within 2 days of onset and in 32% (13/41) of specimens collected on days 3–12, but this difference was not statistically significant ($P = .4$).

Serology

Although MuV was not detected in any swab specimen, 17% (12/70) of available mumps IgM test results were positive (Table 1). A higher percentage of mumps IgM test results was positive in patients in whom a virus was detected (23% [6/26]) than in patients in whom a virus was not detected (14% [6/44]), but this difference was not significant ($P = .3$). Among the

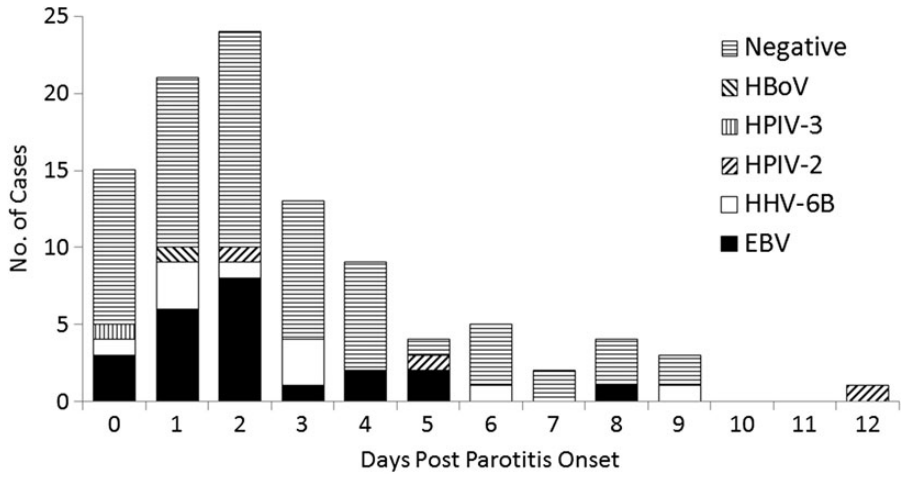

Figure 1. Timing of swab collection. The number of cases is shown in bars by the number of days after parotitis onset on which the swab specimen was collected. Horizontally striped bars represent cases in which no virus was detected. Abbreviations: EBV, Epstein-Barr virus; HBoV, human bocavirus; HHV, human herpesvirus; HPIV, human parainfluenza virus.

Table 1. Mumps Immunoglobulin M Results by Detected Virus

Assay	Total, No. of Mumps IgM Positive (%)	No Virus Detected, No. of Mumps IgM Positive (%)	Virus Detected, No. of Mumps IgM Positive (%)	EBV+, No. of Mumps IgM Positive (%)	HHV-6B+, No. of Mumps IgM Positive (%)	HPIV-2+, No. of Mumps IgM Positive (%)	HPIV-3+, No. of Mumps IgM Positive (%)	HBoV+, No. of Mumps IgM Positive (%)
Capture EIA	2/22 (9)	1/15 (7)	1/7 (14)	1/6 (17)	0/1 (0)	0/0	0/0	0/0
Indirect EIA	1/16 (6)	0/7 (0)	1/9 (11)	0/5 (0)	1/2 (50)	0/1 (0)	0/0	0/1 (0)
EIA unknown	3/6 (50)	2/5 (40)	1/1 (100)	0/0	0/0	0/0	1/1 (100)	0/0
IFA	3/5 (60)	1/2 (50)	2/3 (67)	1/1 (100)	1/2 (50)	0/0	0/0	0/0
Unknown	3/21 (14)	2/15 (13)	1/6 (17)	1/4 (25)	0/2 (0)	0/0	0/0	0/0
Total	12/70 (17)	6/44 (14)	6/26 (23)	3/16 (19)	2/7 (29)	0/1 (0)	1/1 (100)	0/1 (0)

Abbreviations: EBV, Epstein-Barr virus; EIA, enzyme immunoassay; HHV, human herpesvirus; HPIV, human parainfluenza virus; IFA, immunofluorescence assay; IgM, immunoglobulin M.

6 serum specimens that tested positive for mumps IgM obtained from patients in whom a virus was detected, 3 (50%) were obtained from a patient in whom EBV was detected, 2 (33%) were obtained from a patient in whom HHV-6B was detected, and 1 (17%) was obtained from a patient in whom HPIV-3 was detected. A higher proportion of IFAs had a positive result for mumps IgM than EIAs (60% vs 6%–50%).

Patient Characteristics

The median age of all patients was 19 years (range, 4 months to 76 years; Table 2). The median age of patients in whom a virus was not detected (22 years) was significantly different from that of patients in whom a virus was detected (16.5 years; $P = .0065$). Although EBV was detected among patients of all age groups, the greatest proportion (9/23 [39%]) was detected among patients 18–24 years of age (Table 3). All 3 patients in whom HPIV-2 was detected were aged <8 years. Although the median age of patients in whom HHV-6B was detected was 6 years, the range spanned age 4 months to 35 years.

Of all 101 patients with parotitis, 46 (46%) were female (Table 2). There was no statistical difference by sex between patients in whom a virus was not detected and those in whom a virus was detected ($P = .8$).

Vaccination status for mumps was documented for 64% (65/101) of all patients, and of these, 62% (40/65) had received 2 doses of measles-mumps-rubella (MMR) vaccine, 20% (13/65) had received 1 dose, and 18% (12/65) were unvaccinated (Table 2). Where vaccine status was known, there was no statistical association between vaccination profile and detection of a virus. Mumps IgM was detected in the same percentage of vaccinated (16% [6/37]) and unvaccinated (17% [1/6]) patients.

Seasonality

Viruses were detected in specimens collected from patients whose parotitis onsets ranged from May 2009 through October 2011, but no seasonal trends were apparent (Figure 2). Among the 41 cases that occurred during the months of January through May (typical mumps season) [7], a virus was not detected in 24 (59%).

DISCUSSION

Our results indicate that non–mumps viruses could be isolated from patients with parotitis and without a known exposure to mumps. Previous studies have found an association between parotitis and EBV, HPIV, AdV, EV, HHV-6, influenza A, and parvovirus [11–14]. However, another study found no difference in the rate of detection of HHVs, including EBV and HHV-6A and HHV-6B, between children with and without parotitis [22], whereas a different study found a similar prevalence of non–mumps viruses among individuals with and without parotitis [23]. As was observed in other studies [11,

Table 2. Patient Characteristics

Virus Detected	Median Age, y (Range)	Female Sex, No. (%)	0 MMR Doses, No. (%) 1 MMR Dose, No. (%) ≥2 MMR Doses, No. (%) Unknown MMR Doses, No. (%)	State/Jurisdiction[a] (No.)
All patients (N = 101)	19 (0.3–76)	46 (46)	12 (12) 13 (13) 40 (40) 36 (36)	AZ (6), CA (4), KS (13), MI (33), NC (15), PHL (10), TN (1), WA (19)
No virus detected (n = 63)	22 (3–76)	28 (44)	6 (10) 9 (14) 20 (32) 28 (44)	AZ (5), CA (1), KS (4), MI (24), NC (10), PHL (6), WA (13)
Virus detected (n = 38)	16.5 (0.3–71)	18 (47)	6 (16) 4 (11) 20 (53) 8 (21)	AZ (1), CA (3), KS (9), MI (9), NC (5), PHL (4), TN (1), WA (6)
EBV (n = 23)	19 (1–71)	12 (52)	3 (13) 2 (9) 12(52) 6 (26)	AZ (1), CA (1), KS (5), MI (5), NC (4), PHL (3), WA (4)
HHV-6B (n = 10)	6 (0.3–35)	5 (50)	1 (10) 2 (20) 5 (50) 2 (20)	CA (2), KS (3), MI (2), NC (1), TN (1), WA (1)
HPIV-2 (n = 3)	5 (4–7)	0 (0)	1 (33) 0 (0) 2 (67) 0 (0)	KS (1), MI (2)
HPIV-3 (n = 1)	21 (N/A)	0 (0)	0 (0) 0 (0) 1 (100) 0 (0)	PHL (1)
HBoV (n = 1)	3 (N/A)	1 (100)	1 (100) 0 (0) 0 (0) 0 (0)	WA (1)

Abbreviations: EBV, Epstein-Barr virus; HBoV, human bocavirus; HHV, human herpesvirus; HPIV, human parainfluenza virus; MMR, measles-mumps-rubella vaccine.

[a] AZ, Arizona; CA, California; KS, Kansas; MI, Michigan; NC, North Carolina; PHL, Philadelphia (Pennsylvania); TN, Tennessee; WA, Washington State.

23], EBV was detected most often in our project (in 23% of specimens), followed by HHV-6B (10%), HPIV-2 (3%), HPIV-3 (1%), and HBoV (1%). While these viruses (except HBoV) are known to cause parotitis, an etiologic relationship should not be assumed in our survey, as the carriage rate among similar healthy individuals was unknown, and the absence of a MuV infection is difficult to prove. Other factors, including timing of swab collection, mumps serology results, mumps vaccination status, and month of disease onset, should also be taken into account when considering a mumps diagnosis.

Timing of specimen collection is important to consider in interpreting laboratory results. The sensitivity of mumps RNA detection by rRT-PCR declines when samples are collected >2 days after onset. Beyond the second day after onset, the positivity rate declines to approximately 22%–41% [15]. MuV-negative swabs collected within 2 days of parotitis onset more reliably predict a nonmumps etiology than do MuV-negative swabs collected ≥3 days after onset. Fifty-nine percent of our specimens were collected within 2 days of parotitis onset, and so these patients' illnesses were less likely caused by MuV. Negative mumps IgM results may occur when serum is collected prior to day 3 after clinical presentation [15, 24–26]. Patients who mount a secondary immune response, as occurs in the majority of vaccinated mumps cases, may not have an IgM response, or it may be transient and not detected depending on timing of specimen collection. Failure to detect mumps IgM in previously vaccinated individuals has been well documented [4–6, 15].

Commercial IFA and indirect EIA IgM tests are less sensitive than mumps IgM capture assays [15, 24, 27]. A recent study of 205 well-characterized cases that were confirmed by virus isolation showed that IgM capture assays detected 29%–52% of cases whereas an indirect EIA and an IFA detected only 12%–15% of culture-confirmed cases. When stratified by MMR dose,

Table 3. Viral Detection by Patient Age Group

Age Group, y	EBV	HHV-6B	HPIV-2	HPIV-3	HBoV	Total
0–4	3	4	1	0	1	9
5–9	1	3	2	0	0	6
10–17	4	1	0	0	0	5
18–24	9	0	0	1	0	10
25–39	3	2	0	0	0	5
≥40	3	0	0	0	0	3
Total	23	10	3	1	1	38

Data are presented as No. of patients.

Abbreviations: EBV, Epstein-Barr virus; HBoV, human bocavirus; HHV, human herpesvirus; HPIV, human parainfluenza virus.

all the IgM assays performed well when detecting IgM in unvaccinated cases; however, among previously vaccinated individuals, the indirect EIA and the IFA detected only 9%–10% of cases [15]. A capture EIA also tends to be more specific than an indirect EIA and an IFA [24, 27, 28]. In our survey, of the 22 serologic specimens that were tested with a capture EIA, 9% were positive for mumps IgM. For the 16 specimens tested by indirect EIA, 6% were positive, and 60% of the 5 specimens tested by IFA were positive. False-positive reactions can be caused by rheumatoid factor, specific IgG, and cross-reacting IgM in the specimens [24, 26]. Heterotypic IgM antibody responses may occur in individuals infected with other viruses, particularly EBV, which produces a polyclonal B cell stimulation, and sera from these patients may give false-positive IgM results [26, 29, 30]. Furthermore, finding mumps IgM in the serum from the patient in whom HPIV-3 was detected was not surprising, as MuV and HPIV-1 and HPIV-3 are known to have cross-reactive epitopes [31, 32]. However, in our set of specimens with mumps serologic testing, there was no statistical difference between the mumps IgM positivity rate among patients in whom a virus was not detected (14%) and among those in whom a virus was detected (23%). Furthermore, if the mumps IgM-positive specimens that were obtained from patients in whom EBV was detected were excluded, the mumps IgM positivity rate among patients in whom a virus was identified would have been 13%.

Estimates for mumps vaccine effectiveness are high: approximately 77% (range, 64%–88%) for 1 dose and 88% (range, 79%–95%) for 2 doses [33–36]. Therefore, the cause of parotitis in a vaccinated patient is less likely to be MuV than in an unvaccinated patient. Among our parotitis patients with known vaccination status, 53 were vaccinated with at least 1 dose of mumps-containing vaccine. Among these 53 vaccinated patients, who had a lower likelihood of having mumps, another virus was detected in 24 (45%). Furthermore, because mumps IgM is detected more often among unvaccinated mumps patients than among previously vaccinated mumps patients [4–6, 15], finding a higher rate of mumps IgM among our unvaccinated parotitis patients might suggest a mumps etiology. However, we observed the same rate of IgM positivity among our vaccinated and unvaccinated parotitis patients.

The time of year in which the case occurred may also affect the likelihood of a sporadic case of parotitis being mumps. Endemic mumps has a late winter through early spring seasonal pattern [7]. Sporadic cases of parotitis of unknown etiology

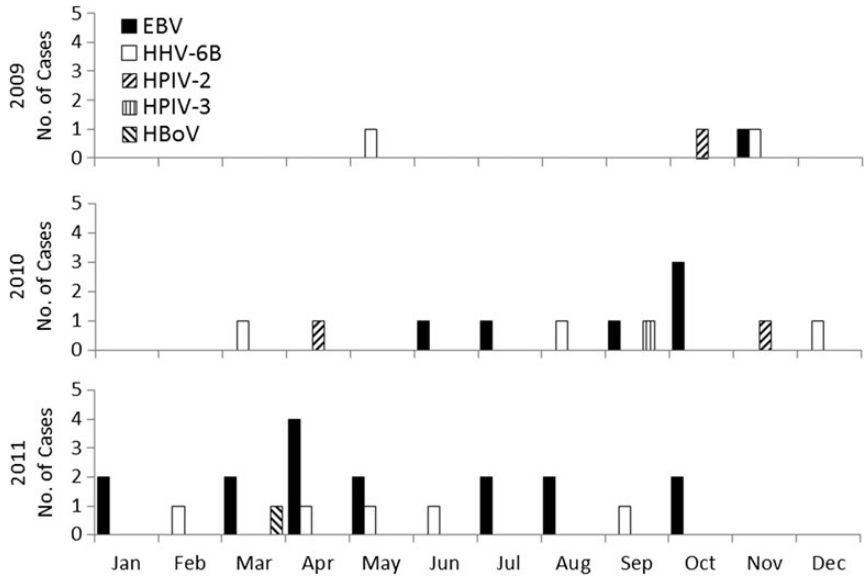

Figure 2. Viruses detected by onset month. The number of cases is shown in bars by the month and year in which parotitis onset occurred. Only cases in which a virus was detected are shown. Abbreviations: EBV, Epstein-Barr virus; HBoV, human bocavirus; HHV, human herpesvirus; HPIV, human parainfluenza virus.

occurring from January through May could have a higher likelihood of being mumps cases. Among our specimens collected during January through May, a virus was not detected in 59%. HPIV-1 and HPIV-2 disease peak in the fall (odd years for HPIV-1), whereas HPIV-3 peaks from April through June [37]. Two of our 3 HPIV-2 cases fit this pattern, but the HPIV-3 case we identified occurred in September. HBoV disease appears to peak during the late fall and winter [38], and the case we detected occurred in March. HHV-6 and EBV do not have remarkable seasonal patterns [39, 40], nor was any pattern identified in our specimens. However, during each progressive year of this project (2009–2011), more EBV was detected. AdV also does not show a marked seasonality in the United States [41], but we did not detect any AdV infections. According to data reported to the National Respiratory and Enteric Virus Surveillance System, more AdV was reported during the time period of this project (2009–2011) compared with 1990–2008, but less HPIV-1 and HPIV-3 were reported during 2009–2011 compared with 1990–2008. There was no difference in reporting of HPIV-2 between the 2 time periods.

Although none of our patients reported recent travel history, travel to areas of the world with high levels of circulating MuV should also be considered when assessing a mumps etiology in a patient with parotitis. Although Finland is the only country to have documented eliminating endemic mumps transmission [42], 62% of countries included the mumps vaccine in their immunization schedules as of the end of 2012 [43]. Levels of circulating MuV are likely to be lower in these countries, but mumps outbreaks have been reported among vaccinated populations [44–46].

This project had several limitations. Because a passive surveillance system was used, some cases of parotitis were likely missed. Similarly, viruses identified from this convenience sample may not be representative of the population. Causation could not be assumed, as the presence of these viruses in a control group without parotitis was not assessed. Some viral specimens were not collected within 2 days of parotitis onset, which is the ideal collection window; thus, some viruses may not have been detected. Other etiologies for parotitis exist, including HIV, *Bartonella henselae* (cat-scratch disease), and influenza [10, 12, 13], but we did not test for them. HBoV has not been previously associated with parotitis, but it was included in this viral panel for hypothesis-testing purposes. Thus, if HBoV is not truly associated with parotitis, including the HBoV-positive case with the cases in which a virus was detected when analyzing viral associations with parotitis would have been a misclassification error, biasing results away from the null.

Despite these limitations, the findings of this project offer a point for consideration. MuV was not detected in any specimen, and another virus associated with parotitis was detected in 38% of specimens. This may suggest that sporadic cases of parotitis may have a lower likelihood of being cases of mumps. Indeed, the zero percent detection rate (95% confidence interval [CI], 0%–3.6%) observed here was well below the 71% detection rate (95% CI, 65.1%–75.7%) reported among outbreak-related cases and the 94% detection rate (95% CI, 90.0%–96.9%) reported among culture-confirmed, outbreak-related cases using the same assay [15]. The combination of a high vaccine efficacy and high vaccination coverage (91.1% for 2 doses of MMR among adolescents 13–17 years of age in 2011) may also suggest on a national level a lower likelihood that sporadic cases of parotitis are mumps [33–36, 47]. If it is true that the majority of sporadic cases of parotitis are not caused by MuV, then the annual number of cases of mumps reported in the United States may be artificially high. During 2009–2011, 91% of non-outbreak-related cases of mumps reported to the CDC via the National Notifiable Diseases Surveillance System were not epidemiologically linked to another case of mumps. However, at the same time, it is estimated that 30% of mumps cases are asymptomatic, and furthermore, in a study of a college outbreak during 2006, only 14% of case patients could identify the source of their exposure [33]. A better understanding of the role viruses play in causing parotitis, as well as improved laboratory diagnostics, would be useful in guiding public health investigations. As sufficient criteria for confidently excluding a mumps diagnosis in a sporadic case of parotitis do not currently exist, all such cases should be thoroughly investigated on the assumption that they are cases of mumps in an effort to prevent a potential outbreak.

Notes

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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