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Clinical Infectious Diseases

MAJOR ARTICLE

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(See the Major Article by Rolfes et al on pages 485–92 and the Editorial Commentary by Pavia on pages 502–3.)

Background. During the 2014–2015 US influenza season, 320 cases of non-mumps parotitis (NMP) among residents of 21 states were reported to the Centers for Disease Control and Prevention (CDC). We conducted an epidemiologic and laboratory investigation to determine viral etiologies and clinical features of NMP during this unusually large occurrence.

Methods. NMP was defined as acute parotitis or other salivary gland swelling of >2 days duration in a person with a mumps-negative laboratory result. Using a standardized questionnaire, we collected demographic and clinical information. Buccal samples were tested at the CDC for selected viruses, including mumps, influenza, human parainfluenza viruses (HPIVs) 1–4, adenoviruses, cytomegalovirus, Epstein-Barr virus (EBV), herpes simplex viruses (HSVs) 1 and 2, and human herpes viruses (HHVs) 6A and 6B.

Results. Among the 320 patients, 65% were male, median age was 14.5 years (range, 0–90), and 67% reported unilateral parotitis. Commonly reported symptoms included sore throat (55%) and fever (48%). Viruses were detected in 210 (71%) of 294 NMP patients with adequate samples for testing, ≥2 viruses were detected in 37 samples, and 248 total virus detections were made among all samples. These included 156 influenza A(H3N2), 42 HHV6B, 32 EBV, 8 HPIV2, 2 HPIV3, 3 adenovirus, 4 HSV-1, and 1 HSV-2. Influenza A(H3N2), HHV6B, and EBV were the most frequently codetected viruses.

Conclusions. Our findings suggest that, in addition to mumps, clinicians should consider respiratory viral (influenza) and herpes viral etiologies for parotitis, particularly among patients without epidemiologic links to mumps cases or outbreaks.

Keywords. non-mumps viral parotitis; non-mumps parotitis; parotitis.

Acute, viral non-mumps parotitis (NMP) is an infrequently recognized illness that occurs sporadically and has been associated with multiple etiologic agents, including adenoviruses, enteroviruses (coxsackieviruses, echoviruses), Epstein-Barr virus (EBV), human herpes virus (HHV) 6A and 6B, influenza A(H3N2) and influenza B viruses, human parainfluenza viruses (HPIVs) 1–3, and parvovirus B-19 [1–9]. While there is no systematic surveillance for NMP, results of several studies have suggested EBV is the most frequently detected virus among patients with NMP, followed by HPIV3, HPIV2, and adenoviruses [6–9]. During January 2015, approximately 17 cases of NMP were reported to the Centers for Disease Control and Prevention (CDC) from several Midwestern states. Although small in number, these temporally related reports represented an unusual occurrence of viral NMP.

The only known cause of epidemic parotitis among humans is mumps, a vaccine-preventable disease caused by mumps virus, a member of the *Rubulavirus* genus of the *Paramyxoviridae* family [10]. Prior to the licensure of mumps vaccine in 1967 and its subsequent routine use in the United States, mumps was one of the most frequently reported diseases during childhood [11, 12]. Since 1990, the Advisory Committee on Immunization Practices to the CDC has recommended children routinely receive 2 doses of measles–mumps–rubella vaccine (MMR) [13]; the effectiveness against mumps following 2 doses of MMR is approximately 88% (range, 66%–95%) [14, 15]. This vaccine recommendation had a powerful impact on reducing mumps occurrence from more than 150 000 cases reported annually during the 1960s to a nadir of approximately 250 cases reported annually during 2000–2005 [16].

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Laboratory testing includes serologic assays to detect mumps immunoglobulin M (IgM), virus culture, or conventional or real-time reverse transcription polymerase chain reaction (RT-PCR) to detect mumps viral RNA. However, confirming mumps virus infection can be challenging among persons with immunity induced by prior vaccination or infection. Upon infection, patients with prior immunity may not mount an IgM response or may have low viral load, thus a negative RT-PCR or serologic test result does not rule out mumps in a patient with compatible signs and symptoms [17].

Because of the unusual occurrence of viral NMP during the 2014–2015 influenza season and the importance of pursuing laboratory confirmation when acute parotitis occurs and mumps is suspected, enhanced understanding of the epidemiologic and clinical features of acute NMP would improve the accuracy of diagnosis among clinicians evaluating suspected mumps cases and result in more timely treatment and public health action when appropriate. During February 2015, we initiated a multistate epidemiologic and laboratory study to describe the etiologic, demographic, epidemiologic, and clinical features of all reported cases of NMP and a parallel multistate case-control study to examine risk factors for the occurrence of NMP caused by influenza A(H3N2) viruses that circulated during the 2014–2015 season. Here, we present the results of the epidemiologic and laboratory study.

METHODS

Case Ascertainment and Epidemiologic Investigation

On 22 December 2014, the CDC's Influenza Division was notified by the Indiana State Department of Health of a cluster of patients with influenza-associated parotitis. On 9 January 2015, after additional state health departments reported similar occurrences of viral NMP, the Influenza Division notified state and local health departments of the occurrence of influenza-associated parotitis through the Epidemic Information Exchange and requested notification when a patient with non-mumps parotitis associated with influenza was identified and the illness met the case definition [18]. On 4 February, state and local health departments and public health laboratories were invited to participate in a multistate investigation of NMP. States could participate in the case-control study of influenza-associated parotitis and/or the epidemiologic and laboratory investigation of NMP regardless of etiology. The methods and results of the case-control study are presented elsewhere [18].

For the epidemiologic and laboratory investigation of NMP, a case was defined as clinical signs or symptoms compatible with acute parotitis or other salivary gland swelling of >2 days duration in a patient with illness onset from 1 October 2014 through 31 May 2015, who had no known epidemiologic linkage to a laboratory-confirmed case of mumps, did not have a laboratory-confirmed diagnosis of mumps infection (was either mumps-negative or not tested for mumps), and either had a laboratory-confirmed non-mumps viral infection (using a recommended test, including RT-PCR or viral culture) or had a buccal swab specimen available for viral testing at the CDC. Surveillance methods for eligible patients varied among states; methods included contacting clinicians using the Health Alert Network, using clinician email listservs, enhancing existing influenza surveillance activities, and passive reporting of suspected mumps cases.

Case ascertainment and investigation were designated as public health surveillance and were given a nonresearch determination by a CDC institutional review board. A questionnaire was administered by telephone to consenting eligible persons or their guardians. Information collected included patient demographic information; signs and symptoms; testing for mumps, influenza, and other viral agents; past medical history; self-reported current and previous seasonal influenza vaccination; self-report of MMR vaccination; hospitalization during the past 12 months; and recent travel.

Laboratory Testing and Analysis

The CDC Division of Viral Disease laboratories conducted testing for mumps virus, HPIV 1–4, adenoviruses, and herpes family viruses, including cytomegalovirus (CMV), EBV, herpes simplex virus (HSV) 1 and 2, HHV6A, and HHV6B. The CDC Influenza Division laboratories conducted testing for influenza viruses.

Mumps Virus

The real-time RT-PCR assays to detect mumps RNA were performed as previously described [19].

Herpes Family Viruses

HHV6

A conventional PCR method coupled with gel electrophoresis was used to screen samples for the presence of HHV6. The primers are from the immediate early gene, *U90*, and are designed to discriminate HHV6A from HHV6B based on a deletion in the U1102 strain. HHV6A-positive samples are determined by a band size of 325 bp; whereas a band size of 553 bp is the result for HHV6B-positive samples [7, 20].

EBV

Specimens were screened using a real-time florescence resonance energy transfer (FRET)–based PCR method that uses 2 florescent probes, the anchor and the detector. When the target is present, these bound probes are in close proximity and release a detectable signature florescence. The target for this method is the BamHI region of EBV [7].

HSV1/2

FRET technology was used to discriminate HSV-1 from HSV-2 in this real-time PCR method targeting the glycoprotein B, *UL27*, gene. This 2-probed system can discriminate type 1 from type 2 based on melt curve analysis. A sample is considered HSV-1 positive if the melt temperature (Tm) is 56°C and HSV-2 positive if the Tm is 63°C (CDC, unpublished method).

Influenza Viruses

Influenza virus infection was confirmed and typed/subtyped using RT-PCR with standard protocols or next-generation sequencing. RT-PCR assays to detect influenza viral RNA were performed as previously described [21] or next-generation sequencing was conducted using a MiSeq platform and the Iterative Refinement Meta Assembler [22]. Study sequences were compared to viral reference sequences and sequences from other circulating viruses.

Adenoviruses and Human Parainfluenza Viruses 1–4

Sample nucleic acid extracts were tested using CDC singleplex real-time RT-PCR assays for adenoviruses and parainfluenza types 1–4 [23]. Threshold cycle values were determined by manually adjusting the fluorescence baseline to fall within the exponential phase of the amplification curves and above any background signal. A positive test result was considered a well-defined curve that crossed the threshold cycle within 40 cycles.

Statistical Analyses

Statistical analyses included use of χ^2 test to compare proportions and Wilcoxon rank-sum tests to compare medians. Analyses were performed with SAS® version 9.3 (SAS Institute, Cary, NC).

RESULTS

Virus Detections

From 1 October 2014 through 31 May 2015, 323 cases of NMP among residents of 21 states were reported to the CDC. The geographic distribution of viruses detected during testing at the CDC of buccal samples from 294 NMP patients from 19 states is summarized in Figure 1 and Table 1. Influenza A(H3N2) virus was detected in 156 (53%) patient samples, including ≥1samples from all 19 states with reported cases. HHV6B was detected in 42 (14%) samples from 10 states. Six other viruses were detected, including adenovirus (1%), HPIV2 (3%), HPIV3 (0.7%), EBV (13%), HSV-1 (1.4%), and HSV-2 (0.3%), primarily in specimens from Midwestern and Northeastern states (Table 1). Multiple viruses were detected in 13% of samples. Mumps virus, CMV, HHV6A, HPIV1, and HPIV4 were not detected in any sample.

Patient Characteristics

Data regarding demographic and clinical features and exposure and vaccination history from 320 NMP patients (with sufficient data) are summarized in Tables 2–4. Among these patients, most were male (65%), median age was 14.5 years (range, <1–90; [interquartile range (IQR), 8–30 years]), and 64% were aged <20 years (Table 2). There were significant differences in sex and median age by virus detection category, which includes single virus detected in the sample (4 categories: influenza A(H3N2), other respiratory viruses, HHV6B, and EBV), virus codetection, and no virus detected (Table 2). The percentage male was greatest among patients with influenza virus single detections and codetections (32 of 37 codetections included influenza virus) and least among patients with no virus detected. Younger median age was associated with HHV6B detection, other respiratory virus detection (HPIV2/3 and adenovirus), and virus codetection, while older median age was associated with EBV and no virus detected (Table 2).

Among the 294 patients with buccal samples tested, 232 (79%) were aged 5–49 years. Single detections of influenza A(H3N2) virus occurred in all age groups, but 76 (61%) occurred among patients aged 5–19 years (Figure 2). Among single detections of other viruses, 14 (74%) HHV6B detections and all other respiratory virus detections occurred among younger patients (aged <14 years), and 14 (78%) EBV detections occurred among

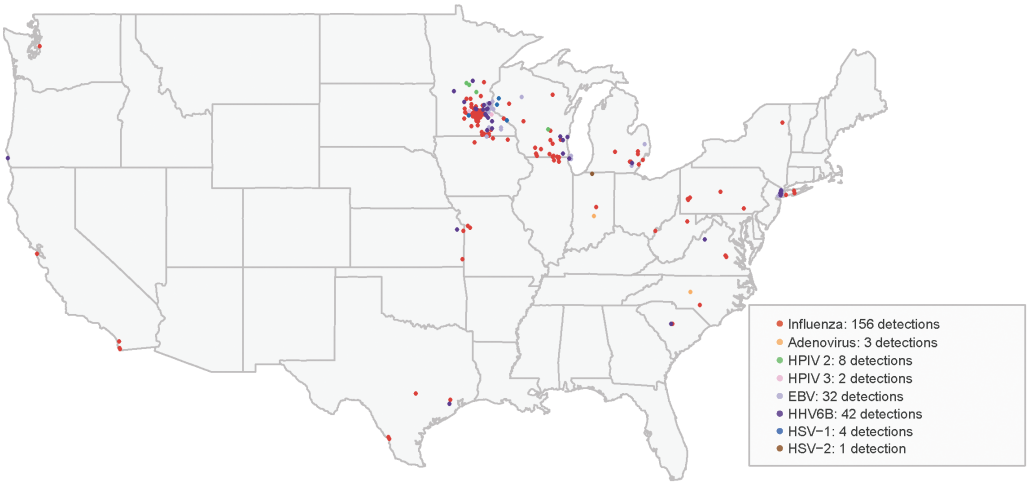

Figure 1. Geographic distribution of viruses detected among patients with non-mumps viral parotitis, with samples tested at the Centers for Disease Control and Prevention, United States, 1 October 2014–31 May 2015. Abbreviations: EBV, Epstein-Barr virus; HHV, human herpes virus; HPIV, human parainfluenza virus; HSV, herpes simplex virus.

Table 1. Viruses Detected in Samples from Patients With Non-mumps Viral Parotitis Tested at the Centers for Disease Control and Prevention and Number of Detections by Virus and State, United States, 1 October 2014–31 May 2015

State	Influenza A(H3N2) Virus (N = 156)	Adenovirus (N = 3)	HPIV2 (N = 8)	HPIV3 (N = 2)	HHV6B (N = 42)	EBV (N = 32)	HSV1 (N = 4)	HSV2 (N = 1)
California	4	0	0	0	0	0	0	0
Indiana	1	1	1	0	0	0	0	1
Maine	3	0	0	0	3	0	0	0
Massachusetts	3	0	0	0	0	0	0	0
Michigan	10	0	0	0	2	2	0	0
Minnesota	71	0	3	2	17	16	4	0
Missouri	5	0	0	0	1	0	0	0
New Hampshire	6	0	1	0	2	1	0	0
New Jersey	4	0	0	0	0	0	0	0
New York[a]	4	1	2	0	9	9	0	0
North Carolina	1	1	0	0	0	0	0	0
Oregon	1	0	0	0	1	1	0	0
Pennsylvania	5	0	0	0	0	0	0	0
South Carolina	2	0	0	0	1	0	0	0
Texas	4	0	0	0	0	0	0	0
Virginia	4	0	0	0	1	0	0	0
Washington	1	0	0	0	0	0	0	0
West Virginia	2	0	0	0	0	0	0	0
Wisconsin	25	0	1	0	5	3	0	0

Abbreviations: EBV, Epstein-Barr virus; HHV, human herpes virus; HPIV, human parainfluenza virus; HSV, herpes simplex virus.

Two viruses were codetected in each of 36 samples. The codetection pairings included 19 samples with influenza A(H3N2) virus and HHV6B detected, 10 with influenza A(H3N2) virus and EBV, 2 with EBV and HHV6B, 2 with influenza A(H3N2) virus and HSV-1, 1 with EBV and HPIV2, 1 with HHV6B and HPIV2, and 1 with HPIV2 and HSV-2. Three viruses were detected in 1 sample: influenza A(H3N2) virus, EBV, and HHV6B. Eighty-four samples from patients with non-mumps parotitis that were tested at the Centers for Disease Control and Prevention had no viruses detected. These samples were from patients from 8 states: Indiana, 1; Michigan, 2; Minnesota, 38; New Hampshire, 1; New York, 20 (19 from New York City and 1 from New York State); Texas, 1; Virginia, 1; and Wisconsin, 20.

[a]Represents New York City (36 samples) and New York State (9 samples).

older patients (aged >19 years). Among patients with no virus detected, 47 (56%) were aged >19 years (Figure 2, Table 2).

Among all patients, 67% reported unilateral parotitis and 40% reported influenza-like illness (ILI; fever [temperature ≥100°F] or feeling feverish and cough or sore throat). Unilateral parotitis was less frequent among patients with no virus detected. Patients with influenza virus detection more frequently reported ILI and other symptoms preceding parotitis onset than patients with EBV or no virus detected (Tables 2 and 3). Among all patients, 46% reported receiving antibiotics during their illnesses; with the exception of patients with EBV detection, little difference in percentage with antibiotic receipt was noted by virus detection category (Table 2). Among all patients, 5% reported complications and 11% were hospitalized; hospitalization was most frequent (22%) among patients with EBV detection, although numbers were small.

Most samples (69%) were collected within 2 days after parotitis onset. Specimens with no viruses detected were more likely to be collected >2 days after parotitis onset than specimens with viruses detected (Table 3).

Overall, 141 (44%) patients reported having an underlying medical condition, and asthma (23%) and obesity (18%) were the most common reported conditions. There was little difference in frequency of underlying conditions by virus detection category (Table 4).

There was little difference in history of mumps virus infection, parotitis, respiratory syncytial virus infection, or mononucleosis during the past year by virus detection category (Table 4). History of strep throat during the past year was more frequently reported among patients with virus codetection, although numbers were small (Table 4). Prior hospitalization during the past year was more frequent among patients with EBV detection.

Except for lower frequency of MMR vaccination among patients with EBV detected, there were no significant differences in MMR or influenza vaccination history by virus detection category (Table 4).

DISCUSSION

We report the largest known survey of sporadic cases of NMP and influenza-associated NMP, including 294 patients with interviews and sufficient samples available for further testing. Influenza viruses and viruses in the herpes family were commonly detected among these patients. All illness onsets occurred during the 2014–2015 US influenza season (October–May). Eight viruses were detected, and 210 (71%) of the samples tested were positive for at least 1 virus. The most frequently

Table 2. Demographic Features, Self-reported Signs and Symptoms, and Other Clinical Characteristics Among 320 Patients With Non-mumps Parotitis by Virus Detection Category, United States, 1 October 2014–31 May 2015

Variable	Total Non-Mumps Parotitis (N = 320)	Influenza A(H3N2) Virus[a] (N = 124)	Other Respiratory Virus[a,b] (N = 10)	Virus Codetection[c] (N = 37)	Human Herpes Virus 6B[a] (N = 19)	Epstein-Barr Virus[a] (N = 18)	No Virus Detected (N = 84)
Demographic features, n (%)[d]							
Male	207 (65)	92 (75)[e]	5 (50)	27 (73)	12 (63)	10 (56)	43 (51)[e]
Age, median years	14.5	14	7[f]	10[f]	5[f]	35[f]	26[f]
Range	<1–90	<1–84	1–12	2–77	<1–37	<1–90	1–74
Interquartile range	8–30	8–23	6–8	6–18	2–9	16–60	11–40
Self-reported signs and symptoms, n (%)[d]							
Influenza-like illness[h]	129 (40)	64 (52)[e]	3 (30)	13 (35)	5 (26)	4 (22)	23 (27)
Fever/feverish[i]	153 (48)	73 (59)[e]	6 (60)	14 (38)	5 (26)	5 (28)	33 (39)
Chills	116 (38)	56 (45)	8 (80)	13 (35)	4 (21)	5 (28)	24 (29)
Muscle ache	100 (31)	40 (33)	4 (40)	9 (24)	2 (11)	4 (22)	28 (33)
Headache	124 (39)	49 (40)	5 (50)	15 (41)	3 (16)	5 (28)	13 (15)
Cough	118 (37)	62 (50)	4 (40)	19 (51)	4 (21)	3 (16)	11 (13)
Wheeze	39 (12)	17 (14)	2 (20)	4 (11)	1 (5)	2 (11)	8 (10)
Sore throat	177 (55)	67 (55)	4 (40)	18 (49)	9 (47)	5 (29)	47 (56)
Runny nose	98 (31)	37 (30)	5 (50)	17 (46)	1 (6)	2 (11)	18 (21)
Ear pain	121 (38)	46 (37)	6 (60)	7 (19)	10 (53)	5 (29)	34 (40)
Rash	24 (8)	8 (7)	0 (0)	3 (8)	4 (21)	1 (6)	5 (6)
Facial swelling	239 (75)	97 (79)	7 (70)	28 (76)	11 (58)	15 (83)	62 (74)
Gland swelling	213 (67)	80 (65)	4 (40)	26 (70)	11 (58)	10 (56)	61 (73)
Unilateral parotitis	215 (67)	84 (68)	7 (70)	29 (78)	16 (84)	11 (61)	49 (58)[e]
Bilateral parotitis	91 (28)	37 (30)	2 (20)	6 (16)	2 (11)	7 (39)	28 (33)
Clinical characteristics, n (%)[d]							
Hospitalized during illness	34 (11)	9 (7)	1 (10)	5 (14)	2 (11)	4 (22)[e]	9 (11)
Experienced complication from illness[g]	16 (5)	3 (3)	0 (0)	3 (9)	0 (0)	1 (6)	7 (8)
Received antibiotics during illness	150 (46)	62 (50)	4 (40)	16 (43)	8 (42)	5 (28)	40 (48)

Included are 210 patients with non-mumps parotitis (NMP) who had buccal specimens from which 1 or more viruses were detected. These patients were subsequently defined as having non-mumps viral parotitis. Also included are 84 patients with NMP who had specimens from which viruses were not detected.

[a]Unless otherwise noted, virus detection indicates single detections of a virus in a sample.

[b]Other respiratory viruses include human parainfluenza virus 2 (HPIV2) detected in 5 samples, HPIV3 detected in 2 samples, and adenovirus detected in 3 samples.

[c]Two viruses were codetected in each of 36 samples. The codetection pairings included 19 samples with influenza A(H3N2) virus and human herpes virus 6B (HHV6B) detected, 10 with influenza A(H3N2) virus and Epstein-Barr virus (EBV), 2 with EBV and HHV6B, 2 with influenza A(H3N2) virus and herpes simplex virus-1 (HSV-1), 1 with EBV and HPIV2, 1 with HHV6B and HPIV2, and 1 with HPIV2 and HSV-2. Three viruses were detected in 1 sample: influenza A(H3N2) virus, EBV, and HHV6B.

[d]Unless otherwise noted.

[e]The χ^2 test *P* value < .05. Reference group consists of patients not in the category; for example, patients with HHV6B detected were compared with patients with samples in which HHV6B was not detected.

[f]Wilcoxon rank-sum test *P* value < .05. Reference group consists of patients not in the category; for example, patients with HHV6B detected were compared with patients with samples in which HHV6B was not detected.

[g]Self-reported complications included ear infections, testicular pain, pneumonia, and abdominal pain.

[h]Influenza-like illness defined as fever (temperature ≥100°F) or feeling feverish and cough or sore throat.

[i]Temperature ≥100°F or self-report of feeling feverish.

detected viruses were influenza A(H3N2), 156 detections in patients from 19 states; HHV6B, 42 detections; and EBV, 32 detections. Codetections of influenza A(H3N2) virus with HHV6B or EBV viruses were also common.

Investigators in other Northern Hemisphere countries have also reported on viral etiologies of NMP during the 2014–2015 influenza season [24–26]. While 2 of these investigations [25, 26] restricted their laboratory investigation to influenza viruses, a survey in the United Kingdom tested children for a broad panel of respiratory viruses, identifying influenza A(H3N2) virus in 16 (15%) samples and respiratory syncytial virus A with codetection of influenza A/H3 in 1 sample [26]. Similarly, we found an increased occurrence of influenza A(H3N2) virus–associated parotitis in this cohort, which might be an artifact of enhanced surveillance and case-finding efforts or a reflection of the dominance of influenza A(H3N2) virus in North America and Europe during the 2014–2015 season [27].

When included in the test panels, EBV was the most frequently detected virus in studies investigating etiologies of NMP prior to the 2014–2015 influenza season. Among 5

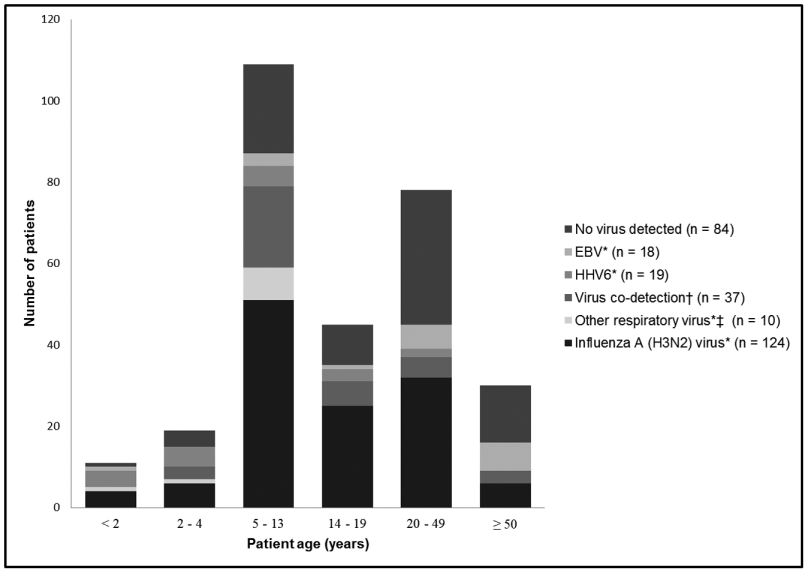

Figure 2. Virus detection among patients with non-mumps parotitis by age group, United States, 1 October 2014–31 May 2015. * Unless otherwise noted, virus detection indicates single detections of a virus in a sample. †Two viruses were codetected in each of 36 samples. The codetection pairings included 19 samples with influenza A(H3N2) virus and human herpes virus 6B (HHV6B) detected, 10 with influenza A(H3N2) virus and Epstein-Barr virus (EBV), 2 with EBV and HHV6B, 2 with influenza A(H3N2) virus and herpes simplex virus1 (HSV-1), 1 with EBV and human parainfluenza virus 2 (HPIV2), 1 with HHV6B and HPIV2, and 1 with HPIV2 and HSV-2. Three viruses were detected in 1 sample: influenza A(H3N2) virus, EBV, and HHV6B. ‡ Other respiratory viruses include HPIV2 detected in 5 samples, HPIV3 detected in 2 samples, and adenovirus detected in 3 samples. Abbreviations: EBV, Epstein-Barr virus; HHV, human herpes virus.

such studies, the average EBV detection rate was 20% (range, 6%–25%); however, EBV test methods varied [6–9, 28, 29]. We detected EBV in 13% of samples; however, the lower frequency reported here might have resulted from the initial surveillance focus on influenza-associated NMP.

The second most commonly detected virus among patients tested during this 2014–2015 study was HHV6B. Investigators in the United States and Finland screened patients with NMP during 2009–2011 and 1993–1998 for HHV6, respectively, with comparable results [7, 8]. The US study used a PCR-based molecular

Table 3. Timing of Sample Collection and Symptom Onset Among 320 Patients With Non-mumps Parotitis by Virus Detection Category, United States, 1 October 2014–31 May 2015

Variable	Total Non-Mumps Parotitis (N = 320)	Influenza A(H3N2) Virus[a] (N = 124)	Other Respiratory Virus[a,b] (N = 10)	Virus Codetection[c] (N = 37)	Human Herpes Virus 6B[a] (N = 19)	Epstein-Barr Virus[a] (N = 18)	No Virus Detected (N = 84)
Timing of sample collection, n (%)[d]							
≤2 days after any symptom onset	148 (46)	48 (39)	4 (40)	14 (38)	12 (63)	13 (72)	37 (44)
≤2 days after parotitis onset	222 (69)	89 (72)	7 (70)	29 (78)	14 (74)	13 (72)	44 (52)[e]
Timing of symptom onset, n (%)[d]							
Symptom onset preceded parotitis onset	154 (55)	71 (63)[e]	5 (50)	23 (62)	6 (32)	4 (27)[e]	24 (29)[e]
Symptom onset at same time as parotitis onset	106 (38)	38 (34)	3 (20)	8 (22)	6 (32)	7 (47)	38 (45)
Parotitis onset preceded other symptom onset	8 (3)	0 (0)	2 (20)	0 (0)	0 (0)	2 (13)	5 (6)

Included are 210 patients with non-mumps parotitis (NMP) who had buccal specimens from which 1 or more viruses were detected. These patients were subsequently defined as having non-mumps viral parotitis. Also included are 84 patients with NMP who had specimens from which viruses were not detected.

[a]Unless otherwise noted, virus detection indicates single detections of a virus in a sample.

[b] Other respiratory viruses include human parainfluenza virus 2 (HPIV2) detected in 5 samples, HPIV3 detected in 2 samples, and adenovirus detected in 3 samples.

[c] Two viruses were codetected in each of 36 samples. The codetection pairings included 19 samples with influenza A(H3N2) virus and human herpes virus 6B (HHV6B) detected, 10 with influenza A(H3N2) virus and Epstein-Barr virus (EBV), 2 with EBV and HHV6B, 2 with influenza A(H3N2) virus and herpes simplex virus 1(HSV-1), 1 with EBV and HPIV2, 1 with HHV6B and HPIV2, and 1 with HPIV2 and HSV-2. Three viruses were detected in 1 sample: influenza A(H3N2) virus, EBV, and HHV6B.

[d]Unless otherwise noted.

[e]The χ^2 test P value < .05. Reference group consists of patients not in the category; for example, patients with samples in which HHV6B detected were compared with patients with samples in which HHV6B was not detected.

Table 4. Underlying Medical Conditions, Exposure History, and Vaccination History Among Patients With Non-mumps Parotitis and Non-mumps Viral Parotitis by Virus Detection Category, United States, 1 October 2014–31 May 2015

Variable	Total Non-Mumps Parotitis (N = 320)	Influenza A(H3N2)[a] (N = 124)	Other Respiratory Virus[a,b] (N = 10)	Virus Codetection[c] (N = 37)	Human Herpes Virus 6B[a] (N = 19)	Epstein-Barr Virus[a] (N = 18)	No Virus Detected (N = 84)
Underlying medical condition, n (%)[d]							
Had any underlying medical condition	141 (44)	61 (50)	4 (40)	11 (30)	3 (16)[e]	8 (44)	40 (48)
Asthma	72 (23)	29 (24)	4 (40)	5 (14)	2 (11)	4 (22)	21 (25)
Chronic obstructive pulmonary disease or chronic lung condition	7 (2)	2 (2)	0 (0)	1 (3)	0 (0)	2 (11)	1 (1)
Cardiovascular condition	13 (4)	6 (5)	0 (0)	1 (3)	0 (0)	0 (0)	2 (2)
Diabetes	14 (4)	4 (3)	0 (0)	2 (5)	1 (5)	2 (11)	4 (5)
Renal condition	3 (0.9)	1 (0.8)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Immunosuppressive condition	7 (2)	3 (3)	0 (0)	0 (0)	0 (0)	0 (0)	2 (2)
Chemotherapy in past year	5 (2)	3 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Neurologic/neurodevelopmental condition	13 (4)	8 (7)	0 (0)	0 (0)	0 (0)	0 (0)	3 (4)
Rheumatoid arthritis	8 (3)	2 (2)	0 (0)	1 (3)	0 (0)	0 (0)	4 (5)
Sjogren's syndrome	2 (0.6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Obesity	55 (18)	20 (17)	0 (0)	5 (14)	2 (11)	2 (11)	20 (24)
Other condition[f]	16 (5)	6 (5)	0 (0)	0 (0)	0 (0)	2 (11)	8 (10)
Exposure history, n (%)[d]							
History of mumps virus infection	19 (6)	3 (3)	0 (0)	5 (14)	0 (0)	2 (11)	8 (10)
History of parotitis	18 (6)	2 (2)	0 (0)	3 (9)	1 (6)	2 (11)	7 (8)
Strep throat in past year	41 (13)	22 (18)	3 (30)	1 (3)[e]	3 (16)	1 (6)	10 (12)
Respiratory syncytial virus or mononucleosis in past year	2 (0.6)	0 (0)	0 (0)	0 (0)	0 (0)	2 (11)	0 (0)
Hospitalization for other illness in past year	26 (8)	8 (7)	1 (10)	3 (8)	0 (0)	5 (28)[e]	1 (1)
Dentist/oral surgeon visit within 2 weeks before illness	8 (3)	3 (2)	0 (0)	1 (3)	0 (0)	0 (0)	3 (4)
Sinus procedure within 2 weeks before illness	1 (0.3)	1 (0.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Aware of others with parotitis/mumps	44 (14)	6 (5)	0 (0)	4 (12)	1 (11)	2 (11)	10 (12)
Travel within 2 weeks before illness	24 (8)	19 (16)	2 (20)	4 (12)	2 (6)	1 (6)	11 (13)
Vaccination history, n (%)[d]							
Influenza vaccine: 2013–2014 season	195 (62)	84 (69)	7 (70)	21 (58)	10 (53)	11 (61)	45 (54)
Influenza vaccine: 2014–2015 season[g]	179 (56)	67 (55)	5 (50)	18 (49)	14 (74)	10 (56)	47 (56)
Measles–mumps–rubella vaccination[h]	280 (89)	113 (93)	10 (100)	33 (89)	18 (95)	11 (61)[e]	69 (82)

[a]Unless otherwise noted, virus detection indicates single detections of a virus in a sample.

[b]Other respiratory viruses include human parainfluenza virus 2 (HPIV2) detected in 5 samples, HPIV3 detected in 2 samples, and adenovirus detected in 3 samples.

[c]Two viruses were codetected in each of 36 samples. The codetection pairings included 19 samples with influenza A(H3N2) and human herpes virus 6B (HHV6B) detected, 10 with influenza A(H3N2) and Epstein-Barr virus (EBV), 2 with EBV and HHV6B, 2 with influenza A(H3N2) and herpes simplex virus 1 (HSV-1), 1 with EBV and HPIV2, 1 with HHV6B and HPIV2, and 1 with HPIV2 and HSV-2. Three viruses were detected in 1 sample: influenza A(H3N2), EBV, and HHV6B.

[d]Unless otherwise noted.

[e]The χ^2 test *P* value < .05. Reference group consists of patients not in the category; for example, patients with HHV6B detected were compared with patients with samples in which HHV6B was not detected.

[f]Other conditions included hepatic disease.

[g]Received influenza vaccine at least 2 weeks before symptom onset.

[h]Reported receiving at least 1 dose of the measles–mumps–rubella vaccine.

assay, while the Finnish study used a serologic assay; the HHV6B detection rate was 4%–10%. In the US study, the median age of patients with HHV6B detection was 6 years (range, 0–35), while testing for HHV6 was limited to children aged <4 years in the Finnish study. In our investigation, patients who had NMP with HHV6B had an age distribution similar to the range in the prior US study and were predominately male. HHV6 is found to infect almost all individuals during early childhood and, similar to other herpes viruses, is capable of reactivation in both normal and immunocompromised persons [30]. Interestingly, HHV6 appears to persist in salivary glands and viral DNA can be routinely detected in saliva using PCR [30]. Furthermore, HHV6B is the predominant strain found in both normal and immunocompromised hosts, which might explain the high frequency of HHV6B detection in our case series.

Of note, our rate of codetection of viruses in patient samples was 14%, and each of the 37 codetection samples included a herpes virus (HHV6B, EBV, HSV1, or HSV2) with either a respiratory

virus (influenza A(H3N2) virus, 32 samples or HPIV2, 3 samples) or another herpes virus (2 samples). Results of 1 study included codetection with EBV and respiratory viruses [9]; another reported codetection with respiratory viruses, with codetection rates ranging from 2% to 8% [6]. Results of prior studies suggest that infection with influenza and other respiratory viruses might reactivate herpes family viruses [31, 32]. In our study, patients with codetections did not report higher frequency of complications, hospitalizations, or underlying medical conditions compared with patients having samples with single virus detection.

It is challenging to determine the etiologic agents among sporadic cases of parotitis occurring in regions with a low incidence of mumps. Information regarding parotitis onset and timing of sample collection is important when interpreting laboratory results. In our study, 69% of oral samples were collected during the first 2 days following parotitis onset; among those samples, viruses were detected in 156 (70%), and the most frequent viruses detected were influenza A(H3N2) virus, HHV6B, and EBV. Further, detection of mumps virus by RT-PCR decreases >2 days following onset of swelling independently of the vaccination status. In one study, the sensitivity of RT-PCR for mumps virus detection decreased from 87% among oral samples collected during day 1 of swelling and 78% among samples collected during day 2 to 41% among samples collected during day 3 [22]. To enhance detection and diagnostic accuracy among patients with NMP, public health laboratories should consider additional respiratory virus panel and herpes family viral testing if resources permit.

Our investigation is subject to multiple limitations. First, it did not include testing for bacterial causes and noninfectious causes of parotitis, such as parotid stones [10]. This was intentional because the study focus was to characterize and describe viral etiologies of NMP. Second, while buccal swab specimens are the best diagnostic samples for suspected mumps, they are less sensitive than nasopharyngeal (NP) swab specimens for detection of respiratory viruses [33, 34]. This suboptimal sampling using buccal specimens might have resulted in an underestimation of the true prevalence of these viruses among our study population. Third, detection of remnant genetic material from previous infections could result in overestimation of the prevalence of certain viruses. Fourth, viruses that were not tested for, including echoviruses and parvovirus B19, which are known but rarely reported etiologies of viral NMP, potentially could have contributed to clinical presentations among these patients. Fifth, only samples associated with completed patient questionnaires were analyzed. This might have resulted in underreporting of certain viruses. Sixth, our initial case-finding strategy focused on influenza-associated viral NMP. This might have resulted in a higher-than-previously-reported occurrence of cases associated with influenza A(H3N2) virus and a lower-than-previously-reported frequency of NMP cases associated with EBV.

In conclusion, we investigated a large occurrence of nonmumps parotitis during the 2014–2015 US influenza season. Possible viral etiologic agents other than mumps virus were detected in a high proportion of samples tested. These detections resulted, in part, from enhanced surveillance, including additional respiratory testing at state public health laboratories and active case-finding efforts. To correctly exclude mumps virus as the etiology of parotitis with mumps-negative RT-PCR results, obtaining additional NP swabs for viral testing within 2 days of parotitis onset should also be considered, particularly among patients without epidemiologic links to mumps cases or outbreaks. Testing for illnesses that mimic mumps might result in more timely and appropriate treatment, including antibiotic cessation and public health response. Additional investigations of NMP are warranted to better understand the etiologic, clinical, and epidemiologic features of outbreak-related and sporadically occurring cases.

Notes

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