Clinical and Vaccine Immunology® Published 2006-2017

Clin Vaccine Immunol. 2017 Feb; 24(2): e00542-16. PMCID: PMC5299122
Published online 2017 Feb 6. Prepublished online 2016 Dec 21. doi: 10.1128/CVI.00542-16 PMID: 28003216

Challenges in Interpretation of Diagnostic Test Results in a Mumps Outbreak in a Highly Vaccinated Population

L. A. Trotz-Williams,[a] N. J. Mercer,[a] K. Paphitis,[a] J. M. Walters,[a] D. Wallace,[a] E. Kristjanson,[b] J. Gubbay,[b] and T. Mazzulli[c]

Patricia P. Wilkins, Editor
Patricia P. Wilkins, CDC;

[a]Wellington-Dufferin-Guelph Public Health, Guelph, Ontario, Canada
[b]Public Health Ontario, Public Health Laboratories, Toronto, Ontario, Canada
[c]Department of Microbiology, Mount Sinai Hospital, Toronto, Ontario, Canada
[*]Corresponding author.
Address correspondence to L. A. Trotz-Williams, Lise.Trotz-Williams@wdgpublichealth.ca.

Citation Trotz-Williams LA, Mercer NJ, Paphitis K, Walters JM, Wallace D, Kristjanson E, Gubbay J, Mazzulli T. 2017. Challenges in interpretation of diagnostic test results in a mumps outbreak in a highly vaccinated population. Clin Vaccine Immunol 24:e00542-16. https://doi.org/10.1128/CVI.00542-16.

Received 2016 Dec 1; Revisions requested 2016 Dec 7; Accepted 2016 Dec 14.

ABSTRACT

In spite of a greatly reduced incidence rate due to vaccination, mumps outbreaks continue to occur in several areas of the world, sometimes in vaccinated populations. This article describes an outbreak in a highly vaccinated population in southwestern Ontario, Canada, and the challenges encountered in interpreting the results of diagnostic tests used in the outbreak. During the outbreak, patients were interviewed and classified according to the outbreak case definition, and specimens were collected for

diagnostic testing according to Ontario guidelines. Twenty-seven individuals were classified as confirmed cases (n = 19) or suspect cases (n = 8) according to the case definition, only 9 of which were laboratory-confirmed cases: 7 confirmed by reverse transcriptase PCR (RT-PCR) and 2 by IgM serology. All 19 confirmed cases represented patients who were associated with secondary schools in the local area and had been vaccinated against mumps with one (n = 2) or two (n = 17) doses of the measles-mumps-rubella (MMR) vaccine. This is the first published report of an outbreak of mumps in Ontario in which all confirmed cases had been vaccinated against the disease. It highlights the limitations of and difficulties in interpreting current mumps diagnostic tests when used in vaccinated individuals.

KEYWORDS: mumps, MMR, mumps vaccination, mumps diagnostic tests, immunized population, mumps serology

INTRODUCTION

Mumps outbreaks still occur in North America and in other areas of the world with high vaccination rates, and several such outbreaks have been reported in the literature in recent years. Outbreaks among unvaccinated groups are easily explained, but, interestingly, there have been several reports of outbreaks among highly immunized groups (1,–4), some of which included cases of patients previously immunized with two doses of the measles-mumps-rubella (MMR) vaccine (2, 4,–8). In light of the high efficacy of the MMR vaccine against mumps, the reason for these outbreaks is unclear. In addition to the increased level of exposure to the virus that occurs in an outbreak setting, current theories for vaccine failure include secondary vaccine failure, i.e., waning immunity in older teens and young adults, with genotype mismatch between the vaccine (genotype A) and wild-type virus being one possible cause (9,–14).

Current diagnostic testing for mumps in Ontario uses two approaches: identification of the organism by reverse transcriptase PCR (RT-PCR) in a buccal or throat swab or urine specimen, and serological analysis for immunoglobulin M (IgM) and IgG. Of these two tests, RT-PCR is considered the more sensitive and specific; however, virus is most likely to be detected in specimens taken from day 7 before to day 9 after the onset of symptoms, with one study reporting that the likelihood of detection of RNA, despite the use of a relatively sensitive technique, declined for specimens collected from a highly vaccinated outbreak population more than 2 days after symptom onset (3, 15, 16). The recommended collection time window for testing buccal and throat swabs in Ontario provincial guidelines is ≤9 days after symptom onset and, for urine, ≤14 days after onset (17). The Centers for Disease Control (CDC) *Vaccine-Preventable Diseases Surveillance Manual* recommends collection of buccal and throat specimens within 3 days and no more than 8 days after onset of parotitis and, because levels of virus in urine are often too low for successful detection, does not recommend testing urine for mumps diagnosis (18). With respect to serology, interpretation of results depends in part on the immunization history of the individual and the local prevalence of mumps, with most IgM-positive results in low-prevalence populations being false positives. Results of serological tests for IgM are often negative in individuals with acute wild-type mumps virus infections who have previously been vaccinated (16, 19). In general, IgM analysis is considered acceptable as a diagnostic confirmatory test only if used in a patient who has been to a country where mumps is endemic or who is a contact of a patient with a confirmed case.

Interpretation of laboratory tests for mumps, therefore, depends on the time of specimen collection relative to symptom onset and on the immunization history of the individual. Local prevalence of the disease at the time of testing (which affects the positive and negative predictive values of a test), and the presence or absence of epidemiological links to a laboratory-confirmed case, may also affect the interpretation of a mumps test result.

In spring 2015, a cluster of mumps cases (genotype G) occurred in southwestern Ontario involving students at several high schools located within the local area. Vaccination rates for mumps at all the schools were high (over 90%), and most individuals identified as cases by Wellington-Dufferin-Guelph Public Health (WDGPH/Public Health) had been fully vaccinated against mumps (with two doses of MMR). This report describes the outbreak and discusses the limitations of current laboratory testing methods and interpretation of test results in accurately detecting and classifying cases associated with the cluster.

RESULTS

For a description of methods used in conducting this investigation, including case definitions, please see Materials and Methods below.

Description of cases.

Thirty-two possible cases of mumps were reported to WDGPH during this outbreak. Individuals reported were aged 3 years to 66 years (median, 16 years). Of the 32 individuals reported, 23 (71.8%) were male and 9 (28.1%) female.

Of the 32 possible cases reported, 27 fit the outbreak case definition as either confirmed or suspect cases.

Nineteen cases were classified as confirmed. Those individuals ranged in age from 13 years to 38 years (median, 17 years). Five (26.3%) were female and 14 (73.7%) male. Seventeen (89.5%) individuals presented with parotitis, while the remaining 2 reported general respiratory symptoms only. Of the 19 confirmed cases, 9 were laboratory confirmed, with at least one positive diagnostic laboratory test each (7 [all of whom had parotitis] by RT-PCR and 2 by positive IgM serology). The other 10 confirmed cases, which included the two cases without parotitis, tested negative but were classified as confirmed because of epidemiological links to laboratory-confirmed cases ($n = 7$), epidemiologically linked confirmed cases ($n = 1$), and/or specified outbreak exposure sites ($n = 2$). Typing of isolates from five laboratory-confirmed cases identified genotype G strains as the cause of the outbreak (MuVs/Ontario.CAN/20.15 [$n = 3$], MuVs/Ontario.CAN/24.15 [$n = 1$], and MuVs/Ontario.CAN/18.15 [$n = 1$]).

All 19 confirmed cases had known links (either direct or via a laboratory-confirmed or otherwise confirmed case) to one or more of three high schools, which were among the specified places of exposure used in the outbreak case definition. Among the 19 individuals, 17 (89.5%) had received two doses of mumps vaccine and 2 (10.5%) had received a single dose.

No cases were classified as probable cases. However, eight individuals, all of whom tested negative for mumps, were classified as suspect cases. These ranged in age from 5 years to 66 years (median, 8 years). Four (50.0%) of the eight were male, four (50.0%) were female, and all eight individuals reported parotitis. All eight were classified as suspect cases because although parotitis had

occurred, no epidemiological link to a laboratory-confirmed case or known place of exposure could be identified. Immunization status was known for seven of the eight individuals. Of these seven, six (85.7%) had received two doses of mumps vaccine and one (14.3%) had received three, with the initial dose received before the subject was 12 months of age.

Figure S1 in the supplemental material shows an epidemiological curve, by week of onset, that includes all confirmed and suspect cases.

The remaining 5 of the 32 individuals reported during the outbreak did not align with any of the case definition categories and therefore remained unclassified. Two of these five reported parotitis and had been fully immunized with two doses of the MMR vaccine, while the other three, who had received one, two, and three doses of the vaccine, respectively, experienced general symptoms of a respiratory infection without parotitis. One of the two with parotitis tested positive for influenza B virus by multiplex PCR and the other for respiratory syncytial virus (RSV) type B; both individuals were epidemiologically linked to laboratory-confirmed outbreak cases. None of the five unclassified individuals had positive mumps diagnostic test results. Table S2 in the supplemental material summarizes reasons for the five individuals being left unclassified.

Figure S2 illustrates relationships between the 32 individuals (confirmed and suspect cases, and unclassified individuals) and the various exposures identified in the investigation.

Results of laboratory tests. Table S3 summarizes the results of laboratory diagnostic tests performed on specimens collected from all patients during the course of the outbreak.

In addition to the results shown was the identification of influenza B and RSV, respectively, in specimens from two of four individuals tested for other respiratory pathogens by multiplex PCR. As mentioned above, both of these cases were unclassified. No pathogens were detected in specimens from the other two individuals, both of whom were classified as confirmed according to the outbreak case definition.

The vast majority (22 of 27) of the individuals tested, including all 9 laboratory-confirmed cases, were found to be serologically "immune," with IgG reactivity indicative of humoral immunity.

DISCUSSION

As in this outbreak, most cases of mumps in vaccinated populations have occurred in individuals vaccinated over 10 years previously and among large groups with close person-to-person contact, such as in teenagers and university-aged populations. The reason is unclear, but, as previously mentioned, waning immunity has been postulated as a possible cause (9, 10, 13, 14). One study, which found that some countries were more likely to experience outbreaks of mumps than others, concluded that administration of doses of a highly immunogenic vaccine 4 to 8 years apart appeared to be the best way to reduce the likelihood of mumps outbreaks (14). However, no correlation could be found between mumps seroprevalence and the likelihood of outbreaks. Several studies have brought into question whether measuring antibody levels following vaccination is an effective method of

assessing resistance to vaccine-preventable viral infections (12, 20), against which a cell-mediated immunity response appears to provide protection in addition to humoral immunity (14, 21). It should be noted, however, that there does seem to be some correlation between levels of humoral antibody and the ability to resist infection (13). Nevertheless, the reported outbreaks in vaccinated populations may indicate that the immunological and virological features of such outbreaks need to be studied, with the aim of better explaining the reasons for the apparent vaccine failure, and thus to examine whether a review of the mumps vaccination schedule might be worth some consideration by public health authorities.

The investigation of this outbreak demonstrated the difficulties of using recognized diagnostic tests for mumps in individuals who have been immunized. Not surprisingly, since the majority of individuals included in the investigation were fully immunized, 22 of 27 serology specimens tested early after symptom onset—only 5 of which had been tested at >5 days, the latest Public Health Ontario (PHO)-recommended testing time for mumps virus IgG diagnostic serology—had elevated IgG levels to mumps virus (see Table S3 in the supplemental material [footnote]). In vaccinated individuals, IgG levels are usually already elevated; therefore, seroconversion usually cannot be demonstrated. This is especially so where an enzyme immunoassay (EIA) is used as the diagnostic serology test, as this does not enable accurate quantification of antibody responses (18). Detection of IgM also presents diagnostic difficulties in vaccinated individuals, as a demonstrable increase in IgM levels following infection is often delayed or altogether absent in such individuals, even among those with positive RT-PCR results (16, 18, 22). The fact that the three IgM-positive serology specimens (see Table S3 [footnote]) had all been collected at ≥8 days after the onset of symptoms may be an indication of the need for delayed specimen collection when using IgM detection as a diagnostic test for mumps virus infection in vaccinated individuals. However, the low percentage of positive tests (11.5% overall and only 1 of 6 RT-PCR-positive individuals who were tested for IgM), even with most of the individuals having parotitis and a known link to the outbreak, may show that a demonstrable IgM response is often altogether absent in cases in vaccinated individuals, even with delayed specimen collection, and that false-negative IgM test results (i.e., negative IgM results in mumps-infected cases) are very likely to occur in such cases (3, 16, 18).

Twenty-five percent of the buccal swabs and 21.4% of throat swabs collected from symptomatic individuals tested positive for mumps virus RNA by RT-PCR (Table S3). This test is considered the gold-standard for mumps diagnosis (3, 22). However, the success of detecting the virus depends on the technique used to collect and transport specimens as well as on the time of collection. PHO guidelines recommend collection of specimens within 3 to 5 days after onset of symptoms (17). However, the *Vaccine-Preventable Diseases Surveillance Manual* of the CDC recommends that specimens should ideally be collected within 3 days after symptom onset, especially in cases where individuals have been vaccinated (18, 22), and this recommendation is supported by published research (16). In this outbreak investigation, only 7 of the 29 symptomatic individuals tested gave positive results by RT-PCR. Whether this could have been due to low levels of virus in buccal and throat secretions among the cases (some of whom were tested beyond the CDC-recommended 3-day window), to the low sensitivity of the RT-PCR protocol relative to that used by the CDC (16), or perhaps to poor or inconsistent methods of specimen collection and/or transportation is unclear. There is some evidence that levels of virus in mumps-infected vaccinated individuals may be very low and that the virus may be only briefly present, even in cases with parotitis (22); in at least one study, this was apparent in both vaccinated and unvaccinated

outbreak cases (16). This may explain the fact that fewer than half of the RT-PCR-positive specimens cultured in this investigation yielded virus (Table S3). The even lower yield of the urine specimens cultured for virus (3.3%) may also have been a result of this, although culture of mumps virus from urine is well recognized as being less likely to yield virus than culture from throat or buccal swabs (18).

Most of the individuals who were confirmed and suspect cases in this outbreak (i.e., 88.5% of confirmed cases, including all of the laboratory-confirmed cases, and 100.0% of the suspect cases) experienced parotitis. As usual in mumps outbreaks, parotitis with no other apparent cause was considered to be the main indication of whether an individual might be considered to be a possible case of mumps, although a few individuals with more general respiratory symptoms but no parotitis were also tested for infection. It is well documented that only about two-thirds of individuals with mumps develop parotitis (15); therefore, it is very likely that up to one-third of all infected cases in this outbreak may have remained unidentified and undiagnosed within the community. The identification of mumps cases was further complicated by the fact that this outbreak occurred in spring, when influenza virus and other respiratory pathogens were still circulating in the community, albeit at lower levels than they would have been earlier in the year. This was illustrated by the identification of influenza B virus and RSV, respectively, in two of four individuals tested for other respiratory pathogens. Both individuals had parotitis but were excluded as cases and remained unclassified because of the presence of other respiratory pathogens. Parotitis in cases of influenza B virus and RSV infection is likely relatively rare compared to parotitis associated with mumps; there appear to be few published reports, if any, of these viruses being isolated from individuals with parotitis. In one study in Spain where specimens from 101 patients with parotitis were tested for several viruses, including influenza virus and RSV, only one patient tested positive for RSV, and no evidence of influenza B virus was found in any of the specimens (23). During the investigation described here, the decision was made to adhere to the criteria specified in the case definitions and thus allow those two individuals to remain unclassified (i.e., noncases); however, it is recognized that it is quite possible that they were in fact mumps cases. Further, a limitation of the investigation and of the classification of cases was that only four individuals were tested for pathogens other than mumps virus, so this criterion could not be applied across all individuals in a standardized manner.

Thus, the presence of other respiratory pathogens in the community and the fact that many individuals with mumps do not experience parotitis, in addition to the relatively low sensitivity of the various diagnostic tests in vaccinated populations, all made the detection and classification of cases in this outbreak very difficult. Moreover, media coverage of the outbreak may have resulted in an increase in the presentation of individuals with parotitis, and also of those with no parotitis and only general respiratory symptoms, to health care providers. This in turn may have increased not only the ability of the health unit to capture true cases but also the likelihood that some of the test-negative immunized individuals with parotitis, even with identified links to the outbreak, may not have been true cases of mumps. As discussed above, the poor performance of diagnostic tests in cases in vaccinated individuals presented a barrier to ruling out the latter.

This outbreak investigation illustrated the challenges of creating an effective case definition for an outbreak of mumps in a highly vaccinated population, in contrast to definitions for use in unvaccinated or undervaccinated populations, where more conservative criteria may suffice. Although the definition was revised and broadened as the investigation proceeded and more information became available, it is very likely that at least some true cases may have remained unreported to Public Health or may have been incorrectly classified as noncases by Public Health. If so, then there might have been individuals with existing cases of mumps in the community who were not advised to self-isolate at any point. For example, any infected individuals who had been fully vaccinated and experienced general respiratory symptoms but not parotitis may not have been considered possible mumps cases and therefore may never have been reported to Public Health. Furthermore, as discussed previously, it is possible that the two individuals reported to Public Health who were ruled out as cases of mumps because of having tested positive for other respiratory pathogens were in fact mumps cases. Although serious complications of mumps infection, especially in vaccinated populations, are relatively rare, there could possibly be negative consequences if such misclassification is repeatedly allowed to occur in such outbreaks over the course of time. With the benefit of hindsight, based on the diagnostic uncertainty illustrated in this instance, it may be advisable in mumps outbreaks in highly vaccinated populations to create an even broader definition for suspect cases than that used in this outbreak, based on either general respiratory symptoms or parotitis, and identified direct or indirect link(s) to an outbreak exposure, and not, as was done in this outbreak, excluding immunized individuals with negative laboratory results or individuals with identified infections with other respiratory pathogens. The presence or absence of epidemiological links should be determined as accurately as possible by repeated interviewing of individuals whenever a new source of potential exposure has been identified. The use of this broader case definition for suspect cases would mean that any individuals potentially infected with mumps virus, even those without parotitis, those testing positive for other respiratory pathogens, and those with negative mumps diagnostic test results, would be advised to self-isolate, reducing the risk of further spread of infections within the community. In addition, to assist in identifying symptomatic individuals for appropriate follow-up by public health authorities, active communication to area physicians in the event of a confirmed case or identified cluster is advisable, with a caution against ruling out mumps as a differential diagnosis based solely on client immunization history, absence of parotitis, or negative diagnostic test results.

Conclusions. In this outbreak investigation, the proportion of specimens that tested positive by any laboratory diagnostic test was very low. This may have been because in vaccinated individuals with mumps, viral shedding is thought to be very transient and to occur at very low levels, and an IgM response to infection less likely than in unvaccinated cases.

During outbreaks in highly vaccinated populations, given the absence of reliable diagnostic tests for mumps in vaccinated individuals with symptoms of respiratory infection and the relative mildness of symptoms compared to those experienced by unvaccinated individuals, consideration should be given to creating broad case definitions for suspect cases based primarily on respiratory symptoms (with or without parotitis) and an identified direct or indirect link to an outbreak exposure site or person. This would allow the isolation of more presumptive cases of mumps, thus reducing the likelihood of spread of the disease within the community by individuals with false-negative test results.

This outbreak added to the growing body of evidence that high levels of MMR vaccine coverage do not provide adequate protection against mumps outbreaks. Outbreaks occurring in such settings should be studied in order to provide information that might better explain the factors that cause them to occur, and to examine whether the current mumps vaccination schedule might need to be reviewed at some point in the future.

MATERIALS AND METHODS

Overview. In May and June 2015, several cases of mumps were reported to Wellington-Dufferin-Guelph Public Health (WDGPH), a local southwestern Ontario health department. The earliest case identified within this cluster was the first laboratory-confirmed case of mumps within the local area in well over a year and was soon followed by several other laboratory-confirmed cases, all of which were eventually determined to be a part of the same cluster of cases.

Public Health follow-up of cases. In accordance with provincial guidelines, WDGPH contacts all reported cases (laboratory-confirmed or presumptive) of any reportable vaccine-preventable disease (VPD), as well as their attending physicians, for further investigation and education. Accordingly, this was done for all cases reported with symptoms compatible with mumps during this outbreak. Information on symptoms, demographics, contacts, and possible exposures was collected for each case. In addition, information was gathered on whether any diagnostic specimens had been collected from the case, and submission of additional specimens for diagnostic testing was arranged where necessary.

Testing of specimens. Specimens collected from all individuals by WDGPH, hospitals, and clinics were tested at the provincial Public Health Laboratory (PHL) in Toronto, Ontario, Canada, and RT-PCR-positive specimens were sent to the National Microbiology Laboratory (NML), Winnipeg, Manitoba, Canada, for genotyping. All specimens (buccal and throat swabs, urine specimens, and blood for serology) were collected according to provincial guidelines (17).

Buccal and throat swabs and urine specimens were processed by RT-PCR using the protocol described by Uchida et al. (24) and Boddicker et al. (25), and attempts were made to culture mumps virus from RT-PCR-positive specimens in rhesus monkey kidney (RMK) and WI-38 fetal lung fibroblast cell lines. Identification of mumps virus was done by monitoring for cytopathic effects (CPE) and hemadsorption using 0.6% guinea pig red blood cells. RMK tubes showing syncytia or a positive hemadsorption test result were tested by an indirect immunofluorescence assay (IFA) using a mumps monoclonal antibody for confirmation (Light Diagnostics Mumps IFA kit; EMD Millipore Corporation, CA, USA).

Blood specimens submitted for serology were tested for anti-mumps virus IgG and IgM using commercially available anti-mumps virus enzyme-linked immunosorbent assays (ELISAs) (Euroimmun AG, Luebeck, Germany).

A subset of throat swabs from four patients were tested by a commercial respiratory viral multiplex PCR assay (Seeplex RV15 ACE; Seegene, USA) for several respiratory pathogens in order to rule out other potential viral causes of parotitis.

Case definitions.

Table S1 in the supplemental material shows the final outbreak case definitions created by WDGPH for the outbreak after modification of earlier, more conservative versions in the initial stages of the investigation as more information became available —notably, that the majority of the individuals had been fully vaccinated against mumps.

SUPPLEMENTARY MATERIAL

Supplemental material:

Click here to view.

FOOTNOTES

Supplemental material for this article may be found at https://doi.org/10.1128/CVI.00542-16.

REFERENCES

1. Cheek JE, Baron R, Atlas H, Wilson DL, Crider RD Jr. 1995. Mumps outbreak in a highly vaccinated school population. Evidence for large-scale vaccination failure. Arch Pediatr Adolesc Med 149:774–778. [PubMed] [Google Scholar]

2. Watson-Creed G, Saunders A, Scott J, Lowe L, Pettipas J, Hatchette TF. 2006. Two successive outbreaks of mumps in Nova Scotia among vaccinated adolescents and young adults. CMAJ 175:483–488. doi:10.1503/cmaj.060660. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

3. Hatchette TF, Davidson R, Clay S, Pettipas J, Leblanc J, Sarwal S, Smieja M, Forward KR. 2009. Laboratory diagnosis of mumps in a partially immunized population: the Nova Scotia experience. Can J Infect Dis Med Microbiol 20:e157–e162. [PMC free article] [PubMed] [Google Scholar]

4. Vareil MO, Rouibi G, Kassab S, Soula V, Duffau P, Lafon ME, Neau D, Casanave C. 2014. Epidemic of complicated mumps in previously vaccinated young adults in the South-West of France. Med Mal Infect 44:502–508. doi:10.1016/j.medmal.2014.09.006. [PubMed] [CrossRef] [Google Scholar]

5. Kancherla VS, Hanson IC. 2006. Mumps resurgence in the United States. J Allergy Clin Immunol 118:938–941. doi:10.1016/j.jaci.2006.07.033. [PubMed] [CrossRef] [Google Scholar]

6. Cortese MM, Jordan HT, Curns AT, Quinlan PA, Ens KA, Denning PM, Dayan GH. 2008. Mumps vaccine performance among university students during a mumps outbreak. Clin Infect Dis 46:1172–1180. doi:10.1086/529141. [PubMed] [CrossRef] [Google Scholar]

7. Kutty PK, McLean HQ, Lawler J, Schulte C, Hudson JM, Blog D, Wallace G. 2014. Risk factors for transmission of mumps in a highly vaccinated population in Orange County, NY, 2009–2010. Pediatr Infect Dis J 33:121–125. doi:10.1097/INF.0000000000000020. [PubMed] [CrossRef] [Google Scholar]

8. Ladbury G, Ostendorf S, Waegemaekers T, van Binnendijk R, Boot H, Hahne S. 2014. Smoking and older age associated with mumps in an outbreak in a group of highly vaccinated individuals attending a youth club party, the Netherlands, 2012. Euro Surveill 19:20776. doi:10.2807/1560-7917.ES2014.19.16.20776. [PubMed] [CrossRef] [Google Scholar]

9. Vandermeulen C, Roelants M, Vermoere M, Roseeuw K, Goubau P, Hoppenbrouwers K. 2004. Outbreak of mumps in a vaccinated child population: a question of vaccine failure? Vaccine 22:2713–2716. doi:10.1016/j.vaccine.2004.02.001. [PubMed] [CrossRef] [Google Scholar]

10. Date AA, Kyaw MH, Rue AM, Klahn J, Obrecht L, Krohn T, Rowland J, Rubin S, Safranek TJ, Bellini WJ, Dayan GH. 2008. Long-term persistence of mumps antibody after receipt of 2 measles-mumps-rubella (MMR) vaccinations and antibody response after a third MMR vaccination among a university population. J Infect Dis 197:1662–1668. doi:10.1086/588197. [PubMed] [CrossRef] [Google Scholar]

11. Kaaijk P, van der Zeijst B, Boog M, Hoitink C. 2008. Increased mumps incidence in the Netherlands: review on the possible role of vaccine strain and genotype. Euro Surveill 13:pii=18914 http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=18914. [PubMed] [Google Scholar]

12. Rubin SA, Qi L, Audet SA, Sullivan B, Carbone KM, Bellini WJ, Rota PA, Sirota L, Beeler L. 2008. Antibody induced by immunization with the Jeryl Lynn mumps vaccine strain effectively neutralizes a heterologous wild-type mumps virus associated with a large outbreak. J Infect Dis 198:508–515. doi:10.1086/590115. [PubMed] [CrossRef] [Google Scholar]

13. Cortese MM, Barskey AE, Tegtmeier GE, Zhang C, Ngo L, Kyaw MH, Baughman AL, Menitove JE, Hickman CJ, Bellini WJ, Dayan GH, Hansen GR, Rubin S. 2011. Mumps antibody levels among students before a mumps outbreak: in search of a correlate of immunity. J Infect Dis 204:1413–1422. doi:10.1093/infdis/jir526. [PubMed] [CrossRef] [Google Scholar]

14. Eriksen J, Davidkin I, Kafatos G, Andrews N, Barbara C, Cohen D, Duks A, Griskevicius A, Johansen K, Bartha K, Kriz B, Mitis G, Mossong J, Nardone A, O'Flanagan D, DE Ory F, Pistol A, Theeten H, Prosenc K, Slacikova M, Pebody R. 2013. Seroepidemiology of mumps in Europe (1996–2008): why do outbreaks occur in highly vaccinated populations? Epidemiol Infect 141:651–666. doi:10.1017/S0950268812001136. [PubMed] [CrossRef] [Google Scholar]

15. American Academy of Pediatrics. 2006. Summaries of infectious diseases: mumps, p 464–465. *In* Pickering LK, Baker CJ, Long SS, McMillan JA. (ed), Red book: 2006 report of the Committee on Infectious Diseases, 27th ed American Academy of Pediatrics, Elk Grove Village, IL. [Google Scholar]

16. Rota JS, Rosen JB, Doll MK, McNall RJ, McGrew M, Williams N, Lopareva EN, Barskey AE, Punsalang A Jr, Rota PA, Oleszko WR, Hickman CJ, Zimmerman CM, Bellini WJ. 2013. Comparison of the sensitivity of laboratory diagnostic methods from a well-characterized outbreak of mumps in New York City in 2009. Clin Vaccine Immunol 20:391–396. doi:10.1128/CVI.00660-12. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

17. Public Health Ontario, Public Health Laboratories. April 2010. Diagnostic test recommendations for mumps. https://www.publichealthontario.ca/en/eRepository/Diagnostic%20Test%20Recommendations%20for%20Mumps%20-%20April%202010%20final.pdf Accessed 13 June 2016.

18. Fiebelkorn A, Barskey A, Hickman C, Bellini W. 2012. Chapter 9: Mumps. *In* Roush Sandra W., Baldy LM. (ed), Manual for the surveillance of vaccine-preventable diseases. Centers for Disease Control and Prevention, Atlanta, GA. [Google Scholar]

19. Maillet M, Bouvat E, Robert N, Baccard-Longère M, Morel-Baccard C, Morand P, Vabret A, Stahl JP. 2015. Mumps outbreak and laboratory diagnosis. J Clin Virol 62:14–19. doi:10.1016/j.jcv.2014.11.004. [PubMed] [CrossRef] [Google Scholar]

20. Allwinn R, Zeidler B, Steinhagen K, Rohwäder E, Wicker S, Rabenau HF, Doerr HW. 2011. Assessment of mumps virus-specific antibodies by different serological assays: which test correlates best with mumps immunity? Eur J Clin Microbiol Infect Dis 30:1223–1228. doi:10.1007/s10096-011-1216-z. [PubMed] [CrossRef] [Google Scholar]

21. Dhiman N, Ovsyannikova IG, Jacobson RM, Vierkant RA, Pankratz VS, Jacobsen SJ, Poland GA. 2005. Correlates of lymphoproliferative responses to measles, mumps, and rubella (MMR) virus vaccines following MMR-II vaccination in healthy children. Clin Immunol 115:154–161. doi:10.1016/j.clim.2004.12.010. [PubMed] [CrossRef] [Google Scholar]

22. Bitsko RH, Cortese MM, Dayan GH, Rota PA, Lowe L, Iversen SC, Bellini WJ. 2008. Detection of mumps virus during an outbreak in a population with a high level of measles, mumps, and rubella vaccine coverage. J Clin Microbiol 46:1101–1103. doi:10.1128/JCM.01803-07. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

23. Barrabeig I, Costa J, Rovira A, Marcos MA, Isanta R, López-Adalid R, Cervilla A, Torner N, Domínguez A. 2015. Viral etiology of mumps-like illnesses in suspected mumps cases reported in Catalonia, Spain. Hum Vaccin Immunother 11:282–287. doi:10.4161/hv.36165. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

24. Uchida K, Shinohara M, Shimada S, Segawa Y, Doi R, Gotoh A, Hondo R. 2005. Rapid and sensitive detection of mumps virus RNA directly from clinical specimens by real-time PCR. J Med Virol 75:470–474. doi:10.1002/jmv.20291. [PubMed] [CrossRef] [Google Scholar]

25. Boddicker JD, Rota PA, Kreman T, Wangeman A, Lowe L, Hummel KB, Thompson R, Bellini WJ, Pentella M, Desjardin LE. 2007. Real-time reverse transcription PCR assay for the detection of mumps virus RNA in clinical specimens. J Clin Microbiol 45:2902–2908. doi:10.1128/JCM.00614-07. [PMC free article] [PubMed] [CrossRef] [Google Scholar]