Diagnosis of Acute Mumps Infection during an Outbreak in a Highly Vaccinated Population: Mumps RNA or Mumps IgM Detection?

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Abstract: A large mumps outbreak commenced in Ireland in October 2014. The users of the National Virus Reference Laboratory were informed that oral fluid collection devices would be provided to allow the collection of oral fluid for the diagnosis of suspected acute mumps infection by RNA detection. Both mumps RNA and mumps IgM detection could be undertaken on a single oral fluid sample and hence would be more accurate in acute infection than serology alone. The aim of this study was to retrospectively assess whether changing the algorithm from serological testing for mumps IgM to molecular testing for mumps RNA in oral fluid samples was beneficial for the diagnosis of acute mumps infection during a mumps outbreak in a highly vaccinated population. A total of 1455 serum and 490 oral fluid samples were submitted for laboratory confirmation of mumps virus infection. Of the sera, 448 (30.8%) tested positive for the presence of mumps IgM. A total of 251 (51.2%) oral fluids had detectable mumps RNA. Despite the limitations of this laboratory based audit it is evident that during an outbreak, mumps RNA detection in oral fluid was beneficial for the specific, definitive diagnosis of acute mumps infection in a highly vaccinated population.

Keywords: Mumps outbreaks, Mumps RNA, Mumps IgM, Oral fluid.

INTRODUCTION

Mumps virus an enveloped, single stranded, non-segmented negative sense RNA virus of the *Paramyxoviridae* family, is the etiological agent responsible for an acute viral infection which presents clinically with parotitis, low-grade fever, headache, malaise, anorexia, rash and abdominal pain.

Genotypes G (predominately G5) and J have been highlighted to co-circulate during Irish outbreaks, whilst the current vaccine strain Jeryl Lynn is genotype A [1]. Mumps is a serologically monotypic virus. It was previously thought that an infection or vaccination of any mumps strain would provide lifelong immunity against subsequent reinfection. However, despite the availability and uptake of an effective mumps vaccine, recent and repeated outbreaks have been reported worldwide and in Ireland among young adults at the tertiary stage of education [2, 3]. Routine childhood vaccination with measles-mumps-rubella (MMR) vaccine was introduced in the Republic of Ireland in 1988 for children between 12 to 15 months of age. In 1999, the age for the second dose of MMR2 was reduced to 4 to 5 years following primary-school outbreaks [4].

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Although the diagnosis of mumps is primarily based on clinical symptoms, other viral infections such as parainfluenza can manifest in a similar manner. Therefore, confirmation of mumps infection is important. Serological testing during outbreaks is not truly definitive in individuals who have received mumps containing vaccines. A clear serological cut-off to distinguish between prior vaccination and current infection has yet to be established. Other laboratory tests can be used to diagnosis infection including mumps virus isolation and *in vitro* neutralisation, but these are time consuming and labour intensive. Testing for mumps RNA on the other hand, is considered to be a time-efficient test with high sensitivity and specificity and can also be performed on samples collected non-invasively such as oral fluid samples.

It is important to emphasise that the practicality of a diagnostics test is dependent on its limitations. The detection of mumps RNA within an oral fluid sample is reliant on the time the sample was collected relative to the onset of symptoms. If clinical symptoms are present for less than 3–4 days, PCR to detect mumps RNA should be the preferred test of choice. Although mumps RNA may be detected up to 9 days after onset of symptoms [5], mumps IgM testing for later time periods may also be useful.

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National Virus Reference Laboratory (NVRL) were informed that with the support of the Health Protection Surveillance Centre, ORACOL collection devices (Malvern Medical Developments, United Kingdom) would be provided to allow the collection of oral fluid for the diagnosis of suspected acute mumps infection by RNA detection. Both mumps RNA and mumps IgM detection could be undertaken on a single oral fluid sample and hence would be more accurate in acute infection than serology alone.

The aim of this study was to retrospectively assess whether changing the algorithm from serological testing for mumps IgM to molecular testing for mumps RNA in oral fluid samples was beneficial for the diagnosis of acute mumps infection during a mumps outbreak in a highly vaccinated population.

METHODS

Data was retrospectively extracted from the NVRL laboratory information system to identify all oral fluid and serum samples submitted from October 2014 to May 2015 for mumps RNA and mumps specific IgM testing. The molecular assay for detection of the mumps N gene and the serological assay for mumps specific IgM testing (Microimmune, Biomerieux, Basingstoke, Britain) have been previously described [3,5]. The data were plotted using Microsoft Excel and GraphPad Prism software (version 5.04).

RESULTS

A total of 1455 serum and 490 unpaired oral fluid samples were submitted to the NVRL for laboratory confirmation of mumps virus infection. Of the sera, 448 (30.8%) tested positive for the presence of mumps IgM. A total of 251 (51.2%) oral fluids had detectable mumps RNA (Figure **1**). Paired serum and oral fluid was received for only one patient. The oral fluid showed detectable mumps RNA and the serum was mumps IgM negative.

A subset of the samples that had detectable mumps RNA were analysed further for mumps-specific IgM detection. Of the oral fluid samples that mumps RNA was detected (n=95), the presence of mumps IgM was 23.2% (22/95). Of the oral fluids that did not have detectable mumps RNA, 8.1% (5/62) had detectable mumps IgM.

Of the 490 oral fluid samples tested, 91 were from college students in three third level institutions. In 63 (69.2%) of these oral fluids, mumps RNA was detected and of these 11 were tested for mumps IgM. Within this group, 3 were IgM positive (27.3%). Of the 28 (30.8%) oral fluids that had no detectable mumps RNA, only 5 were tested for mumps IgM and all were negative.

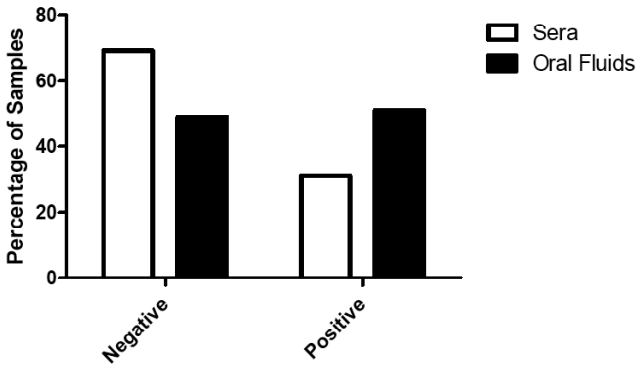

Figure 1: Results of Mumps specific IgM testing in 1455 sera and Mumps RNA testing in 490 oral fluid samples is shown.

Patient test request forms that are provided with the sample collection kits provide space to allow the capturing of vaccination record and date of clinical onset. Of all the samples received, only 7 of the 88 (8%) request forms that were audited had recorded a vaccination history, and 28/88 (31.8%) had recorded onset of symptoms.

DISCUSSION

Traditional mumps virus detection methods by culture have their limitations, such as being insensitive, costly, and time-consuming. The use of an oral fluid sample to detect mumps virus RNA and IgM offers a major improvement over serological diagnosis in acute infection in both non-vaccinated or partially vaccinated individuals, and has the advantage that specimens are collected non-invasively [1]. Therefore, mumps RNA provides a preferred frontline diagnostic test to mumps IgM testing as RNA can be detectable within the first week of clinical symptom onset and has the capability to provide a definitive result.

In this study during a mumps outbreak, the rate of mumps RNA (N gene) detection in oral fluids in the current study was found to be higher (51.2%) compared to the rate of mumps RNA (SH gene) detection previously reported of 13.9% [1] and 9.2% [6]. However, this may also reflect the timing of sample collection from the date of onset of clinical symptoms. The limitations of the study include the lack of paired sera and oral fluid samples from patients. It would be beneficial to collect both sample types simultaneously

in individuals to help define the transitional point where mumps-specific RNA can be sufficiently detected.

Mumps occurred in children between 5-15 years of age in the pre-vaccination era, however in a highly vaccinated population such as Ireland, the age of mumps infection are students in tertiary education. In the Netherlands, which experienced similar outbreaks as observed in Ireland it has been shown that older age is an independent risk factor for mumps infection, [3, 7, 8]. It has been also documented that in the years between the outbreaks, mumps cases were most prevalent in individuals ≥30 years of age, suggesting that this may be the cohort maintaining a reservoir for transmission [7].

The World Health Organisation's recommendation of mumps vaccine uptake and thus protection is 95%. It is estimated that 80-85% of 15-24 year olds in Ireland are immune to mumps through either natural immunity or immunization [9], however it is believed that this number could be an underestimation of immunity. Despite being within herd immunity ranges (75-86%), the shift to repeated outbreaks within young adults in a highly vaccinated population (≥2 doses of MMR vaccine) implies a waning of vaccine induced immunity. [10]. This effect has also been seen in children after receiving their second dose of the MMR vaccine (99% at administration of 3-5 years versus 86% at 11-12 years) [11].

The vaccine currently provided in Ireland is the Jeryl Lynn (genotype A) strain vaccine. Two doses of this MMR vaccine are thought to be approximately 88% (66-95%) effective in protecting against the clinical manifestation of mumps [10]. However, the predominant mumps virus strain responsible for the outbreaks in Ireland belongs to a genotype phylogenetically distinct from the vaccine strains employed (G5). Despite the fact that this vaccine has been shown to be effective in outbreaks caused by MuV belonging to genotype G, it may not confer complete protection [12].

The efficacy of the vaccine is uncertain, as there are gaps in the vaccination records and vaccine uptake within the Irish population. Improvements are needed to document vaccinations, and also to provide this information with the date of clinical symptoms onset when serum/oral fluids samples are sent for mumps RNA/IgM testing. In addition, compulsory documentation of provider-verified month/day/year immunization records for all matriculating full-time students can clarify vaccination status and has been successfully instigated in some universities in Iowa [13].

Although a third MMR vaccine is unlikely to address waning immunity, a third dose of MMR may benefit certain individuals with a low level of mumps virus–neutralizing antibody, especially in the context of an outbreak or other high-risk setting [14, 15]. This was successfully demonstrated following a large additional dose MMR vaccination campaign in universities in Iowa, as fewer mumps cases occurred overall in the target population [16].

CONCLUSION

Despite the limitations of this laboratory based audit it is evident that during an outbreak, mumps RNA detection in oral fluid was beneficial for the specific, definitive diagnosis of acute mumps infection in a highly vaccinated population. For future work it would be beneficial to incorporate this non-invasive, more efficient and cost effective frontline test for mumps into diagnostic protocol, as it will allow for efficient diagnosis of mumps of an individual prior to the development of mumps-specific IgM. It should also be noted that further improvements in establishing cut-off points to differentiate acute infection from prior vaccine response will only occur when details of vaccination status and date of clinical symptom onset are provided with the samples.

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