Indian J Med Res 143, January 2016, pp 8-10
DOI:10.4103/0971-5916.178576

Commentary

Importance of reporting sequence & serological data from mumps outbreaks in unvaccinated populations

In this issue, Vaidya *et al*[1], describe the cross-protective effect of circulating wild type mumps viruses in comparison with the mumps vaccine strain, Leningrad-Zagreb (genotype N). The authors investigated a mumps outbreak within an unvaccinated population in India where two different wild type mumps viruses were isolated (genotypes C and G). Mumps virus is the aetiological agent of mumps, a highly contagious disease which is characterized by pain and swelling in one or both of the parotid glands and often accompanied by complications such as meningitis, deafness and orchitis. Humans are the sole reservoir for mumps virus. Mumps disease is vaccine-preventable and live attenuated mumps-containing vaccines have been used worldwide since the 1960s[2]. In many countries, mumps vaccination is included in the routine childhood immunization schedule. This has resulted in a reduction in the incidence of mumps infections (<1 case per 100,000 population), however, in the absence of routine vaccination, annual incidences of mumps range from 100 to 1000 per 100,000 population[3]. Mumps is historically considered to be a childhood disease, although over the past 20 years there has been an increase in the incidence of mumps outbreaks within vaccinated populations. In these vaccinated populations, the infection is now typically observed in young adults who are in university or military settings and residing in close proximity[4,5]. These outbreaks have been the subject of further studies into the possibility of waning immunity or to identify if there may be antigenic differences between vaccine strains and circulating wild type viruses which may result in immune escape of mumps viruses[6,7]. In countries such as India, where mumps is not included in the routine immunization schedule, there is limited information from outbreaks of the disease and a lack of reporting on the neutralizing antibody responses generated in patients during or after infection with wild type mumps virus and whether the level of cross-protection is different between those who have been exposed to wild type or vaccine viruses.

There are 12 recognized mumps genotypes which are designated A-N, with the exception of E and M which are now classified as genotypes C and K, respectively[8]. Mumps virus genotype is assigned based on the sequence diversity of the small hydrophobic (*SH*) gene and haemagglutinin-neuraminidase (*HN*) gene. The haemagglutinin-neuraminidase protein is the major antigenic protein and the cell surface target for neutralizing antibodies which are thought to be important for protective immune response[9,10], therefore, it is used to determine antigenic differences between mumps strains[11]. There are nine N-linked glycosylation sites within the HN protein which play an important role in defining antigenic properties with amino acid positions aa265-288, aa329-340 and aa352-360 known to be antigenic[10,12,13]. However, much of what is known about mumps HN structure is inferred from other paramyxoviruses[14]. Mumps virus is serologically monotypic[2] and cross-neutralization between genetically distinct mumps strains is observed. This feature is most notable in the use of mumps strains for vaccine production. Genotypes A, B and N are most commonly used in vaccine production worldwide. These have been effective in reducing mumps infections globally despite their use in regions where the circulating wild type mumps viruses are frequently genotypes C, G, H, J and K in the western hemisphere and genotypes B, F, I and L in Asia. Phylogenetic analysis suggests that genotype A is more distant from the other mumps genotypes, it has not been detected as a wild type virus since the 1990s, most likely due to its use as a vaccine strain[15].

The study by Vaidya *et al*[1] confirms findings which have been documented in the wider vaccinated

global population but have not been described in an unvaccinated population. The authors identified that those people who had been infected with wild type virus had neutralizing antibody titres against wild type mumps viruses that were lower than the titres against the vaccine strain. Despite the low neutralizing antibody titres there was good cross-neutralization between the mumps strains. In other studies from outbreaks in vaccinated populations, it has been shown that low neutralizing antibody titres against a vaccine strain are capable of neutralizing wild type mumps virus[16] and that neutralization is observed across the spectrum of mumps genotypes, providing no evidence for immune escape in the vaccinated population[17]. The study by Vaiyda *et al*[1] confirmed these findings for an unvaccinated population. Sequencing of the *HN* gene from the wild type isolates revealed no differences in the known neutralizing epitopes, aa265-288, aa329-340 and aa352-360 of the wild type or vaccine strains. However, the loss of a potential glycosylation site at aa12-14 in both wild type isolates was identified, which has also been observed in other mumps isolates[18] and may suggest that some of the antigenic properties of wild type mumps viruses may be different to vaccine strains.

This investigation highlights that reporting information from mumps outbreaks in unvaccinated populations is a valuable resource, which is currently limited and may help to explain the occurrence of outbreaks in vaccinated populations. The observation of low neutralization titres to wild type strains between vaccinated and non-vaccinated individuals is of interest. Previous studies have shown that low neutralizing antibody titres to wild type mumps infection may be due to the challenge virus and cell type used in assays[19]. It is generally believed that infection with wild type virus confers long term immunity[20], although a correlate of protection to mumps virus, in terms of neutralizing antibody is unknown. The higher neutralizing antibody titre to the vaccine strain could be due to the possibility that the patients may have received a Leningrad-Zagreb-containing vaccine. This point requires further clarification. However, if the patients were unvaccinated, the findings may reflect the attenuation status of the vaccine virus used in the neutralization assays. Further cross-neutralization studies using acute or convalescent serum from patients could help in the identification of a genetic marker for the attenuation of mumps viruses. In addition, the loss of a glycosylation site within the HN protein of the wild type viruses described in this study and previously identified in other wild type isolates, may also identify potential markers for the attenuation of mumps viruses. This may also support the identification of additional antigenic properties of wild type mumps viruses which differ from the current vaccine strains, providing useful information to facilitate the development of future mumps vaccines. Recently, at least two neutralization epitopes in the F protein have been identified, antibodies to these epitopes have been shown to effectively neutralize mumps virus *in vitro*[21]. More thorough genetic characterization of mumps virus isolates is required to provide important information on not only the epidemiology of mumps viruses in the non-vaccinated population which is currently limited but also to the fundamental understanding of the pathogenesis of mumps viruses in both vaccinated and unvaccinated populations.

Sarah Connaughton
National Institute for Biological Standards & Control
South Mimms, Potters Bar, EN6 3QG
United Kingdom
sarah.connaughton@nibsc.org

References

1. Vaidya SR, Dvivedi GM, Jadhav SM. Cross-neutralization between three mumps viruses & mapping of haemagglutinin-neuraminidase (HN) epitopes. *Indian J Med Res* 2016; *143* : 37-42.
2. Plotkin SA, Rubin SA. Mumps vaccine. In: Plotkin SA, Orenstein WA, Offit PA, editors. *Vaccines*, 5th ed. Philadelphia: Saunders; 2008. p. 435-65.
3. WHO. *Weekly Epidemiol Rec* 2007; *82* : 49-60.
4. Centers for Disease C, Prevention. Brief report: update: mumps activity - United States, January 1-October 7, 2006. *MMWR Morb Mortal Wkly Rep* 2006; *55* : 1152-3.
5. Eick AA, Hu Z, Wang Z, Nevin RL. Incidence of mumps and immunity to measles, mumps and rubella among US military recruits, 2000-2004. *Vaccine* 2008; *26* : 494-501.
6. Crowley B, Afzal MA. Mumps virus reinfection - clinical findings and serological vagaries. *Commun Dis Public Health* 2002; *5* : 311-3.
7. Nojd J, Tecle T, Samuelsson A, Orvell C. Mumps virus neutralizing antibodies do not protect against reinfection with a heterologous mumps virus genotype. *Vaccine* 2001; *19* : 1727-31.
8. WHO. Mumps virus nomenclature update: 2012. *Wkly Epidemiol Rec* 2012; *22* : 217-24.
9. Houard S, Varsanyi TM, Milican F, Norrby E, Bollen A. Protection of hamsters against experimental mumps virus (MuV) infection by antibodies raised against the MuV surface glycoproteins expressed from recombinant vaccinia virus vectors. *J Gen Virol* 1995; *76* : 421-3.

10. Cusi MG, Fischer S, Sedlmeier R, Valassina M, Valensin PE, Donati M, *et al*. Localization of a new neutralizing epitope on the mumps virus hemagglutinin-neuraminidase protein. *Virus Res* 2001; *74* : 133-7.

11. Yates PJ, Afzal MA, Minor PD. Antigenic and genetic variation of the HN protein of mumps virus strains. *J Gen Virol* 1996; *77* : 2491-7.

12. Kovamees J, Rydbeck R, Orvell C, Norrby E. Hemagglutinin-neuraminidase (HN) amino acid alterations in neutralization escape mutants of Kilham mumps virus. *Virus Res* 1990; *17* : 119-29.

13. Orvell C, Alsheikhly AR, Kalantari M, Johansson B. Characterization of genotype-specific epitopes of the HN protein of mumps virus. *J Gen Virol* 1997; *78* : 3187-93.

14. Kulkarni-Kale U, Ojha J, Manjari GS, Deobagkar DD, Mallya AD, Dhere RM, *et al*. Mapping antigenic diversity and strain specificity of mumps virus: a bioinformatics approach. *Virology* 2007; *359* : 436-46.

15. Jin L, Orvell C, Myers R, Rota PA, Nakayama T, Forcic D, *et al*. Genomic diversity of mumps virus and global distribution of the 12 genotypes. *Rev Med Virol* 2014; *25* : 85-101.

16. Rubin SA, Qi L, Audet SA, Sullivan B, Carbone KM, Bellini WJ, *et al*. 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* 2008; *198* : 508-15.

17. Rubin SA, Link MA, Sauder CJ, Zhang C, Ngo L, Rima BK, *et al*. Recent mumps outbreaks in vaccinated populations: no evidence of immune escape. *J Virol* 2012; *86* : 615-20.

18. Lim CS, Chan KP, Goh KT, Chow VT. Hemagglutinin-neuraminidase sequence and phylogenetic analyses of mumps virus isolates from a vaccinated population in Singapore. *J Med Virol* 2003; *70* : 287-92.

19. Pipkin PA, Afzal MA, Heath AB, Minor PD. Assay of humoral immunity to mumps virus. *J Virol Methods* 1999; *79* : 219-25.

20. McLean HQ, Hickman CJ, Seward JF. Immunization, vaccines and biologicals - mumps. *The immunological basis for immunization series.* vol. 16. Geneva: World Health Organization; 2010.

21. Santak M, Orvell C, Gulija TK. Identification of conformational neutralization sites on the fusion protein of mumps virus. *J Gen Virol* 2015; *96* : 982-90.