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Perspective

Emergent lineages of mumps virus suggest the need for a polyvalent vaccine

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ABSTRACT

Mumps outbreaks among vaccinated patients have become increasingly common in recent years. While there are multiple conditions driving this re-emergence, convention has suggested that these outbreaks are associated with waning immunity rather than vaccine escape. Molecular evidence from both the ongoing American and Dutch outbreaks in conjunction with recent structural biology studies challenge this convention, and suggest that emergent lineages of mumps virus exhibit key differences in antigenic epitopes from the vaccine strain employed: Jeryl-Lynn 5. The American and Dutch 2016–2017 outbreak lineages were examined using computational biology through the lens of diversity in immunogenic epitopes. Findings are discussed and the laboratory evidence indicating neutralization of heterologous mumps strains by serum from vaccinated individuals is reviewed. Taken together, it is concluded that the number of heterologous epitopes occurring in mumps virus in conjunction with waning immunity is facilitating small outbreaks in vaccinated patients, and that consideration of a polyvalent mumps vaccine is warranted.

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Mumps virus (MuV) is a member of the *Paramyxoviridae* and a cause of fever and viral parotitis. Less frequently, it is associated with orchitis, encephalitis, aseptic meningitis, deafness, and pancreatitis (Rubin et al., 2015). Routine immunization against mumps is part of the recommended series for children in the USA and Europe, and is given in combination with measles and rubella immunization (MMR) (M-M-R II; Merck & Co., West Point, PA, USA) or as measles, rubella, and varicella zoster immunization (ProQuad; Merck & Co., West Point, PA, USA). MuV exhibits moderate genetic heterogeneity (Ivancic-Jelecki et al., 2008), and 12 genotypes (A–N, excluding E and M) currently or historically circulate in different parts of the world (Jin et al., 2015). Multiple vaccine strains have been used in different locations; however, the discussion here is restricted to the genotype A vaccine strains used in Western Europe and the USA: Jeryl-Lynn (JL) lineages 2 and 5.

Increased instances of mumps outbreaks in vaccinated individuals have been seen in recent years, with those on college campuses disproportionately affected (Albertson et al., 2016; Cortese et al., 2008; Patel et al., 2017). Reasons for this increase are likely multifaceted, and include declining levels of vaccine-derived immunity (LeBaron et al., 2009; Davidkin et al., 2008; Gu et al., 2017) and a significant reduction in the natural 'boosters' received by vaccinated individuals as MuV has become less prevalent in the increasingly vaccinated population. The possibility of gradual immune escape by MuV variants has been discussed previously (Nöjd et al., 2001), but was confounded by laboratory findings demonstrating neutralization of wild-type MuV strains representing diverse genotypes by serum from JL-vaccinated children (Gouma et al., 2016a; Rubin et al., 2012). The decrease in antibody titers over time following vaccination with live, attenuated viruses is not unique to mumps; however, the recent tendency toward outbreaks in vaccinated individuals seems to be.

This prompted the present authors to (1) carefully examine the literature describing protective MuV epitopes, neutralization of heterologous strains by JL hyperimmune sera, and the natural history of MuV, and (2) perform a computational analysis of the emergent outbreak strains currently circulating in the Netherlands and the USA, in order to fully explore the potential for MuV vaccine escape.

Of the nine MuV proteins, the most thoroughly explored are the hemagglutinin–neuraminidase (HN), the fusion protein (F), and the small hydrophobic protein (SH). The SH protein exhibits elevated levels of diversity relative to the rest of the MuV genome, and for this reason it is frequently used for genotyping and epidemiological surveillance (Orvell et al., 1997; Ströhle et al.,

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1996; Yeo et al., 1993). Sera from vaccinated individuals and convalescent patients indicate that the immunodominant antigens are HN and F (Cusi et al., 2001; Kulkarni-Kale et al., 2007; Šantak et al., 2015).

The robustness of in vitro serum neutralization assays against HN and F were measured by generating chimeric MuV constructs wherein JL and wild-type genotype H strain 88-1961 backbones were supplemented with the reciprocal copy of HN and F. JL bearing 88-1961 F was neutralized by hyperimmune sera at equivalent levels to native JL, indicating that vaccine-derived antibodies against F are fully cross-reactive (Rubin et al., 2012). Neutralization of JL bearing the 88-1961 HN protein by JL hyperimmune serum was significantly different from JL and the JL/88-1961 F chimera, indicating that biologically relevant distinctions existed between at least some immunogenic epitopes in HN (Rubin et al., 2012). Similarly, cross-neutralization between strains was full in strains featuring no amino acid changes from the relevant vaccine strain, and partial in strains where changes in protein sequence were apparent (Gouma et al., 2016a; Vaidya et al., 2016). These findings are suggestive of retention of certain HN epitopes across MuV strains and variation in others, but the threshold between lower capacity for neutralization in vitro translating into protection versus failure in vivo is unclear. Importantly, Rubin et al. note that the neutralizing sera used in their study were collected 6 weeks post-vaccination, and that antibody titers are not likely to be representative of the infected, vaccinated patients involved in recent outbreaks (Rubin et al., 2012). The investigators also note that T-cell involvement in protective immunity was not assessed, which Homen and Bremel described as likely to be important (Homan and Bremel, 2014).

The lower capacity for neutralization of HN across heterologous strains may very well mean that vaccine-induced immunity drops below the threshold required for in vivo protection in the face of declining antibody titers. This scenario reflects the current state of mumps outbreaks, but would be bolstered by a computational examination of immunogenic protein sequences from outbreak strains in vaccinated populations for validation. Such an analysis is directly possible with publicly available MuV surveillance data from the Netherlands (Gouma et al., 2016b), and indirectly with surveillance data from the USA (Benson et al., 2017). The crystal structure of MuV HN was recently described by Kubota et al., who noted that some of the previously noted three-dimensional immunogenic epitopes involve residues that are mutable across strains (Kubota et al., 2016).

In the present study, multiple sequence alignments were assembled using the HN amino acid sequence from the outbreak strains in the Netherlands for the years 2013–2015 and from JL, the vaccine strain used in the country. The outbreak strains are largely clonal from the standpoint of HN; more than 60 of the >100 isolates available in GenBank collected in the Netherlands over that time period share 100% amino acid identity, and another 16 differ by only a single substitution of a similar residue (lysine to arginine). Twenty Dutch isolates with sequences available in GenBank were selected and their sequence diversity examined (Benson et al., 2017; Sievers and Higgins, 2014; dataset available as Supplementary material supplemental dataset S1 and at doi: 10.13140/RG.2.2.28761.42088), antigenic epitopes predicted (via http://imed.med.ucm.es/Tools/antigenic.html), and secondary structure computed (Garnier et al., 1996) to address the probability of immune escape in a predictive way. The findings were then extrapolated to SH sequences from current USA outbreak strains.

Only five of the 19 Dutch strains examined contained amino acid substitutions relative to consensus (10 total substitutions), indicating that these strains are highly homologous. While all but one of the changes were in predicted antigenic epitopes, only one generated a predicted change in secondary structure (Table 1). This alanine to valine change is conserved in two isolates collected in the Spring of 2015, and generates a predicted change from an α-helix to a linear β-strand. This suggests the loss of an antigenic epitope rather than the introduction of a novel one. These results indicate that the level of amino acid diversity is extremely low within the collection of Dutch outbreak strains. That said, comparison of their sequence, antigenic, and structural patterns to those of JL demonstrated a marked diversity between the strain generating immunity and the strains causing disease. This divergence was not uniform across the HN protein. Of the 25 predicted antigenic epitopes, 13 were 100% identical in sequence, antigenicity, and secondary structure between outbreak strains and JL. These conserved epitopes likely explain the observation of some neutralization of heterologous strains by JL hyperimmune serum (Gouma et al., 2016a; Rubin et al., 2012; Vaidya et al., 2016).

The remaining 12 epitopes all feature at least one divergent residue from JL among the outbreak strains, and 11 of these result in a predicted structural change (Table 2). It is notable that the number of divergent sites often generated a disproportionately large number of predicted structural changes, indicating that the impact of MuV diversity may be underestimated simply by tabulating the number of changes. This structural diversity suggests that antibodies raised against the JL epitopes may no longer interact with the analogous outbreak strain epitopes. Two of three divergent epitopes found in a recent genotype G isolate that facilitated loss of neutralization by sera from JL-immunized guinea pigs were identified in the computational analysis, validating the approach (Šantak et al., 2013). The tendency of vaccine-derived antibody titers against MuV to decline over time (LeBaron et al., 2009) makes it is highly plausible that the recent Netherlands outbreaks in vaccinated individuals resulted from antibodies against the conserved epitopes falling below the protective threshold given their small number.

Similar outbreaks have occurred in the USA in 2006, 2009–2010, and starting in 2014, continuing through 2017. Outbreak strains are typed and surveilled using the SH sequence, which varies at a higher rate than the rest of the MuV genome (Orvell et al., 1997; Yeo et al., 1993; Takeuchi et al., 1991). SH is not known

Table 1
Hemagglutinin–neuraminidase (HN) diversity among outbreak strains.[a]

Divergent strain	Number of sites	Divergent site[b]					Structural change[c]				
Leiden 15	5	A13S	N25D	A37V	T130S	S462T	No	No	H → E	No	No
Heerhugowaard 13	1	K317R					No				
Hilversum 14	1	K317R					No				
Purmerend 14	2	T97S		K317R			No		No		
Hengevelde 15	2	N25D		A37V			No		H → E		

[a] Divergence indicates difference from the consensus HN sequence of 19 Dutch outbreak strains examined. No small hydrophobic protein (SH) sequences featured changes in amino acid sequence across all American outbreak strains; therefore, SH diversity is not included in this table.
[b] Divergent sites are described by the amino acid of the consensus sequence, followed by the residue number, followed by the amino acid of the noted strain.
[c] Secondary structures are abbreviated as follows: H = helix; E = beta strand; C = coiled coil.

Table 2
Divergence between vaccine strain JL5 and outbreak strains.[a]

Epitope	Protein	Sequence[b]	% Divergent sites	% Structural divergence
1	HN	PSKFFTISDSATFAPGPVSNA PSKLFIMLDNATFAPGPVVNA	33%	19%
2	HN	TFRTCFRILALSVQAVTLILVIVTLGELVR TFRTCFRILVLSVQAVTLILVIVTLGELIR	10%	63%
3	HN	LSNQLSSI	0%	N/A
4	HN	ESATMIASAVGVMNQVIHGVTVSLPL ESAAVIASAVGVMNQVIHGVTVSLPL	8%	27%
5	HN	NQLLATLATICTSQKQVSNCSTNIPLVND NQLLSTLATICTNRNQVSNCSTNIPLIND	17%	7%
6	HN	ATHDFSIGH	0%	N/A
7	HN	GCTRIPSFSLKTHWCYTHNVIN	0%	N/A
8	HN	SNQYVSMGILVQTA SNQYVSMEILAQTA	14%	71%
9	HN	KTLKIQYLS	0%	N/A
10	HN	NRKSCSIATVPDGCAMYCYVST	0%	N/A
11	HN	PPTQKLILLFYN PPTQKLTLLFYN	8%	58%
12	HN	WATLVPGVGSG WATLVPGAGSG	9%	0%
13	HN	FENKLIFPAYGGVLPNSTLGVKSAR FENKLIFPAYGGVLPNSTLGVKLAR	4%	24%
14	HN	FFRPVNPYNPCSGP	0%	N/A
15	HN	ALRSYFPS	0%	N/A
16	HN	FSNRRIQSAFLVCAWNQILVTNCELVVPS FSSRRVQSAFLVCAWNQILVTNCELVVPS	7%	3%
17	HN	EGRVLLINNRLLYYQ	0%	N/A
18	HN	WPYELLYEIS	0%	N/A
19	HN	SGENVCPTACVSGVYLDPWPLTPYSH SGENVCPIVCVSGVYLDPWPLTLYRH	15%	38%
20	HN	FTGALLN	0%	N/A
21	HN	VNPTLYVSALNNLKVLAP	0%	N/A
22	HN	GTQGLFAS	0%	N/A
23	HN	TTTTCFQ	0%	N/A
24	HN	DASVYCVYIM	0%	N/A
25	HN	ASNIVGEFQILPVLTR ASNIVGEFQILPVLAR	6%	31%
SH	SH	MPAIQPPLYLTFLLLILLYLIITLYVWIILTVTYKTSVRHAALYQRSFFHWSFDHSL MPAIQPPLYLTFLVLILLYLIITLYVWTILTINYKTSVRYAALYQRSFSRWGFDHSL	14%	5%

N/A: not applicable.
[a] Divergence reported in Table 2 reflects only changes in predicted antigenic epitopes. Additional divergent sites are found in non-antigenic regions.
[b] Top rows contain the consensus sequence across outbreak strains; lower rows contain the JL5 sequence.

to be an antigenic protein, as antibodies against SH are rarely found in the serum of vaccinated or convalescent patients (Ivancic-Jelecki et al., 2008; Rubin et al., 2012). As with HN in the Netherlands, the SH amino acid sequences from American outbreak strains indicate that the ongoing outbreak is associated with an emergent clonal lineage belonging to genotype G that is markedly diverse from JL. Previous reports indicate that phylogenetic clustering of strains is consistent whether based on SH, HN, or F, indicating that mutations are largely genotype-specific (Jin et al., 2015; WHO, 2013). It should therefore be possible to extrapolate findings from HN diversity and potential immune escape to SH. In such a case, sequence diversity or conservation of SH could be considered predictive of diversity in HN, which in turn would have implications for cross-protection or the lack thereof. It is thus potentially prudent to consider that detected variance between outbreak strains and JL in SH is likely mirrored by variance between outbreak strains and JL in the protective epitopes of HN. This argument is bolstered by the current mumps outbreaks in vaccinated individuals in the USA, and the observation that vaccinated mumps patients did not have clear-cut differences in antibody titer from vaccinated, non-patients (Cortese et al., 2011).

Given that at least one American cluster of cases in Arkansas among vaccinated young adults led to an explosion of pediatric cases in a neighboring community with suboptimal vaccine coverage (Majumder et al., 2017), the urgency of mumps vaccine efficacy is pressing. As voluntary exemptions from routine vaccinations continue to rise, all rapid and practical measures to ensure full and complete protective immunity among the vaccinated must be considered. Suggestions of a third boost in young adulthood have been made; however, Fiebelkorn et al. demonstrated that the impact of an additional immunization had a negligible long-term effect on antibody titers (Fiebelkorn et al., 2014). The alternative options include the development of a novel vaccine (Xu et al., 2014) or formulation of a polyvalent vaccine. The emergence of near-clonal lineages in countries with highly vaccinated populations, as opposed to the diversity of circulating strains in countries such as India where mumps vaccination is optional (Vaidya et al., 2013), indicates that selection acting on MuV does slowly drive the evolution of new ‘escape variant’ strains. The development of a polyvalent vaccine would be a practical measure that would increase the robustness of vaccine-derived immunity and exponentially decrease the probability of ‘escape variant’-derived outbreaks in vaccinated individuals.

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Ethics statement

This research did not involve the use of human or animal subjects. The authors confirm that all ethical standards for publication have been met.

Conflict of interest

The authors have no conflicts of interest to declare.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ijid.2017.09.024.

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