Emerging Mumps Infection

Steven Rubin, PhD,* Richard Kennedy, PhD,† and Gregory Poland, MD†

Mumps is one of the older described infectious diseases, first documented by Hippocrates in the fifth century BC. Before widespread use of mumps vaccines, mumps was a common disease of childhood, with nearly everyone having serologic evidence of prior infection by age 15. The virus is spread by direct contact with respiratory droplets. Salivary gland swelling, usually the parotid, is the most common physical manifestation; however, mumps virus, a paramyxovirus, can disseminate widely throughout the body, including the central nervous system, causing a wide array of medical presentations. For example, in the pre-vaccine era, mumps was the leading cause of viral encephalitis and sudden onset deafness in the United States.

**CLINICAL USE OF MUMPS VACCINE**

In the United States, mumps vaccine (Jeryl Lynn strain) was first licensed in 1967 and has been administered as MMR (measles, mumps and rubella trivalent vaccine) since 1971. Since 1989, MMR has been administered as a 2-dose series, with the first dose at 12 to 15 months and the second at 4 to 6 years. Neutralizing antibody is considered a correlate of protection; however, the level of antibody required has not been established. In contrast, there is no association between the magnitude or nature of currently understood cell-mediated immune responses to the vaccine and protection.

The total prelicensure experience demonstrated that 97% of 6283 initially seronegative children developed neutralizing antibody after vaccination.1 Similar seroconversion rates against mumps virus were observed after administration of MMR. Based on the most recent data available, the median 2-dose MMR vaccination coverage among children in kindergarten in the United States is 94.7% (http://www.cdc.gov/mmwr). The vaccine has proven itself to be highly efficacious, with only a few hundred cases reported annually by the end of the 1990s, compared with well over 100,000 reported cases annually (likely a gross underestimate based on reporting) in the prevaccine era, representing greater than a 99% decline in disease incidence. However, since 2006, there has been a resurgence in reported mumps cases in the United States and in other countries where the disease had previously been under control (Fig. 1). These outbreaks have occurred predominately on college/university campuses and similar close-contact environments where the opportunity for exposure and transmission is high.

**IMMUNE RESPONSES AFTER MUMPS VACCINATION**

Mumps vaccination results in the expansion of antigen-specific B lymphocytes and the production of mumps virus–specific antibody. Primary immune responses are initially IgM, followed by the production of low avidity IgG, whereas secondary responses, having undergone affinity maturation, are marked by the absence of IgM and the presence of high titer, high avidity IgG. However, lymphocyte numbers and antibody titers are typically quite low, much lower than the responses against simultaneously delivered antigens (measles and rubella). Mumps virus antibody titers have also been demonstrated to wane at a higher rate than measles or rubella titers.

Memory T cell responses also develop after vaccination and are presumed to contribute to immunity, although it is likely that full protection requires antibody responses as well. Cellular immunity has not been nearly as well studied as antibody responses; however, the data suggest that mumps-specific T cells are detectable long after vaccination and may actually have greater durability than humoral responses.
MUMPS RESURGENCE: VIEWS

There has been some controversy over what factors contribute to the increasing number of mumps outbreaks. Primary vaccine failure is not likely a cause, given data from numerous clinical trials showing seroconversion in greater than 95% of vaccinees after one dose and nearly 100% after 2 doses. Failure to vaccinate or receipt of only 1 of the 2 recommended doses of MMR is also not a likely factor, given that in some outbreaks nearly all cases occurred in persons with a 2-dose vaccine history. Some have speculated that antigenic differences between the 1967 vaccine strain and contemporary circulating strains might permit immune escape; however, this too seems unlikely given that sera collected from individuals shortly after vaccination have been shown to effectively neutralize a vast array of genetically disparate virus strains. In contrast, the preponderance of available data point toward secondary vaccine failure (waning of vaccine-induced immunity) as a major contributing factor. Numerous studies have associated time after vaccination with declining levels of mumps virus–specific antibodies, decreased vaccine effectiveness and increased odds of contracting disease.

In contrast to mumps, cases of measles and rubella infrequently occur in persons with a documented history of 2 doses of MMR vaccine, suggesting some intrinsic property of mumps vaccine that limits its long-term effectiveness. Indeed, there are a number of qualitative and quantitative differences between the immune response to the mumps component of MMR versus responses to the measles and rubella components. For example, compared with levels of measles- and rubella-specific memory B cells, the number of mumps virus–specific memory B cells in MMR vaccinees have been found to be very low, and the antibodies produced are of lower avidity. Avidity testing of antibodies from mumps cases has revealed that a significant portion of cases have both IgM and high avidity IgG. This indicates previous successful vaccination that was insufficient to prevent subsequent infection. A related finding is the in silico immunoinformatics-based discovery that the amino acid sequence of key regions of the major immunological target of the Jeryl Lynn mumps virus vaccine strain (the hemagglutinin–neuraminidase protein) is not optimal for facilitating the interaction between B cells and CD4 T helper cells that is required for robust immunological memory.

Mumps virus–specific T cell studies have focused on lymphoproliferation and IFN-γ production. A more comprehensive assessment of mumps vaccine–induced T cell subsets (eg, regulatory T cells, Th17 cells and Th1 cells) and function (ie, what other immunologic effector mechanisms are mumps-specific T cells capable of?) would fill an important knowledge gap and may provide key insights into the durability of mumps virus–induced cellular immunity. For example, the documented decrease in neutralizing antibody titers over time may be an indirect result of insufficient or inappropriate T cell help. These expanded studies, as mentioned, should include systems biology or vaccinomics approaches aimed at providing a system-level understanding of not just the development but also the waning of mumps-specific immunity. It is likely that the complex interconnected environment and signaling pathways activated during live viral vaccination are critical determinants of how robust and how durable the resulting immune responses will be. We (G.A. Poland and R.B. Kennedy) and others have suggested a vaccinomics paradigm using system biology approaches to further the science in this regard.

Although it is possible that the initial priming conditions for mumps elicit suboptimal immunity, mumps vaccination occurs simultaneously with delivery of measles and rubella virus. There are no studies indicating that the 3 components of the MMR vaccine are distributed, processed or presented differently—an aspect of MMR vaccination that should be examined. An alternative explanation is that mumps antigens are inherently less immunogenic or perhaps are present at a much lower abundance because of a slower or different viral life cycle. Understanding why immune responses to mumps are weaker than responses to other pathogens should be a research priority because new and more effective vaccines are unlikely to be created without this fundamental understanding. Recent advances in testing and developing immunologic adjuvants may provide a solution to the weak immunogenicity of mumps vaccine antigens.

CURRENT CONSIDERATIONS AND FUTURE DIRECTIONS

The hypothesis that waning immunity is a cause of the global resurgence in mumps cases suggests administration of an additional dose of vaccine during adolescence (or later) as a remedy. The merit of such a modification to the current Immunization Practices Advisory Committee–recommended vaccine schedule was recently explored, but was found to not be supportive. In that study, the magnitude and duration of mumps virus neutralizing antibody responses after a third dose of MMR vaccine among 685 young adults were assessed. Although mumps virus–specific antibody titers significantly rose in response to revaccination, the increase was transient, returning to baseline titers within a year. Although this boost did not appear to provide a long-term quantitative benefit in terms of antibody levels, qualitative effects, such as antibody avidity or B cell memory or other markers of cell-mediated immunity, were not examined. Although the authors conclude a lack of compelling data to support a routine third dose of MMR vaccine, the transient boost that occurs after revaccination may be of clinical significance and utility at least over the short term. This is suggested by use of MMR vaccine as a control measure during 2 mumps outbreaks, with mumps attack rates in students receiving the intervention being significantly lower.
substantially lower compared with the attack rate in students not receiving the intervention.\textsuperscript{10,11} However, the data are difficult to rate in students not receiving the intervention. Further investigation of the effectiveness of vaccine use as an outbreak control measure, as well as the potential for a third dose of MMR, to improve long-term vaccine functional performance is needed; however, it is clear that other approaches to improve vaccine effectiveness need to be pursued. Among these, development of new vaccines must be considered. However, such an undertaking requires knowledge of what is responsible for the less than desirable performance of existing vaccines. Why are levels of mumps virus–specific antibody-secreting cells after vaccination significantly lower than the levels induced by natural infection? Why does MMR vaccine result in development of far fewer mumps virus–specific memory B cells than measles- and rubella-specific memory B cells? Are there differences in the site, quantity or quality of mumps, measles and rubella antigen presentation? Why is the avidity of MMR vaccine–induced mumps antibodies much lower than the avidity of the measles and rubella antibodies? Do mumps-specific lymphocyte numbers decline at a more rapid rate than lymphocytes with other antigenic specificities (ie, measles or rubella) or is it a case of simply having too few to begin with? What are the exact roles of CD4 and CD8 T cell responses in long-term protection against mumps re-infection? These and other lines of investigation must be pursued.

Despite the issues raised here with vaccine performance, it is important to emphasize that it is far better to vaccinate than to not vaccinate. Data from investigations of recent mumps outbreaks show that the effectiveness of a single dose of the Jeryl Lynn mumps vaccine is ≈80% and that of 2 doses is ≈88%. Although imperfect, these are nonetheless very good numbers. Further, in those cases of mumps in persons with a history of vaccination, disease symptomatology has been observed to be mild in comparison to cases in unvaccinated persons. Nonetheless, there is room for advancing the science and devising new mumps vaccine candidates.

**REFERENCES**


