Campaign Mode MMR Vaccination to Control Outbreak of Mumps in a Highly Vaccinated Population

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Summary

This study evaluated the effectiveness of a third dose of MMR vaccine for outbreak control, and assessed for waning immunity. Of 20,496 university students who were enrolled during the 2015–2016 academic year, mumps was diagnosed in 259 students. Fisher's exact test was used to compare unadjusted attack rates according to dose status and years since receipt of the second MMR vaccine dose, and multivariable time-dependent Cox regression models were used to evaluate vaccine effectiveness, according to dose status (3 doses *vs* 2 doses, and 2 doses *vs* 0 dose) after adjustment for the number of years since the second dose. The attack rate was lower among the students who had received three doses than among those who had received two doses (6.7 *vs* 14.5 cases per 1000 population, $P<0.001$). Students had more than 9-times the risk of mumps if they had received the second MMR dose 13 years or more before the outbreak. At 28 days after vaccination, receipt of the third vaccine dose was associated with a 78.1% lower risk of mumps than receipt of a second dose (adjusted hazard ratio, 0.22; 95% CI 0.12 to 0.39). The vaccine effectiveness of two doses versus no doses was lower among students with more distant receipt of the second vaccine dose. The authors concluded that students who had received a third dose of MMR vaccine had a lower risk of mumps than those who had received two doses. Students who had received a second dose of MMR vaccine 13 years or more before the outbreak had an increased risk of mumps.

Commentaries

Evidence-based Medicine Viewpoint

Relevance: This study [1] was necessitated by the occurrence of mumps outbreaks in US universities, despite high population-based coverage with MMR vaccine using two doses during infancy and childhood [2-4]. The investigators analyzed the number of confirmed and probable mumps cases that occurred throughout the outbreak and examined the effect of the additional MMR dose. Three major outcome measures were evaluated: (*i*) attack rate of mumps by number of MMR doses received; (*ii*) attack rate by duration since the last dose; and (*iii*) vaccine effectiveness (of the additional dose). Prior to the outbreak, over 98% of the students (age 8-24 years, *n*=20496) had received at least two MMR doses. After the onset of the outbreak, about one-fourth of the students received an additional MMR dose.

There were 259 cases during the outbreak period (August 24, 2015 to May 13, 2016); yielding an attack rate of 12.6 cases per 1000. The attack rate (per 1000) showed a progressive decline with the total number of MMR doses received *viz*. 47.6 with zero doses, 32.8 with one dose, 14.5 with two doses, 6.7 with three doses, and 0 with four and five doses. Further the attack rate also varied by the duration since receipt of the last dose: 1.6 for dose received within 2 years, 3.9 for dose received within 3-5 years, 11.3 for dose received 13-15 years prior, and 17.6 for dose received >16 years prior. The additional dose of MMR vaccine was calculated to have an incremental vaccine effectiveness of 78%.

Critical appraisal: The authors introduced several methodological refinements to their analyses. Prior and additional MMR vaccinations were confirmed by documentary evidence, rather than verbal report. Therefore, the precise number and timing of doses could be recorded. The immunogenic response following vaccination was taken into consideration by calculating the attack rates 7, 14, 21 and 28 days post-vaccination; instead of at one time point.

A formal case definition was used [5,6], although the details were not explicitly stated. The definition describes cases as 'confirmed' or 'probable' based on whether (or not) laboratory confirmation was obtained. However, it is unclear whether cases were detected through passive

surveillance *i.e* students with symptoms reported to health facilities; or active surveillance *i.e.* cases were sought by trained field staff. This can result in a significant difference in the number of cases detected.

It is unclear whether University students represent merely an epidemiological age slab (18-24 years); or whether they represent a cohort of persons with behavior patterns that could prompt and/or promote outbreaks of infectious disease(s). The distinction is important because waning of immunity from infant and childhood MMR vaccination would create a pool of susceptible persons in the next higher age group *viz*. adolescents and young adults. If age is the only issue, cases would be expected among this group, irrespective of whether they attend university or not. On the other hand, if behavior patterns are also responsible, a disproportionate clustering of cases within university campuses is expected. The latter seems to be the case because two-thirds of the mumps cases were reported among university students [7]. This has two potential implications. First, outbreaks would be propagated by the combination of a susceptible cohort, with the added influence of living within a somewhat closed environment (residential, social and epidemiological). This means that merely vaccinating university students (after the onset of an outbreak) without putting into place surveillance systems, isolation facilities and behavior modification strategies through education would be futile. This aspect is especially important because behavior modification (students themselves minimizing contact with cases) after the onset of an outbreak would favorably influence the duration and impact of the outbreak. To be fair, the authors considered these points, reiterating that additional MMR vaccine doses could be one of several potential tools for outbreak control.

Despite the impressive findings highlighted in this study, there are some less emphasized data that merit attention. It appears that even in a developed country like USA with robust vaccination systems and records, there was only about 80% compliance to the MMR vaccination schedules in infancy (first dose) as well as childhood (second dose). However, even this less-than-desirable coverage resulted in substantial reductions in the burden of disease, thereby creating a pool of individuals lacking the opportunity for intermittent natural boosting of immunity. Therefore it is not surprising that the disease burden shifted to the next higher age group *viz*. adolescents and young adults.

Even though students were provided an enabling environment to receive additional MMR vaccination (free clinics, extended hours, health education, campaign mode), only about one-quarter availed this facility, despite the declaration of an outbreak. This behavioral pattern among an educated and empowered cohort augurs poorly for the successful implementation of campaign-mode, voluntary adult vaccination as a public health measure.

This study clearly demonstrated the waning of vaccine-induced immunity (at least for mumps). Even if the immunity is boosted through an additional dose at entry into University, it is possible that once sufficient adolescents and young adults are protected, the disease burden will shift to older age groups. In other words, the overall burden of disease may remain unchanged, merely moving from one demographic bracket to another.

Further, female young adults with insufficient anti-mumps antibody titers are likely to transmit inadequate antibodies to their infants, thereby making young infants susceptible to the disease. Since the first dose of MMR is administered at 12-15 months, there is the likelihood of observing cases in the latter half of the first year of life also. This trend is highly likely given that young mothers (in USA) in the present era, are likely to have received the last dose of MMR vaccine in childhood; and this study shows that vaccination more than 16 years prior was associated with significant decline in immunity.

Conclusion: This analysis suggests that administration of MMR vaccine in a campaign mode, coupled with robust public health measures could mitigate the intensity of a mumps outbreak among highly vaccinated young adults in a University setting. It also demonstrates waning of vaccine-induced immunity and raises the specter of age-shifts in mumps (and possibly other vaccine preventable diseases).

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Pediatrician's Viewpoint

This study [1] reaffirms the need and effectiveness of a 3rd dose of a MMR vaccine to university students to prevent regular outbreaks or breakthrough disease in highly vaccinated adolescents/adults. In recent times, many reports on outbreaks of mumps amongst two dose recipients of MMR vaccine are published [2]. Centers for Disease Control and Prevention (CDC) has also very recently given its recommendations on the utility of using a 3rd dose of MMR during an ongoing outbreaks among college-going students [3]. Earlier, the CDC provided guidance on employing a third dose of MMR for outbreak control but stopped short of making a full recommendation.

What the study fails to provide?

1. The study fails to provide an 'exact' duration of protection offered by a single dose of MMR vaccine against the mumps disease. Though the authors have used a cut-off of 13 years, this is based on the fact that the 2nd MMR dose is usually given at 4-6 years of age in US. In the current study, 81.6% had received 2nd dose at 4-6 years and those who have received three doses, 94.7% were vaccinated at 18-24 years [1]. Since no reliable correlate of protection for the mumps vaccine and disease is known, it would be of paramount interest to know for how long a single dose of mumps vaccine provides protection.
2. The authors have studied attack rates of mumps among students based on both the number of previous doses of MMR vaccine received and the time since the receipt of the last dose of MMR vaccine. It is not clear whether the number of doses received earlier had some impact on the protection or is it the time since the last dose of MMR that only matters. Whether the number of memory B-cells and long lasting plasma cells induced by the previous dose(s) of vaccine have some impact on the durability of protection?
3. The issue of routine 3rd dose of MMR vaccine is still unresolved. Whether the 3rd dose is meant only to offer protection during ongoing outbreaks in colleges/universities or should it be offered routinely at appropriate interval to all 2-dose recipients?
4. Whether different strains of mumps antigens used in different MMR products have different impact on durability of vaccine-induced immunity, a phenomenon referred commonly to as 'immune escape'.
5. In the above study, 77 children have received more than 3 doses of MMR vaccine. Was there any undesirable effect of too many doses of MMR vaccine observed in any vaccinee?

What are the implications for India?

There are some significant differences in the epidemiology of mumps disease and vaccination practices in US and India. Hence, before analyzing any implication of the findings of the study for us, let's first enumerate some peculiar differences in US and Indian scenario.

1. Mumps vaccination is not part of India's UIP despite a significant burden. Only private sector and few smaller states are providing MMR vaccine to children and adolescents. There are no data regarding the coverage of MMR vaccine in the target population;
2. There is no surveillance system to measure/monitor mumps disease in different age groups;
3. A different vaccination schedule of MMR is used in private sector in India than in US where three doses of MMR are given at 9 moths, 15 months, and 4-6 years of age [4].
4. A different mumps antigen (Leningrad-Zagreb) is employed in the most widely used MMR vaccine formulation in India than in US (Jeryl Lynn).
5. In India, the wild mumps virus is still widely prevalent with opportunity of frequent natural boosting in different age groups.

As per the data provided by IDSP and IDsurv, the majority of mumps cases in India occur in more than 5 years of age [2]. There is no information regarding the extent of mumps outbreaks among college-going

students. The coverage of MMR vaccine among this group is also not known, but believed to be miniscule. So, in Indian scenario, the 3rd MMR dose used in US would be equivalent to 4th MMR dose if we go by the IAP immunization schedule [4].

Coming back to the implications for India, first of all, we must stop neglecting mumps disease. It is indeed a serious public health concern [4,5]. The government should establish a surveillance system to monitor/ measure mumps cases. At least two doses of MMR vaccine must be introduced in the UIP in place of Measles-Rubella (MR) vaccine. According to WHO, two doses of the MMR vaccine are sufficient to provide long-term protection against mumps [6]. Even in US, the two-dose schedule has led to a 99% decrease in the incidence of mumps in comparison to pre-vaccine period. Ironically, for the current scenario of frequent outbreaks in college students in many developing countries, the highly successful vaccination programs are to be blamed since there are very little opportunities for sub-clinical natural boosting. There is a need of rescheduling the MMR vaccination schedule for private sector and an adolescent dose of mumps-containing vaccine should be provided to adolescent/pre-adolescent children. Development of a more potent mumps antigen with new formulations like mono- or bi-valent products is also urgently needed.

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Virologist's Viewpoint

The robustness of an immune response after the completion of primary immunization at stated dose and interval loses its verve with the passing of time. Sustained protection is maintained by periodic boosters of vaccines in many diseases, including poliomyelitis, hepatitis B, whooping cough and tetanus. It is not yet fully understood why some vaccines such as hepatitis A and B are effective for a fairly prolonged period, and others require boosters. One view is if the immune system responds rather rapidly to primary vaccine dose, the time gap available for the body is rather insufficient to develop adequate memory response resulting in low level persistence of memory cells in germinal centers. Route of administration and quantum of dose influence the outcome in some instances [1]. Natural immunity in general is longer lasting than vaccine-induced immunity. The risks of natural infection far outweigh the risks of immunization for every recommended vaccine. In this observational study, Cardemil, *et al*. [2] reported their observations on a mumps outbreak in adult student population of a university in the US where proof of vaccination is mandatory for enrolment as student and two doses MMR vaccine coverage exceeds 90%. Waning of vaccine-induced protection, effectiveness of two-dose regimen at 66-95% for mumps, and accumulation of susceptible hosts forgather resulting in increased risk of exposure and intense respiratory transmission of the virus. A difference in sero-response to measles component of MMR vaccine has been documented, and a second dose restored protective levels of antibody response. Host, agent and ethnic factors may account for such differences [3]. The seminal findings of the present report are:

1. Mumps attack rate is lower in recipients of three doses of MMR.
2. Third dose of MMR improved mumps outbreak control.
3. Risk of mumps is higher in vaccines who had received second dose 13 years or earlier.
4. Vaccine effectiveness of two doses *versus* no doses was lower among students who had received the second dose in the distant past, enlisting waning protection.

Government of India's decision to remove the mumps component from MMR in its Universal Immunization Program is not supported by Indian Academy of Pediatrics & Advisory Committee on Vaccination & Immunization Practices [4]. Any momentous decision should perhaps be effectuated after a careful analysis of disease burden and ancillary consequences. The touchstones that need to be examined are: (*i*) Is mumps a cause of significant burden?

(*ii*) Is immunization an optimal and desirable means of reducing disease burden? (*iii*) In the absence of immunization, can mumps be controlled? (*iv*) Are there any unique operational problems in mumps immunization? The answer to first two questions is "YES" and the other two, "NO."

Though usually mild in its presentation, many patients may present with serious complications like aseptic meningitis and encephalitis, resulting in disability or death. Permanent deafness, orchitis, and pancreatitis are other untoward effects of mumps, besides its purported role in Type1 diabetesmMellitus. Further, of the 12 genotypes of the virus, Genotype C and D circulating in Sweden are said to be more neuropathogenic than genotype A. An association with CNS disease was also found for the Odate-1 strain which is isolated in Japan and sub-clusters within the genotypes C and H. Prudence demands a review of the decision to withdraw mumps component from MMR for Indian children. Beneficent elements of this study can be purposefully adopted for instituting health management policy, after a scrutiny of the following findings of the NEJM report:

1. Protective immunity wanes with time and boosters are necessary to sustain durable protection.
2. In the absence of augmented immunization, vulnerability to infection sets in and virus targets such population with ease thereby initiating and propagating an outbreak.
3. MMR is useful in outbreak control.

Factoring the cost of a susceptible adult population that may have escaped infection during childhood to fresh mumps attack with its attendant complications in a growing economy needs consideration while designing a region-specific health management system.

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