Vaccine xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Review

Knowledge gaps persist and hinder progress in eliminating mumps

R. Ramanathan, E.A. Voigt, R.B. Kennedy, G.A. Poland *

Mayo Vaccine Research Group, Mayo Clinic, Rochester, MN 55905, USA

ARTICLE INFO

Article history:
Received 5 March 2018
Received in revised form 10 May 2018
Accepted 12 May 2018
Available online xxxx

Keywords:
Mumps
Mumps vaccine
Mumps virus
Measles-mumps-rubella vaccine
Polymorphism, genetic
Cytokines
Receptors, cytokine
Antibodies
Immunity, humoral

ABSTRACT

Mumps, a common childhood disease in the pre-vaccine era that causes swelling of the parotid salivary glands, can lead to orchitis, viral meningitis, and sensorineural deafness. While the incidence of disease decreased dramatically after the vaccine was added to standard vaccination schedules, the disease has made a substantial resurgence in recent years. As a result, it becomes critical to examine the factors involved in recurring outbreaks. Although low and incomplete vaccination coverage may be a key reason, it does not fully explain the issue due to the high rate of occurrence in populations with high vaccination coverage rates. Multiple studies suggest that waning immunity and secondary vaccine failure play a large role, the effects of which were previously masked by subclinical boosting. Significant knowledge gaps persist around the exact role and mechanism of waning immunity and demonstrate the need for more research in this area, as well as a reevaluation of mumps vaccine policy.

Contents

1. Introduction

Mumps causes fever, muscle pain, and swelling of the parotid salivary glands. Severe complications can arise from mumps infection, leading to sensorineural deafness, viral meningitis in children, and orchitis and oophoritis, with orichitis occurring in up to 30% of cases [1]. Though a closely related virus has been isolated in bats [2], humans are the only reservoir of mumps. Mumps spreads through respiratory droplets and contact. Initial vaccines contained inactivated virus and, while effective, did not induce long-lasting protection [3]. Cases of mumps in the United States dropped sharply after the introduction of the attenuated mumps vaccine in 1967 [4]. The monovalent vaccine was combined with the measles and rubella vaccines, creating the MMR-I vaccine. In 1971, a new version of the vaccine, MMR-II, was approved by the FDA for use [5]. Although only one dose was initially required, recurrent

* Corresponding author at: Mayo Vaccine Research Group, Mayo Clinic, Guggenheim 611C, 200 First Street SW, Rochester, MN 55905, USA.
E-mail address: poland.gregory@mayo.edu (G.A. Poland).

https://doi.org/10.1016/j.vaccine.2018.05.067
0264-410X/

outbreaks of measles led to the establishment of a second dose of MMR-II vaccine for all children in 1989, resulting in a drop of mumps cases [6]. Mumps (R_0 = 4–7) is not as highly contagious as measles (R_0 = 12–18), and most of the current outbreaks occur in settings such as schools and military dormitories, indicating that close contact is required for outbreaks to occur in highly vaccinated populations. Epidemiological calculations suggest immunization coverages of 79–100% may be necessary to achieve herd immunity [5,7]; however, outbreaks continue to occur in countries like the US, where vaccine coverage has remained >90%, suggesting that our understanding of the factors influencing mumps transmission is incomplete.

Despite the availability of a vaccine and recommendations for its use, outbreaks of mumps continue to occur in industrialized countries with high vaccine coverage rates and excellent healthcare systems [1–4]. Since the early 2000s, a surge of mumps cases in vaccinated populations has occurred worldwide; outbreaks have been documented across the United States, the Netherlands, the United Kingdom, Sweden, Belgium, and elsewhere [8–11]. In the United States, a large outbreak occurred in 2006 and then subsided. In 2012 and 2014, further mumps outbreaks occurred, with the Centers for Disease Control and Prevention (CDC) reporting 229 and 1151 cases, respectively. The number of cases has subsequently ballooned over the last two years: 5833 and 5629 mumps cases were reported in 2016 and 2017, respectively, in the United States (as of December 31, 2017). These are reported cases; the actual number of cases is unknown due to under-reporting and asymptomatic infections. These outbreaks largely affected professional sports teams, students on college campuses, religious communities, military populations, and adolescent/young adult populations with typically high vaccine coverage [12]. Given the trend depicted in Fig. 1, it is likely the United States will continue to experience large-scale outbreaks.

While measles and rubella have been the subject of considerable research efforts, mumps has not been studied as thoroughly—likely because of historically small numbers of cases in the vaccination era and the perceived lack of significant morbidity and mortality compared to that of measles and rubella. However, given the dramatic increases in mumps cases worldwide with associated morbidity even in highly vaccinated populations, this perspective is now changing. The scientific community increasingly recognizes the existence of substantial knowledge gaps in the generation and long-term maintenance of immune responses to mumps vaccine. These knowledge gaps hinder the ability of public health systems to protect populations against mumps outbreaks. The increasing appearance of mumps outbreaks necessitates a reprioritization of mumps vaccine research to help explain why mumps outbreaks continue to occur in healthy, highly vaccinated populations. Research to date suggests that this trend is likely due to a combination of low/incomplete vaccine coverage, primary vaccine failure, and secondary vaccine failure—the effects of which were likely suppressed due to subclinical boosting when mumps virus widely circulated. Below we explore the effect of each of these factors.

2. Potential factors contributing to mumps outbreaks

2.1. Low/incomplete vaccine coverage

Many factors have been suggested as possible causes of mumps outbreaks, with low vaccine coverage emerging as an obvious concern. Many mumps outbreaks have occurred in populations with either low or incomplete vaccine coverage. During a 2004 outbreak in the United Kingdom, almost 70% of the mumps cases occurred in those who had not received the vaccination at all [13]. This trend was also observed in outbreaks in Sweden and Canada [10,14].

Vaccine hesitancy and resistance has grown in recent decades, in part due to misinformation spread by the anti-vaccine movement [15], contributing to a decrease in vaccine confidence and coverage in many communities. The impact of vaccine hesitancy can be seen most clearly in Japan, where the vaccine was removed in 1993 from standard vaccination schedules due to concerns about adverse events after administration of the MMR vaccine. It is worth noting that Japan used the Urabe strain, which has been associated with aseptic meningitis. Since then, mumps cases in Japan have skyrocketed [16], and significantly higher numbers of mumps cases have continued compared to countries that have retained the MMR vaccine as a part of the immunization schedule. Japan serves as an important case study for the rest of the world, demonstrating the significant impact of low vaccine coverage on a population.

Low vaccine coverage is unlikely to be a major contributing factor to recent outbreaks of mumps disease in the United States. Vaccination rates for the MMR vaccine in the United States are generally above 90%, and yet outbreaks have occurred in highly

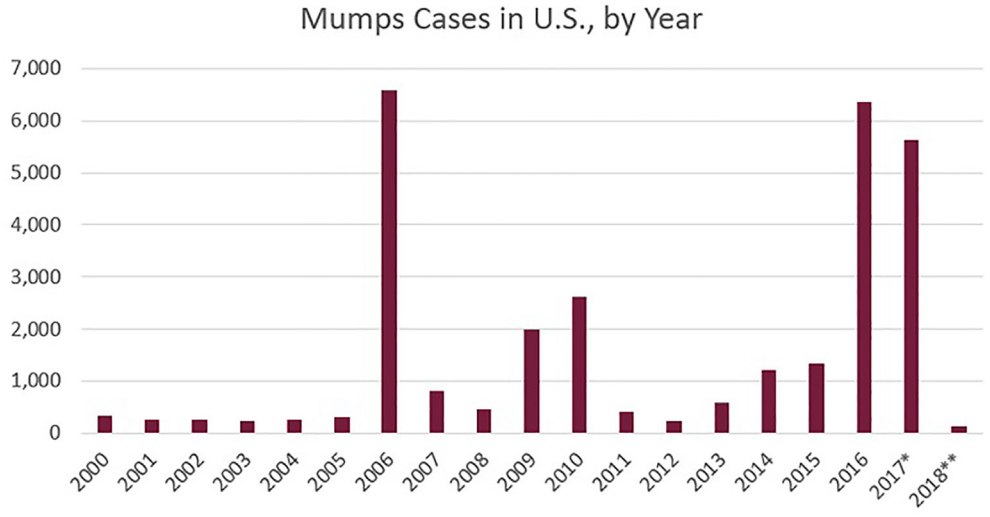

Fig. 1. Reported cases of mumps in the United States by year. This figure, from the Centers for Disease Control and Prevention, outlines the number of mumps cases by year. *Case count is preliminary. **Cases as of January 27, 2018.

Please cite this article in press as: Ramanathan R et al. Knowledge gaps persist and hinder progress in eliminating mumps. Vaccine (2018), https://doi.org/10.1016/j.vaccine.2018.05.067