

Mumps Outbreaks in Vaccinated Populations: Are Available Mumps Vaccines Effective Enough to Prevent Outbreaks?

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Increased reports of mumps in vaccinated populations prompted a review of the performance of mumps vaccines. The effectiveness of prior vaccination with 1 dose of vaccine ranged from 72.8% to 91% for the Jeryl Lynn strain, from 54.4% to 93% for the Urabe strain, and from 0% to 33% for the Rubini strain. Vaccine effectiveness after 2 doses of mumps vaccine was reported in 3 outbreaks and ranged from 91% to 94.6%. There was evidence of waning immunity, which is a likely factor in mumps outbreaks, aggravated by possible antigenic differences between the vaccine strain and outbreak strains. Inadequate vaccine coverage or use of the Rubini vaccine strain accounted for the majority of outbreaks reviewed; however, some outbreaks could not be prevented, despite high vaccination coverage with 2 doses of the Jeryl Lynn vaccine strain. Our findings indicate the need for more-effective mumps vaccines and/or for review of current vaccination policies to prevent future outbreaks.

Mumps is an acute communicable disease characterized by fever, headache, and lethargy, followed by painful swelling of the salivary glands, typically the parotid. In the prevaccine era, mumps was a leading cause of viral meningitis and the most common cause of unilateral acquired sensorineural deafness in children [1]. Use of mumps vaccine in routine pediatric immunization schedules has significantly reduced the incidence of mumps, although outbreaks can occur even among highly vaccinated populations. In the United States, the incidence of mumps decreased from >100 cases per 100,000 population in most years in the prevaccine era (before 1967) to 10 cases per 100,000 population in 1977 [2, 3]. After the 1989 institution of a 2-dose measles, mumps, and rubella vaccine schedule, the number of reported mumps cases further decreased to 1 case per 100,000 population in 1992 and to 0.1 case per 100,000 population in 2001 [4] (figure 1). On the basis of the success of the mumps vaccination program, a national health objective

to eliminate indigenous transmission of the virus by 2010 was instituted [5]. Although similar success in the control of mumps has been achieved in other countries through high vaccine coverage [6, 7], the recent resurgence of mumps in the United States, where outbreaks have occurred in the context of high 2-dose vaccination coverage [8–10], raised the question of whether available mumps vaccines are sufficiently effective to prevent outbreaks and achieve disease elimination. In this review, we summarize the data to date on outbreaks of mumps in vaccinated populations to evaluate the effectiveness of 1 and 2 doses of different mumps vaccine strains and aim to provide a balanced assessment of factors potentially impacting vaccine effectiveness.

METHODS

Published studies of mumps outbreaks among vaccinated populations were identified through a comprehensive search of the PubMed and EMBASE databases with use of the search term “mumps” in conjunction with “mumps vaccine” or “measles-mumps-rubella vaccine” and “epidemic” or “outbreak.” Only articles about outbreak investigations with information on the proportion of cases that occurred among vaccinated persons or on vaccine effectiveness were selected for the analysis.

The following information was abstracted from the selected articles: year, place, setting (e.g., school), number of cases, percentages of persons who received 1 and 2 doses of vaccine,

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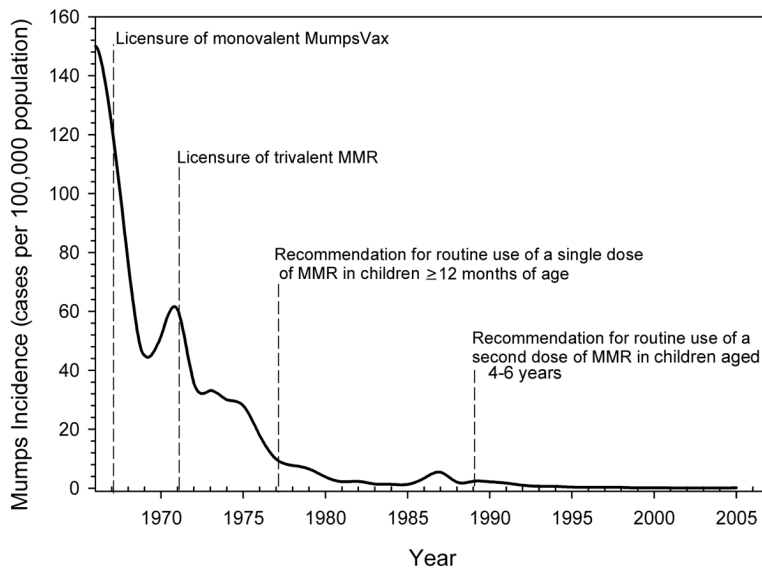


Figure 1. Mumps incidence in the United States over the past 40 years. Incidence rates adapted from the Centers for Disease Control and Prevention [3] and McNabb et al. [4]. MMR, measles-mumps-rubella vaccine.

vaccine effectiveness, type of vaccine used, genotype of circulating viruses, and vaccination coverage for the setting. When available, the percentage of vaccinated persons with documented number of doses was considered. In addition, information on time since vaccination was also collected to assess possible occurrence of waning immunity. Rates of primary vaccine failure were determined on the basis of published studies of mumps vaccine immunogenicity trials, which were identified in PubMed with use of the search terms “measles-mumps-rubella vaccine” or “mumps vaccine” in conjunction with “antibodies” or “immunogenicity.” The search was limited to studies involving at least 25 initially seronegative children who were tested for neutralizing antibody 4–8 weeks after vaccination.

Studies that examined antigenic differences between mumps virus strains were identified and reviewed through a comprehensive search in PubMed with use of the search term “mumps” in conjunction with “neutralization,” “variation,” “genotype,” or “antigenic.” Only studies reporting neutralizing antibody titers against different mumps virus strains in serum samples from vaccinated persons were included.

For all literature searches, no language, article type, or date restriction was imposed. A manual search was also performed for references cited in relevant articles.

RESULTS

The search produced 47 articles on mumps outbreaks among vaccinated populations. Three articles described 2 outbreaks; therefore, information on 50 outbreaks is presented. Of these, 13 outbreaks occurred among populations vaccinated only with the Jeryl Lynn strain (table 1); 14 outbreaks occurred among

populations vaccinated with multiple strains, including Jeryl Lynn, Urabe, Rubini, Toitsukabu, and Torii (table 2); and 21 outbreaks occurred among populations vaccinated with a vaccine strain that could not be identified (table 3). There were no evaluable reports of mumps outbreaks among recipients of other vaccines. The studies included outbreaks in the United States (11 outbreaks), Canada (5), Europe (29, occurring in the United Kingdom, Switzerland, Italy, Spain, Austria, Belgium, Sweden, Ireland, Czech Republic, and Moldova), and Asia (5, occurring in Singapore, Korea, and Japan). The outbreaks included in this review occurred during the past 31 years (1977–2008). Articles reporting 27 (54.0%) of the 50 outbreaks contained information on populations vaccinated with 2 doses; of these 27 outbreaks, 10 (37.0%) involved the Jeryl Lynn vaccine strain, 13 (48.1%) involved a vaccine strain that was not identified, and 4 (14.8%) involved multiple vaccine strains.

The percentage of total cases among individuals previously vaccinated with 1 dose of vaccine was highest (98.7%) in an outbreak in Kansas [15], where vaccination coverage in schools in the county where the outbreak occurred was 99.8%. In general, the proportion of cases among vaccinated patients tended to increase with higher vaccination coverage rates. In outbreaks involving patients vaccinated with different vaccine strains, the percentage of cases among vaccinated patients was highest among those vaccinated with the Rubini strain and lowest among those vaccinated with Urabe strain (table 2). The percentage of cases among individuals vaccinated with 2 doses was generally lower; however, in 1 investigation of this outbreak at a large university in Kansas, the percentage of cases among patients vaccinated with 2 doses was 99.3% (when counting

Table 1. Characteristics of the outbreaks involving patients vaccinated with Jeryl Lynn strain vaccine.

Study (outbreak year)	Setting	No. of cases assessed	Proportion of patients who had received		Vaccine effectiveness, %		Vaccination coverage, ^a %	Virus genotype isolated	
			No. of cases	Proportion of patients who had received	2 doses	1 dose			2 doses
Lewis et al. [11] (1977)	Ontario, Canada (school)	84	84	NA	9.5	NA	NR	20.5	NR
Sullivan et al. [12] (1981)	Ohio (middle school)	62	57	NA	54.4	NA	72.8 ^b	81.7	NR
Chaiken et al. [13] (1983)	New Jersey (school)	63	24	NA	20.8	NA	91	68	NR
Wharton et al. [14] (1986)	Tennessee (high school)	332	194	NA	17	NA	78	48 ^c	NR
Hersh et al. [15] (1988–1989)	Kansas (school, community)	269	79	1.3	98.7	NR ^d	83	99.8	NR
Cheek et al. [16] (1990)	Texas (high school)	54	54	1.9	96.3	NR	82	99.7	NR
Briss et al. [17] (1991)	Tennessee (high school)	68	68	5.9	92.6	NR	NR	97.6	NR
Whitman et al. [18] (1997–1998)	New York City (community)	119	111	62.2	29.7	NR ^e	81	≥1 dose: 98; 2 doses: 62	NR
Schaffzin et al. [19] (2005)	New York (summer camp)	31	29	55.2	13.8	91.6	79.7	2 doses: 86.8; ≥1 dose: 95.9	None
Boxall et al. [51] (2005–2006)	Czech Republic (community)	5998	5933	70.6	1.1	NR	NR	99.6 in a highly affected cohort ^f	NR
Schmid et al. [20] (2006)	Austria (community)	214	169	10.7	40.2	NR	NR	NR	NR
CDC [21] (2006)	Iowa (community)	1798	1252	70.6	19.6	NR	NR	NR	G
Cortese et al. [10] and Bitisko et al. [22] (2006)	Kansas (university)	174	140	99.3 ^g	0.7	NR	NR	2 doses: ≥95	G
Dayan et al. [9] (2006)	United States (community)	6584	3115 ^h	62.5 ^g	24.8	NR	NR	2 doses: 87 ⁱ	G

NOTE. CDC, Centers for Disease Control and Prevention; NA, not applicable; NR, not reported.

^a Vaccination coverage with 1 dose, unless otherwise specified.

^b Vaccine effectiveness was 81.2% when persons with a history of mumps were excluded from the analysis.

^c Among control subjects with provider or written parental record.

^d Recipients of 2 doses of vaccine were at lower risk than were recipients of 1 dose.

^e One-third greater effectiveness with 2 doses, compared with 1 dose.

^f Vaccine coverage by no. of doses not available.

^g Data are for persons who received ≥2 doses.

^h Only cases in patients from Iowa, Illinois, Kansas, Minnesota, Missouri, Nebraska, South Dakota, and Wisconsin.

ⁱ Does not include vaccination coverage among all cohorts of the outbreak.

Table 2. Characteristics of the outbreaks involving patients vaccinated with multiple-strain vaccines or with strains other than the Jeryl Lynn strain.

Study (outbreak year)	Setting	No. of cases assessed	Proportion of patients who had received		Vaccine effectiveness, % (strain)		Virus genotype isolated	
			No. of cases assessed	of vaccine (strain)	1 dose			
					2 doses	1 dose		2 doses
Paccaud et al. [23] (1991)	Switzerland (kindergarten)	9	NA	77.7 (R), 11.1 (U)	NA	22 (R), 93 (U)	96.2 ^b	NR
Paccaud et al. [23] (1992–1993)	Switzerland (community)	112	NA	44.6 (R), 0.9 (other)	NA	33 (R), NR (other)	61.2	NR
Germann et al. [24] (1992–1993)	Switzerland (community)	102	NA	77.5 (R), 6.9 (JL)	NA	NR	61	NR
Oda et al. [25] (1994–1995)	Japan (school, community)	236	NA	6.5 (T/T)	NA	NR	21.6	NR
Mussini et al. [26] (1995)	Italy (community)	152	NA	78.9 (R), 3.3 (U), 3.9 (other)	NA	NR	79 ^b	NR
Limón et al. [27] (1997)	Spain (community)	256	NA	31.1 (R), 7.4 (JL), 34.8 (other)	NA	59 ^c	87 ^c	NR
Goh et al. [28] (1998)	Singapore (community)	592	NA	24.3 (R), 7.1 (JL), 1.5 (U), 10.6 (other)	NA	0 (R) ^d	91.4 ^d	NR
Pons et al. [29] (1998–1999)								
Study 1	Spain (community)	106	NA	83.8 (R), 11.4 (U, JL)	NA	<0 (R), 85 (U, JL)	95.9	NR
Study 2	Spain (community)	43	NA	94.7 (R)	NA	40 (R)	96.8	NR
Ong et al. [30] (1999)	Singapore (school)	235	NA	63.8 (R), 3.4 (JL), 2.1 (U), 15.7 (other)	NA	-55.3 (R), 80.7 (JL), 54.4 (U)	87.1	NR
Montes et al. [31] (2000)	Spain (school)	35	5.7 ^e	77.1 (R), 8.6 (JL), 8.6 (other)	NR	NR	≥1 dose: 100; 2 doses: 16.4	H
Barroso et al. [32] (2005)	Spain (community)	145	10.1 (R), 8.3 (JL), 30.3 (R, JL)	10.1 (R), 11.0 (JL)	NR	NR	2 doses: 48.9 ^f	G1
Gerstel et al. [33] (2006)	Spain (community)	19	50 (R), ^g 33.3 (other)	0	NR	NR	NR	NR
Ortuondo et al. [34] (2006)	Spain (school, community)	63	1.9 (R), 5.8 (JL)	38.5 (R), ^h 53.8 (JL) ^h	NR	NR	NR	G1
Schlegel et al. [35] (NR)	Switzerland (community)	66	NA	80.3 (R), 7.6 (JL), 4.5 (U)	NA	-4 (R), 78 (JL), 87 (U)	95	NR

NOTE. JL, Jeryl Lynn vaccine; NA, not applicable; NR, not reported; R, Rubini vaccine; T/T, Toitsukabu or Torii strain; U, Urabe vaccine.

- ^a Vaccination coverage with 1 dose, unless otherwise specified.
- ^b For R, vaccination coverage was 36% in the 1991 study by Paccaud et al. [23] and 77% in the study by Mussini et al. [26].
- ^c For an estimated 87% vaccination coverage.
- ^d Calculated among 2304 children attending 5 childcare centers.
- ^e The percentage of cases in vaccinated patients, by strain, was not available.
- ^f Does not include vaccination coverage among all cohorts of the outbreak.
- ^g R was administered as the second dose
- ^h First dose of the 2-dose schedule.

Table 3. Characteristics of the outbreaks involving patients vaccinated with an unidentified vaccine strain.

Outbreak year	Setting	No. of cases assessed	No. of patients who had received 2 doses of vaccine	Proportion of patients who had received 1 dose of vaccine	Vaccine effectiveness, %		Vaccination coverage, ^a %	Virus genotype isolated	
					2 doses	1 dose			
Arnedo et al. [36] (1987)	Spain (school, community)	104	95	NA	4.2	NA	89.6	0.0–77.9 among different age groups	NR
Guimbao et al. [37] (1989–1990)	Spain (community)	52	28	NA	32.1	NA	74.7	NR	NR
Brianti et al. [38] (1994–1995)	Italy (community)	466	466	NA	51.7	NA	41.1	64.5	NR
Vandermeulen et al. [39] (1995–1996)	Belgium (school)	105	105	NA	81	NA	61	91.8	NR
Visser et al. [40] (1996)	Spain (school, community)	897	897	NA	13	NA	97.7 and 69.4 ^b	98.7 and 80.0 ^{b,c}	NR
Lopez et al. [41] (1997)	Spain (school, community)	283	81	NR	90.1	NR	49	94.7	NR
Van Den Bosch et al. [42] (1998–1999)	England (community)	144	137	2.2	46.7	NR	NR	1–2 doses: 67–86	C
Savard et al. [43] (1998–1999)	Canada (school, community)	37	37	NR	59 ^d	NR	NR	NR	NR
Lee et al. [44] (1999)	Korea (school)	736	344	39.5	53.2	NR	NR	NR	H
Reaney et al. [45] (1999–2000)	Northern Ireland (community)	729	316	0.9	58.2	NR	NR	>94 ^c	NR
Pugh et al. [46] (2000)	England (community)	200	200	18.5	49.5	NR	NR	87.1 ^c	NR
Sartorius et al. [6] (2004)	Sweden (community)	42	23	NR	NR	91	65	>90 ^c	NR
Mackenzie et al. [47] (2004)	Scotland (school)	50	20	10	45	NR	NR	NR	G2
Cohen et al. [48] (2004–2005)	England (community)	312	312	31.1	16.7	94.6	87.8	1 dose: ≥59.4; 2 doses: ≥55.8	NR
CDC [49] (2004)	England and Wales (community)	16367	NR	3.3	30.1	NR	NR	1 dose: 82, ^c 2 doses: 75 ^c	NR
Watson-Creed et al. [50] (2005)									
Study 1	Canada (school)	13	13	69.2	30.8	NR	NR	NR	G
Study 2	Canada (university)	19	19	5.3	94.7	NR	NR	NR	G
Park et al. [52] (2006)	Korea (school)	15	15	20	73.3	NR	NR	≥1 dose: 95.1; 2 doses: 12.2	I
Castilla et al. [53] (2006–2007)	Spain (community)	>1300	143	78.3	NR	NR	NR	2 doses: >90 ^c	NR
NACI [54] (2007)	Canada (community)	555	284	9	75	NR	NR	NR	G
Bernard et al. [55] (2007–2008)	Moldova (community)	13853	9223	3.8	92.2	NR	NR	≥94 in highly affected cohorts ^c	G5

NOTE: CDC, Centers for Disease Control and Prevention; NA, not applicable; NACI, National Advisory Committee on Immunization; NR, not reported.

^a Vaccination coverage with 1 dose, unless otherwise specified.

^b Among persons aged 1–5 years and 5–10 years, respectively.

^c Does not include vaccination coverage among all cohorts of the outbreak.

^d Patients who had been vaccinated or were indicated as having been vaccinated.

only patients with complete records) or 96.4% (when counting patients with incomplete or missing immunization records as unvaccinated) [10].

Vaccine effectiveness was reported in 23 (46.0%) of the reviewed outbreaks. Vaccine effectiveness after 1 dose ranged from 72.8% to 91% for the Jeryl Lynn strain vaccine, from 54.4% to 93% for the Urabe strain vaccine, and from negative values to 33% for the Rubini strain vaccine (tables 1 and 2). Among the outbreaks in which the strain of the vaccine could not be identified, vaccine effectiveness of a single dose ranged from 41.1% to 97.7% (table 3). The effectiveness of 2 doses of vaccine was reported in 3 articles, and overall, the effectiveness of 2 doses was higher than that of 1 dose (91.6% vs. 79.7% [19], 94.6% vs. 87.8% [48], and 91% vs. 65% [6]), although no statistically significant differences were determined.

Although some studies did not find an association between time since vaccination and increased risk of disease [11, 12, 14, 16], other studies conducted in the United States [15, 17, 19] found persons vaccinated >5 years before the outbreak to be at higher risk of developing disease than persons vaccinated ≤5 years before the outbreak, suggestive of waning immunity. In a recent study conducted at a university in Kansas during an outbreak in 2006, case patients were more likely than their roommates without mumps to have been last vaccinated with the second dose ≥10 years earlier [10]. In addition, studies conducted in the United Kingdom and Europe revealed lower vaccine effectiveness in older cohorts and an increased risk of developing mumps with increased time after vaccination [39, 40, 48].

The genotype of the mumps viruses associated with the reviewed outbreaks was reported in 14 (28.0%) of the outbreaks. Genotype G was isolated in outbreaks in the United States [9, 22, 56], the United Kingdom [47], Canada [50, 54], Spain [34], and Moldova [55]. Genotype C was isolated in 1 outbreak in the United Kingdom [42]. Genotype H was isolated in Korea [44] and Spain [31], and genotype I was isolated in Korea [52].

The extent to which primary vaccine failure (i.e., no seroconversion after vaccination) may contribute to mumps outbreaks was assessed through a review of 30 different studies of neutralizing antibody responses in initially seronegative children after vaccination with the Jeryl Lynn, RIT-4385, Urabe, or L-Zagreb mumps virus strains. Data were not available to adequately assess virus neutralizing antibody activity after vaccination with the Rubini strain or other vaccine strains. Mean rates of primary vaccine failure did not significantly differ for the Jeryl Lynn, RIT-4385, Urabe, and L-Zagreb vaccine strains, ranging from 5.4% to 8.8% (table 4). Although neutralizing antibody responses after vaccination with the Rubini strain have not been adequately reported, ELISA-based data suggest much higher rates of primary vaccine failure. In studies reported by Schwarzer et al. [72, 73], 103 (62.0%) of 166 individuals did

Table 4. Rates of primary mumps vaccine failure after a single dose of vaccine.

Vaccine	No. of studies	Reference(s)	Mean PVF rate, % (95% CI)	Overall PVF rate, % (95% CI)
L-Zagreb	1	[57]	8.8	5.2 (3.6–6.8)
Urabe-AM9	6	[58–62]	7.9 (3.0–12.7)	...
Jeryl Lynn	22	[59–61, 63–70]	5.4 (2.4–8.4)	...
RIT-4385	1	[71]	6.0	...

NOTE. The above data were derived from studies involving at least 25 initially seronegative children who were tested for neutralizing antibody 4–8 weeks after vaccination. All such studies were identified using the following search terms in PubMed: “measles-mumps-rubella vaccine” or “mumps vaccine” and “antibodies.” PVF, primary vaccine failure.

not experience seroconversion after Rubini vaccination; this result was similar to that obtained from a prospective sampling of vaccinated persons in 2 small towns in Cadiz, Spain, where 29 (59.2%) of 49 Rubini vaccine strain recipients were mumps virus antibody seronegative when assessed by ELISA 18–34 months after vaccination [74].

A total of 8 publications were identified that reported neutralization of heterologous wild-type mumps viruses in recipients of different vaccines (Jeryl Lynn, Urabe, Hoshino, and Leningrad-3) [75–82]. In all of these studies, neutralization titers against the wild-type viruses were lower than those to the homologous vaccine virus. In a few instances, serum samples were capable of neutralizing the homologous vaccine virus but not the heterologous wild-type viruses, although this mostly occurred in serum samples from persons with low response to the vaccine.

DISCUSSION

In the outbreaks examined, the effectiveness of 1 dose of the Jeryl Lynn vaccine strain was similar to that of the Urabe vaccine strain and was lowest for the Rubini vaccine strain. These values were similar to those reported in other studies not included in our review (because they were not outbreak investigations), with a vaccine effectiveness ranging from 61.6% to 70% for the Jeryl Lynn strain, from 73.1% to 75.8% for the Urabe strain, and from 0% to 12.4% for the Rubini strain [83–85]. Reviewed articles indicated that the effectiveness of 2 doses of mumps vaccine is higher than that of 1 dose; these results are similar to those from a case-control study conducted in England that revealed vaccine effectiveness of 69% for 1 dose and 88% for 2 doses [86].

Although vaccine effectiveness during outbreaks was lower than that reported during controlled clinical trials, there is no doubt that mumps vaccines confer protection. Compared with attack rates of 31.8%–42.9% among unvaccinated individuals, attack rates among recipients of 1 dose and 2 doses of the Jeryl

Lynn vaccine strain were 4%–13.6% and 2.2%–3.6%, respectively [10, 12, 13, 15, 19].

Other than outbreaks linked to use of the poorly protective Rubini vaccine [23, 26, 27, 30, 85], the major factor in most of the outbreaks reviewed here appeared to be incomplete vaccine coverage. For example, nearly 70% of the 16,367 notified mumps cases in the United Kingdom in 2004 occurred in unvaccinated individuals [49] who had not been targeted by the vaccination program and remained susceptible because of low circulation of mumps caused by high levels of vaccination in younger cohorts. Similarly, a 2004 outbreak in Sweden—a country maintaining a 2-dose vaccine coverage rate of >90% for the past 20 years—occurred almost exclusively among unvaccinated individuals not targeted by the vaccination program [6]. Outbreaks in Canada in 2007 were mostly linked to use of only 1 of the 2 recommended doses of vaccine [87]; however, mumps outbreaks have also occurred among populations with high 2-dose coverage. For example, in 2006, a series of mumps outbreaks occurred in the United States, despite 2-dose vaccination coverage >95%, and in some investigations, >99% of patients had been vaccinated with 2 doses of vaccine [10]. Interestingly, the vaccine strain involved in those outbreaks, Jeryl Lynn, had been responsible for the near elimination of mumps in the United States until that time.

Although the causes of Rubini vaccine failures have not been firmly established, serological studies strongly suggest inadequate seroresponses to vaccination [72–74]. In contrast, robust antibody responses after vaccination with Jeryl Lynn and other vaccine strains have been measured, and primary vaccine failure is relatively uncommon. Furthermore, nearly all of the individuals who failed to produce measurable neutralizing antibody after the first dose of vaccine will experience seroconversion after a second dose [88, 89]; thus, primary vaccine failure in recipients of 2 doses of vaccine appears to be an unlikely cause of mumps outbreaks among vaccinees.

Although the high potential for transmission in densely packed environments (e.g., university campuses) was certainly a factor in recent large-scale outbreaks, our review suggests additional factors, including waning immunity in older vaccinated persons and antigenic variation among mumps viruses. Although a few studies included in our review did not find an association between time after vaccination and increased risk of disease, others revealed age-specific decreases in vaccine effectiveness (for both 1 and 2 doses) [48], increased risk of development of mumps with time after vaccination [10, 39], and higher attack rates with time since vaccination [15, 17, 19]. Furthermore, there are numerous studies documenting decreases in antimumps virus antibody levels with time since vaccination [78, 89–92] and, in some cases, complete loss of seropositivity, even in recipients of 2 doses of vaccine [89, 90, 93]. In 1 study, 28.9% of persons who received 1 dose of vaccine

and 8.4% of persons who received 2 doses of vaccine were seronegative 18–20 and 6–9 years after vaccination, respectively [94]. During the mumps resurgence in the United States in 2006, most cases occurred in cohorts in which the most recent vaccination (second dose) was likely to have been administered ≥ 10 years earlier [9]. Of note, attack rates are not expected to continue to increase in older cohorts, because older individuals are likely to have been repeatedly exposed to wild-type mumps viruses earlier in life, before the dramatic decreases in virus transmission that resulted from implementation of national childhood immunization programs. It is important to mention that a decrease in antibody titer or even an inability to detect antibody does not necessarily imply a loss of immunity. Functional antibody may exist at levels below assay detection limits, and cell-mediated immune responses, which may be protective, have been measured up to 21 years after vaccination, even in seronegative vaccinated persons [63, 95, 96].

Perhaps aggravating the effect of decreasing levels of antibody over time on mumps susceptibility is antigenic variation among mumps viruses. This was most clearly demonstrated in antibody cross-neutralization studies, in which antibody titers to heterologous mumps viruses were often considerably lower than corresponding titers to the homologous virus [75, 76, 78, 79, 81, 82, 97]. Of note, viruses isolated from recent mumps outbreaks differed phylogenically and, possibly, antigenically from the vaccine viruses used. For example, the Jeryl Lynn, RIT-4384, and Rubini vaccine strains are genotype A viruses, whereas wild-type viruses associated with outbreaks occurring in countries using these vaccines belong to genotype groups B, C, D, G, H, and I [31, 32, 52, 56, 98–101]. Likewise, the Urabe, Hoshino, and Torii vaccine strains are genotype B viruses, and viruses isolated during outbreaks in countries using these vaccines have been identified mostly as genotypes C, D, G, J, K, and L (although genotype B viruses have also been isolated) [80, 99, 101, 102]. In individuals responding to vaccination with only nominal levels of neutralizing antibody or in individuals for whom immune responses have waned with time after vaccination, this mismatch between the vaccine genotype and that of circulating mumps virus strains may facilitate immune escape. Of note, these genotype designations are based on sequence variation within the small-hydrophobic gene [103]. Although the small-hydrophobic gene does not play a role in protective immunity, sequence variation in the small-hydrophobic gene is reflective of the virus's overall genetic and antigenic variability, including the hemagglutinin-neuraminidase gene [75, 79, 102], which encodes the major cell-surface target of neutralizing antibody [104–106]. Despite clear evidence of decreasing vaccine antibody levels over time and of reduced vaccine antibody potency to heterologous virus strains, in the absence of a known protective level of neutralizing an-

tibody, whether such quantitative differences are clinically meaningful cannot be asserted.

Our review has several limitations. The data from the articles reviewed was collected and analyzed using different methodologies; therefore, the comparisons made between studies presented here should be interpreted with caution. In many articles, the type of vaccine used before the outbreak was not reported; therefore, conclusions regarding the vaccine strain could not be made. Vaccination coverage was not always available for all of the cohorts involved in the outbreak; therefore, the relationship between vaccination coverage and protection could not be assessed in all cases. When available, we considered the percentage of vaccinated persons with documented numbers of doses. Had we assumed that individuals with undocumented vaccination were unvaccinated, the percentage of vaccinated persons might have been lower.

The cause of mumps outbreaks among vaccinated populations remains unclear, but several potential contributing factors may be involved, as documented in this review. **That outbreaks have recently occurred in populations with >95% 2-dose vaccine coverage strongly suggests that long-term prevention of mumps outbreaks with use of current vaccines and vaccination schedules may not be feasible.** Mathematical modeling including populations highly vaccinated with 2 doses would be important in assessing different vaccination schedules. Additional research is needed to develop more immunogenic and effective mumps vaccines and/or to review current vaccination policies.

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