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Mumps vaccine effectiveness and risk factors for disease in households during an outbreak in New York City

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ABSTRACT

Background and objectives: Mumps outbreaks have been reported among vaccinated populations, and declining mumps vaccine effectiveness (VE) has been suggested as one possible cause. During a large mumps outbreak in New York City, we assessed: (1) VE of measles-mumps-rubella vaccine (MMR) against mumps and (2) risk factors for acquiring mumps in households.
Methods: Cases of mumps were investigated using standard methods. Additional information on disease and vaccination status of household contacts was collected. Case households completed follow-up phone interviews 78–198 days after initial investigation to ascertain additional cases. Mumps cases meeting the study case definition were included in the analysis. Risk factors for mumps were assessed, and VE was calculated using secondary household attack rates.
Results: Three hundred and eleven households with 2176 residents were included in the analysis. The median age of residents was 13 years (range <1–85), and 462 (21.2%) residents met the study mumps case definition. Among 7–17 year olds, 89.7% received one or more doses of MMR vaccine, with 76.7% receiving two doses. Young adults aged 10–14 years (OR = 2.4, CI = 1.3–4.7) and 15–19 years (OR = 2.5, CI = 1.3–5.0) were at highest risk of mumps. The overall 2-dose VE for secondary contacts aged five and older was 86.3% (CI 63.3–94.9).
Conclusions: The two-dose effectiveness of MMR vaccine against mumps was 86.3%, consistent with other published mumps VE estimates. Many factors likely contributed to this outbreak. Suboptimal MMR coverage in the affected population combined with VE may not have conferred adequate immunity to prevent transmission and may have contributed to this outbreak. Achieving high MMR coverage remains the best available strategy for prevention of mumps outbreaks.

1. Introduction

Mumps is a viral infection that commonly presents with fever and parotid gland swelling. An estimated 20–30% of infections may be asymptomatic [1,2]. Complications may include orchitis, aseptic meningitis and, rarely, deafness or encephalitis [3].

Mumps vaccine was first licensed in 1967 and recommended for routine use in children in 1977 [4]; by 1998, the number of reported cases in the United States had declined by over 99% [5,6]. In the United States, mumps vaccine is manufactured using the Jeryl-Lynn strain and administered via subcutaneous injection as a combination measles-mumps-rubella vaccine (MMR) [7]. A first dose is recommended for children at 12–15 months of age, followed by a second dose at 4–6 years of age.

In spite of the dramatic post-vaccine era declines in mumps cases, occasional outbreaks have been reported among vaccinated populations [6,8–10]. A number of hypotheses have been raised to explain these outbreaks including waning immunity, crowding, differences between the mumps vaccine strain and circulating wild strains, diminished mumps vaccine effectiveness (VE), and population immunity below the herd immunity threshold [11–13].

During 2009–2010, a large, multi-state outbreak of mumps occurred among Orthodox Jewish communities in the Northeastern United States. New York City (NYC) has the largest Orthodox Jewish community in the United States and identified the largest number of mumps cases during the outbreak [14,15]. The outbreak presented an opportunity to assess risk factors associated with clinical mumps infection and VE.

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2. Methods

The NYC Department of Health and Mental Hygiene (DOHMH) conducts mumps surveillance via standard methods [1]. Cases are classified according to the 2007 Council of State and Territorial Epidemiologists (CSTE) definition. The clinical case definition is acute onset of unilateral or bilateral swelling of the parotid or other salivary glands, lasting 2 or more days, and without other apparent cause [16]. Index cases in households were identified through mandated electronic reporting of positive test results by laboratories, or clinical reports of suspect disease by providers [17].

Between 2/5/2010 and 4/8/2010, 473 index households were contacted for follow-up. Data was collected using a standard script. An interviewer requested to speak with an adult, who provided information on each household member. A minimum of three call attempts, including at least one evening attempt, were made to each household. During calls, informants were asked: (1) whether each household contact slept in the home, on average, at least 5 nights per week; (2) total number of bedrooms in the household and; (3) for each household contact: birth date, vaccination status, and whether they had been sick with either cheek swelling that lasted for at least two days or a doctor diagnosed case of mumps since September 2009. We defined an affirmative answer as compatible with the CSTE clinical case definition. Informants reporting cases of mumps in their household were prompted to look at a calendar and report date of onset, if possible.

Households with index cases identified through surveillance from 9/1/2009 to 12/31/2009 were eligible for study inclusion. Case households were excluded if: (1) the index case lived alone; (2) the index case did not live in the household (e.g., lived in a dormitory); (3) the index case did not sleep in the home, on average, at least five nights per week; (4) there was not an English-speaking adult in the household; (5) an adult in the household was not able to be contacted; or (6) an adult in the household refused to provide information on household contacts or provided incomplete information.

For this study, a case of mumps was defined as one meeting the CSTE surveillance case definition or a compatible case identified via the phone interview [16]. An index case was defined as the first case in a household to be reported to DOHMH. Primary cases were those with the earliest onset of mumps in the household. We defined household members as being exposed two days before parotitis onset of the primary case, which is the first day that the primary case was infectious. We defined co-primary cases as those with onset within nine days after the primary case's symptom onset. Secondary cases were defined as those reporting onset of mumps 10–25 days after the primary case. Non-secondary cases were defined as those occurring more than one incubation period (>25 days) after the primary case.

Mumps vaccination status was based on documented, valid MMR doses. Acceptable documentation included MMR doses recorded in the NYC Citywide Immunization Registry (CIR) [18] or those obtained directly from an individual's medical provider. CIR, an immunization information system sentinel site for the CDC, maintains high quality completeness and timeliness for which 92% of immunizations are reported within one month and to which 89.5% of providers regularly report [19]. In 2009, CIR contained information on at least 85% of children, from birth to age 18, in NYC [20]. In order to be valid, doses had to be administered in accordance with the recommended vaccination schedule guidelines, meaning the first dose had to be administered no earlier than 4 days before the first birthday and subsequent doses at least 28 days after a previous MMR dose [7]. Individuals lacking MMR documentation from a medical provider and with a record in CIR with at least one reported vaccination, but no recorded MMR doses, were considered unvaccinated with MMR. Individuals with a valid provider recorder with no recorded MMR doses were also considered unvaccinated. Individuals lacking MMR documentation from a medical provider and with no recorded vaccinations in CIR were considered to have unknown MMR vaccination status.

Frequencies were calculated to characterize households and individuals living in households. Overall attack rate (AR) was defined as the number sick divided by the total number of individuals in households. Household-level ARs were defined as total number sick in a household divided by total number living in that household. Household density was defined as total number of people divided by total number of bedrooms in a household. VE and 95% confidence intervals (CI) were calculated using secondary household attack rates (SARs) following standard methods to examine the percent reduction in risk among vaccinated relative to unvaccinated individuals [21]. We similarly examined reduction in risk among those with unknown vaccination status relative to those unvaccinated.

Household members under 5 years of age ($n = 348$) were excluded from the VE calculation because many had not yet received two doses of MMR, and clinical mumps is less common among this age group [22]. The following were excluded from the VE calculation: household members with unknown age ($n = 101$); two households, totaling 6 cases and 15 non-cases, with insufficient information to identify the primary case; and cases for which the date of illness onset could not be exactly determined ($n = 25$). MMR doses administered within 25 days (one incubation period) prior to illness onset of the primary case were not counted, in order to exclude doses potentially administered post-exposure ($n = 3$). Non-secondary cases with onset after 25 days ($n = 40$) were classified as non-cases for the purpose of calculating SARs.

Generalized estimating equations (GEE) were used to examine risk factors for mumps among non-primary cases and non-sick household contacts. Risk factors examined were age group, number of MMR doses received, time from last MMR dose (years), and household density. GEE were used to account for potential correlation between household members [23]. Covariates significant at $p < 0.2$ in a univariate analysis were included in a multivariate model. Stepwise regression was used to create the most parsimonious multivariate model by eliminating covariates not significant at $p < 0.05$. Among the VE analysis cohort, GEE were similarly used to examine two-dose VE adjusted for age group, time from last MMR dose, and household density. All analyses were performed in SAS 9.2 (SAS Institute, Cary, NC).

Data was collected as a part of routine public health surveillance and outbreak response conducted by NYC DOHMH, and household informants were asked to verbally consent to answering additional questions during follow-up phone interviews.

3. Results

Five-hundred-fifty-one cases of mumps residing in 473 households were identified by DOHMH surveillance during the study period. Three-hundred-forty-six (73.2%) households completed follow-up interviews between 78 and 219 days after illness onset of the primary case in the household (Fig. 1). Three-hundred-eleven households (66%) containing 2176 individuals were successfully reached for follow-up and met inclusion criteria.

Households had a median of 7 (range 2–16) residents and 4 (range 1–8) bedrooms. Median household density was 2 people per bedroom (range 0.5–11.0). Median age of all household residents was 13 years [range 0–85, interquartile range = 15.0], with 33.8% aged 10–19 years and 16.7% under 5 years.

Among all 2176 household residents, 462 met our definition of mumps resulting in an overall attack rate (AR) of 21.2%. ARs ranged from 6.7%-100% per household. The mean number of cases

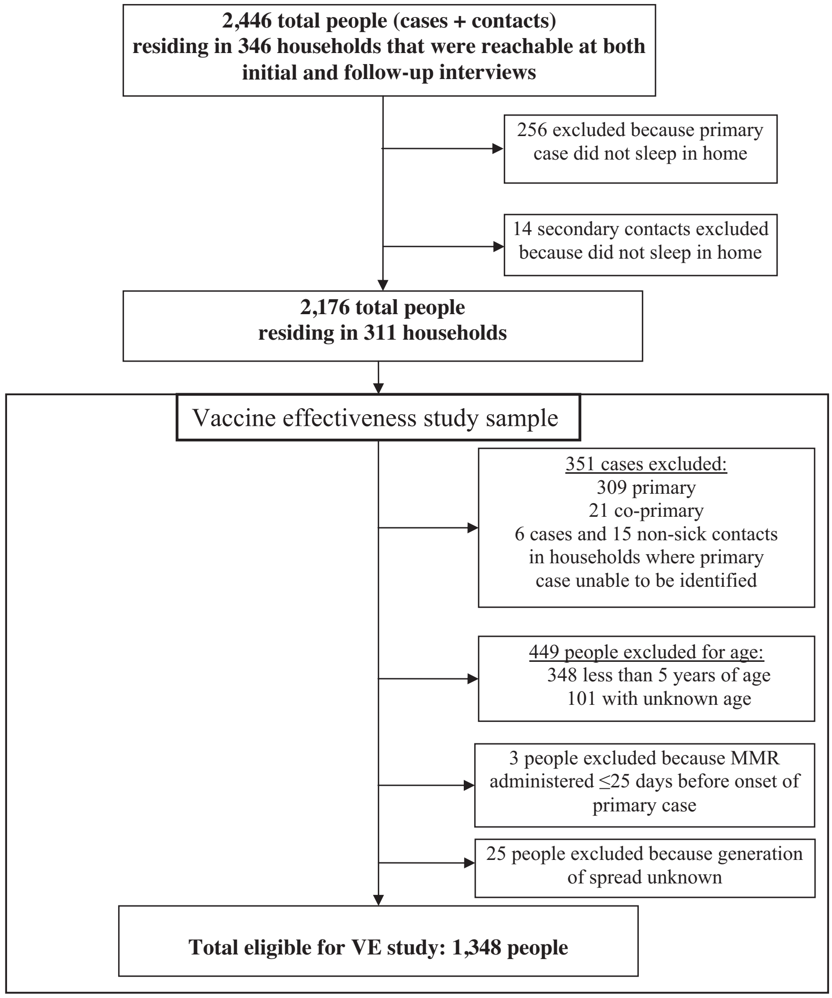

Fig. 1. Household residents included in overall study sample and vaccine effectiveness study sample.

per household was 1.5 (median = 1, range 1–7). Sixty-seven percent of all cases were primary, 4.5% were co-primary, 10% were secondary, 10% occurred later, and 8% had undetermined onset date. Median age was 15 years for primary cases, 14 years for co-primary cases, and 15 years for secondary cases. Over 95% of both primary and co-primary cases and 85.4% of secondary cases were reported via surveillance and confirmed by case investigation (Table 1). Among all non-index cases, 47% had been previously identified

Table 1
Characteristics of individuals living in study households ($n = 2176$).

	Total n (%)	Primary cases n (%)	Co-primary cases n (%)	Cases with undetermined onset date n (%)	Secondary cases n (%)	Later onset cases n (%)	Household contacts without illness n (%)
Total	2176 (100.0)	309 (14.2)	21 (1.0)	37 (1.7)	48 (2.2)	47 (2.1)	1714 (78.8)
Vaccination status[a]							
0 dose	134 (6.2)	12 (3.9)	3 (14.3)	2 (5.4)	5 (10.4)	4 (8.5)	108 (6.3)
1 dose	362 (16.6)	34 (11.0)	0 (0.0)	4 (10.8)	6 (12.5)	9 (19.2)	309 (18.0)
2 dose	921 (42.3)	164 (53.1)	10 (47.6)	11 (29.7)	19 (39.6)	23 (48.9)	694 (40.5)
Unknown	759 (34.9)	99 (32.0)	8 (38.1)	20 (54.1)	18 (37.5)	11 (23.4)	603 (35.2)
Age group (years)							
0–4	363 (16.7)	12 (3.9)	1 (4.8)	8 (21.6)	4 (8.3)	6 (12.8)	332 (19.4)
5–9	377 (17.3)	31 (10.0)	3 (14.3)	3 (8.1)	6 (12.5)	7 (14.9)	327 (19.1)
10–14	410 (18.8)	87 (28.2)	8 (38.1)	4 (10.8)	12 (25.0)	17 (36.2)	282 (16.5)
15–19	326 (15.0)	86 (27.8)	6 (28.6)	7 (18.9)	12 (25.0)	8 (17.0)	207 (12.1)
20+	599 (27.5)	93 (30.1)	3 (14.3)	15 (40.5)	14 (29.2)	8 (17.0)	466 (27.2)
Unknown	101 (4.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.1)	100 (5.8)
Median (range)	13 (0–85)	15 (0–84)	14 (3–53)	18 (0–47)	15 (0–45)	12 (0–46)	12 (0–85)
Mean ± std.dev[b]	17 ± 15	19 ± 12	15 ± 10	19 ± 13	19 ± 12	15 ± 12	17 ± 15
Method of report ($n = 462$ cases)							
Reported via surveillance	386 (83.5)	304 (98.4)	20 (95.2)	3 (8.1)	41 (85.4)	18 (38.3)	0 (0.0)
Self-reported at follow-up	76 (16.5)	5 (1.6)	1 (4.8)	34 (91.9)	7 (14.6)	29 (61.7)	0 (0.0)

[a] Only valid doses considered.
[b] Standard deviation.

Table 2
Household residents by vaccination status and age group ($n = 2075$).

Age group (years) n (%)							
Valid MMR doses	<1	1–3	4–6	7–12	13–17	18+	Total
0	64 (92.8)	38 (17.0)	6 (2.8)	10 (2.2)	8 (1.9)	6 (0.9)	132 (6.4)
1	1 (1.4)	174 (77.7)	54 (25.4)	59 (12.8)	54 (13.1)	19 (2.7)	361 (17.4)
2	0 (0.0)	2 (0.9)	145 (68.1)	365 (79.4)	305 (73.9)	97 (13.9)	914 (44.1)
Unknown	4 (5.8)	10 (4.5)	8 (3.8)	26 (5.6)	46 (11.1)	574 (82.5)	668 (32.2)

via DOHMH surveillance, while 53% were identified via follow-up interview. Thirty-nine (12.5%) households had a secondary case. Non-primary cases with known onset occurred between 10 and 145 days (median = 25 days) after the onset of symptoms of the primary case.

Among those in the study 7–17 years of age, 89.7% had received one or more doses of MMR vaccine with 76.7% receiving 2 doses. Immunization history was not available for 6.8% of household residents less than 18 years of age and 82.5% of those 18 years and older (Table 2).

Among 126 non-primary cases, age group was the only significant risk factor for mumps. Household residents 10–14 years (OR = 2.4, 95% CI = 1.3–4.7) and 15–19 years (OR = 2.5, 95% CI = 1.3–5.0) had the highest odds of mumps compared to the youngest age group. Number of MMR doses ($p = 0.856$) and household density ($p = 0.495$) were not significantly associated with mumps illness in univariate models. Time from last MMR dose was significantly associated with illness in a univariate model (estimate ± SE = 0.073 ± 0.021, $p = 0.0007$) but was no longer significant when included in a multivariate model with age ($p = 0.791$).

VE was assessed among 44 secondary cases and 1304 non-sick household contacts. One and two-dose VE was 82.9% (CI 37.1–95.4) and 86.3% (CI 63.3–94.9), respectively. Individuals with unknown vaccination status experienced an 83.7% (55.9–93.9) reduction in disease compared to unvaccinated individuals. GEE modeling failed to show an effect of age, time from vaccination, or household density on VE (Table 3).

4. Discussion

A large outbreak of mumps provided an opportunity to assess mumps VE and explore reasons for outbreaks among vaccinated populations. While a majority of cases were vaccinated, our estimate of two-dose VE of 86.3% supports the substantial benefit of mumps vaccination.

The 45-year history of mumps vaccine has provided multiple opportunities to assess VE over time. The vaccine efficacy of monovalent mumps vaccine, measured shortly after administration, was 95% in the initial clinical trial [24]. One-dose VE estimates obtained in the United States from 1973 to 1989 ranged from 75% to 91% [25]. Recent point estimates, obtained from 2005 to 2010, have ranged from 64% to 88% for one-dose VE and 83% to 92% for two-dose VE [10,13,26–29]. Our estimates of one (82.9%) and two-dose (86.3%) VE are within the confidence intervals of other published estimates obtained in both the United States and other countries [13,26–30]. Some published literature has suggested that vaccine-induced immunity may wane, for example due to less endemic disease boosting immunity among vaccinated populations [13,31]. However, our VE is in the range of published estimates, suggesting that waning immunity was not likely driving the outbreak.

Low MMR vaccination coverage alone could account for this mumps outbreak. In addition, differences in coverage between the affected community and the surrounding population might account for the limited transmission outside of the community, even in such a densely populated urban area [14]. Among those 13–17 years of age in our study, 73.9% received two doses of MMR vaccine. By comparison, results from the 2010 National Immunization Survey show that 94.5% (95% CI 90.6–96.8%) of adolescents 13–17 years of age in NYC received 2 or more doses of MMR [32]. New York State law mandates at least one dose of mumps-containing vaccine for school attendance [33]. Among NYC's approximately 1.1 million public school children, compliance with immunization requirements is high, with 98.8% being fully vaccinated by the end of the term in the last several years (DOHMH internal data). However, most children in the Orthodox Jewish community attend private religious schools where compliance with immunization requirements appears to be lower.

The estimated herd immunity threshold for mumps vaccination is 75–86% [34]. Mumps VE less than 90% combined with vaccination coverage at the herd immunity threshold, specifically two-dose coverage less than 80% among children and adolescents, could create a synergy in which herd immunity was not adequate to prevent transmission. Mathematical modeling has suggested that VE would need to be >80% to prevent the transmission of mumps in a highly vaccinated population [35]. While our estimates of VE are above this theoretical threshold, estimates are very close to the threshold, and our confidence intervals are broad suggesting that these two factors may have been sufficient to account for our outbreak.

Other factors have been proposed to explain the occurrence of mumps outbreaks. Serological and observational studies have suggested that mumps immunity may wane over time resulting in diminished vaccine effectiveness [12,13,31,36–38], but no association between time from vaccination and mumps was observed in our analysis. Diminished VE of MMR vaccine due to antigenic differences between the strains causing outbreaks and the vaccine strain has also been proposed as a reason for occurrence of outbreaks [38]. However, the mumps viruses associated with the outbreak were all genotype G. In a laboratory study, antibodies against the Jeryl Lynn mumps virus vaccine strain effectively neutralized wild-type genotype G virus [39].

Crowding and intensity of exposure have also been proposed as risk factors for mumps transmission [11]. Other factors relating to intensity of exposure, which we did not measure, may have also played a role in driving this outbreak. We did not find an association between household density and transmission. However, the communities affected by the outbreak engage in frequent gatherings among themselves for religious holidays

Table 3
Mumps vaccine effectiveness (VE) among secondary household contacts 5 years of age and older by number of valid MMR doses ($n = 1348$).

Valid MMR doses	Sick	Not sick	Total	VE (95% CI)
0	4	16	20	–
1	4	113	117	82.9 (37.1–95.4)
2[a]	19	672	691	86.3 (63.3–94.9)
Unknown	17	503	520	83.7 (55.9–93.9)[b]
>= 1	23	785	808	85.8 (62.7–94.6)

[a] Adjusted for age category VE = 86.3 (52.4–96.0), adjusted for household density VE = 86.3 (52.4–96.0), adjusted for years from last MMR using 1 dose as reference group VE = 12.8 (0–69.6).
[b] Reduction in disease in individuals with unknown vaccination status compared to unvaccinated.

and celebrations that may have contributed to a higher intensity of exposure to mumps. In addition, the majority of children in these communities attend religious schools separated by gender. The schools are crowded, and children, especially adolescent boys, spend long hours studying in close contact. While intensity of exposure may have played some role in this outbreak, our household study does not provide any evidence in support of this hypothesis.

A number of limitations to our study should be considered when interpreting our findings. Among secondary cases, 15% were reported by the head-of-household. These cases were not confirmed by investigation or medical record review and may not have fulfilled the CSTE case definition. The time between the index case onset and the follow-up interview may have led to cases being missed due to poor recall. Vaccination coverage estimates are exclusive to households with known mumps disease, and coverage in the overall Orthodox Jewish community may differ. In addition, the study was conducted during a community-wide outbreak, so exposure to mumps may have occurred in other settings besides the home. We did not investigate specific exposures during religious holidays and community celebrations when members of the affected community may have had close contact. Furthermore, the definition of household density, based on number of bedrooms and total people, may not have been sufficiently precise to detect an effect. Our examination of mumps in relation to time from MMR may have been limited by little variability in the number of years from last MMR dose. Most cases in the overall outbreak were male, but the gender of mumps cases identified at follow-up in this study was not ascertained [14]. However, the gender difference in the overall outbreak may suggest that there was not equal exposure to disease among all members of the study households.

With respect to vaccination status, we required documentation of vaccination, and those lacking documentation were classified as unknown. Misclassification of vaccinated and unvaccinated persons into the unknown group may have limited the precision of our VE estimate by excluding those who lacked documentation because they had never been vaccinated, as well as decreased our estimate of the proportion of those who were fully vaccinated. However, the fact that individuals with unknown vaccination status experienced an 83.7% (55.9–93.9) reduction in disease suggests that they were likely vaccinated.

In addition, this study only assessed VE for clinical disease. Given that asymptomatic disease is common, our VE estimates may be overestimates with respect to MMR vaccine preventing infection. There was not a significant difference between our one-dose and two-dose mumps VE estimates; however, this may have been due to insufficient statistical power to detect any incremental increase in protection from a second dose. In spite of the limitations of our study, our results for one and two-dose VE were consistent with estimates previously described in the literature.

While outbreaks of mumps have occurred in vaccinated populations, mumps has declined dramatically since the introduction of mumps vaccination in the United States [2,4]. In the US, high MMR vaccination coverage levels have been achieved; over 90% of adolescents have received two doses of MMR [32]. The high mumps vaccination coverage in the broader NYC population may have limited the scope of this outbreak. In order to achieve mumps elimination in the U.S., a better understanding of factors leading to mumps outbreaks in vaccinated populations and measures to control such outbreaks is required. Better measures of serologic correlates of mumps immunity and the impact of waning immunity need to be explored. Promotion of mumps vaccination in accordance with recommendations from the Advisory Committee on Immunization Practices remains the most effective strategy for controlling mumps [40].

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