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Transmission of mumps virus from mumps-vaccinated individuals to close contacts

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ABSTRACT

During a recent mumps epidemic in the Netherlands caused by a genotype D mumps virus strain, we investigated the potential of vaccinated people to spread mumps disease to close contacts. We compared mumps viral titers of oral fluid specimens obtained by quantitative PCR from vaccinated ($n = 60$) and unvaccinated ($n = 111$) mumps patients. We also investigated the occurrence of mumps infection among the household contacts of vaccinated mumps patients. We found that viral titers are higher for unvaccinated patients than for vaccinated patients during the 1st 3 days after onset of disease. While no symptomatic cases were reported among the household contacts ($n = 164$) of vaccinated mumps patients ($n = 36$), there were cases with serological evidence of asymptomatic infection among vaccinated household contacts (9 of 66 vaccinated siblings). For two of these siblings, the vaccinated index patient was the most probable source of infection. We conclude that, in this particular outbreak, the risk of a close contact becoming infected by vaccinated patients was small, but present.

1. Introduction

Mumps epidemics have occurred in many countries despite national mumps vaccination programs, attacking both unvaccinated and vaccinated individuals [1–3]. In the Netherlands, the combination vaccine against measles, mumps, and rubella (MMR) was introduced in 1987 in the Dutch National Immunization Program (NIP) for all children aged fourteen months and nine years. The two-dose MMR vaccination coverage has been consistently above 93% [4]. There was no widespread mumps among unvaccinated people until the incidence of mumps in the Netherlands suddenly increased in August 2007 [5]. We investigated several hundred clinical cases among people residing in regions where vaccination coverage is considerably lower (due to religious reasons) than it is nationwide. However, clinical mumps infections of people with documented MMR vaccination histories were also reported during this epidemic. Both vaccinated and unvaccinated patients resided mainly in the same geographic areas.

Previous studies have demonstrated that the virus can be cultured from oropharyngeal specimens obtained from infected unvaccinated patients up to 9 days after the onset of parotitis [6,7]. As mumps disease is transmitted by airborne respiratory droplets, the viral mumps titers in oral fluid can be considered an important parameter in characterizing the infectiousness of a mumps patient [8–11]. However, there are very few data available about viral shedding, most particularly of vaccinated mumps patients. The extent to which vaccinated individuals can contribute to viral transmission during an outbreak is not well known [8,12,13]. Some studies have shown that one dose of mumps vaccine is less effective than two doses of the vaccine in conferring protection against infection [14]. The recent mumps epidemic in the Netherlands gave us an opportunity to assess viral shedding by determining the viral titer in oral fluid specimens with real-time PCR. We used the viral titer as a parameter to express the infectiousness of a patient in relation to vaccination status and the duration since last mumps vaccination. Furthermore, to assess virus transmission by vaccinated mumps patients, we checked the household contacts of vaccinated mumps patients for clinical symptoms or high

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mumps-specific immunoglobulin (Ig) G antibodies in oral fluid, which indicate recent mumps infection.

2. Methods

2.1. Data collection

Physicians at municipal health services and hospitals selected patients primarily on the basis of symptoms such as parotitis and orchitis. During the mumps epidemic of 2007–2009, we specifically encouraged these doctors to take samples from symptomatic patients with a mumps vaccination history. We collected patient characteristics such as age, date of onset of disease, and MMR vaccination status, and had samples from symptomatic mumps patients sent to the Laboratory for Infectious Diseases at the National Institute for Public Health and the Environment (RIVM, The Netherlands). Further, we conducted a retrospective study between November 2008 and June 2009 to find evidence of viral transmission in households of vaccinated mumps patients. We invited the patients with laboratory-confirmed mumps and an MMR vaccination history to participate in this study, and we sent them a standardized questionnaire to obtain information about the vaccine and clinical mumps status of their household contacts. We considered parotitis or orchitis reported by a household contact within 1 month after mumps confirmation of the index case to be a clinical secondary case. To pinpoint possible secondary cases of infection via school contacts, we asked the siblings' teachers by telephone whether they had noticed any mumps cases. A sibling with clinical or serological evidence of mumps virus infection, who had attended a school where no mumps had been reported, was considered to most probably be infected by the vaccinated index person. We requested all household contacts, regardless of earlier mumps-related symptoms, to donate oral fluid specimens, so that we could study mumps-specific IgG antibody levels.

2.2. Specimens and handling

Physicians sent in oral fluid samples, throat swabs, and/or urine samples. They used the ORACOL (Malvern Medical Developments, Worcester, UK) sponge device, as the manufacturer instructed, to collect oral fluid. The laboratory technicians directly extracted the oral fluid from the sponge by centrifugation and diluted it for PCR analysis if there was sufficient volume (50 μL or more). Throat swab specimens were collected in viral transport medium (4 mL) and concentrated for PCR analysis as previously described [15]. Briefly the cellular sediment of 1 mL of throat swab sample was centrifuged for 10 minutes at 300 g. For urine specimens, the sediment of 1 mL of urine was generated by centrifugation (10 minutes at 13.000 g). Sediments were dissolved in 200 μL PBS and lysed for RNA purification using the High Pure Viral Nucleic Acid Kit according to procedures recommended by the manufacturer (Roche).

2.3. RNA detection of mumps virus

We examined the clinical specimens for the presence of mumps virus RNA, using a nested reverse transcriptase PCR technique based on small hydrophobic gene primer pairs as recently described [15]. We refer to this PCR technique as diagnostic PCR. If one or more of the clinical specimens obtained from patients with mumps were positive according to diagnostic PCR, we analysed the specimens quantitatively for the amount of mumps viral RNA with F-gene-specific real-time PCR as Uchida and colleagues describe [16].

The data are expressed as genomic equivalents (geq) of mumps virus by volume. It is important to note that specimens testing positive in diagnostic PCR with relatively high threshold cycle values did not always test positive in real-time PCR because of a slightly lower sensitivity of the real-time PCR method and because of some RNA loss due to storage and repeated testing. We regarded such specimens as having a viral titer of half of the cut-off value for quantitative comparisons (i.e. 2.0 geq/100 μL). For the throat and urine samples, the equivalent cut-off values were set at 20.0 geq/mL, due to the testing of 1-mL specimen volumes for these particular specimens when we compared them to oral fluid.

2.4. Immunoglobulin G determination in oral fluid

We asked siblings of vaccinated mumps patients to fill in a questionnaire and donate an oral fluid sample for mumps-specific IgG determination within 6 months after onset of the disease of the index patient, in order to provide evidence for any recent mumps infection. We used a mumps IgG enzyme-linked immunosorbent assay designed for oral fluid to assess the antibody levels of close contacts and cases, as described earlier [17]. According to the criteria of the immunoassay, a cut-off of optical density (OD) greater than 0.15 is considered indicative of a previous wild-type mumps infection, but only for individuals without any vaccination or infection history. As most household contacts were vaccinated, we had to apply a higher cut-off value and used the most conservative one (OD > 0.40) in order to exclude false positives due to circulating antibodies caused by earlier MMR vaccination. This specific cut-off value (OD > 0.40) was previously shown to define mumps infection with a specificity of 95.6% [95% confidence interval (CI): 90.0–98.0%], albeit at the expense of sensitivity (47.1% [95% CI: 23.0–72.2%]) [17]. The cut-off value of vaccinated individuals (OD > 0.40) is only estimated among children and so adult persons were excluded from further analyses.

2.5. Statistics

We compared the proportions of mumps-positive samples in MMR – vaccinated and unvaccinated patients using the chi-square test. We did this separately for oral fluid, throat swabs and urine samples. Data obtained from once- and twice-vaccinated patients were pooled in a single group in order to increase statistical power.

We further used quantitative values of mumps RNA in individual oral fluid specimens as indicators of the risk of patients with mumps spreading the virus. We used Spearman's test to assess the effect of the sampling delay (i.e., the number of days between the onset of the disease and the time of sampling) on the viral titers. In the remainder of the analysis, we considered the clinical samples obtained between day 0 and day 9 to be most reliable for quantitation of viral titers by PCR and excluded comparisons between the groups if too few data were available.

We used Scholz and Stephens' [18] *k*-sample test to assess the effect of a previous MMR vaccination history on the amount of virus detected in the specimens taking into account the sampling delay. We used linear regression models to examine the relationship between the $\log_{10}$ values of viral titers and MMR vaccination status while correcting for both age and sampling delay. These models were based on the data for 83 patients for whom all the variables were available.

3. Results

3.1. Epidemiological and clinical data

The National Institute for Public Health and the Environment (RIVM) received clinical specimens (oral fluid, throat swabs, urine and/or filter paper blood) for laboratory confirmation from both unvaccinated and vaccinated patients. Of the 341 patients presenting with symptoms consistent with mumps between August 2007 and June 2009, 171 patients (50%) had one or more samples that

Table 1
Proportions of mumps virus RNA samples found positive by diagnostic PCR for the SH-gene.

Vaccination status	Proportions of positive specimens		
	Oral fluid	Throat swab	Urine
No MMR vaccination (n = 111)	0.75 (67/89)	0.68 (34/50)	0.61 (54/88)
MMR vaccination (n = 60)	0.62 (33/53)	0.44 (14/32)	0.28 (15/53)
p-Value of chi-square test	0.10	<0.05	<0.05

MMR: measles–mumps–rubella.

tested positive for mumps (Table 1). Occasionally, we used IgM testing on dried blood spots or sera to confirm clinical diagnosis, but we confirmed most patients' diagnoses (>95%) on the basis of PCR testing. The vaccination coverage of patients who tested mumps negative was the same as for those who tested positive. All 170 patients who tested negative were excluded from further analyses.

Most patients who tested mumps positive (n = 111, 65%) were unvaccinated. The median age of the unvaccinated mumps patients was 15 years. Vaccinated patients had either received one dose of mumps vaccine (n = 27, median age 5 years) or two doses (n = 33, median age 13 years). The median time between the onset of mumps and the most recent vaccination was 4 years in both vaccination groups.

Of the 171 mumps-positive patients, genotype information was available for 134 patients who were all infected with genotype D mumps virus.

3.2. Mumps virus detection by diagnostic PCR

Most patients provided both oral fluid and urine for PCR testing; a smaller proportion of patients also provided throat swab specimens (Table 1). The proportion of PCR mumps-positive patients in the vaccinated group was much smaller than that in the unvaccinated group (Table 1). This difference is statistically significant for the throat swab and urine samples ($p < 0.05$).

3.3. Mumps detection by quantitative real-time PCR

Fig. 1A and B suggests a clear decrease of the viral titer in oral fluid in time after onset of disease. This downward trend of viral content over time is significant in the unvaccinated group ($p < 0.01$ with Spearman's test; Fig. 1A) but not in the vaccinated group ($p = 0.19$, Fig. 1B). This was certainly due to the smaller sample size in combination with the very large interpersonal variation of viral content at each fixed time point (which is evident in both groups).

Viral titers in the oral fluid of unvaccinated patients tend to be higher than those of vaccinated patients (Fig. 2), which suggest that vaccination has an effect in reducing viral titer values. We stratified the data in Fig. 2 by sampling delay – the time elapsed since onset of disease ($\leq$3 days, >3 and <6 days, $\geq$6 days) – in order to correct for the decrease of viral titer over time. According to the permutation version of the Scholz–Stephens k-sample test [18], which accounts for the tied viral titer observations (not visible in the box plots), the difference between the two groups with samples taken within 3 days after the onset of disease is statistically significant ($p < 0.01$) and so is the difference between the two groups sampled after three and before 6 days (p-value of 0.01). No significant difference appeared among the patients who provided samples 6 or more days after the onset of disease. The fact that the number of patients was much smaller and the quantitative PCR values were less discriminative at later stages of the disease (data not shown) may explain this. The relative constancy of viral titer values within the strata, as Fig. 1A shows, suggested the stratifications that we used here. Other choices of strata (including using only two strata) yielded similar results.

To study the $\log_{10}$ of the viral titers in terms of other potential determinants, we used a regression model that accounts for three of the available parameters: (1) vaccination history; (2) age; (3) sampling delay. This model has an adjusted R square of 0.30. The model includes an additive effect of vaccination, linear and quadratic terms of age, and an interaction term between age and sampling delay, all of which are found to be significant (Table 2). The negative coefficient of the vaccination status indicates that vaccination is associated with a lower viral titer ($p = 0.025$). The remaining parameters indicate that the logarithm of viral titers peaks around 19 years of age and is lower both at younger and higher ages (data not shown).

A regression model that separately incorporates additive effects of both the first and second mumps vaccinations gives very similar estimates but the effect of vaccination becomes smaller ($p = 0.10$) for a single vaccination, while the effect of a second vaccination is not significant ($p = 0.98$).

Larger models including "time since last vaccination" provide no evidence for an association of this variable with viral titers. This can be explained by the fact that patients in our study have adhered to the standard Dutch vaccination schedule (MMR vaccination at 14 months and 9 years of age) and therefore the effects of either age or time since last vaccination on viral titers cannot be unraveled.

3.4. Evidence for mumps virus transmission among vaccinated people

Of the 56 households of vaccinated mumps patients contacted, 36 (64%) cooperated and returned questionnaires and oral fluid samples. The households included a total of 92 adults and 68 siblings (Table 3). The oral fluid of 9 of the 66 vaccinated siblings exhibited serological evidence of a recent mumps infection. Seven of the siblings attended a school where mumps had circulated and therefore could have been infected at school. However, the other two siblings (both in the same household) had attended a different school where mumps disease had been neither obviously present nor confirmed. The vaccinated clinical index patient of their household had a relatively high viral titer for oral fluid (484 geq/100 μL at 8 days after onset of disease).

4. Discussion

4.1. Epidemiological and clinical data

During the Dutch mumps epidemic (2007–2009), far more people contracted mumps virus than were clinically reported (and had the diagnosis confirmed in the laboratory). Best estimates suggest that most cases occurred among unvaccinated children from the Dutch Orthodox Reformed community (median age 13 years), for whom only a fraction of the cases were confirmed in the laboratory. When it became clear that some vaccinated children could become symptomatic, general practitioners were specifically encouraged to take samples from vaccinated people with the disease. The total number of vaccinated people with confirmed cases that accrued in almost 2 years of surveillance was small, which suggests only incidental infection among vaccinated people. There was no report of mumps circulation outside the Orthodox Reformed community. Therefore, the vaccinated, infected people represent a small and socially distinct part of the whole Dutch vaccinated population. Children in this community are relatively segregated from other populations as they frequently go to religious schools and usually live in rural areas.

The vaccinated patients with mumps were part of the same religious community and could therefore be considered as being

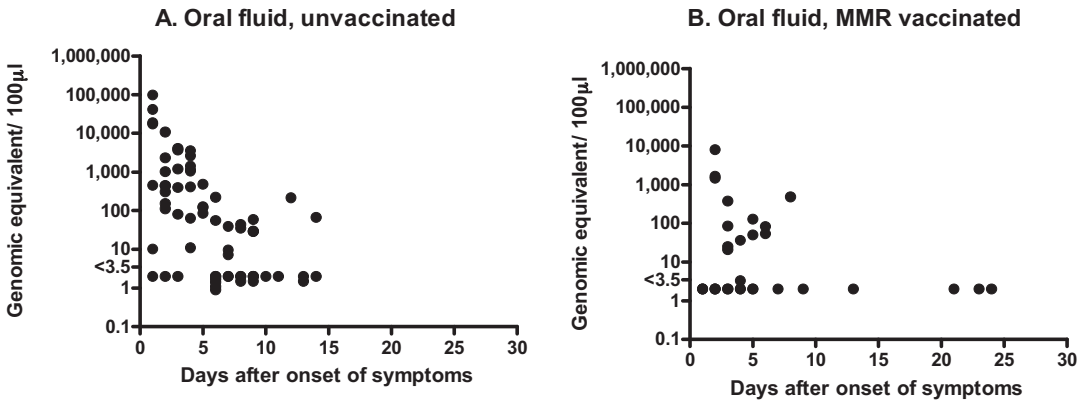

Fig. 1. (A and B) Mumps viral titers in relation to date of onset of clinical symptoms among unvaccinated (A) and vaccinated (B) patients.

Table 2
Potential determinants of viral titers found in regression analysis.

Determinant of viral load	Coefficient estimate (Standard Error)	*p*-Value
Intercept	0.53 (0.47)	0.27
Vaccination	−0.63 (0.27)	0.025
Age in years	0.33 (0.07)	<0.01
Age square (i.e. the square of age)	−0.009 (0.002)	<0.01
Interaction of age with days between onset of disease and sampling	−0.033 (0.007)	<0.01
Interaction of age square with days between onset of disease and sampling	0.0009 (0.0003)	<0.01

contact cases. As this study indicates, they may have led to secondary infections as well.

4.2. Mumps virus detection by diagnostic and quantitative, real-time PCR

On the basis of multiple specimen collection from individual patients (oral fluid, throat swab, and urine), we found that mumps-specific RNA could be detected in a greater proportion of the clinical specimens of unvaccinated patients than of vaccinated patients (Table 1). Apparently, mumps virus is less viraemic in a vaccinated patient with a clinically relevant infection than in an unvaccinated patient, especially regarding urine specimens. Oral fluid samples of both vaccinated and unvaccinated patients most often seem to contain a detectable viral titer and are therefore the most suitable for laboratory mumps confirmation.

Viral titers of oral fluid reached their highest level immediately after the onset of disease (Fig. 1), and the levels were higher for unvaccinated patients than for vaccinated patients, especially when the samples were analysed within the 1st 3 days after the onset of disease (Fig. 2). The multiple regression analysis confirms these two observations by describing the $\log_{10}$ of the titers jointly in terms of vaccination status, age, and sampling delay (i.e. time from onset of disease).

The decrease in titer levels with the sampling delay is consistent with historical data showing that mumps is most often isolated in the first few days of disease and that incidental patients shed the virus from 7 days before symptoms develop up to 9 days after the onset of disease [7,8,19]. Because transmission is associated at least with the duration and the amount of mumps virus secreted in oral fluid, we can expect virus transmission between vaccinated and unvaccinated patients to be at its greatest in the few days around the onset of disease.

Some vaccinated mumps patients have certainly been missed in the analysis, as the diagnostic PCR cannot confirm all the clinically relevant mumps cases because of low virus content in the specimens or an inappropriate sampling time. Hence, vaccinated people who had developed mumps disease are routinely more often excluded from the analysis than unvaccinated people due to lower viral titers at comparable moments of sampling. Detection of specific antibodies in serum does not always fill this diagnostic gap because specific IgM antibodies are hardly detectable in the serum of vaccinated patients in this respect [20]. The fact that almost no IgM is induced during the infection of vaccinated individuals indicates that the pathogenesis of mumps virus infection is different for vaccinated and unvaccinated people.

If waning immunity plays a role in increased susceptibility to mumps infection, then the higher the viral titers for infected people are expected to be, the longer it has been since last vaccination. However, since most of our patients adhered to the standard Dutch vaccination schedule, the putative effect of time since last vaccination is inextricable from that of age and it cannot be used individually to study the phenomenon of waning immunity. Nonetheless, it is interesting to note that the "age square" term in the regression model indicates that the logarithm of viral titers is a concave function of age with a peak at 19 years irrespective

Table 3
Clinical and laboratory data about mumps-infected family members (siblings) of mumps-infected vaccinated patients.

Family members	Number of individuals investigated	Number of mumps sero-positive individuals	Median number of years since last vaccination
Siblings (unvaccinated)	2	0[a]	–
Siblings (vaccinated)	66	9[b]	4.1

[a] Values above the cut-off (optical density >0.15) indicate recent asymptomatic mumps infection. Oral fluid tested with mumps immunoglobulin-G-specific, microimmune ELISA (enzyme-linked immunosorbent assay).
[b] Values above the cut-off (optical density >0.40) indicate recent asymptomatic mumps infection. Oral fluid tested with mumps immunoglobulin-G-specific, microimmune ELISA [17].

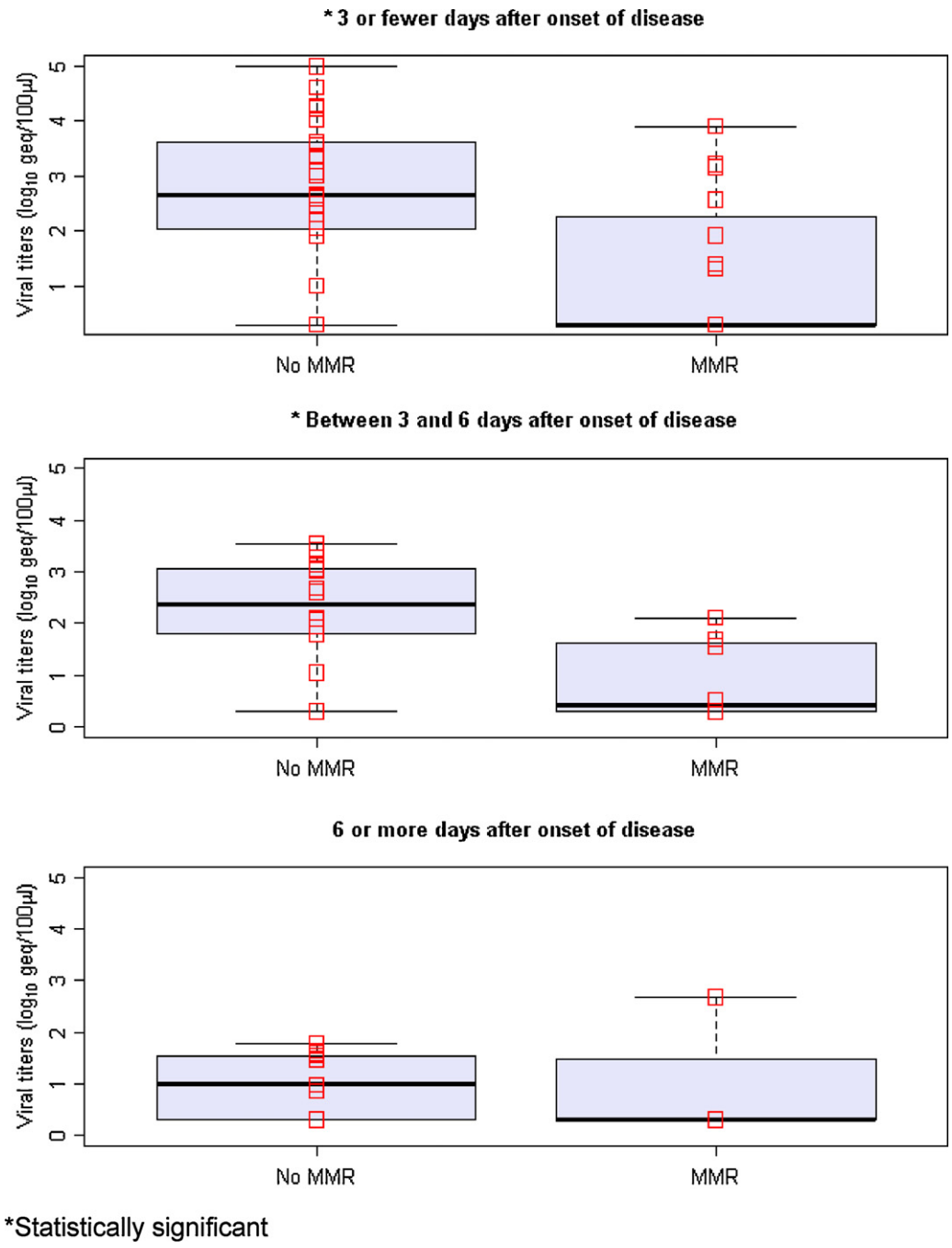

Fig. 2. Comparison of mumps viral titers of oral fluid obtained by quantitative PCR in the two measles–mumps–rubella groups by date of onset of clinical symptoms.

of the sampling delay. In this model, therefore, the viral excretion would increase up to the age of 19 irrespective of vaccination status and the sampling delay. Moreover, the effect of the sampling delay and of vaccination status would essentially be to "pull" the concave curve up or down. Although the confirmation of this pattern would require more data, it is possible that age-related aspects of a patient's immune system or age-dependent virulence factors of the mumps virus also account for the differences in viral titers observed in different patients. If this is so, then age-related effects on viral excretion must be taken into account within discussions about the effect of waning immunity after vaccination.

Our data indicate a much lower impact of virus transmission via vaccinated people than via unvaccinated ones. However, the oral fluid samples from some vaccinated patients occasionally have high viral titers. Recent outbreaks in the USA, Israel, and the Netherlands show that mumps can spread among communities with high vaccination coverage and particularly within student populations [3,21,22]. The spread of mumps among vaccinated students could be due to a longer time since the last MMR vaccination (waning immunity) and/or to more intense and broader social contact than the social contact that their counterparts among the children involved in the outbreak studied here had. Further, the genotype D virus strain caused the Dutch epidemic (2007–2009), whereas the genotype G virus caused the outbreaks among vaccinated students in 2000. The genotype G virus has been documented in many other mumps outbreaks involving vaccinated individuals

[1,23]. Genetic differences between these two virus strains might play a role in the differences in attack rates among vaccinated individuals, although this has yet to be investigated [24,25]. The studies of vaccinated students have published no data documenting the direct transmission of mumps virus from vaccinated patients to vaccinated individuals, though such transmission is deemed possible.

For the Dutch epidemic we describe here, we consider household as well as school contacts as potential risks for mumps virus transmission. It is difficult to prove that a vaccinated patient caused virus transmission because a secondary case could occur by transmission from another unvaccinated mumps patient. In one study, a 34% mumps attack rate was found for household transmission from unvaccinated index patients to susceptible individuals [26]. In our study, screening of members of the households of vaccinated index patients for mumps symptoms did not reveal any symptomatic mumps infection. Nine of 66 vaccinated household contacts (siblings) had mumps-specific antibody levels indicative for recent asymptomatic mumps infection. This is most probably an underestimation of all asymptomatic infections for two reasons: firstly; we screened for mumps-specific antibodies up to 6 months retrospectively. The antibody decrease over time could lead to an underestimation of secondary mumps cases in a household setting. Secondly, the high cut-off (OD > 0.40) gives certainty about positive cases, but can also lead to an underestimation of recent infected contacts who reached antibody levels just below the cut-off. Interestingly, two siblings of these 9 asymptomatic and vaccinated patients did not attend a school where mumps disease had been reported. Household transmission from the vaccinated mumps patient (household index) seems the most plausible explanation for their mumps disease.

This study shows that not only can vaccinated individuals develop mumps symptoms after infection, they can also transmit the virus. However, the overall impact of vaccinated mumps patients on an outbreak remains to be determined. This impact is likely to depend on several factors, which may include social background and waning of vaccination-acquired immunity.

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