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Mumps virus infection in vaccinated patients can be detected by an increase in specific IgG antibodies to high titres: a retrospective study

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SUMMARY

Mumps outbreaks in highly vaccinated populations with genotype G have been reported repeatedly. Detection of these outbreaks can be difficult in a setting with relatively high vaccination coverage when acute cases of mumps are routinely diagnosed by IgM serology since this marker is not reliable for diagnosis of mumps re-infection. To learn whether diagnostic tests performed in a large private laboratory may be useful to detect mumps outbreaks retrospectively, we reviewed the results of almost 7000 mumps tests. Two groups were compared: group 1 comprised of 3438 samples from patients submitted by physicians and clinicians (it was assumed that these patients visited their doctor due to acute disease). Group 2 comprised of 3398 samples submitted from company medical officers and occupational physicians. Since these patients usually attend for routine check-ups and certification of immunity to vaccine-preventable diseases, these samples comprised a control group. From July 2010 to May 2011, a mumps virus outbreak with more than 300 cases occurred in Bavaria, Southeast Germany. Our study includes samples received for serological mumps tests from January 2009 until December 2011 (36 months). The two groups were analysed with regard to the number of IgM-positive cases per month and the level of IgG titre. We found a marked increase for both parameters in group 1 during the time of the outbreak, while the samples submitted by the occupational medical physicians did not display significant alterations. These parameters reflect the outbreak with high accuracy, indicating that a retrospective analysis of IgG titres may be a useful tool for detection of mumps outbreaks when, as was the case in Germany, (i) a nationwide notification system has not been implemented and (ii) a highly vaccinated population is affected.

Key words: Immunization (vaccination), mumps, seroepidemiology, vaccine-preventable diseases.

INTRODUCTION

Mumps virus (MuV) infections lead commonly to fever and parotitis. Older patients often exhibit severe clinical courses and may develop, e.g. meningitis, pancreatitis, orchitis, or epididymitis. The global introduction of MuV vaccination resulted in decreased incidence worldwide. However, multiple outbreaks

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of MuV have affected highly vaccinated communities in crowded settings like religious schools, colleges and universities in recent years [1–5].

Diagnosis of MuV infection can be performed by polymerase chain reaction (PCR) and/or serology (IgM or an increase in IgG in two consecutive sera). Probably due to economic issues, standard diagnostic testing is routinely performed by IgM test in Germany. Detection of mumps-specific IgM works well in immunologically naive individuals, while vaccinated individuals rarely synthesize IgM antibodies or do so only weakly [6, 7]. Thus, diagnosis of MuV re-infection by IgM serology will lead to underascertainment of the actual number of cases when a vaccinated population is affected. To diagnose a MuV infection in vaccinated individuals, use of reverse transcriptase (RT)–PCR and IgM capture tests are recommended.

A nationwide notification system for mumps was introduced in Germany in spring 2013. Mumps cases were notified in earlier years only in the Eastern federal states, which relied on higher vaccination coverage for historical reasons. Consequently only few cases were notified. From July 2010 to May 2011, a large MuV outbreak occurred in Bavaria, a federal state in Southeast Germany, which was highlighted by the high number of mumps-specific IgM-positive samples in unvaccinated individuals and by positive PCR results [8]. This outbreak led to the implementation of a notification system within the federal state of Bavaria, with more than 300 cases being notified; however, a considerable underreporting has been assumed [9].

Since detection of MuV outbreaks is difficult in settings of high vaccination coverage and without nationwide surveillance, alternative tools could prove valuable. This study reviews aggregated data from serological tests performed between January 2009 and December 2011 in a large private diagnostic laboratory. Reviewing serological responses to MuV infections, the results clearly indicate that not only IgM-positive test results but also the appearance of highly positive IgG titres may be useful tools in the detection of outbreaks in a vaccinated population in the absence of a notification system.

METHODS

Study design

The Synlab Medical Care Service Centre, Weiden, Bavaria, analyses laboratory samples submitted by about 40 hospitals and more than 2000 physicians serving outpatients living predominantly in Northern Bavaria [10]. All test results were categorized into four groups: males, females, children aged <14 years, and gender and age unknown (see Table 1).

In the present study, results of mumps IgM and IgG antibody analyses collected between January 2009 and December 2011 were re-evaluated. Two different datasets were created. Group 1 comprised serum samples submitted by Bavarian physicians (predominantly general practitioners, pediatricians and consultants) and hospital laboratories. We assumed that a high proportion of these samples had been submitted for confirmation of suspected mumps cases. To identify patients with repeated submissions for mumps testing in the first group, only samples submitted with the name and the date of birth of the patient were included. When more than one sample from a patient was received, the sample displaying the highest result was used for statistical calculation. This principle was not applied for dataset 2, since the majority of the samples from occupational medicine facilities are submitted anonymously. Moreover, we regarded the probability of repeated antibody testing in this group as low, because these consultations are routine check-ups.

Serological analyses

Bavarian physicians and hospitals (group 1) submitted 3438 samples during 2009–2011 for mumps serology. All samples were tested for mumps-specific IgG antibodies, and 2354 of these specimens were examined for IgM. In group 2, from occupational medicine facilities, 3398 samples were submitted for MuV IgG test, while only 57 serum samples were also tested for mumps-specific IgM (Table 1).

Mumps antibody testing was performed with the BEP III System (Siemens Healthcare Diagnostics, Germany) and Enzygnost ELISA (anti-parotitis virus/IgM and anti-parotitis virus/IgG, Siemens Healthcare Diagnostics). Results of IgM ELISA were given as negative, equivocal, and positive with a cut-off of <0·1, 0·1–0·2 and >0·2, respectively. Results of IgG ELISA were given in geometric mean titres (GMT) as negative (<230), equivocal (230–500), and positive (>500).

Each analysis was performed as requested by the physician in charge. Due to storage limitations, all samples are usually discarded after 21 days. Accordingly, it was not possible to perform additional

Table 1. *Characteristics of patients analysed for mumps virus antibodies in the present study*

	Group 1		Group 2	
	IgG	IgM	IgG	IgM
Analyses (*n*)	3438	2354	3398	57
Gender				
Male, *n* (%)	1082 (31·5)	905 (38·4)	320 (9·4)	7 (12·5)
Female, *n* (%)	1891 (55·0)	1169 (49·7)	2918 (85·9)	45 (80·4)
Children, *n* (%)	462 (13·4)	275 (11·7)	—	—
Unknown (%)	3 (0·1)	5 (0·2)	160 (4·7)	4 (7·1)
Median age (years)	29	28	31	32
IgG antibodies				
Median titre, GMT	1200		1000	
<230 GMT, *n* (%)	615 (17·9)		613 (18·0)	
IgG ⩾ 2500 GMT, *n* (%)	999 (29·1*)		745 (21·9**)	
IgM antibodies, *n*		Negative, 1887 Equivocal, 199 Positive, 268		Negative, 56 Equivocal, 1

GMT, Geometric mean titre.
Group 1 comprised serum from patients of practitioners and consultants in ambulatory and hospital settings. All samples ($n = 3438$) were examined for mumps virus-specific IgG antibodies. Of these, 2354 samples were also examined for IgM antibodies. Serum samples of group 2 patients were submitted from occupational medicine facilities, which are visited for routine check-ups.
* 57·3% and **42·7% of all serum samples (groups 1 and 2) showing IgG antibody titres ⩾2500 GMT from groups 1 and 2 ($n = 1744$).

analyses when an interesting constellation was observed in the retrospective evaluation of the results.

Statistical analyses

The descriptive statistical number and percent, or number and median, were calculated for 3-month time periods. In further analysis, for the continuous parameter IgG, we defined a titre of ⩾2500 GMT as high (positive). This value was the 75% percentile of all IgG values.

To analyse the timely development of IgG and IgM values, we performed two logistic regression analysis with the outcomes IgG ⩾2500 GMT and IgM positive as dependent parameters and time (quarter/year) as independent parameter. To adjust for confounding, the parameters age, sex (gender) and group were considered additionally. Because the outbreak was dependent on time and group, the interaction time × group was also considered. Multivariate logistic regression analysis was performed stepwise forward, with $P = 0{\cdot}05$ for including a parameter in the model and $P = 0{\cdot}10$ for removing a parameter from the model. All analyses were performed using SPSS (IBM SPSS Statistics, USA) and SAS (SAS Institute, USA) software.

RESULTS

From July 2010 to May 2011 a mumps outbreak occurred in the Northeastern part of Bavaria, Germany [8, 9]. Within this region the Synlab Medical Care Centre is the only private laboratory providing testing for inpatients and outpatients. Approximately 40 hospitals and 2000 physicians submit samples to this laboratory [10]. Results of mumps serology analyses were examined retrospectively. Baseline characteristics of mumps antibody test results are summarized in Table 1. In both patient groups the percentage of female patients was higher than the percentage of male patients, but this effect was more pronounced in group 2 (patients of occupational medicine physicians) than in group 1 (patients of practitioners, consultants and hospitals).

Result of IgM tests, 2009–2011

In group 1 the number of positive mumps IgM antibody samples was low in 2009 (10/460, 2·2%) while it was markedly higher in 2010 (Fig. 1*a*; 160/908, 17·6%) and in 2011 (98/988, 9·9%). Of the 268 IgM-positive samples between 2009 and 2011, 65·7% ($n = 176$) originated from male patients, while 34·3%

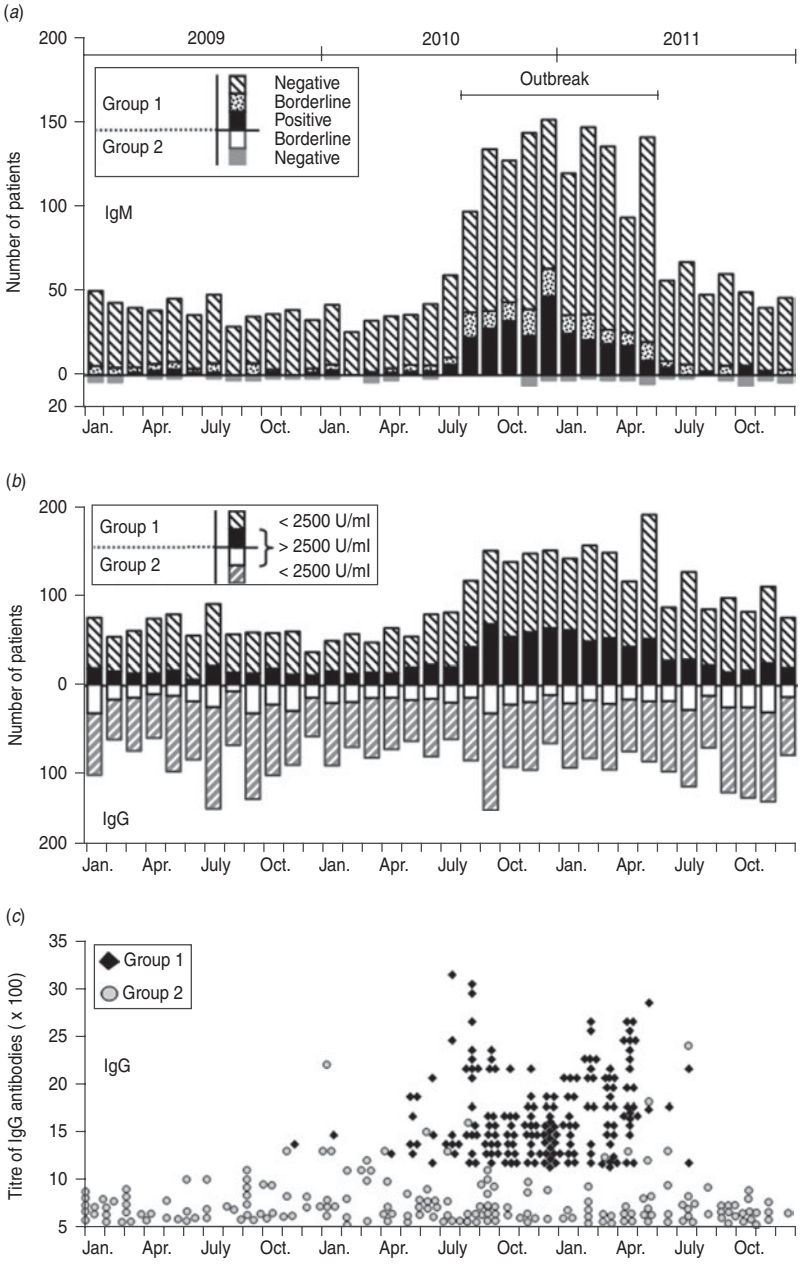

Fig. 1. Results of mumps virus (MuV) serology during 2009–2011. The outbreak period began in July 2010 and lasted until May 2011. Group 1 comprised samples submitted by practitioners and consultants in ambulatory and hospital settings, while group 2 comprised samples submitted by occupational medicine facilities. (*a*) Number of patients tested for presence of MuV-specific IgM antibodies. The samples of group 1 are presented above the x-axis, samples from occupational facilities below. (*b*) Number of patients showing MuV-specific IgG antibodies. The results of both groups are grouped in positive results (titres from 500 to 2500 GMT) and high positive titres (titres $\geqslant$2500 GMT). Results of group 1 patients submitted by practitioners and consultants in ambulatory and hospital settings are indicated above the x-axis, while group 2 patients are given below the x-axis. (*c*) Correlation between top mumps IgG titres and time. The 5% of patients showing the highest MuV-specific IgG antibodies in groups 1 and 2, respectively, are indicated.

($n=92$) were from females. Median age of patients with IgM-positive, equivocal, and negative serum samples was 24, 28, and 29 years, respectively (Table 1). The majority (89·2%, $n=239$) of IgM-positive samples was obtained from July 2010 to May 2011, indicating a period with MuV circulation. This period was characterized by an increase of sera received for IgM testing. Only 56 serum samples had been submitted from occupational medicine facilities for analyses of IgM antibodies (Fig. 1*a*),

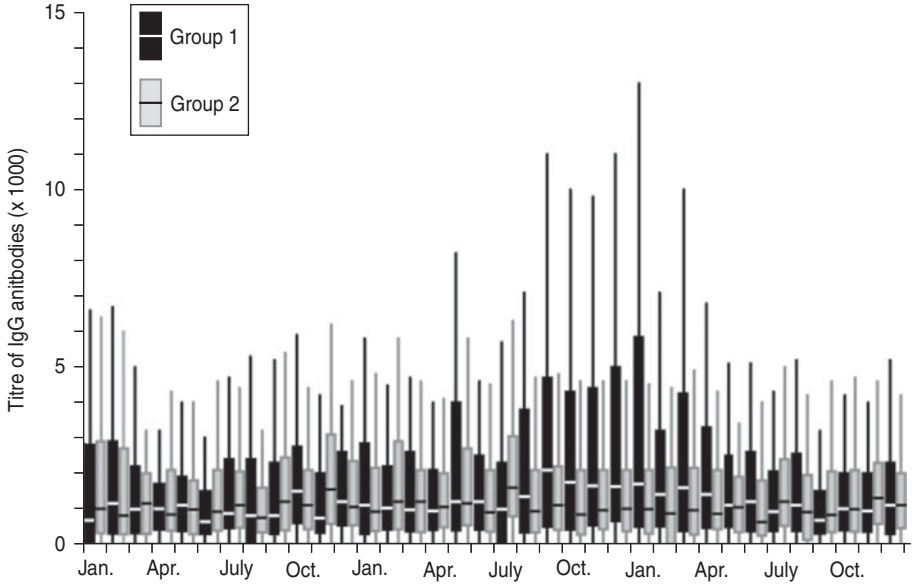

Fig. 2. Box plot showing titres of IgG antibodies per month within the observation period. The outbreak period was from July 2010 to May 2011. Group 1 comprised patients of practitioners and consultants in ambulatory and hospital settings. Serum samples of group 2 patients were submitted from occupational medicine facilities.

thereby verifying our initial hypothesis that persons belonging to group 2 did not exhibit acute signs of mumps. These 56 serum samples were all negative for MuV IgM antibodies with the exception of one sample showing an equivocal result (Table 1).

Results of IgG tests from 2009 to 2011

From January 2009 to June 2010 the median IgG titre per month fluctuated at a low level between 640 and 1200 GMT in group 1 (Fig. 2). During the outbreak period (July 2010 to May 2011) markedly higher values were obtained (median range 1100–2150 GMT), while in the post-outbreak period median IgG antibody titres were comparable to those of the pre-outbreak period (680–1200 GMT). By contrast, increase of median IgG antibody titres was not observed in samples from occupational medicine facilities (group 2).

The interquartile range of all 6836 samples (groups 1 and 2) examined for mumps IgG antibodies was 380–2500 GMT, implying that 75% of all samples presented titres of <2500 GMT. Therefore, a titre of 2500 GMT was used the cut-off value for further statistical analyses of IgG antibody titres. The percentage of patients exhibiting IgG titres $\geqslant$2500 GMT was 29·1% in group 1 and 21·9% in group 2 (Table 1). In group 1, the median age of patients exhibiting IgG antibody titres <2500 GMT was 29 years. Median age of patients showing IgG antibody titres of $\geqslant$2500 GMT was also 29 years. Moreover, the distribution of male patients was similar (38·9% *vs.* 41·9%) in both subgroups of group 1.

In a highly vaccinated population patients will often lack an increase in IgM. Therefore, analyses of IgG titres can be a valuable surrogate marker to detect mumps outbreaks. In group 1 the number of patients showing antibody titre $\geqslant$2500 GMT (black bars, Fig. 1*b*) increased to 999 during the outbreak period. By contrast, in group 2 no increase occurred (white bars). These patients with titres $\geqslant$2500 GMT might be due to the high number of re-infections in vaccinated individuals. This effect was even more marked when a subgroup of each group was analysed, showing 5% of serum samples exhibiting the highest IgG values ('top scorers'). As shown in Fig. 1*c*, 88% (152/172) of the top scorers in group 1 had been collected within the outbreak period, while the high-titre IgG serum samples from group 2 had been collected throughout the observation period. Moreover, the cut-off value for the 5% percentile in group 1 (IgG 12 000 GMT) was markedly higher than that of group 2 (IgG 5600 GMT). Our analysis revealed that during the outbreak the number of sera showing very high IgG titres ($\geqslant$12 000 GMT) was higher in group 1 (n = 175) compared to group 2 (n = 15).

Statistical analysis

Statistical analyses were performed for 3-month periods (quarter I: January–March; quarter II: April–June; quarter III: July–September; quarter IV: October–December). The last quarter of the observation period [IV (2011)] was chosen as the reference period for comparison with other quarters of the observation period. As shown in Table 2, the probability of obtaining a positive or an equivocal IgM test result was significantly increased during the outbreak period [quarters III and IV (2010); quarters I and II (2011)] in group 1. The same holds true when the probability for IgM-positive test results and IgG antibody titres of $\geqslant$2500 GMT are compared. Similar results were seen when matching the probability of obtaining high IgG test titres ($\geqslant$2500 GMT) of group 2 in quarter IV (2011) with that of group 1 in outbreak period quarters (data not shown). A similar comparison for IgM antibody-positive sera was not possible, because IgM-positive sera from group 2 patients had not been observed. Thus, the MuV outbreak in Southern Bavaria was reflected by an increased number of patients who exhibited a positive MuV IgM test result ($n=239$) and by an increased number of patients who exhibited high titres of MuV IgG antibodies.

Patients with repeated submission of serum samples

In further analysis, group 1 patients were identified from whom more than one serum sample for IgM and IgG testing had been submitted, we assumed that this was because physicians suspecting an acute MuV infection would submit samples for further testing, e.g. an increase in IgG titre, or a second test for IgM. Accordingly, IgM antibody test results were correlated to the IgG antibody test results for 87 patients (see Supplementary Table S1, available online).

Several groups were observed: 16 patients exhibited IgM antibodies in the first serum sample. Fourteen patients showed a conversion from negative or equivocal to positive for IgM of 3–29 days (median 7 days) after first sampling. When IgG titres were considered, 10 patients exhibited an IgG titre increase greater than factor 2, and 23 IgM antibody-negative individuals with a highly positive IgG antibody titre ($\geqslant$2500 GMT) were observed. Overall, 63 (72·4%) patients showed a result that was consistent with a case of acute MuV infection or re-infection, while no serological sign of an infection with MuV was observed for 24 (27·6%) individuals.

DISCUSSION

An outbreak of MuV was observed in Northern Bavaria during July 2010 to May 2011. Recognition of MuV outbreaks was difficult in Germany at that time because a nationwide notification system had only been implemented in spring 2013. In this study, MuV IgM and IgG serology was analysed in two different cohorts: group 1 comprised samples submitted by physicians and clinicians treating patients in an ambulatory or hospital setting, while group 2 samples came from occupational physicians seeing patients for routine check-ups. By analysing the IgM and IgG titres against MuV, we clearly demonstrate that group 1 was affected by a MuV outbreak while this was not seen for the control group.

This outbreak was first recognized by an accumulation of positive IgM and PCR results as described previously [8]. Here we show that MuV infection is also reflected in a significant rise of the number of patients with a high IgG titre (Enzygnost $\geqslant$2500 GMT). Moreover, comparison of the 5% percentile sera, the group with the highest IgG antibody titres, showed that for group 1 the cut-off was higher ($\geqslant$12000 compared to 5600 GMT) and the timely distribution coincided with the outbreak. Increase of IgG antibody titre had previously been suspected to be indicative of an increase of mumps cases [4, 11]. Our results demonstrate a significant correlation between increased circulation of MuV and an increase in patients with a very high MuV IgG antibody titre.

A limitation of our study was that we could evaluate only those tests ordered by physicians, while active investigation of cases was not possible, and we were not able to correlate the IgG test results to the corresponding IgM analyses for an individual patient. To circumvent this difficulty, results from patients being tested repeatedly for MuV IgG and IgM antibodies were examined as a correlate of persisting symptoms of mumps. Analysis of this group revealed that serum samples lacking IgG antibodies are rare in MuV-infected patients, which is concordant with relatively high vaccination coverage. Vaccination coverage (one dose of mumps/MMR) in school beginners is 94·6% in Bavaria and 96·3% throughout Germany. Further, consistent with mumps re-infections in highly vaccinated populations, only 25% of these samples were IgM antibody positive. Lacking or delayed IgM response is a well-known feature in MuV re-infection [6, 7].

Table 2. *Adjusted odds ratios (aOR) with 95% confidence intervals (CI) by multivariable logistic regression analysis*

	IgM positive or borderline			IgM positive			IgG ⩾2500 GMT		
Quarter (year)	aOR	95% CI	*P* value	aOR	95% CI	*P* value	aOR	95% CI	*P* value
IV (2011)	1=reference			1=reference			1=reference		
I (2009)	1·48	0·62–3·53	0·378	0·22	0·03–1·93	0·172	1·21	0·78–1·88	0·397
II (2009)	2·01	0·87–4·67	0·103	1·43	0·42–4·88	0·566	0·76	0·48–1·21	0·250
III (2009)	1·71	0·71–4·11	0·229	0·24	0·03–2·1	0·198	1·09	0·7–1·68	0·709
IV (2009)	0·72	0·25–2·05	0·535	0·48	0·09–2·53	0·383	1·18	0·74–1·88	0·483
I (2010)	0·82	0·28–2·34	0·704	0·54	0·1–2·86	0·467	1·39	0·87–2·2	0·164
II (2010)	1·8	0·77–4·23	0·176	1·08	0·3–3·89	0·905	1·4	0·92–2·15	0·118
III (2010)	4·26	2·11–8·6	<0·001	4·77	1·84–12·39	0·001	2·09	1·45–3	0·000
IV (2010)	4·92	2·48–9·75	<0·001	5·49	2·16–13·96	<0·001	2·33	1·64–3·3	0·000
I (2011)	3·37	1·69–6·72	0·001	3·85	1·5–9·9	0·005	1·97	1·39–2·79	0·000
II (2011)	2·58	1·26–5·3	0·010	2·72	1·02–7·28	0·046	1·59	1·11–2·28	0·012
III (2011)	0·99	0·42–2·34	0·973	0·3	0·06–1·57	0·154	0·88	0·59–1·32	0·538

GMT, Geometric mean titre.

Regression analysis was performed for the three outcomes: (i) positive or equivocal mumps IgM antibody test result, (ii) positive mumps IgM antibody test result, and (iii) high mumps IgG antibody titres of ⩾2500 GMT. Quarters I (2009)–III (2011) of group 1 were compared to quarter IV (2011) of group 1.

Grey shading indicates quarters showing significant differences in probability ($P<0·05$).

Logistic regression analysis was performed by variable selection stepwise forward with $P=0·05$ for including a variable in the model and $P=0·10$ for removing a variable from the model. The following variables were considered: age, gender, time (quarter/year).

Besides the interaction time (quarter/year), in all three models sex and age were independent risk factors indicating that only group 1 experienced a mumps outbreak.

Group 1 comprised serum samples submitted from Bavarian physicians (predominantly general practitioners and consultants) and hospitals for laboratory analyses. We assumed that the analyses were mainly performed to confirm clinical diagnoses for patients with acute mumps-like symptoms.

A second limitation of our approach is the lack of clinical information and vaccination data. Socio-demographic details were only known for a very limited number of patients, many of whom were students and/or siblings or roommates of the diseased. In a previous study describing the details of the Bavarian outbreak, clinical data were available and most patients had been vaccinated previously [8, 9].

In the present study the median age of IgM antibody-positive patients was 24 years, corroborating other studies describing mumps outbreaks in young adults [2, 3, 12–15]. The median age of group 1 patients showing highly positive IgG antibodies titre ($\geqslant$12000 GMT) during the outbreak was 22 years while that of patients with lower titres was 29 years. In time periods without circulation of MuV the median age of group 1 top-scorer patients differed only slightly (29 years) from the 95% individuals with lower titres (30 years) confirming the view that young adults were predominately affected within the outbreak. In another analysis of the present outbreak, billing data of affected patients obtained from the Association of Statutory Health Insurance Physicians (ASHIP) for outpatients' median age was 24 years [9], matching the age of IgM-positive patients but not the age of patients with high IgG antibody titres in the present study.

As described by others [2–4, 11, 13, 15, 16], MuV genotype G is presently associated with outbreaks in highly vaccinated groups. Interpretation of these reports indicates that current MuV vaccines do not always protect from MuV re-infection with genotype G and that a positive IgG antibody test cannot be generally equated with immunity against MuV infection. These findings indicate that the aspects indicating increasing susceptibility of 2× MMR vaccination to MuV genotype G re-infection and especially the correlation between MuV-specific IgG antibodies and immunity require further investigation.

This study could demonstrate that in absence of a nationwide surveillance system for mumps, cumulative laboratory data can be used as a correlate to analyse a mumps outbreak retrospectively. By using two cohorts of submissions to a private laboratory, we detected a significant rise in mumps-specific IgG titres during the time of a mumps outbreak, indicating that this type of evaluation is a useful tool and could support surveillance of infectious and vaccine-preventable diseases like mumps.

SUPPLEMENTARY MATERIAL

For supplementary material accompanying this paper visit http://dx.doi.org/10.1017/S0950268813003427.

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