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Mumps vaccine failure investigation in Novosibirsk, Russia, 2002–2004

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ABSTRACT

The aims of this study were to estimate the importance of vaccine failure (VF) in cases of mumps during 2002–2004 in the city of Novosibirsk, Western Siberia, Russia, and to genotype the responsible virus strain. Mumps virus-specific RT-PCR testing of saliva was performed for 18 cases of mumps. Sera were tested for IgM and IgG, IgG avidity, and the ability to neutralise a panel of mumps viruses, including the Leningrad-3 mumps vaccine virus. Of the 12 patients for whom vaccination status was positively determined, 11 showed serological evidence of primary VF. Sequence analysis of virus RNA amplified from saliva revealed a genotype C2 virus in 2002, a genotype H2 virus in 2003, and both genotypes in 2004. Although several vaccinated patients were positive for mumps virus IgG at the time of first sampling, only nominal levels of neutralising antibody were detected, and these were effective in neutralising the vaccine strain, but not genotype C and H mumps virus strains. These results suggest that the majority of cases of mumps in vaccinees are caused by primary VF, defined as either a lack of seroconversion or a lack of IgG maturity, as based on avidity testing. The results also support the hypothesis that sera of low neutralising antibody titre have a limited ability to neutralise heterologous mumps virus strains, suggesting that antigenic differences between circulating and mumps vaccine virus strains may play a role in cases of breakthrough infection. Consistent with previous reports, mumps virus genotypes C and H continue to circulate in Novosibirsk.

Keywords Genotyping, mumps virus, Russia, serology, vaccine failure

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INTRODUCTION

Despite evidence of effective, long-lasting immunity following natural infection or vaccination [1,2], strains of wild-type mumps virus (MuV) continue to circulate worldwide. Recently, two unusually large mumps epidemics have been reported, one in the UK in 2005, involving over 70 000 cases [3], and one in the USA [4], which began in early 2006 and involved 5783 cases (the background number of mumps cases in the USA has been *c.* 250 annually for the past decade). The mumps epidemic in the UK has been attributed mostly to a large cohort of unvaccinated individuals, mostly of college age, who were not eligible for vaccination during childhood. Similarly, the 2006 US epidemic involved mostly college-age students, and has been linked to an insufficient proportion of the population receiving the recommended two-dose schedule of mumps-containing vaccine. In such situations, in which herd-immunity may be lost, outbreaks or epidemics are easily started.

The occurrence of sporadic mumps outbreaks in populations with high vaccine coverage is also a well-known phenomenon. These outbreaks are usually attributed to pockets of unvaccinated individuals and/or vaccine failure (VF), divided into primary (lack of seroconversion) or secondary (waning immunity) failure [5–8]. It has also been suggested that antigenic differences between MuV strains may allow certain strains to escape neutralisation in vaccinees [7,9,10]. While this phenomenon has been demonstrated in the

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laboratory (S. Rubin, personal communication), conclusive evidence of a causal relationship between virus strain-specific antigenic differences and outbreaks or epidemics has not yet been demonstrated. However, for surveillance of vaccine protection against mumps, it is important to follow the distribution of different genotypes of MuV and to measure the genotype-specific immunity in the population. A prospective study to monitor mumps cases was therefore initiated in Novosibirsk, Western Siberia, Russia, in 2002–2004.

Novosibirsk is a large city with a population of *c.* 1.4 million inhabitants. The Leningrad-3 (L-3) mumps vaccine has been used since 1984 in Novosibirsk as part of the national immunisation programme, and the mumps vaccine coverage rate in Novosibirsk has been calculated at 95%. The most widely circulating MuV strains in Novosibirsk between 1994 and 2003 belonged to genotypes C and H [11–14]. According to official data, 142 cases of mumps were reported in Novosibirsk during 2001, 189 cases in 2002, 24 cases in 2003, and 27 cases in 2004. The large decrease in the number of cases in 2003 and 2004 is probably a reflection of the then-instituted requirement for laboratory confirmation of cases, suggesting that MuV may not actually have caused many of the cases reported before 2003.

Vaccination status was determined for all clinical cases of mumps included in this study, and saliva and acute and convalescent sera were obtained. RT-PCR testing of saliva using primers specific for the MuV SH gene was performed to confirm the presence of the virus and to identify the virus genotype [15]. Sera were tested by ELISA for IgM and IgG antibody titres, and for IgG antibody avidity. In addition, sera were tested for their ability to neutralise the vaccine strain (L-3) and two wild-type viruses isolated previously in Novosibirsk.

PATIENTS AND METHODS

Subjects

The SRC VB Vector Ethical Committee approved the study (IRB00001360). Informed consent was obtained from the parents of all children and from the adult patients. The patients' ages and their vaccination status, taken from the official medical records, are presented in Table 1. In total, 18 patients (aged 3–56 years; six females, 12 males) were enrolled in the study. Of the 18 patients, 12 (67%) had been immunised with the L-3 mumps strain vaccine. All 18 patients were diagnosed clinically with mumps according to the WHO case definition (http://www.who.int/vaccines/globalsummary/timeseries/tsincidenceMUM.htm). Clinical signs of meningitis (severe headache, vomiting, nuchal rigidity) were observed in patients P_1/2002, P_3/2003, P_8/2004, P_9/2004, P_{16}/2004 and P_{18}/2004, but spinal taps were not performed; thus, the diagnosis could not be confirmed. Pancreatitis was diagnosed

Table 1. Serum levels of mumps virus (MuV) IgM, IgG, IgG avidity and neutralising antibody in mumps patients

Patient	Age (years)	Status[a] (years)	Days sera were taken[b]	Serum IgM	Serum IgG (titre)	IgG avidity (%)	PRN L-3 (titre)	PRN H (titre)	PRN C (titre)	RT-PCR[c]	MuV genotype
P_1/2002	8	R (1.5)	5/26	+/–	1:900/1:2000	27	1:4/1:8	0/1:4	0/1:8	+/–	C
P_2/2002	4	V (2.5)	5/26	+/–	1:2000/1:8200	31	1:4/1:4	0/0	0/1:8	+/–	C
P_3/2003	18	V (4)	5/11/27	–/+/–	neg/neg/1:500	ND/8	0/1:4	0/1:8	0/0	+/+/–	H
P_4/2003	16	R (4)	4/26	+/–	1:1500/1:9000	29	1:4/1:4	0/1:8	0/0	+/–	H
P_5/2003	15	R (4)	5/26	+/–	1:8500/1:17 300	26	1:4/1:4	0/1:8	0/0	+/–	H
P_6/2003	25	V (4)	5/26	+/–	1:5700/1:11 800	30	1:4/1:8	0/1:8	0/1:4	+/–	H
P_7/2004	17	Unknown	5/26	+/–	1:600/1:1300	32	1:4/1:8	0/1:8	0/1:4	+/–	H
P_8/2004	49	NV	5/26	+/–	neg/1:800	ND/10	0/0	0/1:4	0/0	+/–	H
P_9/2004	20	V (5)	4/26	+/–	neg/1:300	ND/6	0/1:4	0/1:8	0/0	+/–	H
P_{10}/2004	17	Unknown	5/26	+/–	1:500/1:900	32	1:4/1:4	0/1:4	0/0	+/–	H
P_{11}/2004	35	NV	2/25	+/–	neg/1:500	ND/11	0/0	0/1:4	0/0	+/–	H
P_{12}/2004	9	R (2.5)	3/25	+/–	1:1400/1:3000	27	1:4/1:8	0/1:8	0/1:4	+/–	H
P_{13}/2004	28	V (5)	5/26	+/–	1:1400/1:3000	28	1:4/1:8	0/1:8	0/1:4	+/–	H
P_{14}/2004	18	V (5)	5/26	+/–	neg/1:300	ND/4	0/0	0/1:4	0/0	+/–	H
P_{15}/2004	22	V (5)	5/26	+/–	1:300/1:800	29	1:4/1:4	0/1:4	0/0	+/–	H
P_{16}/2004	30	NV	3/24	+/–	neg/1:1000	ND/14	0/1:4	0/1:4	0/1:8	+/–	C
P_{17}/2004	3	V (2)	3/25	+/–	1:1500/1:3000	34	1:8/1:8	0/1:4	0/1:8	+/–	C
P_{18}/2004	56	NV	3/24	+/–	neg/1:500	ND/13	0/1:4	0/0	0/1:8	+/–	C

[a]Vaccination status: V, vaccinated with one dose; R, re-vaccinated (two doses); NV, not vaccinated. Figures in parentheses indicate the time (years) since the most recent vaccination.
[b]Relative to day of fever onset. The first sample was taken upon admission to the hospital and the second was taken following discharge (except P_3/2003).
[c]RT-PCR results are shown for saliva samples.
PRN, plaque reduction neutralisation assay; ND, not detectable; neg, negative.