Increased mumps incidence in the Netherlands: Review on the possible role of vaccine strain and genotype

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As reported in a recent issue of Eurosurveillance, a mumps outbreak is ongoing in the Netherlands despite high vaccination coverage of 90-95% [1]. The reported mumps cases are restricted to geographic regions with a high percentage of residents who are members of a religious community that rejects vaccination. Consequently, two thirds of the mumps patients were not vaccinated. However, also vaccinated individuals in these regions were affected [1]. Since 1987, the measles-mumps-rubella (MMR) combination vaccine produced by the Netherlands Vaccine Institute (NVI) is part of the Dutch national immunisation programme and administered at the ages of 14 months and nine years.

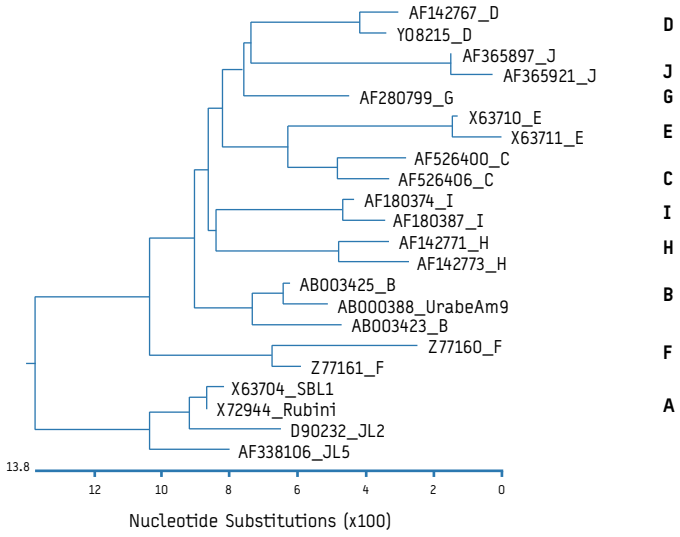
NVI's MMR vaccine contains the Jeryl Lynn mumps strain. The Jeryl Lynn strain consists of two distinct viral isolates (JL-2 and JL-5). Clinical studies have demonstrated 80-100% seroconversion after a single dose of the Jeryl Lynn mumps vaccine [2]. Outbreak-based studies have shown an effectiveness of the Jeryl Lynn mumps vaccine ranging between 63% and 96%, depending on the number of vaccinations given [2-4]. The Jeryl Lynn strain has consistently been shown to be very safe [4,5]. Table 1 shows an overview of available mumps vaccine strains.

The RIT 4385 mumps strain was derived from one of the two distinct virus populations of the Jeryl Lynn strain. Comparative studies of the RIT 4385 and Jeryl Lynn vaccines showed similar seroconversion rates, although the geometric mean titre was significantly higher among recipients of the Jeryl Lynn vaccine [2]. Several vaccines derived from the Urabe AM9 mumps strain were withdrawn from the market due to an excessive number of vaccine-associated aseptic meningitis [6]. The effectiveness of the Urabe vaccine ranges between 54 and 87% [3,5]. Another vaccine strain, Rubini, has shown to be less potent with respect to effectiveness [2,3,5]. For this reason, the WHO recommends that the Rubini strain should not be used in national immunisation programmes [2]. The Leningrad-3 strain was developed in former Soviet Union and its protective efficacy has been estimated to be 91-99% [2,4]. Unfortunately, aseptic meningitis is a particularly common event among recipients of this vaccine strain [4,7]. Furthermore, it has been reported that the Leningrad-3 strain can be transmitted horizontally, causing symptomatic disease [7]. Consequently, Leningrad-3 vaccine has not gained much attention outside former Soviet Union republics. The Leningrad-3 strain was further attenuated in Croatia and was renamed L-Zagreb, which showed equivalent good clinical protection [2]. Unfortunately, an association with aseptic meningitis has also been a matter of concern for the L-Zagreb strain as well as symptomatic transmission of the vaccine virus [4,8,9]. Several other strains have been used for mumps vaccination, but most of them on a limited scale. Therefore, little information is available on their safety and effectiveness. Based on the safety and efficacy data available for the vaccine strains, it can be concluded that the Jeryl Lynn strain has the most favourable benefit-risk profile.

A mismatch between the genotype of the circulating wild-type mumps virus and the vaccine strain may influence the efficacy of the vaccine. At present, the molecular epidemiology of mumps virus is characterised by the co-existence of 13 different genotypes named A–M [10]. Those genotypes are defined on the basis of the most variable part of the mumps virus genome, i.e. the gene encoding the small hydrophobic (SH) protein [10].

Figure

Phylogenetic tree of published sequences of 53 mumps virus strains, based on the nucleotide sequence of the small hydrophobic gene (SH)



Source: Figure obtained from Muhlemann, 2004 [11]

The designated genotypes A–J are indicated on the right.
JL2 and JL5 represent the two subpopulations of the Jeryl Lynn strain (genotype A).
Leningrad-3 and L-Zagreb vaccine strains constitute a distinct group, but no genotype has been ascribed to these strains. These strains are therefore not presented in the figure.

The currently available vaccine strains belong to a few different genotypes (see Table 1). Antigenic differences have been observed between different genotypes which result in incomplete cross-neutralisation [11]. The antigenic differences were largest between genotype A and genotypes B–D and G–I, which correlates well with the relative phylogenetic distance between these genotypes (see Figure 1) [10,11].

At present, there is no clinical evidence that a genotype mismatch leads to vaccine failure or may have epidemiological significance. For example, both the mumps virus in the outbreak in the United States (US) and Canada in 2005-2006 and the virus responsible for the mumps outbreak in the United Kingdom in 2004-2005 belonged to genotype G [4,12,13]. Nevertheless, the MMR vaccine based on genotype A (Jeryl Lynn) appeared to be effective during these outbreaks [12]. The mumps strains responsible for the current mumps outbreak in the Netherlands are of genotype D, and a previous outbreak in an international school in the Netherlands in 2004 [14] was caused by genotype G (R. van Binnendijk, personal communication), whereas the mumps vaccine strain (Jeryl Lynn) belongs to genotype A*. Although cross-protection after vaccination with genotype A might not be as effective after infection with genotype G, no further transmission took place during the outbreak in 2004*. This suggests that vaccine-induced (herd) immunity was

Table 1*

Available mumps vaccine strains

Vaccine strain	Genotype	Manufacturer	Mumps or MMR vaccine	Main distibution area
Jeryl Lynn	A	Merck /Aventis Pasteur MSD	Mumpsvax® (mumps only) M-M-RVaxpro® (Europe) M-M-R II® (US)	United States and Europe
		Netherlands Vaccine Institute (NVI)	BMR vaccin®	Netherlands
		GSK (RIT 4385 strain obtained from Jeryl Lynn)	Priorix®	Worldwide
		Sevapharma Inc. Company	Pavivac (mumps only) Trivivac (MMR)	Czech Republic
Urabe AM9	B	Sanofi Pasteur	Trimovax®	Especially in developing countries, withdrawn in several European countries, United States and Canada
		GSK	Pluserix®	withdrawn by GSK
		Biken (Japan)		Japan
Rubini	A	Swiss Serum Institute		Not recommended by WHO due to low potency
Leningrad-3		Moscow Bacterial Medicine Institute		Russia
L-Zagreb		Institute Immunology Zagreb		Croatia, Slovenia
		Serum Institute India	Tresivac®	India
S79		Dalian Jinjang-Andi Bioproducts (China)		China
Sofia-6		Centre Inf Parasitic Dis (Bulgaria)		Bulgaria (suspended)
Hoshino	B	Kitasato Institute (Japan)		Japan, Korea
Miyahara	B	Chemo-Sero Ther Research Inst (Japan)		Japan
Torii		Takeda Chemicals (Japan)		Japan
NK M-46		Chiba (Japan)		Japan
S-12		Razi State Serum & Vaccine Inst (Iran)		Iran
		Berna Biotech (BBM-18 strain obtained from S-12)		Europe

Source: Netherlands Vaccine Institute (NVI), June 2008

Table 2*

Recent mumps outbreaks with identified responsible wild-type virus (genotype)

Country	Year	Vaccine strain (genotype)	Responsible virus (genotype)	Reference
The Netherlands	2004	Jeryl Lynn (A)	(G*)	[14]
	2007-2008	Jeryl Lynn (A)	(D)	[1]
Canada/United States	2006-2007	Jeryl Lynn (A)	(G5)	[4,12]
United Kingdom	2004-2006	Jeryl Lynn (A)	(G5)	[13]
Russia	2002-2004	Leningrad-3	(C2) (H2)	[15]
Belarus	2001-2003	until 1996: Leningrad-3 since 1996: Urabe (B)	(H1)	[16]

* R. van Binnendijk (personal communication)
Source: Netherlands Vaccine Institute (NVI)

high enough to prevent further circulation of the mumps virus. On the other hand, it is striking that the viruses responsible for reported mumps outbreaks belong to genotypes of that are phylogenetically distinct from the vaccine strains used in the area of the outbreak (see Table 2). Therefore, the possibility that the mumps virus might evolve under selection pressure from the vaccine warrants surveillance of genotype distribution.

Finally, waning vaccine-induced immunity may contribute to a reduced effectiveness of the vaccine. Previously, it was assumed that mumps vaccination induces life-long immunity against mumps. However, increasing evidence shows that vaccinated individuals and possibly also naturally infected individuals, become more susceptible with time after the last exposure to the mumps virus [4,12,13]. Examples are two mumps outbreaks that occurred among vaccinated students in an international school in the Netherlands [14] and on college campuses in the US [12]. Therefore, stronger precautions should be taken to avoid an increase in susceptible adolescents and adults that are more at risk for mumps-related complications such as orchitis and meningitis. Catch-up immunisations should be considered for unvaccinated individuals and susceptible vaccinated people, especially for those living in groups in close contact.

In response to a mumps outbreak, several countries such as Ireland have decided to move the second MMR vaccination forward to the age of four or five years (instead of between nine and 14 years) to decrease the risk of waning immunity between the two vaccinations. However, other outbreaks show that waning immunity may also occur after the second vaccination. Moreover, by decreasing the age of the last MMR vaccination, the susceptibility of women for rubella during their fertile period may increase, which potentially leads to more cases of congenital rubella syndrome.

Conclusion

The first priority should be to avoid clustering of unvaccinated people by making an effort to convince people to get vaccinated. Although a number of mumps cases have occurred in vaccinated individuals, no other mumps vaccine strain is available at present with equivalent or better effectiveness and similar safety profile than the currently used Jeryl Lynn strain. However, the impact of a genotype mismatch between the wild-type virus and the vaccine virus on the mumps vaccine effectiveness as well as the possibility of waning vaccine-induced immunity should be further explored.

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*Authors' correction:

The entry about the Czech republic was moved to the second line in Table 1 and corrected as follows:

- Vaccine strain: The incorrect vaccine name "Pavivivac" was removed from this field and replaced by the strain name "Jeryl Lynn";
- Genotype: Type "A" was added to this field;
- Manufacturer: The entry was corrected to read "Sevapharma Inc. Company"
- Mumps or MMR vaccine: "Pavivac (mumps only)" and "Trivivac (MMR)" was added to this field.

The genotype responsible for the mumps outbreak in 2004 was not of genotype D, but of genotype G. This was corrected in Table 2 and in the text. Previously, the two relevant sentences read: "The mumps strains responsible for the current mumps outbreak in the Netherlands and a previous outbreak in an international school in the Netherlands in 2004 [14] were both of genotype D, whereas the mumps vaccine strain (Jeryl Lynn) belongs to genotype A. Although cross-protection after vaccination with genotype A might not be as effective after infection with genotype D, no further transmission took place during the outbreak in 2004."

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