

EDITORIAL

Mumps vaccines—current status

All mumps vaccines in use today contain live, attenuated virus. As is the case with most other live viral vaccines, the process of attenuation from a wild-type mumps isolate to a “safe” vaccine strain has been empirical; the virus underwent serial passage in various cell lines at non-optimum growth temperatures. The candidate vaccine virus was then tested for safety, reactogenicity and efficacy in animals and human volunteers. There are numerous vaccine strains favoured by different manufacturers but the basic attenuation procedure is the same. The molecular basis for the attenuation is unknown in every case. In fact, the study of the mumps virus at the molecular level is in its infancy, particularly when compared with viruses such as polio and influenza.

Mumps is a member of the *Paramyxovirus* genus and is an enveloped virus containing a non-segmented, single stranded RNA genome of the negative sense. The nature and size of the genome were determined in the early 1970s but detailed sequence data were not available until the mid-1980s. The surface glycoproteins responsible for the fusion (F) and haemagglutination-neuraminidase (HN) activities of the virus are important antigenic determinants and the genes encoding these proteins were the first to be investigated.^{1,2} The sequence of other mumps genes has been elucidated more recently. Much of this work was done on laboratory strains of virus and it was only after the occurrence of vaccine-associated adverse reactions in the 1990s that interest focused on vaccine strains.

In the UK, monovalent mumps vaccine has been available for many years but was not used extensively. In 1988, the national vaccine strategy was changed and a tri-valent measles, mumps and rubella (MMR) vaccine was introduced into the childhood vaccination programme. Three manufacturers have supplied MMR vaccines to the UK market; two produce vaccines containing the Urabe mumps strain and one manufactures vaccine containing the Jeryl Lynn mumps virus. MMR vaccine is aimed at all children aged between 12 and 15 months but may be given at any age. Uptake was good and the incidence of measles, mumps and rubella infections in the UK has declined. However, problems have arisen due to the occurrence of meningitis associated with vaccines containing the Urabe mumps strain. Sporadic cases began to be reported in the UK in 1989, and in some patients there was virological evidence of the involvement of a mumps virus since this virus was isolated from the cerebrospinal fluid.³ At the time there was no

method for differentiating a mumps vaccine virus from a wild strain which could have been infecting the vaccinee co-incidentally. Conventional serology cannot distinguish between mumps strains, and the monoclonal antibodies available were unable to differentiate between vaccine and wild virus. Efforts are now being concentrated on the use of sequence analysis for virus characterisation. Several groups have performed such studies and, although details may vary, the basic principle is that a small region of the genome is amplified by PCR then sequenced, either directly or after cloning. Suitable regions of the genome must be chosen which show variability between strains. The first gene to be used was that of the F protein.⁴ Examination of a small region of *c.* 100 nucleotides provided sufficient information to distinguish between different vaccine strains, between vaccine and wild strains and between wild strains from different geographical areas. Subsequently, genes encoding the phosphoprotein⁵, the HN⁶ and the hyper-variable but putative small-hydrophobic protein⁷ have been used successfully.

In all cases of post-vaccination meningitis where an isolate from the CSF was characterised as being a vaccine strain, this strain was identified as Urabe. The problem with the Urabe strain has been seen in a number of countries including Canada, where the first cases were reported and Japan, where the strain originated. The rate of post-vaccination meningitis varies from study to study and probably depends on the intensity of efforts to find such cases. A rate of one case per several thousand vaccinations can be expected. This is less than the rate of meningitis associated with wild mumps infection and all vaccine-associated cases have been mild with no sequelae. However, children were hospitalised and lumbar punctures performed. The outcome has been that vaccines containing the Urabe strain are no longer used in many mass vaccination campaigns.

The MMR vaccine containing the Jeryl Lynn strain of mumps has been used in the USA for many years and is now the sole source of mumps vaccine in numerous countries including the UK. Despite its widespread use, there has been no case of post-vaccine meningitis from which the Jeryl Lynn strain has been isolated. Other strains of mumps vaccine such as Rubini, Leningrad-3 and Leningrad-Zagreb have been developed but either the number of doses used is relatively small or the follow-up of vaccinees is poor and an accurate estimate of adverse reactions has not been made.

The propensity to cause meningitis appears to be associated with the Urabe strain itself rather than any production factors. Cases were associated with vaccine from both manufacturers, even though one vaccine is produced in chick embryo fibroblast cells and the other in egg amnion. Cases were also associated with many different production batches. The molecular basis of why one strain should be more reactogenic than another is still unknown and more work is needed in this area. Sequencing studies have given information on the geographical and temporal distribution of mumps strains;⁸ additionally it has been

shown that the Jeryl Lynn vaccine is composed of two distinct virus populations.⁹ The clinical significance of this finding is also unknown but the ratio of these virus populations appears remarkably constant throughout production batches of Jeryl Lynn. If nothing else, this demonstrates the consistency of production by this manufacturer. Such molecular studies may become increasingly relevant to the quality control of this type of product in the future.

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