The antigenic diversity of foot and mouth disease FMD viruses is well known and frequently prompts questions on the selection and potential efficacy of inactivated vaccines. A common benchmark to assess the probable efficacy of a given vaccine strain in relation to a field isolate is the range of definitions published by the World Reference Laboratory for FMD (Ferris and Donaldson, 1992) and based on the $r_1$ value derived from the neutralisation of the field virus by sera raised against the vaccine strain. The definitions are as follows:

$r_1 = 0$ to 0.19. These values represent a highly significant serological variation from the reference vaccine strain. Where possible, it would be advisable to use a vaccine strain with a closer relationship to the field virus. However, in an emergency, a potent vaccine of the type used as a reference in the test may provide adequate protection, especially if administered on more than one occasion.

$r_1 = 0.2$ to 0.39. These values represent an area of concern. They show significant differences from the reference strain, but protection may be satisfactory if a sufficiently potent vaccine is employed.

$r_1 = 0.4$ to 1.00. These values are not significantly different from the reference vaccine strain as measured by the particular test system used.

Thus a low $r_1$ value gives cause for concern and will often stimulate the development of a new vaccine strain. Against this background, a critical question is the extent to which significant antigenic variant viruses emerge and the cover or otherwise which could be expected from current vaccine strains.

There are two reasons to develop a new vaccine strain. Firstly, there is the recognition by experts, including the vaccine producers and the reference laboratories, that a significantly different virus has appeared in a region and may/will warrant the development of a new vaccine strain. This recognition is invariably based on a serological assay such as the virus neutralisation test but may be supported by sequence analysis of the VP1 protein. One such example was the emergence of a new A strain in Iran in 1996. Merial responded by developing a new vaccine strain, referred to as A Iran 96, which is now widely used in the Middle East as well as being the choice of some antigen banks. The second reason is concerned with those countries where regular vaccination programmes are employed and the epidemiological situations are relatively stable. Such situations support the obvious concept of preparing a vaccine strain from a local field isolate so that the field viruses and vaccine strains are matched as closely as possible. In this paper, the focus will be on the emerging strains and the threat they represent to world animal health.

Contrary to some ‘opinions’ on the fringes of foot and mouth disease vaccine research and development, antigenic variation does not represent an insurmountable problem in terms of the ability of the manufacturers to keep pace with the commonly observed level of variation in the field. Additionally, evasion of vaccine-induced protective immunity by selection of escape mutants does not appear to be a common phenomenon. There is both a large amount of anecdotal as well as experimental evidence to support these statements including the highly successful vaccination programmes employed in southern South America and Western Europe, prior to these regions deciding to stop vaccination to facilitate, inter alia, exports of animals and animal products. Nevertheless, these general statements require expansion with particular respect to the properties of the different serotypes of the virus.

The O serotype is the most widespread and certainly shows moderate levels of strain variation in the field with, occasionally, more extreme variants. Nevertheless, there are two main lineages of vaccine strains represented by the old (in excess of 30 years since their development) O strains of Europe and South America (OBFS 1860, O Lausanne and O Campos) and the equally old strains of the Middle East and Asia (represented by strains such as O Manisa and O-3039). In the case of the latter group of viruses, there are other valuable strains of O serotype in use. However, established virus strains such as O Manisa provide good cover for many first occurrence situations. Indeed, we found an exceptionally good $r_1$ match between the UK 2001 outbreak strains and our Manisa vaccine strain within two days of the first report of the disease.

The A serotype is quite different, exhibiting a broad range of antigenic variants including the A24 strains typified by the Cruzeiro 1955 isolate which is widely used in South America, the A22 viruses, typically A22 Iraq 24/64 which is quite widely used in the Near and Far East, and the more recent A
variants emerging in the Middle East (A Iran 94, 96, 99 and 2001) and Asia (A Malaysia 97). With the A serotype, it is certainly advisable to use vaccine strains appropriate for the local field isolates. However, a more careful examination of the A serotype distribution worldwide does appear to indicate some stability of the situation in South East Asia and South America whereas the Middle East appears at first sight to represent a ‘hot-spot’ where, until recently, significant variants have emerged reasonably frequently. It is tempting to speculate that this apparent frequency may be due to increased sampling within the region as a result of the very positive actions of veterinary authorities, notably those of Iran. With the A serotype, it very much remains a position of continued vigilance.

The antigenic diversity of both the C and Asia1 serotypes is considerably less. In the case of the C serotype, it was common practice to use only one of several C strains during the period that this serotype was more prevalent and, nowadays, reports of the virus are very infrequent. In the case of the recent isolation of a C virus in Northern Brasil, there seems no basis to assume that the conventional C South America vaccine strains will not adequately cover the situation. While more prevalent, Asia1 field strains are very well covered by a single strain such as Asia1, Shamir. This is consistent with the report of Samuel and Knowles (2001) which pointed to the constraints that appear to be operating with the Asia1 serotype where all viruses described since 1954, the date that the serotype was first described, are members of a single topotype.

In the case of the SAT viruses, the sequence data alone points to significant variation within each of the three serotypes (Vosloo, 1992) which would give very great cause for concern if any field strains substantially escaped from Africa and established in the Middle East or further afield. In recent years, only SAT2, the most prevalent of the three serotypes, has threatened to do this with excursions into Saudi Arabia and North Africa. To date, it seems that an appropriate vaccine, SAT2 Eritrea, along with other control measures, have kept these field viruses in check. Nevertheless, there is a critical need to continue to monitor the SAT serotypes and determine more precisely the efficacy of existing SAT vaccine strains in relation to their ability to protect against significantly different field isolates.

In this article, it has been stated that antigenic variation does not represent an insurmountable problem in relation to protection by vaccination. An important prerequisite in this respect is the need to monitor comprehensively the antigenic characteristics and worldwide distribution of field viruses so that vaccines can be selected or developed within an acceptable time frame. Despite this approach, new antigenic variants occasionally emerge with little warning and there is no option but to use an existing vaccine strain while a more appropriate vaccine strain is developed. While this is a relatively infrequent event, evidence exists which demonstrates that protection can be achieved using a high potency vaccine where the level of homology between the vaccine and field/challenge viruses is low. One of the most recent anecdotal examples was the situation during the 1996 outbreak in the Balkans when A22 Iraq vaccine was used, apparently successfully, against a field isolate which was substantially different from the vaccine. Experimental reports have primarily focussed on the O and A serotypes using one or two way challenge studies in cattle. Barteling et al (1997) demonstrated that O Manisa vaccine made from European Bank antigens gave 6.7 PD50 against challenge with a significantly different O virus, O Greece 1994. It must be added that the O Manisa vaccine gave approximately 20 PD50 when tested by homologous challenge. Protection between distantly related O strains has also been demonstrated with O Lausanne vaccine followed by O Lausanne or O Manisa challenge (96% for homologous protection against 64% for the heterologous protection. Lombard et al, 1979). Given the recognised antigenic variability of the A serotype, it is perhaps more surprising to observe cross-protection with A virus vaccines. Using A22 Iraq vaccine and A Saudi 23/86 challenge virus, Schermbrucker demonstrated greater than 85% protection with two consecutive doses of vaccine, 85% representing the level of protection equivalent to 3 PD50 (cited by Doel, 2003). Heterologous protection has also been demonstrated with other A serotype viruses. In the case of A Iran 96 vaccinated cattle challenged with A Iran 99, Bruckner and Griot (2002) showed good levels of protection after a double dose, single dose or 1/3 dose of vaccine. Similar results were reported by Favre et al (1981) who demonstrated 99.5% homologous and 40% heterologous protection using A5 Allier vaccination and A5 Allier or A24 Argentina challenge. A similar result was seen when A24 vaccinated cattle were challenged with A24 Argentina (94% protection) or A5 Allier (79% protection). Clearly, it would be valuable to extend these early studies to some of the more recent field isolates and vaccine strains with particular reference to the SAT viruses and the use of high potency vaccines typically found with antigen banks.

Finally, it is important to recognise that vaccine strain development, when it is required, may not be a simple matter. Table 1 lists some of the issues to be considered in developing a new vaccine strain. One particular issue is the availability of field isolates and it is, regrettably, a frequent problem that only a few viable samples are obtained from a new outbreak of the disease. In this sense, perhaps the greatest vulnerability in terms of ability to respond rapidly and effectively to an emerging disease situation in a region (and, therefore, its potential spread beyond the borders of the region) is our
ignorance of the viruses circulating in the field. The frequent and timely submission of field samples to the reference laboratories and the corresponding availability to the vaccine producers is, without doubt, one of the most important weapons in the control of the disease by vaccination.

References


Table 1. Some of the Issues and Problems with Development of New FMD Vaccine Strains

1. Lengthy time scale, logistics and high cost with particular respect to full regulatory testing and licensing.

2. Failure to adapt to suspension culture. Some isolates only grow in monolayers.

3. Failure to grow to commercially viable yields.

4. Screening hampered by insufficient quality, quantity, numbers of field isolates.

5. Rare properties such as 146S sensitivity to inactivant (eg. Sat 2 Kenya 227/66) and propensity to aggregate which compromise process recoveries.

6. Slow growth at scale-up thus reducing the annual production capacity.

7. Disqualification of an isolate because of a high risk of rejection by regulatory authorities. (e.g. use of a bovine isolate from a country recognised as 'high risk' in terms of BSE).