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Virus Research 91 (2003) 145–161
Virus Research
www.elsevier.com/locate/virusres

Review

Foot and mouth disease in wildlife

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Keywords: Species; Transmission; Control; Viral relationships; Lesions; Fences; International trade

1. Introduction

Occasionally foot and mouth disease (FMD) can be destructive of wildlife, as apparently occurred in South Africa in the late 19th century where large numbers of impala *Aepyceros melampus* succumbed, and more recently in Israel where high mortality occurred in mountain gazelles *Gazella gazella* (Macaulay, 1963; Shimshony, 1988). More usually, as is often the situation with domestic livestock in extensive production systems, infection of wildlife with FMD results in a relatively mild disease from which affected animals recover in a week or two. The significance of the disease for wildlife lies largely in the potential that cloven-hoofed wild animals have for transmitting the disease to domestic livestock where, especially in intensive farming situations, the disease may be severely debilitating and result in serious economic losses for farmers. Perhaps more significant is the effect the presence of the disease (more precisely, the infection) has on international trade in livestock and livestock products. Therefore, the indirect effects of the infection often far outweigh the direct effects that it has on animals themselves, be they wild or domestic. Some wild ruminants also have the potential to become carriers of the infection i.e. the virus may persist in the absence of any obvious sign of disease. These animals, albeit extremely rarely, transmit the infection to cohorts of the same or other species with which they are in close contact.

Until the end of the 19th century FMD was widespread throughout the world, but from the early 20th century the disease was progressively eradicated from the developed world because of its severe economic impact on intensive livestock production. Presently, North America, most of Europe, Australia and New Zealand among the major livestock rearing areas of the world are free of FMD. It persists currently in South America, most African countries, the Middle East, and many parts of south, central and south-east Asia. Major re-incursions of the disease have occurred recently in south-east Asia (Taiwan, Japan, South Korea and Indonesia), South America (Argentina, Uruguay and Brazil) and western Europe (UK, The Netherlands, France and Ireland). In some cases this has involved the transcontinental spread of the so-called pan-Asian topotype O virus from Asia. This occurred in September 2000 in South Africa (Sangare et al., 2001) and in February 2001 in the UK (Samuel and Knowles, 2001). Wildlife, however, has not been responsible for any of these re-incursions and, as far as is known, none became infected by either direct or indirect contact with domestic livestock during these incidents. On the other hand, fear of spread of the infection into collections of rare and valuable species, including zoological collections, has resulted in much conjecture as to how to protect these animals in the event of an epizootic. Furthermore, what the consequences would be in the event that measures taken to prevent infection prove ineffective is currently a subject of considerable debate. There has been a strong lobby to vaccinate such animals to protect them from infection but how effective that would be is a matter of opinion. Such action could interfere with the trading status of the country concerned. For countries that are members of the *Office International des Epizooties* (OIE), the international animal health organisation that sets international trading norms with respect to animals and animal products, to achieve the most favourable trading status (freedom from FMD without vaccination), no animals vaccinated against FMD within the last 12 months should be present on the territory of the country concerned. No distinction is made between wildlife and domestic live-

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0168-1702/02/$ - see front matter
PII: S0168-1702(02)00263-0

stock. Requirements relating to vaccination on the part of the OIE are, however, under review.

A general observation has been that wherever in the world FMD has been eradicated from livestock, it has also generally disappeared from wildlife in those regions. An exception exists in parts of sub-Saharan Africa where African buffaloes *Syncerus caffer* serve as maintenance hosts for the South African Territories (SAT) types of foot and mouth disease virus (FMDV) (Condy et al., 1985). It is clear that these viruses are able to survive independently of livestock although SAT viruses affect cattle commonly in many parts of sub-Saharan Africa (Thomson, 1996). There is, conversely, so far no evidence of infection of African buffaloes with the other three virus types (A, O and C) prevalent in Africa, although it must be admitted that this aspect has been insufficiently investigated. The maintenance of FMDVs by wildlife in sub-Saharan Africa makes the eradication of these viruses from large parts of the African continent impossible for the foreseeable future without the destruction of large numbers of African buffaloes which is both ecologically and morally untenable.

Countries in which FMD does not occur restrict imports of livestock and their products, and also of susceptible wildlife, from countries where the disease is prevalent. Hence, it is a challenge for African nations to maintain their rich wildlife heritage without compromising development of livestock industries especially in the arid regions of the continent where the potential for crop production is limited or even non-existent. The presence of FMD is a major constraint to the commercialisation of livestock production—because FMD generally has its greatest effect where intensive livestock production is practised, which is often a requirement for commercialisation. More especially, the presence of FMDVs limits access of the continent's livestock and livestock products to international markets. However, there are other diseases that contribute to this situation. FMD also limits the viability of attempts at integrating livestock production with wildlife conservation. In southern Africa, where commercialisation of livestock production is more developed than elsewhere on the African continent, minimising the effect of FMD in order to enable international trade in beef and other products has been largely achieved by segregation of wildlife and livestock using fencing. However, fences have significant environmental, social and economic costs and it is sometimes argued that the costs outweigh the benefits (Scott Wilson Resource Consultants, 2000).

2. Epidemiology

Essentially all cloven-hoofed animals and Camelidae (i.e. members of the order *Artiodactyla*) are susceptible to infection with FMD viruses but the facility with which different species and even breeds of animals develop clinical disease varies. This variation extends to susceptibility to infection (i.e. the amount of infectious virus required to establish infection) and the routes and rates of viral excretion by different species once they are infected (Thomson, 1994). This variation is largely quantified in the case of domestic animals but for most species of wildlife their relative susceptibility is unknown. Furthermore, it should be appreciated that in this respect different strains of FMD viruses may interact differently with different species of animals. Among wildlife species, only African buffaloes have been shown to serve as long-term maintenance hosts and then only for the SAT types of the virus (Hedger et al., 1973; Hedger, 1976; Condy et al., 1985).

Hedger (1981) tabulated wildlife species that have been recorded with clinical FMD as a result of natural or experimental infection, not always confirmed by virus isolation. These include 22 members of the Bovidae, 10 Cervidae, 4 Suidae, one species of Tayasuidae, and 4 Camelidae among the Artiodactyla. Among the Insectivora there were two species of Erinaceidae and one among the Talpidae. Other species recorded were one species of Dasypodidae among the Xenarthra (Edentata); a member of the Leporidae among the Lagomorpha; two Sciuridae, one Bathyergidae (Rhizomyidae), 4 species of Muridae, one Hystricidae, one Hydrochaeridae, one Capromyidae, one Dasyproctidae, and one Chinchillidae among the Rodentia. There were also two species of Elephantidae in the Probiscidea; one species of Procaviidae in the Hyracoidea; one species of Ursidae among the Carnivora and various marsupials and monotremes. Since that time, FMD has been reported in nyala antelope *Tragelaphus angasi* (Bengis, 1983) and the mountain gazelle *Gazella gazella* (Shimshony et al., 1986) among the Bovidae, and giraffe *Giraffa camelopardalis* (Bengis, 1984) in the Giraffidae. Recently, Schaftenaar (2002) has reviewed the published occurrence of FMD in zoological collections between 1931 and 1990. This list, derived from events in Europe, Israel and India, emphasises the diversity of species susceptible to infection with only three of the 7 serotypes (A, O and C).

With a few exceptions, excretion and transmission of FMD by wildlife has not been studied in any detail. For that reason much of what is currently accepted in that regard has been extrapolated from what is known to occur in domestic species. Generally, high levels of FMD virus occur in oro-nasal secretions for 1–3 days prior to, and for 7–14 days after the development of lesions (Sellers, 1971; Donaldson, 1983; Thomson, 1994). Urine and faeces were reported to contain little virus (Hyslop, 1970) but more recent studies have contradicted that finding (Kitching, 1992). FMD is occasionally spread mechanically by contaminated ani-

mal products (e.g. milk and meat) or by fomites, vehicles and people contaminated with the virus. Rarely, FMD has been transmitted over long distances by air-borne aerosols (Gloster et al., 1982; Donaldson, 1983) but this has usually required high concentrations of infected domestic pigs to generate a plume of virus-containing aerosols derived from expired air. There is no reason to believe that wildlife, including warthogs *Phacochoerus africanus* (R.G. Bengis, M.D. Gainaru and G.R. Thomson, unpublished data), are capable of generating significant levels of aerosolised virus.

Roe deer *Capreolus capreolus*, fallow deer *Dama dama*, sika deer *Cervus nippon*, red deer *Cervus elaphus* and muntjac *Muntiacus muntjac* excreted FMD virus following experimental infection in approximately the same quantities as sheep and cattle (Gibbs et al., 1975). It has furthermore been shown that infection between deer and domestic livestock may occur in either direction, viz. deer infecting livestock or vice versa (Sutmoller, 2001). However, at the time the studies by Gibbs et al. (1975) were conducted, deer were considered unlikely to be important in the maintenance and spread of the infection in the UK should an outbreak occur, because they were rarely in close contact with livestock. This may be different today with numbers of deer being held to have increased significantly although, as already indicated, there is no reliable evidence that deer became infected during the recent widespread epizootic in the UK (A.I. Donaldson, personal communication, 2001). Routes of virus excretion by African buffaloes also resembled those of cattle but excretion persisted for up to 28 days. Aerosol excretion of low levels of virus was sometimes detected (Gainaru et al., 1986).

There are no reports of the dose of FMD virus required to infect wildlife. In cattle and sheep the minimal infectious dose by the respiratory route is 25 and 10 cell culture infective doses, respectively (Gibson and Donaldson, 1986; Donaldson et al., 1987), while the dose required for oral infection is about 10 000 times higher (Burrows et al., 1981; Sellers, 1971). However, aerosols containing as little as one cell culture infective dose established infection in impala (R.G. Bengis and G.R. Thomson, unpublished data). This sensitivity to infection may contribute to the epidemics of FMD in impala in the Kruger National Park (KNP) of South Africa described below and explain why this species alone suffers regular epidemics of disease.

Transmission of FMD by carrier animals has been debated for years. FMD carriers are defined as animals in which the virus persists, often at barely detectable levels, in the pharynx for 4 weeks or longer (Salt, 1993, 1998). By 4 weeks, recoverable virus has disappeared from all other secretions, excretions and tissues of animals that have passed through the acute stage of the infection. However, there is a report describing the detection of viral RNA by reverse transcriptase polymerase chain reaction in a range of tissues from cattle for up to 2 years after recovery from experimental infection (Bergmann et al., 1996). The significance of this finding is difficult to interpret because it is unexpected and has not been corroborated. Carrier status appears to occur only in ruminants (Terpstra, 1972). Although many susceptible ruminants may presumably become persistently infected (i.e. carriers) only African buffaloes have so far been shown conclusively to transmit FMD while in that state (Dawe et al., 1994a,b; Vosloo et al., 1996).

Fallow and sika deer regularly developed persistent infection following experimental exposure, while red deer did so occasionally; roe and muntjac deer, on the other hand, did not (Forman et al., 1974; Gibbs et al., 1975). Persistent infection developed in experimentally infected kudu *Tragelaphus strepsiceros* (Hedger, 1972). Excretion of FMDV for a little over 4 weeks has also been shown in wildebeest *Connochaetes taurinus* (Anderson et al., 1975) and sable antelope *Hippotragus niger* (Ferris et al., 1989).

In all parts of the world with the exception of sub-Saharan Africa, FMD in free-ranging or captive wildlife appears to have been an extension of the disease in livestock. This has been documented for free-ranging moose *Alces alces* (Magnusson, 1939), as well as in fallow (Bartels and Claasen, 1936), roe and red deer in Europe (Cohrs and Weber-Springe, 1939). In the former Soviet Union, FMD was described in free-ranging reindeer *Rangifer tarandus* (Kvitkin, 1959Ogryzkov, 1963) and saiga *Saiga tatarica* (Khukorov et al., 1974), while in India severe clinical signs and mortality were reported in blackbuck *Antilope cervicapra* (Kar et al., 1983). High morbidity and mortality also occurred in free-ranging mountain gazelles in Israel (Shimshony et al., 1986). All these episodes in wildlife occurred during epidemics in cattle. Similarly, outbreaks of FMD in zoological gardens in Paris (Urbain et al., 1938), Zurich (Allenspach, 1950) and Buenos Aires (Grosso, 1957), coincided with outbreaks of FMD in domestic animals. Even in sub-Saharan Africa, where wildlife are clearly involved in the maintenance of FMD, livestock sometimes transmit the infection to wildlife rather than vice versa (Hedger, 1976; Thomson et al., 1984; Anderson et al., 1993).

The only locality in which overt FMD has been reported regularly in wildlife over the last 60 years is the KNP in South Africa, where there have been 31 recorded outbreaks in impala since 1938, and 23 since routine surveillance was introduced in the mid 1960s. Eight (26%) were caused by SAT1, 15 (48%) by SAT2, three (10%) by SAT3, and five (16%) were untyped. However, since 1983, nine of the 10 outbreaks in impala were caused by SAT2. Sequence analysis of the SAT2 viruses involved has shown that these outbreaks were causally distinct (Vosloo et al., 1992; Bastos et al., 2000).

FMD in impala appears to occur generally in localities where high densities of this species occur. Also because impala depend on water, infection frequently has spread along water courses in the KNP, i.e. it is assumed that the virus is not transmitted through the water itself but by contact between animals congregated along rivers and streams. With few exceptions, obvious clinical disease has not occurred in other species in the vicinity of outbreaks in impala (Bengis, 1983; Keet et al., 1996). Direct contact between impala inside the KNP and domestic animals outside the park is largely prevented by a perimeter fence, and cattle immediately outside the fence are vaccinated every 6 months. Perimeter fencing and vaccination of cattle close to the perimeter are presumed to have prevented many FMD outbreaks in cattle raised close to the KNP (see below).

There is some uncertainty about the dimensions of fences required to prevent the spread of FMD in southern Africa, particularly in view of the potential for air-borne spread of FMD virus. In south-eastern Zimbabwe, double fence lines with a defoliated zone about 10 metres wide between the two lines were used to form the perimeters of commercial wildlife conservancies. The idea is that direct transmission across the fence lines would be precluded by prevention of direct contact between animals on either side of the fence. In the initial design, one of the fence lines was at least 1.8 m in height to prevent antelope from jumping over the fence (Thomson, 1999; Hargreaves et al., in press). An analysis of the risks posed by such a system to the livestock industry of Zimbabwe was conducted soon after the establishment of three such conservancies (Sutmoller et al., 2000). This showed that there was a risk that, despite the double fence line and the height of the fence, impala and kudu antelope would be able to get out of the conservancies in significant numbers by jumping the perimeter fences. Conversely, the risk of air-borne spread across the perimeter fences was found to be insignificant. A few months after the risk analysis was completed an outbreak of FMD caused by a SAT2 virus occurred in cattle immediately adjacent to one of the conservancies. Subsequent investigation, which included genome sequencing of viruses involved in the outbreak, showed that the virus that caused the outbreak had been introduced into the conservancy 2 years previously by African buffaloes translocated from the Hwange National Park in western Zimbabwe (Hargreaves et al., in press). There was strong circumstantial evidence that the herd of buffalo introduced from Hwange had infected antelope (impala and kudu) in their vicinity and that the antelope had subsequently transmitted the infection to cattle outside the conservancy (Hargreaves et al., in press).

Although African buffaloes in the KNP in South Africa have been shown to be the usual source of infection for impala on the basis of sequencing studies (Bastos, et al., 2000; Bastos, 2001), persistent infection in impala has not been demonstrated (Anderson et al., 1975; C. de W. van Vuuren, personal communication, 1997). However, FMD epidemics caused by identical viruses have recurred in impala 6–18 months after the original outbreak (Vosloo et al., 1992; Keet et al., 1996) indicating that the virus may have been maintained within the impala population. Were that so, the mechanism whereby the viruses survived in interepidemic periods remains to be explained. The alternative explanation is that the same virus has been transmitted on more than one occasion from buffalo to impala in the same vicinity.

Infection and attack rates have varied in outbreaks of FMD in impala that have been studied, with the latter sometimes much lower than the former, indicating that subclinical infection is common, as has been seen in impala experimentally (R.G. Bengis and G.R. Thomson, unpublished data).

Paradoxically, clinical FMD has not been diagnosed in impala other than in the KNP (this species is widely prevalent in sub-Saharan Africa), although there is serological evidence of infection in other parts of the subcontinent (Anderson et al., 1993). It is assumed that the reason for this is that in the KNP, unlike most other parts of sub-Saharan Africa where impala occur, active surveillance for clinical FMD is conducted routinely.

African buffaloes were recognised as major reservoirs of SAT type viruses in the 1970s (Hedger et al., 1972) although it seems that these animals rarely develop clinical FMD in natural circumstances. In this respect SAT type viruses affect buffaloes and impala in the KNP differently. Persistence of the viruses in some individual buffaloes for at least 5 years probably explains why FMD virus persisted for over 20 years in a small isolated group of buffaloes (Condy et al., 1985). However, persistence of infection in individual buffaloes is probably not life-long (Hedger, 1976).

Infection of individual animals within breeding herds of buffalo usually occurs when maternal immunity starts to wane at 2–4 months of age (Condy and Hedger, 1978). Calves are not necessarily infected by their dams (Condy and Hedger, 1974), and it is presumed that SAT viruses spread mainly during minor epidemics among young animals in breeding herds, with carriers ensuring that the viruses survive interepidemic periods (Thomson et al., 1992). Since most buffaloes in southern Africa are born in mid summer, they become susceptible to infection more-or-less synchronously during the dry winter months when passively acquired antibody wanes. Other susceptible species, principally impala, probably become exposed while infection is circulating among buffalo calves, possibly around permanent water points, where animals congregate. It is assumed, therefore, that there is a time during each year when breeding herds of

buffalo are a potent source of infection for other species of animals that come into contact with them, even though there is no obvious clinical disease within such herds.

Transmission of SAT type viruses between individual buffaloes appears to occur by two processes: (1) contact transmission between acutely infected and susceptible individuals which is likely to account for most infections and (2) occasional transmission between carrier buffalo and susceptible individuals. However, the mechanism whereby carrier transmission occurs between buffaloes is obscure. A possibility, for which the evidence is still tenuous, is sexual transmission (Bastos et al., 1999). In a study conducted in the KNP samples were collected from the uro-genital tracts of 20 buffalo bulls. SAT3 virus was recovered from the semen and sheath-wash of a 3.5-year-old animal with measurable circulating antibody to all three SAT type viruses. This suggests that carrier bulls may shed SAT viruses in their semen. Buffalo bulls in the field have been observed by farmers to mount domestic cows on occasion (S. Hargreaves, personal communication) and it is possible that sexual activity may be a way in which SAT-type viruses are transmitted from African buffaloes to cattle.

It appears that the rate at which the three SAT viruses circulate within buffalo populations in the KNP differs. SAT1 viruses were consistently recovered at a higher rate than the other two SAT viruses over a 10-year period from probang specimens collected from buffaloes (Table 1). Studies into circulating antibody levels in the same population showed that antibody to SAT1 rose consistently sooner in young animals than for the other two types (Thomson et al., 1992; Thomson, 1994). This indicates that SAT1 viruses in the KNP circulate more rapidly than SAT2 and 3.

Genome sequencing studies conducted over the last 10 years in southern Africa have shown that buffalo populations in different geographic locations maintain distinct lineages of SAT-type viruses, i.e. so-called topotypes. For SAT2 and SAT3, four topotypes have so far been identified within each type while for SAT1 only three were distinguishable (Vosloo et al., 1995; Bastos, 1998; Bastos et al., 2001; Bastos and Sangare, 2001). Figs. 1 and 2, as an example, show the geographic distribution of the three SAT1 topotypes in southern Africa. Topotype I comprises viruses from north-eastern South Africa, southern Zimbabwe and Mozambique; Topotype II is represented by viruses from northern Zimbabwe, Malawi and Zambia; whilst Topotype III contains viruses originating from western Zimbabwe, Namibia and Botswana. The geographic distribution of the SAT2 and 3 topotypes are similar (Bastos, 2001). This demonstrates clearly that SAT topotypes are in a process of evolving independently in buffalo in different wildlife locations. The natural geographic distributions of intratypic variants within each SAT type are therefore now clearly recognised in southern Africa. Similar work

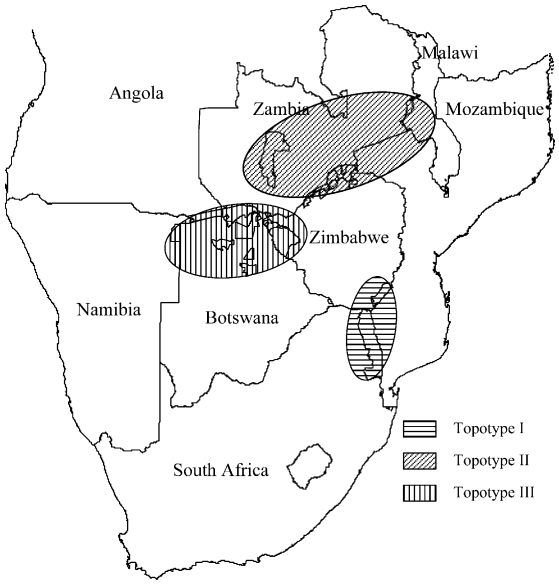

Fig. 1. Map of southern Africa depicting the geographical distribution of SAT1 FMD buffalo virus topotypes.

Table 1
Summary of FMD viruses recovered from probang samples of buffaloes in the KNP (1986–1996)

Year	No. of SAT1 isolates (%)	No. of SAT2 isolates (%)	No. of SAT3 isolates (%)	Total for year
1986	4 (40)	3 (30)	3 (30)	10
1987	3 (100)	Nil	Nil	3
1988	6 (46)	5 (38)	2 (15)	13
1989	24 (73)	8 (24)	1 (3)	33
1990	3 (43)	2 (28)	2 (28)	7
1991	35 (61)	14 (24)	8 (14)	57
1992	8 (89)	1 (11)	Nil	9
1993	5 (62)	2 (25)	1 (12)	8
1994	3 (43)	Nil	4 (57)	7
1995	4 (67)	2 (33)	Nil	6
1996	4 (27)	1 (7)	10 (67)	15
1986–1996	99 (59)	38 (23)	31 (18)	168

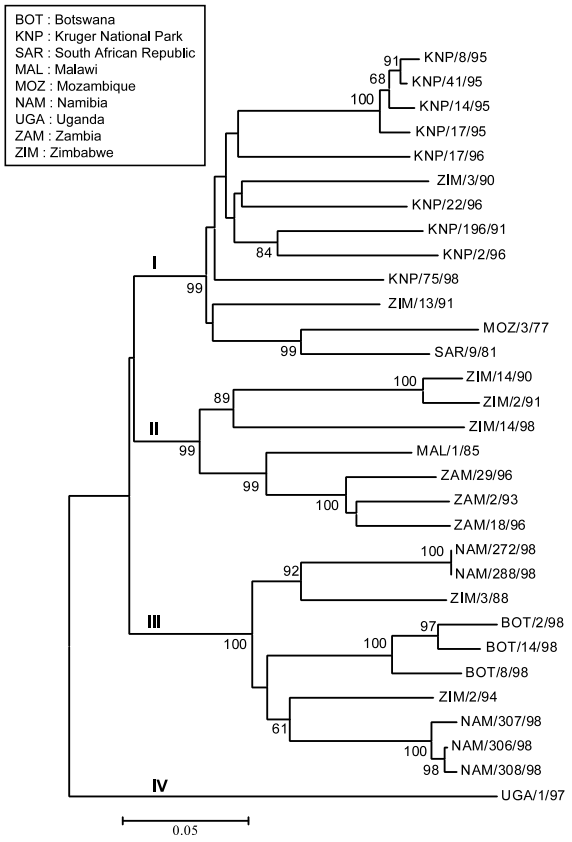

Fig. 2. Neighbor-joining tree depicting VP1 gene relationships of SAT1 type foot-and-mouth disease viruses in southern Africa. The three southern African buffalo virus topotypes (I–III) are indicated, with topotype IV representing an East African lineage.

in other regions of Africa is needed. At the applied level this has enabled the source of outbreaks of FMD in cattle in southern Africa to be traced to their origin in individual buffalo populations (Vosloo et al., 2002a,b) and has been used to trace the origin of captive buffalo moved illegally (Vosloo et al., 2002b). It also enables selection of appropriate virus strains for inclusion into vaccines used to protect cattle in the vicinity of infected buffalo populations (Hunter et al., 1996).

However, there is a paradox in understanding the transmission of FMD viruses from buffaloes to other species. While SAT1 viruses appear to circulate more rapidly within buffalo herds in the KNP (see above), most FMD outbreaks in impala within the KNP as well as in cattle adjacent to the KNP have been caused by SAT2 viruses (Thomson, 1994; Bastos et al., 2001). A possibility is that impala as well as cattle are, in general, more susceptible to infection by SAT2 viruses than SAT1 but there is no direct evidence for this.

Two recent outbreaks of FMD in cattle in the Mpumalanga and Limpopo Provinces of South Africa serve to show conclusively that the infections were derived from contact with buffaloes that escaped across the perimeter fence of the KNP (Vosloo et al., 2002b).

The first of these outbreaks occurred initially in communal cattle in the Nkomazi area immediately south of the KNP in November 2000 (Fig. 4). Unfortunately, this SAT1 infection spread to a feedlot near Middelburg (Mpumalanga), about 200 km to the east, before it was detected and thence to an abattoir at Manzini in Swaziland by cattle exported from the feedlot for slaughter. The outbreak also spread across the border between South Africa and north-eastern Swaziland by illegal transborder movement of cattle from Nkomazi. These events were deduced by comparison of partial 1D nucleotide sequences of viruses obtained from the various localities (Fig. 3) and investigation on the ground. The sequencing results clearly show that the Swaziland and South African outbreak viruses share >99% sequence homology and that these viruses are most closely related to a southern KNP buffalo virus genotype, represented by KNP/22/96 (99% bootstrap support) (Fig. 3). The FMD outbreaks were preceded by a devastating 1:100-year flood in eastern Mpumalanga that destroyed the perimeter fence of the KNP in many places and allowed buffalo to escape into adjacent farming areas. The significance of the flood is demonstrated by the fact that after the flood of 2000 a total of 468 buffalo were chased back into the KNP by helicopter or destroyed during the third quarter of the year in comparison with significantly smaller

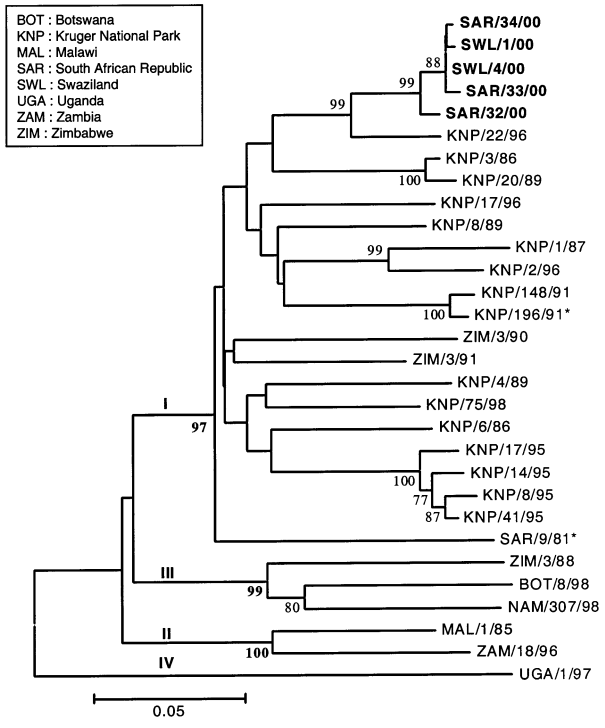

Fig. 3. VP1 gene tree depicting genetic relationships of SAT-1 viruses from the 2000 cattle outbreak (indicated in bold) with those from African buffalo sampled between 1985 and 1998 in different Southern African regions. Vaccine strains are denoted by a * and buffalo virus topotypes I–IV (corresponding to Figs. 1 and 2) are indicated.

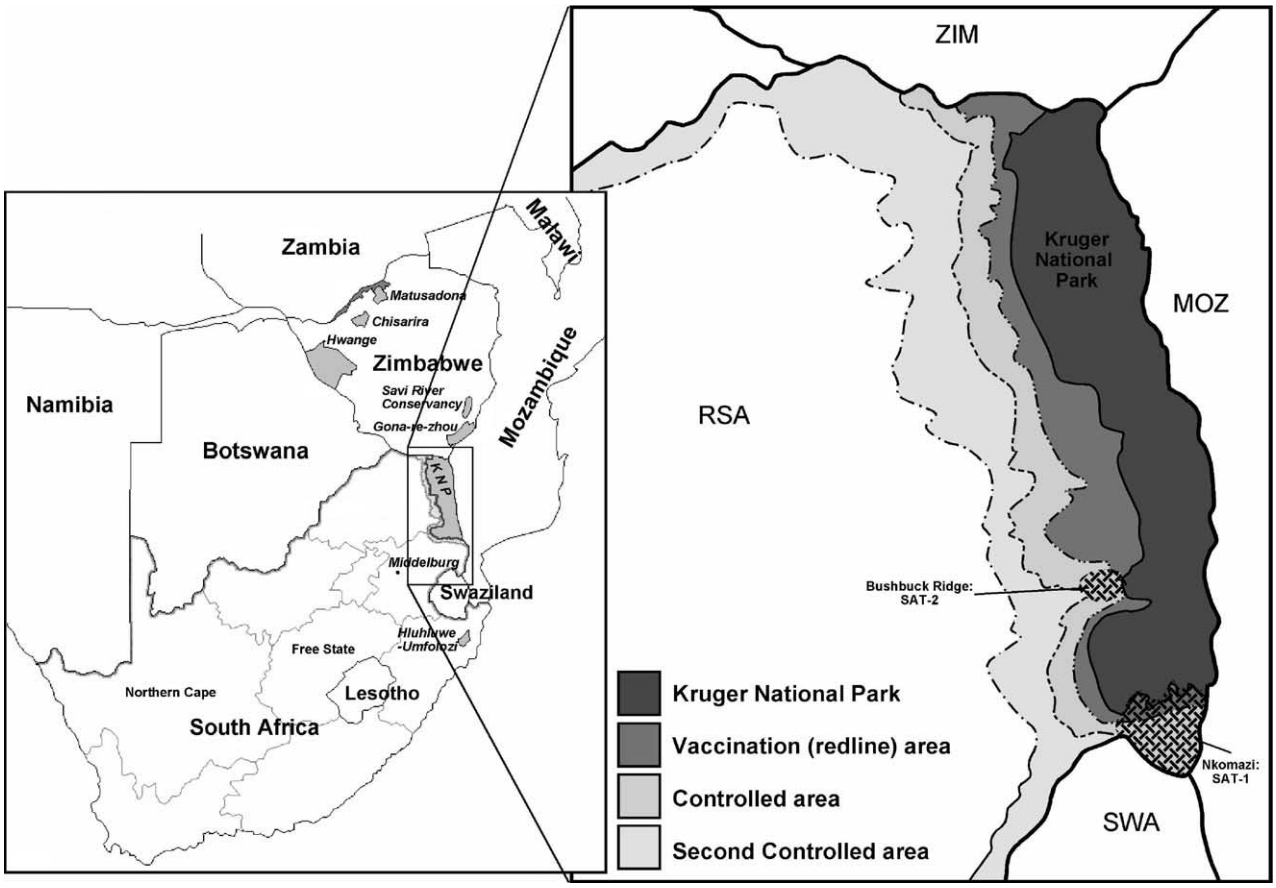

Fig. 4. Map of the Kruger National Park and associated FMD control zones in South Africa.

numbers in the 4 previous years (Fig. 5). Some of the escaped buffalo were observed to have mingled with cattle in the surveillance zone adjacent to the KNP (Fig. 4), where vaccination is not practised. As indicated above, the SAT1 virus causing the outbreak was shown to be closely related to SAT1 viruses isolated from buffalo in the southern part of the KNP (Fig. 3).

The other FMD outbreak, caused by a SAT2 virus, occurred at Bushbuck Ridge—in Limpopo province, also adjacent to the KNP—in February 2001 (Fig. 4).

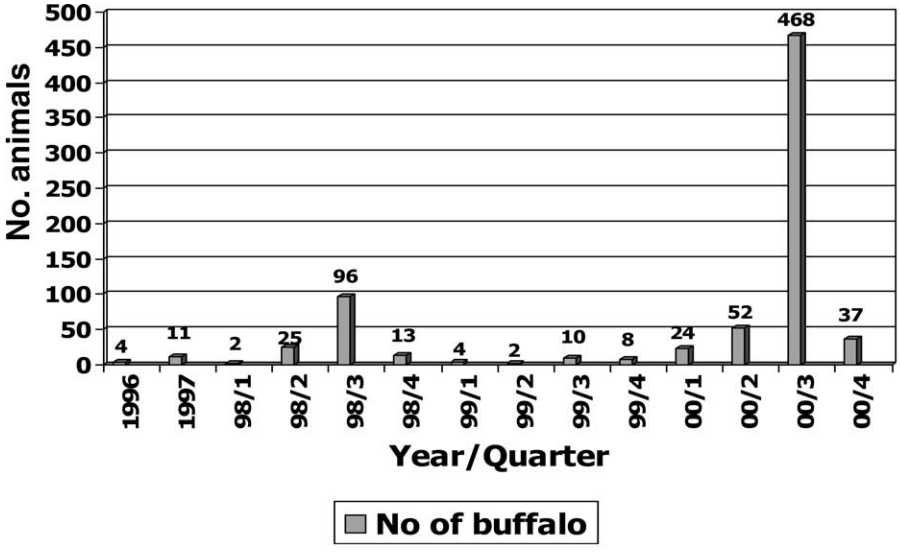

Fig. 5. Recorded escapes of buffaloes from the Kruger National Park.

This outbreak was similarly attributed to the escape of buffaloes from the KNP following the unusual flood of the previous year. The virus involved was shown by partial 1D sequencing to be closely related to SAT2 viruses previously isolated from buffalo in the nearby Orpen Gate area of the KNP (data not shown).

There is evidence suggesting transmission in both directions between cattle and European hedgehogs *Erinaceus europaeus*, and for latent infection of hibernating hedgehogs (Hulse and Edwards, 1937; McLaughlin and Henderson, 1947; Macaulay, 1963). However, these reports should be viewed with caution, because there is no evidence that hedgehogs have participated in the propagation of FMD viruses in Europe or Africa in recent times.

Capybaras *Hydrochaeris hydrochaeris* are susceptible to FMD and they may play a role in the epidemiology of FMD in cattle in South America (Gomez and Rosenberg, 1984/1985). Although laboratory mice *Mus musculus* and guinea pigs *Cavia porcellus* are highly susceptible to infection with FMD virus following needle inoculation, and neonatal mice frequently develop fatal disease (Subak-Sharpe, 1961), there is no evidence that mice or other small rodents have been involved in the spread of FMD in the field.

The position of elephants is confusing. Natural cases of FMD have been reported in captive African elephants *Loxodonta africana* and Asian elephants *Elephas maximus* (Piragino, 1970; Pyakural et al., 1976; Hedger and Brooksby, 1976; Rahman et al., 1988), and African elephants are susceptible to needle inoculation with FMD (Howell et al., 1973). However, African elephants did not become infected when exposed to artificially infected cohorts or cattle (Howell et al., 1973; Bengis et al., 1984). Furthermore, there was no serological evidence for infection in elephants culled in KNP over a period of 30 years (Bengis et al., 1984). In southern Africa, African elephants are not considered susceptible to FMD in natural circumstances, and they are not subject to the restrictions on movement imposed on ruminants from FMD-endemic areas.

Although hippopotami *Hippopotamus amphibius* are artiodactyls, which are generally susceptible to FMD, they have not been proven to suffer from FMD, and serology on 877 of these animals in the KNP failed to detect evidence of infection (R.G. Bengis, personal communication). Rhinoceros *Ceratotherium simum* and *Diceros bicornis* are perissodactyls, which are generally refractory to FMD.

3. Pathogenesis

The pathogenesis of FMD has been studied mainly in cattle and pigs (Burrows et al., 1981; Brown et al., 1995, 1996). Acquisition of infection, other than in pigs where it is normally oral, usually occurs by inhalation and the initial site of virus replication is thought to be the respiratory bronchioles of the lung (Brown et al., 1996). However, an earlier study showed initial replication occurred in the mucosa and possibly the lymphoid tissues of the pharynx, particularly in the tonsillar region of the soft palate (Burrows et al., 1981). The virus then spreads via the bloodstream to Langerhans cells (macrophage-like dendritic cells) in epithelia (Di Girolamo et al., 1995), and all epithelial cells in contact with an infected Langerhans cell become infected (Brown et al., 1995). An interesting demonstration of this phenomenon (i.e. infection of dendritic macrophages of the Langerhans type) is the effect that prior African swine fever virus infection has on subsequent exposure of pigs and dendritic cell cultures to FMD virus. Both in vivo and in vitro, ASF virus is able to prevent or at least reduce the capacity of FMD virus to cause infection (Gregg et al. 1995a,b).

In infected animals FMDV is disseminated to many epidermal sites, but lesions only develop in areas subjected to mechanical trauma or physical stress (Gailiunas and Cottral, 1966).

A number of mechanisms have been proposed for persistent infection with FMD virus (Salt, 1993; Woodbury, 1995). The pharynx is probably the site of viral persistence and in persistently infected ruminants virus can be routinely recovered from cells and secretions collected from the pharynx and anterior oesophagus using 'probang cups' (Sutmoller and Gaggero, 1965). Recent studies in cattle have shown that virus persists in the basal layer cells of the pharyngeal epithelium, particularly of the dorsal soft palate (Zhang and Kitching, 2001). It is not present in the more superficial layers of those epithelia and it is not clear how the virus is excreted into the pharynx. Bergmann et al. (1996) found FMD virus-specific genetic sequences in multiple sites, but not in pharyngeal specimens, in cattle up to 2 years after infection. This finding contradicts previous observations based on detection of live virus and its significance is therefore uncertain.

4. Clinico-Pathology

FMD in wildlife varies from completely inapparent to acutely lethal infection. Death due to FMD has been described among mountain gazelles in two Israeli nature reserves (Shimshony et al., 1986; Shimshony, 1988), and it also has occurred in impala (Hedger et al., 1972), blackbuck (Kar et al., 1983), saiga (Kindyakov et al., 1972), white tailed-deer (McVicar et al., 1974), and warthogs (R.G. Bengis, personal communication). The case fatality rate among mountain gazelles in one outbreak was greater than 50% and at least 1500 animals died. Death was presumed to be due to a

combination of heart failure (due to viral myocarditis) in the more acute cases, and *diabetes mellitus* (as a result of pancreatitis) in cases of longer duration (Shimshony, 1988; Perl et al., 1989).

It is becoming increasingly apparent that some wildlife, African buffalo particularly, as is the case for sheep and goats among domestic animals, frequently suffer infection that is not apparent. They may nevertheless excrete FMD virus while in the acute stage of the infection (Gainaru et al., 1986).

The signs of FMD in wildlife are generally similar to those in domestic animals (Thomson, 1994). In FMD, vesicles (blisters, or aphthae) develop at multiple sites, generally on the feet and in the mouth (Sutmoller, 1992; Barker et al., 1993). Severe lesions occur where there is mechanical stress on infected epithelial surfaces. This varies with the species. Thus, suids, which have a high ratio of body-weight to foot-size, and which root with the nose, tend to have the most severe lesions on the feet and on the rostrum of the snout. In warthogs, which tend to 'kneel' while grazing, lesions are common in the skin covering the carpal joints (R.G. Bengis, personal communication). In ruminants, oral lesions can be severe. In impala (Fig. 6), as in small domestic ruminants, mouth lesions are usually most severe on the dental pad (Fig. 7), but may occur elsewhere, especially on the tongue; (Fig. 8) foot lesions begin as a coronitis, sometimes vesiculating around the entire coronet (Fig. 9). Vesicles at any site rupture early in the course of disease, so that the blisters are often eroded by the time that an animal is examined.

Young animals of any species may die acutely of myocarditis, which appears grossly as whitened streak-like areas in the myocardium.

Most infections in African buffaloes caused by SAT type viruses are thought to be subclinical because few of over 47 000 buffalo examined after being culled in the KNP, where FMD is endemic, had clinical signs or lesions suggestive of FMD (R.G. Bengis, personal communication). Furthermore, no FMD virus was recovered from suspect material examined in the laboratory. Absence of clinical FMD or signs of healed lesions in buffalo in Botswana, Zimbabwe and Uganda has also been reported (Hedger et al., 1969; Hedger, 1972; Hedger et al., 1973). Following experimental infection of young buffalo, typical small lesions were described, particularly of the feet, although infection in the absence of clinical disease also occurred (Anderson et al., 1979; Gainaru et al., 1986). More severe lesions occurred in a small group of buffalo recently captured in the KNP for reasons unrelated to FMD and held in pens there. Typical mouth lesions of FMD developed in what appeared to be a natural outbreak caused by a SAT1 virus (D. Keet, personal communication, 2001). Five of the 30 animals were seen to chew constantly and had white foam at the corners of the mouth although drooling of saliva was not seen. The animals were clearly uncomfortable but did not stop feeding. On closer examination, 6 were found to have lesions in the

Fig. 6. Photograph of impala showing piloerection.

Fig. 7. Photograph of a dental pad lesion in an impala.

Fig. 8. Photograph of a tongue lesion in an impala.

Fig. 9. Photograph of a foot lesion in an impala.

mouth. These occurred on the tongue, insides of the cheeks and, in one case, on the hard palate. Some lesions were large (70 × 30 mm), foul smelling and the affected epithelium was brittle and came off in granules (Fig. 10). Within a week, ulcers/erosions formed with rounded epithelial edges and a clear pink floor. After 2 weeks the tongue lesions were visible as pale, weakly circumscribed areas with poorly developed papillae. Foot lesions did not occur in any of the animals. This account accords with an earlier observation, also made in the KNP, among a group of 8 buffalo captured and kept in pens (Young et al., 1972). Initially, three of the animals showed malaise, diminished appetite, pyrexia and a painful gait. The disease spread rapidly and within 7 days 7/8 animals showed some lameness in one or more feet and, in some, salivation. In the most severe cases chewing motions, protrusion of the tongue and severe salivation were observed. Vesicles and ulcers were small (10 mm in diameter), while in one animal a lesion on the hard palate measured 25 mm. Lesions in the mouth were confined to the dental pad, palate, dorsum of the tongue and lips. On the feet, lesions were found on the coronary band and in the interdigital cleft. Within 3 weeks the animals had recovered fully.

From the above, it is clear that while some, possibly most, infections of buffalo with SAT viruses do not cause disease, in some circumstances at least, typical FMD may result. However, disease has not been reliably recorded in free-living buffalo.

Histologically, vesicles begin as clusters of hypereosinophilic degenerating keratinocytes in the stratum spinosum. Intercellular edema fluid accumulates, forming a vesicle which soon ruptures, leaving an eroded surface (Barker et al., 1993). The epithelium in the mouth often regenerates completely within a week, but foot lesions heal more slowly. Myocardial lesions consist of multifocal myocardial degeneration and necrosis with a predominantly lymphocytic cellular response.

Some impala may develop severe, although usually non-fatal FMD, while others remain clinically normal (Thomson et al., 1984; Keet et al., 1996). In the acute stages animals may develop piloerection, (Fig. 6) probably due to fever, and locomotor signs relating to foot lesions. These vary from mild 'walking on eggs', with arched back and head held low, to severe 'carrying leg' lameness. Other signs include licking or shaking of the feet, shifting weight from one leg to the other, holding one hoof off the ground, lagging behind the herd, and lying down with reluctance to rise. Similar signs have been observed in kudu, bushbuck *Tragelaphus scriptus*, nyala, warthogs and giraffe (R.G. Bengis and D.F. Keet, personal communication). In very severe cases, hooves of impala and wild suids may slough (R.G. Bengis, personal communication). Secondary bacterial infection of foot lesions is sometimes crippling.

Discontinuity of the skin/hoof junction results in a 'break' or fault in the hoof wall as the hoof grows, which is useful for estimating the time since the acute phase of the disease. In impala it takes 5–6 months for this fault to grow out completely.

Salivation is uncommon in antelope, even in animals with severe mouth lesions (R.G. Bengis, personal communication).

Unusual signs include progressive emaciation as a result of exocrine and endocrine pancreatic atrophy in mountain gazelles (Perl et al., 1989), loss of horns (Shimshony et al., 1986), erosions at the base of the supernumerary digits in wild suids and kudu (R.G. Bengis, personal communication) and lesions on the kneeling pads of warthogs and bushpigs (R.G. Bengis, personal communication).

Lesions of the udder or teats have not been documented in wildlife but are common in livestock, particularly dairy cows.

In white-tailed deer FMD was very similar to that seen in cattle, with vesicles on both oral and foot epithelium (McVicar et al., 1974). However, they tended to form preferentially on the bulbs of the heel rather than in the interdigital cleft. White-collared peccaries *Tyassu tajucu* were very susceptible, but the course of the disease was milder and of shorter duration than that in domestic pigs. Vesicles occurred on the snout, tongue, coronary band, and interdigital clefts (Dardiri et al., 1969). Nine-banded armadillos *Dasypus novemcinctus* developed vesicular lesions on footpads and toes (Wilder et al., 1974).

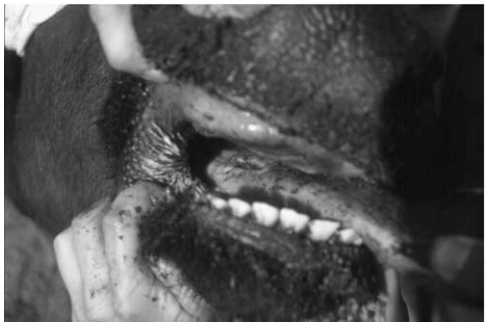

Fig. 10. Photograph of mouth lesion in a captive buffalo.

5. Diagnosis

The diagnosis of FMD in wildlife is more complicated than in domestic stock because the variation in severity of presenting signs is greater than in domestic animals. It is sometimes important to demonstrate infection, or the absence thereof, in wildlife where no disease is apparent either because it tends to be subclinical for the particular species/virus combination or because thorough physical examination of wild animals in the field

is difficult to accomplish. Laboratory support is therefore even less dispensable in situations involving wildlife than in the case of infection in domestic livestock.

Persistent infections in ruminants may be identified by collection of specimens of pharyngeal secretions and cells using a 'probang cup' (Sutmoller and Gaggero, 1965; Kitching and Donaldson, 1987). This material is then inoculated into sensitive cell cultures that enable any viable virus present to replicate and cause cytopathic effects. However, because the test may fail to detect virus in some animals—the virus appears to be present intermittently and in varying quantities—it cannot be relied upon to detect all persistently infected individuals. Therefore, where persistent infection is suspected, as many animals as possible should be sampled. Alternatively, animals that produce negative results should be resampled at least twice at weekly intervals. Another reason why probang specimens frequently provide false negative results is that they are badly taken and stored. For example, it is important to avoid contamination of the collected material with blood (caused by excessively vigorous sampling) or ruminal fluid and to store the collected material (after mixing with an equal volume of buffered saline or phosphate at pH 7.4) in liquid nitrogen or dry ice immediately after collection.

Sera should be collected from as many suspect animals as possible. Positive serological results may provide conclusive evidence of infection because wildlife is usually not vaccinated and therefore significant levels of antibodies to FMD virus result only from infection or, in young animals, ingestion of colostrum containing such antibodies. Virus neutralisation and liquid-phase blocking ELISA (lpbELISA) (Hamblin et al., 1986) are commonly used for all species. However, the lpbELISA tends to produce false positive results with giraffe sera, especially against SAT2 (J.J. Esterhuysen, personal communication). Serological tests that detect antibodies to the non-structural proteins of FMD viruses, such as the 3ABC ELISA, are particularly useful in wildlife because they are not vaccinated and therefore positive results are indicative of infection with one of the aphthovirus serotypes. However, some commercial kits that have been tried in this respect have a low sensitivity and therefore their use cannot be recommended on a large scale as yet (Vosloo, unpublished data). Furthermore, these test still need to be validated and the duration of detectable antibody responses in different species determined.

The differential diagnosis of FMD in wildlife is complicated because of the many species potentially involved as well as the vast number of infectious and non-infectious diseases associated with these species in different parts of the world.

6. Immunity

The duration of immunity following FMD infection seems to vary among wildlife (Hedger et al., 1972), but there are almost no reliable data. In cattle, antibody concentration reflects immune status (McCullough et al., 1992). Immunity in cattle lasts 1–3, and occasionally more than 4 years (Bachrach, 1968; Brooksby, 1982). When immunity is challenged by another viral subtype, the duration of immunity is reduced; the degree of antigenic difference and the duration of immunity are inversely related (Pay, 1983).

Although animals that have recovered from infection or been vaccinated rapidly develop virus neutralizing antibody, protective immunity against FMD virus is probably also effected by antibody-dependent phagocytosis by cells of the reticuloendothelial system (McCullough et al., 1992).

7. Control and management

Control strategies for FMD in wildlife depend largely on the locality and the type of livestock husbandry practised in that locality. Because of the potential impact of FMD on the livestock economy, the effect on wildlife is often secondary in the eyes of authorities responsible for animal health. In most countries FMD is a scheduled or controlled disease and how it is dealt with is stipulated in legislation or animal health regulations. Furthermore, international norms with respect to FMD and other important livestock diseases, intended to facilitate trade in animals and animal products, are published by the OIE (International Animal Health Code, 2002).

In regions normally free of the disease, the first line of defence is to prevent introduction of FMD viruses into susceptible populations. This is accomplished by prohibition of, or strict controls on, the importation of animals and animal products from FMD-endemic areas; these sanctions extend to wildlife and their products (International Animal Health Code, 2002). In practice, however, this is increasingly difficult to accomplish for two reasons. Firstly, the volume and diversity of trade in animals and animal products, consequent to some extent on the expansion of free trade zones, is so enormous that it is difficult to police effectively. Compounding this fact is the tendency for traders and private individuals to avoid both tariff and non-tariff barriers by smuggling meat and meat products into countries where the prices of these commodities are high or where particular types of meat are unavailable. As an example, the smuggling so-called 'bush meat' into developed countries by immigrants and their friends and relatives from the Developing World has been held to be a particular problem. Bush meat clearly poses a risk to the countries

into which it is imported but whether this really presents risks comparable with those posed by large-scale commercial smuggling of potentially infected domestic animals and their products is doubtful. It should be remembered that even if such illegal imports contain FMDV, that virus would need to infect a susceptible animal for FMD to be propagated as an 'outbreak'. In practice this requires feeding the product, or leftovers thereof, to pigs because other susceptible domestic species are herbivorous and so unlikely to be exposed. For that reason, it has long been a requirement in developed countries that swill fed to pigs be heat-treated to inactivate FMD and other infectious agents. The difficulty in ensuring that such requirements are followed in practice is now resulting in complete bans on the feeding of swill to pigs. This in turn creates another divide between developed and developing countries because in developing countries pigs are extremely efficient at converting human detritus into high quality protein and swill-feeding bans would be counter productive in many circumstances.

In southern Africa, where wildlife are reservoirs of FMDV, the historic approach has been, firstly, to separate domestic livestock from wildlife, usually by means of fences (increasingly, double fence lines that preclude direct contact between animals on either side—see above). In addition, cattle in localities adjacent to wildlife areas are usually vaccinated bi-annually against FMD. This generally has been successful in preventing transmission of FMD from wildlife to livestock (Thomson, 1995). However, the use of fencing has been severely criticised by conservationists, because the fences sometimes have blocked migration routes and access of wildlife to water, resulting in ecological disturbance and wildlife mortality (Owen and Owen, 1980; Taylor and Martin, 1987). The necessity for fencing is increasingly questioned; the argument being that vaccination alone should be sufficient to protect livestock from infection.

A recent study on the environmental, social and economic impact of fences aimed at animal disease control in Ngamiland (north-western Botswana) has highlighted the complexities of the issues involved. Essentially, the economic, social and environmental costs and benefits are viewed differently by the various affected parties, e.g. local communities with a livestock tradition, commercial farming interests, the tourist industry and the environmental lobby (Scott Wilson Resource Consultants, 2000). Wildlife management may be further complicated by restrictions placed on areas where particular species such as buffalo may be farmed or ranched; on wildlife translocation; and on the distribution of products derived from wildlife, such as meat, hides and trophies.

Routine vaccination of cattle against FMD in areas adjacent or close to wildlife areas has been practised in southern Africa since the early 1970s and was regularly conducted in zoos in Europe between 1950 and 1990 (Schaftenaar, 2002). However, because even the best FMD vaccines are relatively inefficient it has been shown by experience in southern Africa that reliance on vaccines exclusively is dangerous. The reasons for this are two-fold. Firstly, immunity following primary vaccination is ephemeral (3–4 months only in cattle when the vaccine contains alhydrogel/saponin as the adjuvant; oil-adjuvanted vaccines may be more effective in this respect). Only when individual cattle have received several inoculations does the level of immunity engendered remain high against challenge with the homologous virus. Thereafter annual vaccination is required to keep levels of immunity at a satisfactory level. The second problem is that of antigenic variation. It is well established that animals recovered from infection with one FMDV type are susceptible to re-infection with any of the other 6 virus types. Within the three SAT types of FMDV associated with buffalo in southern Africa, there is considerable intratypic variation with variants being more or less restricted to particular localities, i.e. so-called topotypes as described above (Vosloo et al., 1995; Bastos, 1998; Bastos et al., 2001; Bastos and Sangare, 2001). The variation in nucleotide sequence in the portion of the genomes studied may be reflected in dramatic intratypic differences in antigenicity (Thomson et al., 1992; Vosloo et al., 1996). Therefore, it is essential to vaccinate cattle against the types and subtypes of viruses that are circulating in wildlife, buffalo particularly, in that locality in order to be sure that the vaccines will protect the cattle effectively. This raises another two difficulties: only in southern Africa has this phenomenon been studied in any detail so that elsewhere in Africa the situation on the ground is largely unknown (i.e. occurrence and distribution of topotypes). The other problem is that even in southern Africa vaccines are not available against all the topotypes that are known to exist. Furthermore, there is little incentive for vaccine manufacturers to develop vaccines against all topotypes because the veterinary authorities that purchase the vaccine rarely go beyond specifying the types of FMD virus that need to be included in the final product.

Vaccination of wildlife against FMD in Africa has so far not been seriously considered. A pilot study was conducted into the possibility of vaccinating buffalo calves within breeding herds in a wildlife reserve in South Africa with high antigen-payload vaccines containing an oil adjuvant in an attempt to prevent them from becoming infected with SAT-type viruses (Hunter P., personal communication, 1997). The results were inconclusive.

In earlier studies, circulating antibody responses to vaccination of eland *Taurotragus oryx*, impala and buffalo were measured. However, because the resistance

of these animals to subsequent challenge was not investigated, all that can be concluded is that the serological responses were broadly similar to those observed in cattle but of a lower order (Hedger et al., 1980). Consequently it was suggested that these wildlife species should receive double the dose of vaccine normally administered to cattle. It is therefore difficult in the light of existing information to be sure how effective vaccination of wildlife is, particularly insofar as protection against infection—as opposed to disease—is concerned. However, there is nothing to suggest that wild herbivores react fundamentally differently to FMD vaccines in comparison with domestic species.

In Europe, following the recent incursion of the pan-Asian O topotype into the UK and subsequent spread to The Netherlands, France and Ireland there has been considerable debate on how animals in zoological collections, including animals representing important genetic material for endangered species, should be protected from infection. This debate has included consideration of exceptionally valuable domestic animals such as those involved in long-term studies into bovine spongiform encephalopathy. As is the way in the age of electronic communication, many people, some knowledgeable and others not, have expressed opinions via the Internet and in the press on the advisability of using vaccines in such situations. Basically, the issue has revolved around saving healthy animals from slaughter and incineration or burial and the effect this would have on the subsequent ability of the country concerned to trade freely in animals and animal products.

As already indicated, there are no data to suggest that wild ruminants in general react differently from domestic ruminants to conventional FMD vaccines. Superficially therefore, there is no reason why such vaccines should not be used in wildlife. The question, however, is: What would be the objective of vaccinating wild animals in captivity? In general, it seems that the objective is to protect the animals in question from infection. If so, that presents a difficulty because, while it may be possible to protect wild animals from this relatively mild disease, it is well established that FMD vaccines are less efficient at preventing infection, including development of persistent infection (i.e. carriers), in ruminants (De Leeuw et al., 1979; Donaldson et al., 1987; Donaldson and Kitching, 1989; Salt et al., 1996). Therefore, the problem with vaccinating wildlife lies in the possibility that, should they become infected, persistent infection may result and they could become a potential source of future outbreaks. Two arguments are advanced to counter this contention:

- it is now possible to differentiate between vaccinated animals and those that have been vaccinated and subsequently infected because inactivated vaccines do not, in general, induce antibody responses to some of the non-structural proteins encoded during viral replication (Bergmann et al., 1993; De Diego et al., 1997; Meyer et al., 1997; Mackay et al., 1998; Silberstein et al., 1997; Sorensen et al., 1998);
- persistently infected animals very rarely, if ever, transmit the infection (Thomson, 1996).

As far as detection of animals that become infected despite being vaccinated is concerned, it is presently generally accepted that while this can be done on a herd basis, the tests have not yet been shown to be reliable (sufficiently specific and sensitive) in individual animals. Therefore, there is presently no assurance that vaccinated animals that subsequently become infected will be detected. This is particularly relevant to animals in zoological collections and others that have high individual value and which are traded or exchanged between countries. On the other hand, unvaccinated animals, even if they did not develop obvious disease following infection, would be easy to detect by serological testing.

Animals that are infected despite vaccination may become carriers and therefore pose a small but identifiable risk as outlined above. Because of this, trade restrictions are sometimes imposed on countries where there is a possibility that such animals exist. Even if that likelihood were to be addressed by the current review of OIE recommendations, it would probably complicate the exchange of such animals between zoological collections located in different countries. The argument that carrier animals transmit FMD virus so infrequently as to be epidemiologically insignificant and that this possibility can be safely ignored, is possibly dangerous in view of the enormous economic repercussions that could result if such an unlikely possibility came to pass (Muckspreader, 2001). Considering all the above, vaccination of wildlife with currently available vaccines should be avoided, even in the face of an outbreak, and efforts directed instead towards protecting such animals against exposure to infection. Hopefully, technical developments in vaccine preparation (purification of viral antigens to the extent that non-structural viral proteins are excluded from the final vaccine, with appropriate certification) and companion serological tests, will soon enable animals, including wildlife, that have been vaccinated and subsequently infected, to be differentiated from animals that have been vaccinated but not infected. Once that is achieved, vaccination of wildlife to protect them against FMD should not constitute a problem in terms of international trade.

Acknowledgements

The Director of OAU–IBAR is thanked for permission to publish this paper. Dr B. du Plessis kindly

provided data on buffalo escapes from the KNP for Fig. 5. Dr D. Keet provided the information on the occurrence of FMD in captured buffaloes in the KNP as well as photographs of the lesions (Fig. 10). Photographs used in Figs. 6–9 were provided by Dr R. Bengis. We are grateful to Ms E. Kirkbride for the graphic work used in Fig. 5. Drs Roy Bengis and Dewald Keet are especially thanked for many years of fruitful and friendly collaboration.

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