FOOT-AND-MOUTH DISEASE VIRUS TYPE C SITUATION: THE FIRST TARGET FOR ERADICATION?

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After its first description in Europe in 1926, the Waldmann C foot-and-mouth disease (FMD) serotype, later referred to simply as type C, was for many years a significant component of the FMD complex in Europe, South America, South Asia, the Philippines and parts of East Africa and was included in preventive vaccination programmes. The outbreak areas in different continents were often linked by trade in meat products and vaccines. However, for reasons which are obscure, this FMD virus type, never perhaps as robust as other FMD virus types, has been in decline for some 30 years and its distribution has become severely limited in the last decade. This situation has led to an understanding that FMD virus type C could be considered as a candidate for eradication. Drawing on molecular epidemiological data this report briefly describes the recent history of FMD type C occurrence and presents the epidemiological determinants to be understood if eradication is to be attempted. Recommendations are made with respect to the actions which need to be taken.

1. INTRODUCTION

What became known by international agreement as Waldmann type C FMD virus was first described in 1926 (Waldmann and Trautwein) in Germany. Historically the type C FMD virus has had a relatively narrow distribution compared to the other European types O and A and type Asia 1, being found principally in Europe and South America with reported occurrence in South Asia and Africa. Although it became relatively widespread, and was an important component of the global FMD situation, it had always a relatively restricted distribution and was never perhaps as robust as other types of FMD. In Africa it has been reported, and then only infrequently, from Kenya (from 1957 almost every year until 1988), Ethiopia (initially in 1957, then from 1971 to 1983) and Uganda (after 1970 and 1971 and possibly until 1979). In North Africa outbreaks were confirmed in Tunisia in 1965, 1967 and 1969, however, other anecdotal reports from Algeria in 1971 and 1972 were never confirmed.

The recent history of type C foot-and-mouth disease (FMD) virus occurrence indicates a greatly reduced incidence of outbreaks and geographic distribution compared to the mid-twentieth century situation. This has led some workers to suggest that the current situation lends itself to contemplating global eradication of this virus type in the near future. However, this enthusiasm needs to be tempered by a realisation that the areas where FMD virus type C outbreaks were last detected in Asia and Africa and surrounding countries are not well covered by surveillance. Here, and in Latin America, where surveillance is considered to be relatively effective, the epidemiology of FMD virus type C occurrence is enigmatic. This paper explains the elements of the enigma and suggests that without a knowledge of the determinants of virus persistence between outbreaks in the foci where the virus has occurred in recent years it is difficult to assess with certainty the actual status of these foci and the likelihood that the virus could be eliminated from each of them.

2. MATERIALS AND METHODS

RNA was extracted from virus-containing preparations using the RNeasy Kit (Quiagen) and a one-step amplification of the VP1-coding region was performed (primer sequences available on request to the authors) using Ready-To-Go™ RT-PCR beads (GE Healthcare) with amplicon clean-up using ExoSAP-IT (USB Corp.). Cycle sequencing used the CEQ Quick Start Kit and the CEQ8000 automated sequencer (Beckman Coulter). The region amplified is depicted in Figure 1. Phylogenetic analysis using MEGA 4.0 (Tamura et al., 2007) enabled the construction of mid-point rooted Neighbor-joining trees.
3. RESULTS

3.1 A brief history of recent FMD virus type C occurrence

In the last 20 years the type C virus has been restricted to four countries or geographic clusters of countries, namely: South America, The Philippines, South Asia and Eastern Africa (records of the FAO World reference Laboratory for FMD, Institute of Animal Health, Pirbright Laboratory, UK). Several factors constrain identification of the epidemiology of FMDV type C. These relate to the insensitivity of surveillance programmes combined with the dubious quality of laboratory diagnostics in some countries especially in the relatively remote areas which constitute foci of type C occurrence and related to this the paucity of type C viruses or samples presented in a timely manner for confirmation and characterisation. The comments which follow must be viewed in the light of this constraint.

3.2 The South American Focus

Type C FMD viruses were rapidly identified from South America after their identification in Europe having spread through livestock movements and through the use of vaccines. Two serogroups were relatively widespread and prevalent in South America in the 1950s to 1970s. The most persistent was the sero-group designated C₃ but related viruses were last detected in Argentina in 1993. An indication of the results of phylogenetic analysis is given in Figure 2.

It is important to note the clustering of South American type C FMD viruses around two strains extensively used as vaccines i.e. C₃/Resende/BRA/55 [AY593807] and C₃/Indaial/BRA/71 (78) [M90376] and the close relationship between C₃ Resende and C₃ Philippines. Notwithstanding the fact that the formerly overtly persisting type C FMD viruses were not seen after 1993, an outbreak occurred in September 2004 in buffaloes and cattle on an island in the Amazon River in the Municipality of Careiro da Várzea, Amazonas, Brazil (FAO, 2005). The area concerned was within a routinely-vaccinated (trivalent A, O and C vaccine) zone of the country. According to PANAFTOSA, VP1 gene sequencing led to the conclusion that the virus was “historically endogenous to the continent”, “... it was not possible to establish a close relationship with any of the isolates of the PANAFTOSA-PAHO/WHO data bank (maximum homology of 89 per cent)” and “... comparison between the isolates C₃/Careiro and C₃/Indaial/BRA/71 (vaccines strain) showed a genetic difference of 13 per cent in the region studied. This result precludes the hypothesis that the virus resulted from an escape from the vaccine industry.” Thus, although the virus groups within the C₃ clade, it is a distinct virus and its provenance remains unknown. One must ask not only "Where did the virus originate?" but also "Where has it been until now?" This is clearly an enigma which unless it is resolved casts doubt on any claims that the type C virus has been eliminated. Clearly the answer will relate to the statements "Amazon region is in the northern livestock crescent where the animal health and veterinary delivery systems are not as effective as those in other parts of the country. The area as a whole depends on the import of animals and meat from other parts of the country." (FAO 2005).
3.2 The Philippines Focus

The close relationship which existed earlier between the swine and animal health industries in South America and The Philippines, with transfer of animals and vaccines, are believed to have provided the means for the movement of C3 Resende-like type C viruses to The Philippines in the 1970s or earlier. The viruses display an evolutionary continuum over more than 10 years from 1984 to 1994 explicable as the evolution of a single clade of virus (Figure 3). This is quite remarkable because from 1991 to 1994 FMD (not just type C FMD) was not detected in The Philippines despite intensive active surveillance including sero-surveillance being conducted in 1993/4 (P.L. Roeder, personal observation). When FMD was again detected in Quezon City of Manila in September 1994 it was identified as belonging to type C. However, it was only the first case detected which yielded type C FMD virus, the epidemic which evolved to engulf the island of Luzon for the next 10 years was, with three exceptions, always type O belonging to the “CATHAY” topotype. The three exceptions were in Cavite, close to Manila, in June 1995 and Bulacan, far south of Manila in January and March 1995. The relationship, if any, between these outbreaks could not be determined; unfortunately these viruses were not subjected to phylogenetic characterisation. The Philippines veterinary authorities have pursued FMD elimination vigorously for more than 14 years and in recent years have conducted extensive serological studies to support an application for accreditation of freedom from FMD without finding any evidence of FMD virus circulation. Once again we are faced with an enigma – that of where this virus had been in the period between its last sighting in 1991 and its reappearance in 1994; it clearly was not re-introduced from vaccine.
3.3 The Eastern African Focus

Type C FMD virus was first recorded in sub-Saharan Africa in Kenya and Ethiopia in 1957. With the exception of an Angolan outbreak in 1973, clearly linked to South America phylogenetically, (see Figure 2; C/ANG/3/73), the early isolates show independent lineages with a common origin possibly representing a single introduction. All other isolates emanate from East African countries, primarily Kenya, and the Kenyan isolates are closely related to the vaccine strain K267/67. The virus was last detected in Ethiopia in 1983 and was clearly endemic in Kenya until 1988 but the later situation is uncertain.

3.4 The South Asia Focus

The type C FMD virus was probably introduced into the sub-continent in 1950s through the use of vaccines prepared in Europe. All the later viruses from India are closely clustered but outbreaks have not been detected since 1996 (see Figure 5). Reports from Pakistan and Afghanistan of type C viruses are highly unlikely to be correct. Viruses from the other South Asian countries (Nepal, Bangladesh, Pakistan, Sri Lanka and Bhutan) reflect the situation in India. The observed situation is suggestive of a relationship between outbreaks and vaccine use but vaccine strains in use are needed to confirm this and the information is not available.
Figure 4: Phylogeny of eastern African isolates of Type C FMD virus.

Figure 5: The phylogeny of South Asian viruses related to the European/South American groups.
4. CONCLUSIONS AND RECOMMENDATIONS

4.1 Feasibility of eradication

There is no reason to suspect the presence of type C FMD virus outside the foci described. The virus could well have been eliminated from The Philippines, where it was last seen more than 13 years ago, and might have ceased to circulate in South Asia and East Africa, where it was last seen more than 10 years ago. The proximate analysis presented here suggests that latterly the persistence of virus in the reservoirs where it was occurring was related largely to vaccine use and less to livestock trade than it had been earlier. If type C vaccine use is discontinued in East Africa and South Asia it seems likely that the disease will not return to those areas. Similarly, the best way to determine what is happening in South America is to cease using type C FMD vaccine and intensify surveillance.

Bearing in mind the analysis presented above, however tentative it might be at this stage, it is possible to examine the feasibility of eradication of type C FMD virus. It is axiomatic that an eradication programme is unlikely to succeed unless it is founded on a sound understanding of the epidemiology of the disease targeted. In the case of FMD type C and the areas in which it has occurred until recently, there are serious deficits in understanding which could compromise eradication. These are the issues relating to where the virus had been in Brazil and The Philippines prior to the disease reappearing in 1994 and 2004, respectively – and where it is now. Without significant improvements in surveillance and intensive efforts focussed at disclosing any remaining occult virus transmission uncertainty will remain.

The global eradication of FMD virus type C is probably feasible but it requires a coordinated effort with a strong active surveillance and epidemiological component and economic justification.

4.2 Recommendations

If a serious attempt is to be made to achieve verified eradication of type C FMD virus - or at least its elimination from three of its former reservoirs in South Asia, The Philippines and eastern Africa – the following actions appear to be essential:

1. Elaborate a sound justification for undertaking the exercise and a coordination mechanism.
2. Cease all use of type C FMD vaccine.
3. Maintain type C FMD vaccine bank(s) within an emergency preparedness programme to be deployed if type C FMD re-emerges.
4. Strengthen FMD surveillance in the foci of attention where the virus was last seen and include an active virological and serological search for type C FMD virus.
5. Strengthen the availability of laboratory diagnostic capability (antigen trapping and typing ELISA, solid phase blocking ELISAs, PCR) and access to Reference Laboratory services.

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6. REFERENCES