EPIDEMIOLOGICAL DEVELOPMENTS AND CONTROL OF FOOT AND MOUTH DISEASE IN ASIA

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Summary: *In the Asia region, foot and mouth disease (FMD) outbreaks are predominantly caused by FMD virus (FMDV) serotype O. The two main topotypes involved are 'South-East Asia' (SEA) and 'Middle East – South Asia' (ME-SA). FMDV of the SEA topotype (Mya-98 lineage) is widespread in South-East Asia and East Asia. FMD outbreaks due to serotype A have been sporadically observed in recent years. Serotype Asia 1 newly appeared in Pakistan from 2010 and Bahrain and Iran in 2011. Member Countries should take note that no matching vaccine is currently available for this Asia 1 serotype. Early detection of the disease and virus matching to ensure use of the most appropriate vaccine is therefore of paramount importance for disease control purposes. In the absence of suitable candidate vaccines, other control methods are required to prevent pandemic outbreaks and reduce the risk of economic disasters.*

The economic impact of FMD in East Asia (People's Republic of China, Japan and Korea) has been severe in the period 2010–2011. Pigs play an important epidemiological role in FMD outbreaks in this region since they act as an amplifier of the disease, excreting 100- to 2000-fold more FMDV than cattle and sheep. Preliminary trials have been conducted with an antiviral agent of T-1105 as a possible alternative way to inhibit virus excretion from FMDV infected pigs. Preliminary results appears to be promising, indicating efficacy within 1 hour after administration by the oral route.

Key words: *Asia – East Asia – foot and mouth disease – FMDV – pigs – T-1105 – FMD vaccine*

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1. Introduction

Foot and mouth disease (FMD) outbreaks caused by FMD virus (FMDV) serotypes O, A and Asia 1 have continuously occurred in the Asia region. Recent years have seen a significant increase in economic activity in the region. This has resulted in far more cross-border movements of people, domestic animals and animal commodities. In these circumstances, the risk of spread of animal infectious diseases has also increased. For example, FMD, one of most important transboundary diseases, now has the capacity to spread within the region in shorter period of time than before. Livestock numbers in the Asia region are also on average higher than in other regions of the world, such as Europe, Africa and the Americas. Furthermore, the human population of the region is more than 4.15 billion, accounting for more than 60% of the world's population. It is predicted that the consumption of animal products will increase more and more with the increase in the human population in the region.

Given these circumstances, there is clearly an opportunity for transboundary animal diseases such as FMD to spread quickly and widely within the region.

This report will outline the characteristics of FMD outbreaks and the important epidemiological role played by susceptible animals and will refer to the use of vaccines as a control tool for FMD outbreaks. In addition, details will be provided of a potential novel control method for FMD in pigs. FMD outbreaks in pigs —a category of livestock considered to be an amplifier for FMD— are often on a very large scale and can cause serious economic damage. Preliminary trials on the use of an anti-viral agent gave promising results as an alternative method to inhibit virus excretion from FMDV-infected pigs.

2. Characteristics of recent FMD outbreaks in the region

In the Asia region, FMD appears to have been spreading more quickly than before and this could be linked to the increasing economic activity among Member Countries. An example of the tendency for FMD to spread across countries is the spread of FMDVs of the South-East Asia (SEA) topotype (Mya-98 lineage) within South-East Asia and East Asia [4]. Severe outbreaks caused by viruses of this topotype have occurred in the East Asia region (People's Republic of China, Japan and the Republic of Korea) in 2010–2011. To control these FMD outbreaks, countries had to use FMD vaccines. A description of the FMD outbreaks in Japan will be given below as an example.

FMD was first suspected in Miyazaki Prefecture in the southern island of Kyushu in Japan on 20 April 2010. It was the first FMD outbreak in Japan since the year 2000. In 2000, the FMD outbreaks had been caused by the Middle East – South Asia (ME-SA) topotype (PanAsia) [5]. It was subsequently shown that the isolated virus had low virulence for susceptible animals, such as cattle, pigs, sheep and goats. The source of the virus was considered to be imported hay or straw from the Asia region. The infection did not spread widely and only three outbreaks occurred. The main reason for the small number of outbreaks was considered to be the low virulence of the agent [6].

The FMD epidemic in 2010, however, had a severe effect on livestock farming in the affected prefecture, which had a high density of cattle and pigs. The epidemic forced the prefecture to slaughter some 220 000 pigs and 68 000 cattle (including all vaccinated animals), and impose a ban on the transfer of livestock. Japan's FMD control policy, similar to most other FMD-free countries where vaccination is not practised, is based upon stamping out without vaccination. However, when FMD outbreaks occurred in several pig farms in early May, it took time to kill and bury the animals and the number of outbreaks rapidly increased. Therefore, in the middle of May, to control the spread of infection, Japan decided to vaccinate livestock within a 10-km radius of affected farms in the four Miyazaki Prefecture towns of Tsuno, Kawaminami, Takanabe, and Shintomi. No new FMD cases have been detected in Miyazaki Prefecture since 4 July 2010, date of the last case (No. 292), which occurred in Miyazaki city. The sequence of events relating to the discovery of FMD in Japan in 2010 was as follows.

A private veterinarian discovered a suspicious case in the affected farm and reported it to the local government Veterinary Service on 9 April 2010. The same day, an official veterinarian visited the farm and observed that one of the cows had fever, anorexia, salivation and erosions in the oral cavity but that the others had no clinical signs. Since two other suspicious cases were found on the same farm on 16 April 2010, the Veterinary Service conducted examinations for diseases such

as bluetongue, bovine viral diarrhoea/mucosal disease, infectious bovine rhinotracheitis and Ibaraki disease, but the PCR test results for these diseases obtained on 19 April 2010 were all negative. On the same day, the Veterinary Service submitted samples to the National Institute of Animal Health (NIAH). On 20 April, PCR tests conducted by NIAH showed that the cattle were infected with FMDV. An epidemiological survey revealed that the initial FMD infection took place at a water buffalo farm in Tsunocho in Miyazaki Prefecture as early as mid-March 2010. More than 10 farms had been infected with FMD by 20 April 2010. The isolated virus, FMDV type O, SEA topotype (Mya-98 lineage), had recently been widely detected in South-Eastern and Eastern Asian countries, such as the People's Republic of China, the Republic of Korea, Mongolia and Russia. However, no specific routes of virus entry to Japan have yet been identified.

The disease also led to the temporary closure of some public facilities and the cancellation of nearly 300 sporting and other public events, and the prefectural government asked residents in and around the affected areas to refrain from going out unless absolutely necessary.

3. Vaccine matching of FMD and the necessary conditions for the vaccine

According to the reports of OIE/FAO Reference Laboratory for FMD [11], FMDV isolates which belong to O SEA topotype (Mya-98) show antigenic matching with O Manisa, O Ind R2/75 and O Taw 98, but some of the recent isolates from Hong Kong (2011) did not match with O Manisa and O Taw 98. All isolates (2009-2010) from Iran, Pakistan and the United Arab Emirates which belong to ME-SA topotype (PanAsia-2) were matched with O Manisa, O IND R2/75, O TAW 98 and O BFS.

FMDV isolates (2009-2010) from Iran that showed a close match with A TUR 06. FMDV isolates from Afghanistan (2010-2011) were antigenically matched with type A vaccine strains of A IRAN 05 and A TUR 06. Type A isolates from the People's Republic of China and the Republic of Korea showed antigen matching with Mya-97.

FMDV type Asia 1 isolates (2010-2011) from Bahrain, Pakistan and Iran showed no antigenic matching with vaccines Asia 1 IND 8/79, Asia 1 Shamir and Asia 1 WBN. Member Countries in the region should take note of FMD outbreaks involving this strain. Early detection of FMD caused by this serotype is important for control purposes.

With regard to FMD vaccine, the following general conditions and conditions specific to the region should be considered:

a) The FMD vaccine must be an inactivated vaccine. In the past, FMD live vaccines were developed but all the trials and experiments resulted in failure [9].

b) The vaccine selected should be a good antigenic match for field isolates. For this reason it is very important to send samples to FMD Reference Laboratories for virus isolation and sequencing.

c) Whenever FMD vaccine is used, in an emergency to control FMD outbreaks or routinely, it is essential to be able to determine whether FMDV antibodies are the result of infection or vaccination. The vaccine should be produced in accordance with the OIE *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals*. Under the terms of the OIE *Terrestrial Animal Health Code* definition for regaining FMD free status after an outbreak if vaccination has been used, the Member has to examine the vaccinated animals for antibody against FMDV non-structural protein (NSP). Likewise, Members wishing to be recognised as FMD-free 'with vaccination' have to show that vaccinated animals are free from antibody to NSPs arising as a result of infection.

d) Cooperation and research collaboration on FMD diagnosis and vaccine production are important between Member Countries to control FMD in the region.

e) In order to be able to differentiate between antibody due to infection and antigen due to vaccination, there is an urgent need to continue striving to produce pure vaccines to limit the effect of NSPs when evaluating surveillance results.

4. The epidemiological role of susceptible animals in foot and mouth disease

Generally speaking, each category of susceptible livestock, such as cattle, pigs and sheep, seems to have a unique role in the epidemiology of FMD.

Cattle

Cattle are the most susceptible category of livestock to FMDV. Generally, the minimum infectious dose for cattle is 101.0 ID_{50} by respiratory route of infection [10]. The comparable figure for pigs is 102.6 ID_{50} by the same route. Cattle are consequently referred to as 'detectors' in FMD outbreaks. In the FMD outbreaks in 2000, only Japanese black cattle were infected. It is considered likely that they were infected as a result of extremely low amounts of FMDV adhering to imported hay or straw.

Pigs

To become infected, pigs require a larger amount of FMD virus than cattle and sheep (see above). However, once they are infected, pigs excrete very large quantities of the virus (100- to 2 000-fold more than cattle and sheep). Whereas the maximum amount of FMDV that a head of cattle, a sheep or a goat excretes from its respiratory tract is 105 ID_{50}/day, a pig excretes more than 108 ID_{50}/day [1]. This explains why pigs are referred to as an 'amplifier' in FMD outbreaks. FMD outbreaks in Taiwan in 1997 [2] and in Japan and Korea in 2010 are examples of this type of outbreak.

Sheep

In sheep, FMD usually produces mild or un-apparent clinical signs, making early detection of FMDV infection difficult. In 2001 in the United Kingdom, infected sheep continued to be moved without giving rise to any suspicion of FMD. As a result, within a short period FMD had spread to many parts of the country [3].

5. A novel tool to control FMD in pigs by an antiviral agent

The role of pigs in FMD outbreaks has already been described above. It has been demonstrated that an antiviral agent of pyrazinecarboxamide derivatives, T-1105, whose mechanism of action is considered to be the inhibition of RNA-dependent RNA polymerase activity, has a strong antiviral effect against FMDV both in vitro and in vivo. This antiviral agent could therefore be considered as a tool for reducing the expansion of FMD outbreaks, as opposed to FMD control by the vaccine approach.

The antiviral activity of T-1105 was determined as 1.6 µg/ml by means of a 50% plaque reduction assay with FMDV O/JPN/2000 in vitro [7].

T-1105 was administered by oral route, mixed with feed, to 4 pigs (T-1105 group) at a dose of 200 mg/kg twice a day for 6 days with inoculation of 106 $TCID_{50}$ of FMDV O/JPN/2000 just 1 hour after the initial administration of T-1105 (Fig. 1); 2 other pigs (control group) were inoculated only with the same dose of FMDV. The control group showed typical clinical signs such as fever, vesicles on their feet and lameness. In the T-1105 group, no clinical signs of FMD were observed throughout the period of the experiment (Table 1). The virus was not detected from nasal swab samples collected from the T-1105 group, tested by virus plaque assay and real-time PCR; in this group, the antibody titres of both the liquid phase blocking (LPB) ELISA (Fig. 2) and the virus neutralisation tests increased very little when compared to those of the control group [8].

Fig. 1.– In-vivo experiment demonstrating anti-viral activity of T-1105 in pigs inoculated with FMD virus

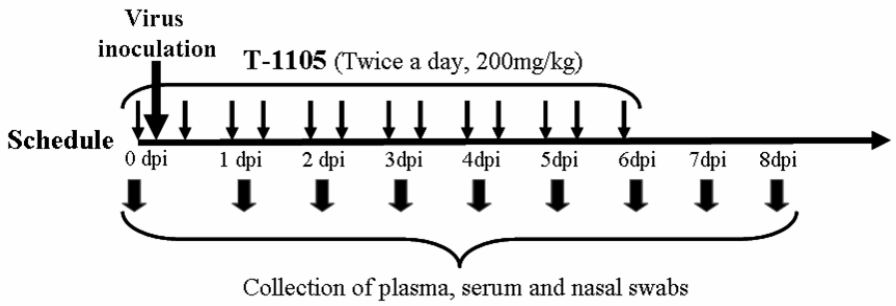


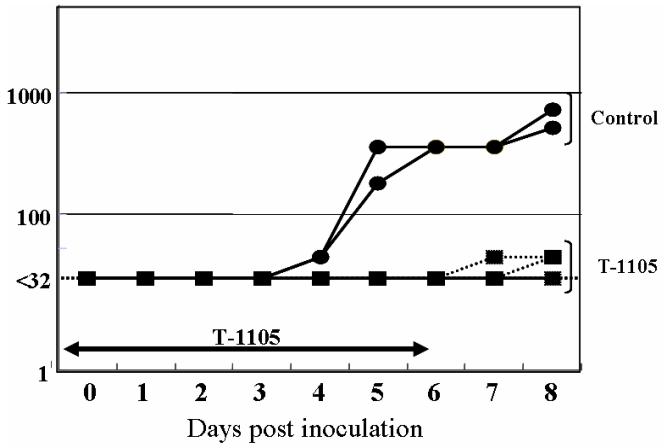
Table 1.– Clinical signs in T-1105 group and control group following FMD virus inoculation

Treatment	No.	Days post inoculation								
		0	1	2	3	4	5	6	7	8
T-1105	1	–	–	–	–	–	–	–	–	–
	2	–	–	–	–	–	–	–	–	–
	3	–	–	–	–	–	–	–	–	–
	4	–	–	–	–	–	–	–	–	–
Control	5	–	–	+	++	++	++	++	++	++
	6	–	–	–	+	+	++	++	++	++

\+ Blister formation
++ Rupture

Lameness / Dysstasia

Fig. 2.– LPB ELISA antibody titre in the T-1105 group and control group



Since the viraemia stage was not detected by real-time PCR with the plasma samples, and since the increase in FMDV antibodies was so slight, it was considered that there had been no virus replication in the T-1105 group of pigs. These results suggest that the antiviral agent inhibited FMDV excretion from the virus-inoculated pigs.

The use of vaccine in pigs during an outbreak to limit or decrease virus excretion is common practise to limit the spread of FMDV during outbreaks of FMD where pigs are involved. Preliminary trials with the use of an antiviral agent of pyrazinecarboxamide derivatives, T-1105 gave promising results. However, further work need to be undertaken to investigate this as an alternative or complimentary to vaccination to control outbreaks by limiting virus excretion. Clarity is also needed on the acceptance of this possible alternative method in terms of OIE standards.

6. Global perspective to the control of foot and mouth disease

There are on-going discussions between country and regional organisations representatives as well as experts and representatives of OIE and FAO in preparation of an FMD Global Control Strategy under the hospices of the FAO/OIE GF-TADs mechanism.

The objectives, underlying principles, major tools, activities and expected results of this strategy have been presented and discussed during the 79th OIE General Session, in May 2011 [12]. The process to be followed in preparation of this Global Strategy has been presented also during that General Session. A resolution has been voted in support of this initiative. A first draft of the strategy was discussed during a seminar held in Paris from 2 to 4 November 2011. The interactions with the country and regional organisations representatives and experts will continue during the coming months in order to progress in the development of the global strategy while making sure it will encompass regional specificities. The final strategy document will be presented during the FAO/OIE Global Conference on Foot and Mouth Disease Control to be held in Bangkok from 27 to 29 June 2012.

In that context, work being done under regional programmes such as SEACFMD and OIE/JTF Project on FMD Control in Asia, under the overall coordination of the regional GF-TADs, is of paramount importance in the evolution of a regional FMD control strategy that is in line with the global strategy under development.

7. Conclusion

In the Asia region, FMD outbreaks have continued to occur widely, associated with the rapid increase in economic activity. Although FMD serotype O is still predominant in outbreaks in the region, outbreaks due to serotypes A and Asia 1 also occur sporadically but widely. In most cases, good matching vaccines are available for the FMD serotypes occurring in the region and they can be selected based on the information provided by OIE/FAO Reference Laboratories for FMD. In some cases, however, such as recent outbreaks due to Asia 1 and SEA topotypes, no matching vaccines are currently available. Member Countries should therefore be aware that a good matching vaccine is not always available and make every effort to develop an effective early detection system for such FMD outbreaks.

Another crucial way and also an obligation of OIE Member Countries to reduce the spread of FMD in the region is to immediately notify any occurrence of FMD to the OIE and neighbouring countries. Phylogenic analysis has revealed that there are strong links between FMD outbreaks occurring in different Members of the region.

Further research is needed in vaccine development and the possible use of antiviral agents in pigs as an alternative or complimentary control measure to limit the excretion of virus during FMD outbreaks.

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