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Potential of antiviral therapy and prophylaxis for controlling RNA viral infections of livestock

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Abstract

With intensification of trade, livestock are increasingly exposed to severe animal diseases caused by a range of RNA viruses. Recent prime examples include outbreaks of foot-and-mouth disease (FMD), peste des petits ruminants, Rift Valley fever and bluetongue. To minimise their impact, controlling the spread of virus is of utmost importance. Good quality, reliable vaccines exist for some, although not all, of these diseases, but suffer from a set of drawbacks, not the least of which being the time needed to trigger the immune response (i.e. "immunity-gap"). Effective, rapid control tools are, therefore, urgently needed and antiviral compounds could serve this purpose. Although limited in vitro and in vivo research has been performed, encouraging results for FMD suggest that livestock could be protected against infection within 24 h following antiviral treatment and up to 12 h post-infection. Such prophylactic/therapeutic antiviral drugs could complement emergency vaccination in a previously disease-free setting or be applied to treat valuable zoological collections and breeding stocks in endemic and previously disease-free regions alike. This paper will primarily focus on the effects of FMD on livestock and other sectors, and on appropriate control tools. The outlined principles can be extrapolated to other RNA viral diseases.

Keywords: RNA virus; Control; Stamping out; Vaccination; Antiviral; Foot-and-mouth disease; Rift Valley fever; Classical swine fever; Avian influenza; Newcastle disease; Peste des petits ruminants; Rinderpest; Swine vesicular disease; African horse sickness; Bluetongue; Vesicular stomatitis; Livestock

1. Introduction

Highly pathogenic RNA viruses of livestock can be defined as those RNA viruses that cause highly contagious or transmissible animal diseases which have the potential for very severe and rapid spread, irrespective of national borders, which are considered to be of serious socio-economic and/or public health consequence, and which are of major importance in international trade of animals and their products (i.e. transboundary animal diseases or TADs; Domenech et al., 2006). By definition, these diseases closely relate to the former World Organisation for Animal Health (OIE) List A diseases (OIE, 2004). Of the 15 diseases described, 11 are caused by RNA viruses from 7 different families (Table 1). Additionally, nearly 30% of all other OIE-listed diseases of terrestrial animals are attributed to RNA viral infection which highlights the threat these agents pose to the livestock industry.

"Livestock" is a collective term used for any breed or population of animals kept by humans for subsistence or commercial interest. Worldwide, the sector accounts for 40% of the agricultural gross domestic product (Steinfeld et al., 2006). For the purpose of this paper, however, the term will be restricted to cattle, pigs, sheep and goats. The focus will, thus, be put on Rift Valley fever (RVF) virus, classical swine fever (CSF) virus, peste des petits ruminants (PPR) virus, rinderpest (RP) virus, foot-and-mouth disease (FMD) virus, swine vesicular disease (SVD) virus, bluetongue (BT) virus and vesicular stomatitis (VS) virus (Table 1).

The aim of the present paper is to describe the impact of highly pathogenic RNA viruses on livestock and the community at large, to summarise existing control measures and to inquire into the possibility of using antiviral drugs, as an adjunct to available measures for disease control in livestock, both in disease-free and disease-enzootic settings. Although there has been considerable interest in antiviral therapy for humans who are infected with H5N1 or other highly pathogenic

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Table 1
RNA viral family, genus and species of former World Organisation for Animal Health List A diseases

Family	Genus	Species	Disease	Main affected livestock species					Zoonotic agent
				Cattle	Pigs	Sheep	Goats	Others	
Bunyaviridae	*Phlebovirus*	Rift Valley fever virus	Rift Valley fever	X	–	X	X	–	X
Flaviviridae	*Pestivirus*	Classical swine fever virus	Classical swine fever	–	X	–	–	–	–
Orthomyxoviridae	*Influenza A virus*	Avian influenza virus	Avian (bird) flu	–	–	–	–	Avian	X
Paramyxoviridae	*Avulavirus*	Newcastle disease virus	Newcastle disease	–	–	–	–	Avian	X
	Morbillivirus	Peste des petits ruminants virus	Peste des petits ruminants	X[a]	X[a]	X	X	–	–
	Morbillivirus	Rinderpest virus	Rinderpest	X	X	X	X	–	–
Picornaviridae	*Aphthovirus*	Foot-and-mouth disease virus	Foot-and-mouth disease	X	X	X	X	–	–
	Enterovirus	Swine vesicular disease virus	Swine vesicular disease	–	X	–	–	–	–[b]
Reoviridae	*Orbivirus*	African horse sickness virus	African horse sickness	–	–	–	–	Equidae	–[c]
	Orbivirus	Bluetongue virus	Bluetongue	X	–	X	X	–	–
Rhabdoviridae	*Vesiculovirus*	Vesicular stomatitis virus	Vesicular stomatitis	X	X	X	X	Equidae	X

The viruses are listed in alphabetical order starting at the family level.
[a] Can become infected. However, no clinical signs or virus transmission has been observed.
[b] Sporadic laboratory infections have been recorded.
[c] Occasionally through intranasal exposure to certain vaccine strains.

influenza viruses (De Clercq and Neyts, 2007) through exposure to ducks or chickens, antiviral drugs should not be used to treat influenza-infected poultry, as this may favour the emergence of drug-resistant viruses. Avian influenza therefore will not be discussed.

2. Impact of FMD outbreaks on agriculture and livestock

The FMD virus (FMDV) is a classic example of a highly contagious RNA virus that affects multiple species, has an extremely high mutation rate (Domingo et al., 2003) and is very disruptive to normal life and economic activity. Moreover, FMDV is globally ranked by veterinary authorities as the first and foremost priority (Domenech et al., 2006). Hence, FMDV will serve as a model throughout the paper and its control module will be extended to that of the above-listed RNA viruses.

The impact of FMD differs significantly between disease-free and disease-enzootic countries/zones (Perry and Rich, 2007), and is largely dependent upon the trade status of the respective country/zone. Economic considerations and access to lucrative trade markets are indeed by far the major incentives for controlling FMD (FAO, 2006).

The main concern of FMD-free regions is to prevent virus introduction. Despite all efforts to control the borders, outbreaks will occur, as exemplified by the 2001 FMD outbreak in the United Kingdom (UK) and the 1997 outbreak in Taiwan (Yang et al., 1999), both suspected to be the result of illegal movement of infected animals or animal products and/or the use of illegal consignments of contaminated feed (Donaldson, 2002; Kitching and Alexandersen, 2002). The 2001 epidemic generated costs totalling £8–9 billion, of which £3.1 billion represented direct losses to agriculture and the food chain (Thompson et al., 2002). Indirect losses to tourism were estimated to be as high as £5 billion (Campbell and Lee, 2003). The direct economic consequences of the Taiwan outbreak (US$ 3.31 billion) consisted of a ban in export trade to Japan of 6 million pig carcasses and the purchase of emergency vaccines. Similarly high revenue impact figures are predicted in case of FMD incursions in Australia, New Zealand and the United States of America (Belton, 2004; Garner et al., 2002; Paarlberg et al., 2002).

Moreover, the 2001 epidemic had a profound impact on society at large. Farmers in the affected countries saw 4.4 million animals destroyed (OIE, 2007a), had to cope with decreased livestock prices, standstills were imposed (Scudamore, 2001), road blocks put up, social events cancelled and there even was a 1-year ban on fox-hunting (Baker et al., 2002). The resulting human tragedy unfortunately led to farmer suicides (Nerlich et al., 2002).

Although not always as apparent, FMD also has diverse, albeit unmistakeable impacts in FMD-endemic settings (usually developing countries), as livestock contribute to the livelihood of roughly 70% of the world's poor (DFID, 2000). Controlling FMD would have positive market and non-market benefits, such as healthier animals (e.g. increased fertility, Hugh-Jones, 1979; increased meat quality and quantity), additional income through renting of animals, increased milk production (Sarma et al., 2004) and eventually improved market access (Perry and Rich, 2007). All leading to the conclusion that poverty – in terms of hunger eradication, child mortality reduction and improved human health – can be reduced by improved animal health (Perry and Sones, 2007). The incentive for FMD control, however, varies and its cost is weighed against the benefits of controlling diseases such as PPR, contagious bovine pleuropneumonia and haemorrhagic septicaemia that, unlike FMD (although mortality in young animals may reach 50%; Bachrach, 1985), induce high mortality rates in susceptible animal populations.

3. Existing FMD control measures

The current version of the OIE Terrestrial Animal Health Code makes provision of zoo-sanitary measures (i.e. disin-

fection, decontamination and cleaning of the animal holding facilities, their surroundings, transport vehicles and equipment), movement restrictions, "stamping out" (i.e. culling and disposal of all infected and susceptible "contact" livestock) and/or vaccination to control outbreaks and regain FMD-freedom (OIE, 2007b). Until recently, most FMD-free countries/zones not practising routine vaccination favoured a "stamping out" policy accompanied by zoo-sanitary measures and movement restrictions (e.g. Council Directive 90/423/EEC), mainly because of the short 3-month waiting period to recover FMD-free status (OIE, 2007b). As a result of the mass slaughter of animals during the 2001 epidemic, however, "stamping out" has been the topic of heated debate. Consequently, and accelerated by the availability of reliable "marker" vaccines and DIVA tests (i.e. tests that *d*ifferentiate *i*nfected from *v*accinated, uninfected *a*nimals) (Bergmann et al., 2000; Brocchi et al., 2006), both OIE and European guidelines were amended to facilitate the use of emergency vaccination (Council Directive 2003/85/EC) and to reduce the waiting period from 12 to 6 months when applying such vaccination (OIE, 2007b).

Although "stamping out" has proven successful as a first line of defence, some of its shortcomings merit consideration. First, it can only be successfully applied when FMD is quickly recognised and diagnosed. Logistically it is less feasible with widespread disease in a densely populated livestock area and intensive surveillance is needed to identify infected and dangerous "contact" premises (Barteling and Sutmoller, 2002). Insufficient decontamination of equipment and improper biosecurity measures contribute to the further spread of the disease (Honhold, 2006). Additionally, pre-emptive culling of "contact" animals often leads to the unnecessary death of thousands of healthy animals and poses a threat to zoological collections and breeding stocks, not to mention the human trauma related to the burning, and the images thereof, of thousands of carcasses (Nerlich et al., 2002).

In FMD-endemic and FMD-free-with-vaccination countries/zones, outbreaks are primarily controlled by vaccination (Lubroth et al., 2007). Apart from having to ensure a cold chain (FMD vaccine must be stored at 4 °C to guarantee stability), the logistics needed to carry out a vaccination campaign are relatively simple. Vaccination could be performed by farmers (Barteling and Sutmoller, 2002) which would greatly reduce the risk of cross-contamination between infected and disease-free premises. The current vaccine is fairly cheap (€3 per vaccinate) (Umans and Deleu, 2001) and proper application prevents clinical signs (Cox et al., 2005; Orsel et al., 2007) and animal suffering. Moreover, FMD vaccination reduces virus transmission (Cox et al., 1999; Orsel et al., 2005; Salt et al., 1998) and new outbreaks may cease within a week (Barteling and Sutmoller, 2002).

Nevertheless, some drawbacks persist when relying on (emergency) vaccination. Because of the existence of seven FMDV serotypes and multiple subtypes (Belsham, 1993) with little or no cross-protection among them, the efficacy of this policy depends on vigilant epidemiological monitoring to identify new strains and on the selection of an appropriate vaccine to match the circulating field isolate (Paton et al., 2005). Therefore, a suitable vaccine will probably not be available during the first few days of an outbreak. Moreover, even the best available vaccines only confer complete clinical protection 7 days post-vaccination because of the time needed to trigger the immune response (i.e. "immunity-gap") (Eblé et al., 2006; Golde et al., 2005). Delays in vaccine availability and in the onset of protection implies that during the critical initial stage of an outbreak, livestock will remain highly susceptible to infection. Furthermore, in FMD-endemic regions, vaccination of animals less than 6 months of age is hindered by the existence of maternal antibodies (Condy and Hedger, 1978). Table 2 summarises the advantages and limitations of the FMD "stamping out" and vaccination policy.

4. Potential for anti-FMD antiviral drug therapy and prophylaxis

To address some of the gaps in the current control measures (e.g. "immunity-gap", serotype-dependence, animal welfare, public opposition to mass pre-emptive culling, maternal antibodies), alternative and/or supplementary methods need to be investigated, developed and marketed. During recent years there has been an upsurge in papers dealing with the potential use of both specific and non-specific antiviral agents for rapid inhibition of FMDV replication and the early onset of protection against the disease. The success of such antiviral regimens, however, depends on the potency (efficacy), selectivity (specificity), safety (possible side-effects) and drug-resistance profile of the agents used. This section reviews substances that have been shown to be active against FMDV and discusses their potential advantages and disadvantages as prophylactic (i.e. significant reduction in the number of diseased animals) and therapeutic (i.e. significant reduction in the duration/severity of disease) tools.

4.1. Non-specific anti-FMDV agents

In 1977, Cunliffe et al. demonstrated that interferon inducers, such as polyriboadenylic–polybouridylic acid and polyriboninosinic–polyribocytidylic acid (poly-IC), respectively enhanced the immunological response of guinea pigs and pigs to FMD vaccination (Cunliffe et al., 1977). Pre-treatment of pigs with 1 mg/kg poly-IC alone, however, was unable to stimulate resistance to FMDV infection. Nevertheless, the paper highlighted the potential for non-specific inhibition of FMDV replication in vivo by interferon, which was put to the test some 25 years later. Research demonstrated that pigs were protected against FMDV within 1 day following 10^9 pfu/animal of adenovirus-expressed porcine type I interferon (Ad5-PoIFN-α) inoculation. None of the treated pigs developed clinical signs or had detectable viremia, and only low levels of FMDV-specific neutralising antibodies were observed (Chinsangaram et al., 2003). Moreover, protection lasted for 3–5 days (Grubman, 2005). However, when cattle were inoculated with 10^{10} pfu/animal of Ad5-PoIFN-α, the appearance of lesions and fever was delayed and disease was less severe, but none of the animals was completely protected (Wu et al., 2003). The

Table 2
Advantages and limitations of "stamping out" and vaccination as foot-and-mouth disease control policies

Policy	Advantages	Limitations
Stamping out	Recovery to OIE FMD-free status after 3 months	Expensive when applied on large-scale
	Good first line of defence	Logistically difficult in case of widespread disease
	Favoured cost–benefit policy if applied during a short period of time	Logistically difficult in densely populated livestock areas
		Active and intensive surveillance needed to track infected and dangerous "contact" premises
		Insufficient decontamination of equipment contributes to the spread of FMDV
		Increased risk of "through the gate" or indirect contact infection
		Strict bio-security measures are needed for the disposal of the carcasses
		Animal welfare and bio-ethical issues
		Human tragedy and traumatic experience for all those directly or indirectly involved
Vaccination	Relatively cheap	Recovery to OIE FMD-free status after 6 months
	Logistics are rather simple	Vaccine is serotype and to lesser extent subtype specific
	Vaccination by farmers is feasibly and reduces the risk of cross-contamination	Vaccine probably unavailable during first few days of an epidemic (formulation period)
	Outbreaks cease within a week after application of potent FMD vaccine	Vaccine requires cold chain to maintain its stability and efficacy
	Minimal socio-economic consequences if vaccination is not suppressive (vaccinate-to-life)	FMD live virus escapes from vaccine production facilities have contributed to past outbreaks
	Prevents clinical disease and animal suffering	Immunity-gap during first 4–7 days
		Duration of immunity is limited to 6 months
		Marker vaccine and DIVA diagnostic test must be available

studies were subsequently expanded by combining interferon types I and II. Results indicated that both types of interferon acted synergistically to inhibit FMDV replication in vitro and in vivo (Moraes et al., 2007). The duration of protection both in swine and in cattle was prolonged by a single-shot delivery of a replication-defective human adenovirus type 5 expressing both porcine interferon alpha and a capsid-FMDV subunit vaccine (Moraes et al., 2003; Pacheco et al., 2005), combining the benefits of antiviral treatment (early onset of protection) and vaccination (long-lasting immunity).

Other significant anti-FMDV activity was observed using a potent stimulator of the innate immune response, *in casu* oligonucleotides containing unmethylated CpG motifs (CpG ODN) which stimulate cytokine synthesis and cellular activation. Subcutaneous inoculation of this non-specific antiviral agent in mice 4 days prior to viral challenge was found to reduce viremia, generalised disease and death for five of the six FMDV serotypes tested, but failed to protect against serotype SAT3 (Kamstrup et al., 2006). The effect was observed even when CpG ODN was administrated up to 12 h post-infection and lasted for 14 days. In vitro experiments with CpG ODN in which no inhibitory effect on FMDV replication could be demonstrated, further supported the assumption that CpG ODN protection is immune-system modulated (Kamstrup et al., 2006).

Cytokines such as interferon and non-specific stimulators of innate immunity such as CpG are broad-spectrum antimicrobial agents. Although the above-mentioned compounds are safe since natural host defence mechanisms are stimulated and exert potent antiviral activity against FMDV in limited controlled experimental settings with healthy animals, no data are available about their efficacy in the field. It is at present unclear if their lack of selectivity would not reduce the demonstrated potency against FMDV when administered to animals already immune-compromised due to prior infections of viral, bacterial or fungal origin.

4.2. Specific anti-FMDV agents

More specific FMDV inhibitors were recognised in 1987, when De la Torre et al. reported on the antiviral effects of the nucleoside analogue ribavirin [1-β-D-ribofuranosyl-1*H*-1,2,4-triazole-3-carboxamide] which was found to eliminate FMDV – measured by both virus yield assays and infectious intracellular RNA quantification – from acutely and persistently infected BHK-21 cell cultures at 50% effective concentrations (EC_{50}) of 30–50 μg/ml and 3–6 μg/ml, respectively (De la Torre et al., 1987). Subsequent research demonstrated that the mode of action of ribavirin against FMDV involved at least two mechanisms: direct mutagenesis driving the virus to error catastrophe (i.e. increase in the error frequency during viral replication that results in loss of viral infectivity) (Airaksinen et al., 2003; Crotty et al., 2002) and inhibition of inosine 5′-monophosphatase (IMP) dehydrogenase, a cellular enzyme engaged in viral RNA synthesis and in balancing guanine nucleotides (Airaksinen et al., 2003). Since it partially targets a host enzyme on which the infecting virus itself has little or no influence, ribavirin is notable for not generating drug resistance (De Clercq, 2006) and to our knowledge resistance of FMDV replication has not been reported.

Related mutagenic base analogues, such as 5-fluorouracil and 5-azacytidine, reduced FMDV progeny by 50–100-fold in vitro. Both compounds are readily incorporated into RNA strands and interfere with RNA processing and translation causing abundant nucleoside transitions and virus mutants, resulting in a loss of

Table 3
Small molecules reported to inhibit the replication of FMDV

Antiviral compound	In vitro activity (EC_{50})	In vivo activity
Ribavirin	30–50 μg/ml (De la Torre et al., 1987: lytic infection); 214 ± 124 μg/ml (Goris et al., 2007: lytic infection); 3–6 μg/ml (De la Torre et al., 1987: persistent infection)	Remains to be explored
5-Fluorouracil	100–1000 μg/ml (Sierra et al., 2000)	Remains to be explored
5-Azacytidine	10 μg/ml (Sierra et al., 2000)	Remains to be explored
2′-*C*-Methylcytidine	1.7 ± 1.0 μg/ml (Goris et al., 2007)	Remains to be explored
T-1105	1.6 μg/ml (Sakamoto et al., 2006)	Pigs, mixed with feed, 200 mg/kg (Sakamoto et al., 2006)

viral fitness and infectivity (Sierra et al., 2000). Despite these promising developments, safe application of error catastrophe as an antiviral strategy requires addressing issues like toxicity to cellular enzymes and the potential provocation of virus mutants with unpredictable biological properties as a result of insufficiently high concentrations of mutagenic agents (Domingo et al., 2005). However, combining the effects of mutagens and other inhibitors that exert different antiviral effects can induce high-fitness FMDV extinction as demonstrated in vitro by Pariente et al. (2005). These results support observations made in the treatment of *Mycobacterium tuberculosis* and HIV infections where combination regimens achieve greater benefit than each drug given individually, reduce the likelihood of resistance development and might allow individual doses to be lowered, thereby diminishing adverse effects (De Clercq, 2006).

Further in vitro studies identified a 50–140-fold more potent inhibitor of the FMDV replication, namely the nucleoside analogue 2′-*C*-methylcytidine which is active against all seven FMDV serotypes and is suspected to target the FMDV RNA-dependent RNA polymerase (Goris et al., 2007). Moreover, since FMDV is a member of the *Picornaviridae* family in which viruses causing important human diseases are also classified (e.g. poliovirus and rhinoviruses), it may be possible to implement strategies that have been developed to inhibit these human viruses. For instance, several drugs (e.g. pleconaril) have been developed (although none of them are being used clinically) that block the host cell attachment and/or uncoating events of picornaviruses. Other drugs target the viral 2A gene product (enviroxime), the viral 2C gene product(s) (TBZE-1) or the viral 3C protease (rupintrivir) (De Clercq, 2006; De Palma et al., 2007).

Although no in vivo testing of the aforementioned agents has been performed, work on pyrazinecarboxamide derivates, and in particular T-1105, both in vitro (EC_{50} = 1.6 μg/ml) and in pigs clearly underlines the potential applicability of such compounds as alternative and/or supplementary control tools, since all animals were protected against clinical disease and FMDV could not be recovered from nasal swabs (suggesting a reduction in virus excretion and transmission). Very low anti-FMDV antibody titres were detected when the compound was administered to pigs at concentrations of 200 mg/kg twice daily for 6 days, starting one hour before challenge, by mixing it with their feed (Sakamoto et al., 2006).

Another antiviral strategy that is being pursued is the feasibility of controlling FMD outbreaks using gene expression silencing by RNA interference (RNAi). Plasmids expressing short hairpin RNA targeted to the highly conserved non-structural protein 2B coding region are capable of inhibiting the replication of multiple FMDV serotypes in porcine cells by approximately 97–98% (de los Santos et al., 2005), whereas FMDV serotype-specific inhibition was obtained by RNAi targeting the VP1 gene (Chen et al., 2004). Moreover, the use of different delivery systems for mediating RNAi such as adenovirus vectors is being studied (Chen et al., 2006). However, one may question whether a technology such as RNAi is applicable in a field situation since the concept is yet to be validated for human use. Table 3 provides a non-exhaustive overview of agents that have been reported to inhibit FMDV replication, either in vitro or in vivo.

Even if antiviral protection is short-lived, it may prove sufficient to bridge the "immunity-gap". Moreover, given the rapidity with which FMD spreads in susceptible animal populations, treatment before and/or early in the course of infection is likely to offer maximum effect. However, antiviral regimens will probably have to be limited in time so as to prevent the development of viral resistance to the drugs in question.

5. Scenarios for anti-FMDV antiviral therapy and prophylaxis

One or a combination of potent, selective antiviral agents might be beneficial in previously FMD-free countries/zones in the following scenarios:

- Prophylactic antiviral drugs could be used as an adjunct to emergency FMD vaccination to bridge the "immunity-gap" and hence reduce viral replication, excretion and transmission.
- The best currently available DIVA tests are not sufficiently sensitive and specific to allow the detection with 95% confidence and 5% prevalence of a single FMDV-infected animal in a vaccinated herd of less than 30 ruminants (the "small herd problem"). Proposed strategies to circumvent this problem include avoiding vaccinating such herds in the first place (Paton et al., 2006). In that case, an effective antiviral could be used prophylactically to protect such herds against infection and subsequent culling.
- Antiviral therapy and prophylaxis could be used when precious zoological collections and rare breeding stocks are infected or are in danger of being so.

In FMD-endemic countries/zones, the large-scale applicability of antiviral therapy and prophylaxis at present will dependent on the ease of storage and administration and on cost. Small-scale usage, however, is not unthinkable. Recently, the Thiruvananthapuram zoo (India) lost 19 of its animals, among which were blackbucks (endangered antelope species) and mithuns (rare bovine species), to an endemic FMDV serotype O infection (ProMED-mail, 2007). Maybe these losses could have been avoided by the availability of antiviral compounds that reduce or inhibit virus replication. In rural settings and if considered advantageous (cost/benefit analysis), young animals could also be treated which would overcome the current problem associated with insufficient immunisation conferred by vaccination due to the presence maternal antibodies.

6. Extending antiviral drug therapy and prophylaxis to other highly pathogenic RNA viral infections of livestock

Approximately 60 countries officially reported to the OIE the occurrence of one or more of the above-mentioned TADs, excluding FMD, on their territories in 2006 (OIE, 2007c). Their presence was quite surprising at times as shown in North West Europe where BT caused an extensive epidemic while virus transmission by the available *Cullicoides* vector was unexpected given the moderate climate conditions (Toussaint et al., 2007). During the first half of 2007, almost half a million susceptible animals have been exposed to these agents, of which 10% either succumbed to the disease or were destroyed or slaughtered (OIE, 2007c). Case fatality rates ranged from 0% (SVD) to as high as 74–76% (CSF and PPR). The true, unofficial, incidence was most certainly higher.

Like FMD, these diseases are usually controlled by "stamping out" (e.g. SVD in Portugal in 2007), vaccination (e.g. Global RP Eradication Programme) or a combination of both. With the exception of SVD for which no vaccine is on hand (De Clercq and Goris, 2004; Dekker, 2000), live attenuated and/or inactivated virus vaccines are available (BT: Bréard et al., 2003; CSF: Dewulf et al., 2004; PPR: Diallo, 2003; RVF: Gerdes, 2002; VS: House et al., 2003; RP: Roeder and Taylor, 2002). However, apart from the disadvantages listed in Table 2, these vaccines do not always cover all virus serotypes (e.g. BT virus), nor do all of them, and in particular live attenuated virus vaccines, meet "marker" requirements to differentiate vaccinated from infected animals (e.g. BT, RVF, PPR, limited sensitivity of the DIVA test for CSF: Floegel-Niesmann, 2003). Additionally, inadequate attenuation of live virus vaccines has been shown to cause serious disease in the field (e.g. BT: Monaco et al., 2006).

As in the case of FMD, alternative/supplementary disease control tools are, thus, urgently needed. Limited research has been directed towards the development of antiviral therapies in vitro. For instance, known FMDV inhibitors have shown to inhibit RP virus (5-fluorouracil: Ghosh et al., 1996), SVD virus (2′-*C*-methylcytidine: Goris et al., 2007) and RVF virus (ribavirin: Peters et al., 1986), whereas two *S*-adenosylhomocysteine (SAH) hydrolase inhibitors, 3-deazaguanine and 3-deazauridine, have proven active against BT virus (Smee et al., 1981), two additional SAH inhibitors, neplanocin A and 3-deazaneplanocin A, interfere with the replication of the VS virus (De Clercq et al., 1989). Inhibition of other cellular enzymes, such as the oritidine 5′-phosphate (OMP) decarboxylase, using pyrazofurin and derivatives thereof has been observed for RVF virus (Canonico et al., 1982; Goebel et al., 1982). 5-[(4-Bromophenyl)methyl]-2-phenyl-5*H*-imidazo[4,5-*c*]pyridine (BPIP), a known inhibitor of the viral RNA-dependent RNA polymerase of pestiviruses (Paeshuyse et al., 2006), inhibited CSF viral replication in vitro (Vrancken et al., 2008) and inhibition of the RNA polymerase of the PPR virus was demonstrated using uracil derivates (El-Sabbagh et al., 2007).

Antiviral strategies based on iRNA are also being considered for most viruses (VS: Barik, 2004; PPR and RP: Servan de Almeida et al., 2007; BT: Wirblich et al., 2006). In addition, interferon inducers and interferon inhibited the majority of highly pathogenic RNA viruses, confirming their broad-spectrum antiviral activity (SVD: Amadori et al., 1987; VS: Basu et al., 2006; BT: Coen et al., 1991; RP: Fujisaki et al., 1968; RVF: Peters et al., 1986).

Table 4
Viral and/or cellular targets for specific antiviral molecules against highly pathogenic RNA viruses

Virus family	Viral target	Cellular target
Bunyaviridae (RVF virus)	RNA polymerase: remains to be explored	IMP dehydrogenase: ribavirin (Peters et al., 1986); OMP decarboxylase: pyrazofurin (Canonico et al., 1982; Goebel et al., 1982)
Flaviviridae (CSF virus)	RNA polymerase: BPIP (Vrancken et al., 2008)	Remains to be explored
Paramyxoviridae (PPR and RP virus)	Fusion polypeptide: remains to be explored; RNA polymerase: RP virus: 5-fluorouracil (Ghosh et al., 1996); RNA polymerase: PPR virus: uracil derivates (El-Sabbagh et al., 2007)	Remains to be explored
Picornaviridae (SVD virus)	Viral capsid: remains to be explored (Verdaguer et al., 2003); viral 3C protease, viral 2A and 2C gene products: remains to be explored; RNA polymerase: 2′-*C*-methylcytidine (Goris et al., 2007)	Remains to be explored
Reoviridae (BT virus)	Remains to be explored	IMP dehydrogenase: ribavirin (Smee et al., 1981); SAH hydrolase: 3-deazaguanine, 3-deazauridine (Smee et al., 1981)
Rhabdoviridae (VS virus)	RNA polymerase: remains to be explored	SAH hydrolase: neplanocin A, 3-deazaneplanocin A (De Clercq et al., 1989)

Clearly, most of this work is far from ready for field applicability. Nevertheless, the basic scenarios for controlling FMD, listed in the above paragraph, in which the availability of an antiviral drug might prove beneficial can also be envisaged for other highly pathogenic RNA viral infections. Drug delivery in pigs could be envisaged by mixing the compound with pig feed as demonstrated by Sakamoto et al. (2006), whereas injectable or bolus compounds will most likely have to be developed for administration to ruminants. It should be noted, however, that bridging the "immunity-gap" may be less realistic when a live attenuated virus vaccine is used, as the antiviral compound might hinder vaccine efficacy. Table 4 presents the viral and/or cellular targets for specific antiviral molecules against the RNA viral infections highlighted in this review. References to appropriate sources of reading are also included.

7. Concluding remarks

The control of TADs remains of paramount importance to protect livestock against severe and sometimes lethal diseases, many of which are induced by highly pathogenic RNA viruses. Existing control measures include "stamping out", vaccination or a combination of the two, accompanied by zoo-sanitary measures and severe movement restrictions. Recently, thanks to encouraging developments in antiviral therapy, we may be witnessing a paradigm shift in controlling TADs as conventional control tools are no longer regarded as the "Holy Grail". Some questions concerning the use of antiviral compounds (efficacy, selectivity, safety, route of administration, uptake and clearance of the compound in the animal, development of drug-resistant mutants, possible risk to humans of residual compound in food-producing animals, etc.), however, will need to be addressed, and further in vivo research will be required before antiviral compounds are readily available and taken up in contingency plans. Moreover, to get antiviral therapy or prophylaxis accepted by the competent authorities, controlled field trials might need to be set up in regions where TADs are endemic. Nevertheless, their potential for early protection and their serotype-independence make antiviral drugs highly attractive candidates for pro-active research.

In conclusion, given the severe socio-economic consequences related to RNA viral infections, it is not unreasonable for public/private partnerships to spend a few millions euros to find out how antiviral compounds might help to cure, control and eradicate disease, and possibly a few million more to stockpile an effective therapy for emergency use, either in a disease-free or disease-endemic setting. Moreover, as some of these livestock viruses are zoonotic agents (Table 1) and also pose a threat to human health (from December 2006 to May 2007 alone RVF caused four times more human casualties in Kenya, Somalia and Tanzania than HPAI did globally during the entire 2006 epidemic; WHO, 2007), the development of prophylactic and/or therapeutic agents is of utmost importance. There is thus a great opportunity for closer collaboration between human and veterinary scientists to enhance developments in this field of research.

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