

Rift Valley fever – a growing threat to humans and animals

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Received: July 23, 2020 Accepted: January 19, 2021

Abstract

Rift Valley fever (RVF) is a zoonotic, vector-borne infectious disease of ruminants and camels transmitted mainly by the *Aedes* and *Culex* mosquito species. Contact with the blood or organs of infected animals may infect humans. Its etiological factor is the Rift Valley fever virus (RVFV) of the *Phlebovirus* genus and *Bunyaviridae* family. Sheep and goats are most susceptible to infection and newborns and young individuals endure the most severe disease course. High abortion rates and infant mortality are typical for RVF; its clinical signs are high fever, lymphadenitis, nasal and ocular secretions and vomiting. Conventional diagnosis is done by the detection of specific IgM or IgG antibodies and RVFV nucleic acids and by virus isolation. Inactivated and live-attenuated vaccines obtained from virulent RVFV isolates are available for livestock. RVF is endemic in sub-Saharan Africa and the Arabian Peninsula, but in the last two decades, it was also reported in other African regions. Seropositive animals were detected in Turkey, Tunisia and Libya. The wide distribution of competent vectors in non-endemic areas coupled with global climate change threaten to spread RVF transboundarily. The EFSA considers the movement of infected animals and vectors to be other plausible pathways of RVF introduction into Europe. A very low risk both of introduction of the virus through an infected animal or vector and of establishment of the virus, and a moderate risk of its transmission through these means was estimated for Poland. The risk of these specific modes of disease introduction into Europe is rated as very low, but surveillance and response capabilities and cooperation with the proximal endemic regions are recommended.

Keywords: Rift Valley fever virus, vector-borne disease, mosquitoes, haemorrhagic fever.

Introduction

Rift Valley fever (RVF) is a zoonotic, vector-borne infectious disease classified as a haemorrhagic fever. The aetiological factor of the disease is the Rift Valley fever virus (RVFV), considered one of the most important pathogens in Africa (15, 16). RVFV belongs to the *Bunyaviridae* family and *Phlebovirus* genus with nine other species including Punta Toro virus, sandfly fever virus, and severe fever with thrombocytopenia syndrome virus (72). RVF is a lethal illness, with high rates of mortality and abortion, causing economic losses in affected regions. RVFV infects cattle, sheep, goats and camels in an age-dependent manner, where young animals are significantly more likely to suffer than adults. RVFV primarily affects animals but can also cause sickness in humans. The virus is transmitted by mosquitoes (mainly of the *Aedes* and *Culex* genera). Humans usually get RVF through contact with infected

livestock, but also can through bites from infected mosquitoes (48, 62). As other arboviral infections (e.g. dengue, chikungunya and Zika), RVF may emerge worldwide as a result of globalisation's distribution effect on arthropod vectors, mainly mosquitoes, which transmit an increasing number of unrecognised and new viruses efficiently. The risk is real of arbovirus introduction to continents including Europe and North America with the possibility of co-circulation (53). The World Organisation for Animal Health (OIE) has designated RVF a notifiable disease (78), and it is also classified as an overlap select agent by the Centers for Disease Control and Prevention (CDC) and the United States Department of Agriculture (USDA). In 2020, the European Food Safety Agency (EFSA) published a report on the risk of RVFV's introduction to Europe due to the emergence of the fever in new territories and reported seropositivity in animals in Turkey and Tunisia (60). Evidence of seropositivity in sheep and goats that

have not lived through an RVF outbreak suggests that low-level circulation of the virus can occur in livestock (64).

Epidemiology

RVFV was first isolated in 1931 during an epidemic among sheep in the Rift Valley in Kenya (16). Since then, major outbreaks affecting livestock and humans have occurred in several countries in Africa, including Egypt, Kenya, South Africa, Madagascar, Mauritania, Senegal, and Gambia (29, 40, 59, 66, 68). The occurrence of severe epidemic RVF has been considered to be related to climate conditions, periodic flooding, a higher greenness of vegetation index, and the consequent emergence of mosquito vectors infecting susceptible ruminant hosts (59). Nevertheless, in the last decade, RVF epidemics have been occurring more frequently in West Africa and in other sub-Saharan countries. In 2000 and 2001, a major outbreak of RVF was reported for the first time outside the African continent, in Saudi Arabia and Yemen (67).

In Mayotte, an overseas department of France and part of the Comoros archipelago in the Indian Ocean, human cases of RVF were detected for the first time in 2007. Retrospective serological studies demonstrated the presence of RVFV in livestock since 2004. RVF re-emerged in 2018, when 142 human cases and several clusters of ruminants were reported (3, 81).

Recent studies carried out in the countries surrounding the Mediterranean (Turkey, Tunisia, Iran, Iraq, and Algeria) and in the Western Sahara, where neither a human nor animal case of the disease has ever been reported, indicate the presence of a certain level of seropositivity in animals and in humans (2, 8, 18, 28, 35, 57, 80). In most of these studies, the sample size and areas of origin of the tested animals were limited, so inference from the results may be difficult.

In January 2020, two RVF outbreaks were notified in the south-eastern Libyan region of Al Kufrah. In each outbreak (one in sheep and the other in sheep and goats), one case was declared, and regarded only serological positivity. No deaths were reported (60).

Virion structure

RVFV is an enveloped virus with the genome in the form of segmented negative-sense RNA, comprising large (L), medium (M), and small (S) segments. The L segment encodes viral RNA polymerase and the M segment encodes the Gc and Gn envelope glycoproteins and the NSm1 and NSm2 nonstructural proteins (10). The S segment shows an ambisense strategy and encodes the nucleoprotein (N protein) and the NSs nonstructural protein (32). Genomic segments make up the viral ribonucleoprotein complexes and are associated with multiple copies of the N protein and RNA-dependent RNA polymerase (10). RVFV has

an envelope composed of a lipid bilayer and the Gn and Gc glycoproteins forming heterodimers, which further assemble into pentamers and hexamers with icosahedral symmetry (37).

RVFV attaches to cells via interaction between the Gn and Gc viral glycoproteins and DC-SIGN and I-SIGN cellular C-type lectins (79). Being exposed on the outer surface of the virus, the Gn and Gc glycoproteins are recognised by the host immune system and induce neutralising antibody production. Cells are infected by receptor-mediated endocytosis of the virus, followed by pH-mediated fusion of viral and endosomal membranes resulting in the release of nucleocapsids into the cytoplasm, where transcription, translation, and genome replication occur. The non-structural protein NSs is known to be a major virulence factor allowing the virus to escape the host innate immune response through suppression of the type I interferon response (43).

Vectors

RVFV has been isolated from more than 53 species in eight genera within the *Culicidae* family, where the *Aedes* and *Culex* genera are considered to be the main vectors (48, 50). Primary vectors such as floodwater *Aedes* (e.g. *Ae. mcintoshi*, *Ae. ochraceus*, *Ae. sudanensis*, and *Ae. dentatus*) maintain the virus' viability in their eggs in dry soil even during dry periods. Vertical transmission (adult to egg) is hypothesised to allow the virus to persist during inter-epidemic and overwintering periods (47, 55). When the rainy season begins, infected eggs hatch and infected adult female mosquitoes initiate transmission to nearby animals, and then disease outbreaks may occur. Another group of secondary vector mosquitoes mainly from the *Culex* (*Culex pipiens*, *Culex poicilipes*, and *Culex univittatus*), *Anopheles*, and *Mansonia* species may move into sites with infected animals, and thus virus transmission continues, which may result in wider geographical coverage of the disease (66). Secondary vectors of RVFV transmit the virus horizontally from highly viraemic animals to humans. Epidemic transmission of RVFV has been related to heavy and prolonged rainfall primarily due to the El Niño Oscillation. Secondary vectors are highly abundant when stagnant floodwaters are colonised by *Culex* and *Mansonia* species and this increases transmission to domestic animals and humans (36).

Transmission

Direct transmission is possible among animals and from animals to humans, and its vertical mode has been described in humans, animals and vectors (Fig. 1). The main route of human infection is contact with blood, body fluids, or tissues and organs of infected animals and aborted animal fetuses. Infection can occur by inhaling aerosols of infectious body fluids. Therefore, various forms of employment cannot avoid exposure as

an occupational hazard and in particular skinning or slaughtering of infected animals and veterinary practices are among the activities the least safe from RVFV infection risk. Consumption of raw or unpasteurised milk has also been identified as a risk factor for RVFV infection (77). Grossi-Soyster *et al.* (34) suggest that exposure to raw milk might contribute to a significant number of cases of RVF, especially during outbreaks and in endemic areas. Mosquito bites are also considered

a risk factor for RVFV infection in humans. There is no documented direct horizontal human-to-human transmission, although sporadic RVFV vertical transmission from mothers to their newborns has been reported (1). Considering wild animals as an RVFV reservoir, the possibility of African buffalo (*Syncerus caffer*) or other wild native or endemic ruminants, wild rodents or bats participating in the spread of the virus is not proven but also not discounted (4, 27, 42, 76).

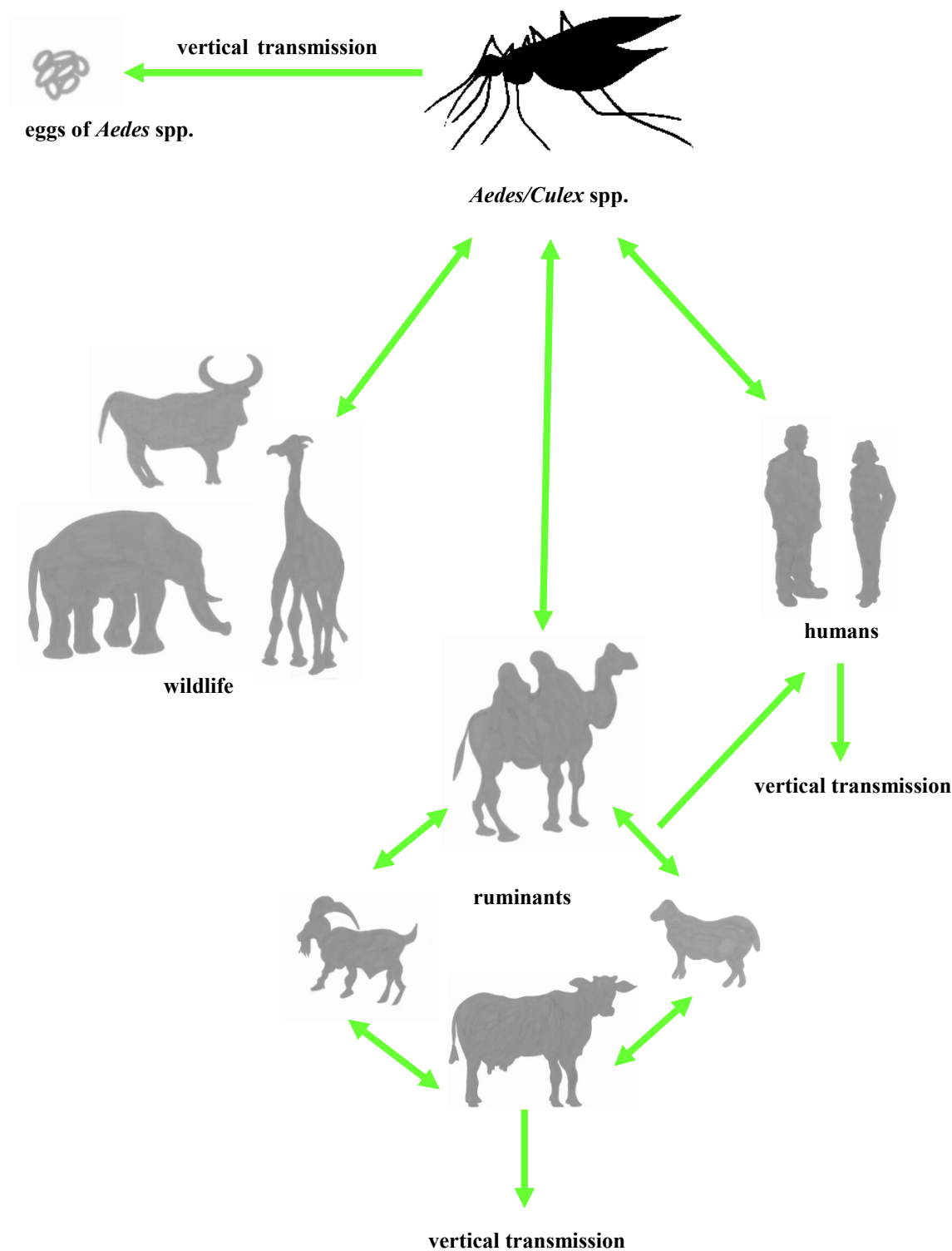


Fig. 1. The scheme of RVF transmission. Vectorial transmission is to humans, ruminants, and wildlife; direct transmission is between ruminants and from ruminants to humans; and vertical transmission is in humans, ruminants, and *Aedes spp.*

Pathogenesis

Although infection shows unique pathogenesis in each animal model (39), generally three types of infection pattern are observed (in both naturally infected and experimentally infected animals), depending on the sensitivity or resistance of the animals. It can be a severe acute infection with uncontrolled viraemia, when high blood viral load is significantly associated with fatal outcome and the infected animal dies quickly. The second pattern, with mild to asymptomatic infection, is one in which the viraemia decreases quickly. The third pattern, with delayed onset of infection complications, has fever and viraemia in the first phase, and in the second phase an additional fever episode may occur. The virus may spread to other organs in this pattern, especially to those of the central nervous system after crossing the blood-brain barrier and to the retina, which is often associated with serious long-term consequences. In both animals and humans, RVFV-induced lesions occur predominantly in the liver. This finding is consistent among severe cases and has been clearly demonstrated by histopathological examination of tissues of experimentally infected sheep (14, 62). The tropism of the virus is limited to hepatocytes and monocytes. Infection can lead to hepatocellular changes progressing to necrosis, which is manifested by increased levels of liver enzymes, leukopaenia or thrombocytopenia (30).

Clinical symptoms of RVF include high fever, lymphadenitis, nasal and ocular secretions in adult animals, haemorrhagic diarrhoea, vomiting, abdominal colic, lasting prostration, dysgalactia, jaundice, increased abortion frequency (“abortion storms”) and a high mortality rate in young animals (39). A clear distinction is observed regarding the susceptibility to and progression of RVF between young animals and adults.

Sheep and goats are the most susceptible animals to RVFV infection and show similar clinical symptoms. In sheep, the incubation period of the disease is 24–36 h. Post-mortem analysis revealed multi-focal liver necrosis and occasional mild splenomegaly (24). Adult sheep mortality after experimental infection is between 20 and 30%, while in newborn lambs it is much greater at 95–100% (22); the risk of abortion in pregnant ewes is close to 100% (39). In goats, the course of the disease can be somewhat more variable, with viraemia and symptoms inconsistent after infection. Peak viraemia in the blood of goats is also significantly lower than in lambs of identical age after experimental infection. Unlike lambs, goats do not always experience febrile illness. In goats, the formation of hepatic lesions, which are more focal in adults, is followed by necrotic hepatitis.

Cattle are less susceptible to disease than sheep and goats. RVFV infections in adults are usually asymptomatic but can also manifest as an acute disease with mortality rate up to 5 % (39, 75). A recent study has

demonstrated that the onset and duration of fever, in addition to other aspects of the disease including viraemia and liver pathology, are less consistent than in sheep (75).

Camels in turn seem to be less susceptible than cattle, with the vast majority of infections being asymptomatic. However, acute RVFV infection may still result in a severe disease course and death. Symptoms can include ocular discharge, haemorrhages, foot lesions and abortions (29).

Infection in humans primarily causes a self-limiting febrile illness. Approximately 50% of infected humans have no clinical signs, while others may experience flu-like symptoms. A small percentage may develop severe clinical forms, involving haemorrhagic fever with hepatic disease, encephalitis or ocular complications (22, 39).

Diagnosis

The techniques used for the diagnosis of RVF include detection of specific IgM or IgG antibodies, virus isolation, and detection of RVFV nucleic acids. The enzyme-linked immunosorbent assay (ELISA) is a reliable and sensitive test to detect antibodies against RVFV. A number of ELISAs of different formats are commercially available or under development (26, 41). They are used routinely in many countries for single case diagnosis, outbreak management, and surveillance. Both IgG and IgM ELISAs are available for most species. Depending on the type of ELISA used, it is possible to distinguish between recent (presence of IgM) and past (presence of IgG) infection and to differentiate between vaccinated and infected animals (DIVA). In naturally occurring infections, an antibody response against both N and NSs would be expected, whereas in individuals vaccinated with the attenuated vaccines only an antibody response to the N protein would be observed (54). Therefore, a dual-target ELISAs has been developed with two viral proteins, N and NSs, for DIVA.

Virus isolation or detection of viral RNA is performed from whole blood or serum samples taken during the acute (febrile) stage of the disease, or various post-mortem organs such as the brain, liver or spleen taken from fresh carcasses or aborted foetuses. The virus can be detected in milk, although tests are not specifically designed for this material (unpublished results from the COOPADEM farmers’ association in Mayotte). Different highly sensitive molecular tests have been developed for RVFV: nested RT-PCR (65), quantitative real-time PCR (6, 20, 31), multiplex PCR-based microarray assay (70), RT loop-mediated isothermal amplification (46), and recombinase polymerase amplification (23). Molecular tests have also been used for the detection of RVFV in mosquitoes in the Kenyan surveillance program (44, 73). Conventional and real-time RT-PCR assays are currently the most rapid and sensitive tests for the detection and

quantification of RVFV during outbreaks (31). Methods based on next-generation sequencing approaches, colorimetry, or TaqMan array cards have been developed recently, but most of these techniques are expensive and require dedicated trained personnel (11, 49, 82).

Isolation of RVFV is usually conducted by inoculation of suckling mice or various susceptible mammalian or invertebrate cell cultures (African green monkey kidney of Vero lineage, BHK-21 baby hamster kidney, and AP61 mosquito cells). A cytopathic effect is usually observed within 5 days post-inoculation, the presence of RVFV being confirmed by immunostaining (19).

A pen-side test or lateral flow immunochromatographic strip test for detection of the nucleoprotein of RVFV was developed. This type of assay helps to better manage the early diagnosis and control of RVF in the case of ongoing outbreaks (13).

Vaccine

In endemic and non-endemic areas, vaccination of livestock against RVF is an important disease control tool. Different strategies have been used to develop RVF vaccines. The earliest vaccines, such as inactivated vaccines and the live-attenuated Smithburn preparation, were developed from virulent RVFV isolates (25). The first RVF vaccine was formalin-inactivated and was based on the NDBR103 Entebbe strain isolated from a mosquito in Uganda (63). This was further developed into TSI-GSD200, a new generation of formalin-inactivated RVFV vaccine manufactured by the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID). The RVFV vaccine inactivated with formalin or ethyleneamine has been prepared for veterinary use by passage in BHK-21 hamster kidney cells. Repeated immunisation schedules and high costs are the main disadvantages of inactivated vaccines (25).

The live attenuated Smithburn vaccine is one of the oldest and most widely used vaccines for the control of RVF. The strain was isolated in 1944 in Uganda from *Eretmapodites* spp. (38). Despite its potency and low cost, the Smithburn vaccine has several disadvantages like residual pathogenicity, causing abortion and foetal malformations and not precluding its possible return to full virulence. Live attenuated vaccines are prohibited in pregnant animal prophylaxis and restricted to use in RVFV-free countries. There is also a possibility of reassortment when the vaccine is used during outbreaks, leading to increased diversity of the virus (9).

The next live attenuated vaccine, MP-12, was developed by the USAMRIID for both human and veterinary use exploiting the virulent ZH548 and ZH501 strains isolated from Egyptian patients and passaging them serially 12 times in MRC-5 cells in the presence of 5-fluorouracil as a mutagen. The MP-12 strain is temperature-sensitive and carries redundant mutations in

all three genomic segments. Generally, MP-12 has the ability to produce antibody titres sufficient to protect vaccinated animals against RVFV and there is a potential beneficial effect of immunising pregnant animals, which is the protection of newborns (12).

The natural deletion of 549 nucleotides (70%) of the NSs gene led to the development of the Clone 13 attenuated vaccine. This vaccine is based on the 74HB59 plaque-purified clone isolated in the Central African Republic. Clone 13-vaccinated animals can be easily differentiated from naturally infected animals using the DIVA test. The mutant virus is unable to replicate efficiently in vaccinated animals and does not produce a long-term immune response, which is the main disadvantage of the vaccine (58).

A group of new vaccines, produced using recombinant nucleic acid technology, includes subunit protein vaccines, DNA vaccines (45, 69), virus-like particles (VLPs) (51), virus replicon particle vaccines (61), virus vectored vaccines (74), and genetically modified live vaccines (developed from recombinant viruses engineered using reverse genetics) (5). The solutions with most promise seem to be the recombinant protein-based vaccines, VLPs, and DNA vaccines that are DIVA-compatible, because they are highly safe and a minimal environmental risk (25). Currently, no vaccines have been authorised for use in the European Union (EU) and none of the vaccines have been made available for human use.

Risk of the introduction of RVFV into the EU

The mechanisms by which RVF has moved to new geographic areas are unknown. Mosquitoes involved in RVFV transmission do not appear to migrate or move appreciable distances (47). Migrating or windblown vectors, movements of viraemic mammals, phoresy of RVFV-infected ticks on migratory birds, or movement of infected humans or vectors by aircraft have come under consideration. Studies on birds have demonstrated that they do not become infected or develop antibodies (17).

The wide distribution of competent vectors, the availability of susceptible ruminants, and global climate change combine to seriously threaten the rest of the world with the transboundary spread of RVFV. At least nine vector species able to transmit RVFV are known to be present in Europe and neighbouring countries. Among them, *Aedes caspius* and *Culex pipiens* are assumed to be the most efficient vectors (7, 21, 52, 56, 71). This should be taken into consideration in the design of surveillance and control programs which should operate in Europe (33).

According to an EFSA report (60), movements of infected animals and vectors (shipped by air, sea container or road transport) are considered other plausible pathways for the introduction of RVFV into Europe. The risk of its introduction into the EU was

assessed using a model called MINTRISK (Method to INTeegrate all relevant RISK aspects). MINTRISK estimates derive from the combination of pathogen entry rate, level of transmission (as the basic reproductive number) and the probability of the establishment of RVF in the EU (associated with the presence of susceptible hosts and conditions) along appropriate pathways for disease introduction. For Poland, the authors of the report estimated a very low risk of introduction of the virus through an infected animal or vector, a moderate risk of virus transmission through an infected animal or vector and a very low risk of establishment of the virus (60).

The overall risk of introduction of RVF into the EU through the movement of infected animals is very low in all the EU regions (assessed as less than one outbreak every 500 years). The same level of risk of introduction in all regions through the movement of infected vectors was also found, with the highest level for Belgium, Greece, Malta, and the Netherlands (one epidemic every 228–700 years), mainly linked to the number of connections by air and sea transport with African RVF-infected countries. However, taking into account the risk of the spread of RVF in countries neighbouring the EU and the potential introduction of infected vectors, the EFSA suggests that EU authorities should strengthen their surveillance and response capabilities, as well as cooperate with the countries of North Africa and the Middle East (60).

Conflict of Interests Statement: The authors declare that there is no conflict of interests regarding the publication of this article.

Financial Disclosure Statement: This study was funded by the statutory activity of the National Veterinary Research Institute in Puławy.

Animal Rights Statement: Not applicable.

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