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Development and planning of measures to reduce the risk of the foot-and-mouth disease virus spread (case of the Republic of Kazakhstan)

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ABSTRACT

The current epizootic situation of foot-and-mouth disease (FMD) in the world indicates the need to organize measures for its prevention and elimination among agricultural and wild animals. The present study aimed to develop and plan measures to reduce the risk of spreading FMD virus in Kazakhstan. In epizootiological studies, the authors used the periodic bulletins of the World Organization for Animal Health, statistical data on the epizootic situation of FMD in Kazakhstan, geographical data of the territories of the regions of Kazakhstan included in the zones with vaccination and acceptable FMD status, and other necessary information. FMD monitoring was carried out by serological and virological studies of blood serum samples by detecting antibodies to the nonstructural protein of FMD virus and the reproductive pathogen or its antigenic components. According to the results of epizootiological monitoring, serological studies established the highest sero-positivity (25.3%) in cattle during 2021. Repeated virological studies of samples from these animals did not established signs of the presence and persistent circulation of FMD virus. However, in 2022, a case of FMD was recorded in the Karaganda region of Kazakhstan in the zone without vaccination. It was found that the immunogenicity of FMD vaccine among vaccinated cattle, goats and sheep was 85% or higher. However, the intensity of post-vaccination immunity persisted for about 3 months, instead of the 6 months guaranteed by the manufacturer. The extensive type of animal husbandry did not reduce the threats of the spread of FMD virus. The authors have identified logistics corridors through which the penetration and spread of FMD virus is possible. It is not possible to minimize the threat of spread using vaccination alone. Therefore, the authors have developed measures that include elements of biosecurity, surveillance and rapid diagnostics, animal movement control, and international cooperation.

Keywords: Foot-and-mouth disease, Virus, Animals, Epizootiological situation, Nonstructural protein.
Article type: Research Article.

INTRODUCTION

Significance of the spread of foot and mouth disease

Diseases of farm animals and plants are a serious obstacle to economic growth, poverty reduction and food security of the country, as well as the achievement of the principles of sustainable development (Gusmanov *et al.* 2023; Miswar *et al.* 2023). One of the most serious animal diseases is foot-and-mouth disease (FMD; Mubarak *et al.* 2024). FMD (*aphthae epizooticae*) is an acute viral highly contagious disease of domesticated and wild artiodactyls, characterized by fever, aphthous lesion of the mucous membrane of the oral cavity, skin, udder, and interungulate cleft of the extremities. In young animals, myocardial and skeletal muscle damage is observed. Sometimes people also suffer from FMD, especially children (Sorensen *et al.* 2000). FMD epizootics can spread over vast territories in a short time. From infected animals, the aerosol virus can be spread by wind over a distance

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of over 250 km (Sorensen *et al.* 2000). Cattle are the main source of FMD spread, although the virus can affect all artiodactyl animals. The high contagiousness of FMD, the tendency to global spread, a wide range of susceptible animals, a variety of immunological types and subtypes of the pathogen, a variety of ways of its isolation and spread, and the ability to persist for a long time both in the external environment and in the body of animals cause several complex problems of a veterinary, sanitary and economic nature. The FMD epidemic in 2000-2001 had an impact on the global economy and the socio-political life of almost all states. The total economic damage to the Republic of Kazakhstan as a whole is estimated at $31 billion. In the UK in 2001, the damage from an outbreak of FMD was estimated at 9-13 billion USD (Thompson *et al.* 2000; Scudamore & Harris 2002). The outbreak of FMD in 2010-2011 in South Korea led to the death of about 3 million cattle and pigs, and the economic damage as a result of this outbreak is estimated at 3 trillion won (2.7 billion USD; Joo *et al.* 2002; http://www.koreatimes.co.kr/www/news/opinon/2011/10/137_97523.html). Economic damage includes 100% morbidity of animals, loss of fatness, milk, as well as a decrease in product quality (Ahmad Zaki *et al.* 2018; Zhanabayev *et al.* 2022). FMD epizootics hinder the normal economic activity of entire districts, regions, and even states (King 2016). Forced quarantine measures to eliminate FMD disturb the normal economic activities of agricultural and processing enterprises and affect public, economic, and interstate relations.

Spread of FMD in Kazakhstan

From 2011 to 2013, 18 cases of FMD were registered in Kazakhstan, including five in 2011, 10 in 2012, and three in 2013. Data analysis showed that 15 outbreaks were caused by the type O FMD virus, while the remaining outbreaks were caused by the type A. Out of these, two outbreaks in 2012 were caused by the type A/Iran-05HER-10 FMD virus, and four outbreaks in 2013 were caused by the type A/Sea-97. In 2015, nine northwestern regions of Kazakhstan received the status of an FMD-free zone without vaccination. The pathogen of the disease spread from the territories of the People's Republic of China and Russia to the East Kazakhstan region; from the Kyrgyz Republic to the Zhambyl and Almaty regions; and from the Republic of Uzbekistan to the Kyzylorda region through the joint pastures of susceptible animals with animals of neighboring countries endemically risky for FMD; as well as through the transportation and drift of contact animals across the border from the territories of the People's Republic of China and Russia to the East Kazakhstan region; from the Kyrgyz Republic to the Zhambyl and Almaty regions; and from the Republic of Uzbekistan to the Kyzylorda region. Serological studies have established that the circulating FMD virus of A or O types corresponded to the types of virus circulating in the border areas of the People's Republic of China, the Russian Federation, Kyrgyzstan, and Uzbekistan. The recurrence of such cases of FMD in Kazakhstan and neighboring countries will be possible in the absence or in the case of improper implementation of measures to prevent the disease. The probability of FMD penetration into Kazakhstan remains high. The current FMD epizootic situation in Kazakhstan requires close monitoring of susceptible animals, control of possible ways of introducing infection into the territory, and, if necessary, taking timely measures to prevent the occurrence of infection and further study of the behavior of the FMD virus in nature.

FMD prevention measures

Vaccination is one of the most common measures to prevent FMD. Until recently, FMD prevention was carried out by vaccinating animals in threatened areas, and the elimination of epizootic outbreaks was performed by killing sick and contact animals in the epizootic focus, as well as incomplete monitoring of antibodies to nonstructural proteins (NSP) of the FMD virus in safe territories (Gulenkin 2008; Paton *et al.* 2006). Every year, more than 2 billion doses of FMD vaccines are used worldwide to control FMD outbreaks and for prophylactic purposes to limit disease incursions and the spread of the virus in endemic regions (Knight-Jones & Rushton 2013). Since unrefined FMD vaccines were often used to immunize animals, post-vaccination antibodies are antibodies against both structural proteins and NSP of the virus. This complicates the task of differentiating vaccinated animals from asymptomatic virus carriers or convalescents. In safe territories where there was no outbreak of FMD and vaccination was not carried out, antibodies against FMD virus NSP are detected among animals, but they may be the result of non-sterile immunity or may indicate the circulation of the FMD virus among animals that are asymptomatic virus carriers (Karaulov *et al.* 2001). According to the requirements of the Terrestrial Animal Health Code of the World Organization for Animal Health (OIE), it is prohibited to export animals and animal products to foreign countries from territories with an FMD danger. This is allowed only after the territory or region has been declared FMD-free. Obtaining such a status requires the implementation of a set of anti-epizootic measures, which include monitoring and establishing the existing epizootic situation due to illness, eliminating the disease, establishing the absence of circulation of the reproductive virus in the body of susceptible animals, and controlling the epizootic situation (urgenbayev *et al.* 2021; Ivanov *et al.* 2021). The main purpose of FMD monitoring is the early detection of changes in disease spread prevention based on the identification of incidents, which allows us to identify the number of sources of the infection pathogen (patients and carriers) in a particular population and the number of newly emerged foci of the infection pathogen (Ponamarev *et al.* 2006). The scope and methods of FMD monitoring and measures taken to maintain the acceptable status regarding this disease, including diagnosis, prevention, and control, should meet the requirements of the OIE prescribed in the Terrestrial Animal Health Code (Kodeks zdorovya nazemnykh zhivotnykh MEB 2019). Our review of the literature showed that monitoring should include:

(i) Biosecurity (control over the movement of animals, quarantine of new or returning animals, and compliance with strict sanitary procedures for people and equipment entering and leaving the farm);

(ii) Observation and rapid diagnosis (diagnostic technologies, such as real-time reverse transcription polymerase chain reaction (RT-PCR), allow fast and accurate detection of FMD virus);

(iii) Outbreak response plan (availability of a well-developed and proven outbreak response plan which should include procedures for isolating infected animals, eradicating the disease and safely disposing of carcasses to prevent further spread);

(iv) Education and training (animal breeders and veterinarians should be aware of the symptoms of FMD and the necessary actions in case of suspected disease);

(v) International cooperation (the World Organization for Animal Health (OIE) plays a crucial role in coordinating these international efforts).

This study aimed to develop and plan measures to reduce the risk of spreading the FMD virus in Kazakhstan.

MATERIALS AND METHODS

Ethical approval

The research protocol was discussed and approved at the meeting of the local ethical committee of the Kazakh Research Veterinary Institute of the Science Committee of the Ministry of Education and Science of the Republic of Kazakhstan on August 29, 2017.

Study period and location

The design strategy of our study included qualitative and quantitative research methods. We performed a literature search from 1995 to 2022 to study the world experience in monitoring the epizootic situation and prevention of FMD based on published journals, papers, and reviews. The Internet search included academic scientific journals, PubMed, and Google Scholar, and was conducted on papers that had the terms "foot-and-mouth disease" and "epizootiology" in the secondary headline. Papers in English and Russian were selected in the search results. The study of the epizootic situation of FMD in cattle was carried out in Kazakhstan from 2018 to 2022. Experimental studies on laboratory diagnosis of FMD were carried out at the Kazakh Research Veterinary Institute in Almaty.

Methods of epizootic monitoring

Epizootic monitoring for FMD in farm animals was conducted according to the Epizootic Research Methods and Theory of the Epizootic Process (Karaulov 2001). The epizootic situation regarding FMD in Kazakhstan was studied based on the materials of the official veterinary statistics provided by Committee for Veterinary Control and Supervision (CVCS) in the Ministry of Agriculture of the Republic of Kazakhstan. The sampling of biomaterial from animals was carried out with the permission of the authorized body in the field of veterinary medicine (CVCS). In epizootiological studies, we used materials from the OIE periodic bulletins on cases of FMD registration in various countries of the world, statistical data on the epizootic situation of FMD in Kazakhstan, as well as data on the geography of the territories of the regions included in the zones with vaccination and an acceptable FMD status. To monitor FMD, data from epizootiological and clinical studies were used to identify animals with symptoms similar to FMD, serological studies to determine antibodies to the NSP of FMD virus, and virological studies to isolate the reproductive pathogen and/or its antigenic components, as well as antibodies to post-vaccination structural proteins. Epizootiological analysis of these territories was carried out according to the historical and existing epizootic situation of the disease under study, the geographical location of this territory, and the applied technology of animal husbandry, considering the risks of the occurrence and

spread of FMD. Data on the epizootiological situation and the clinical condition of animals were presented by the district and regional divisions of the Republican Governmental Agency (RGU), CVCS of the Ministry of Agriculture of the Republic of Kazakhstan, as well as the Institute's branches located in 11 regions of Kazakhstan.
To assess the epizootic status of the region for FMD, serological and virological studies of blood serum samples from cattle, goats, and sheep were carried out. Serological monitoring involved collecting blood serum samples from a set sample size of target animals and testing them for the presence of antibodies to FMD virus NSP in the enzyme-linked immunosorbent assay (ELISA). The sample of epizootic units (EUs), and then the sample size of animals in each EU, were determined according to the formula recommended by the OIE based on 10% prevalence. Blood samples were taken from young animals (from 3 to 12 months old) susceptible to FMD annually in the spring before the animals were driven to pastures and in the autumn after their return to the stall. Identification of animals seropositive for antibodies to the NSP of FMD virus was carried out in five epizootiological zones (zones with vaccination and an acceptable FMD status) in East Kazakhstan, Almaty, Zhambyl, Turkestan, and Kyzylorda regions of Kazakhstan.

Blood sampling

Blood serum samples were obtained from the jugular veins of the animals and placed in vacutainers. Afterward, at the Virology laboratory of the Kazakh Scientific Veterinary Institute (KazSRVI) Limited Liability Partnership (LLP; Almaty, Kazakhstan), studies were conducted for the presence of antibodies to NSP by ELISA [ID vet: Id Screen FMD NSP Competition, PrioCHECK, FMDV NS Ab Strip Kit, Thermo Fisher, the Netherlands, as well as a set of reagents for the detection and identification of FMD virus RNA by real-time polymerase chain reaction (RT-PCR), OM-Skrin-Yaschur-RV, Russia]. For the period from 2018 to 2022, 16,840 blood samples were taken from animals. In the case of confirmation of suspicious and/or positive results of blood serum samples, primary analysis for antibodies to FMD virus NSP, to assess the epizootic status of animals, blood serum samples were taken again together with swipes of the pharyngeal mucosa and esophagus from positive animals to check for the persistent presence of a reproductive pathogen. In total, samples from 146 animals were additionally examined.
A suspension was prepared from swipes of the mucous membrane on a sterile Hanks solution with antibiotics. The resulting suspension was subjected to gradient purification from mechanical impurities at 2,000 g for 20 minutes by centrifugation. If necessary, the test samples were sterilized using sterilizing membrane filters. Virus isolation was carried out in cell culture and on laboratory animals. The presence of the virus was determined by the cytopathogenic effect in cell culture and pathology caused in the bodies of laboratory animals. Identification of the isolated virus was carried out using a neutralization reaction in cell culture or on susceptible laboratory animals. To study the intensity of immunity, a trivalent FMD vaccine (strains A/Iran-05, A/Sea-97, O/PanAsia, O/PanAsia-2, and Asia-1/Shamir, 6 PD50 for each valence) manufactured by the All-Russian Research Institute for Animal Health (VNIIZh) was administered subcutaneously to 10 cattle heads by 3 mL, and in 10 sheep by 1 mL each. Blood serum samples were taken from animals before vaccination, and also 21 and 56 days after vaccination for ELISA testing with VNT and SP (specific antibodies) to detect FMD virus-neutralizing and structural protein-specific antibodies. Antibodies specific to the structural protein of the FMD virus were measured for three serotypes of FMD virus (O, A and Asia 1) using commercial kits for ELISA [PrioCHECK, Thermo Fischer, Waltham, Massachusetts, USA and Istituto Zooprofilattico Sperimentale della Lombardia e dell Emilia Romagna (IZSLER), Brescia, Italy].

Data analysis

The resulting digital data were statistically processed in the Excel software. Maps of the Kazakhstan territory zoning were obtained by us from Internet resources and processed using PowerPoint software.

RESULTS

Epizootiological analysis of the zones with an acceptable FMD status with vaccination

The acceptable veterinary and sanitary status of Kazakhstan regarding FMD can be reached with the help of a set of measures reflected in the dossier compiled with the OIE rules for each epizootiological zone. According to the zoning, the territory of Kazakhstan was divided into areas with two zoo-sanitary statuses: (i) zones without vaccination and with an acceptable FMD status and also (ii) zones with vaccination and an acceptable FMD status. The first area, the northwestern territory of Kazakhstan, previously qualified and having the official OIE-confirmed status as a zone with an acceptable FMD status without vaccination, was divided into five smaller zones with the same zoo-sanitary status for economic and anti-epizootic purposes (Fig. 1). At the OIE World Assembly

on May 28, 2019, certificates of acceptable FMD status without vaccination were received for the following zones:
Zone 1 (yellow on the map): West Kazakhstan region, Atyrau region, Mangystau region, south-western part of Aktobe region;
Zone 2 (red on the map): the north-eastern part of the Aktobe region, the south of Kostanay region, and the western part of the Karaganda region;
Zone 3 (brown on the map): the central part of the Kostanay region, the western part of the North Kazakhstan region, and the Akmola region;
Zone 4 (green on the map): the eastern part of the North Kazakhstan region, the northern part of the Akmola region, and the Pavlodar region;
Zone 5 (pink on the map): the central and eastern parts of the Karaganda region, the south of the Akmola region, and the Pavlodar region.

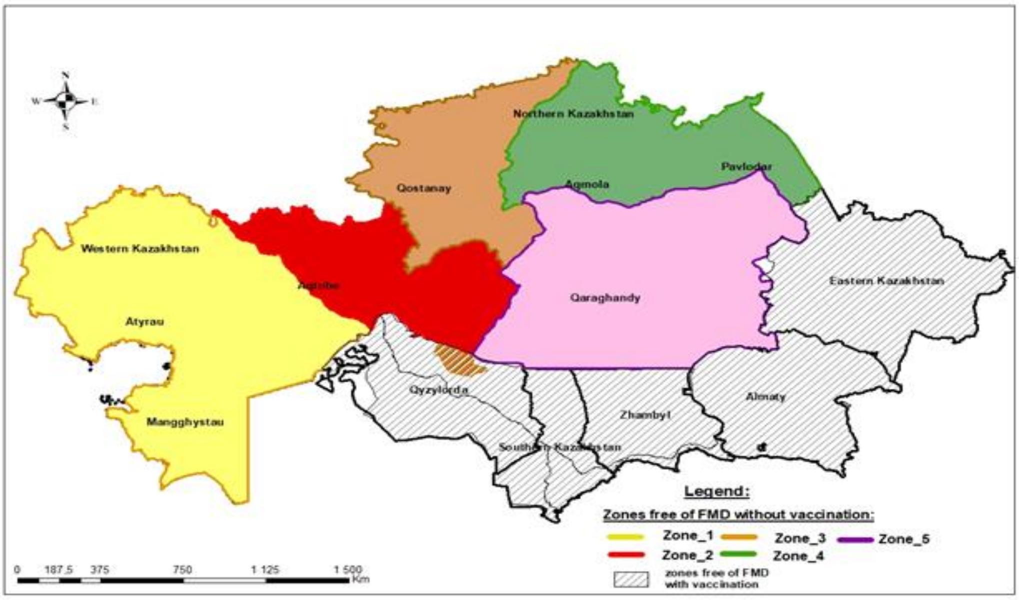

Fig. 1. Zoning of the territory of Kazakhstan regarding FMD in 2020.

The second area, the southeastern territory of Kazakhstan, has five safe zones for FMD with vaccination. In the zone with vaccination and an acceptable FMD status of Kazakhstan, active immunization of animals susceptible to FMD is carried out with a trivalent vaccine against types A, O, and Asia-1 purified from NSP of the FMD virus (manufactured by the Shchelkovsky Biocombinat, Russian Federation). The vaccine is made from an inactivated FMD virus, a strain of several serotypes (A Iran-05, A Sea-97, O PanAsia, O PanAsia-2, and Asia-1 Shamir) obtained in a suspension of VNK-21 cells, aluminum oxide hydrate, and saponin adjuvant. The zones with acceptable FMD sanitary status with vaccination are shown in Fig. 2.

Fig. 2. Sanitary zones/regions of Kazakhstan regarding FMD [Source: https://www.oie.int/en/disease/foot-and-

mouth-disease/#ui-id-2].

Zone 1: the territory of Almaty region;

Zone 2: the territory of the East Kazakhstan region;

Zone 3: the northern territories of Zhambyl, Turkestan, and Kyzylorda regions;

Zone 4: the southern and south-western regions of Turkestan and Kyzylorda regions;

Zone 5: the southern border regions of Turkestan and Zhambyl regions.

Five south-eastern regions of Kazakhstan (East Kazakhstan, Almaty, Zhambyl, Turkestan, and Kyzylorda regions) were included in the zone with an acceptable FMD status and with vaccination. Geographically, all these five regions occupy the eastern and southern outskirts of Kazakhstan and consistently border each other. The outer limits are bordered by the Russian Federation from the north, the People's Republic of China from the east, and the Kyrgyz Republic from the south. The geography of the location of the zone with an acceptable FMD status and with vaccination and also its adjacent territories is shown in Fig. 3.

Fig. 3. Kazakhstan and neighboring countries with FMD risk areas (red arrows) in the interstate border.

Study of vaccinated animals for the presence of NSP

The results of our laboratory studies on ELISA showed that out of 1,380 animal serum samples taken in 2018, 163 samples were positive for antibodies to the FMD virus NSP, which equals 11.8%. The incidence of EUs and administrative districts seropositive for antibodies to the virus NSP was 64.7%. In 2019, 2,799 samples of blood serum from cattle, goats, and sheep were collected and examined in the zones with an acceptable FMD status and vaccination. The results of our laboratory studies on ELISA showed that 164 samples of animal blood serum were positive for antibodies to FMD virus NSP, which equals 5.86%. The incidence of EUs and administrative districts for animals seropositive for antibodies to the virus NSP was 44.7%. In 2020, 2,070 samples of blood serum from cattle, goats and sheep were collected and examined in the zones with an acceptable FMD status and vaccination. As a result, 356 samples were positive for antibodies to FMD virus NSP, which is 17.1%. The incidence of EUs and administrative districts for animals seropositive for antibodies to the virus NSP was 41.4%. In 2021, 5,370 samples of cattle blood serum were examined in the zones with an acceptable FMD status and vaccination, of those, 1343 were seropositive for NSP, which equals 25.3%. The incidence of EUs with animals seropositive for antibodies to FMD virus NSP was 47.2%. In 2022, in the zone with an acceptable FMD status and vaccination in 5 southeastern regions of Kazakhstan, 5,221 samples of cattle blood serum were taken and analyzed with ELISA. 1,186 animals positive for NSP were detected (22.7%), and the incidence of EUs (64 EUs out of 90, animals that reacted to NSP were detected) was 71.1%. The results of the conducte As a result of the laboratory tests, 146 samples taken additionally from NSP-positive animals did not show the FMD virus. Sero-positivity for antibodies to the FMD virus NSP was detected in regions bordering the People's Republic of China, the Kyrgyz Republic, and the Republic of Uzbekistan due to animal contact, and border areas of the southern regions, with the pathogen of the disease coming from abroad, from the countries where FMD outbreaks occasionally appeared. This situation indicates that in the border regions of the five south-eastern regions of Kazakhstan, which belong to the zones that have an acceptable FMD status with vaccination, there are risks of introduction and development of the disease among non-immune livestock or the persistence of the pathogen in the body of animals slightly immune and non-immune to FMD. Thus, in 2019, in the Trans-Baikal Territory in the eastern part of Russia, a case of FMD was detected that had been caused by a new line for this region (O/ME-SA/Ind-2001e) closely related to viruses found in China (2018). d studies are shown in Fig. 4. As shown in Fig. 4, in 2021, compared with 2018, there was a twofold increase in the number of animals positive for NSP, and the largest number of cases was noted in the Zhambyl and Turkestan regions. The most favorable epizootic situation for FMD in Kazakhstan as a whole was observed in 2019.

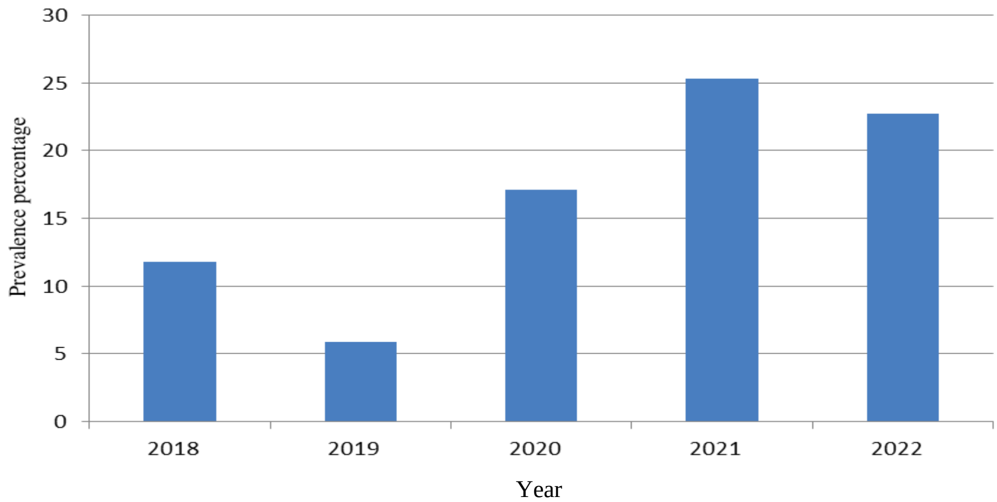

Fig. 4. Results of bovine blood serum analysis for NSP in five southeastern regions of Kazakhstan.

Only from January to February 2020, six outbreaks caused by the O/SEA/Mya-98 serotype FMD virus were registered in the Primorsky Territory of the Russian Federation. In December 2021, it was reported to the OIE about the detection of the O/ME-SA/Ind-2001 serotype in an FMD outbreak in cattle in the Orenburg region of the Russian Federation. In January 2022, a case of an outbreak of FMD among cattle was registered in Kazakhstan in the Kiikty village in the Shetsky district of the Karaganda region. The FMD virus was identified as type O/ME-SA/Ind-2001d by the molecular biological method of studies in the selected samples by reverse transcription PCR (RTr-PCR). The infected 25 heads of cattle with clinical symptoms of FMD in the infection focal point were slaughtered. After the notification of the case of infection of animals with FMD on the OIE website, the zone including the Karaganda region has been declared unsafe for FMD since 2022 (Fig. 5). The cause of the outbreak of FMD in January 2022 in the Karaganda region, as well as the outbreak in December 2021 in the Orenburg region of the Russian Federation, was the same strain of O/SE-MA/Ind-2001d of the FMD virus, the route of movement of which from the Middle East had been previously predicted by King (2016). To control the epizootic situation for FMD in 2022 in the Karaganda region, we collected 99 samples of blood serum from cattle in nine EUs located in three administrative districts and investigated them for the presence of NSP with ELISA. As a result, seropositive antibodies of FMD virus NSP were detected in blood serum samples in only one EU. The incidence of EUs seropositive for antibodies to the virus NSP was 11.1%. Ninety nine samples were taken from the sheep and goats, of those, 12 samples were seropositive for antibodies to the FMD virus NSP. The incidence rate was 22.22%.

Study of immunity stress in vaccinated animals

In the regions with an acceptable FMD status with vaccination, a total vaccination of susceptible livestock (cattle, goats, and sheep, as well as pigs) was carried out with a sorbed mono- and polyvalent FMD vaccine prepared from a virus grown in a culture of VNK-21 cells produced in the Russian Federation against FMD type A (SEA-97, Iran-05 subtypes), type O (PanAsia, PanAsia-2 subtypes), and type Asia-1. According to the research of the KazSRVI, in 2017, 21 days after vaccination, the level of immunity among cattle in East Kazakhstan, Almaty, and Zhambyl regions ranged from 80 to 100% against all three types of FMD virus. However, the immunity rate among goats and sheep during these periods was low and amounted to 0 - 10% in the East Kazakhstan region, 15 - 25% in the Almaty region, and 15 - 65% in the Zhambyl region.

Fig. 5. According to the OIE, zone 5, which includes the Karaganda region, has been unsafe for FMD since 2022 [Source: https://www.oie.int/en/disease/foot-and-mouth-disease/#ui-id-2]

After 90 days, the level of group immunity against FMD among cattle significantly decreased and ranged 25 - 75% in the East Kazakhstan region, while 30 - 60% in the Zhambyl region. For goats and sheep during this period, immunity ranged 20 - 50% in the East Kazakhstan region and 25 - 80% in the Zhambyl region. The obtained research data indicate that the vaccine stimulates the formation of immunity of sufficient intensity among cattle for 21 days after application against all three types of FMD virus, however, after 90 days it decreases to a level of 25-30% against type A, 35 - 45% against type O and 60 - 75% against type Asia-1. For goats and sheep, the immunogenicity of the FMD vaccine on the 90th day reached 20-25% against type A, 45-50% against type O and 35-80% against type Asia-1. In 2018, according to the results of ELISA on blood serum samples taken from vaccinated cattle, the presence of specific antibodies to the type Asia-1 FMD virus was found in Kyzylorda region in 199 samples out of 230 (86.5%); in Almaty region in 39 out of 40 studied samples (97.5%); and in West Kazakhstan region in 33 out of 37 samples from goats and sheep (89.2%). In total, of the 307 samples examined, 271 showed the presence of antibodies (88.27%). In 2019-2020, KazSRVI and Pirbright Institute (Great Britain) performed a study of immunity stress in cattle and sheep after a single vaccination against FMD with a trivalent vaccine containing serotypes A, O, and Asia-1 produced by Federal State Budgetary Institution (FGBU) VNIIZh (Russia), using the reaction of neutralization of ELISA after 0, 21, and 56 days after immunization. As a result of the study, on the 21st day after vaccination, 50% of specific antibodies were formed for type O, 30% for type A, and 40% of specific antibodies for type Asia-1. On the 56th day after vaccination, up to 20% of specific antibodies had decreased for type O, 10% remained for type A, and up to 30% had decreased for type Asia-1, although, according to manufacturers, the vaccine should prevent FMD infection of animals for 180 days. These data indicate that the FMD vaccine manufactured by VNIIZh caused full-fledged immune protection of cattle against all three types of FMD virus for only 21 days. In subsequent periods, the level of immunity in these animals decreased and conditions for the development of the infectious process could arise. For goats and sheep, on the 21st day after vaccination, 90% of specific antibodies were formed for type O, 10% were formed for type A, and 70% for type Asia-1. On the 56th day after vaccination, 90% of specific antibodies remained for type O, no specific antibodies were detected for type A, and only 20% remained for type Asia-1. In the experiment of testing the FMD vaccine made by the Shchelkovsky Biocombinat on cattle 21 days after vaccination, the formation of immunity for type O equaled 30% of specific antibodies, 10% for type A, and nothing for type Asia-1. On the 56th day after vaccination, 20% of specific antibodies in the blood serum of animals remained for type O, nothing were found for type A, and 40% for type Asia-1.

DISCUSSION

Serological monitoring data indicate that FMD may appear spontaneously, regardless of the time of year and conditions of animal husbandry, among animals that lack immunity or have weakened post-vaccination immunity.

Therefore, it is necessary to develop measures to reduce the risks of the spread of the FMD virus, consisting of preventive measures (prevention of spread) and emergency measures (during an outbreak). Studies show that it is necessary to develop monitoring of the epizootic situation to reduce potential risks (Myrzhieva *et al.* 2020; Karmaliyev *et al.* 2020; Almansorri *et al.* 2023; Hassanzadeh Khanmiri *et al.* 2023). Strengthening biosecurity measures can prevent the spread of the disease (Bekezhanov *et al.* 2021; Martinez Durango & D'Amato Castillo 2022). The corridor of the probable FMD pathogen introduction risk from neighboring countries is present at the places of crossing/passage of the interstate border along international and interstate highways, and the directions of vectors of this factor correspond to the geography of traffic along these highways (Woldemariyam *et al.* 2023). Therefore, it is important to monitor the movement of animals, quarantine new or returning animals, and observe strict sanitary procedures for people and equipment entering and leaving pastures and animal breeding sites. Disinfection of vehicles and shoes can also help prevent the spread of the disease. According to the results of our study, it has not been proven, but also not refuted, that the illegal transportation of live cattle and meat from one region to another is an increased risk factor even for regions located in a safe zone, based on the level of vaccination of animals. For instance, there is a possibility of such a movement of livestock from the Kyrgyz Republic to the Zhambyl and Turkestan regions. Such data give reason to believe that these cases are a possible etiology of the appearance of animals seropositive for antibodies to FMD virus NSP in zones with an acceptable FMD status of vaccination. In addition, the spread of the FMD virus could be facilitated by the settlement of migrants from the southern regions of Kazakhstan in its northern territories, as they transport pets and farm animals from zones with a different epizootic status. Among the migrants to the northern territories, many immigrants from China, Mongolia, and other countries often bring their livestock, which can also be a source of infectious diseases. The intensification of animal husbandry and the increased number of animals in Kazakhstan are important risk factors for FMD. Thus, the Ministry of Agriculture of Kazakhstan implements various programs (Sybaga, Senim) to involve the population of the country in the development of the livestock industry. As a result of the implementation of these programs, animals from various countries are purchased on preferential terms and reproduce in farms in various regions of Kazakhstan. Purchasing and moving animals from different countries with different epizootic backgrounds and collecting them in one herd can lead to the recurrence of "dormant" infections, including FMD. Against the background of global changes in the world, climate warming due to the active intervention of human activity on the environment, alterations in the epidemic (Covid-19), and epizootic situation (FMD) began to be observed (Feng Jiang *et al.* 2020; Karim *et al.* 2021). Pathogens of exotic, previously unknown diseases with an acute course of the infectious process began to be observed in different parts of the globe. Therefore, it is important to develop a system of measures for monitoring and rapid diagnosis, as well as the international exchange of information received. Rapid diagnosis in case of suspicion is crucial to prevent and control the outbreak. At the 3rd meeting within the framework of the epidemiological and laboratory networks on FMD for the countries of Western Eurasia held on August 17-18, 2021, D. King, Head of the Vesicular Disease Reference Laboratory Group of the OIE World Reference Laboratory for foot-and-mouth disease (Pirbright Institute; OIE & FAO 2022) presented a forecast of the risk of introduction and spread to Kazakhstan of new strains of FMD virus circulating in China, such as Type O-May-98, Type O-Ind-2001d, as well as a new isolate Type A-GVII circulating in the countries of the Middle East. Forecasts on the probable vectors of the spread of the FMD virus have been confirmed in Kazakhstan. Thus, in January 2022, a case of an outbreak of FMD among cattle was registered in the Kiikty village in the Shetsky district of the Karaganda region. In the infection focal point, 25 heads of cattle with clinical symptoms of FMD were slaughtered. The FMD virus was identified as type O/ME-SA/Ind-2001d, similar to the cause of the FMD outbreak in December 2021 in the Orenburg region of the Russian Federation, by the RTr-PCR molecular biological method of analysis in the selected samples. To assess the activities of the Veterinary service of the Republic of Kazakhstan on the prevention of FMD, an OIE expert, a fellow of the Pirbright Institute (Great Britain), Paton *et al.* (2006) presented recommendations on further preventive measures against FMD in Kazakhstan. Thus, animal immunization should be carried out with a trivalent vaccine (O, A, Asia 1), which should protect against the following strains that are considered dangerous: Group 1: O/SEA/Mya-98; A/ASIA/Sea-97; O/ME-SA/Ind2001; O/Cathay; O/ME-SA/PanAsia; Group 2: O/ME-SA/PanAsia2; A/Asia/Iran-05; A/Asia/G-VII; Asia 1/Sind-08; O/ME-SA/Ind-2001. The selected vaccine suppliers to Kazakhstan should provide evidence that there is a good prospect that their vaccine will be able to protect animals against strains threatening Kazakhstan. The experiments aimed at testing the FMD vaccine manufactured in Russia showed low protective properties of FMD vaccine. The FMD vaccine manufactured by

VNIIZh caused full immune protection of cattle against all three types of FMD virus only for 21 days. In subsequent periods, the level of immunity in these animals decreased and conditions for the development of the infectious process could arise. The practical conclusions of our study allowed the CVCS of the Ministry of Agriculture in the Republic of Kazakhstan to apply to the OIE for permission to vaccinate susceptible animals against FMD in these regions and change their status to zones with vaccination. These actions will contribute to the preservation of an acceptable situation regarding the spread of FMD in the northwestern territories of Kazakhstan in 2023. In addition, CVCS, together with the staff of the KazSRVI, considering the results of our study, has developed a strategy against FMD, which implies the following activities throughout Kazakhstan:

(i) the activity of the vaccine should be at least 6PD50 for each valent dose;

(ii) the vaccine should be purified, not causing the formation of antibodies to FMD NSP in vaccinated animals

In five zones without vaccination including Akmola, Atyrau, Aktobe, North Kazakhstan, West Kazakhstan, Pavlodar, Kostanay, Karaganda, and Mangystau regions, it is necessary to carry out 100% immunization of susceptible animals (cattle, goats, sheep, and pigs) against FMD with a monovalent vaccine from the strain of the FMD virus type O Ind-2001. The first vaccination should begin at 4 months for cattle and 3 months for goats and sheep. The animals should be vaccinated every three months until the age of 18 months. Further vaccination is carried out every 6 months. By the time, the animal reaches one year of age, it will have been vaccinated 3 times, by 2 years, 5 times, by 3 years, 7 times, by 5 years, 9 times, etc. In five south-eastern regions (Almaty, East Kazakhstan regions, Zhambyl, Turkestan, Kyzylorda), considering the experience of controlling the spread of FMD and the existing epizootic situation in the country, vaccination should be carried out with a vaccine that has the following characteristics:

- contains viruses of type O, A, and Asia-1, antigenically related (with an antigenic correspondence/affinity coefficient r1 greater than 0.30) with variants of type O-Ind-2001 and Pan-Asia 2, Type A SEA97 and Iran-05, and type Asia-1-Shamir, capable of providing intensive immunity in vaccinated animals against these types.

To assess the compliance of the purchased vaccine with the requirements, it is recommended to evaluate the expected characteristics of the vaccine by examining representative animals from the target population. This assessment should be carried out before making a final decision on the purchase of the vaccine. A simple and cost-effective approach is to purchase and vaccinate animals, take serum samples on-site and send them to a reference laboratory to measure antibody titers.

CONCLUSION

On the one hand, with the emergence of a new genetic line of the type A FMD virus, vaccines used against FMD in many countries have proved ineffective against this genetic line of the pathogen. On the other hand, we have established a certain incidence of antibodies to FMD virus NSP among cattle susceptible to this disease, although the epizootic status of such animals according to the results of virological and genomic studies turned out to be acceptable. This allows us to assert that although vaccination is the most common or one of the most common measures to prevent FMD, it is necessary to develop measures to prevent the spread of the FMD virus to increase the sustainability of the development of territories and the safety of people and animals. When developing these measures, we did not investigate the system of raising awareness of specialists, livestock breeders, and veterinarians, as well as farm workers on the epizootic situation of the spread of FMD in the region, the level of awareness of the symptoms of FMD and the necessary actions in the case of suspicion of the disease. Regular training can provide a quick and effective response to potential outbreaks. Therefore, we consider it necessary to conduct a separate study in the future to look at the possibility of including an information and training system in the structure of the measures we have developed.

Authors' Contributions

KAT: Conception and design, acquisition of data, analysis, and interpretation of data, critical revision of the manuscript, final approval. AMA: critical revision, final approval. AMB: first draft, zoning map design. VVK: analysis and interpretation of data, zoning map design. ASK: FMD vaccine strain study, setting the ELISA serological reactions. YKO: FMD vaccine strain study. SBM: sample selection. PBA: laboratory testing of samples, PCR analysis. EEB: setting the ELISA serological reactions. SYK: sample selection. MKT: sample selection, setting the ELISA serological reactions. BST: sample selection, zoning map design.

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Conflict of interest
The authors declare that they have no conflict of interest.

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