UDC 619:616.98:578.821.2:636.22/.28(4-014/-015)


# To the problem of nodular dermatitis of cattle//News of agrarian sciences.

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**The purpose.** To study epizootic situation and possible paths of spread nodular dermatitis, and also to determine measures on control of infestation. **Methods.** Data of International epizootic office and national databases on safety and quality of animal production are analyzed; stuffs and publications connected to the problem of nodular dermatitis are studied. **Results.** Analysis is made of state-of-the-art epizootic situation on nodular dermatitis in the world. Features of development of disease are mapped and data about the virus which is etiological agent of nodular dermatitis are generalized. Also the vector of spread of the infestant to the continental Europe is specified. Possible ways of on control of infestation with nodular dermatitis are outlined. **Conclusions.** Considering high contageousness, transboundary of nodular dermatitis, its prompt extending to the countries of the continental Europe, real threat of hit of the infestant in Ukraine from neighbouring states is determined.

***Key words:*** *nodular dermatitis, cattle, virus Neethling, stamping-out, specific prophylaxis, homologous vaccines, heterologous vaccines.*

Nodular dermatitis of cattle (Lumpy skin disease, Dermatitis nodulares) is a viral contagious, emergent ones, transgenic bovine cattle disease characterized by fever, hypodermic tissue edema, internal organs and extremities, the formation of typical, prone to necrotic collapse of nodules in the skin and mucous membranes of the digestive canal and respiratory tract, eye damage and generalized lymphadenitis [1, 2].

The aforementioned disease is economically significant, as it causes a temporary decrease in the milk productivity of infected animals, temporary or permanent infertility of bulls, skin damage, and the death of animals due to considerations of bacterial infection. Besides, a significant element of unprofitability of livestock branch, on condition of spread of a disease, are costs of conducting monitoring and diagnostic tastings, the organization of preventive and liquidating measures in case of threat or developing of a disease and also trade restrictions that take root for prevention of her distribution.

For the first time, the disease was registered in Zambia in 1929, and in the future, the area of the disease spread to Southern and Eastern Africa (Zimbabwe, South Africa, Botswana, South Rhodesia, Swaziland, Mozambique, Namibia, Malawi, Congo, and Kenya). Since the 1960's, nodular dermatitis has been registered in 29 countries of Central and South Africa, extending to North Africa (Egypt, Oman, and Bahrain) and the Middle East (Israel, Palestine, and Lebanon), and was first registered in Turkey in 2013. For a long time, the aforementioned disease was considered to be exotic for European countries. In the territory of the former Soviet Union, until recently, the aforementioned disease has not been registered in any country, including Ukraine [2].

For a long time, it was believed that the etiological agent of the disease is a group of viruses, which, by virulence, immunogenicity and cytopathogenic effect, are divided into three types: *Orpheling* (BLD),

*Allerton* and *Neethling*. Subsequently, it has been shown that Orpheling (BLD) and Allerton viruses are not critical for the pathogenesis of bovine cattle disease on nodular dermatitis. The main cause of the disease is the Neethling virus, which according to the International Committee on Taxonomy of Viruses (ICTV) refers to the genus Capripoxvirus, the subfamily Chordopoxvirinae, the Poxviridae family. In addition to the causative agent of nodular dermatitis, the genus Capripoxvirus includes sheep pox viruses and goat pox virus. Representatives of the above-mentioned kind are closely related, have an antigenic affinity and morphological identity. The peculiarity of the pathogens of the genus Capripoxvirus is that they have a cross-linked immune response. This is of great practical importance for addressing the issue of prevention and control of nodular dermatitis. Virions of the Neethling Virus are shaped like a brick with rounded edges, a dual sheath, and a dense core. The size of the virions varies within 180-320 nm [2, 3].

The virus is cultivated on chorioallantoic membrane of 5-7-day chick embryos, causing small varioliform affection on its surface, as well as in primary cell cultures. To isolate and cultivate the virus, cultures of the cattle dermis cattle with a support medium containing fetal blood serum of cattle are used [4].

In addition, the cattle virus nodular dermatitis can reproduce in the culture of testicular and kidney cells of calf and lamb, adrenal glands of the lamb, kidney of the embryo of the sheep, fetal lamb and calf muscle cultures, in the adult meristic line (AVK58) and in the cells of the Syrian Kham kidney line The bar (VNK / 21). It should be noted that in the primary isolation of the pathogen in the culture of the renal cells of the lamb cytopathogenic changes are observed only after 11-12 days, and have extremely slow flow, whereas under the conditions of passage of the virus in the above-mentioned culture, cytopathogenic changes, manifested by the formation of individual tricks or increased refractive activity, cytopathogenic action is observed after 48-72 hours [5]. Taking into account that the virus of nodular dermatitis and sheep and goat poxviruses are of the same genus, and for the production of the vaccine against the latter, the widely used transfusion culture of goat cells of gonads was adapted and the degree of accumulation of the *Neethling* virus type in the above cell culture was studied. The maximum cytopathogenic changes are observed in it in 48-72 hours, and according to the results of virus titration, its activity by the infectious action is 5.5 lg TCD50 / cm. [6].

According to OIE, susceptible to nodular dermatitis, there are cattle (*Bos taurus* and *Bos indicus*), as well as Asian buffalo (*Bubalus bubalis*) [7]. It has been determined that livestock animals are more susceptible to infection than meat, especially during lactation [8]. According to individual authors, besides cattle, nodular dermatitis is affected by giraffes, impulse, sheep, and goats [3, 9]. In the case of laboratory animals, rabbits and guinea pigs are susceptible to experimental infection. Man is not susceptible to the virus of nodular dermatitis [7].

The Neethling virus is fairly stable in the external environment. It has been established that in the affected areas of skin it is stored for at least 33 days, in sperm 22 days, in saliva 11 days, in blood and internal organs - 4 days. Warming the virus for 5 days at 37 ºC does not reduce its virulence, and at a temperature of 4 ºC, it is stored for 6 months [10]. The virus is stable at pH 6.6-8.6. Inactivation of the causative agent of nodular dermatitis occurs at a temperature of 55 ºC for 2 hours and at a temperature of 65 º C - for 30 minutes. Given that the Neethling type virus is an envelope, it is sensitive to such fatty solvents as ether and chloroform. In order to inactivate the nodular dermatitis virus, use 1% solution of formalin, 2% phenol solution or 2-3% solution of sodium hypochlorite [3].

According to the OIE data contained in the Code of Health of Terrestrial Animals [11], the incubation period of nodular dermatitis is defined as 28 days, whereas according to some authors [2] for an experimental infection - from 2 to 10 days. At the same time in the cattle, there is a fever, painful swelling at the injection site of the pathogen and regional lymph nodes. The skin develops deep necrotic processes with significant tissue infiltration by monocytes and histiocytes containing cytoplasmic inclusion cells [2, 3, 5].

The main source of the causative agent of nodular dermatitis is the sick, diseased animals and virus carriers. From the organism of infected animals, the virus is excreted with repelled fragments of the affected skin, saliva, nasal leaks, sperm, milk, and blood. There are two ways of spreading the virus of nodular dermatitis beyond the epizootic center. First, these animals are the source of infection (patients,

reconvalescents, carriers). That is, the source of infection not only allocates but also spreads the virus at considerable distances. Second, it is a mechanical transmission to the pathogen with contaminated livestock products, feeds, vehicles, service personnel and animal care items. The role of blood-sucking insects, including flies (Stomoxys calcitrans and Biomyia fasciata), mosquitoes (*Culex mirficens* and *Aedes natrionus*) [12], ixodic ticks (*Rhipicephalus decoloratus*, *Rhipicephalus appendiculatus* and *Amblyomma hebraeum*) [13, 14], as a mechanical factor virus transfer. In addition, the risk factor for nodular dermatitis is a warm humid climate, strong winds, and the presence of reservoirs, although it is established that the disease may also occur in the winter. The tropism of the pathogen to the epithelial cells of the respiratory organs indicates the probable role in the common nodular dermatitis of the airborne mechanism of transmission of the pathogen [15].

Given the high contagious nature of nodular dermatitis, and given the steady state of the disease, it can be manifested as an epizootic or sporadic. In fresh cells, the disease manifests itself in the form of an epizootic, occurs suddenly and simultaneously in several herds, which can be located at a considerable distance. In the initial occurrence of nodular dermatitis in the herd, the incidence can reach up to 70-90%, although, usually in endemic cells, the incidence is 5-50%, and mortality does not exceed 5-10% [3].

The high contagiousness of the disease, the rapid expansion of its nose, and significant economic losses led to the inclusion of nodular dermatitis in the list of the International Office of Epizootics - this provides for mandatory notification of cases of registration of the disease in one or another territory [11].

Until the mid-80s, nodular dermatitis was an endemic disease for the African continent, and then cases were registered in Bahrain, Kuwait, Oman, and Yemen. Since July 2012 in Israel, 232 nodules of nodular dermatitis have been identified. Since then, the disease has been registered in Lebanon (November 2012) - 34 cells, Palestine (February 2013) - 58 cells, Jordan (April 2013) - 2 cells, Iraq (August 2013) - 28 cells, and from August 2013 - in Turkey (236 cells) (Fig. 1).

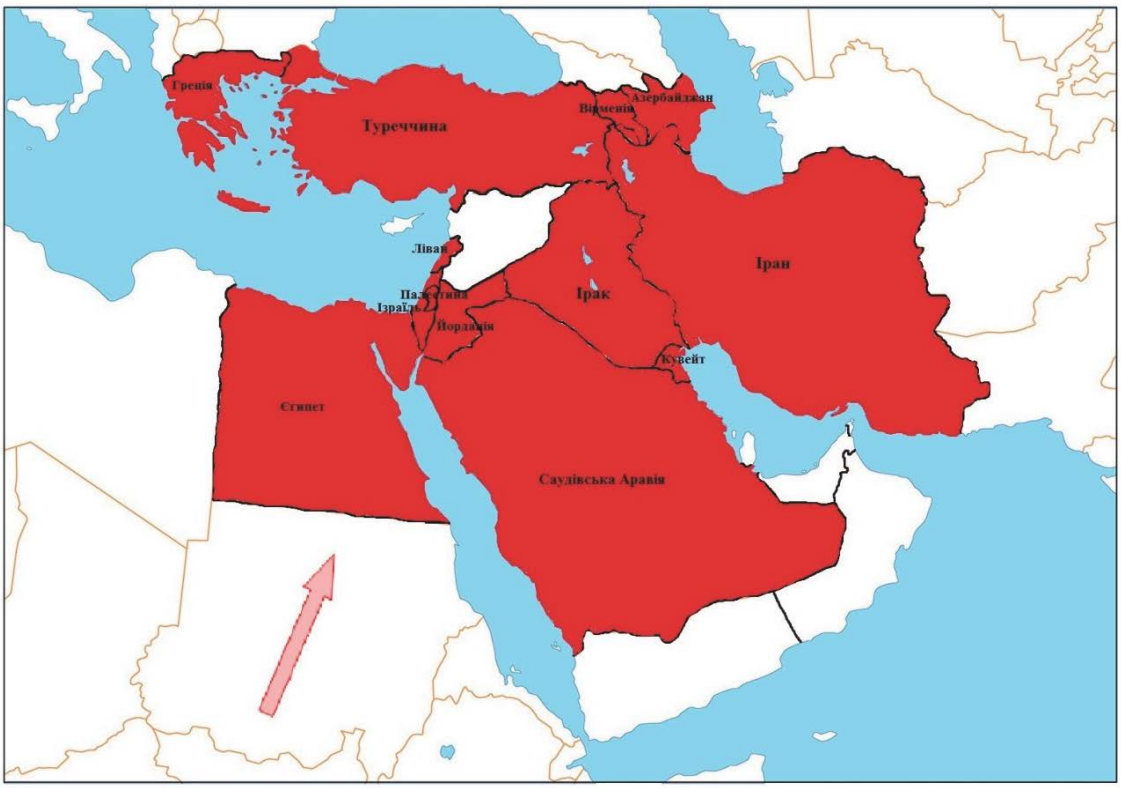


*Figure 1 - Distribution of nodular dermatitis in the countries of the Middle East in 2012-2014 (according to OIE)*

The first cases of nodular dermatitis in Turkey were registered in August 2013, on the border with Syria (the province of Kahramanmaras and Batman). Significant numbers of cases were registered in the southern provinces and in those bordering Iraq. The spread of the disease was characterized by

significant distances of individual cells from the main epizootic center (400-500 km.). In addition, the disease in animals was registered in high altitude areas (Sivas province), at an altitude of 1300 m above sea level and average winter temperature minus 5 ºC.

According to the reports of OIE, the possible reason for the spread of nodular dermatitis may be the illegal movement of animals. It is precisely the inadequate control of the spread of the disease in Turkey that led to the pathogen of nodular dermatitis to continental Europe.

Subsequently, the disease spreads to Iran (May 2014), where 6 cases of nodular dermatitis, Kuwait (November 2014, 5 cells) and Azerbaijan (July 2014, 16 cells) were detected. Thus, the long-term vector of distribution of nodular dermatitis of bovine animals in the direction of the south (Africa) to the northeast (Middle East) was confirmed. This was the basis for predicting the incidence of the disease from Turkey, and in the future from Azerbaijan to the Russian Federation [3], where the first cases of the disease were registered in June 2015 in the highland villages of Dagestan. Subsequently, clinical signs of the disease were detected in Chechnya, North Ossetia, the Republic of Kalmykia, Astrakhan region, Stavropol and Krasnodar Territories. In total, in September 2016, 235 cases of the disease were registered in the Russian Federation, with the latter cases occurring on the territory of Voronezh (200 km from the border with Ukraine) and Tambov regions.

In addition to the spread of the disease from the territory of Turkey to the Russian Federation had a manifestation of another vector of the spread of the disease, namely, the countries of southern Europe. Thus, in August 2015, nodular dermatitis is registered in Greece (a total of 218 cells), and, despite the measures envisaged by quarantine, the control of the movement of susceptible livestock, the zoning of the disease territories has spread to the continental Europe. Already in April 2016, nodular dermatitis was registered in Bulgaria (a total of 217 cells) and Macedonia (178 cells), while in June and July 2016 it was in Albania (57 cells), Serbia (219 cells), and Montenegro (63 cells ) Given the large number of susceptible animals in the region and the prevalence of the disease in the Balkan Peninsula (recorded almost throughout the territory of each disadvantaged country), it is safe to assert that rooting of the disease in this area and the possible risk of spreading it to neighboring countries. And given the peculiarity of the spread of nodular dermatitis in the direction from south to northeast (from Africa to the Middle East, from Turkey to the Russian Federation) there is a possible risk of this disease through Romania to Ukraine (Figure 2).


*Figure 2 - Probable ways to get into the pathogen of nodular dermatitis on the territory of Ukraine*

Thus, the significant spread of the disease between neighboring states, both in the territory and in time, confirms the allegation of high contagiousness and transboundary nodular dermatitis. This, in turn, raises concerns about the risk of nodular dermatitis in Ukraine from neighboring countries (the Voronezh region and the Krasnodar Territory of the Russian Federation, as well as through Romania from the territory of Bulgaria).

It is precisely for this reason that issues of monitoring and ensuring measures to combat nodular dermatitis are becoming relevant today. In order to establish a diagnosis of bovine nodular dermatitis, an integrated approach is used that involves an epizootiological examination in conjunction with clinical and laboratory confirmation of the presence of the pathogen. For the laboratory confirmation of nodular dermatitis, the identification of the pathogen using molecular genetic methods (PCR), electron microscopy (detection of typical virions), isolation of the virus in the cell culture followed by its identification in the PCR, immunodiffusion, indirect fluorescence and neutralization are used. It should be noted that the neutralization reaction is the most specific serological test, but it is not sufficiently sensitive. Agar gel immunodiffusion and indirect fluorescence reactions are less specific due to cross-reactions with antibodies to other poxviruses. The use of Western blotting is sensitive and specific but difficult and costly to conduct. Efforts have been made to detect antibodies to the pathogen, but at present OIE do not recommend this method, which is explained by the use in some countries of live vaccines against nodular dermatitis [7]. Thus, today, for monitoring and diagnosis of the disease, the most expedient application of PCR is both real and quantitative in real-time (real-time), which, in comparison with other methods, has clear advantages - availability, sensitivity and specificity [16].

A country is considered to be safe from nodular dermatitis if there have not been confirmed cases of the disease in the past three years and no vaccination has been carried out against the aforementioned pathogen during this period. Under the conditions of registration of the disease, after the mandatory notification of the disease in the OIE, anti-epizootic measures are carried out. To date, there are several principal schemes for controlling nodular dermatitis, which include both general and special measures (Table 1).

In order to eliminate the infection site, the slaughter of all susceptible animals is carried out, the disposal and destruction of their corpses, the purification, and decontamination of farms are the so-called stamping-out method. It is through this method that the eradication of the disease centers in Greece, Bulgaria, and Macedonia is carried out. However, this method is expensive and, given the emergence of new cells of nodular dermatitis in the above-mentioned countries, is not effective enough [17]. Another method of emergency flash control is a modified stamping-out that involves the slaughter of sick and infected animals, as well as the introduction of circular vaccination of buffer areas within a radius of 25-50 km from infected areas (has been successfully applied in Israel during outbreaks in 2013).

**Table 1 - A set of measures for the elimination of nodular dermatitis in countries where diseases were recorded (according to the OIE).**

| Country | Antiepyzootic measures |
|---|---|
| Armenia | disease notification, border measures, monitoring, screening, general surveillance, internal movement control, zoning, vector control |
| Azerbaijan | disease notification, border measures, monitoring, general surveillance, domestic movement control, official vaccination, vectors control |
| Bulgaria | disease notification, border guard measures, general observations, targeted surveillance, internal movement control, stamping out, zoning, prohibition of vaccination |
| Macedonia | disease notification, border measures, general surveillance, stamping out, prohibition of vaccination |
| Greece | notification of illness, border measures, screening, targeted surveillance, internal movement control, stenting, zoning, prohibition of vaccination |
| Russia | notification of illness, border guard measures, screening, targeted surveillance, control of movement within the country, zoning, control of vectors |

| | |
|---|---|
| Serbia | notification of a disease, precautionary measures at the borders |
| Turkey | disease notification, border measures, general surveillance, domestic movement control, stamping out, zoning, official vaccination, vectors control |
| Iran | disease notification, border guard measures, monitoring, screening, general surveillance, targeted surveillance, internal movement control, stamping out, zoning, vectors monitoring |
| Iraq | notification of a disease, border measures, monitoring, official vaccination |
| Israel | disease notification, border measures, screening, general surveillance, internal movement control, modified stenosis, zoning, official vaccination, vectors control |
| Jordan | disease notification, border measures, monitoring, screening, general surveillance, official vaccination |
| Kazakhstan | communication about the disease, border measures, general surveillance, control of movement within the country |
| Kuwait | disease notification, border measures, screening, internal movement control, modified stemming, official vaccination, vectors control |
| Lebanon | border disease surveillance, monitoring, general surveillance, internal movement control |
| Palestine | borderline surveillance, monitoring, screening, general surveillance, control of movement within the country, zoning, official vaccination, control of vectors |
| Saudi Arabia | disease notification, border guard measures, monitoring, targeted surveillance, domestic movement control, modified stem-out, vectors control |

Analyzing the effectiveness of anti-epizootic measures in nodular dermatitis, it has been established that despite the peculiarities of methodological approaches to fighting the disease (stamping out, modified stamping out or vaccination) in unsuccessful countries, cases of recurrence of the disease were established several months after the normalization of the epizootic situation (Azerbaijan, Greece, Russia, Iran, Kuwait and Saudi Arabia). That is, it is not possible to argue about the superiority of a particular methodological approach to the fight against nodular dermatitis, but, of course, in addition to special measures, the operational efficiency of the veterinary service of a country and the amount of state support for anti-epizootic measures is of great significance.

It should be noted that despite the different schemes of struggle against nodular dermatitis, the only effective way to combat this disease, in countries where it is endemic, is vaccination [14]. To date, two groups of vaccines are used in the world, namely homologous and heterologous. The composition of preparations for specific prevention of nodular dermatitis of the first group includes a viral mass based on a live attenuated strain of a Neethling virus [1]. The market for homologous agents for specific prevention is represented by the following drugs:

- Lumpy Skin Disease Vaccine, based on the Neethling strain of the nodular dermatitis virus (manufactured by Onderstepoort Biological Products, South Africa);
- Lumpivax, based on the attenuated field strain of the nodular dermatitis virus (produced by Merck Animal Health and Intervet, South Africa;
- Herbivac LS, based on the Neethling strain of the nodular dermatitis virus (manufactured by Deltamune, South Africa).

In addition, taking into account the antigenic affinity and the cross-immune response of viruses of the genus Capripoxvirus to prevent nodular dermatitis, the sheep and goat vaccine virus is used as a heterologous means of specific disease prevention [14]. It is believed that many sheep and goat strain strains are suitable for preventing nodular dermatitis [18], but the immunization dose for bovine animals should be 3-10 times the dose for immunization of sheep and goats [1]. To date, for the prevention of nodular dermatitis, the following vaccines from the attenuated strains of the smallpox of sheep and goats are used:

- Jovivac, based on attenuated strain RM-65 of sheep pox virus (manufactured by Jovac, Israel). Effective in a ten-fold dose for sheep;

- LSD Vaccine, based on attenuated strain of RM-65 sheep flock virus (manufactured by Abic-Phibro, Israel (ten times the sheep dose);

- Poxvac ™, from the attenuated Bakirköy strain of the smallpox virus (produced by Vetal Animal Health Products, Turkey. Effective when the sheep dose is increased three to four times;

- SPPV vaccine, from an attenuated strain of Romanian sheep pox virus (produced by the Saudi Arabian Veterinary and Vaccine Institute, Saudi Arabia).

In case of immunization of cattle with a vaccine based on O-240 and O-180 strains of Kenya smallpox sheep, post-vaccine complications with clinical manifestations of the disease are recorded, which is a certificate of non-compliance of the abovementioned preparations with a safety criterion, therefore they are not recommended for bovine animals [19].

According to the results of studies conducted in Israel to determine the efficacy of Neethling strains of the nodular dermatitis virus and the strain of RM 65 vaccine avian influenza virus, it was found that the homologous preparation was 4 times more effective than its heterologous analogue [14, 20].

Thus, a significant variation in the immunogenic and protective properties of vaccines, which today are used to prevent nodular dermatitis, are contradictory in their harmlessness and efficacy [19, 20, 21]. In addition, the immunization of bovine animals with attenuated vaccines may lead to post-human reactions that are manifested by local reactions at the place of introduction of the vaccine, an increase in body temperature and a temporary decrease in milk yield, and in addition, in certain animals (<10%), the clinical signs of nodular dermatitis . Instead, sheep vaccine vaccines almost do not cause complications in cattle, hence immunization with a heterologous vaccine and subsequent vaccination with the Neethling strain helps to avoid complications in the use of live vaccines and to increase the effectiveness of specific prevention.

It should be noted that live attenuated nodular dermatitis vaccines are not recommended for use in countries free of biosecurity because of the possible occurrence of lesions on the skin of immunized animals were a high-level virus can accumulate in the environment [22]. In addition, the use of live attenuated vaccines complicates the diagnosis of the disease (it is not possible to differentiate between the vaccine and the field virus) and leads to a restriction of international trade in animals and livestock products [23]. In addition, the possibility of reversing the attenuated vaccine strain with the use of live vaccines due to the peculiarities of the epizootic situation in the region, the technology of keeping and keeping livestock, should not be excluded.

Thus, given the high degree of contagiousness, the transdermal nature of nodular dermatitis, its proliferation from the African continent, first to the Middle East, and in the future through Turkey to continental Europe, there is a real threat of a pathogen from entering the territory of Ukraine from neighboring countries. That is why the urgent issue of the present is the development of measures to control nodular dermatitis and prevent epizootics in Ukraine.

**Conclusions.**

Considering high contageousness, transboundary of nodular dermatitis, its prompt extending to the countries of the continental Europe, real threat of hit of the infestant in Ukraine from neighbouring states is determined.

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