

Review

## Dirofilariasis in Russian Federation: a big problem with large distribution

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**Abstract:** Dirofilariasis caused by *Dirofilaria spp.* is an important vector-borne and largely zoonotic disease. In Russia, dirofilariasis is caused by two agents *D. immitis* and *D. repens*. The present article provides detailed analyses of human and canine dirofilariasis methods of diagnosis, treatment, and prevention of the disease, with particular reference to the control programmes. Information has been summarised from literature in different languages that are not readily accessible to the international scientific community.

Human dirofilariasis was first registered in Russia in 1915, and recent reports showed that the total number of infected humans increases on average by 1.8 times every three years. Human dirofilariasis was registered in 42 federal subjects. Totally 1162 cases of subcutaneous dirofilariasis were registered in the Russian Federation between 1915-2013, the most frequently type of subcutaneous dirofilariasis was ocular dirofilariasis (more than 50% cases). Seven cases of pulmonary dirofilariasis were registered in Russia. The treatment of human dirofilariasis includes surgical removal of worms only; in result preventive measure have major importance for reducing risk of *Dirofilaria* infection. Control programmes have been implemented by the government at all administrative levels including diagnosis and treatment of patients, identification, isolation, and treatment of infected dogs, monthly chemoprophylactic of dogs during spring-summer periods, and regular vector control.

**Keywords:** dirofilariasis, heartworm diseases, human, Russia

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### Introduction

Dirofilariasis is an important vector-borne and globally distributed zoonotic disease [1-3] and it is a single vector-borne disease caused by a nematode in the Russian Federation [4]. The disease is caused by roundworms in the genus *Dirofilaria* (Nematoda: Onchocercidae) and is naturally transmitted by mosquitoes. The *Dirofilaria* life cycle includes an invertebrate host and a vertebrate definitive host [5, 6]. Six of 40 species from the *Dirofilaria* genus are responsible for affecting humans [7]. Two main filarid species, *D. repens* and *D. immitis*, were found in the Russian Federation, and these species also have the high prevalence, veterinary and medical importance worldwide [1, 8, 9].

The *D. repens* and *D. immitis* life cycles include mosquito vectors from the *Culicidae* and final hosts of different domestic and wild carnivorous animals [10, 11]. Both *Dirofilaria* species demonstrate low host specificity and can affect many mammals. Humans are accidental hosts for *Dirofilaria*, thus adult nematodes do not reach maturity in their heart or skin [1, 12-14]. *D. repens* and *D. immitis* follows that of other *Dirofilaria* species in that infected mosquitoes, introduce third-stage larvae (L3) into the vertebrate host during a blood meal. The L3 larvae molt first into fourth-stage larvae (L4) and then adults within the vertebrate host

[15, 16]. Canine dirofilariasis, caused by *D. repens*, induces such clinical signs as a pruritus, dermal swellings, subcutaneous nodules, alopecia and erythema [17-20]. Canine infestation caused by *D. immitis* is frequently asymptomatic, depending on worm burden and duration of infection [21, 22]. Heavy infestation with a high worm burden can produce clinicopathologic manifestations, including pulmonary endarteritis, hypertension, thromboembolism and pneumonitis [23-26].

There are three types of dirofilariasis distinguished in humans, depending on clinical signs: subcutaneous dirofilariasis (SD), ocular dirofilariasis (OD) and pulmonary dirofilariasis (PD) [27-29]. SD usually manifests as a single subcutaneous nodule, which is caused by macrofilaria trapped by the immune system [27]. Subcutaneous migration of the worm may result in local swellings with changing localisation (creeping eruption) [31]. In addition, rare cases of organ manifestation have been reported, affecting the scrotum, male genitals, female breast, lymphatic glands and peritoneum [2, 32-38]. OD is a variation of subcutaneous dirofilariasis with parasite localisation in the eye area [30]. Eye involvement may be periocular, sub-conjunctival, subtenons, or intraocular [39-42]. PD caused by *D. immitis* is a less frequent type of dirofilariasis. Clinical signs include a single pulmonary nodule forming around immature macrofilaria [43, 44]. In rare cases, multiple lesions have also been described [45, 46].

**Table 1** *Dirofilaria* prevalence in mosquitoes

Region	Mosquito vector	Prevalence	Refs
Moscow Federal District (n=1554)	Total prevalence – 2.4%	<i>D. repens</i>	[52]
Astrachan (n=334)	<i>Aedes</i> – 3.3%, <i>Anopheles</i> – 1.9%, <i>Culex</i> – 5.8%	<i>Dirofilaria</i> spp.	[55]
Tula (n=2277)	<i>Cx. pipiens</i> – 0.01–0.08%, <i>Ae. caspius</i> – 0.02–0.08%, <i>Ae. dorsalis</i> – 0.02–0.08%, <i>An. messeae</i> – 0.01–0.04%	<i>D. repens</i>	[54]
Rostov on Don (n=482)	<i>Aedes</i> – 0%, <i>Anopheles</i> – 0.86%, <i>Culex</i> – 1.37%	<i>Dirofilaria</i> spp.	[58]
Chabarovsk (n=1284)	<i>Aedes</i> – 3.7%, <i>Anopheles</i> – 10%, <i>Culex</i> – 4.1%	<i>Dirofilaria</i> spp.	[56]
Anapa (n=550)	<i>Aedes</i> – 0.44%, <i>Culex</i> – 0.46%	<i>Dirofilaria</i> spp.	[51]
European Part of Russia (n=45714)	<i>Cx. pipiens</i> – 0.01–0.08%, <i>Ae. caspius</i> – 0.02–0.08%, <i>Ae. aegypti</i> – 0.01–0.06%, <i>An. maculipennis</i> – 0.01–0.04%	<i>D. repens</i>	[url*]
	<i>Cx. pipiens</i> – 0.01–0.08%, <i>Cx. modestus</i> – 0.01–0.06%, <i>Ae. caspius</i> – 0.01–0.08%, <i>An. maculipennis</i> – 0.01–0.06%	<i>D. immitis</i>	[51]

n – total number of mosquitoes investigated. *Cx.*, *Culex*; *Ae.*, *Aedes*; *An.*, *Anopheles*. [url\*], <http://fguz-volgograd.ru/component/content/article/1197>.

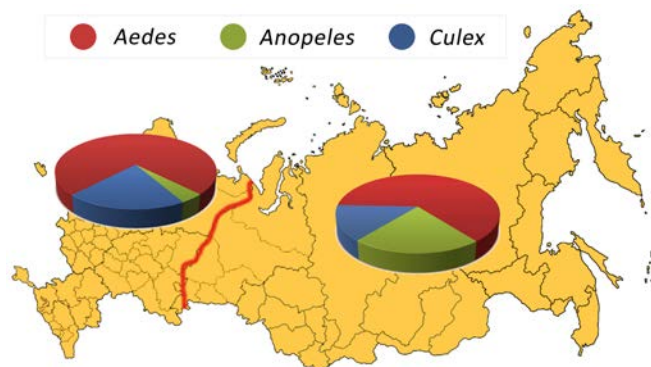
**Table 2.** Mosquitoes species that are involved or potentially involved in the transmission of *Dirofilaria* spp.

Species	Part of Russia [Refs]
<i>Aedes aegypti</i>	European, Asian [51]
<i>Aedes albopictus</i>	European, Asian [52]
<i>Aedes caspius</i>	European, Asian [51, 53]
<i>Aedes dorsalis</i>	European, Asian [51, 53]
<i>Aedes koreicus</i>	European, Asian [50]
<i>Anopheles maculipennis</i>	European [52]
<i>Anopheles messeae</i>	European, Asian [54]
<i>Culex pipiens</i>	European, Asian [51, 54]

of infestation among domestic dogs and cats, and humans.

References for this review were collected by searching Elibrary (elibrary.ru), Google Scholar, PubMed, and the ISI Web of Knowledge. Search terms used included “dirofilariasis,” “*Dirofilaria repens*,” “*Dirofilaria immitis*,” “canine dirofilariasis,” “feline dirofilariasis,” “dirofilariasis Russia”. Relevant articles or book chapters in English and Russian were also consulted. Epidemiological data were obtained from the articles cited, and reports released by the Ministry of Health of the People’s Russian Federation. The search of these databases was completed in 2016, when this review was prepared. During revision of the manuscript, additional citations brought to our attention were added. There were no restriction on the type of study design. Following the initial screening, the references of all eligible studies were examined to identify any other potentially relevant articles. Because this is not a systematic review evaluations of methodological quality were not used to exclude papers from the study.

The review was divided in five parts: in part 1 publishing studies about mosquitoes transmitted *Dirofilaria* in Russia were included; in part 2 publishing epidemiologic studies that reporting *Dirofilaria* prevalence, symptoms of dirofilariasis in domestic dogs were included. In part 3 all included reports were focused of human dirofilariasis in Russia; in part 4 studies about diagnostic methods and treatment of dirofilariasis both in humans and animals were included. In part 5 studies summarised controls and prevention procedures of dirofilariasis provided in Russia were included.



**Figure 1.** Distributions of mosquitoes from the Culicidae family in the Asian (left) and European (right) parts of Russia (the data shown from references [48-50]).

### Vector species in Russia

Mosquitoes from the *Culicidae* family serve as vectors to transmit *Dirofilaria* spp. The L1 stage larvae are ingested by feeding mosquitoes, then larvae moult twice over 8-17 days, and this time highly depends on temperature. For L3 development stage larvae, the average temperature is at least 20°C for two weeks. It has been experimentally demonstrated that the development of infectious L3 larvae requires 8-10 days at 28-30°C, 11-12 days at 24°C, and 16-20 days at 22°C. Below 14°C, development arrests, although it can be restarted when the temperature increases above this threshold. Consequently, the climate and associated changes can determine the presence and dynamics of transmission of dirofilariasis in temperate regions. If the temperature is inadequate, development of L3 stage larvae does not occur [1, 46].

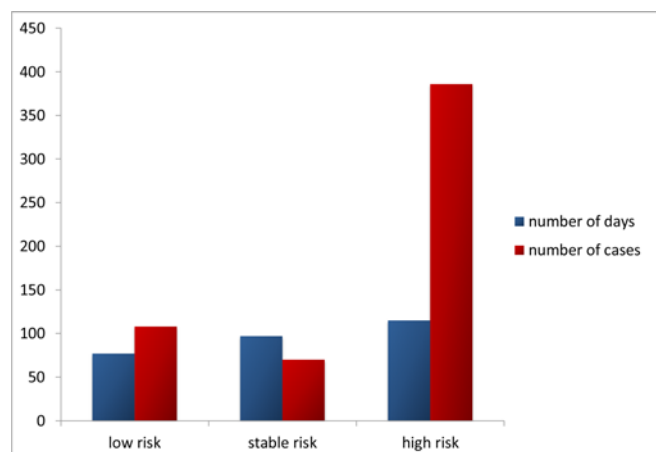
The *Culicidae* family is a large group including more than 3000 species globally distributed [47]. Nevertheless 31 mosquito species from the *Culicidae* family, including the genera *Aedes meigen*, *Culex linne*, *Anopheles meigen*, *Culiseta feit* and *Ochlerotatus lynch-arribalzaga*, transmit *Dirofilaria* spp [1]. In the Russian Federation, *Culicidae* fauna includes 94 species with diversity in both the European and Asian parts of Russia (Figure 1) [48-50]. However, the importance of different species in *Dirofilaria* spp. transmission is underestimated. Sporadic reports indicate different prevalence rates of *Dirofilaria* spp. in mosquitoes from three genera: *Aedes*, *Culex* and *Anopheles*, and prevalence rates of *Dirofilaria* spp. in mosquitoes are significantly different in different regions (Table 1). However, eight species of mosquito from the *Culicidae* family are most frequently involved in the transmission of *Dirofilaria* spp. In Table 2, we present the list of species found in Russia, which have the capacity to transmit *Dirofilaria* based on data published in the Russian Federation [50-54].

This review summarises the current status of dirofilariasis in Russia, with particular focus on the impact of control and prevention

**Table 3. *Dirofilaria* spp. prevalence in domestic dogs**

Region (n)	<i>Dirofilaria</i> species and prevalence (%)	Age group	Sex	Refs
Novgorod region (n=108)	<i>Dirofilaria</i> spp. – 28.7%	–	–	[61]
Altay region (n=3535)	<i>Dirofilaria</i> spp. – 11.7%	–	–	[62]
Moscow Federal District (n=3371)	<i>D. repens</i> – 0.65%, <i>D. immitis</i> – 3.4%	2-3 years old – 11%, 4-6 years old – 14.0%, 7-9 years old – 78.3%, older than 9 years – 2.4%	female – 42.6%, male – 57.4%	[63]
Kirov region (n=233)	21.8%	8 months old – 2.4%, 2 years old – 4.9%, 3-6 years old – 56.1%, older than 7 years – 34.1%	–	[64]
Voronezh region (n=424)	<i>D. immitis</i> – 36.5%, <i>D. repens</i> – 63.5%	–	–	[65]
Barnaul (n=121)	<i>Dirofilaria</i> spp. – 33.3%, <i>D. immitis</i> – 10.5%, <i>D. repens</i> – 3.9%	1-3 years old – 15.4%, 4-6 years old – 42.3%, 7-9 years old – 30.8%, older than 10 years – 11%	males – 65.4%, females – 42.3%	[66]
Krasnodar (n=3366)	<i>D. immitis</i> – 28%, <i>D. repens</i> – 0.12%	1-3 years old – 15.6 - 29.9%, 4-8 years old – 26,9 - 39.2%	male – 27.0%, female – 28.4%	[67]
Astrakhan region (n=5729)	<i>Dirofilaria</i> spp. – 2.9%	–	–	[56]
Anapa (n=38)	<i>D. repens</i> – 15.7%, <i>D. immitis</i> – 5.3%, <i>D. repens</i> + <i>D. immitis</i> 5.3%	2 years old – 10%, 5-7 years old – 80%, 8 years old – 10%	males – 60.0%, females – 40.0%	[57]
Chabarovsk (n=41)	<i>Dirofilaria</i> spp. – 29.2%	1-3 years old – 29.2%, 4-5 years old – 16.7%, 6-8 years old – 66.7%	males – 65.8%, females – 34.2%	[68]
Yakutsk (n=14*, n=33)	<i>Dirofilaria</i> spp. – 51.5%, <i>D. repens</i> – 21.4%, <i>D. immitis</i> – 47.8%	1-3 years old – 10.0%, 4-8 years old – 33.3%, older than 9 years – 3.33%	–	[69]
Penza (n=1269)	<i>Dirofilaria</i> spp. – 9.1%	–	–	[url*]
Perm (n=125)	<i>D. immitis</i> + <i>D. repens</i> – 0.8%, <i>D. repens</i> – 3.2%	–	–	[70]
Kalmyk Republic (n=180)	<i>D. repens</i> – 24.4%	–	–	[71]
Kostromskoi Region (n=234)	<i>Dirofilaria</i> spp. – 33.0%	2-3 years old – 57.0%, 4 years old – 14.0%, 7-8 years old – 29.0%	male – 54.0%, female – 46.0%	[72]

n, total number of investigated animals. [url\*], [http://58.rospotrebnadzor.ru/rss\\_all/-/asset\\_publisher/Kq6J/content/id/290168](http://58.rospotrebnadzor.ru/rss_all/-/asset_publisher/Kq6J/content/id/290168). \*Postmortern examination.



**Figure 2. The number of days (blue) and the number of cases (red) for each zone of transmission □ low risk, stable risk, and high risk of human dirofilariasis (The data summarized from reference [4]).**

### Geographical distribution of dirofilariasis in Russia

The area of spread of *Dirofilaria* spp. in Russia depends on the source of infection and the area of spreading of vector-mosquitoes *Anopheles*, *Aedes* and *Culex*. *Dirofilaria* spp. were found in 42 federal subjects of the Russian Federation, where mean temperature in July is at least 17°C in the north zone and at least 24°C in the south zone [4, 60]. The number of days with temperature higher than 15°C was 60-70 per year in the north and more than 120 days in the south. Three zones of *Dirofilaria* spp. transmission are distinguished in Russia. This classification is based on geographic and climatic conditions, and determines the

development of vectors (Figure 2). The zone of stable risk of transmission includes 11 subjects in the European part of Russia (41-56 N), the south border of which is located on the foothills of the Kaucazian Mountains. The high risk of *Dirofilaria* spp. transmission depends on high temperatures in July (20-24°C), and temperatures higher than 15°C for 110 days; the transmission season is approximately 3-5 months. This zone includes five Federal Subjects: Rostov Federal District, Volgograd Federal District, Astrakhan Federal District, Saratov Federal District and Krasnodar region. The mean risk of transmission zone (51-55 N) includes 18 federal subjects, including the territories of Tatarstan Republic, Chelyabinsk and Kurgan Federal Districts (56 N), Far Eastern Federal District (42-52 N), Chabarovsky region, Amursky District, and European Jewish Autonomic District, Prymorsky Region. The average temperature in July is 19-21°C and the temperate is higher than 15°C for 90-105 days. The low risk of transmission zone (54-58 N) includes 12 federal subjects. The maximum temperature in July is 17.5-19°C and the temperature is higher than 15°C for 60-90 days [4, 55].

### Canine dirofilariasis

Both species, *D. immitis* and *D. repens*, were found in dogs in Russia. The first cases of canine dirofilariasis caused by *D. repens* were registered in Soviet Union territories in the Kharkov region (Ukraine), near the border of the Rostov region, in the Bukhara Region and in the Rostov region. *D. immitis* was firstly reported in dogs from the territory of the Azerbaijan Republic. Later, this species were also identified in the Turkmenistan Republic, in the Far East Ussuri region and in Abkhazia [61, 62]. Recently, dirofilariasis was registered in dogs from 17 regions [56, 57, 61-

73]. The minimum prevalence was 0.12% and the maximum prevalence was 63.5% (Table 3). There was no common tendency for differences in the prevalence for sex; the prevalence in males and females fluctuated in different regions. In the Ulyanovsk region, male and female dogs had equal prevalence rates; in Barnaul and Anapa, female dogs were more frequently affected than male dogs (Table 3). Conversely, the *Dirofilaria spp.* prevalence was higher in males than in females in the Chabarovsky region [68]. Dirofilariasis was found in dogs of different age groups. However, cases of *Dirofilaria spp.* infestation were not found in puppies younger than six months old (Table 3). High infection rates were found in dogs between four and six years old and the lowest prevalence was found in one-year-old dogs. Dogs older than six years had the lower *Dirofilaria spp.* prevalence than dogs between four and six years old (Table 3). Dirofilariasis in dogs can be asymptomatic, and in some cases, *Dirofilaria spp.* infection causes disorders with different clinical symptoms, depending on parasite species and intensity of infection. Cardiopulmonary dirofilariasis caused by *D. immitis* is frequently fatal for dogs [73, 74]. Totally three clinical forms of dirofilariasis are distinguished:

- i) Mild (asymptomatic). Dogs with this form of disease do not have clinical signs. Dirofilariasis was determined by blood sample analyses. However, laboratory tests frequently show eosinophilia, proteinuria, and increased lactate dehydrogenase rates.
- ii) Moderate. Cardiopulmonary disease with chronic renal pathology. All animals tire easily; the lack of breath and cough frequently appear. Radiography shows expansion of pulmonary arteries. Ultrasonography of the heart and abdominal organs shows an increase in the right ventricle and renal sucker, and prostate cyst is also appeared. Echocardiography shows arrhythmia.
- iii) Caval syndrom. Cardiopulmonary disease with thromboembolic, chronic renal and hepatic pathology. Animals in this group have fatigue, cough, and shortness of breath, weight loss, jaundice, and ascites. Radiography shows an increase in heart borders and expansion of pulmonary arteries. Heart ultrasound revealed an increase in right ventricular infarction and thinning of fluid in the pericardium. Ultrasound of the abdominal cavity shows increased size liver and hepatic veins, enlargement of the spleen, and expansion of the renal pelvis, prostate cysts and ascites. Violation of the heart and sinus arrhythmia appears in echocardiography. This form is found frequently among affected dogs.

*D. repens* causes subcutaneous dirofilariasis in dogs and less pathogenicity than *D. immitis*. Canine subcutaneous dirofilariasis is frequently asymptomatic. Clinical manifestations are classified into two clinical forms: multifocal nodular dermatitis and papular dermatitis. Both clinical forms frequently present with leukocytosis, proteinuria and increased alkaline phosphatase. Both clinical forms have equal frequency among affected dogs [73-75].

#### Human dirofilariasis

The first case of human dirofilariasis was reported in 1915 by A.P. Vladychenskiy, who found filaria in a nodule between the orbital wall and eyeball [101]. Regular researches were produced after 1930, when columnist of Soviet Helminthological School, K.I. Skriabin, completely described ocular dirofilariasis [76].

Dirofilariasis was first included in Russian Sanitary Regulations and Standards (No.3.2.1333-03 "Profilactic of parasitic diseases in Russian Federation") in 2003. Now dirofilariasis was registered in 42 federal subjects. In total, 1093 cases of human dirofilariasis were registered in 1915-2012 [59]. Early reports were published mainly in southern regions of Russia: in Chabarovsky region, the first case of human dirofilariasis was registered in 1929 [76]; in Astrahan District in 1951 [78]; in Altay Region in 1989 [79] and in Ryazansky District and Irkutsky District in 1997 (data from: <http://cgje.62.rospotrebnadzor.ru/info/91828>). The latest reports published from south regions [80-84] were Penzensky District (2000); Ivanovsky district, Permsky District (2004); Smolensky District (2007); Kirovsky District (2008).

A stable tendency for increasing numbers of cases of human dirofilariasis is observed in Russian Federation. During 1996-2001, a total of 152 cases of *Dirofilaria* infestations were registered, whereas 227 cases were registered between 2011-2012 [85-87]. The total number of infected humans increases in average by 1.8 times every three years [87]. However, the real number of affected people is underestimated, due to low quality of diagnostic procedures, difficulty of filaria extraction, and incomplete data of *Dirofilaria* infestations. In 2013, a new form of dirofilariasis, found in Rosstat, was reported [59]. From 1915, the date of the first Russian reported case of dirofilariasis, to 2014, most reported cases were found in a restricted number of southwestern administrative units [59]. Nevertheless, data analysis revealed three regions with high levels of dirofilariasis. The Rostovsky region had the highest *Dirofilaria* infestation rates – 242 cases [8, 58, 59, 88, 89], Nizhegorodsky region had the second highest – 129 cases [58], and Volgogradsky district had the third highest – 93 cases [59, 90]. Warm climate conditions and high infestation rates of *Dirofilaria* in mosquitoes and dogs in Rostovsky and Volgogradsky regions contribute to high prevalence rates of human dirofilariasis. High levels of *Dirofilaria* infestation were found in people from the Nizhegorodsky region associated with kennel dogs, which delivered infected mosquitoes from Chechensky Republic [59]. There is lack information about gender and age distribution of people infected *Dirofilaria spp.* in Russia. Data reported by Ministry of Health show, that in 2012 years 143 cases of dirofilariasis were registered in people between up 1 year to 87 years old. Dirofilariasis was registered in 76 % woman (109 cases) and 24% man (34 cases) (data from: [http://rospotrebnadzor.ru/documents/details.php?ELEMENT\\_ID=651](http://rospotrebnadzor.ru/documents/details.php?ELEMENT_ID=651)). The most frequently registered infection was subcutaneous dirofilariasis. In total, 1162 cases of SD were registered in the Russian Federation between 1915-2013 [91] and 782 described cases were caused by *D. repens* [91]. Map of *Dirofilaria* spreading in Russian Federation were presented by Ermakova et al. (2014) [8]. *Dirofilaria spp.* were frequency localised in the ocular area (more than 50% cases) [8, 79, 81, 83, 84, 88, 89-102] follow head and face [8, 81, 88-92, 96], upper limbs [8, 88, 89, 92, 96-100], stomach [8, 88, 89], genitals [8, 83, 84, 88, 89, 91, 106, 107], breast and knees [8, 67, 88, 89, 91, 92, 104, 108] (Figure 3).

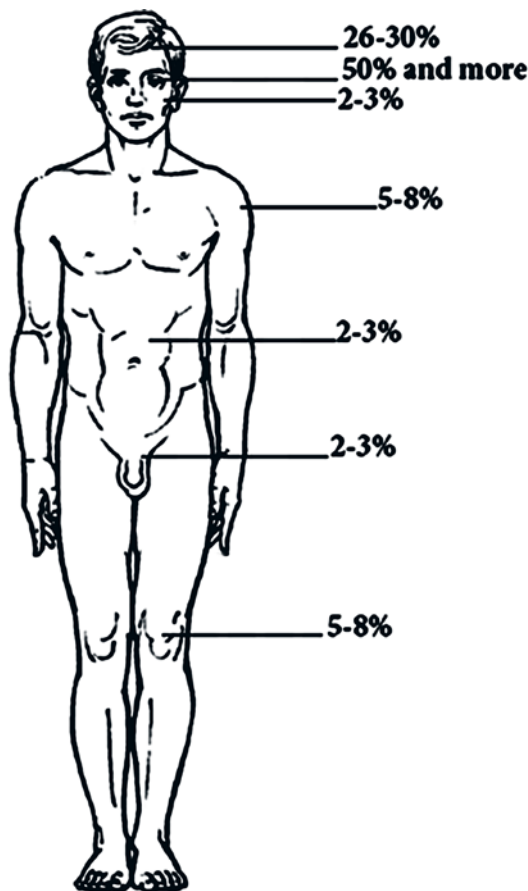
#### Rare cases of human dirofilariasis

Three unusual types of human dirofilariasis were registered in the Russian Federation [108-110]. In one case *Dirofilaria spp.* was extracted from intracerebral haematoma via autopsy from a 41-year-old patient, who had stenosis and occlusion of major carotid vessels, venous sinus and bone destruction of the skull base [109].

Typical signs of subcutaneous dirofilariasis (nodules, lymphatic and optical fields, creeping eruption) were not present. Other case of subcutaneous dirofilariasis was described in a 49-year-old female, with dirofilariasis of the tendinous sheath of the extensor pollicis longus [110]. The patient was admitted to hospital with a diagnosis of dorsal hand ganglion cyst, and correct diagnosis was made after worm extraction. The first case of microfilaria detection in a patient in the Saratov region, who had clinical manifestations of a *D. repens* infestation, was described in the Moscow region by Supriaga et al. [111].

**Table 4. Pulmonary dirofilariasis in Russia**

Patient	Dirofilaria species	Clinical signs
Male, 40 years old	<i>D. repens</i>	Pain in the chest, lack of breath, cough
Male, 34 years old	<i>Dirofilaria</i> sp.	Pain in the chest, body temperature 39°C
Female, 60 years old	<i>D. repens</i>	Pain in the chest, cough, body temperature 37.2-37.6°C
Female, 75 years old	<i>D. repens</i>	No clinical signs
Male, 47 years old	<i>D. repens</i>	Pain in the chest, cough, body temperature 39°C



**Figure 3. Areas of *Dirofilaria* spp. localisation**

### Human pulmonary dirofilariasis

In total, seven cases of pulmonary dirofilariasis were registered in Russia. Six cases were described in the Ivanovo region and one case was described in Moscow. Single pleural nodules were found in five patients [112, 113] (Table 4); two cases were autochthonous pulmonary dirofilariasis with the development of recurrent exudative pleurisy and "nummular" pulmonary nodules [114, 115].

### Dirofilariasis diagnostic procedures

#### Diagnostic of canine dirofilariasis

Canine dirofilariasis diagnostic in Russia is conducted by standard procedures, including the blood sample analysis, immunoassay tests and polymerase chain reaction (PCR) analysis, which are also complement by ultrasonography, radiography and clinical sign analysis. The blood test analysis include standard procedures: methods of direct microscopy of the fat blood drop, Knott's method, Wyllie's method, which are used worldwide [1]. Due to the fact that the blood test analysis and ultrasonography and radiography used both for humans and animals we don't distinguish this chapter in two parts.

Some modified blood samples analyses for *Dirofilaria* diagnostic use in Russia. For example, Supryaga & Andreenkov [116] proposed a dirofilariasis diagnostic method for medical practice for patients with a low density of microfilariae in the blood. The authors proposed a modification whereby microfilariae are detected using stained ultrafilters, which are domestically produced. In this method, haemolysed blood passes through ultrafilters under vacuum.

Another method was proposed by Kolesova et al [69]. Blood samples are left at low temperature (4-15°C) for 20-24 hours with K<sub>2</sub>-EDTA (Editor's comment: EDTA, Ethylenediaminetetraacetic acid) added. Blood is divided into plasma and sediment, which forms a funnel-like cavity containing microfilaria on the boundary between plasma and sediment. Blood samples (15-20 ml) are taken from the bottom of the funnel and mixed with Lughole 1% solution, followed by microscopy investigation.

V.B. Yastreb suggested modified Knott's technique [117]. Blood samples (2-3 ml) were mixed with 5% sodium citrate (1:20). Then, 1 ml samples of canine and feline blood aliquots were placed in a 10-ml centrifuge tube with 9 ml distilled water added. The tubes were left at room temperature for at least 5 min for erythrocyte haemolysis, with further centrifugation at 2000 rpm for 5 min. The supernatant was then discarded, and sediment (0.5 ml) retrieved in the microscopic fields was identified on the basis of differential morphometric (i.e. length and width) and morphological (i.e. head and tails) features of canine and feline filariae under light microscopy at 200x, 400x and 1000x magnifications. This method is as effective as the classic Knott method and has a number of advantages: 1) larvae in the sediment are alive and microfilariae viability can be studied according to the conditions and timing of blood storage, which is especially important in the preparation of secretory antigens of the parasite; 2) microfilaria drug efficacy can be estimated in vitro and in vivo conditions. In addition, modified quality tests were suggested by Arkhipova & Arkhipov [118] using a mixing pipette and a Fucs-Rozanthal counting chamber. Blood taken from the ear vein was placed into the mixing pipette up to mark I, and filled to mark II with solution containing glacial acetic acid,

fuchsin solution, and distilled water (ratio of 3:4:93). The coverslip glass was ground in a clean and dry Fuchs-Rosenthal chamber until the so-called Newton's rings were visible. The mixing pipette with the blood and solution was shaken and a blood drop (not the first) was applied to the middle of the chamber plate and checked using a microscope. The numbers of microfilariae in all squares were counted. Immunoassay tests are the "gold standard" for diagnosis of *Dirofilaria* infection both in pets and humans. Diagnosis can also be performed using Elisa kits. However, high cost and low accessibility of this kit has limited its large-scale use. In addition, PCR tests were conducted according to the standard procedure [89, 119].

Due to limitations, it is necessary to use home-produced immunoassay tests. Beskrovnaya et al. [120, 121] suggested a procedure for somatic *Dirofilaria* antigen extraction. Pure somatic antigen was extracted from immature female *D. repens* worms. Removed worms were homogenised mechanically followed by ultrasound sonication and then extraction of proteins in 0.25 M aqueous sucrose solution. Samples were subject to further purification from lipids in acetone solution by centrifugation, and then the supernatant is discarded. The sediment was dried under vacuum and diluted in potassium phosphate buffer (pH 6.4) with further purification by centrifugation. Derived antigen was used at a concentration of 40 µg/ml in a volume of 100 µl per well. The sensitivity and specificity values of indirect immunofluorescent-antibody test (IFA) were 84.0% and 86.4%, respectively [120, 121].

However, immature *Dirofilaria* female specimens are not frequently found in clinical practice, thus another immunoassay analysis was conducted using somatic antigens from *Setaria labiotopapillosa* and *Setaria equina* [122]. Protein spectra for both species contained identical antigens for *Dirofilaria* antigens that are used in the diagnosis of *Dirofilaria* spp. infections. Both methods mentioned above used for *Dirofilaria* detection in dogs. However, immunoassay tests can produce false-negative results, especially for cats [1]. Molecular biotechnology has also been evaluated for diagnosing dirofilariasis in Russia. For example, MALDI-TOF MS (*Editor's comment*: MALDI is the abbreviation for "Matrix Assisted Laser Desorption/Ionization"; TOF MS is the abbreviation for "Time of Flight Mass Spectrometry") has been used for the identification of *D. repens* and *D. immitis* in dogs [123]. The analytical procedure does not require large material or labour expenditures, nor does it require experience of taxonomic studies in parasitology. The main obstacle for application of MALDI-TOF MS is the cost of the apparatus, but this expense is covered from the economical point of view. However, this method is rarely used in Russia, due to the high cost of the apparatus. It is therefore necessary to use combined diagnostic methods for *Dirofilaria* detection.

#### Human dirofilariasis diagnostic

Opposite to canine dirofilariasis diagnostic, identification of *Dirofilaria* worms in humans is usually spontaneous and it is often performed by patients, appeared worm in subcutaneous area in body or in the eye. *Dirofilaria* worms are also extracted using surgery of subcutaneous nodules. How it was mentioned above, humans are accidental hosts for *Dirofilaria*; so direct blood samples analyses for microfilaria are not useful for diagnostic of human dirofilariasis [1]. Human pulmonary dirofilariasis is a great medical importance problem, due to the absence of specific symptoms. Patients can be asymptomatic or have signs of

respiratory diseases; diagnosis is performed by surgical biopsy of pulmonary nodules, using radiography. PCR diagnosis of dirofilariasis is sporadically used in Russia [89]. There are also absent any commercial IFA tests for *Dirofilaria* diagnostic in humans, however non-commercial immunoassay tests have been performed in some studies [8, 120].

#### Treatment

##### Canine dirofilariasis treatment

Dirofilariasis treatment for dogs is based on clinical signs, the intensity of infection and data on laboratory tests (blood and urine analyses, ultrasonography, echocardiography) [1]. There are two methods of dirofilariasis treatment: macrofilaria therapy, and microfilaria therapy. Macrofilaria therapy is a complex treatment, which has high risk of side effects, due to massive destruction of adult worms in the bloodstream. Melasormine hydrochloride is used for macrofilaria treatment worldwide, according to standard protocol. To prevent anaphylactic shock due to adult helminths deaths, the antihistamine Tavegilum is administered to dogs at a dose of 0.05 mg/kg twice per day for five days after the beginning of treatment [124].

Supportive therapy includes immunomodulators (Ribotan, Ronkoleykin), hepatoprotectors (Karsil, Essenciale), analeptics (Sulphocamphokain), drugs improving blood microcirculation (Trental), drugs influencing metabolic processing in cardio musculature (Riboxin, Cocarboxylase), infusion solutions (salt and colloid solutions). Supportive therapy is provided based on clinical signs after evaluation of the individual situation for each animal. Restriction of physical activity is also used for avoiding the risk of pulmonary thromboembolism. For microfilaria therapy, macrocyclic lactones (avermectins, milbemycins, ivermectin (ivomec) are frequently used. Angiotensin-converting-enzyme (ACE) inhibitors are also used in supportive therapy for reducing renal vascular resistance. To exclude the possibility of an anaphylactic reaction due to high microfilaremia, therapy is combined with antihistamine drugs (tavegil, diphenhydramine, suprastin, among others) [124, 125].

Surgical extraction of filaria from subcutaneous nodules is used for treatment of canine dirofilariasis. Recently, surgical therapy has also been performed on dogs with vena cava syndrome [1] using flexible alligator forceps introduced via the jugular vein [126].

##### Human dirofilariasis treatment

Anthelmintic therapy is not usually recommended for human dirofilariasis treatment. The surgery is used in most cases because worm extraction from subcutaneous nodules is a simple procedure [105]. However, treatment of pulmonary dirofilariasis is complex procedure, which included extraction of filaria from nodules in the pleura and lungs using videothoracoscopy and chemotherapy using Albendazole [112]. One case of human microfilaremia was successfully treated with Doxycycline, Albendazole and Diethylcarbamazine [127].

##### Control and prevention

Recently, dirofilariasis was included in Russian Sanitary Regulations and Standards (No.3.2.1333-03) in the category of «Rare helminthiasis». The current Russian Sanitary Regulations and Standard No.3.2.3215-14 regulates the order of organisation

of preventive measures for dirofilariasis. The prevention of human and animal infestations is based on the interruption of vector-borne transmission of infestation: the extermination of mosquitoes, identification and treatment of domestic dogs and cats infected with *Dirofilaria spp.*, the prevention of mosquito contact with domestic animals and man, regular monitoring of phenology, ecology of mosquitoes that potentially transmit *Dirofilaria spp.* [128]. In addition, complex measures against larvae of mosquitoes in ponds or houses using insecticide are regularly provided in centres of *Dirofilaria* infection. Yearly monitoring of *Dirofilaria spp.* infestation rates in domestic dogs and cats are conducted in spring-summer time. Chemoprophylaxis is provided for dogs that reside in regions where canine dirofilariasis is endemic [86].

### Xenomonitoring

Average xenomonitoring is provided by entomologists [129].

Entomological monitoring of vector species, including mosquito collection, determination of species, evaluation of population distribution, evaluation of seasonal and daily population dynamics, epidemiological importance of individual species, definition of hatching larvae spaces and concentration of imago [129].

Investigation of *Dirofilaria spp.* prevalence in mosquitoes is based on microscopy and molecular diagnostics methods. For evaluation of the epidemiological situation of controlled timing of the epidemic season of dirofilariasis in territories of the high prevalence (start and end dates of seasons with infected mosquitoes and effective transmission of dirofilariasis) and determination of the number of generations of larvae of *Dirofilaria*-carrying mosquitoes are calculated.

The transmission period of *Dirofilaria spp.* is calculated based on average temperature data. Calculation begins from the day when the established daily average temperature is 14°C (0 units of *Dirofilaria* development (HDU, heartworm development units)), and at a temperature exceeding the threshold (14°C), HDU are accumulated. The season of infected mosquitoes began when HDU was 130. Other parameters such as the period of L3 development in mosquito species and the total number of *Dirofilaria spp.* larva generation (N) are also calculated [129].

Measures of mosquito population control include entomological and sanitary surveys, realisation of prevention works, and destroying of mosquito larvae [129].

### Pet infestation prevention measures

According to high morbidity among infected animals and difficulty of dirofilariasis therapy, prophylactic and preventive measures are very important. Complex preventive procedures include:

- i) Yearly monitoring of microfilaria in the blood of domestic cats and dogs, with the total number of investigated animals being at least 200 specimens in a Federal District.
- ii) Microfilaria therapy of affected animals.
- iii) Veterinarian practitioners and epizootologists provide explanatory works for heartworm disease prevention measures with pet owners.

- iv) Monthly chemoprophylactic with Dironet starts one month prior to the transmission period and finishes one month after this period ends.
- v) In the spring-summer period it is highly recommended to use repellents for protecting dogs against mosquitoes.
- vi) It is necessary to conduct further training for heartworm disease diagnosis and treatment of veterinarian practitioners especially in interdistrict clinics and laboratories [130, 131].

### Dirofilariasis prognosis

Latest published studies of the epidemiological situation of dirofilariasis in Russian Federation have shown an unfavourable outlook [132]. Data for dirofilariasis in the Russian Federation are incomplete and randomly published. Due to this the absence of adequate forms of dirofilariasis reports, which was introduced only in 2013, it is difficult to estimate a clear epidemiological situation. Reports of canine dirofilariasis have been published from 17 regions, whereas human dirofilariasis have been registered in 42 regions [132]. Moreover, most surveys were conducted using only blood sample microscopy, so the prevalence of each *Dirofilaria* species was not estimated [56, 60-62, 72]. High sensitivity methods, such as immunoassay tests (gold standard for dirofilariasis diagnosis) and PCR, are available for only a few large veterinary centres [119-121]. Clinical epidemiology and treatment of canine dirofilariasis are considerable, but not thoroughly studied [73, 74]. The role of wild carnivorous mammals is also underestimated. Studies of obligate mutualistic endosymbiont bacteria *Wolbachia* identification and influence of dirofilariasis pathogenicity in animal and humans are not provided in Russia, whereas detection of *Wolbachia* antigens is a major tool for *Dirofilaria* infection diagnostic [133, 134]. More studies about the transmission of both *Dirofilaria* species by mosquito vectors are clearly needed. Although monthly chemoprophylactic in dogs was successful at reducing *Dirofilaria spp.* infestation among dogs, prophylactic and preventive procedures are not provided in all regions where dirofilariasis is found. Control programmes are mainly implemented in zones with high and stable risks of infection, whereas zones with low risk of infestation rarely have control procedures. In addition, there are no published reports that help to estimate results of control and prevention programmes. Inadequate diagnosis and treatment in rural areas and towns also contributes to high levels of dirofilariasis.

### Conclusion

This review shows the difficult epidemiological situation of dirofilariasis in Russia. Preventive procedures are major importance for decreasing of *Dirofilaria* infection rates in dogs and humans. The success of control and prevention programmes was only evident when all aspects and steps of procedures were thoroughly performed for a considerable number of years. Regular monitoring of dirofilariasis infestation cases among domestic pets, humans and wild carnivorous mammals help to create an epidemiological map of dirofilariasis in Russia, and helps to evaluate the effect of the control programmes. It is necessary to support programmes of public health education, modernisation of veterinary clinics, especially in rural areas, regular training of veterinarian practitioners, epidemiologists, medical employers and public health workers with diagnosis, treatment and prophylactic

of dirofilariasis skills. All these gaps present obstacles to the effective integration of the knowledge of dirofilariasis in Russia.

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