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VERSITA

Human dirofilariasis due to *Dirofilaria repens* in Ukraine, an emergent zoonosis: epidemiological report of 1465 cases

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Abstract

The filarial nematode *Dirofilaria repens* is currently considered to be one of the most extensively spreading human and animal parasites in Europe. In Ukraine, reporting cases of dirofilariasis has been mandatory since 1975, and the disease was included in the national surveillance system for notifiable diseases. Up until December 31st 2012, a total of 1533 cases have been registered, with 1465 cases occurring within the previous 16 years. Most of the cases of dirofilariasis were registered in 6 regions: Kyiv, and the Donetsk, Zaporizhzhya, Dnipropetrovsk, Kherson and Chernihiv oblasts. In the years 1997–2002 the highest incidence rate was noted in the Kherson oblast in the south of the country (9.79 per 100 000 people), and the lowest in western Ukraine (0.07–1.68 per 100 000 people). *D. repens* infections were registered in all oblasts. Parasitic lesions were most often located in the head, the subconjunctival tissue and around the eyes. *D. repens* lesions were also found in the limbs, torso, male sexual organs, and female mammary glands. Dirofilariasis was diagnosed in persons aged from 11 months to 90 years old, most often among people between 21–40 years of age. Most patients had only one parasitic skin lesion; the majority of isolated nematodes were female. The results of our analysis point to a constant increase in *D. repens* dirofilariasis incidence in humans in Ukraine. Despite educational efforts, infections have become more frequent and the territory in which the disease occurs has enlarged to encompass the whole of Ukraine. Nevertheless, the Ukrainian sanitary-epidemiological services managed to achieve some measure of success, e.g. by creating a registration system for *D. repens* infections and establishing proper diagnostics for the disease.

Keywords

Dirofilariasis, *Dirofilaria repens*, human, epidemiology, Ukraine, Europe

Introduction

The filarial nematode *Dirofilaria repens* is an etiological agent of dirofilariasis, a vector-borne zoonosis. The reservoirs for these nematodes are dogs and some other carnivores, with mosquitoes serving as vectors, and humans being accidental hosts. In humans, adult nematodes can settle in the subcutaneous tissue in various parts of the body, as well as in the subconjunctival tissue. *D. repens* is currently considered to be one of the most extensively spreading human and animal parasites in Europe (Genchi *et al*. 2011*a*). In the previous decade, dirofilariasis has been registered in areas previously considered free of infection, e.g. in Austria, Germany, Slovakia and Poland. The rising number of cases in Europe is connected with climate change, the increase of mosquito populations and the intensification of international animal trade (Genchi *et al*. 2011*b*, Simón *et al.* 2012).

In Ukraine, dirofilariasis has been known for a long time. The first cases of *D. repens* infection were noted over one hundred years ago by N. Iv. Petropavlovskij among dogs in

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Kharkiv (Petropavlovskìj 1904), whereas the first human infection was discovered in 1927 in Kharkiv as well (Skrâbin *et al*. 1930). According to our data, Ukraine is the only European country with a system of mandatory registration of dirofilariasis cases, functioning since 1975, as well as a national register of *D. repens* human infections cases. Sanitary-epidemiological services provide active education on the subject. Much attention is given to the proper training of specialists regarding the diagnosis, treatment and prevention of dirofilariasis.

The aim of this paper is to evaluate the current epidemiological situation of *D. repens* human infection in Ukraine.

Materials and Methods

Study design. An analysis was conducted of epidemiological data from the years 1997–2012, collected in reports from 27 regional sanitary-epidemiological stations owned by the Ministry of Health. The regions in the reports included 24 Ukrainian oblasts, the cities of Kyiv and Sevastopol, as well as the Autonomous Republic of Crimea.

Setting. Cases of dirofilariasis were classified on the basis of the following clinical and laboratory criteria.

Clinical criteria: subcutaneous dirofilariasis – the presence of lesions in the subcutaneous tissue; ocular dirofilariasis – subconjunctival lesions and other lesions around the eyes.

Laboratory criteria: microscopic confirmation of the species of nematodes isolated from subcutaneous or ocular lesions, based on morphological characteristics such as: size, the presence of characteristic elongated ridges on the cuticle, the location of the vulva and anus, the length of spicules in males (Fig. 1A–D).

The case was confirmed when both the clinical and laboratory criteria were fulfilled. A detailed analysis of clinical data gathered during the years 2009–2012 – a total of 755 cases – was conducted.

Molecular methods. Molecular analysis of 8 randomly selected nematode specimens (cases 97♀/2011, 116♀/2011, 144♂/2011, 146♀/2011, 164♀/2011, 167♀/2011, 206♀/2011, 26♀/2012), isolated in 2011–2012 from patients inhabiting various parts of Ukraine, was conducted in order to confirm that the species were recognised correctly. The alignment of *D. repens* (GenBank: AM749230–749234) and *D. immitis* (AM749226–749229) cytochrome oxidase subunit I gene sequence was performed with CLC Main Workbench software. Primers RepIm-F0 5′-TCAGATTAGTATGTTTGTTTGAA CTTCTTATTT-3′ and RepIm-R0 5′-ACAGCAATCCAAA TAGAAGCAAAAGT-3′ were designed manually, based on the multiple alignment, within the DNA sequence regions identical for *D. immitis* and *D. repens*. 1 µl of DNA solution obtained from worms was added to every PCR reaction, yielding a final volume of 20 µl, containing 1× concentrated Sso-FastTM EvaGreen Supermix and 500 nM primers RepIm-F0 and RepIm-R0, for all PCR samples. Human DNA was used as the negative control and DNA isolated from an adult *D. repens* worm was used as the positive control; *D. immitis* DNA was another positive control used in PCR. Amplification was performed as follows: initial denaturation 95°C 3 min followed by 45 cycles of three-step reaction: 95°C 15 s, 61°C 20 s, 72°C 40 s. Signal was acquired in the green channel at the end of each cycle. After the completion of PCR, premelt conditioning for 90 s in 70°C was performed, followed by high-resolution melting (HRM) in a temperature range from 70°C to 84°C in 0.05°C temperature increments for 2 s at each step. The PCR products were purified using the Kucharczyk TE Clean-Up kit (cat. no. 400-043) and subjected to sequencing with primer RepIm-F0.

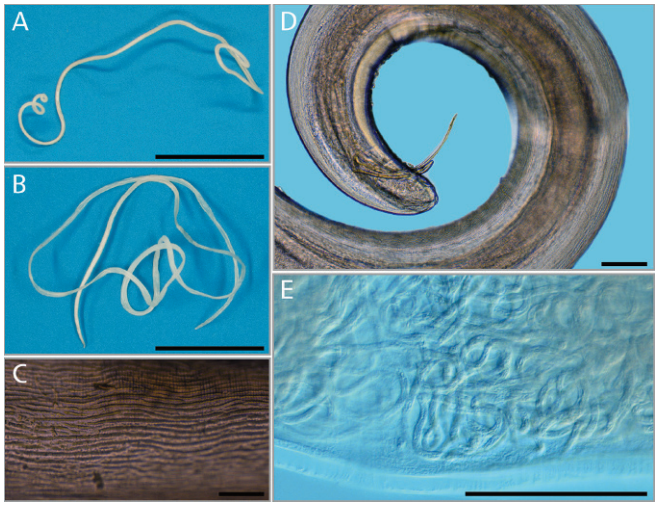

Fig. 1. *D. repens* nematodes isolated from patients in Ukraine. A – male (case 179♂/2012); B – female (case 219♀/2012); C – surface of the cuticle (characteristic longitudinal ridges visible; case 174♂/2012); D – posterior end of male specimen (spicule visible; case 174/2012); E – fragment of a uterus filled with microfilariae (Nomarski differential interference contrast, case 50♀/2012). Scale bars: A, B = 10 mm, C–E = 100 µm

Statistical methods. A hierarchical cluster analysis using the average linkage method (UPGMA) was conducted in relation to the frequency of registering dirofilariasis in all the oblasts of Ukraine.

Results

Within a period of 16 years, between January 1st 1997 and December 31st 2012, 1465 confirmed human cases of *D. repens* dirofilariasis were registered. The majority of the cases were noted in Kyiv (149; 10.2%), and the Donetsk (135; 9.2%), Zaporizhzhya (132; 9.0%), Dnipropetrovsk (120; 8.2%), Kherson (109; 7.4%) and Chernihiv (100; 6.8%) oblasts. Over half (50.8%) of all the cases registered within this period were noted in these 6 regions.

As a result of hierarchical cluster analysis of the incidence rate in all of the Ukrainian oblasts, the country has been divided into 5 regions with substantially different ranges of

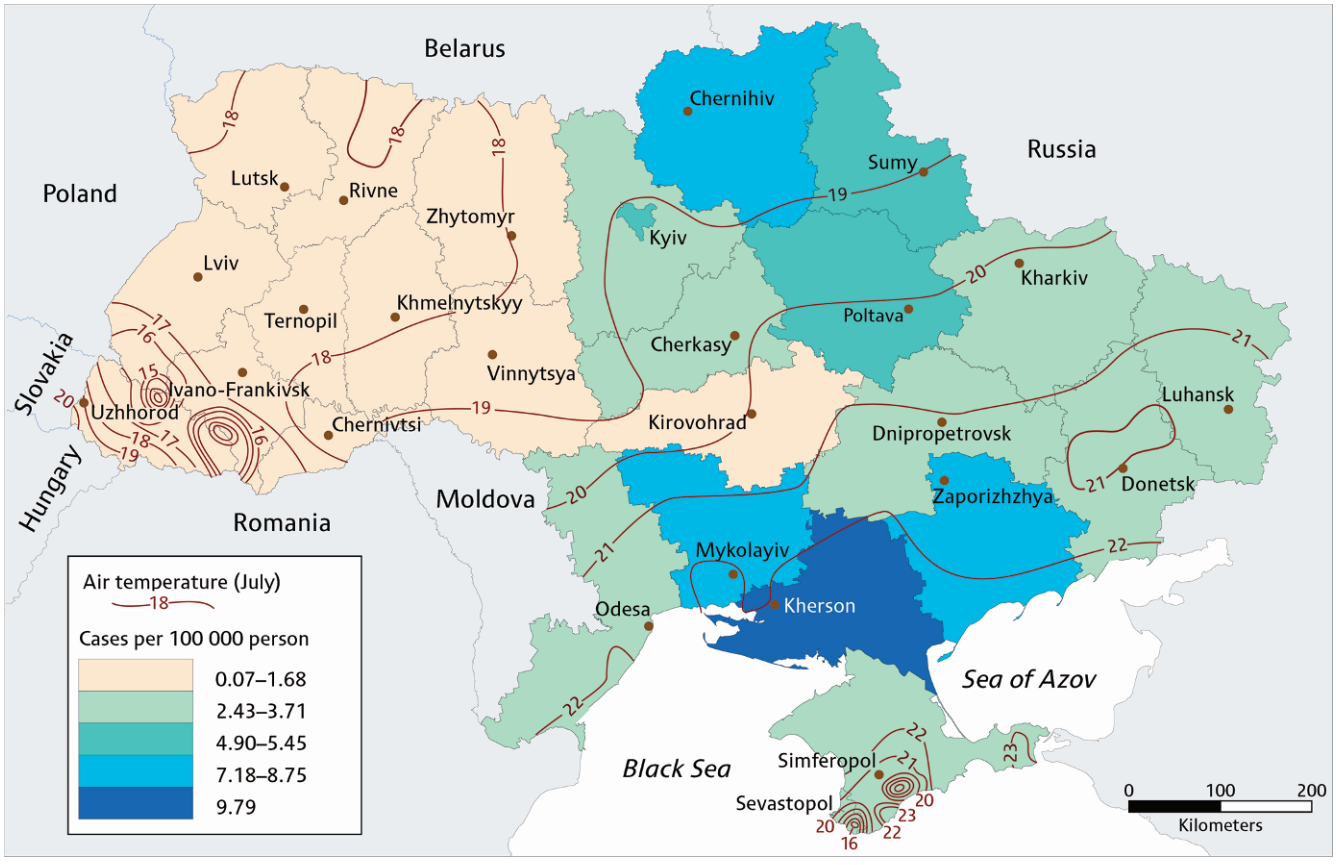

Fig. 2. Occurrence of *D. repens* in humans in Ukraine in the period 1997–2012 (climatic data from Babičenko *et al*. 2007)

incidence rates. The highest incidence rate, 9.79 per 100 000 people, was noted in the Kherson oblast in the south of the country, and the lowest, between 0.07 and 1.68, in western Ukraine. *D. repens* infection was noted in all the oblasts of Ukraine plus Crimea, Kyiv, and Sevastopol (Fig. 2)

The incidence of new cases of dirofilariasis changed over time. The period 1997–2001 was characterized by a low number and increased rate of registered cases; a total of 64 cases were registered, primarily in the south-eastern part of the country. From 2004 until 2008 the number of newly registered cases was somewhat stable over time, but exhibited high variation and clearly noticeable increase in the following period.

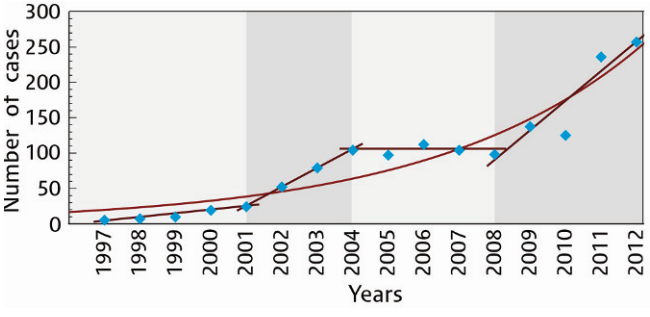

Fig. 3. Number of human dirofilariasis cases detected in 1997–2012 (red lines illustrate trends)

In 2011 a sharp increase in the number of infections in comparison to the previous year occurred, with the Ternopil oblast remaining as the only region without registered dirofilariasis cases. In 2012 the number of *D. repens* infections continued to rise, and cases were registered in all oblasts. Taking into consideration the whole studied period of 1997–2012, the increase in case numbers was exponential (Figs 3, 4).

Analysing clinical data (755 cases), it was determined that in 488 cases (64.6%) the parasitic lesions were located in the head, including 297 cases of lesions around the eyes. Dirofilariasis of the limbs and torso constituted a lower percentage of cases – 9.0% and 11.8% respectively. *D. repens* were also detected in the sexual organs of men (31 cases), and in female mammary glands (19 cases). In 16 cases (2.1%) the location of the parasite was not specified in the data (Fig. 5).

Dirofilariasis was most frequent among patients aged 21–40 (325, 43.0%); the youngest patient was 11 months old, and the oldest was 90 years old.

Women constituted 67.4% (509), and men 32.1% (242) of the infected. In 4 cases (0.5%) no data regarding the sex of the patient were provided in questionnaires.

Dirofilariasis was initially diagnosed by means of clinical symptoms in 565 patients out of 755 analysed (75%). The majority of these patients (752) had one parasitic lesion, and three patients had two lesions. Each of the examined lesions contained

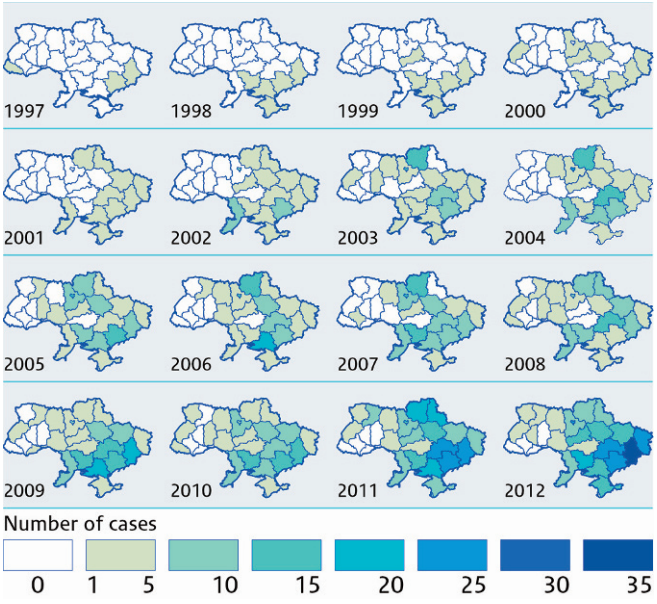

Fig. 4. The spread of *D. repens* infections in Ukraine from 1997–2012

one parasite; a total of 725 *D. repens* females and 33 males were found. The length of the females varied from 6–17.5 cm, the length of the males from 3–6.3 cm. No cases of both female and male nematodes co-occurring in the same lesion were noted.

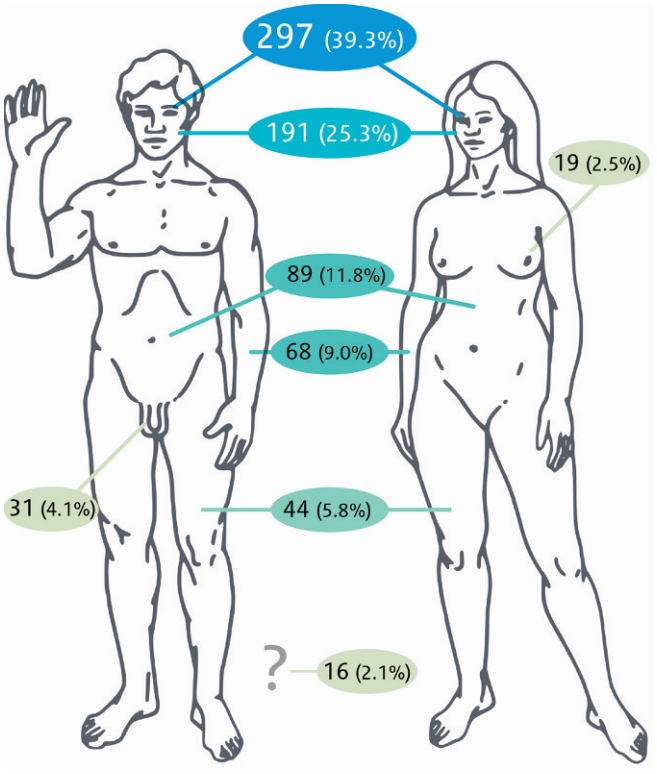

Fig. 5. Location of parasitic lesions on 755 patients infected with *D. repens* (human silhouettes credit: NASA; GRIN DataBase Number: GPN-2000-001623)

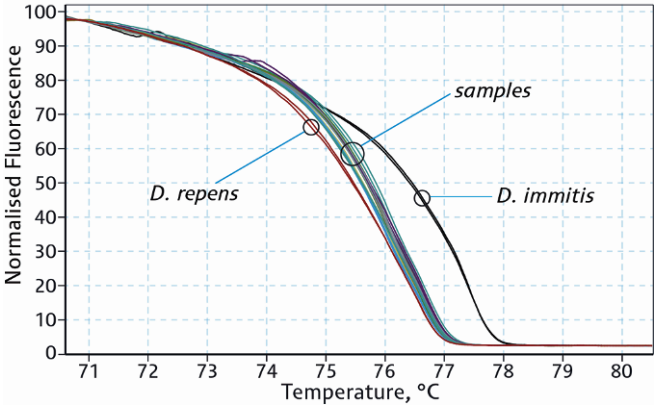

Fig. 6. Graph of normalized fluorescence versus temperature. HRM curves of PCR products obtained from DNA isolated from nematodes: '*D. repens*' – positive control of *D. repens* DNA amplification; '*D. immitis*' – positive control of *D. immitis* DNA amplification; 'samples' – samples obtained from the worms isolated from Ukrainian patients

In two cases, females measuring 10.7 and 11.2 cm had uteri filled with living microfilariae. These nematodes were isolated in 2012 from the eyes of two women, aged 28 and 65, living in the Donetsk oblast (Fig. 1E).

HRM curves of the PCR products amplified from the DNA isolated from the worms had a shape similar to the HRM curve of the *D. repens* positive control (Fig. 6). Clean sequencing reads were obtained for 225 bases of all eight analyzed products, and all eight products had identical DNA sequences with the bases 345–567 of *D. repens* cytochrome oxidase subunit I gene sequence (JF461458.1) and homologous regions of the following *D. repens* COI gene sequences: AM749234.1, AM749233.1, AM749232.1, AM749231.1, AM749230.1, DQ358814.1. The positive control DNA amplification product had 99% identical bases with the COI sequences mentioned above, within the 225-bases-long region used for analysis.

Discussion

Since the first case of human dirofilariasis was noted in 1927, only 16 cases were described in the literature through 1974 (Skrâbin *et al*. 1930, Gerbil′skij 1951, Gerbil′skij and Dorogan′ 1961, Šupik *et al*. 1967, Rozenbaum 1970, Gogina 1970, Mel′ničenko and Prosvetova 1971, Prosvetova and Mel′ničenko 1971, Èngel′štejn *et al*. 1973, Sušarnik and Peremykin 1975, Mukvoz and Belozerskaâ 1975, Anonymous 1975, Bolgarenko 2001, Žaboedov and Šupik 1976). From 1975 onwards, cases of human dirofilariasis have been registered in official statistics. In the years 1975–1996, 52 cases were registered (our data), thus with an average incidence of approximately 2.5 cases annually. Within the last 16 years the number of infected people exceeded 1.4 thousand; an average of 91.5 new cases are detected every year. In this period, a notable increase in *D. repens* infections was observed in other European

countries as well. Analysing data collected from published studies, Genchi *et al*. (2011*a*) concluded that a three-fold increase in annual dirofilariasis cases took place in Italy during the period between 1999–2009, compared to the period between 1986–1998.

Dogs and some wild carnivores are reservoirs of *D. repens*. However, the dissemination of dirofilariasis is related to climatic and geographical conditions. The main factors in determining the population of vectors and the parasites they carry are temperature, rainfall and relative humidity. The time required for the microfilariae of *D. repens* to reach the invasive L_3 stage in a mosquito is governed by temperature, and it cannot exceed 1 month (the maximum lifespan of a mosquito). Studies conducted in Ukraine confirmed the possibility of the parasite reaching the invasive L_3 stage within 2 weeks in the natural conditions of Kyiv during the summer (Kuzmin *et al*. 2005). It is estimated that depending on the region, 1 to 6 generations of *D. repens* can develop annually in Ukraine (Genchi *et al*. 2009). For most of the country, the approximate length of the transmission period of *D. repens* is 3–4 months per year (Simón *et al*. 2012).

Most of the nematodes isolated from humans are immature. So far, only singular cases of mature *D. repens* females carrying microfilariae have been described (Suprâga *et al*. 2004, Poppert *et al*. 2009). Two new cases from Ukraine in which gravid females were discovered may confirm the assumption that the full development and fertilisation of *D. repens* in humans is possible (Simón *et al*. 2012).

Among the inhabitants of Ukraine, the parasites were most often detected in the head (64.6%), primarily around the eyes (39.3%). This is the location of *D. repens* most frequently described in the literature (Simón *et al*. 2012), probably because parasitic lesions located elsewhere are more difficult to detect by the patient and/or are trivialized. The high percentage (75%) of correctly diagnosed infections is a sign of good clinical diagnostics available to primary care physicians.

An uneven distribution of *D. repens* infection throughout the country was discovered, based on our epidemiological analysis. One of the oblasts with the highest prevalence – the Kherson oblast (9.79% per 100 000) – is located in the southern part of Ukraine, next to the Black Sea, where from May to October the climatic conditions allow for 4–6 generations of *D. repens* to develop (Simón *et al*. 2012). The oblast with the second-highest prevalence – Chernihiv, 8.75 per 100 000 – lies in the northeast, where the average temperature is lower. The majority of this region, however, is damp, with excellent conditions for mosquitoes to thrive.

In EU countries, registering cases of *Dirofilaria* infection is not mandatory, therefore the evaluation of the epidemiological situation is based on data published in the literature. In Poland, Ukraine's western neighbour, autochthonous human infections have been noted since 2010 (Cielecka *et al*. 2012). The three cases detected so far occurred in the environs of Warsaw, where infections of dogs by *D. repens* have been detected since 2007. In the regions of Ukraine bordering Poland cases of infection began occurring relatively late: since 2008 in the Lviv oblast, and 2010 in the Volyn oblast. In the Zakarpattya oblast, which shares borders with Poland, Slovakia, Hungary and Romania, and is separated from the rest of Ukraine by a mountain range, infections are irregular: the first human case was noted in 1997, with two more following in 2008 and 2010. The first autochthonous Slovakian human case was described in 2008 in the western part of the country (Babal *et al*. 2008). In Hungary autochthonous human infections have been suspected since 1879 (Babes 1879, Babesiu 1880) and confirmed in 2000 (Szénási *et al*. 2008). Only a few human cases of *D. repens* infections have been discovered in Romania as of 2012 (Mănescu *et al*. 2009, Popescu *et al*. 2012), and in the bordering Ukrainian oblasts, apart from Zakarpattya, one case was registered in Ivano-Frankivsk and Chernivtsi each, in 2007 and 2009 respectively. In Moldavia, which borders Ukraine in the southwest, *D. repens* infections are most likely not a major epidemiological issue, since in the available literature we have found only two described human cases (Gudumac *et al*. 2011, Novak *et al*. 2010).

Among the northern regions of Ukraine the highest incidence rate for dirofilariasis is noted in the Chernihiv oblast, where cases of infection have been registered every year since 1997. In the adjoining Belarusian Gomel oblast, the first 10 cases of human infection were registered in 1997–2008, 8 of which were classified as autochthonous (Naralenkova 2004).

Through 2011, 701 cases of human dirofilariasis have been detected in Russia. The Rostov oblast, which borders eastern Ukraine, and Krasnodar Kray, located near the Black Sea and the Sea of Azov, both lie in the area with the highest incidence rate (Sergiev *et al*. 2011). In Ukraine, the regions around the Black Sea and the Sea of Azov have the highest dirofilariasis incidence rate, ranging from 6.12 to 8.94 per 100 000 inhabitants.

In his evaluation of the data published on human dirofilariasis, Pampiglione concluded that through 2000 the number of dirofilariasis cases in Ukraine did not exceed 100 (Pampiglione *et al*. 1995, 2000). Endemic regions of *D. repens* are located in many areas in Europe, however the total number of cases described so far has been surprisingly low – 600 (Masny *et al*. 2013) in comparison to Ukraine's 1533. Therefore, it appears that in order to achieve a proper outlook on the epidemiological situation, it would be necessary to introduce mandatory registration of *D. repens* dirofilariasis cases in EU countries.

The change in the epidemiological situation in Ukraine that occurred in the previous decade has been noticed by sanitary-epidemiological services and described in domestic literature (Pavlikovs′ka and Nikolaênko 2011). English language journals, however, still provide data from before 2000.

In conclusion, the results of our analysis point to a steady increase in *D. repens* dirofilariasis infections of humans in Ukraine. Despite educational efforts, the incidence rate increased and the disease spread to encompass almost the entire country. Nevertheless, the Ukrainian sanitary-epidemiological services managed to achieve some measure of

success, e.g. by creating a system of registering *D. repens* infections and establishing proper diagnostics for the disease.

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