A Descriptive Spatiotemporal Analysis of Rabies in Domestic Carnivores and Wildlife in 2012-2018 in Ukraine

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ABSTRACT

Ukraine leads Europe in the number of rabies cases reported in both wild and domestic animals. Endemic rabies in Ukraine poses a threat for spreading rabies into non-endemic neighboring countries including Poland, Slovak Republic, Hungary, and Romania. This study is the first to collate and analyze rabies cases at the national level in Ukraine. Spatial and temporal analysis was used to identify space-time clusters of rabies cases using collated national rabies surveillance from 2012 to 2018. In the study period, 10,717 rabies cases were confirmed with the majority in domestic carnivores (49.5%), the remaining primarily in foxes (34.0%). Rabies epidemic curves identified peak rabies incidence in October to December for foxes and October to March for domestic carnivores. The kernel density of rabies for all species estimates a permanently high density in southwest Ukraine and lower in northeast Ukraine. The highest rabies case density in foxes is concentrated in oblasts bordering European countries while domestic carnivores are concentrated near the border with the Russian Federation. The analysis identified 13 statistically significant clusters located in the same higher density areas from the kernel. This national-level analysis of rabies provides the first statistical evidence to support rabies prevention, surveillance and eradication strategies across Ukraine.

INTRODUCTION

Rabies is responsible for 59,000 human deaths globally annually, particularly in developing countries (Fahrion et al, 2017, WHO, 2018, Robardet et al., 2019). Historically, *Carnivora* and *Chiroptera* species are the primary hosts of Rabies Virus (RABV); however, rabies affects both domestic and wild animals (Fooks et al., 2017, Fisher et al., 2018, Brookes et al., 2019). The World Health Organization's Rabies Information System reports that Ukraine, the Russian Federation, and the Republic of Belarus account for the highest number of rabies cases in Europe (Rabies Bulletin Europe, 2021).

While rabies cases are subject to mandatory reporting in all European countries, including Ukraine, rabies control and surveillance efforts significantly vary among EU and non-EU European countries (Cliquet et al., 2010, Taylor and Nel, 2015, Picot et al., 2017). During the last century, the positive trend in control measures and active implementation of the oral rabies vaccination (ORV) programs for sylvatic rabies in European countries facilitated to eliminate fox mediated rabies (Franka and Wallace, 2018, Müller and Freuling, 2020, Calvelage et al., 2020).

In Ukraine, the first ORV program for wild carnivores was introduced in the early 2000s, however, due to limited funding, this program was targeted to areas with the highest rabies incidence (Polupan et al., 2019). ORV campaigns were usually carried out 1-2 times per year only across these targeted areas. For instance, during 2012-2014 from 4 to 9 oblasts (among 24) were covered by ORV vaccination in spring and autumn, during 2015-2017 from 3 to 6 oblast were cover by ORV only once per year, but during 2018 ORV deployed across the whole territory of Ukraine but again, only once (in autumn). As reported by Freuling et al., 2013 in order to eliminate rabies in wild animals, ORV campaigns should be carried out twice a year. The parenteral vaccination campaigns for domestic carnivores in Ukraine were launched in 1954, and remain ongoing, but are not viewed as very effective in controlling wild rabies (Botvinkin and Kosenko, 2004). Despite conducting ORV and parenteral vaccination campaigns, Ukraine remains endemic for rabies (Golik et al., 2015, Polupan et al., 2019, Flis, 2020).

Unlike other countries in Eastern and Central Europe, Ukraine has a high circulation of rabies in domestic carnivores (including stray dogs and cats) with as many cases of rabies in wild (Rabies Bulletin Europe, 2021, Riccardi et al., 2021). As noticed by Cliquet et al. 2014 in Europe during 2012, the proportion of rabid domestic animals (3,088 cases) was almost analogous with reported in wildlife, with domestic cases dominated in Ukraine (1,161 cases) and in the Russian Federation (893 cases), that suggest that rabies monitoring need concentrate around domestic species.

According to Kornienko et al. 2019 between 1998 and 2018 in Ukraine, there were 33,079 cases of rabies among animals, including 19,687 (59.5%) and 13,392 (40.5%) cases in domestic (10 species) and wild animals (18 species), respectively. Among these cases, domestic cats (25.3%), dogs (19.3%), foxes (36.7%) and cattle (13%) accounted for 94.5% of animal rabies cases. Among wild animals, the highest number of cases was recorded in foxes (12,136; 90.6%) with a significantly lower number of cases recorded from other wild species. In domestic animals, cats accounted for the highest proportion of cases (8,384 cases, 42.6%), with dogs (6,375 cases, 32.4%), cattle (4,311 cases, 21.9%), and sheep and goats (419 cases, 2.1%) accounting for the remaining cases (Kornienko et al., 2019).

The aim of this study was to investigate the spatial and temporal dynamics of rabies in animal populations (primarily fox and domestic carnivore populations) at the national level in Ukraine between 2012-2018. To date, no previous studies have explored spatial and temporal dynamics of rabies at the national level, likely due to the lack of a centralized national database of rabies cases which contains GIS data. Initial attempts to consolidate rabies case data for GIS analysis were made in 2016, however, this study was limited to 4 of 24 oblasts, or regions, of Ukraine (Polupan et al., 2019). Since this initial effort, our research group has made significant efforts to compile a national-level database of rabies cases, with the support and approval of Ukrainian authorities. This database contains data on rabies cases across Ukraine starting from 2012. This study represents the first spatial and temporal analysis of rabies incidence at the national level in Ukraine. Results of this work are particularly relevant to planning effective rabies control measures and implementing more targeted awareness campaigns in both veterinary and public health sectors.

MATERIALS AND METHODS

Study location

Ukraine is located in Eastern Europe with area 603,628 km^2. The total length of Ukraine's land borders is 5,684 km, of which 2,590 km fall on the borders with Central and Western Europe, including Poland, Slovakia, Hungary, Romania, Moldova, Republic of Belarus. In the east and northeast, Ukraine borders Russia Federation; in the south, Ukraine's maritime borders are in the Black Sea and the Sea of Azov.

Most of Ukraine's land borders do not have natural boundaries that would hinder animal migration. In the country itself, such a boundary is the Dnieper River, which divides the country from north to south into 2 parts, the left bank and the right bank. Along the river, there are 6 reservoirs with a maximum width of 7 km to 28 km (Fileccia et al., 2014).

The country is administratively divided into 24 oblasts **(Figure 1)**, each oblast is subdivided into administrative districts called rayons. The estimated human population about 42 million of people, human density 73.8 persons per km^2 (FAO, 2015).

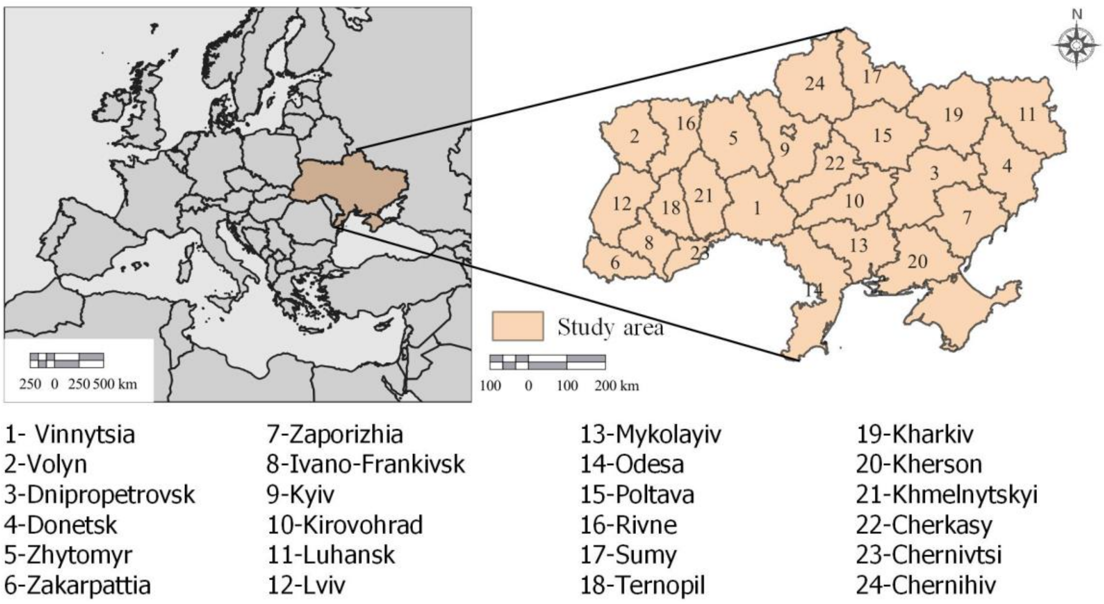

Fig. 1. Map of the study area with the boundaries and names of oblasts of Ukraine.

With regards the animal population, there are 116 species of mammal fauna across all Ukraine. Specific to this study, the more abundant predatory species include foxes, wolves, badgers, raccoon dogs, raccoons, martens, jackals. They counted about 468 thousand heads in 2018, from which accounted about 50 thousand heads of foxes, 11 thousand of raccoon dogs, 2 thousand of wolves, other there are small predatories according to State Statistics Service of Ukraine (SSSU, 2021).

Disease data

Ukraine conducted passive surveillance which covers the whole country. It is based on testing indicator animals each year; indicator animals are generally animals that show clinical signs (or abnormal behaviour suggestive of rabies), animals found dead, road kill and animals which have potentially exposed humans to rabies. Active monitoring is used to monitor the effectiveness of oral vaccination campaigns (ORV) in wild animals and provided by hunters. This active monitoring occurs one month after vaccination when foxes are shot at the rate of 2–4 foxes per 100 km^2 of vaccinated area and the carcasses (head) send to the laboratory and tested.

The State Regional Laboratories of Veterinary Medicine (SRLVM) had received samples from animals as part of passive surveillance. In general fresh carcasses of small animals, or heads and brains of large animals, are delivered by oblast (rayon) veterinary specialists to the SRLVM along with supporting documentation indicating animal species, name and address of the sender, animal owner person who was in contact with the animal, any known vaccination status of the animal, anamnesis, clinical and epidemiological information if available (Preventive measures against rabies of animals, 1994). Rabies diagnosis was performed on each sample using fluorescent antibody test (FAT) or bioassay test in white mice; samples with positive results in either test were considered positive (OIE, 2018). In case of testing of vaccine intake by foxes, the lower jaw and serum samples of foxes are sent to State Scientific Research Institute of Laboratory Diagnostics and Veterinary and Sanitary Expertise the delivery messenger with the appropriate accompanying document, where they indicate the species of animal, the address of the land where the shooting took place, the date vaccination, date of blood sampling, name and series of vaccine, which used for immunization (Polupan, 2018).

Rabies surveillance data for the study period (2012-2018) were collected from the official annual reports of the State Regional Laboratories of Veterinary Medicine of the State Service of Ukraine for Food Safety and Consumer Protection and from the State Scientific Research Institute of Laboratory Diagnostics and Veterinary and Sanitary Expertise. Data regarding positive samples included the serial number of cases, animal species (fox, dog, cat, raccoon dog, badger, cattle, etc.), location (oblast, district, settlement) and the date of the rabies diagnosis confirmation. The geocoordinates of each case we found additionally. The data of negative samples were collected by laboratories only as a general number per oblast annually without location and date, thus we could not find geocoordinates and conduct more deep spatial and temporal analysis.

Although every effort was made to integrate data into the dataset accurately, there are limitations to the data collection stemming from the lack of clearly marked as to the surveillance method (e.g., active and passive surveillance). Since the data sets are mixed, this limits study analysis. To address some of these limitations, the analysis were performed and presented separately for the different species.

Descriptive Statistical Analyses

Rabies data were classified into four groups: foxes, domestic carnivores (including stray cats and dogs), other wild animals (e.g., raccoon dogs, martens, wolfs, ferrets, rats, bats), and other domestic animals (e.g., cows, horses, goats, and pigs) **(Table 1)**. Foxes were allocated into a separate group due to their main role as a rabies reservoir (Polupan et al., 2019). Dogs and cats (both domestic and stray) were combined into one group as they are a major source of human rabies infection in Ukraine (Kornienko et al., 2019). The percentage of positive samples with exact binomial confidence interval in each group was calculated using epitools package in R and are shown in **Table 2, Supplemental Table 1, Supplemental Table 2.** To assess the difference in percentage of positives in each group across the years we used Pearson's Chi-squared test in R (Aragon, 2012). The statistically significant results were considered at $p<0.05$. Epidemic curves of rabies cases among wildlife and domestic animals have been created by monthly period for all oblasts **(Figure 2)**.

Spatial and Temporal Analysis

The spatial and temporal analysis was conducted for all species of animals and separately for foxes and domestic carnivores. Kernel density estimation (QGIS 3.4.6, Heatmap) of cases was used to describe spatial heterogeneity in rabies distribution on an annual basis as described previously (Chainey, 2013). The optimal search radius responsible for smoothing power was calculated according to Fotheringham et al. (2010).

The number of samples from animals were mapped as an indicator of monitoring efforts (active and passive) by oblasts and shown as choropleth maps (Figure 6, 7) for foxes and for domestic carnivores separately. In order to increase the comparability of surveillance efforts between regions in Ukraine, an index of surveillance efforts in Ukraine was also calculated as the number of tested animals over the human population (i.e. unit of 100.000 inhabitants) in each oblast (Taylor, 2021). Human population data were obtained from the State Statistics Service of Ukraine (SSSU, 2020).

Spatial-temporal clusters of rabies cases were identified using SaTScan software 9.6. Dataset limitations (lack of location and geocoordinates respectively for all negative samples, absent GIS information on fox and domestic carnivores population) restricted the analysis tool selection to the space-time permutation model limitations (Kulldorff et al., 2005; Kulldorff, 2018). This model permits analysis of cases without controls (negative samples) which allowed for data analysis despite the dataset limitations. Maximum spatial cluster size and maximum temporal cluster size were set to 50% of the population at risk and 50% of the study period respectively. The time aggregation parameter was defined up to 14 days.

All maps and Shapefiles of all georeferenced were generated in QGIS 3.4.6. using projection CRS: EPSG:102013 – Europe_Albers_Equal_Area_Conic. Vector layers of Ukraine`s borders were obtained using GADM (http://gadm.org/).

RESULTS

Descriptive Statistical Analysis

Between 2012 and 2018, 81,314 samples of 28 different species were tested on rabies in oblasts laboratories. Of these, 10,717 samples tested positive. Table 1 details rabies cases across the four species groups within the study period. Among all species of animals, cases in domestic carnivores were the highest - 5,309 cases (49.5%), with 3,051 cases (28.5%) reported from cats and 2,258 cases (21.1%) from dogs. In other domestic animals, 1,214 rabies cases (11.3%) were confirmed, out of which a large majority were reported from cattle (1,038 cases, 9.7%). Among all wild animals, the vast majority were reported from foxes - 3,653 cases (34.0%), with 541 cases (5.1%) confirmed in other wild animals (Table 1).

Table 1. Number of rabies cases in Ukraine for 2012–2018

Figure 2 shows epidemic curves for all species identified in sample metadata. For monthly variations, the last months of autumn and first months of winter displayed the highest proportion of reported cases for all species of animals, and spring and summer months had the lowest reported cases each year (Fig. 2).

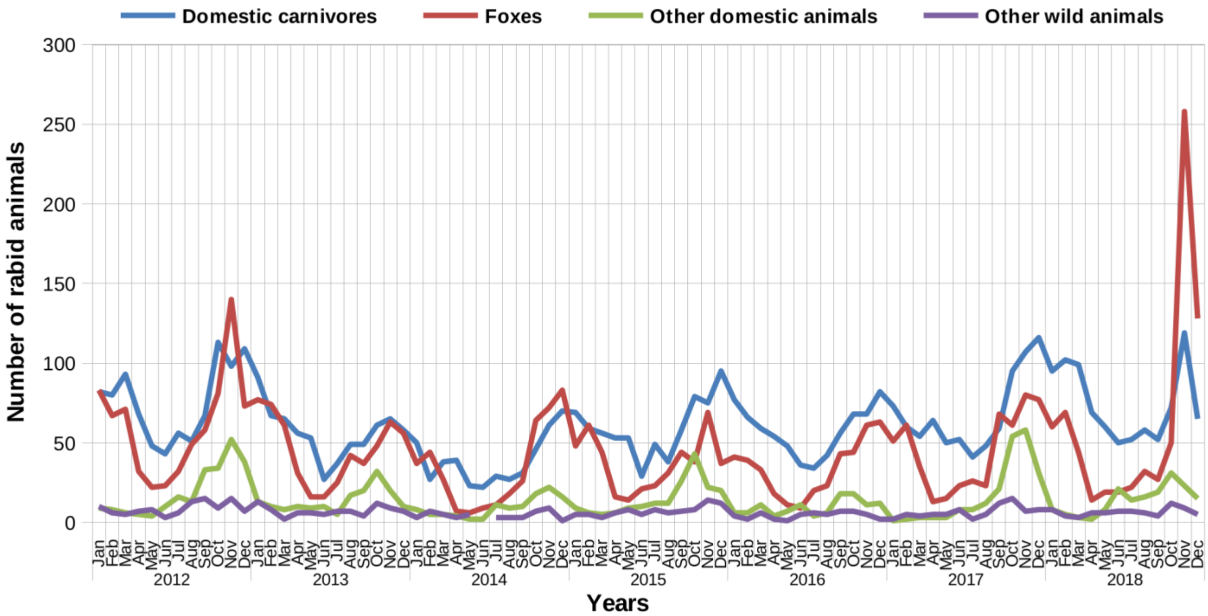

Fig. 2. Epidemic curves of rabies cases among wildlife and domestic animals in Ukraine, by month, 2012–2018.

The highest number of rabies cases in foxes (among all species) were observed from 2012 to 2014 and in 2018. In general, the fox`s epidemic curve shows a consistent rabies incidence increase from October through December for each year of the study period.

The epidemic curve in domestic carnivores shows a consistent incidence increase in October through March for each year with the highest annually picks (among all species) from 2015 to 2017. The full list of rabies prevalence, with 95% exact binomial confidence interval over the years of the study for foxes, domestic carnivores, and other domestic and wild animals is described in Table 2.

Table 2. Rabies prevalence by year (2012–2018) with 95% exact binomial confidence interval (BCI).

As shown in Table 2, the percentage of positive cases in foxes was not consistent across all years of observation (χ 2 =74.291, df =6, p-value=5.371e-14). From 2012 to 2013, a reduction in the percentage of cases was observed (2012 – 7.58%, 2013 – 6.13%), followed by an increase during the following 2 years (2014 – 9.03%, 2015 – 9.96%), a reduction in 2016 (6.76%), and an increase in the last 2 years of the study (2017 – 7.29%, 2018 – 8.39%).

The percentage of positive cases in domestic carnivores was also inconsistent across the years of observation (χ 2 = 192.7, df =6, p-value< 2.2e-16). The lowest percentage of positive rabies cases was observed in 2013 and the highest in 2015. From 2012 to 2014, a reduction in the percentage of positive rabies cases in domestic carnivores was observed (2012 – 21.02%, 2013 – 17.55%), followed by an increase during the following 2 years (2014 − 24.15%, 2015 − 29.50%), a decrease in 2016 (18.26%) and an increase in the last 2 years of the study (2017 – 21.02%, 2018 – 21.25%) (Table 2).

Spatial and Temporal Analysis

In general, the highest density of rabies cases among all animal species across 2012–2018 was concentrated in southwestern Ukraine (primarily Vinnytsia oblast) close to the border with Moldova (Fig. 3). High density of rabies cases were observed in central Ukraine (in the eastern part of the Cherkasy oblast) and in eastern Ukraine (Zaporizhzhia, Donetsk, Lugansk, Dnipropetrovsk, and Kharkiv oblasts), near the border with the Russian Federation.

Interestingly, two southern oblasts (Odesa and Kherson) showed decreasing rabies case density among all species in the study period while several other areas in eastern and western Ukraine showed an increasing density of cases during the study period (Luhansk, Sumy, Kharkiv, Kirovograd, Khmelnytskyi and Lviv oblasts). Across Ukraine, only two locations: northeast Ukraine (Poltava oblast) and southwest Ukraine (Zakarpattia oblast) showed consistently low rabies case density year-over-year for the study period.

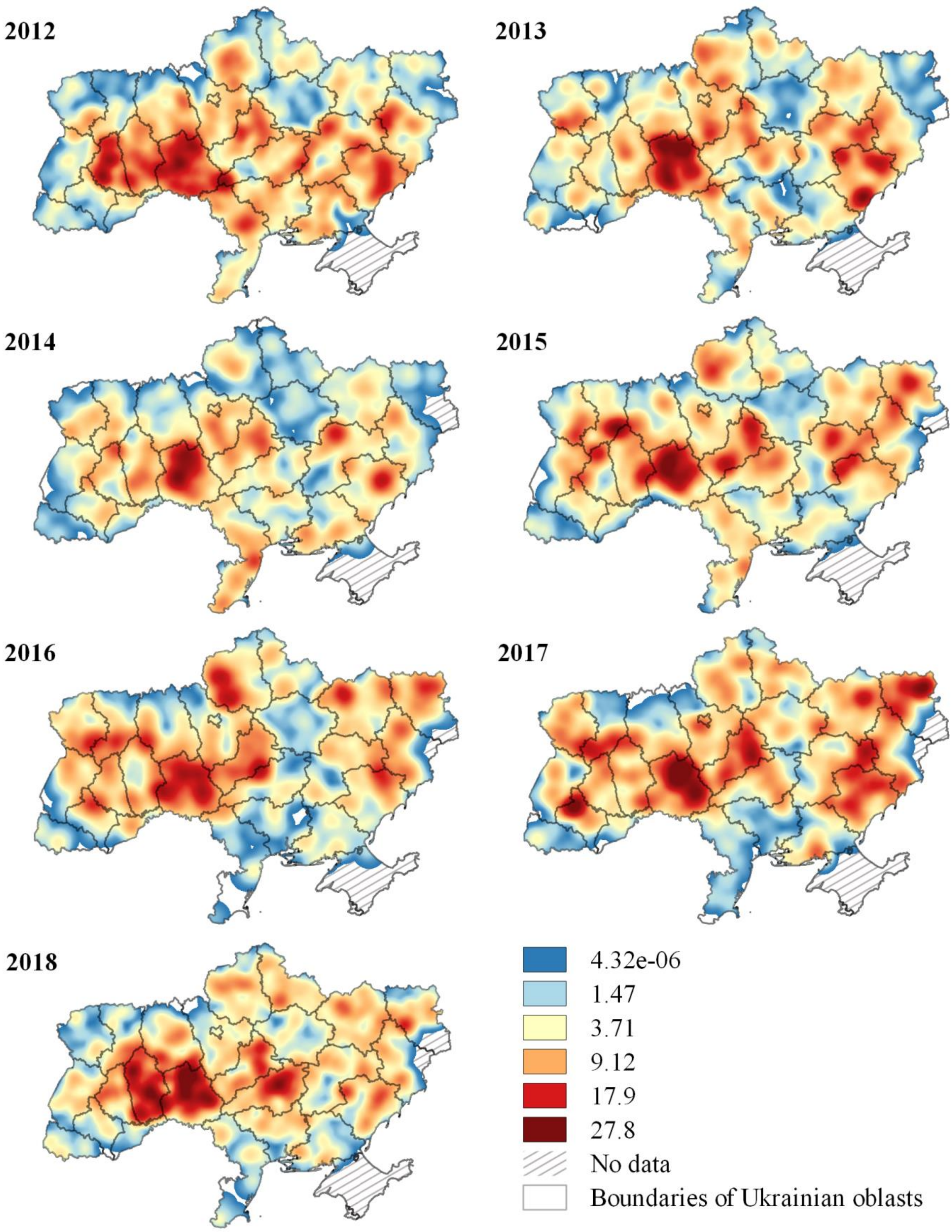

Fig. 3. Kernel density estimation of animal rabies cases for 2012–2018.

When we conducted Spatio-temporal analysis separately for fox and domestic carnivore data, we identified that the density of rabies cases in foxes (Fig. 4A) was mostly concentrated in three areas: southwestern Ukraine (especially in Vinnytsia Oblast, near the border with Moldova), western Ukraine (Khmelnytskyi, Ternopil and Ivano-Frankivsk oblasts), and close to the border with Poland (Lviv and Volyn oblasts). Lower density of rabies cases among foxes was observed in central Ukraine (Zhytomyr, Chernihiv, Cherkasy, Kirovograd, Dnipropetrovsk, and Zaporizhzhia oblasts).

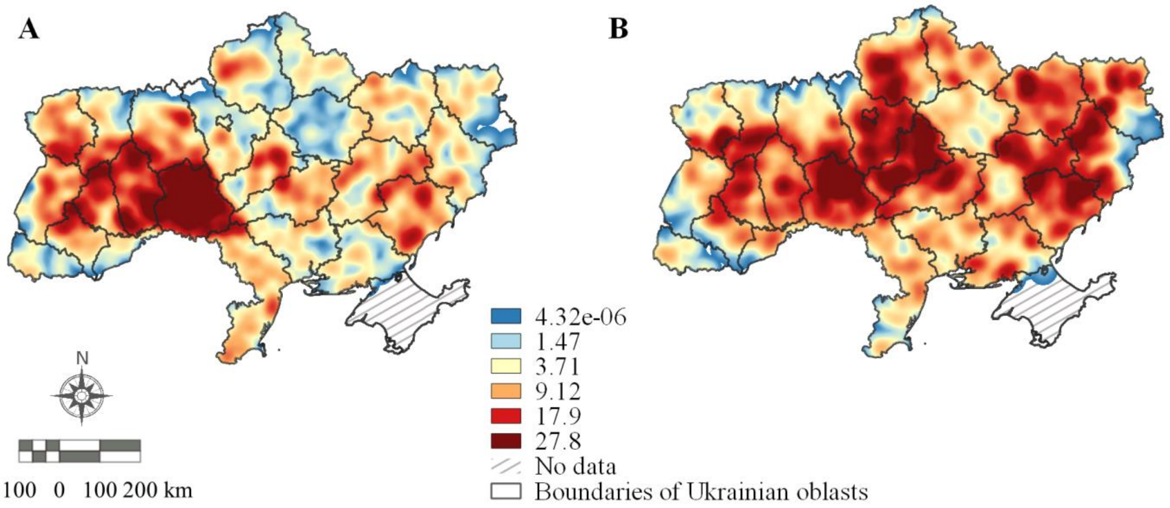

Fig. 4. Kernel density estimation of rabies cases in foxes (A) and in domestic carnivores (B) for 2012-2018.

Areas of the high density of rabies cases in domestic carnivores (Fig. 4B) was more uniformly distributed across Ukraine than that observed for the fox case data. Rabies cases peaked in central (Kirovograd, Kyiv oblasts), west (northern section of Vinnytsia oblast) and east Ukraine (Zaporizhzhia, Donetsk, Luhansk, Kharkiv oblasts) along the border with the Russian Federation and near the border with the Republic of Belarus (Chernihiv oblast). Year-over-year density for foxes rabies cases (Supplemental Fig. 1) and domestic carnivores (Supplemental Fig. 2) was also analyzed separately during the full study period (2012–2018) and confirmed the permanent localization rabies cases among foxes in the west of Ukraine and regarding pets mostly in the central part.

Space-time cluster analysis

Figure 5 shows the spatial-temporal clusters using the permutation space-time model. Ten statistically significant clusters were detected in foxes (Table 3) with the earliest cluster on January 3, 2012, in western Ukraine (Ternopil oblast). In domestic carnivores, we detected three likely clusters (Table 4) with the earliest cluster on January 30, 2012, also in western Ukraine which intersected in space and time with the cluster in foxes.

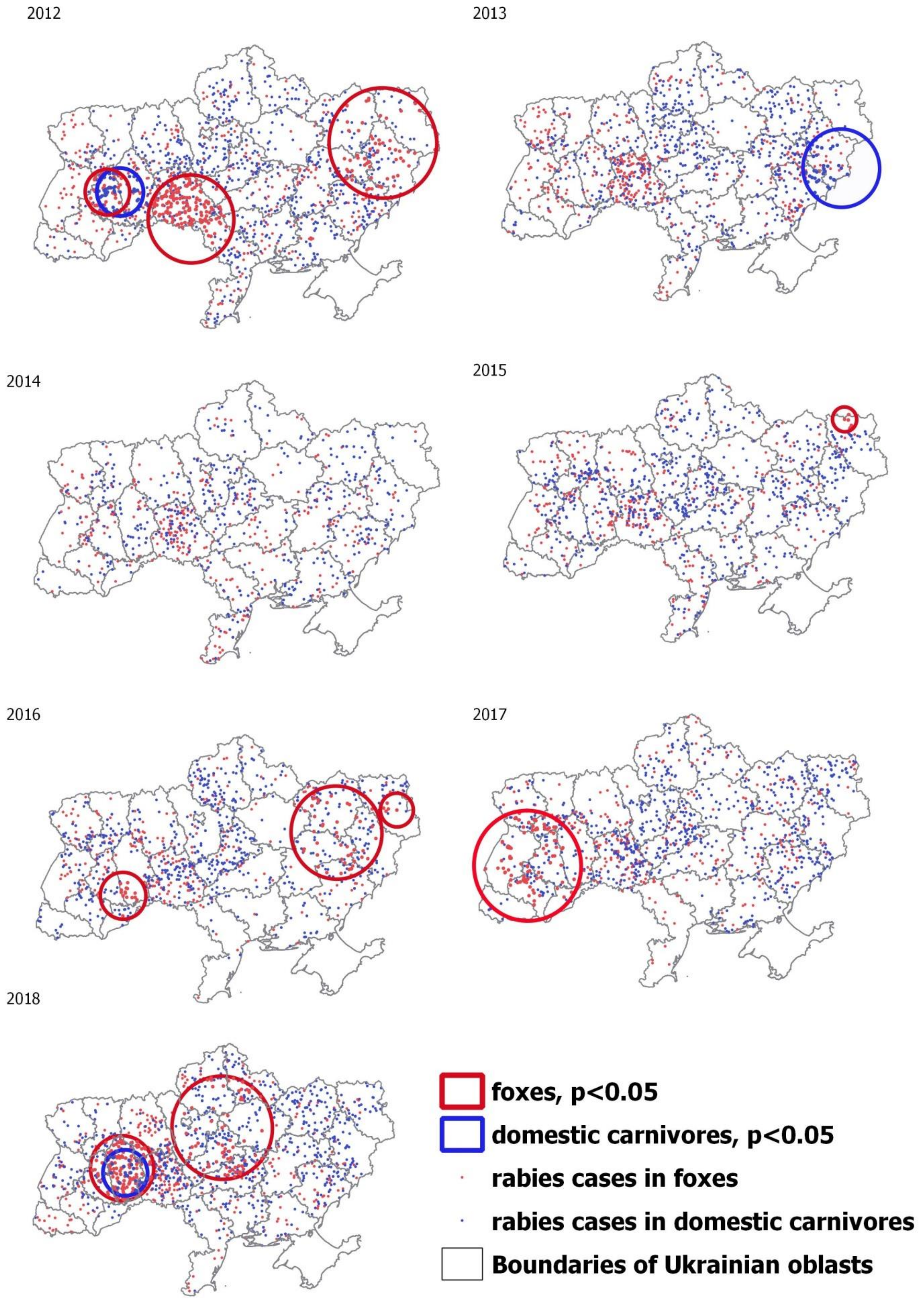

Fig. 5. Spatiotemporal clustering of rabies cases in foxes (red circles) and domestic carnivores (blue circles) from 2012 to 2018 were detected using space-time permutation model in SaTScan.

The majority (7/10) of the clusters in foxes and one cluster (1/3) in domestic carnivores coincides with high kernel density locations. These overlapping areas are indicated in the Table 3 and Table 4.

Table 3. Space-time clusters of fox rabies cases in Ukraine from 2012 to 2018. * The asterisk (*) shows those clusters that overlap with higher density from the kernels.

Table 4. Space-time clusters of rabies cases among domestic carnivores in Ukraine from 2012 to 2018. * The asterisk (*) shows those clusters that overlap with higher density from the kernels.

The number of samples from foxes (Fig. 6) and domestic carnivores (Fig. 7) show the monitoring efforts in Ukraine. With regards to foxes data, the majority of oblasts provided a moderate to a high number of samples. Only in few oblasts monitoring efforts/year were more intense (~1000–2000 samples per oblast) (Fig. 6).

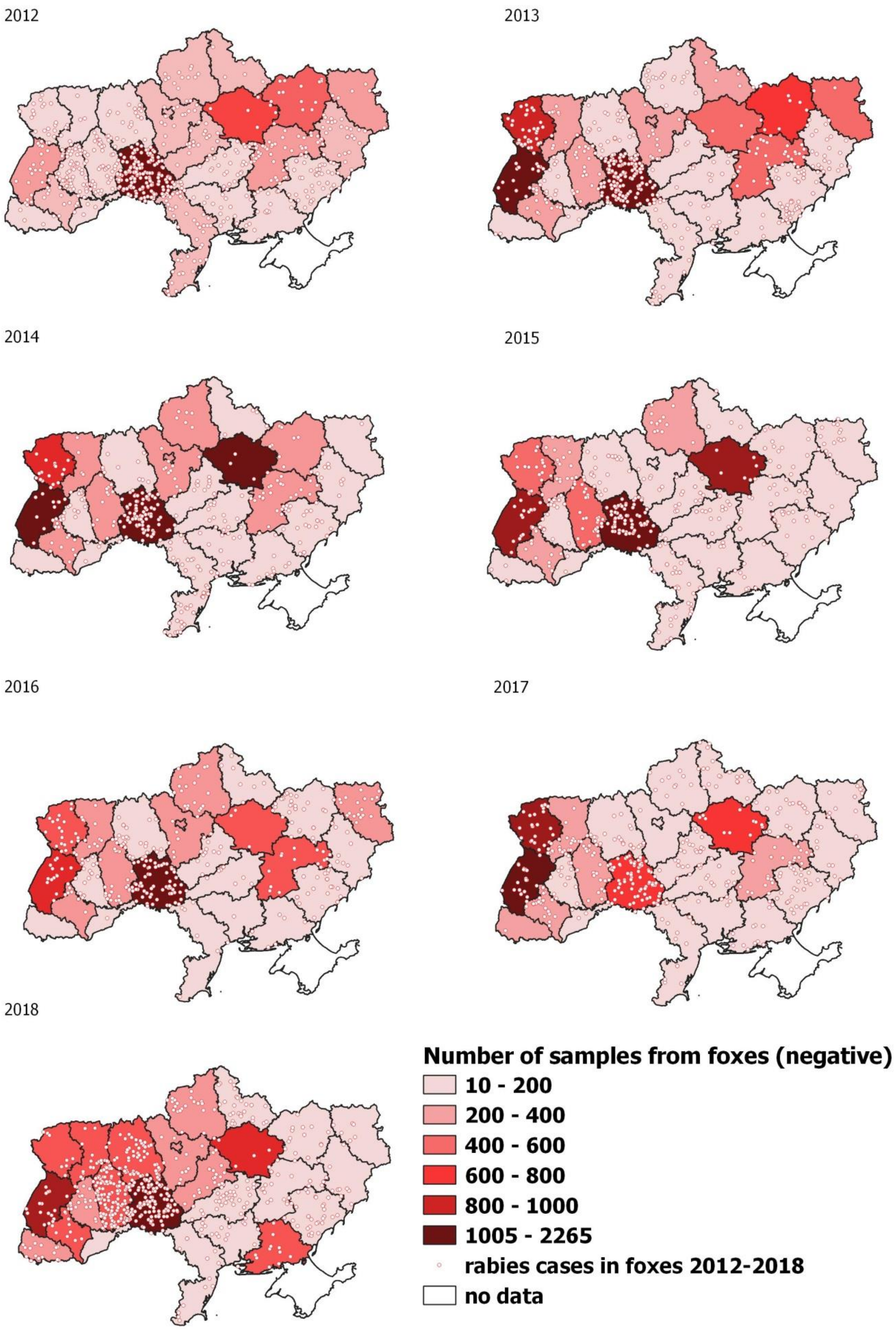

Fig. 6. Collection of fox samples by oblast between 2012–2018.

The number of samples collected from domestic carnivores were much lower than those collected from foxes across all Ukraine, with only central (Kyiv, Kirovograd) and western

(Vinnytsia) Ukraine collecting moderate numbers of samples (~300–350 samples per oblast) (Fig. 7).

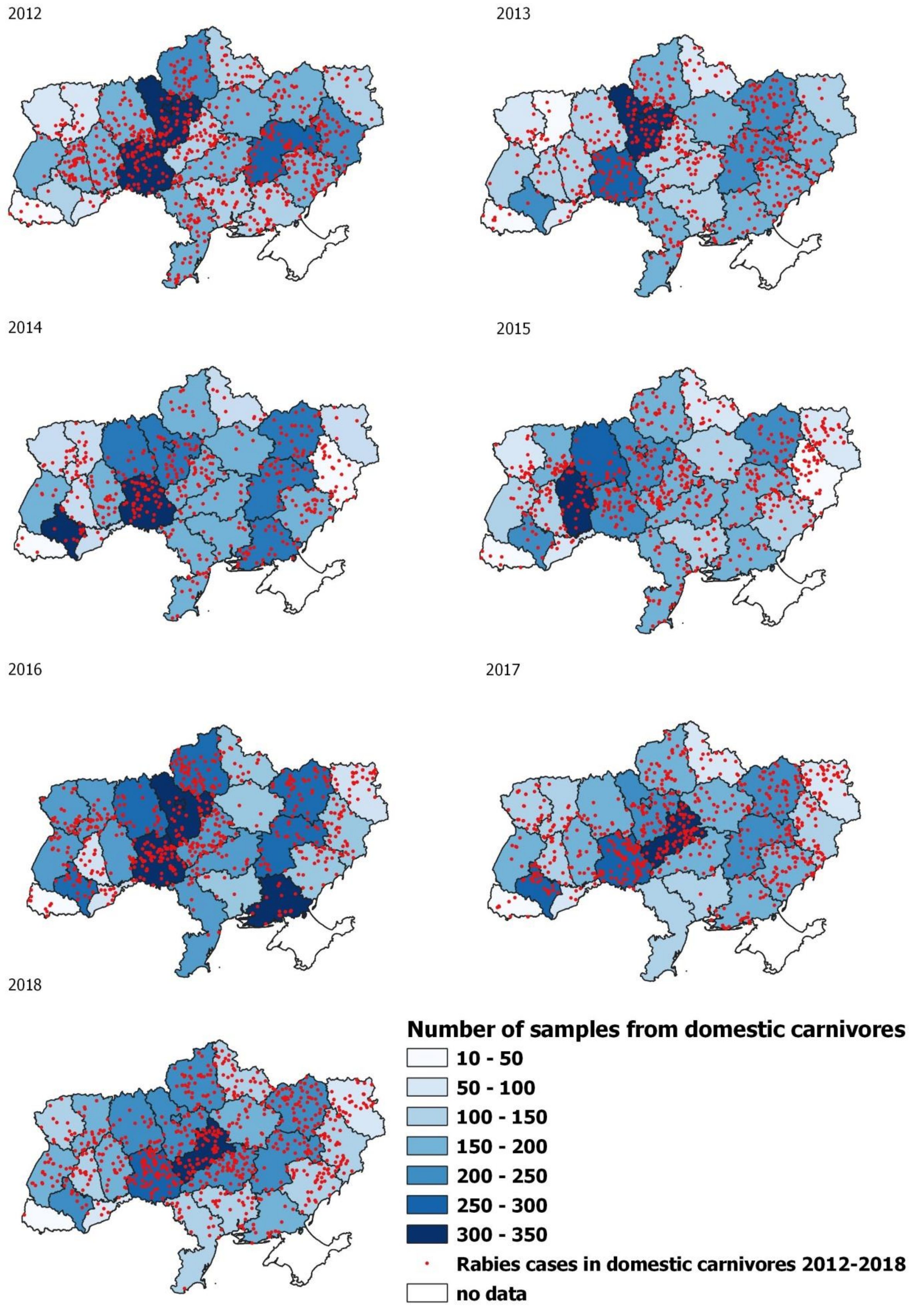

Fig. 7. Collection of domestic carnivore samples by oblast between 2012–2018.

In some oblasts with intense monitoring efforts (1000-1500 samples) the rabies incidence was also higher (up to 500 cases). This was not always the case and in some oblasts (i.e. Poltava), despite the intense monitoring efforts, the incidence of rabies was consistently low (up to 10 cases).

The level of surveillance of animal rabies in Ukraine for the entire study period (number of samples per 100,000 people) among foxes and domestic carnivores is described in Table 5. Among foxes, the index of surveillance efforts varied from 1.86 to 79.59 samples. The highest index was observed in the west and centre of the country (Vinnytsia, Volyn and Poltava oblasts), and the lowest level in the east and south of Ukraine (Donetsk, Odesa, and Zaporizhia oblasts). The level of sampling from domestic carnivores was low in all oblasts and the index ranged from 2.06 to 17.30, with the lowest rates observed in the east (Donetsk, Luhansk) and in one oblast in the west (Zakarpattia).

Table 5. The level of surveillance in Ukraine from 2012 to 2018.

DISCUSSION

This study describes, for the first time, temporal and spatial dynamics of rabies epidemic in domestic and wild carnivore populations across all of Ukraine. Our study used the newly developed national dataset for rabies, which incorporates data obtained between 2012–2018 from multiple sources; the dataset contains a remarkable amount of data. Between 2012 and 2018, more than 78,000 samples were analyzed and more than 10,000 cases from different species were confirmed.

The analysis performed in this study showed that, in addition to foxes about 50.0% of rabies cases (5,309 cases) were observed in domestic carnivores, a pattern which is different from other regions of Europe where wild carnivores are primarily affected (Flis, 2019, Taylor et al., 2021). Our results show that, within the domestic carnivores, cats (28.5%) are more affected than dogs (21.1%). This result is primarily explained by the high-density population of domestic carnivores, especially cats and the less obligatory rabies full vaccination in cats at the national level (mentioned by Kornienko et al., 2019). According to the Instruction of control rabies, cats need to be vaccinated in the area of outbreaks which limited to quarantine zones. While most pets in Ukraine are under at least some veterinary supervision, thus rabies (or suspected rabies) cases in domestic carnivores are often identified. Interestingly, the inverse was reported in Poland between 2012–2018 with only 5.4% of cases reported in cats (38 cases) in comparison to 8.1% of cases in dogs (57 cases) (Rabies Bulletin Europe, 2021). This opposite situation may be connected with the most responsible of owners and the absence of stray domestic carnivores in Poland.

During the study period, the highest number of rabies cases was reported in 2012 (1,979 cases), with the lowest number of cases (1,070) reported in 2014. Reduction in 2014 may be due to the Russian Federation occupation in eastern Ukraine (particularly in the Luhansk and Donetsk oblasts) and the annexation of the Autonomic Republic of Crimea. These acts affected rabies surveillance strategies in those areas, including reducing the number of samples and data collected across Ukraine, and also increased uncertainty within the reporting from those three regions.

The epidemic curves for foxes and domestic carnivores are remarkably similar (Fig. 2). Rabies epidemic peaks in autumn and winter (from October to February) in fox populations are driven mainly by fox ecology, with peak case numbers coinciding with fox resettlement in relation to breeding and habitat expansion, aggressive behaviour which facilitates fighting over territory (Domnich et al., 2011, Golik, 2016). Fluctuations in fox number also depend on the availability of food and the number of infected individuals in the population (Brusentsova, 2019). In addition to the ecological explanations, the disease dynamic in foxes may be partially influenced by hunting and culling practices in Ukraine. These are concentrated in autumn and therefore result in an increased number of samples (and positive cases). Although culling occurs throughout Ukraine, each oblast differently regulates the cull, resulting in large regional variations in fox population density across Ukraine. Despite that veterinary and sanitary requirements target fox population density of 0.5–1 head per 1000 ha territory at the end of culling, in most oblasts (in the western and central part of Ukraine) fox population density exceeds that rate up to 3–3.5 head per 1000 ha territory (Novitskyi et al., 2017). The measures for evaluation of the effectiveness of the ORV, which conducted by hunters mainly in autumn in different numbers, also influencing the reporting efforts depending on each oblast. In domestic carnivores, our data identified a seasonal distribution in the epidemic curve of rabies incidence, with higher incidence in the period between October and March of every year, similar to that identified in the fox data. The reason for this temporal pattern in domestic carnivores is not completely clear and deserves further attention. One possibility is the synantropization of foxes (proximity of foxes to human habitats), a well-known phenomenon in Ukraine (Drozhzhe, 2015, Levkivsky et al., 2016, Makovska, 2020). As reported by the Ministry of Health of Ukraine, 500–600 people per year report to medical facilities as a result of fox attacks (Antonova, 2021). This statistic suggests that foxes may attacks domestic animals as well as humans, which could lead to an increase in domestic carnivore rabies. A similar correlation between domestic carnivore and fox rabies was observed in Germany between 1995 and 2005, where a reduction of rabies cases in domestic carnivores correlated with a reduction of rabies cases in foxes (Freuling et al., 2013). Therefore, the high incidence of stray domestic carnivores provides an environment conducive to rabies spillover between foxes and domestic carnivores (Roebling et al., 2014; Velasco-Villa et al., 2017). It is, therefore, plausible to assume that in rural or suburban areas the interaction between foxes and domestic carnivores (both domestic and stray) may potentially influence to some extent the seasonal patterns described above. However additional ecological study on contact patterns and genetic analysis of animals populations is necessary to further study this hypothesis.

Prevalence data varied between species with fox and domestic carnivores presenting narrower intervals (min-max) across the years (6.1% – 8.4% in foxes and 17.5% – 29.5% in carnivores) compared to other species. It is also clear that rabies prevalence differs between oblasts and across years in each oblast (see Table 1, 2 in the supplementary documentation) and the factors influencing these differences may be very different and results, as mentioned above, influenced by the surveillance mechanisms in place.

Data from foxes were obtained primarily through active monitoring from hunters, and official veterinarian in case of reported bites of foxes to humans or other animals. In addition data from the ORV monitoring are only generated from oblasts where vaccination campaigns were implemented. Data from domestic carnivores was obtained primarily from suspected rabies cases based on clinical symptoms and in case of bites to humans or other animals.

As some data on the population density of domestic and stray carnivores, as well as foxes, is missing, this determined the choice of the permutation model for the cluster detection. Similarly, kernel density estimation of cases did not take into consideration the underlying population of domestic or wild animals. Extraction mapping is a valuable methodological option to address this limitation and should be considered for future works considering population data (Picado et al., 2010).

While the dataset was able to capture data from all oblasts across Ukraine, variability in surveillance methods and reporting is inherent in these systems, which principally depends on the frequency of ORV campaigns and quality of control measures checking the vaccine effectiveness. As a consequence, samples submitted from each oblast are inconsistent in terms of numbers (from 20 to 2,000 samples), thus reporting peaks disconnected from the disease dynamic. As can be seen from Supplemental Table 1, in Vinnytsia, Volyn, Ivano-Frankivsk, Lviv and Poltava oblasts, the laboratories received more samples from foxes, respectively they could identify the higher number of cases in foxes. In other oblasts (Kyiv, Kirovograd, Odesa, Mykolaiv), where active monitoring in foxes is weaker, fewer confirmed rabies cases were identified. These data are also influenced by the size of territory, number of foxes population and epizootic situation within each oblast.

The kernel density estimates of cases in foxes and domestic carnivores revealed a consistent presence of rabies across years in most of the oblasts of Ukraine, however different density intensities were seen. Density differences are likely explained by ecological and environmental features, presence of natural barriers (for instance, the Dnipro River which divides the territory of Ukraine into two parts, mountains in west Ukraine, etc.). On another side, the different impact of ORV campaigns and vaccination of domestic carnivores. Moreover, the ORV campaigns should be carried out twice a year but due to the limited finance in most of the oblasts, the campaigns are implemented irregularly and only in autumn

With regards to rabies in foxes, the higher density of cases was found in southwestern Ukraine (especially Vinnytsia oblast). It must acknowledged that reporting efforts may have influenced this pattern, as the number of samples analyzed were larger in the west of Ukraine (Supplemental Table 1) compared to other regions. In Vinnytsia and other southwestern regions, the higher density of cases may be influenced by the higher fox population (Novitskyi et al., 2017). The lower density of rabies cases in the western regions near the border with EU countries (especially Zakarpattia oblast) may be due partially explained by the mountainous environment which can influence fox presence and density, and may limit wild animal movement, resulting in slower progression of rabies. In addition, these oblasts (Lviv, Volyn, and Zakarpattia) benefited in recent years (2012–2016) from regular ORV campaigns with the support of the EU.

In these eastern oblasts of Ukraine, where the ORV campaigns were implemented regularly (especially in Poltava oblast), we identified lower circulation across the years. As noticed by Kornienko et al. (2019) in 2011–2014, spring and autumn oral vaccines campaigns were used on hunting grounds in Luhansk, Kharkiv, Donetsk, Sumy, Poltava, and Dnipropetrovsk regions. In these areas between 2011-2014, there was a significantly decreased intensity of rabies. In addition, the natural barriers in these areas (Dnipro River and Kremenchuk Reservoir) decreased infected animal dispersion from the endemic western parts and likely reduced the spread of rabies. As reported by Zecchin et al. (2019) the presence of natural or artificial barriers may have an influence on the ecology of reservoirs of rabies and, as a consequence, on the dynamic of the infection. The above-mentioned was determined by Picard-Meyer et al. (2012) during their study. Previously Ivanov et al., 2013 showed that the Dnieper River served as a natural barrier to rabies virus movement, due to the rabies isolates circulating on either side of the Dnieper River belonged to two separate clusters, suggesting that similar environmental barriers may influence the dynamics of rabies spread.

Density plots of cases in domestic carnivores were also consistently present in most of the oblasts but especially in the central and eastern regions and along the border with the Russian Federation. The highest density was observed in Khmelnytskyi, Vinnytsia, Cherkasy, Kirovohrad, Zaporizhzhia, Donetsk, and Luhansk oblasts. These regions are highly industrialized, characterized by larger human density, large numbers of domestic carnivores within towns surrounded by vast suburban areas (Dnipro, Kharkiv, Zaporizhzhia). Due to the high density of domestic carnivores in these oblasts, there was sub-ideal vaccination coverage. In general, approximately 2 million cats and 3.5 million dogs are immunized against rabies annually in Ukraine (Makovska, 2020). But this is not enough coverage due to the extremely high density of pets. Various sources estimate up to approximately 6 million dogs and 7.5 million cats (including stray animals) are kept in Ukraine (Kornienko et al., 2019). The low vaccination rate is attributed to multiple factors including poor owners' commitment, lenient laws on cat non-vaccination and the lack of penalties for non-vaccination of household pets (Makovska et al., 2018). The lowest density of rabies cases in domestic carnivores was detected in Poltava, Odesa, Mykolaiv, and Zakarpattia oblasts as results of better cover by campaigns of parenteral vaccination.

Categories were split to evaluate clusters within each and determine the presence of overlapping clusters. The space-time cluster analysis identified a total of thirteen clusters in wild and domestic carnivores during 2012–2018. The majority of the clusters in foxes and one cluster in domestic carnivores are located in high kernel density locations (Tables 3 and 4). In western oblasts (Khmelnytskyi, Ternopil) in 2012 and, more clearly, in 2018 (Vinnitsia, Khmelnytskyi, Ternopil), clusters of rabies in domestic carnivores intersected with clusters in foxes during the same time period (partial in January – February 2012, and November – December 2018). These findings may suggest regions with higher risks of rabies transmission between species. However, we acknowledge that, although intriguing, this result may be a function of differences in surveillance efforts across the two species; additional data from a consistent surveillance program is needed to verify. Ideally, molecular surveillance, including typing of rabies virus isolates in the context of contact pattern studies is needed to test this hypothesis.

The risk factor data in the dataset, including ecological (i.e. foxes density, interaction pattern with domestic populations), environmental and humans related factors (i.e. human density, artificial barriers, vaccination of domestic populations) were not thoroughly and statistically analyzed in the current study, as the focus was a descriptive study detailing the spatial and temporal dynamics of rabies. The intent of this project was to support the Ukrainian authorities in improving rabies control through the identification of high-risk regions at the national level. This study also described some of the limitations in the current dataset and rabies surveillance measures.

CONCLUSIONS

This study analyzed national level data, which revealed limitations of the current rabies control measures implemented in Ukraine. These analyses show that current methods are not slowing rabies case numbers in wild or domestic animals. The current rabies control current in Ukraine should be revised to use a data-driven strategy for monitoring and surveillance. The authors recommend increasing compliance with animal welfare requirements, enforcing pet vaccination, improving monitoring wild, domestic, and stray animal population density, and improving the effectiveness of vaccination campaigns (including ORV strategies twice a year) in wild animals. Additionally, we recommend improving current rabies surveillance and monitoring systems to integrate GIS technologies to enable improved monitoring of the effectiveness of the programs.

The results presented here, and taking into consideration the limitations in surveillance efforts across Ukraine, support efforts by the Ukraine State Food and Consumer Service to develop a risk-based national control program for rabies. Pillars of the revised control programs will improve surveillance strategies and prioritize regular ORV campaigns in regions at a higher risk for rabies cases and spread. The interaction between domestic carnivores and foxes could potentially influence the disease dynamic in some regions of Ukraine and should be further studied.

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Supplemental Figure 1. Kernel density estimation of rabies cases in foxes by years. Areas with the highest density of rabies cases are highlighted in red, and the areas with the lowest density are blue across all years.

Supplemental Figure 2. Kernel density estimation of rabies cases in domestic carnivores by years. Areas with the highest density of rabies cases are highlighted in red, and the areas with the lowest density are blue across all years.

Supplemental Table 1. Rabies prevalence in foxes for each oblast with 95% exact binomial confidence interval (BCI). The table represents the results of the percentage of positive samples in foxes from each of the oblasts by year (2012–2018).

Supplemental Table 2. Rabies prevalence in domestic carnivores for each oblast with 95% exact binomial confidence interval (BCI). The table represents the results of the percentage of positive samples in domestic carnivores from each of the oblasts by year (2012–2018).

Table 1. Number of rabies cases in Ukraine for 2012-2018

Species	2012	2013	2014	2015	2016	2017	2018	Total
1) Domestic carnivores	905 (45.7%)	693 (45.6%)	489 (45.7%)	723 (49.9%)	747 (56.1%)	845 (50.7%)	907 (53.2%)	5309 (49.5%)
• Cat	548	393	274	415	437	504	480	3051
• Dog	357	300	215	308	310	341	427	2258
2) Fox	739 (37.3%)	564 (37.1%)	414 (38.7%)	450 (31.1%)	415 (31.2%)	521 (31.3%)	548 (32.2%)	3651 (34.1%)
3) Other domestic animals	237 (12.0%)	174 (11.5%)	117 (10.9%)	186 (12.8%)	117 (8.8%)	215 (12.9%)	167 (9.8%)	1214 (11.3%)
• Cow	204	153	106	155	99	185	136	1038
• Goat	25	13	10	26	16	24	28	142
• Horse	7	7	0	1	2	3	2	22
• Pig	1	1	0	4	0	3	0	9
4) Other wild animals	98 (4.9%)	88 (5.8%)	50 (4.6%)	89 (6.1%)	53 (4.0%)	84 (5.0%)	83 (4.8%)	545 (5.1%)
• Badger	6	11	6	7	4	4	7	45
• Bat		3	1		3	1	1	9
• Beaver	3	1	1		1	3	2	11
• Elk			1	2		1		4
• Ferret	2	5	2	3	1	1	1	15
• Hamster	7	2		3	1	3		16
• Jackal				3	2	1	3	9
• Lynx					1	1		2
• Marten	31	30	12	14	6	9	14	116
• Domestic cavy			1	1				2
• Muskrat	1		1	2		1	1	6
• Otter				1		1	1	3
• Raccoon	3	2	1	2	4	5	5	20
• Raccoon dog	27	27	15	36	25	35	33	198

• Rat	4	3	1	3	2	6	3	22
• Roe deer	1		1	1	1	2	2	8
• Saiga antelope			3					3
• Squirrel							2	2
• Weasel	1		1	1			1	4
• Wild boar	1	1		1				3
• Wolf	11	3	3	9	2	8	7	43
Total	1979	1519	1070	1448	1332	1665	1704	10717

Table 2. Rabies prevalence by year (2012-2018) with 95% exact binomial confidence interval (BCI).

Species	Year	Positive	Samples	Prevalence, (%)	Lower 95% BCI	Upper 95% BCI
Foxes	2012	681	8988	7.58	7.04	8.14
	2013	561	9150	6.13	5.65	6.64
	2014	414	4586	9.03	8.21	9.89
	2015	450	4518	9.96	9.10	10.87
	2016	419	6194	6.76	6.15	7.42
	2017	520	7133	7.29	6.70	7.92
	2018	700	8347	8.39	7.80	9.00
Domestic carnivores	2012	862	4100	21.02	19.79	22.30
	2013	689	3926	17.55	16.37	18.78
	2014	489	2025	24.15	22.30	26.07
	2015	723	2451	29.50	27.70	31.35
	2016	747	4090	18.26	17.09	19.48
	2017	851	4049	21.02	19.77	22.31
	2018	887	4174	21.25	20.02	22.52
Other domestic animals	2012	214	378	56.61	51.45	61.67
	2013	172	316	54.43	48.76	60.02
	2014	117	137	85.40	78.36	90.85
	2016	115	181	63.54	56.07	70.55
	2017	207	295	70.17	64.59	75.33
	2018	165	245	67.35	61.09	73.18
Other wild animals	2012	98	600	16.33	13.46	19.54
	2013	84	687	12.23	9.87	14.91
	2014	50	259	19.31	14.68	24.65
	2015	89	304	29.28	24.22	34.74
	2016	58	477	12.16	9.36	15.43
	2017	75	475	15.79	12.63	19.39
	2018	120	439	27.33	23.22	31.76

Table 3. Space-time clusters of fox rabies cases in Ukraine from 2012 to 2018. The asterisk (*) shows those clusters that overlap with higher density from the kernels.

Custer No.	Start date	End date	Observed/ expected = ratio	Radius, km	p-value
One*	January 3, 2012	April 8, 2012	43/19.44 = 2.21	69.81	p = 0.019
Two	August 27, 2012	November 4, 2012	37/15.14 = 2.45	168.54	p = 0.011
Three*	November 5, 2012	December 30, 2012	92/52.70 = 1.75	134.35	p = 0.020
Four	December 3, 2015	December 16, 2015	6/0.28 = 21.14	40.02	p = 0.00050
Five*	November 5, 2016	November 18, 2016	6/0.43 = 13.89	54.48	p = 0.012
Six	November 19, 2016	December 30, 2016	36/12.81 = 2.81	150.27	p = 0.000049
Seven*	November 19, 2016	December 16, 2016	14/2.77 = 5.05	75.53	p = 0.0024
Eight*	January 30, 2017	February 26, 2017	36/14.42 = 2.50	174.43	p = 0.0026
Nine*	February 11, 2018	June 30, 2018	37/14.42 = 2.57	176.70	p = 0.0031
Ten*	November 4, 2018	December 15, 2018	204/105.79 = 1.93	111.42	p = 1e-17

Table 4. Space-time clusters of rabies cases among domestic carnivores in Ukraine from 2012 to 2018. The asterisk (*) shows those clusters that overlap with higher density from the kernels.

Custer No.	Start date	End date	Observed/ expected=ratio	Radius, km	p-value
One *	January 30, 2012	February 12, 2012	14/2.19 = 6.39	73.11	p = 0.00061
Two	August 14, 2013	August 27, 2013	9/1.22 = 7.37	131.05	p = 0.028
Three	November 18, 2018	December 15, 2018	17/3.49 = 4.87	78.60	p = 0.0014

Table 5. The level of surveillance in Ukraine from 2012 to 2018 (e.g. No of tested animals/100.000 humans).

№	Oblasts	The average number of the human population during 7 years	The average number of samples domestic carnivores and foxes	The average number of samples(negative) domestic carnivores and foxes /per 100.000 humans	The average number of samples(negative) from foxes	The average number samples from foxes /per 100.000 humans	The average number of samples from domestic carnivores	The average number samples from domestic carnivores /per 100.000 humans
1	Vinnytsia	1595985,00	1545,29	96,82	1270,29	79,59	275,00	17,23
2	Volyn	1037732,14	725,86	69,95	612,57	59,03	113,29	10,92
3	Dnipropetrovsk	3261931,57	544,43	16,69	330,71	10,14	213,71	6,55
4	Donetsk	4274368,71	196,14	4,59	79,57	1,86	116,57	2,73
5	Zhytomyr	1251246,86	332,14	26,54	137,00	10,95	195,14	15,60
6	Zakarpattia	1254407,29	218,29	17,40	192,43	15,34	25,86	2,06
7	Zaporizhia	1755218,71	316,29	18,02	153,43	8,74	162,86	9,28
8	Ivano-Frankivsk	1377686,71	573,57	41,63	357,14	25,92	216,43	15,71
9	Kyiv	1728721,43	457,71	26,48	206,29	11,93	251,43	14,54
10	Kirovohrad	969650,00	289,00	29,80	121,29	12,51	167,71	17,30
11	Luhansk	2209247,29	287,43	13,01	201,14	9,10	86,29	3,91
12	Lviv	2516805,29	1156,14	45,94	1001,00	39,77	155,14	6,16
13	Mykolaiv	1157929,43	230,00	19,86	109,00	9,41	121,00	10,45
14	Odesa	2379265,29	299,14	12,57	147,14	6,18	152,00	6,39
15	Poltava	1434079,71	959,14	66,88	810,43	56,51	148,71	10,37
16	Rivne	1158635,71	443,43	38,27	317,00	27,36	126,43	10,91
17	Sumy	1116179,43	251,14	22,50	150,43	13,48	100,71	9,02
18	Ternopil	1062600,14	282,71	26,61	157,86	14,86	124,86	11,75
19	Kharkiv	2703744,71	547,29	20,24	334,71	12,38	212,57	7,86
20	Kherson	1062019,86	365,57	34,42	188,86	17,78	176,71	16,64
21	Khmelnytskyi	1292369,29	521,00	40,31	338,86	26,22	182,14	14,09
22	Cherkasy	1241660,00	402,57	32,42	202,14	16,28	200,43	16,14
23	Chernivtsi	904816,57	177,43	19,61	99,43	10,99	78,00	8,62
24	Chernihiv	1040871,57	409,71	39,36	233,00	22,39	176,71	16,98