Current issues and gaps in the implementation of rabies prevention in Ukraine in recent decades

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Introduction

Rabies is a fatal viral disease that can be prevented by a vaccine (Fooks et al., 2017, 2018, World Health Organization, 2018). Rabies is transmitted to humans through contact with sick animals whose saliva contains the virus. The main carriers of rabies for humans are unvaccinated domestic carnivores that can get rabies (Rupprecht & Salahuddin, 2019; Klein et al., 2020). Many countries have managed to get rid of rabies, the agent of which is transmitted mainly through dog bites, or to significantly improve the endemic situation (Franka & Wallace, 2018; Meyerhoff et al., 2021). This success has been achieved primarily by the use of effective policies and programmes that focus on campaigns for vaccination of dogs, public awareness-raising, widespread use and availability of post-exposure prophylaxis (PEP) (Calveleto et al., 2020; Meyerhoff et al., 2021). Although mass vaccination of dogs is expected to be an important part of any effective strategy, the most important issue in preventing human rabies is the vaccination of people living in rabies-endemic countries before and after exposure (Baghi et al., 2019; Brookes et al., 2019; Gholami & Alamdary, 2020). In addition, human rabies occurs more than in 150 countries and territories (Fooks et al., 2017; Fisher et al., 2018). Dog rabies produces around 59,000 human deaths, more than 3.7 million people with disability adjustments and $ 8.6 billion of economic damages every year around the globe (Shwiff et al., 2013; Robardet et al., 2019; Yoder et al., 2019). As reported by Hamppson et al. (2015), the biggest component of the economic burden relates to premature death (55.0%), under which direct expenses for prevention measures (PEP, 20.0%) and medicines are included in the PEP (15.5%), with limited costs for vaccination of animals (1.5%) and extra expenses associated with livestock loss (6.0%). Besides this, all consequences also combine losses correlated with the risk of human fatality, which leads to total economic damages caused by canine rabies of $ 120 billion (Reges, 2017; Anderson et al., 2019). In Ukraine, the prescribed course of anti-rabies vaccinations costs about $ 215 per human, depending on the severity of the bite. In general economic costs of treating rabies are enormous: the cost of the vaccine consumed annually

Keywords: epidemiology of rabies; rabid animals; dog bites; rabies exposure; rabies vaccines; spatial distribution.

Rabies is a fatal viral disease that can be prevented by a vaccine (Fooks et al., 2017, 2018, World Health Organization, 2018). Rabies is transmitted to humans through contact with sick animals whose saliva contains the virus. The main carriers of rabies for humans are unvaccinated domestic carnivores that can get rabies (Rupprecht & Salahuddin, 2019; Klein et al., 2020). Many countries have managed to get rid of rabies, the agent of which is transmitted mainly through dog bites, or to significantly improve the endemic situation (Franka & Wallace, 2018; Meyerhoff et al., 2021). This success has been achieved primarily by the use of effective policies and programmes that focus on campaigns for vaccination of dogs, public awareness-raising, widespread use and availability of post-exposure prophylaxis (PEP) (Calveleto et al., 2020; Meyerhoff et al., 2021). Although mass vaccination of dogs is expected to be an important part of any effective strategy, the most important issue in preventing human rabies is the vaccination of people living in rabies-endemic countries before and after exposure (Baghi et al., 2019; Brookes et al., 2019; Gholami & Alamdary, 2020). In addition, human rabies occurs more than in 150 countries and territories (Fooks et al., 2017; Fisher et al., 2018). Dog rabies produces around 59,000 human deaths, more than 3.7 million people with disability adjustments and $ 8.6 billion of economic damages every year around the globe (Shwiff et al., 2013; Robardet et al., 2019; Yoder et al., 2019). As reported by Hamppson et al. (2015), the biggest component of the economic burden relates to premature death (55.0%), under which direct expenses for prevention measures (PEP, 20.0%) and medicines are included in the PEP (15.5%), with limited costs for vaccination of animals (1.5%) and extra expenses associated with livestock loss (6.0%). Besides this, all consequences also combine losses correlated with the risk of human fatality, which leads to total economic damages caused by canine rabies of $ 120 billion (Reges, 2017; Anderson et al., 2019). In Ukraine, the prescribed course of anti-rabies vaccinations costs about $ 215 per human, depending on the severity of the bite. In general economic costs of treating rabies are enormous: the cost of the vaccine consumed annually
for humans is about $1 million, excluding rabies immunoglobulin used for the combined course of vaccinations (Antonova et al., 2021). In addition, about $3 million during the last 10 years in Ukraine were lost due to livestock rabies, while there are also considerable losses from funding vaccination campaigns for wild and domestic carnivores which unfortunately were ineffective (Kornienko et al., 2019; Taylor et al., 2021).

During the last few decades, more than 100,000 people (almost 210 per 100,000 population) turned to medical institutions for treatment of animal bites annually. Every year, up to 23,000 people have been prescribed rabies vaccinations (Kornienko et al., 2019; Polupan et al., 2021).

Historically, before 1970, dogs were a common reservoir and sources of rabies in Ukraine, however, due to the increasing population of wildlife, the main reservoir and source of rabies in Ukraine became red foxes (Vulpes vulpes) (Botvinkin & Kosenko, 2004; Baker et al., 2020). As reported by Makovska et al. (2020) from 2000 to 2019 foxes accounted for 88.3% of wildlife rabies cases and 36.5% of general rabies cases. Besides these, domestic carnivores (including stray) were additional sources of rabies. Cats accounted for 25.5% and dogs for 19.3%. The last high peak of the incidence of rabies in animals was recorded in 2007 with the number of laboratory confirmed cases 2,932. Since 2007 the number of rabies cases among domesticated companion animals has increased and in 2016 the number of rabies cases in cats was higher than in foxes (Drozdzhe, 2015; Makovska et al., 2018; Kornienko et al., 2019).

The difficult epizootic situation with rabies in animals poses a permanent threat of complicating the epidemic situation in Ukraine. Based on the results of epizootiological laboratory monitoring, there has been a pronounced tendency with respect to human rabies infections: reduction of manifestations of rabies among foxes and an increase among cats and dogs. Thus, during 1997–2017, cats were the source of rabies for humans in 39.6% of cases, dogs – in 29.3% and foxes – only in 20.7%, others – 8.7%, bats – 1.7%. The most meaningful factors of the increasing role of domestic carnivores as a source of rabies for humans are low levels of specific rabies prevention in domestic animals and the increased density of the population of stray dogs and cats (Polupan et al., 2021). Among the most important preventive measures which need to be covered by monitoring are problems of irresponsible pet ownership, stray dogs and cats, the possibility of full immune prophylaxis of rabies (both in humans and animals). Lack of reliable information is one of the main obstacles to effective prevention and control of human rabies, not only at the global but also at the national level (Grigoryan & Metlin, 2016; Acharya et al., 2020).

In this respect, the aim of our study is to indicate the problems, gaps and failures in rabies prevention, the main reasons for human rabies cases and highlighting the risk of animal attacks in view of their species and geographical distribution on all territory of Ukraine during 1996–2020.

Materials and methods

In Ukraine, the function of the implementation of epidemiological surveillance of rabies is entrusted to 24 oblast laboratory centres of the Ministry of Health of Ukraine. The post-exposure prophylaxis prescription takes place at 726 units and 22 centres of rabies assistance (points of PEP) operating under traumatological or surgical units of health facilities of the Ministry of Health at rayon or oblast levels. First aid to those affected by animals is provided at any health facility with further referral to the PEP unit. Constant components of monitoring include recording the number of cases when patients refer to healthcare facilities with injuries resulting from animal attacks or from other dangerous contacts with animals. The number of cases is recorded by the species of animals that attacked people. Information about post-exposure prophylaxis is taken into account too. Monthly official statistical reports on cases of infectious diseases in humans and animals are prepared. There is constant monitoring of indicators of surveillance and exchange of information between the Ministry of Health of Ukraine facilities and veterinary medicine facilities regarding the epidemic and epizootic situation of rabies, the cases of animal attacks on people and the results of diagnosis of rabies in these and other animals, the need for and results of quarantine of attacking animals, PEP scope and other preventive measures. Monitoring involves the constant exchange of information between different institutions. The relationship between institutions that implement epidemiological surveillance, medical care, and veterinary medicine is particularly close.

Consolidated data from various sources were used to analyze problems and gaps in knowledge about rabies. Sources of primary data were the following archival materials about human rabies cases reported in Ukraine from 1996 to 2020; state statistical reporting from national reports of infectious diseases in humans, information from epidemiologists’ reports about investigations of human rabies cases and monitoring data for rabies surveillance from the Ministry of Health of Ukraine. Information about the human population was obtained from the State Statistics Service of Ukraine. The data regarding visits to health facilities by patients who suffered from animal attacks and the post-exposure prophylaxis scope were available from national monitoring tables (2007–2019) with indicators of epidemiological surveillance for rabies. Information on age, sex, localization of injuries, incubation period, laboratory confirmation was in some cases incomplete. Specific case descriptions were taken from the above analytical references, reports of cases of rabies, data of oblast level monitoring, scientific publications, personal experience. We also used available data about the animals, wild or domestic, if they had an owner, vaccination against rabies. The data included the number of attacks on people by rabid animals, as well as the number of cases of using post-exposure prophylaxis and implementation of other preventive measures. The veterinary medicine oblast departments of the State Service of Ukraine for Food Safety and Consumer carried out epizootiological surveillance of rabies in Ukraine. Data on the epizootic situation were obtained from official annual reports of the oblast laboratories of veterinary medicine and oblast departments of the state veterinary service for the period from 2007 to 2019. Only laboratory-confirmed cases of animal rabies were recorded.

All mentioned data were aligned and consolidated by time and geographic affiliation for visualization and analysis of the problem of rabies in Ukraine. For spatial analysis free QGIS 3.4.6 (the USA, 2019) software were used. The choropleth maps were created using projection CRS: EPSG:102013 Europe Albers Equal Area Conic. Vector layers of Ukraine’s borders and oblasts were obtained using free spatial data Diva-Gis (www.diva-gis.org/Data).

Results

In Ukraine, for the period 1996–2020, there were 63 cases of human deaths from rabies. Among these 63 fatal cases, there were 51 adults and 12 children (aged from 3 to 17). In terms of spatial distribution, human rabies cases were observed in the majority of administrative oblasts of Ukraine (Fig. 1).

Fig. 1. Dispersion of rabies cases in humans per oblast during 1996–2020 according to the official statistical data of the Ministry of Health of Ukraine

Frequency of reported cases varied between 1 to 7 cases per year. The higher peaks were registered in 2007. There were no cases reported
In 62 out of 63 cases, there were typical clinical manifestations, and rabies was diagnosed intra vitam, based on anamnesis of animal bites and clinical signs and in the majority of cases (50) confirmed by laboratory information regarding the PEP failures described in Table 3.

Fig. 3. The proportion of animal species involved in the 63 human rabies cases in Ukraine (1996–2020)

The differentiation of the main reasons of rabies cases in humans in Ukraine (1996–2020), %

Table 1

| Failure Reason                              | Number of Cases | %     |
|---------------------------------------------|-----------------|-------|
| Not seeking medical assistance after animal attacks | 603             | 9.5   |
| Errors in diagnosis of rabies               | 95              | 1.5   |
| Animal bites not verified                   | 3.2             |       |
| Errors in post-exposure prophylaxis         | 6.3             |       |
| Failure to prescribe rabies                 | 4.8             |       |
| Post-exposure prophylaxis                   | 15.9            |       |

As presented in Table 2, some requirements of the instructions until 2016 did not always correspond to the WHO position on rabies vaccines. Particularly, it was regulated to start the post-exposure prophylaxis only in the case of the animal showing clinical signs of rabies or disappearance of the animal (without rabies immune globulin (RIG) or with RIG depending on the location, depth and number of injuries). Due to observance of this practice the onset of vaccination was delayed, or vaccination was not conducted. At the same time, for 15 patients the chance of survival was lost, as the post-exposure prophylaxis was not carried out. The following causes of failures despite seeking medical assistance were reported: errors during animal quarantine (9.5%); errors in diagnosis of rabies in animals (3.2%); the refusal of PEP by the patient (6.3%); failure to prescribe post-exposure prophylaxis (4.8%) (Table 1, Table 2). The remaining 10 patients out of 25, who applied to health institutions, received post-exposure prophylaxis, but it turned out to be ineffective as was mentioned in Table 1.

As can be seen from Table 3, the most common reasons for failure were scheme breach, late start of course of vaccination and absence of rabies immune globulin. In total, the analysis of visits by patients who suffered from contact with animals and the provision of post-exposure prophylaxis was carried out according to monitoring data for 13 years. During this period (2007–2019), from 65,916 to 106,496 victims of animal attacks were registered annually. An average of 84,148 people (187.4 per 100,000 of the population) was affected by animals every year, among which 2,155 people (4.8 per 100,000 of the population) suffered from contact with animals and the provision of post-exposure prophylaxis was carried out according to monitoring data for 13 years. Among these patients, 2,155 people were victims of rabid animals. Post-exposure prophylaxis was prescribed annually, on average, for 21,434 patients (25.4% of those who came for assistance after animal attacks). Among them, 2,155 people were victims of rabid animals as confirmed by the laboratory. By the end of each year, 14,619 patients or 68.0% of those who had been prescribed the vaccination completed the course and were immunized, and 14.3% continued the course of the vaccination. The course of vaccination was stopped by doctors in 7.7% of the

Fig. 2. The annual number of rabies cases in humans in Ukraine according to the official statistical data of the Ministry of Health of Ukraine (1996–2020)

Fig. 4. Changes in the role of different animal species as sources of human rabies cases in ever 5-year period in Ukraine during 1996–2020
cases after the laboratory exclusion of rabies in the animal or after the quarantine period for animals was over. In 9.0% of cases, patients refused vaccinations or arbitrarily interrupted the course. 1.0% of those who received vaccination were lost to surveillance, possibly due to changing residence. In addition, by 2015, for post-exposure prophylaxis, predominantly, a Cocav vaccine, 6 doses into the shoulder muscle under the Essen regime (daily for 1 dose on 0, 3, 7, 14, 30 and 90th days) was used. Since 2015, other vaccines for 6 and 5-dose prophylactic vaccination (Indirah, Verorah, Rabipur) have been used more often (Table 2). Taking into consideration the number of prescriptions of the combined course, the annual need for rabies immune globulin was on average 69 L, and for vaccines more than 110,300 doses. The amount of vaccine used in practice was almost 3,000 doses less than the total need because the vaccine was not used in cases of refusal to vaccinate or after interruption of courses. Since 2011, there has been a sharp decline in the use of the vaccine in combination with rabies immune globulin (Fig. 5).

Table 2
The type of rabies vaccines used for humans in Ukraine from 1996 to 2020 according to the official statistical data of the Ministry of Health of Ukraine

| Name of vaccine | Description | Years of use | Manufacturer | Base | Active ingredient/dose activity, IU*/mL | Dose, injection site | Mode of administration | Delaying the start of the PEP** |
|----------------|-------------|--------------|--------------|------|----------------------------------------|----------------------|------------------------|------------------------------|
| Cav (Cav)      | Rabies culture inactivated dry vaccine for human immunization (Rabies-Vnukovo-32) | Till 2004 | Microgen, Russia; Breed Service, Ukraine | Primary culture of the kidney cells of Syrian hamsters | Rabies virus Vnukovo-32 strain ≥ 0.5 | 3.0–5.0 mL by intramuscular | 7–12 days; booster dose on the 10th, 20th day after the main course | Yes |
| Cocav (Cocav) | Rabies culture inactivated concentrated purified dry vaccine | From 1999 to 2014 | Microgen, Russia | Primary culture of the kidney cells of Syrian hamsters | Rabies virus Vnukovo-32 strain ≥ ≥ ≥ 2.5 | 1 mL intramuscular (deltoid area) | 0, 3, 7, 14, 30, 90 days | Yes |
| Verorab (Verorab) | Rabies vaccine for human use, prepared on ceI culture (inactivated) | Since 2004 | Sanofi Pasteur, France | Vero cell culture | Rabies virus, Wistar Rabies PM/W138–1503–3M strain (inactivated) ≥ ≥ ≥ 2.5 | 0.5 mL intramuscular (deltoid area) | WHO: Essen regimen: 0, 3, 7, 14, 28, 30 days. Zagreb regimen: 2, 11 (0, 2, 7, 21) | No |
| Indirab (Indirab) | Rabies, inactivated, whole virus Pitman Moore | Since 2010 | Bharat Biotech International limited, India | Vero cell culture | Rabies virus Pitman Moore strain ≥ ≥ ≥ 2.5 | 0.5 mL intramuscular (deltoid area) | WHO: 5-dose 0, 3, 7, 24, 28 days | Yes, till 2016 |
| Rabipur (Rabipur) | Rabies, inactivated, whole virus | Since 2016 | Kybion Bering Vaccines Private, India | Primary culture of fibroblasts of chicken embryos | Inactivated rabies virus Fluro LEP strain ≥ ≥ ≥ 2.5 | 1 mL intramuscular (deltoid area) | WHO: 5-dose 0, 3, 7, 24, 28 days (since 1997) Abbreviated: 2, 1, 10, 7, 21 days | No |

Notes: * IU – International Unit; ** – delayed start of the post-exposure prophylaxis means start of vaccinations with the appearance of signs of an animal’s disease or its disappearance in accordance with requirements of "The instructions of the Ministry of Health of Ukraine".

Table 3
List and possible causes of post-exposure prophylaxis failures in 10 rabies victims in Ukraine (1996–2020)

| Year | Age | Source/rabies test result | Localization of injuries | PEP day after attack | Drugs received* | Incubation period | Recommendations for vaccine guidelines: category of injuries; drug administration scheme | Possible causes of PEP failures |
|------|-----|--------------------------|-------------------------|---------------------|---------------|----------------|---------------------------------------------------------------|--------------------------------|
| 1997 | 49  | fox/negative             | face, fingers, forearms, body | 1 main treatment course | 30 days | Bad case; Rabies immune globulin (RIG) +Cav 5.0 × 21 days. Revaccination on the 10th, 20th, 35th day after main treatment course | Inadequate assessment of the contact nature, inadequate PEP course (without RIG). The effect of acute respiratory infection when receiving PEP is not excluded | Scheme breach: RIG was not administered (not available) |
| 2001 | 11  | home cat/positive         | shin                     | 2 Cav 3.0.x12=2      | 32 days | Light injuries; Cav 3.0 × 12 days. Revaccination on the 10th, 20th day after the main treatment course | This category of risk does not include RIG administration. No RIG administration due to underestimation of risk. Stitching the wound. | Scheme breach: RIG was not administered |
| 2001 | 27  | fox/no test data not available | shin                     | 1 RIG, Cav main treatment course | data not available | Light injuries; Cav 3.0 × 12 days. Revaccination on the 10th, 20th, 35th day after the main treatment course | This category of risk does not include RIG administration. No RIG administration due to underestimation of risk. Stitching the wound. | Scheme breach: RIG was not administered |
| 2003 | 44  | stray dog/no test         | shin                     | 1 Cav 3.0.x12=2      | 105 days | Light injuries Cav 3.0 × 12 days. Revaccination on the 10th, 20th day after the main treatment course | This category of risk does not include RIG administration. No RIG administration due to underestimation of risk. Stitching the wound. | Scheme breach: RIG was not administered |
| 2004 | 32  | fox/no test data not available | nose                    | 2 4 Cocav           | 34 days | Category III b*** RIG Cocav 0, 3, 7, 14, 30, 90 | Late PEP start. Scheme breach: RIG was not administered | Scheme breach: RIG was not administered |
| 2005 | 68  | home dog/no test data not available | fingers of the hand      | 4 Cocav             | 42 days | Category III a** RIG + CoCav 0, 3, 7, 14, 30, 90 | Late PEP start. Not enough RIG dose CoCav – the next day Alcohol drinking during PEP. | Scheme breach: RIG was not administered |
| 2007 | 41  | fox/positive              | fingers of the hand      | 5 RIG, 4 Cocav, 6 RIG, 103 days | 27 days | Category III RIG Cocav 0, 3, 7, 14, 30, 90 | Low immunizing power of the vaccine | Early PEP start. Scheme breach: RIG was not administered (not available). Different vaccine |
| 2013 | 34  | stray cat/positive        | hand fingers             | 8 2 Cocav 4 Indirab  | 150 days | Category III The mode of joint use of Cocav and Indirah is not regulated | Late start of PEP, Scheme breach: RIG was not administered (not available). Different vaccine | Scheme breach: RIG was not administered (not available) |
| 2014 | 63  | fox/test data not available | face                   | 1 4 Cocav           | 45 days | Category III RIG Cocav 0, 3, 7, 14, 30, 90 | Late PEP start. Scheme breach: RIG was not administered (not available). Different vaccine | Scheme breach: RIG was not administered (not available) |

Notes: * – Cav, Cocav, Indirah – cultural rabies vaccines; the assertion that “vaccines from different manufacturers for the prevention of the same infectious diseases can be interchangeable” does not apply to vaccines Cocav and Indirah; ** – category III a: any bite or slobbering of any localization made by a wild carnivorous animal or a bat; *** – Category III b: slobbering of damaged mucous membranes, any bite in the head or face, neck, fingers of the hands, perineum, genital wide or deep bites of any localization, multiple (2 or more) bites of a domestic animals.

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During 1996–2010 in Ukraine, there were about 37,338 cases of rabies among 18 species of wild and 10 species of domestic animals. Most of these cases were identified from domestic carnivores. However, most often rabies was detected among foxes – 37.3%, and among other wild animals – 2.9%. The share of rabid dogs was more than 19.3%, cats – 24.7%, farm animals – 15.8%. According to the results of epidemiological surveillance for rabies during 2007–2019, the largest proportion of animal attacks on people was from dogs (77.7%); the highest proportion of attacking animals actually diagnosed with rabies virus occurred in cats (32.9% of all rabid animals, Table 4).

Table 4

| Species of animals which attacks humans | Attacks by all animals | Attacks by rabid animals |
|----------------------------------------|------------------------|-------------------------|
| Total number of attacks                | 1,079,182               | 85,014                  |
| Dogs                                   | 838,635                 | 64,510                  |
| Cats                                    | 196,128                 | 15,087                  |
| Farm animals                           | 11,525                  | 886                     |
| Wild predators                         | 11,986                  | 923                     |
| Bats                                   | 1,407                   | 108                     |
| Rodents                                | 14,130                  | 1,110                   |
| Other                                  | 5,071                   | 300                     |
| Total number of attacks                | 1,079,182               | 85,014                  |

Discussion

This article includes for the first time long-term data on the causes of human deaths from rabies, the most important problems and gaps in knowledge on measures to prevent rabies and an assessment of the risk of...
animal attacks in view of their species and geographical distribution, taking into account the epizootic and epidemic situation of rabies in Ukraine in 1996–2020.

During 25 years, 63 people died of rabies, and unfortunately, this trend is intensifying over the years. The situation is not quite defined, as the possibility of incomplete accounting of cases due to underdiagnosis is not excluded. Due to limited laboratory capabilities for diagnosing rabies in humans, rabies could occur under other diagnoses. Quoting Chikanya et al. (2020) the incidence of human rabies in Europe is very low, both for cases contracted in Europe and imported from endemic countries. In contrast to the animal data, the global trend of reported human data over time suggests relative stability in the number of cases reported. Indigenous cases were mostly reported from Eastern Europe, corresponding to patients bitten by stray or aggressive domestic dogs or foxes.

The current definition in Ukraine of confirmed cases according to diagnostic criteria, when there are clinical manifestations and laboratory confirmation of rabies, includes 50 cases. The remaining 13 cases were probable, without laboratory research, but with an epidemiological link and met the clinical criteria for the diagnosis of rabies (acute encephalitis, and at least two of the following symptoms: change in sensitivity at the site of the bite, paresis or paralysis, muscle spasms, fear of water, delirium, convulsions, anxiety). The highest number of human rabies cases was observed in 2007 (n = 7). This could be explained by the peak of rabies cases in animals in 2007 (Fig. 6). Due to an increase of over 100% in the number of cases of animal rabies in 2006–2007 compared to 2005, the frequency of requests for medical assistance also increased – 4,732 humans were affected by rabid animals in 2007. After that, the number of such attacks and their victims slowly decreased by 2019 to 1,161. According to Yoder et al. (2019), the increase in rabies in dogs by 10.0% is associated with an increase in human morbidity by 6.3%. In our study, the number of rabies cases among attacking dogs increased by 2007 to 1,121 and then decreased by 2019 to 337 (by 33.0%). But during all this time, 40 people died from rabies and the source of the rabies virus for 24 of them was dogs. In the 12 years preceding 2007, 23 people died and only 2 after dog attacks. Regarding geographical distribution, the largest number of human rabies cases was confirmed in the east of Ukraine (Donetsk
neighbouring countries with endemic rabies, such as the Russian Federa-
estern oblasts can be linked with sick animals which can move from
the rabies transboundary disease, the permanent endemic situation of
dogs was associated with closeness to potential food sources such as
higher human population there is a higher number of stray domestic car-
human population with a high density of domestic carnivores, there are
by the lack of conducting vaccination measures, so the risk of transmission
of rabies from dogs remains the most anticipated.

Geographical features of animal attacks also have certain patterns.
For instance, in the territories of eastern Ukraine, where there is a large
human population with a high density of domestic carnivores, there are
more attacks by dogs and cats (Makovska, 2020a). Also in places of the
higher human population there is a higher number of stray domestic carn-
ivores. As noted by Warenbourg et al. (2021) the higher density of stray
dogs was associated with closeness to potential food sources such as
commercial food places and a university restaurant. Besides this, due to
the rabies transboundary disease, the permanent endemic situation of
eastern oblasts can be linked with sick animals which can move from
neighbouring countries with endemic rabies, such as the Russian Federa-
tion and the Belarus Republic (Mogilevsky, 1997; Makovska et al., 2018).
Quoting Baker et al. (2020), incursions from other regions account for less
than 1.0% of cases but allow for re-emergence of the disease. The afore-
mentioned also was submitted by Polupan et al. (2021) during their study,
the genetic sequences of the studied samples from Ukraine are characteris-
tic of isolates isolated in the Russian Federation, South-Eastern Europe,
Western Siberia, and Kazakhstan. Similar results were received by Picard-
Meyer et al. (2012) when they investigated samples from Ukraine. In the
central and western oblasts, where population density is lower and there
are more fields and forests, there was a large number of fox attacks, as was
evidenced previously by another author (Freuling, et al., 2013; Makovska,
2020b).

Besides this, we determined that for a long time, cats were the main
source of rabies for people in Ukraine. But, over the past 20 years, the role
of dog transmission of the rabies virus to humans has increased signifi-
cantly to 66.7% (Fig. 4). The beginning of the increase was observed in
2003. It can be explained by the reduction in efforts for vaccination of
domestic carnivores and reduction in attention paid to pets due to the start
of the ORV campaign in 2001 (Makovska et al., 2020). In addition, the
risks of human infection with the rabies pathogen transmitted by dogs are
increasing due to their owners’ failure to comply with the rules of animal
keeping, a lower level of vaccination of pets, low-level of public aware-
ness and absence of expert appraisal and increasing of the dog population.
As reported by Kornienko et al. (2019) according to various estimates,
there are between 6–8 million dogs kept in Ukraine and the number of
homeless animals of this species can be 10–20 thousand per city (oblast
centre). As asserted by Roebling (2014), responsible pet ownership, uni-
iversal rabies vaccination of pets and removal of stray remains integral
components to control rabies and other diseases.

In general, control of rabies in domestic carnivorous remains relevant.
Among the human victims of rabies, 24 had dangerous contact with dogs
and 22 with cats. Among these animals, 19 were homeless and 25 had
owners. No animal was vaccinated against rabies. Twelve patients out of
63 who died of rabies died following attacks by wild animals, including
1 from a bat and 11 from foxes. It is known that the incubation period for
victims of fox attacks in one case lasted 3 years. The sources of rabies in
5 patients out of the 63 cases studied are unknown. In one case, rabies
was diagnosed in the laboratory after the death of the patient, in another –
the diagnosis occurred during life, but the history is unknown. Three did not
remember contact with the animals. A total of 12 children aged 3 to 17
died of rabies. Young children tend to be attacked by animals due to
neglect, and older children are afraid to confess to their parents about an at-
tack. But in all cases, the precondition was the ignorance of both adults
and children about the dangers of contact with animals. The behaviour of
the majority of victims in relation to medical treatment was rather poor,
more than 60.0% (27 adults and 11 children) did not apply for post-
exposure prophylaxis, almost 25.0% suffered from their own pets. Ob-
viously, the people were not sufficiently informed about rabies – clearly,
there is a need to implement educational prevention campaigns. The fact
that 12 victims of rabies were children and that among their parents there
were medical and veterinary professionals suggests that children should be
included in the target audience, and the training of professionals should
be improved. Ignorance can also be seen in the fact that only 7 animals that
attacked rabies victims were examined in the laboratory. In other cases,
when animals were killed or killed after the attacks on people, these events
were not reported anywhere, visits to medical facilities did not take place.
As a result, in 38 cases, people died due to ignorance, irresponsible own-
ship of animals, neglect of their own health and people’s neglect of the
health of other people and animals. They lost their chance to survive be-
cause they did not seek help to obtain a post-exposure prophylaxis.
The remaining 25 patients out of 63 sought help after animal attacks.
Because rabbits can be prevented in a person who has had dangerous con-
tact with a sick animal with the help of post-exposure prophylaxis, this
should be done as soon as possible after dangerous contact with the ani-
mal, and the amount of PEP should correspond to the category of damage.
But the vaccine was not always available during the study period.

Since 2003 rabies vaccines for human immunization have not been
produced in Ukraine. From the same year, deliveries of rabies immuno-
globulin to medical institutions were suspended and deliveries of rabies
vaccine financed from the state budget were significantly reduced. The
function of providing immunoglobulin was entrusted to local bud-
gets. In recent years, the volume of vaccine supplies from the state budget
has increased. But not all local budgets are ready to spend on rabies im-
munoglobulin (Antonova et al., 2021). As noticed by Grigoryan & Metlin
(2016) in countries where there is no local production of anti-rabies vac-
cines, governments and other donors are likely to subsidize a limited
number of doses of rabies vaccine, which will reduce their availability.
This situation can be exacerbated by two factors: 1) the lack of rabies
immunoglobulin for treatment; 2) the fact that pharmaceuticals must be
imported, which leads to a lack of access due to the high price.

Due to limited budgets, disruptions in the manufacture of rabies im-
munoglobulin in Ukraine, hospitals have not always provided a permu-
nant supply of rabies vaccines and immunoglobulin, thus patients have not
always been able to buy drugs in the pharmaceutical network due to their
high cost. This situation has caused the unwillingness of adequate (timely
and in full) provision of medical care by medical staff; loss of access and
unequal access to patient care, as a result we have experienced non-
vaccination, refusal, or incomplete vaccination without the use of rabies
immunoglobulin (n = 8). Due to incorrect requirements in the instructions
(Table 2), the observation of animals was mistakenly conducted on other
animals than the ones which were the source of the biting attack, and in
the other 3 cases, the animals concerned were killed or their death within
10 days of the attack on a person was not reported (Table 1). Thus, the
main reason for post-exposure prophylaxis failures is not the quality of
vaccines, but the violation of vaccination schemes, non-use of immuno-
globulin. This statement is confirmed in our study. The greater number of
people did not receive immunoglobulin, although they suffered from
attacks by foxes and stray animals and suffered an injury to dangerous
locations. Only one case of PEP failure was related to the ineffectiveness
of the Covac vaccine, but the evidence was not convincing. An important
element of rabies surveillance is the diagnosis of the disease in both hu-
mans and animals. In 2 cases, the reasons for rabies developing in humans
were a delay in the verification of animal rabies in combination with de-
laying the onset of PEP and waiting for laboratory results. In such a situa-
tion, medical prophylaxis of rabies is the last chance, when the salvation of
people’s lives depends on the organization and quality of practical imple-
mentation.

The role of animals is found for each case, which is ensured by the
close interaction of two sectors of health care: humans and animals. Every
year more than 80,000 victims of animal attacks occur, about 20,000
people are vaccinated. In addition, 71.5% of victims of the attack suffer
from dogs and cats that had owners. Thus, irresponsible possession of

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animals occurs due to imperfect legislation in this area. The share of attacks from stray cats and dogs was 27.4%, but it was due to attacks from homeless animals that about 17,000 people a year had to be vaccinated as a high-risk group, because of the impossibility of observing homeless animals and also of conducting post-mortem laboratory tests on them in order to exclude rabies. Such a difficult situation regarding stray animals described in the literature (Clapet et al., 2014; Roebling et al., 2014). According to the investigation of Chikanya (2021), in some countries of southeastern Europe, homeless dog populations also very high and their supervision difficult. This carries a high risk of threatening human health and animal welfare.

The highest number of attacks was in 2008, which can be explained by the highest peak among animals in 2007. This contributed to the wider spread of the disease among animals, which increased the incidence of rabies, animal aggression and, consequently, the number of attacks on humans. A similar statement is confirmed in the works of Yoder et al. (2019). The results show a positive relationship between current reported contacts and rabies cases in dogs and humans in the previous year. This suggests that past cases of rabies in humans and dogs are important events for assessing the risk of current exposure, which showed that the disease resonates over the next year. The smaller number of attacks in 2014 is explained by the beginning of political conflicts on the territory of Ukraine, which affected the quality of monitoring, both among animals and among people. Besides this as suggest by Antonova et al. (2021) given that as a result of hostilities some territories of the eastern regions of Ukraine, as well as the Crimean Peninsula were separated from Ukraine to Russia, the total number of attacks and requests for medical aid has decreased accordingly. Due to the difficult political situation between Ukraine and the Russian Federation, which previously provided us with its vaccines, an absence of a vaccine was observed, also cases of redistribution of vaccine residues between institutions, and a search for drugs in other areas and even abroad. Thus, in 2016, out of 9 administrative areas, 786 cases were reported when patients did not receive PEP or PEP was not prescribed.

Previously for collaborating in the eradication of rabies in Ukraine, there were programmes aimed at preventing animal rabies. In 2008 the state programme of rehabilitation of the territory of Ukraine from rabies for 2008–2015 was adopted. The crucial task of the Programme was a comprehensive solution to the protection of humans and animals (wild, domestic, farm) from rabies and finally to eradicate this disease in our country. According to Kornienko et al. (2019) despite the conducting of campaigns of oral and parenteral vaccination among wild and domestic animals in Ukraine, they did not achieve great success. In addition, the lack of registration of domesticated companion animals and the ability to control their immune status prevents proper planning and evaluation of the effectiveness of immune prevention of rabies. The last comprehensive programme, which provided for intersectoral cooperation at the state level, was completed in 2010. Since then, the same rabies prevention programs have been developed and implemented at the oblast and rayon levels. The need for coordination at the central level is palpable. Nowadays the deficiencies in the fight against rabies, as well as other zoonoses, are the lack of agreed coordination of inter-sectoral interactions on the central level, the attitude towards zoonoses as non-priority problems, the lack of funding for prophylaxis programs, and the use of old methods of interventions. As noticed by Fadion et al. (2017) for any public health program, permanent funding resources are essential for continuing a rabies control programme, and the lack of those resources is one of the primary barriers to eradicating the fatal disease.

As we compare Ukraine’s experience with that of other countries that have succeeded in overcoming rabies, it is clear that this work takes considerable time. This happens even when the activities are carried out under a comprehensive programme and have financial support (Taylor et al., 2021). The concept of the frame of “One Health” approach has highlighted the integral division of responsibilities between institutions focused on animal health and human health (Wallace et al., 2017; Acharya et al., 2020). We recommend strengthening health applications against rabies by health workers, using a “One Health” approach by multiple stakeholders in Ukraine, and stepping up and monitoring the effectiveness of regular pet vaccination campaigns by the Veterinary Departments in each oblast and conducting further assessments of pets bites and controlling all rabies measures.

Conclusions

Overall, during 25 years (1996–2020) about 37,338 cases of rabies among animals and 63 cases among humans were registered. The leading source of rabies for human cases was dogs (24) and cats (22). The main causes of death were absence of seeking medical assistance after animal attacks (60.3%), error and underestimation of risk during referral for medical assistance after animal attacks (39.7%), errors during animal quarantine (9.5%), errors in diagnosis of rabies in animals (3.2%), refusal of PEP by the patients (6.3%), failure to prescribe PEP (4.8%), failure of PEP (15.9%).

During the last 13 years (2007–2019) on average, about 84,148 people (187.4 per 100,000 population) suffered from animals attacks every year, among which 2,155 people (4.8 per 100,000 population) were affected by rabid animals. PEP was prescribed annually, on average, for 21,435 patients, from which by the end of each year, 14,619 (68.0%) patients had completed the course and were immunized. The frequency of the proportion of the risk of attack by rabid dogs compared to the total number of dog attacks on humans was 1:12 from cats (1:25), wild animals (1:70) and farm animals (1:20), but the largest general proportion of animal attacks on people was from dogs – 838,635 attacks (77.7%). Geographically, the highest frequency of attacks by domestic carnivores was observed in the east of Ukraine, that of attacks by foxes in the central and western oblasts. The majority (71.5%) of victims of attack by dogs and cats were victims of animals that had owners, the share of attacks from stray cats and dogs was 27.4%.

The risks to humans of infection with the rabies virus transmitted by pets are increasing due to their owners’ failure to comply with the rules of keeping animals, increase in the population of stray domestic carnivores, the low level of vaccination of pets, low-level of public awareness and the absence of comprehensive expert assessment. Ensuring the prevention of rabies in humans requires the availability of PEP for the population, the availability of vaccines against rabies and RIG, the readiness of medical staff, high efficacy of rabies drugs, and the need to closely link the two sectors of human and animal health based on a “One Health” approach.

In conclusion, our results confirm the high risk of infection by the rabies virus from wild animals and also from domestic animals, which is a matter of concern to European countries due to the distribution of unvaccinated domestic carnivores and the possibility of transmission of rabies to humans in cases of tourism because most EU countries eliminated rabies in humans many years ago.

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