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Reviewers

contents

editorial

Dear Readers,

The journal "Zdravotníctvo a sociálna práca" (Health and Social Work) was renamed in 2021 to International Journal of Health, New Technologies and Social Work.

Our long-term effort is to gradually acquire for the journal European significance and be included in international databases. Starting with issue No. 4 in 2016, the journal accepted the Harvard style of referencing, and changed guidelines for the authors. The aim of the changes was to move closer to the standard in international journals published in English in the area of health and helping professions. The editors are aspiring for registration in other relevant international databases. Since last 2020 the journal has published all articles in English only.

The journal "Zdravotníctvo a sociálna práca" *(Health and Social Work)* was established in 2006 at Faculty of Health and Social Work blessed to P. P. Gojdič in Prešov and St. Elizabeth University College of Health and Social Work in Bratislava. In 2022, the journal celebrated its 17th year of publication.

Previously professional journal, within 5 years developed into an international, peer-reviewed scholarly journal, published quarterly (4 issues per year). The journal were published by the St. Elizabeth University of Health and Social Work in Bratislava. The journal became international in 2009. The journal was published and distributed in the Slovak Republic and also in the Czech Republic.

Since 2011, the journal is published both in print and as electronic issues, available from: www.zdravotnictvoasocialnapraca.sk. Starting by issue No. 3 in 2014, the scope of the journal has broaden and the journal is covering health sciences, such as Public Health, Nursing, Laboratory Medicine, but also helping professions such as Social Work or Pedagogy. Collaboration with Faculty of Health and Social Work of Trnava University in Trnava was initiated.

The journal is indexed in the following databases: Central and Eastern European Online Library — CEEOL (since 2018), Bibliographia Medica Slovaca (BMS), and Slovak reference database CiBaMed.

The part of journal is Supplementum, to publish abstracts from international conferences organized by the St. Elizabeth University of Health and Social Work in Bratislava. In 2023, the conference will take place in October in Piešťany, in the Slovak Republic.

prof. Miron Šrámka, MD, DSc.
redactor-in-chief

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Epidemiology and therapy of lung endoparasitic infections with a zoonotic potencial

Epidemiológia a terapia pľúcnych endoparazitických infekcií so zoonotickým potenciálom

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ABSTRACT

Introduction: Endoparasitic infections remain a serious public health problem in both developed and developing countries. A wide spectrum of endoparasites affects the respiratory system, especially the lungs. The diagnosis and therapy of these lung infections is difficult, especially because of their wide spectrum of clinical symptoms. They are also caused by a large variety of potential etiological agents and they forms — the current state of their ontogenetic development.

Research objectives: To provide basic information about endoparasitic infections (including zoonotic) that attack the respiratory tract of humans and to describe their epidemiology in the most exposed regions.

Core of the work: Pulmonary endoparasitises of humans are primarily associated with their occurrence in tropical regions. Endoparasitosis of the human respiratory tract is caused by various types of parasites (protozoa, nematodes, cestodes, trematodes and their developmental stages). They are most often accompanied by cough, wheezing, fever and, in some cases, characteristic eosinophilia. Complications due to endoparasitic lung infections occur more often in children, adolescents and immunocompromised individuals.

Conclusion: Pulmonary infections caused by parasites represent the highest risk for children and immunocompromised persons after transplants, with malignancies or for patients with HIV/AIDS. Globalization, travel to exotic locations, migration, animal trade, intensive livestock farming, and global climate change may lead to an increased epidemiological risk of pulmonary endoparasites.

Key words: Endoparasitic infections, pulmonary infections, zoonoses

ABSTRAKT

Úvod: Endoparazitárne infekcie zostávajú aj v súčasnosti závažným problémom verejného zdravia v rozvinutých aj rozvojových krajinách. Široké spektrum endoparazitov postihuje dýchací systém, najmä pľúca. Diagnostika a následná terapia týchto infekcií pľúc je náročná, predovšetkým pre ich široké spektrum klinických príznakov. Tie bývajú spôsobené aj veľkou rozmanitosťou potenciálnych etiologických agensov a formou — momentálnym stavom ich ontogenetického vývoja.

Ciele: Priniesť základné informácie o endoparazitárnych infekciách (vrátane zoonóznych), ktoré atakujú respiračný trakt ľudí a popísať ich epidemiológiu v najviac exponovaných regiónoch.

Jadro práce: Pľúcne endoparazitózy ľudí sú spájané predovšetkým s ich výskytom v tropických oblastiach. Endoparazitózy dýchacieho traktu ľudí sú zapríčinené rôznymi druhmi parazitov (protozoá, nematódy, cestódy, trematódy a ich vývinovými štádiami). Najčastejšie sú sprevádzané kašľom, sipotom, horúčkou a u niektorých charakteristickou eozinofíliou. Komplikácie v dôsledku endoparazitárnych infekcií pľúc sa častejšie vyskytujú u detí, mladistvých a imunokompromitovaných jedincov.

Záver: Pľúcne infekcie spôsobené parazitmi predstavujú najvyššie riziko pre deti a osoby s oslabenou imunitou po transplantáciách, s malignitami alebo pre pacientov s HIV/AIDS. Globalizácia, cestovanie do exotických lokalít, migrácia, obchod so zvieratami, intenzívne chovy hospodárskych zvierat a globálne klimatické zmeny môžu viesť k zvýšenému epidemiologickému riziku výskytu pľúcnych endoparazitóz.

Klúčové slová: Endoparazitárne infekcie, pľúcne infekcie, zoonózy

INTRODUCTION

Endoparasitic lung diseases are specific lung diseases caused by various types of protozoa and helminths. Infections are associated primarily with animals and humans living in subtropical and tropical regions. However, globalization, travel to exotic locations, migration, the increasing number of immunocompromised people in the world, animal trade, intensive animal breeding and global climate changes can lead to the spread of these diseases even outside the endemic areas of their occurrence.

RESEARCH OBJECTIVES

The purpose of this review is to provide basic information about endoparasitic infections (including zoonotic) that attack the respiratory tract of humans and to describe their epidemiology.

ANIMAL PULMONARY ENDOPARASITES

Nematodes affecting the cardiopulmonary system of dogs and cats have recently become the focus of increased attention due to their occurrence in several European countries and their spread to previously non-endemic areas. These are, *Aelurostrongylus abstrusus, Angiostrongylus vasorum, Crenosoma vulpis, Dirofilaria immitis* and *Eucoleus aerophilus* (syn. *Capillaria aerophila*). The importance of lungworm infections (*A. abstrusus, C. vulpis* and *E. aerophilus*) in pet animals is their zoonotic nature and subsequent epidemiological potential. The reasons for the increased incidence of pulmonary parasitosis in domestic animals are not fully understood, but several factors may play a role, such as global warming, changes in seasonal vector population dynamics, and animal migration within Europe. Most of these parasites have an indirect life cycle and therefore require an intermediate host for their development. This is true for *A. abstrusus, A. vasorum* and *C. vulpis*, and mosquito-borne *D. immitis*. *E. aerophilus* can develop either directly in the environment or in earthworms that act as facultative intermediate hosts (Traversa, di Cesare *et* Conboy 2010). Therefore, climate change is likely to have a strong impact on the distribution, development and transmission of parasites. The current trend of increasing temperatures will probably allow nematodes to spread in several countries. In recent years, angiostrongylosis has been reported with increasing frequency in dogs (Traversa, di Cesare *et* Conboy 2010). Some studies indicate the possible spread of *A. abstrusus* and *C. vulpis* into new geographic areas. Especially in Europe, there are endemic areas such as Portugal (Payo-Puente *et al.* 2008) and Italy (Traversa *et al.* 2008). *C. vulpis*, affects wild and domestic canids in Europe and North America. *C. vulpis* is recognized as the cause of respiratory diseases in dogs in various countries of the Europe (Unterer *et al.* 2002; Barutzki *et* Schaper, 2009). Respiratory tract infection of dogs and cats caused by *E. aerophilus* is considered to be sporadic, but clinical cases in animals are now more common (Foster *et al.* 2004) as well as zoonotic transmission to humans (Lalosević *et al.* 2008). In Europe, Cats infected with *A. abstrusus* are often asymptomatic (Payo-Puente *et al.* 2005). If clinical signs are present, this is often an inflammatory response caused by the eggs and the migration of first-stage larvae into the bronchial tree, causing lesions in the pulmonary alveoli. Symptoms are mostly mild to intense coughing, sneezing, mucus-purulent nasal discharge, dyspnea, abdominal breathing with open mouth, death may occur in young or immunocompromised individuals (Tüzer E *et al.* 2002; Ribeiro *et al.* 2014).

Table 1: Overview of lung edoparasites (Source: own processing)

Parasites	Mode of transmission	Infectious form	Animal reserviors	Endemic area of occurrence
Protozoal parasites				
Entamoeba histolitica	Ingescion	Cyst	Mammals	Worldwide
Leishmania spp.	*Phlebotomus* spp. Arthropod-borne	Promastigote	Dogs and cats	Asia, North Africa, Southern Europe, South America
Toxoplasma gondi	Ingestion	Sporulated oocyst, tachyzoite and bradyzoite	Cats	Worldwide
Plasmodium spp.	*Anopheles* spp. Arhropod-borne	Sporozoite	Long-tailed macaques in case of *P. knowlesi*	South America, Africa, Southeast Asia and northern Australia
Fungi				
Pneumocystis jirovecii (originally protozoan)	Airborne	Cyst	No	Worldwide
Nematodes				
Wuchereria bancrofti and Brugia spp.	Mosquitoes Arthropod-borne	Larva	Dogs and cats in case of *Brugia* spp.	Tropical and subtropical areas
Toxocara spp.	Ingescion	Eggs	Dogs and cats	Worldwide
Dirofilaria immitis	Mosquitoes Arhropod-borne	Larva	Dogs	Worldwide
Trichinella spp.	Ingescion	Larva	Mammals	Worldwide
Ascaris spp.	Ingescion	Eggs and larva	Pigs	Worldwide
Strongyloides stercoralis	Skin penetration	Larva	Dogs	Tropical and subtropical areas
Hookworms	Skin penetration	Larva	No	Tropical and subtropical areas
Cestodes				
Echinococcus spp.	Ingescion	Eggs	Carnivores	Worldwide
Trematodes				
Schistosoma spp.	Skin penetration	Larva- cercariae	Dogs and livestock	East Asia, South America and Sub-Saharan Africa
Paragonimus spp.	Ingescion	Larva- metacercariae	Mammals and crustaceans	Asia, South America and Africa

Table 2: The occurrence of endoparasites in the human body and the possibilities of therapy (Source: own processing)

Parasites	Incubation period	Target organ	Organ localization	Treatment
Protozoal parasites				
Entamoeba histolitica	Several weeks to several years	Colon	Liver, lungs, brain, kidneys, spleen and skin	Metronidazole
Leishmania spp.	10 days to 24 months	Liver, spleen and bone marrow	Lungs and kidneys	Antimonials, liposomal amphotericin B and miltefosine
Toxoplasma gondi	5–23 days	-	almost all body organs	Pyrimethamine,suladiazine or trimethoprime
Plasmodium spp.	7 to 30 days	Liver	Lung, brain, bone marrow and spleen	Artemisinin, chloroquine, pyrimethamine and atovaquone
Fungi				
Pneumocystis jirovecii (originally protozoan)	Up to 3 months	Lungs	Rare CNS	Trimethoprim-sulfamethoxazole
Nematodes				
Wuchereria bancrofti and *Brugia* spp.	6 to 12 months	Lymphatic system	Lungs and skin	Diethylcarbamazine
Toxocara spp.	Weeks to months	-	Eyes, liver, lungs and CNS	Albendazole, surgical removal
Dirofilaria immitis	Months to years	-	Lungs	Diethylcarbamazine and surgical removal
Trichinella spp.	1-2 days - enteral phase, 2-8 weeks parenteral phase	Small intestine	Muscles, CNS, heart and lungs	Albendazole
Ascaris spp.	4-6 weeks	Small intestine	Lungs	Albendazole,mebendazole or levamisole
Strongyloides stercoralis	2-4 weeks	Small intestine	Skin, liver and lungs	Albendazole or ivermectin
Hookworms	5-8 weeks	Small intestine	Skin, liver and lungs	Mebendazole or albendazole
Cestodes				
Echinococcus spp.	5-15 years	-	Liver, lung, brain and heart	Surgical removal of cysts and Mebendazole
Trematodes				
Schistosoma spp.	14-84 days	Mesentery and bladder vessels	Liver and lungs	Praziquantel
Paragonimus spp.	65-90 days	Lungs	Brain and muscles	Praziquantel

In farm animals there are several parasitic infectious agents responsible for respiratory diseases. However, dictyocaulosis caused by the parasite *Dictyocaulus viviparus* is considered one of the most common lung diseases of cattle with significant economic losses (Ploeger 2002; Panciera *et* Confer, 2010). Prevalence and mortality depend on the degree of pasture/feed contamination and animal hygiene on farms (Cantacessi *et al.* 2011). Clinical signs in affected animals are: loss of appetite, reduced growth, difficulty breathing and coughing (Mahmood *et al.* 2014). Chronic inflammatory changes in infected lungs are manifested by loss of epithelial and ciliated cells, peribronchiolitis, eosinophilic bronchiolitis and atelectasis (Mahmood *et al.* 2014). The most frequently occurring lung nematodes in small ruminants are *Protostrongylus* spp., *Muellerius* spp. and *Dictyocaulus filaria*. They cause bronchitis, pneumonia and are responsible for lung lesions in ruminants that can be observed during post mortem meat inspection. If only the lungs are affected by lungworms during the post mortem examination, these are removed. But if the infection has caused pneumonia, emaciation, or anemia, then the whole body is discarded (Herenda *et al.* 2000).

Mammomonogamus laryngeus is a nematode in the *Syngamida*e family found in tropical mammals, lifestock and very rarely in humans. For now, approximately 100 cases have been described, nearly half of which came from the Caribbean and Brazil (de Almeida *et al.* 2018; Agossou *et al.* 2021). The adult males and females are found in copula and are bright red in colour, inhabiting the larynx, trachea or bronchi. The mode of infection remains to be elucidated, and thus, life cycle of the parasite is imperfectly known. The nematode commonly causes cough and asthma-like symptoms in the patient, sometimes with haemoptysis (Bhandari *et al.* 2020).

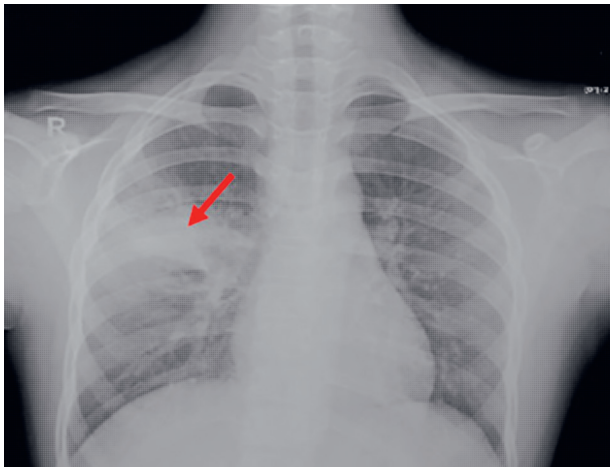
HUMAN PULMONARY ENDOPARASITES

Parasitic infections are associated primarily with human populations living in developing countries in subtropical and tropical regions. However, globalization, travel to exotic locations, migration and the increasing number of immunocompromised people in the world can lead to the occurrence of these diseases even in developed countries (Tab.1). Protozoa and helminths can cause pneumonia especially in at-risk populations, such as young children and immunocompromised individuals. Pneumonia in AIDS patients is often associated with *Toxoplasma gondii* and *Pneumocystis jirovecii* infection (Schäfer *et al.* 2019). Pulmonary strongyloidosis and hyperinfection syndrome on the other hand, is an endemic parasitosis in patients receiving chemotherapy or glucocorticoid therapy (Luvira et a., 2016). The incubation period of endoparasitic diseases varies depending on the type of parasite, from a few days (*Trichinella* spp.) to several years (*Echinococcus* spp.) (Tab.2). Most endoparasites enter the body through ingestion or skin penetration, and their target organs are most often the digestive tract, the liver, less often the lungs or other organs. The lungs are most often infected with migrating stages of endoparasites (*Ascaris lumbricoides*) or as secondary infected organ due to spread of infection from the initially infected organ (liver abscess in case of amebiasis). Lungs are the target organ only for some specific endoparasites such as *Paragonimus* spp. (Tab.2) Helminth infections in the lungs are mainly associated with eosinophilia and the formation of lung infiltrates, especially during the migration phase of helminth larvae (Cheepsattayakorn *et* Cheepsattayakorn 2014). On the other hand, in protozoan infections there is no elevation of eosinophils in the blood or lung tissue as in helminth infections (Vijayan 2008).

Thus, one of the most common manifestations of parasitic lung infections caused by helminths is parasitic eosinophilic inflammation. The first type of such inflammation was described in 1932 by Löffler, as cases with minimal respiratory symptoms, peripheral blood eosinophilia and pulmonary infiltrates, which may be associated with *Ascaris lumbricoides* migration (Lőffler 1932). In addition, this syndrome may be the result of a hypersensitivity reaction to transient migration of parasites into the lungs, which is typical for its picture of pulmonary eosinophilia without other symptoms in the respiratory tract, or it may be associated with very mild symptoms (Fujimura *et al.* 2001) (Fig. 1). Lőffler›s syndrome occurs more often in children than in adults. The most common triggers of this syndrome are *Ascaris lumbricoides, Ancylostoma duodenale, Necator americanus* and *Strongyloides stercoralis* (Riberio *et* Fischer 2002; Al-Tawfiq *et al.* 2022).

Several types of parasites cause a specific hypersensitive reaction of the organism to their presence in the lung tissue. This reaction is directed against microfilariae of species such as *Wuchereria bancrofti* and *Brugia malayi* (Al-Tawfiq *et al.* 2022). This type of organism reaction was described in 1943 by Weingarten as Tropical pulmonary eosinophilia (TPE), later as filarial tropical pulmonary eosinophilia (Weingarten 1943; Joob *et* Wiwanitkit 2020). *W. bancrofti, B. malayi* and *B. timory* are helminths that cause lymphatic filariasis transmitted by several mosquito species as *Culex* spp., *Mansonia uniformis* and *Armigeres subalbatus* (Mulyaningsih *et al.* 2019). TPE occurs only in a small proportion of patients (<0.5 — 1.0 %) infected with filariae, with a higher predominance in men (Santeliz 2019). TPE is characterise by slow onset, which can appear up to several months after the parasite has invaded the body itself, typically with with cough, dyspnea, for several months (Al-Tawfiq *et al.* 2022). *Visceral larva migrans* (VSM) is a syndrome associated with the migration of larvae of the species like *Toxocara canis* and *Toxocara cati*. The syndrome presents with severe dry cough with or without dyspnea, mild chest and abdominal pain with general fatigue with or without eosinophilia (Almatary *et* Bakir 2016).

Figure 1: Chest X-ray with opacity in the right zone in Lőffler syndrome (Source: Kiem Hao et al. 2022)



SCHISTOSOMIASIS

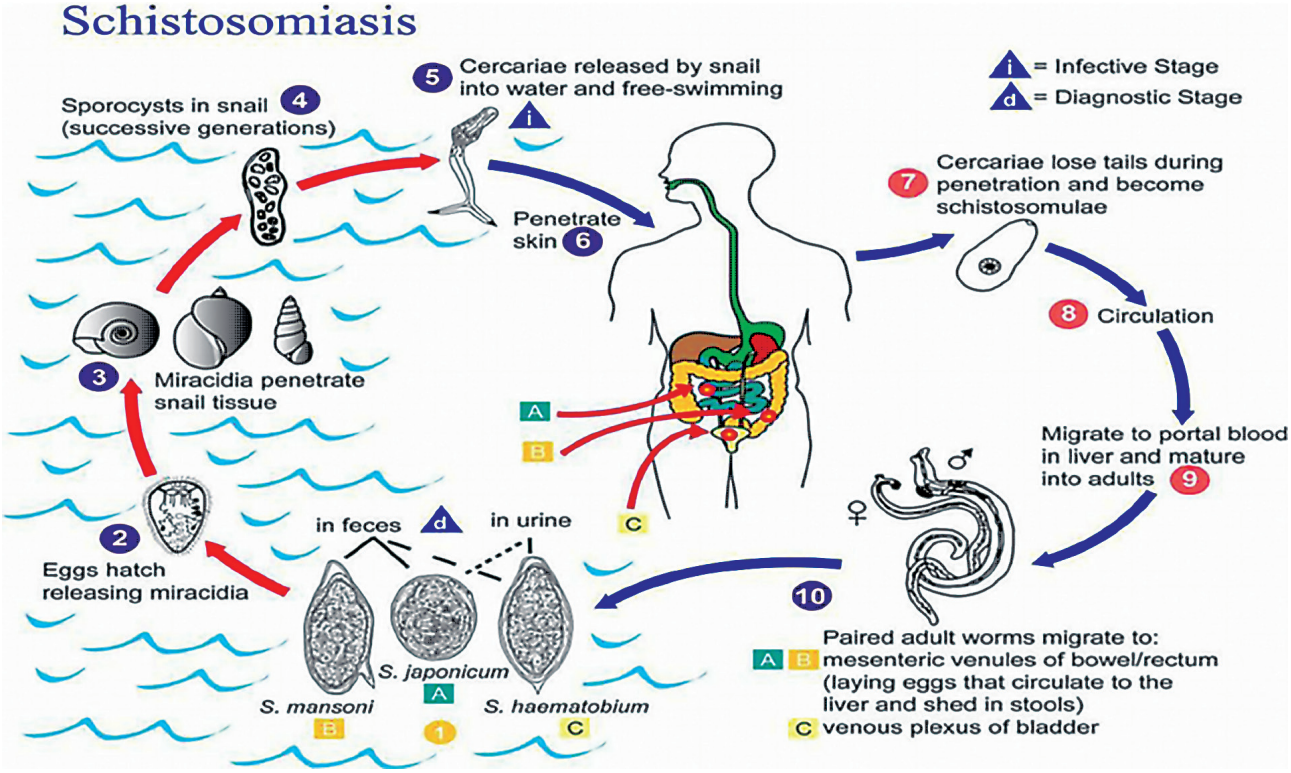
Pulmonary infections caused by parasites represent a significant burden on health care, especially in developing regions of the world. Schistosomiasis is one of these infections, occurring primarily in African, South American and some Asian countries. This tropical disease is caused by trematodes from the genus Schistosoma — *S. mansoni, S. haematobium* and *S. japonicum*. It is estimated that more than 200 million people are newly infected with these species annually (Steinmann 2006). Infection occurs when a person comes into contact with water containing free cercariae that are able to penetrate human skin (Nelwan 2019). Cercariae transform into schistosomula after penetrating the skin. They enter the blood, passing through the lungs and then mature in the portal veins of the liver, where females mate with males. They pass into the mesenteric or urogenital vasculature

depending on the species and lay eggs (Weerakoon, Gordon *et* McManus 2018) (Fig. 2). Schistosomiasis can have an acute or chronic phase. The acute phase is characterized by larval migration, maturation and egg production. In this phase, cercarial dermatitis and Katayama syndrome are observed, mainly in travelers in endemic regions (Houlder *et al.* 2021). The chronic phase is primarily associated with symptoms of egg deposition in several organs, including the lungs. In this phase, not only eggs, but also adults are deposited, which can result in the development of hepatosplenic diseases, obstruction of blood vessels in the lungs, directly by the parasite or indirectly as a result of immune-mediated inflammation with subsequent fatal pulmonary hypertension (Pearce, 2005; Lapa *et et al.* 2009; Porres-Aguilar *et al.* 2012). Nunes and colleagues (2017) also found a high incidence of schistosomiasis-induced pulmonary hypertension in endemic areas. Other symptoms associated with schistosomiasis are pneumothorax, hydropneumothorax and nodular lung lesions (Bamefleh *et* Al-Hussain 2021; Mortier *et al.* 2021). The main forms of treatment used for schistosomiasis are praziquantel and oxaminiquine (da Paixão Siqueira *et al.* 2017) (Tab. 2).

ALIMENTARY TREMATODOSIS

Infections caused by some species of trematodes can be among the important alimentary zoonoses, acquired by consumption of contaminated or insufficiently processed food originating from the aquatic environment. Diseases caused by trematodes that are transmitted through food could become a serious public health problem in the near future, also due to the high demand for fish and other aquatic animals in the world, but also due to the increase fish inland production in aquacultures, especially in Southeast Asia (Madsen *et al.* 2022). The most common foodborne trematodes are *Clonorchis sinensis, Fasciola hepatica, Opisthoorchis viverrini* (liver flukes), *Paragonimus westermani, Paragonimus miyazakii, Paragonimus mexicanus* and *Paragonimus skrjabini* (lung flukes) (Nakamura-Uchiyama, Mukae *et* Nawa 2002; Sripa *et al.* 2010). Eating habits (eating raw freshwater fish, crabs, aquatic plants and algae), but also socio-economic status, contribute to the spread of this type of trematodes. For example, eating raw crab meat is a common part of Korean cuisine (ke-jang) and one of the transmission routes of pulmonary trematodes (Fürst *et al.* 2012). Another delicacy is the uncooked meat of the Japanese wild boar (*Sus scrofa leucomystax*), which can be a paratenic host for *P.westermani*. In some countries of Asian disease occurs among people who eat raw crustaceans, which can be a source of trematodes (Blair *et al.* 2007). The most common type of foodborne fluke associated with lung infestation is *Paragonimus* spp. Endemic areas with paragonimosis are in Asia, Latin America, some parts of North America and Africa (Blair 2022). Adults of *Paragonimus* spp. live in the lungs of a variety of animal species, including dogs, cats, rodents, domestic animals, wild

Figure 2: Life cycle of Schistosoma hematobium, S. mansoni and S. japonicum (Source: U. S. Centers for Disease Control and Prevention)



animals, and humans (Blair *et al.* 2007). *Paragonimus* species have complex life cycles, during which they utilize hosts of three different species of animals (molluscs, crustaceans and mammals). In these animals, reproduction and production of eggs occurs, which reach the oral cavity through sputum and are swallowed and subsequently excreted via stool into the environment. The eggs hatch into miracidia, which are swallowed by water snails and the miracidia are transformed into cercariae. These invade crustaceans with the subsequent formation of infectious metacercariae (Blair 2022). Pulmonary paragonimosis is the most common form of infection with *Paragonimus* spp.. Symptoms of the disease are often cough and expectoration of rust-brown or bloody sputum, chest pain, fever, difficulty breathing and bronchopneumonia. Migrating individuals of *Paragonimus* spp. can cause bilateral pleural effusions and pneumothorax. Chronic paragonimosis most often leads to weight loss and anemia. In general, paragonimosis has high morbidity but low mortality, unless there is complicated infection of other organs (Yoshida, Doanh *et* Maruyama 2019; Coogle Sosland *et* Bahr, 2022). Endobronchial lesions occur in 54 % of patients with the pulmonary form of paragonimosis. The occurrence of these lesions is more common in children (Singh *et al.* 2012). Praziquantel and triclabendazole are usually use for treating paragonimiasis (Richter 2022) (Tab 2).

DIROFILARIOSIS

Dirofilaria immitis is a nematode that primarily infects dogs and other carnivores — foxes, wolves, coyotes, jackals, and sea lions (Biswas *et al.* 2013; Penezić *et al.* 2014; Farriols *et al.* 2020). Man is considered as an accidental host, as *D. immitis* is unable to complete its life cycle in the human body (Biswas *et al.* 2013; Pupić-Bakrača *et al.* 2021). Transmission to humans takes place from dogs through infected mosquitoes — *Aedes* spp. *Anopheles* spp. and *Culex* spp. (Șuleșco*et al.* 2016). In the human body, the larva migrates to the right ventricle of the heart and develops into an immature adult worm, after the worm enters the pulmonary arteries. The worm subsequently dies due to the inflammatory response and the formation of granulomas occurs. Most infected people with pulmonary heartworm disease are asymptomatic (Biswas *et al.* 2013). Nevertheless, some patients develop cough, hemoptysis, fever, dyspnea and eosinophilia (Pupić-Bakrača *et al.* 2021). Pulmonary lesions include solitary or multiple nodules (Saha *et al.* 2022). Dirofilariasis is endemic in North and South America, Australia, Japan and Europe and is particularly widespread in warmer regions.(Lok, 2018).

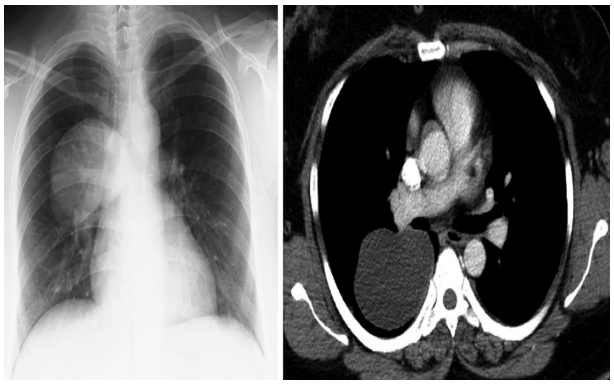
ECHINOCOCCOSIS

Larvae of *Echinococcus granulosus* and *Echinococcus multilocularis*, are the etiological agents of human hydatidosis. Humans become accidental hosts after direct contact with primary hosts, mostly canids or by ingesting food contaminated with faeces containing parasite eggs (Gessese 2020). Adults of *E. multilocularis* live in the small intestine of definitive hosts — foxes, coyotes, wolves and dogs (Deplazes *et al.*2013). In the small intestine, the eggs are released from the pregnant proglottids into the feces, after ingestion by a suitable host (rodents). Oncospheres are released from the eggs, which penetrate the intestinal wall and infect various organs through the circulatory system — predominantly the liver and lungs (Wen *et al.* 2019). In these organs, a cyst is formed, which gradually enlarges, producing protoscolexes and daughter cysts (CDC 2020). The definitive host becomes infected by eating an infected intermediate host. *E. granulosus* goes through a similar life cycle, but with the following differences: the definitive host are dogs and other canids, and the intermediate host is sheep, goat, and swine (CDC 2020). Pulmonary alveolar echinococcosis in humans is most often caused by hematogenous spread of the parasite from a primary hepatic lesion (Kern *et al.* 2003). Clinically, pulmonary echinococcosis presents with cough, dyspnea, chest pain and fever (Sarkar *et al.* 2016). If a hydatid cyst ruptures in a pulmonary bronchus, it may result in expectoration of cystic fluid containing parasitic membrane, hemoptysis, asthma-like symptoms, respiratory distress, persistent pneumonia with IgG elevation, and eosinophilia. In rare cases, rupture of cyst can lead in anaphylactic shock or sepsis (Savani *et* Sharma 2002; Buttenschoen *et al.* 2009; Arminanzas, Gutierrez-Cuadra *et* Fariñas 2015). In case of rupture of the hydatid cyst into the pleural space, effusion, empyema, and pneumothorax are the main symptoms (Kunst *et al.* 2011; Sarkar *et al.* 2016). Radiologically, hydatid cysts in lung tissue vary depending on the species of the infecting echinococcus. *E. granulosus* forms cysts with smooth borders, non-calcified nodules or masses (Garg *et al.* 2016) (Fig. 3). Lobular nodules or masses with calcifications occur in *E. multilocularis* infections (Kantarci *et al.* 2012; Sade *et al.* 2018). Available treatment options for E. granulosus infection include open surgery, percutaneous interventions, and drug therapy. For E. multilocularis infection, the treatment of first choice is aggressive surgery, while pharmacotherapy is used as an adjunct to surgery. Albendazole is the most commonly used drug in the treatment of echinococcosisinfection (Tab. 2).

TRICHINELLOSIS

Trichinellosis is one of the alimentary diseases caused by helminths *Trichinella* spp. The most important species is *Trichinella. spiralis*. Infection occurs when from eating uncooked meat from pigs, game and other animal species (Rostami *et al.* 2017). After ingestion, larvae transform into adults in the duodenum and jejunum. Females produce larvae that penetrate submucosa. Subsequently, they are deposited predominantly in the muscles, but also in various organs, via the blood or lymphatic circulation (Diaz, Warren *et* Oster 2020). In the muscle, the larvae encyst and form a host capsule that can later form calcifications. Infection of

Figure 3: Intact simple cyst: (a) Chest radiograph shows a well-defined cyst located in the upper and middle zones of the right lung. (b) CT image of the cyst.
(Source: Emlik et al. 2015)



a) b)

the respiratory tract is not frequent, but symptoms such as shortness of breath, cough, dyspnea and pulmonary infiltrates may still occur. Dyspnea can also be caused by parasite migration into the diaphragm and respiratory muscles (Pozio *et al.* 2020; Ait-Ammar *et al.* 2022; Rawla *et* Sharma, 2022). Treatment with anthelmintics such as albendazole should be started immediately if possible and by 3 days after infection (Tab. 2). In addition, these drugs inhibit the development of hatched larvae. In most cases, anthelmintic treatment is started only after symptoms of larval invasion. Severe muscle pain usually requires additional analgesic treatment (Diaz, Warren *et* Oster 2020).

STRONGYLOIDIASIS

Strongyloides stercoralis is a common species of helminths with relatively frequent occurrence in tropical regions, but also with occurrence in other climatic zones (Eslahi*et al.* 2021). *S. stercoralis* females produce eggs, the rhabditiform larvae hatching from the eggs are able to penetrate the mucosa and enter the intestinal lumen. These larvae enter the environment in faeces or change into filariform larvae and re-enter the intestinal epithelium or perianally in the skin without leaving the host. This contributes to autoinfection and persistence of infection lasting 20 to 30 years in patients who have left endemic areas (Cheepsattayakorn *et* Cheepsattayakorn 2014). Rhabditiform larvae that enter the environment through feces can undergo two distinct cycles in soil: a) a direct (host-soil-host) cycle and b) an indirect cycle (Vijayan, 2008). In a direct cycle, rhabditiform larvae metamorphose directly into filariform larvae and can infect humans through the skin. In the indirect cycle, rhabditiform larvae mature into free-living sexual forms (males and females) and then produce a second generation of rhabditiform larvae (Vijayan 2008). These rhabditiform larvae then transform into filariform larvae and directly penetrate through the skin into the lymphatic or venous capillaries. They are transported through the blood stream to the heart and lungs. Filariform larvae invade the pulmonary capillaries, enter the alveoli or migrate to the bronchi, trachea, larynx and epiglottis. They are subsequently swallowed back into the digestive tract (Vijayan 2008). Common symptoms in strongyloidosis are wheezing, dyspnea, and hemoptysis (Krolewiecki *et* Nutman 2019). Also in case of larval death the Acute respiratory distress syndrome may occure (Nnaoma, Chika-Nwosuh *et* Engell 2019). In immunocompromised individuals, autoinfection with strongyles can take a form of hyperinfection with subsequent septic infection caused by enteric flora when the parasite penetrates (Namisato *et al.* 2004; Nnaoma, Chika-Nwosuh *et* Engell, 2019; Ang, Villaluna *et* Albay 2020). The prevalence of strongyloidiasis varies by region: 26 — 48 % in Sub-Saharan Africa, 15 — 82 % in Brazil, 1 — 16 % in Ecuador and 4 — 40 % in the USA, 10.1 % in Spain (Genta 1989; Monge- Maillo *et al.* 2018).

HOOKWORM INFECTION

The hookworms *Ancylostoma duodenale* and *Necator americanus* are non-zoonotic parasites of humans. Larvae of hookworms enter the human body by penetrating the skin, often causing a local infection with itching. Infection with the *A. duodenale* can also occur through ingestion (Loukas *et al.* 2016). Larval migration in the human body involves migration through the lymphatic vessels, venules and pulmonary circulation, which can lead to a hypersensitivity reaction and the development of Lőffler's syndrome (Hotez *et al.* 2004). When the larvae penetrate the pulmonary capillaries into the alveola, the development of bronchitis or bronchopneumonia and alveolar bleeding may occurs (Parija, Chidambaram *et* Mandal 2017). Ingestion of large numbers of *A. duodenale* larvae can lead to the development of Wakana disease characterized by vomiting, nausea, dyspnea, cough, laryngeal irritation, hoarseness and eosinophilia (Loukas *et al.* 2016; Chapman *et al.* 2021). Currently, the two most commonly used drugs for the treatment of hookworms worldwide are mebendazole and albendazole (Tab. 2). Pyrantel pamoate and levamisole are alternative drugs, although neither is as effective as albendazole (Loukas *et al*. 2016).

AMEBIASIS

Entamoeba histolytica is the etiological agent that causes intestinal and extraintestinal infections, including liver and lung infections (CDC 2019). Infection occurs through the fecal-oral route, by ingesting mature cysts of the parasite from contaminated water, food or hands. After ingestion, it occurs in the small intestine, release of trophozoites to the large intestine. Trophozoites multiply binary in the large intestine and produce cysts that leave the digestive tract with the stool (CDC 2019). In some cases, trophozoites invade the intestinal mucosa and penetrate into the bloodstream. From there, they are carried to the liver, lungs, and brain, where

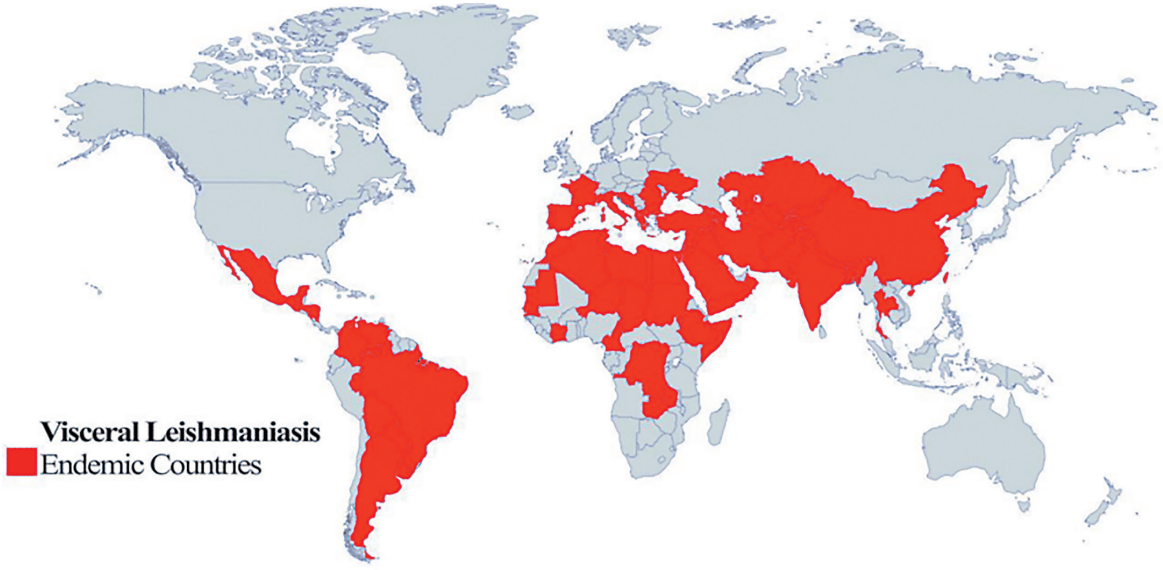
they cause hepatic, pulmonary, and cerebral amoebiasis. Invasive amoebiasis is a specific parasitic disease occurring mainly in immunocompromised patients, primarily with HIV infection (Hsu *et al.* 2008). Pulmonary amebiasis is most often caused by the extension of an amoebic liver abscess (Zulfiqar, Mathew *et* Horrall 2022). Most often, pulmonary amoebiasis is accompanied by fever, pain in the upper right quadrant of the abdomen, cough, chest pain and hemoptysis. Abscess formation and hepatobronchial fistulas can occur in pleuropulmonary amoebiasis (Tanyuksel *et* Petri 2003; Vijayan 2008). Approximately 7 — 20 % of patients with hepatic amoebiasis and 2 — 3 % with another invasive form of amoebiasis also have pulmonary symptoms such as pleural effusion, lung abscess or pleural empyema (Lichtenstein *et al.* 2005; Zakaria *et al.* 2016). Metronidazole is the first-line treatment for intestinal amebiasis, alternatives to metronidazole include tinidazole, ornidazole, and nitazoaxanide. Patients with fulminant amoebic colitis or signs of peritonitis should be started on broad-spectrum antibiotics (Stanley 2003).

VISCERAL LEISHMANIASIS

Visceral leishmaniasis (VL) also called „Kala azar" is a protozoan disease caused by the species *Leishmania donovani, Leishmania chagasi* and *Leishmania infantum*. The disease is transmitted by blood-sucking arthropods *Phlebotomus* spp. from family *Psychodidae* (Bennai *et al.* 2018; Owino *et al.* 2019). Globally, the disease occurs in Asia, Europe, Middle East, Africa, North and South America-Brazil accounting for approximately 90 % of all cases on the South American continent (Bispo *et al.* 2020) (Fig. 4).

Visceral leishmaniasis is a severe, systemic and potentially fatal parasitosis. The most affected organs in VL are the bone marrow, spleen, and liver (Akuffo *et al.* 2018; Ceccarelli *et al.* 2018). VL is parasitic condition characterized by the presence of prolonged fever, hepatosplenomegaly, and anemia (Burza *et al.* 2018). The lungs, like any other organ, can be affected by leishmaniasis. Leishmania amastigotes have been identified in lung septa, alveoli and in bronchoalveolar lavage (BAL) (Davidson *et al.* 2020). Cough is a common symptom in patients with VL. Respiratory symptoms during hospitalization are associated with a worse prognosis in pediatric patients probably due to pre-existing lung infection (de Alvarenga *et al.* 2010). The most common changes in the lung tissue are interstitial pneumonitis and bronchopneumonia. At the same time, they are often described as a complication and cause of death in patients with VL (Daher *et al.* 2015; Ahmed *et al.* 2016; Scarpini *et al.* 2022). The spread of HIV and AIDS in visceral leishmaniasis-endemic areas increases the number of patients living with both types of infection (Alvar *et al.* 2008), suggesting that visceral leishmaniasis is an opportunistic disease in HIV/AIDS-infected patients (Burki 2022). Due to similar immune-compromising mechanisms in *Leishmania infantum* and HIV-1 infections, HIV treatment control may be affected and worsened in patients that are co-infected with visceral leishmaniasis. Compared to patients with visceral leishmaniasis alone, co-infected patients have more serious health problem with increased parasite burden, frequent relapses and resistance to antileishmanial drugs (Sundar, Chakravarty *et* Meena, 2019). Therefore, serological tests for latent infection caused by leishmania should be indicated during pre-transplantation screening from endemic areas (Morales *et al.* 2003). The choice of drugs available for VL is limited to antimonials (sodium stibogluconate and meglumine antimoniate, paromomycin, oral miltefosine, and amphotericin B (Alves *et al.* 2015).

Figure 4: Incidence of visceral leishmaniasis in the world (Source: Sasidharan and Saudagar, 2021)



TOXOPLASMOSIS

Toxoplasma gondi is an intracellular protozoan that primarily infects cats and other felids. People become infected by ingesting uncooked food: unpasteurized dairy products, vegetables or meat contaminated with parasitic cysts (Vijayan 2008). Clinical manifestations are flu-like, with enlarged lymph nodes. Involvement of the respiratory system is most common in patients infected with HIV/AIDS (Vijayan 2008). Toxoplasmosis manifests as interstitial pneumonia, diffuse alveolar damage, or necrotizing pneumonia when lung involvement occurs (Garg *et al.* 2020; Wu *et al.* 2021). Specific cases are obstructive lobar pneumonia or disseminated toxoplasmosis (Schmidt *et al.* 2013; Paruthikunnan *et al.* 2014). If confirmation of pulmonary toxoplasmosis is required in HIV/AIDS-infected patients, diagnosis based on real-time PCR in BAL fluid should be preferred over standard antibody testing (Reischl *et al.* 2003; Davidson *et al.* 2020).

PNEUMOCISTIS PNEUMONIA

Pneumocystis jirovecii (previously *Pneumocystis carinii*) was previously classified as a protozoan. It is currently considered a fungus, based on cell wall composition, key enzyme structure, and gene sequencing (Amber 2017). *P.jirovecii* is thought to be transmitted from person to person through the air. Asymptomatic lung colonization can occur in people with a normal immune system, and they can thus become reservoirs (asymptomatic carriers) of *P.jirovecii*. With an ever-growing immunocompromised HIV-negative population, the overall number of cases of *P.jirovecii* pneumonia (PCP) continues to increase (Buchacz *et al.* 2010; Patterson *et al.* 2017). Patients with oncological diseases, post-transplant patients, with autoimmune and inflammatory conditions receiving immunomodulatory therapies and patients diagnosed with primary immunodeficiency are at increased risk of PCP.

At the beginning of the HIV pandemic, PCP was one of the most common infections associated with AIDS. Today, as a result of prophylaxis and initiation of early antiretroviral therapy (ART), the incidence of PCP in HIV patients has a decreasing trend (Salzera *et al.* 2018). On the other side recipients of organ transplants, stem cell transplants, patients with hematological malignancies and patients with autoimmune diseases are exposed to a significant higher risk of PCP infection (White *et al.* 2019). From 2000 to 2010, there was a decrease in the incidence of PCP in HIV-positive patients, but there was an increase in the incidence of PCP by 30 % in patients with hematological malignancies and by 25 % in renal transplant patients (Maini *et al.* 2013). In a Korean hospital tertiary care also confirmed an increasing number of PCP cases in HIV-negative patients, while PCP cases in HIV-positive patients are decreasing (Lee *et al.* 2019).

The onset of PCP can vary depending on the type of disease. In HIV-positive patients, PCP is the AIDS-defining disease, and it is not possible to predict how long the patient has been at risk of acquiring PCP (ie, how long the patient has had CD4+ < 200). However, in patients with hematological malignancy and after hematopoietic stem cell transplantation (HSCT), it is known that disease can occur between 5 and 587 days after HSCT, with 50 % of patients developing infection between 60 and 270 days after allogeneic transplantation (Williams et al, 2016). In kidney transplant recipients, the risk period is highest 12 months after transplantation (Szydłowicz *et al.* 2018). Symptoms of PCP are generally nonspecific and typically point to pneumonia. Extrapulmonary diseases are rare (White *et al.* 2019). The risk of PCP is reflected in the patient's baseline condition, immune status, and other potential risk factors, especially if other more typical bacterial and viral pathogens have been ruled out. Symptoms include fever, nonproductive cough, worsening chest pain, and dyspnea. Dyspnea and cough may be less common in HIV-negative patients, but respiratory failure may occur more frequently (Salzer *et al.* 2018). In HIV-positive patients, PCP usually manifests over several weeks as a progressively worsening disease associated with significant respiratory distress. Garg *et al.* (2018) found cytomegalovirus (CMV) viremia to be a risk factor for PCP in kidney or pancreas transplant patients, with 90 % of patients having CMV 1 year before PCP and 89 % having active CMV infection at diagnosis of PCP. The diagnosis of PCP is multifactorial and may include clinical suspicion, patient risk factors, laboratory tests, chest radiography, chest computed tomography (CT), sputum examination, evaluation of bronchoalveolar lavage fluid, or lung biopsy. Laboratory findings are mostly nonspecific for PCP, and the most notable finding is elevated serum lactate dehydrogenase (LDH) in HIV-infected patients. In HIV-negative immunocompromised patients, elevated serum LDH levels may also be due to other causes, so LDH is not a diagnostic tool in this patient population (Truong *et* Ashurst 2022). Most fungi, including *P.jirovecii,* contain beta-D-glucagon in their cell walls. An increase in serum beta-D-glucagon in patients with clinical signs and risk factors for pneumonia should raise the suspicion of infection with *Pneumocystis spp*.. In hypoxic patients with tachycardia and signs of respiratory distress, arterial blood gas analysis should be performed to assess the severity of their disease and/or detect an increased alveolar-arterial (A-a) oxygen gradient (Waks *et al.* 2015; Sabbagh *et* Darwich 2018). A chest radiograph typically reveals diffuse bilateral peri-hilar interstitial infiltrates. Other radiographic findings may include solitary or multiple nodules that may progress to cavitary lesions. If there is clinical concern for *P.jirovecii* infection and a negative chest radiograph, a chest CT should be performed (Truong *et* Ashurst 2022). As *P.jirovecii* cannot be cultured, definitive diagnosis requires detection and identification of the organism by PCR from respiratory specimens or staining with fluorescein antibodies

(Truong and Ashurst 2022). A definitive diagnosis of PCP may not always be possible. Immunosuppressed patients without HIV infection are likely to have a lower organism burden in sputum or bronchoalveolar lavage samples, making diagnosis more difficult (Truong and Ashurst 2022). The management of PCP is increasingly complicated also due to the occurrence of *P.jirovecii* resistance (Suárez *et al.* 2017). Mutations in dihydrofolate reductase and dihydropteroate synthase cause resistance to trimethoprim sulfamethoxazole, and the A144V mutation in cytochrome b is associated with resistance to atovaquone (Suárez *et al.* 2017; Argy *et al.* 2018).

CONCLUSION

Globalization, travel to exotic locations, migration, animal trade, intensive animal husbandry, and global climate change may lead to increased occurrence of pulmonary parasitosis in both developing and developed countries. Pulmonary infections caused by parasites pose the highest risk for immunocompromised persons after transplants, with malignancies, or for patients living with HIV/AIDS.

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Conflict of interest
The authors declare there is no conflicts of interest in the connection with published article.

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Lethal course of COVID-19 – morphological findings
Letálny priebeh COVIDu-19 – morfologické nálezy

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ABSTRACT

Objective: Millions of people worldwide have succumbed to the disease of COVID-19 and millions more are suffering from its consequences. As with previous epidemics and pandemics, one of the indispensable tools in the fight against disease is autopsy.

Methods: We monitored pathological findings in 250 patients who died in connection with COVID-19. In the case of a fatal course, it is in most cases the result of lung damage. We therefore focused on changes in the lungs.

Results and Conclusions: In the lungs, the most common finding was diffuse alveolar damage (DAD) in various stages, with foci of bleeding into the alveoli and thrombus. Studying fatal cases of COVID-19 is not a suitable method for clarifying the causes of long-term COVID. However, the findings suggest that in patients with a severe course, it is mainly pulmonary fibrosis, hypoxia, tissue damage and microthrombi.

Keywords: COVID-19, autopsy, immunohistochemistry, microthrombi.

ABSTRAKT

Cieľ: Celosvetovo ochoreniu COVID-19 podľahli milióny ľudí a ďalšie milióny trpia jeho následkami. Tak, ako aj pri predchádzajúcich epidémiách a pandémiách, jedným z nenahraditeľných nástrojov v boji s ochorením je pitva.

Metóda: V našej práci sme sa venovali patologickým zmenám v prípadoch fatálneho priebehu ochorenia. Patologické nálezy sme sledovali u 250 pacientov, ktorí zomreli v súvislosti s COVID-19. Patologické nálezy sme sledovali u 250 pacientov, ktorí zomreli v súvislosti s COVID-19. Pri fatálnom priebehu ide vo väčšine prípadov o následok poškodenia pľúc. Zamerali sme sa preto na zmeny na pľúcach.

Výsledky a záver: V pľúcach bolo najčastejším nálezom difúzne alveolárne poškodenie (DAD) v rôznom štádiu, s ložiskami krvácania do alveolov a tromby. Štúdium fatálnych prípadov COVID-19 nie je vhodnou metódou na objasnenie príčin dlhého COVIDu. Avšak nálezy naznačujú, že u pacientov s ťažkým priebehom je to hlavne fibróza pľúc.

Klúčové slová: COVID-19, pitva, imunohistochémia, mikrotromby

OBJECTIV

Since the outbreak of the pandemic, COVID-19 has become the most common cause of severe viral pneumonia in humans. It soon became clear that, in addition to the lungs, it directly or indirectly affects many organs of the human body. For effective treatment and prevention of complications, it is necessary to know exactly the pathogenesis of the disease. One of the irreplaceable tools for clarifying pathological events is autopsy and analysis of autopsy findings and samples. The aim of this work is to clarify the pathological events taking place in the most affected organs during lethal COVID-19, focusing on lung tissue. Persistent symptoms in patients after overcoming the disease, also called post-covid syndrome or long COVID, are becoming an increasing problem. Even if works describing autopsy findings in patients with a lethal course are not an ideal tool for this, they can contribute to clarifying some events to a certain extent. With the increasing number of patients who have overcome the disease of COVID-19, more and more patients have begun to appear, in whom difficulties persist even more than 4 weeks after overcoming the disease. Although in the vast majority of cases they do not lead to the death of the patient, they represent a serious medical problem. Such a post-acute inflammatory syndrome is not unique to COVID-19. Very similar, although in some aspects different, syndromes have also been described after infections with other viruses, such as Ebola, Dengue, Polio, SARS, Chikungunya, EBV, H1N1, Coxackie B, VZV, but also after other pathogens such as Borrelia, Giardia lamblia and Coxiella burnetti (Choutka J, Jansari V, Hornig et al. 2021). Patients with symptoms of prolonged COVID can be divided into two main groups. It can be patients with a severe course and hospitalization, who suffer from symptoms of the disease after being discharged from the hospital. In these patients, we assume the presence of lung fibrosis, tissue and organ damage caused by virus infection and complications of the disease, such as hypoxia, septic condition, but also therapy, pulmonary ventilation and many others.

MATERIALS AND METHODS

A total of 250 patients who were confirmed to have COVID-19 at autopsy were included in this retrospective study. Of these, in 208 cases, COVID-19 was determined to be the underlying disease that led to death (death due to COVID), in 42 cases the cause of death was another disease and the patient also had SARS-CoV-2 infection (death with COVID). Autopsies were performed at the Institute of Pathological Anatomy of the Faculty of Medicine of Comenius University and University Hospital Bratislava and at other workplaces of the Office for Health Care Supervision of the Slovak Republic in the period from April 2020 to December 2022. Standard necropsy samples of organs and tissues were fixed in 10 % formalin, representative sections were processed by routine technology by embedding in paraffin, and 5 μm thick sections after deparaffinization were stained with hematoxylin and eosin. Histological preparations for imunnohistochemical preparation were evaluated under a light microscope. The tissue sections were first deparaffinized by placing in a thermal oven with a temperature of 60 °C for 15 minutes and then placed in xylene for 2 × 5 minutes. The samples were further rehydrated for 2 × 5 minutes in 96 % and 70 % alcohol and then rinsed with distilled water. Antigen epitopes of the tissues were unmasked by revitalization in the Dako PT Link device (Dako, Glostrup, Denmark), where they were incubated in revitalization solutions for 20 minutes at a temperature of 98 °C. Based on the recommendation of the respective antibody manufacturer, slides were incubated in TRIS-EDTA solution (10 mM TRIS, 1 mM EDTA, pH 9.0) or in sodium citrate solution (10 mM, pH 6.0). After cooling, the samples were rinsed in a physiological buffered saline solution with a pH of 7.2 (PBS) and then incubated at room temperature for 10 min. with endogenous peroxidase inhibitor (Agilent Technologies, Santa Clara, CA, USA). Subsequently, the sections were rinsed in PBS and incubated for 30 min. with primary antibodies that were diluted using Dako REAL antibody diluent (Agilent). After incubation, the slides were washed and placed in PBS solution for 15 minutes, and subsequently incubated at room temperature for 30 minutes with peroxidase-labeled secondary antibody (anti-mouse / anti-rabbit EnVision FLEX / HRP, Dako). The slides were then rinsed and placed in PBS solution for 15 minutes. The reaction was visualized using a solution containing diaminobenzidine (DAB, Dako), which acted for 5 minutes, the reaction was terminated by rinsing with distilled water. The samples were counterstained with hematoxylin, cleared with xylene and covered with a coverslip with PERTEX mounting medium (Histolab AB, Sweden). For the detection of SARS-COV-2 viral RNA by in situ hybridization in histological preparations, we used the RNA Scope® detection system using a probe for genomic RNA encoding the nucleocapsid protein (Advanced Cell Diagnostics, Inc., USA). Histological preparations were evaluated in Motic RED-230 and Eclipse i80 light microscopes (Nikon, Tokyo, Japan).

RESULTS

We observed the most serious organ changes in patients with a lethal course of COVID-19 in the lungs. The changes were most pronounced in patients who died of COVID. However, even in those who were infected with SARS-CoV-2 and died from other causes, we could often observe different stages of the developing disease of COVID-19.

In the first wave, lung involvement was in most cases massive, diffuse, mostly in the acute stage. In the later waves, we could more often observe a focal distribution with the appearance of changes at different stages. Changes were not evenly distributed. The peripheral parts of the lungs were mainly affected. Even in cases with minimal changes in deaths "with

COVID", these were observable in the peripheral parts of the lungs. In the acute exudative stage of the disease, the lungs are heavy, edematous, often with foci of bleeding (Figure 1. A, B). In the later, proliferative stage with organization, the lungs have a stiffer, elastic consistency, and are grayish-red in cross-section (Figure 1. C, D). Common complications in patients with COVID include superinfection with the development of bronchopneumonia and thromboembolic disease and foci of infarctions and hemorrhages (Figure 1. D).

The histological picture corresponded to the typical picture of diffuse alveolar damage in different stages. In the acute, exudative phase, we observed alveolar capillaritis with mixed inflammatory infiltration, interstitial edema and predominantly perivascular inflammatory infiltration by lymphocytes and plasma cells. Congestion and thrombi were often present in the vessels, in places with hypertrophy and proliferation of endothelial cells, up to doubling of the basement membrane (Figure 2, 3). In places, there was a transfer of edema fluid into the alveoli, in places with foci of intra-alveolar bleeding, with the formation of hyaline membranes, activation and exfoliation of pneumocytes (Figure 4). The affected pneumocytes were often separated in chains, sometimes they were accumulated in the alveoli, usually with an admixture of alveolar macrophages. In the later stages of the disease, foci of organization were present. With COVID-19, the bronchial epithelium was often damaged and detached. In this phase, signs of cytopathic effect of the virus were present in many cases, such as significantly enlarged type 2 pneumocytes with an enlarged nucleus and prominent nucleoli, as well as multinucleated pneumocytes. In the later, proliferative stage, squamous metaplasia, organization of septa, and gradual fibrosis of the lung parenchyma often occurred. As a rule, we could observe fibrosis of the lungs after 3 weeks from the onset of the disease.

We proved the presence of RNA virus in epithelial cells using in situ hybridization, which indicates the presence of a replicating virus. We also detected positivity in macrophages and hyaline membranes. In a carefully analyzed case of persistent symptoms of the COVID-19 disease with pulmonary symptomatology for 2 months with a lethal course, we observed foci with signs of the acute phase of damage as well as foci of late organization with massive pulmonary fibrosis. Foci of acute damage consisted of capillaritis with a mixed lympho-neutrophil inflammatory infiltrate in the septa, detached alveolar epithelium, alveolar edema, foci of bleeding in the alveoli, and hyaline membranes (Figure 4).

DISCUSSION

According to the World Health Organization database, 1,866,814 cases of COVID-19 were confirmed in Slovakia by the end of May 2023, including 21,167 deaths (WHO 2023). In our group, we observed the histopathological changes of selected organs in 250 patients, of whom 208 died from COVID and 42 with COVID, that is, from another disease, while SARS-CoV-2 infection was a secondary finding. However, accurate recording of deaths related to SARS-CoV-2 infection can be difficult and has been a source of controversy and inaccuracies in data evaluation since the beginning of the pandemic (Boyle P 2021). At the beginning of the pandemic, autopsy findings were essential for understanding the pathogenesis of fatal cases of the disease, later for determining to what extent and by what mechanism the SARS-CoV-2 infection was involved in the death of a specific patient. Autopsy findings can be divided into macroscopic and microscopic. Both images complement each other. Many pathological events in COVID-19 have a macroscopically non-specific picture and a histological correlate is needed to determine the pathological process. The samples from the first wave (in Slovakia until the end of June 2020) were dominated by diffuse lung damage in the acute phase. In samples from a later period, we found bearing damage in various stages. Such a finding points to the gradual onset of infection in different parts of the lungs. In the literature, we did not find a mention of a similar change in the nature and distribution of histopathological findings. We believe that the change occurred mainly due to modification of treatment, mutations of the virus with changes in virulence.. The first wave was very specific in Slovakia compared to other countries in that we registered only 28 deaths from COVID-19, most of which came from the facility social services, and they were mostly elderly polymorbid patients.

In addition to changes typical of diffuse alveolar damage (DAD), the most common findings included pulmonary thromboembolism, foci of hemorrhage, and pulmonary infarctions. This is in agreement with the findings of other authors (Bösmüller H, Matter M, Fend F,2021). The microscopic image was dominated by the image of DAD at different stages of development. The clinical correlate of DAD is acute respiratory distress syndrome. It is a nonspecific finding that can be caused by other viruses, bacteria, fungi, parasites, toxic substances, prolonged mechanical ventilation, chemotherapy, and many other influences (Suster D, Suster S. 2021). In our cohort, the average time from death to autopsy was more than 40 hours. During this time, morphological changes caused by autolysis and postmortem multiplication of bacteria can already occur (Cocariu EA, Mageriu V, Stăniceanu F et al 2021). In our samples, we found an association with interstitial edema, multinucleated cells and borderline necrotizing bronchitis. Thus, these changes could be at least partially due to autolysis. As a result of autolysis, the boundaries between cells can be blurred, which can mimic multinucleated cells.

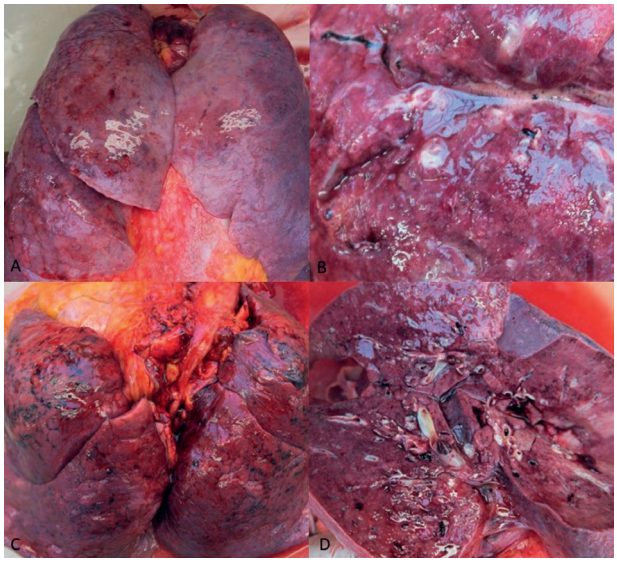
As for the histomorphological picture, data on the exact picture of changes in individual organs during long-term COVID are rare. Pulmonary fibrosis is a known complication

of the severe course of COVID-19, but also of ARDS from other causes. In our case, we were able to prove the presence of the virus more than 2 months after the onset of symptoms, which supports the persistence of the virus as a possible cause of prolonged COVID. There were signs of both fibrosis and acute damage in the lungs.

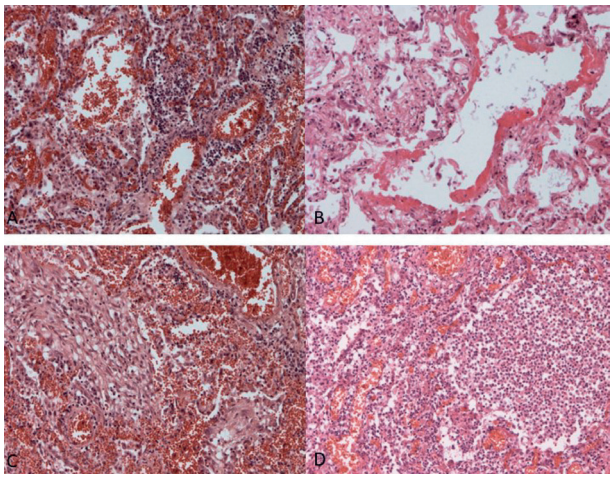
CONCLUSION

Before getting its name, the disease COVID-19 was described as pneumonia of unknown origin. Respiratory symptoms dominate in patients, and even in fatal cases, lung involvement is the most serious. Analysis of necropsy samples showed that the virus affects different organs. This action is complex and includes the virus itself, the body's immune reaction with a tendency to form thrombus, but also changes caused by hypoxia and the severe condition of the patients. Our analysis of 250 cases of fatal COVID-19 shows that the majority of findings are nonspecific, caused mainly by hypoxia, severe disease, and a prothrombotic state associated with microthrombi formation and thromboembolism. Along with non-specific changes, one of the most consistent findings was microthrombi present to varying degrees in virtually all examined organs. We believe that this is a significant contributing factor to the damage to these organs. Findings on the lungs are dominated by DAD in various stages, up to the development of lung fibrosis. It is a non-specific finding that can be caused by various causes. Evidence of the viral origin of the finding is its cytopathic effect, in the case of SARS-CoV-2 it is multinucleated cells and significantly hypertrophied pneumocytes with prominent nuclei. As for long-term COVID, autopsy findings are more telling in cases after a severe course of the disease. Pulmonary fibrosis, tissue damage, hypoxia and microthrombi are probably used in etiopathogenesis.

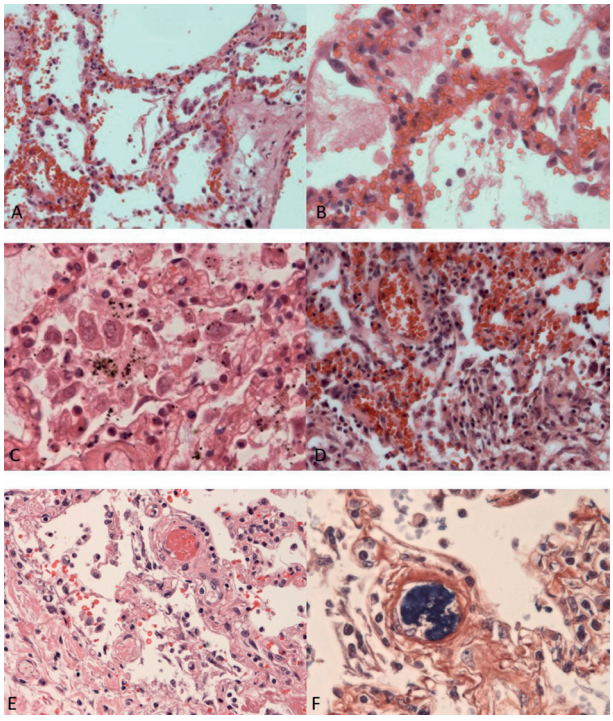
Figures 1.



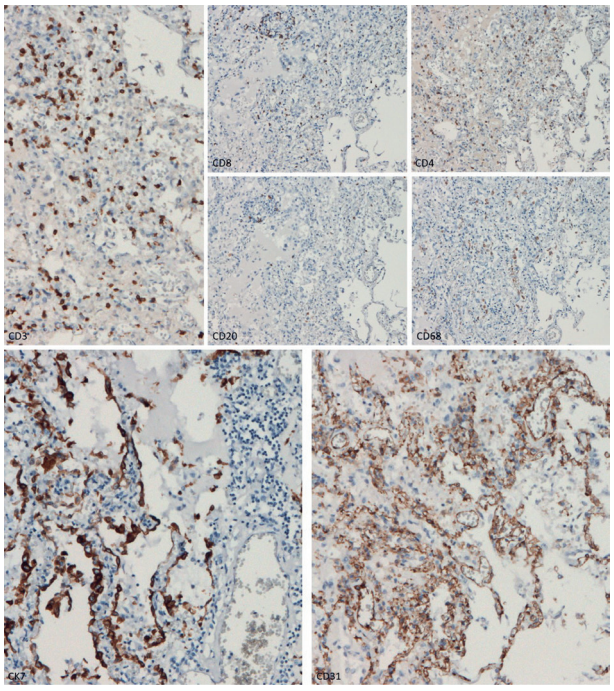
Figures 2.



Figures 3.



Figures 4.



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Authorship

All authors have read and approved the final version of the manuscript, and all author listed as co-workers met the criteria for authorship.

Conflict of Interest
The authors declared no conflict of interest in relation to the article.

Figures legends:

Figure 1. Macroscopic findings on the lungs in COVID-19 pneumonia. A: COVID-19 pneumonia, lung tissue in the acute stage. The lungs are heavy, infiltrated, subpleural foci of bleeding are visible (arrow). B: A large amount of foamy fluid is oozing out on the incision, the lungs are darker, gray-red in color. C: COVID-19 pneumonia, lung tissue in the stage of organization. Lungs are heavy, stiffer, elastic consistency, darker, gray-red color. D: On the section, the lungs are consolidated, gray-red in color. Captured embolization (yellow arrow) to branch a. pulmonalis.

Figure 2. Microscopic changes in the lung parenchyma in COVID-19 disease. A: Focal extravasation of erythrocytes, interstitial lympho-plasmacytic infiltrate. B: Hyaline membranes. C: Foci of erythrocyte extravasation with foci of organization. D: Typical changes may be overlaid by a polymorphonuclear inflammatory infiltrate in superinfection, but activated pneumocytes and a lymphoplasmacytic interstitial infiltrate are present. HE, 100x.

Figure 3. Microscopic changes in lung parenchyma in COVID-19 disease. A, B: Activated pneumocytes separating in chains with formation of hyaline membranes. C: Activated pneumocytes with nuclei with light chromatin and prominent nucleoli. D: Activated, detached alveolar epithelium with extensive accumulation in the alveoli. E, F: Microthrombus highlighted by blue staining in special phosphotungsten hematoxylin staining. HE, 100x (A); HE, 200x (B, D, E); HE, 400x (C); FH, 200x (F).

Figure 4. Inflammatory infiltrate in the lung in COVID-19. CD3 positive is a T-lymphocyte inflammatory infiltrate, composed of CD4+ T-lymphocytes and CD8+ T-lymphocytes concentrated mainly around blood vessels (arrow). Less numerous are CD20+ B-lymphocytes, also around blood vessels, and scattered CD68+ macrophages. DAB, hematoxylin, 200x (CD3), 100x (CD8, CD4, CD20, CD68)

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Optic disc neuropathies and optical coherence tomography

Zmeny terča zrakového nervu a optická koherentná tomografia

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ABSTRACT

Introduction: Optical coherence tomography (OCT) has revolutionized the evaluation and management of optic disc neuropathies by providing objective and quantitative measurements of optic disc parameters and enabling early detection of structural changes. OCT is extensively utilized in the diagnosis, monitoring, and management of glaucoma. It helps in the assessment of optic disc parameters, including cup-to-disc ratio, neuroretinal rim thickness, and retinal nerve fiber layer (RNFL) thickness. It can show the optic disc drusen themselves and their impact on surrounding structures. OCT scans aid in measuring RNFL thickness and assessing optic disc morphology.

Material and methods: Analysis consists of a group of patients monitored at the neuro-ophthalmology outpatient clinic of the Department of Ophthalmology, Faculty of Medicine, Comenius University in Bratislava over a period of one year, from January 2022 to January 2023. Cirrus HD-OCT 5000 was device used to scan optic disc of both eyes, using the optic disc cube 200x200 scanning protocol, the output of which is the RNFL and ONH analysis protocol of both eyes.

Results: Group of 121 patients, of which 60 are men and 61are women, with an average age of 48.57 with a maximum of 92 years and a minimum of 22 years. From data collected so far, 13,0 % were diagnosed with retrobulbar neuritis. In which 61,11 % have had confirmed demyelinating disease.

Conclusion: Serial OCT scans can help monitor changes in oedema severity, evaluate response to treatment, and identify potential complications.

Key words: Optic disc, Optical coherence tomography, optic disc oedema, retinal nerve fibre layer

ABSTRAKT

Úvod: Optická koherentná tomografia (OCT) spôsobila revolúciu v hodnotení a manažmente neuropatií terča zrakového nervu (TZN) tým, že poskytuje objektívne a kvantitatívne merania parametrov TZN a umožňuje tak včasnú detekciu jeho štrukturálnych zmien. OCT sa vo veľkej miere využíva pri diagnostike, monitorovaní a liečbe glaukómu. Pomáha pri hodnotení parametrov optického disku, vrátane pomeru exkavácie k terču zrakového nervu, hrúbky neuroretinálneho okraja a hrúbky vrstvy nervových vlákien sietnice (RNFL). Umožňuje vizualizáciu samotných drúz terča zrakového nervu a ich vplyvu na okolité štruktúry. OCT skeny pomáhajú pri meraní hrúbky RNFL a hodnotení morfológie terča zrakového nervu.

Materiál a metodika: Analýza pozostáva zo súboru pacientov sledovaných na neurooftalmologickej ambulancii Kliniky oftalmológie LF UK v Bratislave počas jedného roka, od januára 2022 do januára 2023. Cirrus HD-OCT 5000 bol prístroj použitý na skenovanie optického disku oboch očí pomocou skenovacieho protokolu optic disc cube 200 × 200, ktorého výstupom je protokol analýzy RNFL a ONH oboch očí.

Výsledky: Súbor tvorí 121 pacientov, z toho 60 mužov a 61 žien, s priemerným vekom 48,57 rokov, maximálne 92 rokov a minimálne 22 rokov. Z doteraz zozbieraných údajov bolo 13,0 % diagnostikovaných s retrobulbárnou neuritídou. V ktorých 61,11 % malo potvrdené demyelinizačné ochorenie.

Záver: Sériové OCT skeny pomáhajú monitorovať zmeny v závažnosti edému TZN a hodnotiť odpoveď na liečbu ako aj identifikovať potenciálne komplikácie.

Klúčové slová: Terč zrakového nervu, Optická koherentná tomografia, Edém terča zrakového nervu, Vrstva nervových vlákien sietnice

INTRODUCTION

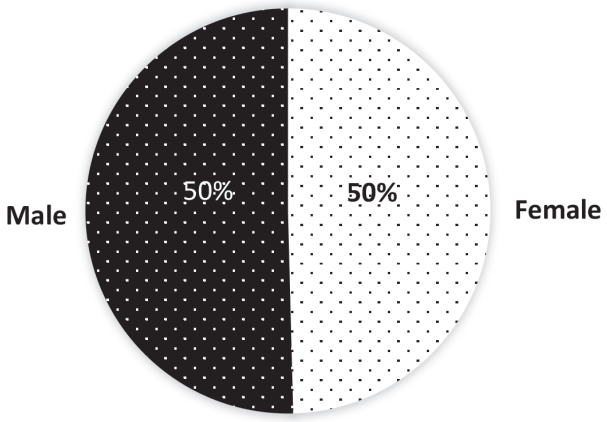
The optic disc is the anterior end of the optic nerve and abnormalities of the optic disc may reflect eye disease, problems in development or CNS disease. Optic disc is the point of exit for ganglion cell axons leaving the eye. Because there are no rods or cones overlying the optic disc, it corresponds to a small blind spot in each eye, is also the entry point for the major blood vessels that supply the retina. Optic disc has an oval shape and its diameter is approximately 1.5 — 2 mm. It located nasally from the fovea, approximately 4 mm. Its colour contrasts with the pink retina, temporally the boundary of optic disc is sharper than nasally, this is due to the arrangement and transition of nerve fibres of ganglion cells. In its centre is a recess called the excavation of the optic nerve. It's important part of cup/disc ratio — C/D ratio, where C cup expresses the excavation in the centre of the optic disc and D disc as the diameter of the entire optic disc. The physiological value of the C/D ratio ranges from 0.0 to 0.3. The ratio is important to correlate with the size of the optic nerve target itself (Krásnik V., 2014, Oláh Z 2017). Optic atrophy is a morphological sequela reflecting the loss of many or all of the axons of the optic nerve. A number of diseases such as hereditary, metabolic, tumour, and increased intracranial pressure can lead to optic atrophy (Sadun and Wang, 2011). Optic disc oedema can be produced by a number of diseases such as optic disc drusen, intracranial masses, orbital tumours, ischemic optic neuropathies, inflammations, and infiltrations before leading to optic atrophy (Sadun and Wang, 2011). Optic disc tilt was found in approximately one-third of young myopic eyes and was independently associated with the presence of glaucomatous optic disc (GOD) (Lee et al., 2017).

Optical coherence tomography (OCT) is a non-invasive imaging technique that has become an essential tool in the diagnosis and management of various retinal diseases. It is a promising tool for evaluating optic disc anomalies. Studies have shown that OCT can be used to quantitate the thickness of the peripapillary retinal nerve fibre layer as an indirect measure of axonal loss or swelling, making it useful in identifying and quantifying papilledema in idiopathic intracranial hypertension (IIH) (Skau et al., 2011). In cases of papilledema, which is optic disc swelling due to increased intracranial pressure, OCT can quantitatively measure the thickness of the peripapillary retinal nerve fibre layer (RNFL). This measurement provides an indirect assessment of axonal loss or swelling, aiding in the identification and quantification of papilledema severity. Monitoring RNFL thickness over time with OCT can help assess the progression of papilledema and response to treatment (Rigi et al., 2015, Hayreh, 1976). OCT can also detect different kinds of abnormalities including shape of cavities, defect of lamina cribrosa, or distance to subarachnoid space in the excavated optic discs anomalies (Ohno-Matsui et al., 2013).

MATERIAL AND METHODS

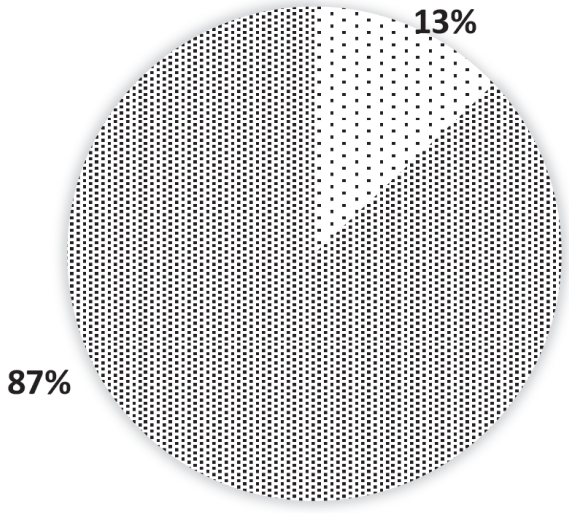
Analysis consists of a group of patients monitored at the neuro-ophthalmology outpatient clinic of the Department of Ophthalmology, Faculty of Medicine, Comenius University in Bratislava over a period of one year, from January 2022 to January 2023. Currently consists of 121 patients, of which 60 are men and 61 are women, with an average age of 48.57 with a maximum of 92 years and a minimum of 22 years.

Graph 1: Group of 121 patients and distribution by gender



From data collected so far, 13,0 % were diagnosed with retrobulbar neuritis, in which 61,11 % have had confirmed demyelinating disease.

Graph 2. Group of 16 patients (13 %) with retrobulbar neuritis (RNB) and 105 patients (87 %) with different diagnosis in the group of 121 patients



Cirrus HD-OCT 5000 was device used to scan optic disc of both eyes, using the optic disc cube 200x200 scanning protocol, the output of which is the RNFL and ONH analysis protocol of both eyes.

DISCUSSION

In the field of optic disc evaluation using optical coherence tomography (OCT) as a non-invasive imagining method, there are several core applications to consider. OCT allows for detailed assessment of optic disc morphology, including disc size, cup-to-disc ratio, neuroretinal rim thickness and optic disc parameters. OCT also provides precise measurements of the thickness of the RNFL, which contains the axons of retinal ganglion cells. RNFL thinning is a hallmark of various optic neuropathies. Quantitative measurements obtained from OCT scans can help in diagnosing and monitoring optic disc abnormalities, such as glaucoma, optic neuropathy and many others. In the further text we will discuss application of OCT imagining method in various neuropathies using published work found in pubmed database.

Optical coherence tomography (OCT) is a non-invasive tool that measures retinal nerve fibre layer (RNFL) thickness based on its optical properties. OCT is a good instrument to diagnose early glaucoma, but cannot be used to exclude it (Pagliara et al., 2008). Bradley et al. estimated the number of OCT scans necessary to detect moderate and rapid rates of retinal nerve fibre layer thickness worsening at different levels of accuracy using a large sample of glaucoma and glaucoma-suspect eyes. They found that to diagnose retinal nerve fibre layer worsening more accurately, the number of OCT scans must be increased compared with current clinical practice. A clustered measurement strategy reduces the number of scans required compared with evenly spacing measurements (Bradley et al., 2023). Some studies suggest that macular and optic nerve head parameters may be useful in tracking progression in patients with advanced glaucoma (Lavinsky et al., 2018) and study by Moghinmi at al found that macular and ONH vessel density may add significant information to the evaluation of the risk of glaucoma progression and prediction of rates of disease worsening (Moghimi et al., 2018). Recent work by Hood et al. suggests that the OCT probability (p-) maps, also known as deviation maps, can play a key role in an OCT-based method for detecting glaucoma. However, artifacts seen on the p-maps of healthy control eyes can resemble patterns of glaucoma damage. These glaucoma-like artifacts are relatively common and are probably due to normal anatomical variations in healthy eyes. A simple anatomical artifact model based upon known anatomical variations can help distinguish these artifacts from actual glaucomatous damage (Hood et al., 2022). OCT can be a useful tool in the diagnosis and management of glaucoma, but it should not be used as the sole diagnostic tool. Clinical examination of the optic nerve and achromatic automated perimetry remain the gold standard for the management of glaucoma. Artificial intelligence (AI) has been used in optic disc OCT to aid in the diagnosis and management of glaucoma. AI algorithms can analyze OCT images to detect changes in the optic nerve head and retinal nerve fiber layer, which are important indicators of glaucoma progression (Ryalat et al., 2023).

Optical coherence tomography can be used to diagnose optic disc drusen (ODD), they are calcified deposits that can cause visual field defects and other complications. Teixeira et al. found that ODD appear as hyporeflective spheroidal elements located in front of the lamina cribrosa, fully or

partially surrounded by a hyperreflective border (Teixeira et al., 2020). Danišová and Fric compared two methods of ODD imaging in paediatric patients and found that swept-source OCT is a promising new "gold standard" in ODD diagnostics (Danišová and Fric, 2021). OCT angiography can detect significant peripapillary microvascular changes in patients with ODD, which correlate with the reduction of retinal nerve fibre layer (RNFL) and ganglion cell complex (GCC) (Engelke et al., 2020). En face multimodal imaging features, such as OCT or colour fundus photography, may provide complementary information about optic disc drusen. OCT can visualize the internal structure of drusen and its impact on the surrounding tissue layers, while colour fundus photography can provide an overview of the optic disc appearance. In study by Yan et al was found that green-light fundus autofluorescence (FAF) had the highest sensitivity in detecting optic disc drusen. FAF imaging captures the natural autofluorescence emitted by various ocular structures, including drusen (Yan et al., 2021).

Optic disc oedema (ODE) is a condition where the optic nerve head appears swollen due to fluid accumulation and optical coherence tomography (OCT) can help differentiate ODE from other conditions such as for example optic nerve head drusen (ONHD/ODD). Some studies have shown that OCT can differentiate ODE from ODD by measuring the thickness of the retinal nerve fibre layer and subretinal hyporeflective space (Johnson et al., 2009, Lee et al., 2011). Swelling of the optic nerve head due to increased pressure in the brain is called papilledema and studies have shown that OCT can provide additional information for detecting papilledema, including parameters such as peripapillary capillary density, peripapillary retinal nerve fibre layer thickness, total retinal thickness, optic nerve head volume, minimum rim width, and Bruch's membrane opening height. These parameters can help differentiate between papilledema and pseudopapilledema, and can also provide a continuous scale of papilledema severity (Jivraj et al., 2021, Pardon et al., 2019, Bassi and Mohana, 2014, Fard et al., 2019). Studies have shown that OCT measurements are influenced by optic disc oedema (ODE) caused by inflammatory optic neuropathies or retinal vein occlusions and show significantly greater thickness values in those patients than in controls (Menke et al., 2005). There is evidence to suggest that OCT can be used to monitor Anterior Ischemic Optic Neuropathy (AION). In AION, OCT may reveal optic disc swelling or oedema, which can be quantified by measuring the thickness of the retinal nerve fibre layer (RNFL) using OCT scans. Several studies have investigated the use of optical coherence tomography (OCT) in monitoring nonarteritic anterior ischemic optic neuropathy (NAION). Contreras et al. found that OCT can diagnose optic disc oedema and monitor retinal nerve fibre layer (RNFL) loss over time, which is correlated with visual function (Contreras et al., 2007) and study by Sharma et al. used OCT angiography (OCT-A) to reveal a global and sectorial reduction of retinal and choroidal peripapillary flow densities at the acute stage of NAION, followed by partial subsequent spontaneous recovery (Sharma et al., 2017).

OCT can be a useful tool in evaluating in retrobulbar optic neuritis (RON), but it should not be used as the sole diagnostic tool. It is important to consider other clinical findings, such as visual acuity and visual evoked potentials, in conjunction with OCT findings. Studies have shown that OCT can identify retinal nerve fibre layer thickness reduction in previous RON and nonarteritic ischemic optic neuropathy (Giambene et al., 2017). Additionally, it can detect generalized RNFL thinning in the affected eye at 3 months after a first episode of acute optic neuritis, most significantly in the temporal quadrant and average thickness (Yau et al., 2013). Also, it can differentiate acute optic neuritis (ON) in myelin oligodendrocyte glycoprotein antibody-associated disorder (MOGAD) from multiple sclerosis (MS) by measuring peripapillary RNFL thickness (Chen et al., 2022).

Nowadays intraocular tumours are treated with radiotherapy (proton beam irradiation, Leksell gamma knife, stereotactic irradiation on linear accelerator) and OCT can be useful to find post radiation changes in the retina, in the macula region but also in the optic disc area (Furdová A, 2014, Furdová et al., 2016, Furdová et al., 2018a). Orbital tumour manifestation can be also monitored on OCT findings (Furdová et al., 2018b).

CONCLUSION

OCT has significantly advanced our understanding of optic disc anomalies by providing high-resolution cross-sectional images of the optic nerve head. Its ability to visualize and quantify structural changes within the optic disc aids in accurate diagnosis, monitoring disease progression, and assessing treatment efficacy. It is however important to interpret OCT findings in the context of the patient's clinical history and other diagnostic tests, as OCT findings alone may not be sufficient to make a diagnosis or guide treatment decisions.

DECLARATIONS

Conflict of interest: The authors declare no conflict of interest.

Competing interests: The authors declare no competing interests.

Consent for publication: The authors consent the publication of this work.

Data availability: The datasets generated during and/or analysed during the current review are available from in PubMed database.

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Rabies

Besnota

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ABSTRACT

Introduction: Rabies is one of the oldest known infectious diseases and is considered to be presents spread remains an actual zoonosis. Rabies is a disease caused by a neurotropicby a virus of the genus Lyssavirus (family Rhabdoviridae, order Mononegavirales), which is transmitted toall mammals. The aim of our article is to provide a comprehensive overview of the epidemiology, transmission, pathogenesis and advances in diagnostics, about vaccination, therapeutic options, prevention and control strategy.

Core of Work: There are many variants (or strains) of the virus, each of which has a specificthe host. All variants are zoonotic. Carnivores and bats are the main hosts reservoir. Most cases of human rabies are caused by dog bites. Regulation the occurrence of rabies in domesticated and free-living animals is based on their vaccination, which the risk of rabies in humans decreases.

Conclusion: For the first time, World Health Organization, World Organization for Animal Health, Food and Agriculture Organization of the United Nations and Global Alliance for Rabies Control are united and determined to reach the strategic plan to prevent human death from dog-transmitted rabies by 2030.

Keywords: rabies, epidemiology, pathogenesis, diagnosis, infection disease control

ABSTRAKT

Úvod: Besnota je jednou z najstarších známych infekčných chorôb a v súčasnosti sa považuje za vážnu zoonozu. Besnota je ochorenie spôsobené neurotropným vírusom z rodu Lyssvirus (čeľaď Rhabdoviridae, rad Mononegavirales), ktorý sa prenáša na všetky cicavce. Cieľom tohto článku je poskytnúť ucelený prehľad o epidemiológii, prenose, patogenéze, pokrokoch v diagnostike, očkovaní, terapeutických možnostiach, stratégii prevencie a kontroly.

Jadro práce: Všetky varianty vírusov sú zoonotické. Hlavnými hostiteľmi sú šelmy a netopiere. Väčšina prípadov ľudskej besnoty je spôsobení uhryznutím psa. Regulácia výskytu besnoty u domestikovaných a voľne žijúcich zvierat je založená na očkovaní, čím sa riziko besnoty u ľudí znižuje.

Záver: Svetová zdravotnícka organizácia, Svetová organizácia pre zdravie zvierat, Organizácia spojených národov pre výživu a poľnohospodárstvo a Globálna aliancia na kontrolu besnoty sa prvýkrát zjednotili a odhodlali dosiatnuť strategický plán na zabránenie ľudskej smrti v dôsledku besnoty prenášanej psom do roku 2030.

Klúčové slová: besnota, epidemiológia, patogenéza, diagnóza, kontrola

INTRODUCTION

World Health Organization (WHO), United Nations Food and Agriculture Organizationand Agriculture (FAO), the World Organization for Animal Health (OIE) and the Global Alliance for Rabies Control (GARC) created the "United Against Rabies" platform in 2015 ("United Against Rabies"), which coordinates worldwide efforts to achieve the global goal "Zero by 30: The Global Strategic Plan to Prevent Human Death from Dog-Transmitted Rabies by 2030"). Rabies Elimination Strategy "Zero by 30" is based on a pragmatic approach of three stages that have set goals (1st stage: beginning of 2018 — 2020; Stage 2: Scale Up, Increase in Effort 1921 — 2025 and Stage 3: Completion, 2026 — 2030) — to gradually eliminate the death of people from rabies. This is the first time that the main playersin the field of human health and animal health have joined their efforts in a common strategy for the elimination of rabies within the "One Health" framework, that is, knowledge, human capacities(public-private cooperation), tools and technologies. It can prevent deaths in human through increasing people's awareness, preventive vaccination of dogs (elimination of the sourceinfections) and effective post-exposure (life-saving) therapy for humans. Therefore, rabies belongs to humanpreventable diseases (Anonymus, s. a.).

In the publication Šimková et al. (2022), we dealt with historical connections of recent effortd, focusing the beginnings of rabies research (L. Pasteur) and the preparation of an attenuated strain (virus fixe), the first serum and vaccination against rabies, efforts to combat rabies in animals in the former Czechoslovakia (Czechoslovak republic) in the periods before the establishment of the republic (1906 — 1910) and after the establishment of the republic (1919 — 1939, 1947 — 2001).

The purpose of this work is to analyse the issue of rabiesfocusing pathogenesis and clinicalsymptoms in animals, laboratory diagnosis and regulatory measures, and elaborate a holistic view of this zoonosis in the concept of "One Health" — international cooperation to achieve optimal health of people, animals and the environment.

ETIOLOGY

Rabies is an acute neurological disease caused by lyssavirus rabies (virus RABV; classical rabies virus; genus Lyssavirus, family Rhabdoviridae, order Mononegavirales), which affects the central nervous system of all terrestrial warm-blooded animals and humans, andwith a fatal course (fatal encephalomyelitis) in all (up to 100 %) individualswith clinical symptoms of the disease.

The dominant reservoir of rabies in humans is the dog and the fox, especially in those countrieswhere rabies in dogs is not under control. Historically, the rabies is associated with hematophagous bats (*Desmondus* sp., especially the vampire — *Desmodus rotundus*) in the Caribbeanarea, in Central and South America (Shipley et al., 2019).

RABV infection in human causes multiple symptoms, behavioral changes, and death. Hydrophobiais a specific symptom of rabies in human. The infection is transmitted by biting (the virus is presentin saliva) from wild and domestic animals. The most serious source (reservoir) of RABV are dogs, which cause a significant problem for people, especially in those countries where dog rabies is not underofficial control and where they are slaughtered for human consumption (Garba et al., 2013; Ajoke et al., 2014).

The genus *Lyssavirus* contains the following species: *Aravan lyssavirus, Australian bat lyssavirus, Bokeloh bat lyssavirus, Duvenhage lyssavirus, European bat 1 lyssavirus, European bat 2lyssavirus, Gannoruwa bat lyssavirus, Ikoma lyssavirus, Irkut lyssavirus, Khujand lyssavirus, Lagos bat lyssavirus, Lleida bat lyssavirus, Mokola lyssavirus, Rabies lyssavirus, Shimoni batlyssavirus, Taiwan bat lyssavirus, West Caucasian bat lyssavirus* (Anonymous, 2019).

Phylogenetic groups of the genus *Lyssavirus*, countries of origin and common reservoir species mammals are summarized in Table 1 (Fooks et al., 2017; Shipley et al., 2019).

Tab. 1: Genus Lyssavirus (Fooks et al., 2017; Shipley et al., 2019)

The rabies virus (Rabies lyssavirus — RABV) belongs to genotype 1 (formerly serotype 1, serologically distinct from other lyssaviruses in this genus). The primary host is carnivores (Carnivora) and bats (Chiroptera). Genetic typing has replaced traditional serological typingmethods of studying the rabies virus and enabled the taxonomic specification of the genus Lyssavirus; variantsRABV, known as "rabies-related" or "non-rabies" lyssaviruses, non-RABV "non-rabies" lyssaviruses (Wunner, 2009).

VIRUS STRUCTURE

RABV and non-RABV lyssaviruses belong to the group of RNA viruses. The RNA genome contains 5 genes that code for 5 structural proteins: N — nucleoprotein (450 amino acid), P — phosphoprotein (297 amino acids), M — matrix protein (202 amino acid), G — glycoprotein (505 amino acids) and L — RNA transcriptase/polymeraseor a large protein (2142 amino acids). These proteins (RABV and non-RABV) number 67 to 74 % of virion weight. RABV particles — virions have a bacillary or projectile form, with one rounded end and the other flattened (planar/flat) end. An average length of an infectious virion is 180 nm (130 — 250 nm) and the average width is 75 nm (60 — 110 nm) (Wunner, 2009).

Table 1: The Lyssavirus genus (Fooks et al. 2017; Shipley et al. 2019)

Species	Virus	Countries of virus isolation	Most common reservoir based on virus detection
Phylogrup I			
Rabies lyssavirus	Rabies virus (RABV)	Global	All mammals
		North and South America	Bats: *Eptesicus fuscus, Desmodus rotundus, Lasionycteris noctivagens, Perimyotis subflavus, Tadarida brasiliensis*
Aravan lyssavirus	Aravan virus (ARAV)	Kyrgyzstan	Bats: *Myotis blythii*
Australian bat lyssavirus	Australian bat lyssavirus (ABLV)	Australia	Bats: *Pteropus alecto, Saccolaimus flaviventris*
Bokeloh bat lyssavirus	Bokeloh bat lyssavirus (BBLV)	France and Germany	Bats: *Myotis nattereri*
Duvanhage lyssavirus	Duvanhage virus (DUVV)	Kenya and South Africa	Bats: *Miniopterus sp., Nycteris thebaica*
European bat 1 lyssavirus	European bat lyssavirus 1 (EBLV-1)	Belgium, Denmark, France, Germany, the Netherlands, Poland, Russian Federation, Slovakia, Spain and Ukraine	Bats: *Eptesicus serotinus*
European bat 2 lyssavirus	European bat lyssavirus 2 (EBLV-2)	Denmark, Finland, France, Germany, the Netherlands, Norway. Switzerland and United Kingdom	Bats: *Myotis daubentonii*
Gannoruwa bat lyssavirus	Gannoruwa bat lyssavirus (GBLV)	Sri Lanka	Bats: *Pteropus medius*
Irkut lyssavirus	Irkut virus ((IKKVP)	China and Russian Federation	Bats: *Murina leucogaster*
Khujand lyssavirus	Khujand virus (KHUB)	Tajikistan	Bats: *Myotis mystacinus*
Phylogroup II			
Lagos bat lyssavirus	Lagos bat virus (LBV)	Central African Republic, Ethiopia, France, Ghana, Nigeria, Senegal South Africa and Zimbabwe	Bats: *Eidolon helvum, Rousettus aegyptiacus, Micropteropus pusillus, Epomops buettikoferi, Nycteris gambiensis, Epomophorus wahlbergi*
Mokola lyssavirus	Mokola virus (MOKV)	Cameroon, Central Africa Republic, Ethiopia, Nigeria, South Africa and Zimbabwe	Rodents and domestic animals
Shimoni bat lyssavirus	Shimoni bat virus (SHIBV)	Kenya	Bats: *Hipposideros commersoni*
Phylogroup III			
Ikoma lyssavirus	Ikoma lyssavirus (IKOV)	Tanzania	African civet *(Civettictis civetta)*
Llieda bat lyssavirus	Llieda bat lyssvisus (LLEBV)	Spain, France	Bats: *Miniopterus schreibersii*
West Caucasian bat lyssavirus	West Caucasian bat virus (WCBV)	Russian Federation, Kenya	Bats: *Miniopterus schreibersii*

Epizootological cycles, forms, variants, geographical distribution, main reservoirs clarified the types and etiology of rabies and other rabies-like lyssavirus diseases (Švrček et al., 2007). From an epizootological point of view, it is recognized: 1. chiropteric cycle (applies tohematophagous, insectivorous, herbivorous, fructiform bats) and 2. terrestrial cycle (sylvatic, urban, mixed and African forms of rabies; carnivores — small mammals).

HOST SPECIES

The following wild animal host species have been found to harbor rabies viruses (Stuchin et al., 2018):

Acinonyx jubatus (slender cheetah, order Carnivora, family Felidae), — *Alces alces* (moosewetland, Cetartiodactyla, Cervidae), — *Alopex lagopus* (Arctic fox, Carnivora, Canidae), — *Antrozous pallidus* (mantle bat, Chiroptera, Vespertilionidae), –*Artibeus cinereus* (Gervais' fruit bat, Chiroptera, Phyllostomidae), — Artibeus fimbriatus (round fruit bat, Chiroptera Phyllostomidae), — *Artibeus jamaicensis* (fruit-eating leaf beetle/Mexican bat, Chiroptera, Phyllostomidae), — *Artibeus lituratus* (largefruit bat, Chiroptera, Phyllostomidae), — *Artibeus phaeotis* (dwarf fruit bat, Chiroptera, Phyllostomidae), — *Artibeus planirostris* (South American species of bat, fruit bat with a flat surface, Chiroptera, Phyllostomidae), — *Atilax paludinosus* (washmarsh, Carnivora, Herpestidae), *Callithrix jacchus* (white bearded marmoset, Primates, Cebidae), — *Canis adustus* (jackalstriped, Carnivora, Canidae), — *Canis aureus* (golden jackal, Carnivora, Canidae), — *Canis latrans* (prairie coyote, Carnivora, Canidae), — *Canis lupus* (predatory wolf, Carnivora, Canidae), — *Canis mesomelas* (dark-backed jackal, Carnivora, Canidae), — *Canis simensis* (wolf, Ethiopian, Carnivora, Canidae), — *Capreolus capreolus* (forest roe deer, Cetartiodactyla, Cervidae), — *Caracal caracal* (lynx caracal, Carnivora, Felidae), — *Carollia perspicillata* (Seba short-nosed bat, Chiroptera, Phyllostomidae), — *Castor fiber* (European beaver, Rodentia, Castoridae), — *Cerdocyon thous* (maikong/crab-eating fox, Carnivora, Canidae), — *Chrysocyon brachyurus* (maned wolf, Carnivora, Canidae), — *Civettictis civetta* (African civet, Carnivora, Viverridae), — *Corynorhinus townsendii* (Townsed's bat, Chiroptera, Vespertilionidae), — *Crocuta crocuta* (spotted hyena, Carnivora, Hyaenidae),– *Cuon alpinus* (dhole, red dog, Carnivora, Canidae), — *Cynictis penicillata* (mongoose fox, Carnivora, Herpestidae), — *Cynomops abrasus* (South American species of bat/cinnamon dogfaced bat, Chiroptera, Molossidae), — *Cynomops planirostris* (southern bat, Chiroptera, Molossidae), — *Cynopterus brachyotis* (Lesser short-nosed fruit bat, Chiroptera, Pteropodidae), *Desmodus rotundus* (red desmod/large vampire, Chiroptera, Phyllostomidae), — *Diaemus youngi* (white-winged bat, Chiroptera, Phyllostomidae), — Diclidurus albus (white/northern bat, Chiroptera, Emballonuridae), — *Diphylla ecaudata* (hairy-legged vampire bat, Chiroptera, Phyllostomidae), *Elephas maximus* (Asian elephant, Proboscidea, Elephantidae), — *Eptesicus brasiliensis* (Brazilian brown bat, Chiroptera, Vespertilionidae), — *Eptesicus diminutus* (serotine, Chiroptera, Vespertilionidae), — *Eptesicus furinalis* (Argentine brown bat, Chiroptera, Vespertilionidae), — *Eptesicus fuscus* (brown bat, Chiroptera, Vespertilionidae), — *Eptesicus serotinus* (late nightingale/late bat, Chiroptera, Vespertilionidae), — *Eptesicus somalicus* (Somali serotine, Chiroptera, Vespertilionidae), — *Erethizon dorsatum* (Canada urzon, Rodentia, Erethizontidae), — *Euderma maculatum* (spotted bat, Chiroptera, Vespertilionidae), — *Eumops auripendulus* (black bat, Chiroptera, Molossidae), — *Eumops glaucinus* (Wagner's bat/chestnut tadarida, Chiroptera, Molossidae), — *Eumops patagonicus* (Patagonian bat, Chiroptera, Molossidae), — *Eumops perotis* (batwestern mastiff bat, Chiroptera, Molossidae), *Felis lybica* (yellow cat, African wild cat, Carnivora, Felidae), — *Felis manul* (steppe cat/manul, Carnivora, Felidae), — *Felis nigripes* (black-footed cat, Carnivora, Felidae), — Felis silvestris (wild cat, Carnivora, Felidae), *Galerella sanguinea* (red gorse, Carnivora, Herpestidae), — *Genetta ghetta* (Civet, Carnivora, Viverridae), — *Giraffa camelopardalis* (giraffe, Cetartiodactyla, Giraffidae), — *Glaucomys volans* (asapan flycatcher, Rodentia, Sciuridae), — *Glossophaga longirostris* (Miller's long-tongued bat, Chiroptera, Phyllostomidae), — *Glossophaga morenoi* (western long-tongued bat, Chiroptera, Phyllostomidae), — *Glossophaga soricina* (long-tongued vampire, Chiroptera, Phyllostomidae), *Herpestes ichneumon* (Egyptian mongoose, Carnivora, Herpestidae), — *Herpestes javanicus* (javan mongoose, Carnivora Herpestidae), — *Herpestes sanguineus* (common slender mongoose, Carnivora, Herpestidae), — *Histiotus macrotus* (big-eared brown bat, Chiroptera, Vespertilionidae), — *Histiotus montanus* (small big-eared, brown batChiroptera, Vespertilionidae), — *Histiotus velatus* (tropical brown bat/tropical big-earedbrown bat, Chiroptera, Vespertilionidae), — *Hyaena hyaena* (banded hyena, Carnivora, Hyaenidae), — *Hydrochoerus chydrochaeris* (Rodentia, Caviidae), — *Hylobates lar* (Primates, Hylobatidae), *Ichneumia albicauda* (mongoose abuvudan/promyka abuvudan, Carnivora, Herpestidae), — *Ictonyx striatus* (mustelidae, Carnivora, Mustelidae), *Lasionycteris noctivagans* (silver-haired bat, Chiroptera, Vespertilionidae), — *Lasiurus blossevillii* (western red bat or southern reddesert red bat, Chiroptera, Vespertilionidae), — *Lasiurus borealis* (eastern batred, eastern red bat, Chiroptera, Vespertilionidae), — *Lasiurus cinereus* (batspiny/hoary bat, Chiroptera, Vespertilionidae), — *Lasiurus ega* (southern yellow bat, yellow bat, Chiroptera, Vespertilionidae), — *Lasiurus egregius* (big red bat, Chiroptera, Vespertilionidae), — *Lasiurus intermedius* (northern yellow bat, Chiroptera, Vespertilionidae), — *Lasiurus xanthinus* (bat/western yellow bat, Chiroptera, Vespertilionidae), — *Leptonycteris curasoae* (forest glossophage/southern long-nosed bat, Chiroptera,

Phyllostomidae), — *Leptonycteris nivalis* (Chiroptera, Phyllostomidae), — *Lepus europaeus* (Lagomorpha, Leporidae), — *Lontra canadensis* (North American otter, Carnivora, Mustelidae), — *Lycalopex griseus* (Pampas fox, Carnivora, Canidae), — *Lycaon pictus* (doghyena, Carnivora, Canidae), — *Lynx lynx* (lynx, Carnivora, Felidae), — *Lynx rufus* (lynx, Carnivora, Felidae), *Macrotus californicus* (Californian bat/leaf bat, Chiroptera, Phyllostomidae), — *Marmota monax* (wood marmot, Rodentia, Sciuridae), — *Martes foina* (rock marten, Carnivora, Mustelidae), — *Martes martes* (marten, Carnivora, Mustelidae), — *Martes pennant* (Carnivora, Mustelidae), — *Meles leucurus* (Aisan badger/ sand badger, Carnivora, Mustelidae), — *Meles meles* (european badger, Carnivora, Mustelidae), — *Mellivora capensis* (honez badger/ratel, Carnivora, Mustelidae), — *Melogale moschata* (grey badger/Chinese ferret-badger, Carnivora, Mustelidae), — *Mephitis mephitis* (striped skunk, Carnivora, Mephitidae), — *Micronycteris megalotis* (little big-eared bat, Chiroptera, Phyllostomidae), — *Molossops neglectus* (bat/rufous dog-faced bat, Chiroptera, Molossidae), — *Molossus molossus* (bat/ tadarida Pallasova, Chiroptera, Molossidae), — *Molossus rufus* (bat/black mastiff bat, Chiroptera, Molossidae), — *Mormoops megalophylla* (ghost-faced bat, Chiroptera, Mormoopidae), — *Mungos mungo* (banded mongoose, Carnivora, Herpestidae), — *Mus mutulus* (house mouse, Rodentia, Muridae), — *Mustela putorius* (black polecat, Carnivora, Mustelidae), — *Myocastor coypus* (river nutria, Rodentia, Myocastoridae), — *Myotis albescens* (bat/ silver-tipped myotis, Chiroptera, Vespertilionidae), — *Myotis austroriparius* (southeastern myotis, Chiroptera, Vespertilionidae), — *Myotis californicus* (bat/California myotis, Chiroptera, Vespertilionidae), — *Myotis chiloensis* (bat, Chilean myotis, Chiroptera, Vespertilionidae), –*Myotis daubentonii* (water bat/Daubenton's bat, Chiroptera, Vespertilionidae), — *Myotis evotis* (bat, long-eared myotis, Chiroptera, Vespertilionidae), — *Myotis grisescens* (batgray bat, Chiroptera, Vespertilionidae), — *Myotis keenii* (Keen's bat, Chiroptera, Vespertilionidae), — *Myotis leibii* (eastern small-footed bat, Chiroptera, Vespertilionidae), — *Myotis levis* (bat, Chiroptera, Vespertilionidae), — *Myotis lucifugus* (bat, little brown bat, Chiroptera, Vespertilionidae), — *Myotis nattereri* (batciliate, Natterer's bat, Chiroptera, Vespertilionidae), — *Myotis nigricans* (dark bat, Chiroptera, Vespertilionidae), — *Myotis riparius* (bat/riparian myotis, Chiroptera, Vespertilionidae), — *Myotis septentrionalis* (bat, northern long-eared bat, Chiroptera, Vespertilionidae), — *Myotis velifer* (Chiroptera, Vespertilionidae), — *Myotis volans* (Chiroptera, Vespertilionidae), — *Myotis yumanensis* (Chiroptera Vespertilionidae), *Nasua nasua* (red nose, Carnivora, Procyonidae), — *Neotoma floridana* (rat, eastern woodrat, Rodentia, Cricetidae), — *Nyctalus noctula* (bat/ rusty morning, Chiroptera, Vespertilionidae), — *Nyctereutes procyonoides* (bear dog, Carnivora, Canidae), — *Nycticeius humeralis* (evening bat, Chiroptera, Vespertilionidae), — *Nyctinomops laticaudatus* (bat, broad-eared bat or broad-tailed bat, Chiroptera, Molossidae), — *Nyctinomops macrotis* (big free-tailed bat, Chiroptera, Molossidae), *Ondatra zibethicus* (musk muskrat, Rodentia, Cricetidae), — *Oryx gazella* (oryxSouth African, Cetartiodactyla, Bovidae), — *Otocyon megalotis* (bat-eared fox, Carnivora, Canidae), *Panthera leo* (desert lion, Carnivora, Felidae), — *Panthera pardus* (spotted leopard, Carnivora, Felidae), — *Papio ursinus* (chakma baboon, Primates, Cercopithecidae), — *Paracynictis selousi* (Selous mongoosis, Carnivora, Herpestidae), — *Phyllostomus hastatus* (bat, large leaf fly, Chiroptera, Phyllostomidae), — *Pipistrellus hesperus* (batcanyon bat, Chiroptera, Vespertilionidae), — *Pipistrellus kuhlii* (bat/southern bat, Chiroptera, Vespertilionidae), — *Pipistrellus subflavus* (tricolored bat, Chiroptera, Vespertilionidae), — *Plecotus auritus* (bat, light-eared bat, Chiroptera, Vespertilionidae), — *Pongo pygmaeus* (Bornean orangutan, Primates, Hominidae), — *Procavia capensis* (South African daman, Hyracoidea, Procaviidae), — *Procyon lotor* (purebred bear, Carnivora, Procyonidae), — *Proteles cristata* (Civet hyena, Carnivora Hyaenidae), — *Pseudalopex vetulus* (hoary fox, hoary zorro, Carnivora, Canidae), — *Pteronotus davyi* (bald bat, Chiroptera, Mormoopidae), — *Pteronotus parnellii* (Parnell's bat, Chiroptera, Mormoopidae), — *Pteropus poliocephalus* (Australian bat, Chiroptera, Pteropodidae), — *Rangifer tarandus* (reindeer/caribou, Cetartiodactyla, Cervidae), — *Rhinolophus ferrumequinum* (bat/horseshoe bat, Chiroptera, Rhinolophidae), — *Rhinolophus pusillus* (horseshoe bat, Least horseshoe bat, Chiroptera, Rhinolophidae), — *Rousettus leschenaultia* (water bat, Leschenault's rouseta, Chiroptera, Pteropodidae), — *Saimiri sciureus* (saimiri squirrel-like, Primates, Cebidae), — *Sciurus carolinensis* (gray squirrel, Rodentia, Sciuridae), — *Sciurus niger* (fox squirrel, Rodentia, Sciuridae), — *Spermophilus tridecemlineatus* (banded ground squirrel, Rodentia, Sciuridae), — *Spermophilus undulatus* (long-tailed squirrel or Eversmann's squirrel, Rodentia, Sciuridae), — *Spermophilus* variegatus (rock squirrel, Rodentia, Sciuridae), — *Sturnira lilium* (smallyellow-shouldered bat, Chiroptera, Phyllostomidae), — *Suncus murinus* (Asian domesticshrew, Eulipotyphla, Soricidae), — *Suricata suricatta* (wavy meerkat, Carnivora, Herpestidae), — *Tadarida brasiliensis* (Guano tadarida, Chiroptera, Molossidae), — *Tamias stratus* (eastern chipmunk, Rodentia, Sciuridae), — *Taurotragus oryx* (moose antelope, Cetartiodactyla, Bovidae), — *Tragelaphus strepsiceros* (great kudu, Cetartiodactyla, Bovidae), — *Urocyon cinereoargenteus* (brown fox, Urocyon, Carnivora, Canidae), — *Uroderma bilobatum* (the tent bat, Chiroptera, Phyllostomidae), — *Vespertilio murinus* (the batvariegated, Chiroptera, Vespertilionidae), — *Vulpes chama* (chama fox, Cape fox, Carnivora, Canidae), — *Vulpes corsac* (foxkorzak, Carnivora, Canidae), — *Vulpes velox* (swift fox, Carnivora, Canidae), — *Vulpes vulpes* (foxrust, Carnivora, Canidae) and — *Xerus inauris* (Cape squirrel, Rodentia, Sciuridae).

Host species of domesticated animals:

- *Bos taurus* (domestic tur, Cetartiodactyla, Bovidae), — *Camelus dromedarius* (one-humped camel, Cetartiodactyla, Camelidae), — *Canis familiaris* (domestic dog, Carnivora, Canidae), — *Capra hircus* (goat domestic donkey, Cetartiodactyla, Bovidae), — *Equus asinus* (domestic donkey, Perissodactyla, Equidae), — *Equus caballus* (domestic horse, Perissodactyla, Equidae), — *Felis catus* (domestic cat, Carnivora, Felidae), — *Ovis aries* (domestic sheep, Cetartiodactyla, Bovidae) and — Sus scrofa (wild boar, Cetartiodactyla, Suidae).

The host species of rabies include *Homo sapiens* (reasonable man, Primates, Hominidae).

GEOGRAPHICAL DISTRIBUTION

The rabies virus is widespread throughout the world, with the exception of some islands. Som ecountries, e.g. England, Ireland, Sweden, Norway, Iceland, Japan, Australia, New Zealand, Singapore, and some Pacific and Indonesian islands have been free of rabies for several years, as a result of targeted surveillance and regulatory measures during importation.

Current categorization of countries according to the risk of rabies transmission to human from terrestrialanimals is not stable and can be subject of change. The Guidance "Rabies risks in terrestrial animals bycountry" is sorting the countries as following (Anonymous, 2020):

High risk: Afghanistan, Albania, Algeria, Angola, Argentina, Armenia, Andaman and Nicobar Islands, Azerbaijan, Bali, Belarus, Belize, Benin, Bhutan, Bolivia, Borneo, Bosnia and Herzegovina, Botswana, Brazil, Burkina Faso, (Burma) Myanmar, Burundi, Chad, Montenegro, China, Dominican Republic, Djibouti, Egypt, Ecuador, Eritrea, Ethiopia, El Salvador, Philippines, French Guiana, Gabon, Gambia, Ghana, Greenland, Georgia, Guatemala, Guinea, Guinea-Bissau, Guyana, Haiti, Honduras, India, Indonesia, Iran, Iraq, Israel, South Africa, Yemen, Jordan, Cambodia, Cameroon, Kazakhstan, Kenya, Colombia, Comoros, Congo (Democratic Republic of the Congo), Korea (North, South), Kosovo, Costa Rica, Cuba, Kyrgyzstan, Laos, Lesotho, Lebanon, Liberia, Libya, Lithuania, Macau (China), Macedonia, Madagascar, Malawi, Malaysia, Mali, Margarita (an island in the Caribbean Sea), Morocco, Mauritania, Melilla (a Spanish enclave in North Africa), Mexico, Myanmar, Moldova, Mongolia, Mozambique, Namibia, Nepal, Niger, Nigeria, Nicaragua, Oman, Pakistan, Palestine, Panama, Paraguay, Peru, Ivory Coast, Poland, Puerto Rico, Equatorial Guinea, Romania, Russian Federation, Rwanda, Saudi Arabia, Senegal, Serbia, Sierra Leone, Somalia, Sri Lanka, Central African Republic, Sudan, Suriname, Svalbard (Svalbard and Jan Mayen, Norway), Swaziland, Syria, Tajikistan, Tanzania, Thailand, Tibet, Togo, Tunisia, Turkey, Turkmenistan, Uganda, Ukraine, Uruguay, Uzbekistan, Venezuela, Vietnam, Zambia, Zanzibar, Western Sahara and Zimbabwe.

Low risk: Bahrain, Brunei/State of Brunei Darussalam, Bulgaria (high in foxesrisk), Czech Republic (within 50 km of the Poland/Slovakia border, high risk for foxes), Chile, Croatia (high risk for foxes), Estonia, Grenada (an island state in the Lesser Antilles), Hong Kong (China), Canada (in foxes, skunks/Mephitidae and procyon lotoris high risk), Kuwait, Lithuania (high risk for foxes), Hungary (high risk for foxes) St. Tomas and Princes Island, Slovak Republic, Slovenia, Taiwan, East Timor, Trinidadand Tobago, United Arab Emirates, USA (low risk; high risk in foxes, skunksand chastity bears).

No risk: American Samoa, Andorra, Anguilla, Antarctica, Antigua and Barbuda, Aruba, Acension, Australia, Azores, Bahamas, Balearic Islands, Barbados, Belgium, Bermuda, BritishVirgin Islands, Cabrera, Cook Islands, Cyprus, Denmark, Dominica, Faroe Islands, Falkland Islands, Fiji, Finland, Formentera (belongs to the Balearic Islands, the island belongs toto Spain), France, French Guiana, French Polynesia, Galapagos, Gibraltar, Greece, Guadeloupe, Guam (Mariana Islands), Hawaii, Netherlands, Netherlands Antilles, Ibiza, Iceland, Ireland, Isle of Man, Jamaica, Japan, Kiribati, Cape Verde, Canary Islands, Cayman Islands, Cocos Islands, Corsica, Madeira, Majorca, Maldives, Malta, Martinique, Mauritius, Mayotte, Menorca, Micronesia, Monaco, Montserrat, Nauru, Niue, Norfolk, Northern Mariana Islands, Channel Islands, Norway (mainland onlypart), New Caledonia, New Zealand, Corsica, Liechtenstein, Luxembourg, Germany, Palau, Virgin Islands, Papua New Guinea, Pitcairn Islands (Pitcairn, Henderson, Ducie and Oenoin the Pacific Ocean), Ivory Coast, Portugal, Austria, Reunion, Samoa, San Marino, United Kingdom (low risk to bats), Solomon Islands, Spain (mainlandand Balearic and Canary Islands), Seychelles, Singapore, St. Helena, St. Kitts and Nevis, St. Lucia, Saint Martin, Saint Pierre and Miquelon, Saint Vincent and the Grenadines, Solomon Islands, Sweden, Italy, Tahiti, Tokelau, Tonga, Turks and Caicos (Islands), Tuvalu (Island), Vanauta, Easter Island, Christmas Island, Wake Island, Wallis and Futuna (groupislands).

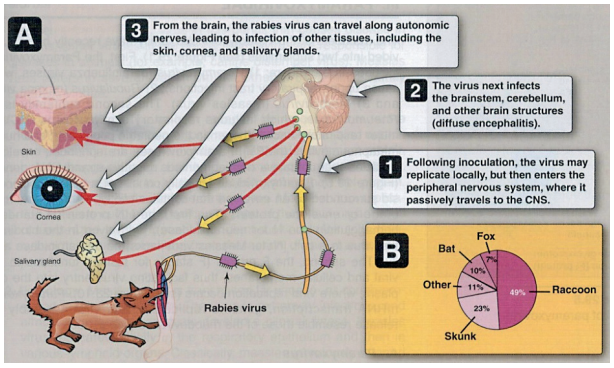
However, rabies or rabies-related lyssaviruses can occur in countries that are declared rabies-free.

TRANSMISSION

Rabies virus (RABV) is a highly neurotropic pathogen. Schematic representation rabies pathogenesis in the Fig. 1 (Cornelissen et al., 2013). The transfer is generally conditionalby penetrating the saliva of a rabid animal into the tissue of a healthy susceptible species, usually through a woundon the skin caused by a bite, scratch or through a damaged mucous membrane.

Using G-protein recipes, the virus hits receptive target cells (myocytes, locallysensory and motor neurons) and also reproduces in muscle cells and macrophages (Tsianget al., 1986). Infection of the salivary glands by a virus from the CNS is of fundamental importance for the viral cycleand the spread of disease. The amount (titer) of the virus in the salivary glands can often be higher thanin the brain. In some animal species, saliva can be infectious even before clinical signs of a CNS infection (Wunner, 2009).

Figure 1. Rabies pathogenesis (Coenelissen et al., 2013)



A. Schematic representation of pathogenesis of rabies infection.
B. Wildlife rabies in the United States.

After being bitten by a rabid animal, the infection spreads through saliva from the wound to susceptible muscles orskin cells on the side of the injury. Within a few days or months, the virus enters theperipheral nerves and is transported to the central nervous system (CNS) of the host. It startsits viral (three-phase) cycle in the infected cell, which has the following sequence: → adsorption, attachment, attachment to a receptive cell of the host; → endocytosis, penetration, embeddingof the virus into the plasma membrane; → unpacking, getting rid of the surface structure, looseningnucleocapsids-nucleocapsid protein; → transcription, transcription, → replication, → construction, assembly, → budding, and → release of the complex virus. The cycle repeats: → adsorption and → release) in host cells and spreads to other target cellsand extracellular space of the host (Wunner, 2009). However, viral cycle in the cell does not cause its death; it affects the symptomatology of the disease, which is conditioned by the disruption of the neurotransmitters'synthesis (Väyrynen, 2020).

RABV overcomes the neuromuscular junctions of peripheral nerves with the help of nicotineof acetylcholine receptors, which are located on the postsynaptic membrane of muscle cells and migrates to the central nervous system via fast retrograde axonal (axoplasmic) transport/current in peripheral motor and sensory nerves, thus, a process that is facilitated by the viral P-protein. The rate of axonal transport can be up to 3 mm/h (Tsiang, 1979; Kelly and Strick, 2000; Wunner, 2009).

From the CNS, the virus spreads centrifugally, using the same mechanism as it spreads to the brain. It affects the dorsal roots of the spinal ganglia and causes inflammatory processes in them, whichthey trigger pain, paraesthesia (itching, numbness, burning in different parts of the body). A virusaffects peripheral nerves; the result is weakness to paralysis, spreading further and reaching dorsallyspinal nerve roots. However, there are also other mechanisms of virus transport (e.g. cell-to-cell and synaptic connections). The ability of the virus to spread from the periphery to the CNS and from the CNS to the periphery is a characteristic feature(neuroinvasiveness) of RABV pathogenicity (Cornelissen et al., 2013).

The virus concentrates in nerve tissue and salivary glands. Saliva and cerebrospinal liquid are extremely risky. Premortal concentration (infectious dose) of the virusin human cerebrospinal fluid can be high (titer > 107-8 copies/ml; (Maier et al., 2010)). From the brain, the virus spreads to the salivary glands, from which it is irregularly secreted into saliva. From salivas, the virus is transmitted (usually by a bite) to other hosts (Cornelissen et al., 2013). Virus in saliva ortissue fluids of infected animals can be present in a few days (e.g. 3 to5 days for dogs), or in more than 18 days. An infection of the salivary glands is caused by the spread of a virusfrom the CNS, which is an important moment in the life cycle of the virus. Regarding the amount of viruspresent in saliva, i. e. with a dose of inoculum, the virus can enter the bloodstream directlyand cause systemic viremia.

RABV isolated from bats with superficial infection (into the epidermis) can rapidlyreproduce at lower body temperatures (34 °C), than the RABV virus isolated from dogs, whichnot related to its neuropathogenicity. Low temperature and reduced pH affect the spread of the virus frombats (Morimoto et al., 1996). Transdermal infection (superficial bites, lacerations, scratching) probably plays a significant role.

Other routes of transmission are intranasal (in sniffing animals) and oralinfection (in bats that live in high population density in caves), and alsotransplant infection via whole organs (cornea, kidneys, liver, heart, lungs), ortissue allotransplantation, especially in African and Asian countries. In donor organs, RABV is present not only on nerve endings, but also in epithelial and glandular cells (Maier et al., 2010; Lu et al., 2018).

The transmission of RABV infection between people (human-to-human transmission) is by bitingtheoretically possible, but unlikely. However, there is at least one report of a humaneencephalitis caused by human bites (Feder et al., 2012). Feces (leftoversundigested food), blood, urine and other body fluids are generally not considered infectious. Standard safety measures when treating sick people, when working in diagnosticsand research laboratories, during the

production of vaccines and during vaccination (live vaccines) can minimize risk of transmission of infection.

The speed of virus spread in nature varies, depending on animal species; it was qualified in foxes (Anderson et al., 1986), skunks (Kuzmina et al., 2013), polar bears (Biek et al., 2007) and bats (Lord et al., 1975). In general, the spreading speed varies from 10 km to40 km per year (Anderson et al., 1981). The disease is spread by the movement of animals, in epizootological casesand migration waves (Lord et al., 1975; Childs et al., 2000; Kuzmina et al., 2013; Benavides a kol. 2016)

INCUBATION PERIOD

The incubation period is quite long, generally unstable. The virus remains at the point of entry intoa receptive organism for a long time. The incubation period is related to the amount (infectious dose) of the virus, virulence (virus strain), inoculation site (the closer to the head — the shorter the incubation period; head versus limbs), depth of inoculation, nature of injury and pre-exposureimmunity. The incubation period for dogs, cats and ferrets is usually more than 10 days, 2 weeks to 3months; cattle 25 days to more than 5/6 months; sheep, goats and pigs 3 to 4 weeks. In humans, the period varies from a few days (generally 15) to several years; 1 to 3 months in most cases (Harnach, 1960; Nižnánsky et al., 1965; Vrtiak et al., 1965; Anonymus, 2010; Spickler, 2012; OIE, 2019) and in extreme cases up to 6 years (Greene and Rupprecht, 2006; Singh et al., 2017). In general, the incubation period after infection by bats is less than 6 months, although the symptom-free period can be longer in individual cases (Spickler, 2012).

CLINICAL SIGNS

All mammals are susceptible to infection and can transmit RABV. However, there is a significant oneinterspecies variability. The primary and global reservoir is carnivorous wild mammals (e.g. brown bear, Procyon lotor), foxes (Vulpes vulpes), skunks (Mephitis mephitis), bats (Chiroptera), animals living in large populations, especially domesticated, asthere are cats, cattle and especially dogs.

All animals show some non-specific symptoms of the disease, including timidity, agitation, restlessness, anorexia or increased appetite, vomiting, diarrhea, mild fever, pupil dilation, hyperactivity, rage and excessive salivation. Animals can searchsolitude. The first symptom after vaccination rabies is usually sparing (weakness) of the limb, towhich the vaccine was administered and neurological signs of rabies. Survival of sick animals is extremely rare.

The 3 stages (forms) of the disease can be identified (Nižnánsky et al., 1965; Vrtiak et al., 1986; Merck Veterinary Manual, 1998; Spickler, 2012; Jimenes Castro et al., 2014). Prodromal stage. After an incubation period (usually 2 to 3 months), the first appear clinical symptoms. This stage lasts 1 to 3 days and inludes behavioral changes such as aggression, loss of shyness, change of activity in the diurnal mode (night versus day), in wild animals loss of the fear of people, or change in appetite (eating foreign objects). Some animalsdie quickly without clinical symptoms. An excitable form of "furious rabies; mad dog syndrome" — manifests itself in aggression. It occurs in all kinds of sick animals. Death is caused as a result of progressiveparalysis. The paralytic form is characterized by progressive paralysis; manifests itself in paralysis of throat and masticatory muscles, often with significant salivation and inability to swallow food and saliva. A drop in the lower jaw is characteristic. Paralysis of the throat causes voice changes. Paralysis progresses quickly to all parts of the body. Ataxia, incoordination of movements is characteristicand ascending spinal paresis. The end of this form is quick death. In both forms of rabiesthere are species differences.

Not all (50 — 90 %) sick animals transmit the virus via bites, which is probably related with the amount of virus in the saliva, the species of animal and the strain of the virus. Excreting the virus with saliva precedes the clinical symptoms of the disease. Rarely in dogs and batsthe disease proceeds without symptoms (asymptomatic).

Surviving individual with clinical and neurological symptoms is rare. Today, likein the past, clinically manifested rabies was and is associated statistically (> 99.9 %) with the fatal course of the disease. The hope for a recovery is minimal. Veterinarians and doctors face a dilemma — euthanasia is the way out for a sick animal, for a sick personisolation and palliative care.

PATHOLOGY OF RABIES

Although rabies manifests with severe neurological and fatal symptoms, pathologicalchanges are not significant or only minimal; therefore, only a mild inflammatory reaction takes place. Afterinfection, pathological changes in peripheral nerves, spinal cord and brain appear. They point outto degenerative changes of ganglion cells; perineural and perivascular are presentnomonuclear cell infiltrations, glial nodules and neurophagy. Degeneration of neurons causes rather their dysfunction than die off. It is in an advanced stage of degenerative changescharacterised by vacuolization of gangliocytes. The significant inflammatory changes are present in the midbrain and spinal cord. Intracellular Negri bodies in the cytoplasm are characteristicneurons, but not in all cases (Spickler, 2012). The pathology of rabiesdescribed in more detail by (Wunner, 2009; Sinhg et al., 2017).

DISINFECTION

Rabies virus is sensitive and can be inactivated by: sodium hydroxide, 45 to 75 % ethanol, iodine preparations,

quaternary ammonium bases, formaldehyde, phenol, ether, trypsin, beta-propiolactone and several detergents. It also can be inactivated by high pH (more than 11) and very low pH (below 3) and ultraviolet radiation. Sunlightand a dry environment (dried blood and secretions) make the virus unable to survive in the environmentlonger time (Spickler, 2012). The virus survives in the bodies of dead animals for several days.

Biological safety

Work in the rabies diagnostic laboratory (keeping experimental animals, dissection, samplingbrain tissue samples, preparation of preparations, sample processing) requires a higher degreebiological protection, considering the fact that rabies is currently an infectious diseasediseases with high mortality. In general, biological protection level 3 is required (virus reproduction, processes that produce a large amount of aerosol, homogenizationtissue, work with new strains of the virus against which prophylaxis is not known). The personalmeans of protection include e.g. special clothing, gloves, eye protection; vaccination of workers is required. National and international standards apply to work in diagnostic workplaces (Šimko and Šimková, 2007), Šimko, 2010) and in thiscase for rabies diagnosis (e.g. mice, mouse inoculation test) and transport of RABV samples.

DIAGNOSTIC TESTS

Clinical diagnosis. Diagnosis is not easy, especially in areas where rabies do not occur. At the beginning of the disease, rabies can be easily mistaken for other diseases. Therefore, alwayswhen rabies is suspected, the laboratory confirmation is necessary. Rabies cannot generally be diagnosed during the incubation period. Rangeand the relevance of diagnostic tests is in the recommendations of the WHO (World Health Organization, Laboratory techniques in rabies) and OIE (World Organization for Animal Health; Manual ofdiagnostic tests and vaccines for terrestrial animals). Early diagnosis is important forconfirmation of disease and prognosis. Diagnostic tests are reviewed by several authors (e.g. Wunner, 2009; Rupprecht, Nagarajan, 2015; Fooks et al., 2017). Rabies diagnostic tests have a history. Microscopic examinations are focusedfor proof of Negri bodies. Staining of impression preparations using the method according to Sellers. Biological experiment on mice or rabbits. For the detection of virus particles and inclusionselectron microscopy can be used for bodies. The direct immunofluorescence method usesanti-rabies conjugate (commercially produced) with a fluorescent substance; this method requiredspecial microscope. Diagnostic tests for rabies in the former Czechoslovakia were complexand some are still practiced until the present (Anonymus, 1962, 1975).

Diagnostic tests are performed from clinical samples such as cerebrospinalfluid, saliva, smears from the nasal mucosa, eyes, throat, impressions from the eye (bulbus oculi) and cornea, biopsy material of skin from the face and neck area; after death from brain tissue (brainbase, cerebellum and hippocampus) of dead animals (Warrel and Warrel, 2004).

Postmortem diagnostic tests

Macroscopic postmortem findings are not characteristic and are used to determine the diagnosisonly a secondary meaning. In some cases, there may be cachexia, injury to the papilla, tongue, broken teeth, etc. Foreign objects may be present in the stomach (pica). There are typicalhistological findings in the CNS (multifocal, mild polioencephalomyelitis and craniospinal ganglionitis with mononuclear perivacular infiltrates). Rabies is characterized by inclusions in the cytoplasm of neurons (usually between the nucleusand neuron protrusion) of the brain and spinal cord, that is, in the place where the replication of the rabies virus takes place. Evidence of cytoplasmic Negri (Babesh-Negri) bodies after Sellers staining (1927; a saturated solution of basic fuchsin and methylene blue in methanol) in brain tissue istraditional method of proof of rabies. Negri bodies are found in some gangliacells of Ammon's horn, less often in the Purkinje cells of the cerebellum. Bodies don't have tobe present in all cases of the disease. They contain rabies virus proteins and RNA; they areacidophilic, round, sometimes oval; their size varies (depending on the animal species) from 0.25 to 27 μm. They are not homogeneous, they have their internal basophilic structure. The finding of Negri bodies does not have to bespecific for diagnosis; it has only a supporting meaning (Wunner, 2009).

Direct evidence of fluorescent antibodies (direct fluorescent antibody technique) isthe gold standard for rabies diagnostic tests because the test is not time-consuming, it is notexpensive and has high sensitivity (Wunner, 2009). Intravital samples from humans for diagnostic purposes. Excretions, biological fluids (e.g.saliva, spinal fluid, tears) and tissues (biopsy samples of skin, hair follicles from the cervicalneck area; nape: back of the neck and shoulders), blood and serum are used for diagnostic purposes. It is advisable to store the collected samples at a temperature of –20 °C or less, or preserve them with glycerin (C3H8 O3, CAS 56-81-5).

Current intravital diagnostic tests (Rupprecht and Nagarajan, 2015; Fooks et al., 2017) are built ondetection of viral nucleic acid; conventional RT-PCR and real time PCR (of the test result 3-4 h and 2-3 h). Advantages: high speed and sensitivity, „one-tube systems"minimizes the risk of contamination; disadvantages (e.g. need for special equipment and risk contamination and — viral neutralization substances: — FAVN (Flourescent antibody virus neutralization) a – RFFIT (Rapid fluorescent focus inhibition test), which give results in 5-8 days. These tests are suitable for control after vaccination. The disadvantage is the long time it takes to know the test results.

Postmortem diagnostic tests (Rupprecht and Nagarajan, 2015; Fooks et al., 2017; Timiryasova et al., 2019).

Viral antigen status tests:

- FAT test (Fluorescent antibody test): test results in a time range of 2-3 h; fasttest with high sensitivity and specificity; disadvantages: the need for an expensive conjugate, speciallight microscope, more complex interpretation of the result,
- DRIT test (Direct immunohistochemical test): 2 — 3 h; light microscope only; interpretation of resultsis more difficult.
- Viral antigen or antibody: — LFD with (Lateral flow devices), 30 — 60 min, required validation.
- Live virus: — RICIT (Rabies tissue culture isolation test): 4 — 6 days, allows determination of characteristics (properties) of the virus; disadvantages: long time, need for specialists.
- Live virus: — MIT (Mouse inoculation test), more than 28 days, allows to determine characteristics (properties) of the virus; disadvantages: very long time, need for specialists, ethical problems related to live models (animals).

HYGIENE OF ANIMAL PRODUCTS

Transmission of RABV, as well as all lyssaviruses, occurs through saliva through compromised integrity of the skin or mucous membranes, generally through wounds (injuries, tears, scratches) orlicking. Transmission by consuming (eating) carcasses of infected animals is also possible. Viral devitalization by gastrointestinal factors may not be effective, especially with violation (abrasion) of the mucous membrane of the oral cavity (Bell and Moore, 1971; Ramsden and Johnson, 1975).

Eating raw meat or other tissues from infected animals is not a source of infection people; however, it is generally not recommended.

VETERINARY MEASURES IN THE FORMER CZECHOSLOVAKIA

According to legal regulationsin the former Czechoslovakia, rabies in food animals had been considered to be one of the most dangerous diseases. It was forbidden to kill animals sick or suspected of rabies. Animals sick or suspected of having this disease was not allowed to deliver to slaughterhouses or ambulance slaughterhouses. Animals suspected of infection that are detected at the slaughterhouse had to be placed in reserved areasand lockable spaces. Meat from animals with rabies is inedible. Decree no. 54/1961 collection of laws of the Czechoslovak Republic had implemented some measures on veterinary caree. g. occurrence of infection or suspicion of it, prohibited the use of milk for human consumption and allowed it tofeed animals only after boiling (Nižnánsky et al., 1965).

When the infection had been detected, or if the suspicion of it has not been ruled out — the official authorities at the timeordered that meat from slaughtered animals had to be sterilized; milk of the sick animals and animals suspected of infection were harmlessly removed, and animals suspected ofinfections boiled or pasteurized before use. Milk for pasteurization had been transported in special containers, marked with the red letter „V". Guideline procedure fordeciding on animal products (excepting meat) from animals with rabiesor suspected of infection required harmless removal (destruction) of skin, bones, hooves, mane, bristles, fur, wool, intestines and milk (Anonymus, 1962; 1965).

The rabies virus does not survive in pasteurized milk and heat-treated meat; is aheat inactivated. In general, it is not recommended to consume animal products fromanimals sick with rabies (Spickler, 2012). There is now no evidence of oral infection of human's from raw meat or other tissues from infected animals, from consuming the virus in food.

EATING DOG MEAT

There are data that in some countries (China, Vietnam, Philippines, Thailand, Laos, Cambodia, Philippines…) rabies virus infection in humans can occurthe food chain by killing dogs and handling their meat. This type of meat ispart of the diet of people in many countries, from the ancient past — to the present (Cambodia, China, Mexico, Italy, South Korea, Thailand, Vietnam, Earth area around poles (Clifton, 2003; Rupert, 2004; Anthony, 2009). The meat of dogs and cats is mainly consumedin Cambodia, China, South Korea, Vietnam, India, Indonesia, Africa (e.g. Ghana, Nigeria, Cameroon) (Garba et al., 2013; Ajoke (2014). Dog meat consumption, for example, in Asia (China, Vietnam, Korea) has a long history. It is not consumed in Western countries, due to moral and cultural norms. There is a ban on killing dogs in Europe; a dog is not a food. However, they do existlocal ethnic minorities (and regional customs) that are historically specificway of life and consume (for various reasons) dog meat and its products (rottenfat, sausages, heat-treated meat). Dog meat is a consumable part of fat and skeletal muscleof animals, which is an important source not only of protein in various countries of the world.

Places for killing dogs for human consumption, especially in Africa and Asia are the source of RABV infection, in relation to the origin of the dogs and their health status(e.g. vaccination, veterinary inspection before, during and after slaughter) and hygienic conditions forthese slaughterhouses. Asia and Africa are also considered areas of significant human mortality nowadays, where 30,000 people die each year; in Asia every 15 min. one Asian dies of rabies (Singh

et al., 2017). The market for live dogs and cats and their meat is often illegal, i.e. withoutofficial control. Estimates from 2014 assume that it is killed and consumed annually worldwide25 million dogs. Elimination of rabies in dogs is a basic preventive measure forthe elimination of rabies in humans in all rabies-endemic countries, within the context of the global program „No Human Death from Rabies by 2030". Basicreproductive number — R 0 is a key indicator that is used for effective countermeasuresthe spread of rabies. Topical R 0 is between 1 and 2 and less (Coleman and Dye, 1996; Hampson et al., 2009; Townsed et al., 2013; Cleavelans and Hampson, 2017).

Places for killing dogs and related processes (handling: catching, transport, method of treatment, waiting time, minimal or no welfare before killing, method of killingand further processing…) represent a significant health risk in the epidemiology of rabies in several Asian and African countries. There exist evidence of rabies transmission from dogs to humansin connection with environmental hygiene, population density, especially in rural areas, communities and overpopulated areas (Atuman et al., 2014).

Risk points for the transmission of rabies to humans arise when handling live dogs (most are unvaccinated and often of unknown origin); inhumane transport and conditionshandling before slaughter, during slaughter, skinning and handling of the carcass of dogs not only forthe „slaughter house" or directly on the market, but also during the cutting, freezing and sale of meat and before heat treatment.

The origin of the dogs „living on the street" (stray dogs) and their health status is unknown or verydoubtful. In most cases, vaccination data are missing. Personnel during the kill, after the kill and meat handling often has minimal education. In some cultures, dog meat or parts of their bodies are traditionally and legally consumed, either as a part of the daily diet, tradition orrituals.

BATS

In America, some species of bats are considered reservoirs of the virusrabies for mesocarnivore species: e.g. striped skunk (*Mephitis mephitis*), teddy bearlynx — *(Procyon lotor*), *Urocyon cinereoargentus* (Canidae), bobcat (Felis rufus), domestic cat (*Felis catus*), wolf (*Canis lupus*), domestic dog (Canis lupus familiaris) and other speciese.g. short-billed crow (*Corvus brachyrhynchos*, Corvidae, Passeriformes), black crow (*Corvus corax*, Corvidae, Passeriformes), rock squirrel (*Otospermophilus variegatus*, Sciuridae, Rodentia), mantled chipmunk (*Eutamias dorsalis*, Sciuridae, Rodentia), chipmunk (*Eutamias cenerollis*), long-tailed hamster (*Peromyscus maniculatus*, Cricetidae, Rodentia), *Peromyscus truci*, *Neotoma albigula* (Critediae, Rodentia), which also feed on dead species, in this case by dead bats (Theimer, et al., 2017).

The results of this workdocument the ecological potential of rabies transmission via the food of carnivorous animal species. A mesocarnivore is an animal whose diet consists of 50 — 70 % meat, with the restconstitute non-vertebrate foods, which may include insects, fungi, fruit, other plant material, andwhatever food is available to them. This group includes species e.g. some families (Canidae, Viverridae, Mustelidae, Procyonidae, Mephitidae, herpestidae), with a smalland medium body weight (< 15 kg) and live in communities in highly differentiated environment (Roemer et al., 2009).

Consumption of bats (mush meat, commercial hunting). Out of all (at least 5416) of mammal species, bats make up more than 20 % (120 species) (Simmons, 2005). They are widespreadin most ecosystems. They are economically important, especially as insect eaters, pollinators of plants and spreaders of their seeds. They also produce organic natural fertilizer (guano, source of N, K and P). Bats belong to the group of small (less than 1 kg) — the so-called „bushmeat" — of animals that are consumed in different parts of the world, mainly in the tropical areas of Asia (e.g. Thailand (Suwannarong and Schuler, 2016)) and Africa, Oceania, parts of Central and Southern America, islands in the Atlantic, Indian and Pacific Oceans (Fricket al. 2019 quote Rocha et al., 2021). Bats are hunted also for other purposes, for the needs of the souvenir market, forethnobiological purposes, human ethnic medicine, zootherapeutic purposes (e.g. in Brazil) and otherscommercial and religious various spiritual purposes; meat is especially popular (blood asaphrodisiac) (Rocha et al., 2021).

Bats in general are divided into two basic types: — megabats (Megachiroptera) and — microbats (Microchiroptera). In some areas of the world they have anothercommercial significance; they are hunted as a source of food for the population ("hunting bushmeat for humanconsumption"; „when people are together, they hunt tiger together"). Some species are the sourceand vectors of infectious diseases of animals and humans, including lyssaviruses (Micklebburg et al.,2009; Cifuentes Jiménez et al., 2017; Shipley et al., 2019; Akem and Pemunta, 2020; Rochaet al., 2021). Bats are also used for animal nutrition at various levels, e.g. birds of prey.
Clinical symptoms of rabies in bats are manifested by disturbances in flight orientation, striking eye expression and behavioral changes, especially aggression. The symptoms are notspecific. The disease must be confirmed only by laboratory tests.

The transmission of rabies by bats (Chiroptera) to humans poses a minor health risk, due to the fact that mostly bats that feed on and fruit and insects (insectiform) are consumed, although these can also be a source of infection. Elimination of human rabies from bats is not controlled by host vaccinationspecies. The transmission of rabies to livestock by some hematophagous species of bats is at leastpartially controlled by vaccination of cattle (e.g. in America).

RABIES IN HUMANS

Clinical signs of human rabies are difficult to interpret, especially in the early stages. An intra vitam diagnosis is rarely definitive. Summary of clinical signs of rabiesin humans according to clinical status is as following (Thraenhart, 2004; Wunner, 2009):

Prodromal status: fever, anorexia — refusal to eat, vomiting, headache, weakness, apathy, anxiety, agitation, depression, pain or paraesthesia (tingling, burning, numbness on the side of the bite injury);

- acute neurological phase: rapid breathing — hyperventilation, hypoxia — deficiency of oxygen in the body, loss of speech — communication disorder, paresis — partial loss of momentum — incompleteparalysis, paralysis — loss of ability to move — muscle paralysis, hydrophobia — fear of water, pharyngeal spasm, excessive salivation (1–1.5 l of saliva/day), other disturbed functions of the centralof the nervous system, confusion, delirium — morbid confusion, delirium, hallucinations — perception disorder, anxiety, agitation, depression, hyperventilation;
- coma (state of deep unconsciousness): pituitary dysfunction, hyperventilation, apnea, hypotension, cardiac arrhythmia, heart block — atrioventricular block anddeath: pneumothorax, intravascular thrombosis and secondary infections.

RABIES AND THE EU COMMUNITY NETWORK

The European Center for Disease Prevention and Control (ECDD) deals with technicaldocumentation on disease definitions that help the Commission of the European Communities indeveloping surveillance and response intervention strategies. The aim of these definitions of diseases is to facilitate the reporting of diseases and special health problems of communicable diseases, including rabies in human (EC Commission Decision, 2008).

Clinical criteria. Any person with acute encephalomyelitis and at least one of theseof seven symptoms: — sensory changes in the place of the passing animal bite, — paresis or paralysis, — hydrophobia, — delirium, — convulsions and anxiety.

Laboratory criteria. At least one of the following four criteria: — Lyssa virus isolationin a clinical sample (e.g. in saliva or brain tissue), — detection of viral antigensusing fluorescence (fluorescent antibody test (FAT)) in a clinical sample, — specific antibody response to Lyssa virus using a serum virus neutralization test orcerebrospinal fluid. Laboratory results must be interpreted according to the vaccinationor immunization status.

Epidemiological criteria. At least one of the following three epidemiological contexts: –transmission from animal to human (animal with suspected or confirmed infection), – exposure to the effects of a common source (same animal) — interhuman transmission (e.g. organ transplantation).

Classification of the disease case. A possible case of the disease — any person who meetsclinical criteria. A probable case of the disease — any person who meets the clinical criteria. Confirmed case of the disease — any person who meets the clinical and laboratory criteria.

CONCLUSION

Summa summarum „It never hurts to look back, we are more aware of changes". A virusrabies has a long history that started long ago (2000 years ago) BCin Mesopotamia, in the time of Aristotle in Egypt, Greece, Persia, and India. In 1804, Zinke straightenedattention to the saliva of dogs recognized their infectious nature. L. Pasteur (1881 — 1885) provedneurotropism of the virus, prepared the vaccine (air-dried spinal cord) and performed the vaccination. This was a milestone in the beginning of modern science and the beginning of the era of targeted infection control and disease prevention. In the next period (1903), Reminger and Riffaz-Bazz identified the structure of the virus. The UK was officially recognized as a rabies-free country in 1920; Finland in 1991. This was followed by the preparation of vaccines and the vaccination of domestic and wild animals. Occurrence of rabies in humans is related to the occurrence of rabies in animals. If there are already clinical symptoms, then it is a diseasefatal to both animals and humans. The control and eradication of rabies in humans is therefore built on struggle against rabies in animals.

A system of modern diagnostics and preventive and control measures has been created, namelyat the national and international level. The fight against rabies in humans is based on the elimination of rabies in dogs, as these animals constitute the biggest risk from a global perspectivefor people's health in the platform of the current fight against this disease. Attenuation of transmitted rabies by bats in some geographical areas of the world is based on host vaccinationspecies, especially domestic (farm) animals. Half of the world's human population lives inthe most rabies-infected area (Asia, Africa) with a large population of dogs (WHO data from 2020). Africa and Asia are at greatest risk of human mortality, accounting for 95 % of global fatalities due to rabies. About 99 % of human rabies cases are associated with dog bites and (more than 80 %) in rural areas.

World Health Organization (WHO), United Nations Food and Agriculture Organizationand Agriculture (FAO), the World Organization for Animal Health (OIE) and the Global Alliancefor Rabies Control (GARC) created the „United

Against Rabies" platform in 2015 ("United Against Rabies"), which coordinates worldwide efforts to achieve the global goal „Zero by 30: The Global Strategic Plan toPrevent Human Death from Dog-Transmitted Rabies by 2030").

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