

PREGLEDNI RAD

ZNAČAJ PASTEROVOG ZAVODA U NOVOM SADU ZA PREVENCIJU I SUZBIJANJE BESNILA U REPUBLICI SRBIJI

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SAŽETAK

Besnilo je smrtonosna zoonotska bolest, koja se javlja u više od 150 zemalja i predstavlja javnozdravstveni problem za više od tri milijarde ljudi u svetu. U Evropi je besnilo kod životinja prisutno u Ukrajini, Belorusiji, Poljskoj, Moldaviji, Rusiji i Rumuniji, a pojedinačni slučajevi su prisutni i u drugim zemljama. Najveći broj slučajeva humanog besnila je prisutan u Aziji i Africi. Cilj ovog preglednog rada je bio da se predstavi značaj Pasterovog zavoda u Novom Sadu za suzbijanje i prevenciju besnila u Republici Srbiji. Podaci za ovaj rad su prikupljeni iz različitih baza podataka (*Web of Science*, *PubMed*, *Google Scholar*), biltena itd. Pasterov zavod u Novom Sadu je Nacionalna referentna zdravstvena ustanova za besnilo u Republici Srbiji. Sve delatnosti potrebne u borbi protiv besnila su zastupljene u okviru ove ustanove: pružanje antirabične zaštite ljudima ugroženim od besnila primenom vakcine protiv besnila sa kulture ćelija i humanog antirabičnog imunoglobulina (HRIG), preventivna imunizacija visokorizične populacije, pružanje stručno-metodološke pomoći i stručni nadzor nad radom 27 antirabičnih stanica (ARS) u Republici Srbiji, snabdevanje HRIG-om i vakcinom protiv besnila svih ARS, utvrđivanje doktrinskih i stručno-medicinskih stavova iz oblasti antirabične zaštite, praćenje kretanja besnila, izrada izveštaja i obaveštavanje ARS i organa vlasti o svakom registrovanom slučaju besnila u zemlji, predlaganje i sprovođenje mera za njegovo suzbijanje, dijagnostika besnila u okviru nacionalne referentne laboratorije za besnilo, kontrola postignutog imuniteta nakon imunizacije ljudi i životinja. Regionalni projekat oralne vakcinacije lisica protiv besnila se od 2010. godine sprovodi na teritoriji Republike Srbije, a od 2011. godine monitoring uspešnosti vakcinacije. U Republici Srbiji, urbano besnilo je eliminisano 1980. godine, kao i poslednji slučaj humanog besnila na teritoriji pokrajine Kosovo i Metohija, dok je poslednji slučaj silvatičnog besnila lisica u Srbiji registrovan 2018. godine. U cilju eradikacije besnila neophodna je sinhronizovana aktivnost zdravstvene i veterinarske službe, kao i saradnja na lokalnom, nacionalnom i internacionalnom nivou.

Ključne reči: Pasterov zavod, besnilo, istorija, epidemiologija, javno zdravlje

Uvod

Prvi Pasterov zavod u Srbiji i na Balkanu je osnovan 1900. godine u Nišu, i to 12 godina nakon osnivanja Pasterovog Instituta u Parizu (1). Odlukom Vojnog ministarstva, dana 25. 12. 1900. godine, novi zavod u Nišu dobija ime „Kraljevski vojni Pasterov zavod” i zvanično biva otvoren za javnost 1. 1. 1901. godine. Za prvog stalnog upravnika imenovan je dr Dragutin Petković. Vakcinacija ljudi protiv

besnila u Srbiji je uvedena još 1890. godine. Prema direktivi kraljevske vlade, sve do otvaranja zavoda u Nišu, ljudi ujedeni od strane besnih životinja su bili upućivani u Budimpeštu na lečenje (2). Stoga je doprinos novootvorenog zavoda u preventivnoj medicini bio velik, naročito nakon započete proizvodnje vakcina protiv besnila i velikih boginja (1).

THE IMPORTANCE OF THE PASTEUR INSTITUTE IN NOVI SAD FOR THE PREVENTION AND CONTROL OF RABIES IN THE REPUBLIC OF SERBIA

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SUMMARY

Rabies is a deadly zoonotic disease that occurs in more than 150 countries and represents a public health issue for over three billion people worldwide. In Europe, rabies in animals is present in Ukraine, Belarus, Poland, Moldova, Russia, and Romania, with isolated cases reported in other countries as well. The highest number of human rabies cases is found in Asia and Africa. The aim of this review paper is to present the significance of the Pasteur Institute in Novi Sad in the control and prevention of rabies in the Republic of Serbia. Data for this paper were collected from various databases (Web of Science, PubMed, Google Scholar), bulletins, etc. The Pasteur Institute in Novi Sad is the National Reference Health Institution for rabies in the Republic of Serbia. All activities necessary in the fight against rabies are covered within this institution: providing anti-rabies protection to people at risk of rabies through the administration of cell culture rabies vaccines and human rabies immunoglobulin (HRIG); preventive immunization of high-risk populations; providing expert methodological assistance and professional supervision of the work of 27 anti-rabies stations (ARS) in the Republic of Serbia; supplying HRIG and rabies vaccines to all ARS; establishing doctrinal and professional medical guidelines in the field of anti-rabies protection; monitoring the occurrence of rabies; preparing reports and informing ARS and government authorities about every registered case of rabies in the country; proposing and implementing measures for its control; diagnosing rabies within the national reference laboratory for rabies; and controlling the achieved immunity following the immunization of people and animals. The regional project of oral vaccination of foxes against rabies has been implemented in the territory of the Republic of Serbia since 2010, and monitoring of vaccination effectiveness has been conducted since 2011. In the Republic of Serbia, urban rabies was eliminated in 1980, as was the last case of human rabies in the territory of the province of Kosovo and Metohija, while the last case of sylvatic rabies in foxes in Serbia was registered in 2018. In order to eradicate rabies, synchronized activities of the health and veterinary services are necessary, as well as cooperation at the local, national, and international levels.

Ključne reči: Pasteur Institute, rabies, history, epidemiology, public health

Introduction

The first Pasteur Institute in Serbia and the Balkans was founded in Niš in 1900, 12 years after the Pasteur Institute in Paris had been founded (1). According to the decision of the Ministry of Defense, the new institute in Niš was named the “Royal

Military Pasteur Institute” on December 25th, 1900, and it was officially opened to public on January 1st, 1901. Dr Dragutin Petković was appointed as the first permanent director. Vaccination of people against rabies in Serbia was introduced as early as 1890.

Dvadesetak godina kasnije, 1921. godine se osniva Pasterov zavod u Novom Sadu, koji će već 1928. godine preuzeti sve poslove ostalih zavoda u Kraljevini Srba, Hrvata i Slovenaca i do danas ostati centralna ustanova za borbu protiv besnila (2,3). Od samog osnivanja, pa sve do danas, osim preventivno-medicinskim radom, Pasterov zavod u Novom Sadu se bavio i istraživanjima, kao i praćenjem kretanja besnila i drugih zoonoza. Značajni naučni rezultati istraživanja su publikovani u brojnim stranim i domaćim časopisima (3). Prvi direktor Pasterovog zavoda u Novom Sadu je bio dr Adolf Hempt, koji je razvio inaktivisanu tj. mrtvu vakcinu protiv besnila, koja je po njemu i dobila ime, i bila u upotrebi od 1925. pa sve do 1989. godine (3). Hemptova vakcina se izvozila u Austriju, Nemačku, Mađarsku i Čehoslovačku, kao i u neke afričke zemlje (3). Posle Drugog svetskog rata, Hemptov rad je nasledio i nastavio njegov učenik dr Milan Nikolić. Jedan od njegovih najznačajnijih radova je bila izolacija virusa besnila iz slepih miševa (3).

Na poziv dr Nikolića, na odeljenje za virusologiju Pasterovog zavoda, u aprilu 1960. godine iz Veterinarskog instituta Novi Sad dolazi dr Miloš Petrović. U tom periodu je u okviru zavoda osnovano nekoliko odeljenja: Odeljenje virusologije životinja, Odeljenje za humanu virusologiju, Odeljenje virusologije insekata, Odeljenje virusologije biljaka i Odeljenje histologije, koje je radilo dijagnostiku besnila. Dr Petrović je postavljen za direktora Pasterovog zavoda u Novom Sadu 1973. godine, gde je najpre učestvovao, a kasnije i rukovodio proizvodnjom vakcine protiv besnila za humanu upotrebu po tehnologiji dr Hempta. Uveo je direktni imunofluorescentni test u dijagnostiku besnila, unapredio rad na kulturi ćelija i rad u vivarijumu, kao i izvođenje bioloških ogleda na miševima. Zaslugama dr Petrovića i zaposlenih, u januaru 1975. godine Savezni komitet za zdravstvo i socijalnu zaštitu u Beogradu proglašava Pasterov zavod za Nacionalnu referentnu laboratoriju za besnilo (3). Radi zajedničke proizvodnje humanog imunoglobulina protiv besnila Pasterov zavod 1988. godine sklapa ugovor sa Zavodom za transfuziju krvi iz Beograda (3). Danas, Nacionalna referentna laboratorija za besnilo Pasterovog zavoda u Novom Sadu već niz godina sertifikuje glavne dijagnostičke metode u ANSES laboratoriji u Francuskoj, koja je referentna laboratorija za besnilo Evropske Unije. Zahvaljujući svojoj bogatoj i vrednoj istoriji Pasterov zavod u Novom Sadu je 2001. godine proglašen i zaštićenim spomenikom kulture (3).

Cilj ovog preglednog rada je bio da se predstavi značaj Pasterovog zavoda u Novom Sadu za suzbijanje i prevenciju besnila u Republici Srbiji.

Metode

U cilju pisanja rada korišćeni su podaci iz baze podataka: *Web of Science*, *PubMed*, *Google Scholar*, *WHO Rabies Bulletin*, publikacija izdata povodom 95 godina rada Pasterovog zavoda u Novom Sadu i Međunarodnog naučnog simpozijuma "Istorija besnila u Srbiji" pod nazivom "95 godina Pasterovog zavoda u Novom Sadu". Ključne reči pretrage uključivale su: "Pasterov zavod", "besnilo", "istorija", "epidemiologija", "javno zdravlje" i "imunizacija". Ova literatura je obuhvatila različite vrste studija, kao što su sistematski pregledi, meta-analize, eksperimentalne randomizovane studije, biografije, istorijske članke, prikaze slučaja i tekstove sa zvaničnih internet sajtova.

Nacionalna referentna ustanova za besnilo u Republici Srbiji

Pasterov zavod u Novom Sadu je Nacionalna referentna zdravstvena ustanova za besnilo u Republici Srbiji, i kada je reč o prevenciji ove zoonoze, vodeća institucija u našoj zemlji, kao i u jugoistočnoj Evropi. Saradnja sa veterinarskom službom predstavlja ključ uspeha u borbi protiv besnila, kako na nacionalnom, tako i na internacionalnom nivou. Sve delatnosti potrebne u borbi protiv besnila su zastupljene u okviru ove ustanove: pružanje antirabične zaštite ljudima ugroženim od besnila primenom vakcine protiv besnila sa kulture ćelija i humanog antirabičnog imunoglobulina (HRIG), preventivna imunizacija visokorizične populacije, pružanje stručnometodološke pomoći i stručni nadzor nad radom 27 antirabičnih stanica (ARS) u Republici Srbiji, snabdevanje HRIG-om i vakcinom protiv besnila svih ARS, utvrđivanje doktrinskih i stručno-medicinskih stavova iz oblasti antirabične zaštite, praćenje kretanja besnila, izrada izveštaja i obaveštavanje ARS i organa vlasti o svakom registrovanom slučaju besnila u zemlji, predlaganje i sprovođenje mera za njegovo suzbijanje, dijagnostika besnila u okviru nacionalne referentne laboratorije za besnilo, kontrola postignutog imuniteta nakon imunizacije ljudi i životinja (3).

Postekpoziciona antirabična zaštita

U Službi za prevenciju i sprečavanje širenja besnila i drugih zaraznih bolesti Pasterovog zavoda

According to the directive of the royal government, people bitten by rabid animals had been sent to Budapest for treatment until the institute was opened in Niš. Therefore, the contribution of the newly opened institute in preventive medicine was great, especially after the production of vaccines against rabies and smallpox started (1).

About twenty years later, in 1921, the Pasteur Institute was founded in Novi Sad, which in 1928 took over all the work of other institutes in the Kingdom of Serbs, Croats and Slovenes and which has remained the central institution for the fight against rabies to this day (2,3). From the moment of its foundation to this day, the Pasteur Institute in Novi Sad has also been engaged in research, as well as monitoring trends in rabies and other zoonoses, in addition to preventive and medical work. Significant scientific research results have been published in numerous foreign and domestic journals (3). The first director of the Pasteur Institute in Novi Sad was Dr Adolf Hempt, who developed the inactivated, that is the dead vaccine against rabies, which was named after him, and which was in use from 1925 to 1989 (3). Hempt's vaccine was exported to Austria, Germany, Hungary and Czechoslovakia, as well as to some African countries (3). After the Second World War, Hempt's work was inherited and continued by his student, dr Milan Nikolić. One of his most important works was the isolation of the rabies virus from bats (3).

At the invitation of dr Nikolić, dr Miloš Petrović from the Veterinary Institute of Novi Sad came to the Department of Virology of the Pasteur Institute in April 1960. During that period, several departments were founded within the institute: the Department of Animal Virology, the Department of Human Virology, the Department of Insect Virology, the Department of Plant Virology and the Department of Histology, which was engaged in the diagnostics of rabies. Dr Petrović was appointed director of the Pasteur Institute in Novi Sad in 1973, where he first participated and later managed the production of rabies vaccines for human use based on dr Hempt's technology. He introduced a direct immunofluorescence technique in the diagnosis of rabies, improved the work on cell culture and the work in the vivarium, as well as biological experiments performed on mice. Thanks to dr Petrović and his employees, the Federal Committee for Health and Social Protection

in Belgrade declared the Pasteur Institute to be the National Reference Laboratory for Rabies in January 1975 (3). The Pasteur Institute signed an agreement with the Institute for Blood Transfusion from Belgrade in 1988 to jointly produce human immunoglobulin against rabies (3). Today, the National Reference Laboratory for Rabies of the Pasteur Institute in Novi Sad has certified the main diagnostic methods in the ANSES laboratory in France for several years, which is the reference laboratory for rabies in the European Union. Thanks to its rich and valuable history, the Pasteur Institute in Novi Sad was declared to be a protected cultural monument in 2001 (3).

The aim of this review article was to present the significance of the Pasteur Institute in Novi Sad for the control and prevention of rabies in the Republic of Serbia.

Methods

In order to write this article, data from the following databases were used: Web of Science, PubMed, Google Scholar, WHO Rabies Bulletin, the publication which was published on the occasion of 95 years of work of the Pasteur Institute in Novi Sad and the International Scientific Symposium "History of Rabies in Serbia" under the title "95 years of the Pasteur Institute in Novi Sad". The key words included the following: Pasteur Institute, rabies, history, epidemiology, public health and immunization. This literature included different types of studies, such as systematic reviews, meta-analyses, experimental randomized studies, biographies, historical articles, case reports and texts from official websites.

The National Reference Health Institution for Rabies in the Republic of Serbia

The Pasteur Institute in Novi Sad is the National Reference Health Institution for rabies in the Republic of Serbia, and when it comes to the prevention of this zoonosis, it is the leading institution in our country and in the Southeast Europe. Cooperation with the veterinary service is the key to success in the fight against rabies, both at the national and international level. All the activities necessary in the fight against rabies are covered within this institute: providing anti-rabies protection to people at risk of rabies through the administration of cell culture rabies vaccines and human rabies immunoglobulin (HRIG), preventive

pruža se antirabična zaštita nakon III kategorije izloženosti u urbanom okruženju, prema Svetskoj zdravstvenoj organizaciji (SZO), koja podrazumeva transdermalno ozleđene sa krvavim ranama, one kod kojih je bilo samo kontakta sa sluzokožom sumnjive životinje, ili ako životinja koja je pokazala agresivno ponašanje i nanela ozledu ne može da se prati, ili uginu tokom 10 dana praćenja (3,4). Besnilo je bolest koja se može sprečiti, kontrolisati i eliminisati vakcinacijom (5). Postekspoziciona profilaksa (PEP) je od ključnog značaja za sprečavanje kliničkih znakova besnila. Ona u Srbiji podrazumeva ispiranje rane, infiltraciju rane humanim imunoglobulinom protiv besnila (HRIG) i davanje vakcina u 4 doze po skraćenom *Essen* protokolu, ili Zagreb šemi (4). Ovaj protokol je zasnovan na preporuci stručnog komiteta iz Centra za kontrolu bolesti (ACIP) u SAD-u, koji je smanjio režim od 5 doza vakcina protiv besnila na 4 doze koje se daju na dane: 0, 3, 7 i 14, u kombinaciji sa imunoglobulinom protiv besnila koji se daje nultog dana (5). Ovo smanjenje broja doza vakcine je zasnovano na kliničkim studijama, epidemiološkom nadzoru i eksperimentalnim radovima na životinjama (6). Od 2018. godine SZO je dodatno smanjila režim vakcinacije na 3 doze (na dane 0, 3, 7 ili 0, 3, 21), dok Američki savetodavni odbor za praksu imunizacije (engl. *U.S. Advisory Committee on Immunization Practices*) i dalje preporučuje 4 doze vakcine u PEP (4).

Uvidom u izveštaje koje ARS u Republici Srbiji šalju u Pasterov zavod, došlo se do podataka da je u periodu od 2015. do 2024. godine vakcinisano ukupno 7580 pacijenata, pri čemu je utrošeno 17.183 doza vakcina i 4.744.644 lJ seruma. Kao izvor podataka korišćeni su Obrasci broj 5 – pojedinačna prijava kojom se prijavljuje mogućnost infekcije virusom besnila, u skladu sa važećim Zakonom (7).

Preekspoziciona antirabična zaštita

Sa druge strane, preventivna (preekspoziciona) imunizacija se sprovodi u okviru visokorizične populacije, kao što su poljoprivrednici, ljudi koji žive u oblastima gde je besnilo endemsko, kod ljudi profesijom izloženih riziku od obolevanja (lovci, veterinari, zaposleni u javno komunalnim službama, čuvari u zoološkim vrtovima, biolozi koji rade sa slepim miševima, zaposleni u laboratorijama za dijagnostiku besnila) i turisti (7). Potreba za preventivnom imunizacijom protiv besnila je naročito

naglašena u slučaju rada sa slepim miševima koje nikada ne bi trebalo da diraju neobučene i nevakcinisane osobe (8). Preventivne mere podrazumevaju vakcinaciju ljudi davanjem intramuskularnih ili intradermalnih vakcina protiv besnila tri doze na dane 0, 7, 21 prema stručno-metodološkom uputstvu, što omogućava brzu aktivaciju imunološkog odgovora kad osoba ponovo dođe u kontakt sa virusom (9).

U Laboratoriji za serološku dijagnostiku Pasterovog zavoda, kod prethodno imunizovanih pacijenata određuje se titar antitela na besnilo u serumu brzim testom inhibicije fluorescentnih fokusa na antirabična antitela (RFFIT – *Rapid fluorescent focus inhibition test*) (3). Njegova pogodnost za profilaksu besnila se ogleda u tome što pouzdano utvrđuje zadovoljavajući nivo antitela od 0,5 IU/ml (internacionalnih jedinica po mililitru) i što pokazuje zadovoljavajuću tačnost, 100% specifičnost, varijabilnost između testova od 21%, varijabilnost unutar testa od 14%, linearnost u opsegu do oko 60 IU/ml (10). U okviru Laboratorije za serološku dijagnostiku određuje se i titar antitela na besnilo u serumu kućnih ljubimaca, vakcinisanih protiv besnila, fluorescentnim testom na neutrališuća antitela na besnilo (FAVN – *Fluorescent antibody virus neutralization*) (3). Ovaj test se izvodi na kulturi ćelija sa živim virusom besnila i zbog toga može da ga izvodi samo laboratorija koju odobri Evropska Unija. Sertifikacija i validacija RFFIT i FAVN testa se vrši jednom godišnje kod referentne laboratorije za besnilo Evropske Unije (11).

Za otkrivanje virusa besnila pre razvoja kliničke slike kod pacijenta nema dostupnih dijagnostičkih testova, zato su dalja istraživanja o dijagnostičkim tehnikama u oblasti besnila od velike važnosti (12). Jedina moguća dijagnostika besnila kod životinja i ljudi je *post mortem* i ona se u Pasterovom zavodu vrši u okviru Laboratorije za dijagnostiku besnila tehnikom direktne imunofluorescencije (FAT – *fluorescent antibody technique*), biološkim ogleđom na miševima (MIT – *mouse inoculation test*) i primenom molekularne tehnike - testom lančane reakcije polimeraze (RT-PCR) (3). FAT se smatra brzim dijagnostičkom metodom i zlatnim standardom u ispitivanju moždanog tkiva na prisustvo virusa besnila uz upotrebu fluorescentnih antitela, a kao potvrdni test se radi izolacija virusa besnila biološkim ogleđom na miševima (MIT) (13). U laboratoriji za dijagnostiku besnila se vrši i ispitivanje potentnosti inaktivisanih vakcina protiv besnila za

immunization of high-risk populations, providing expert methodological assistance and professional supervision of the work of 27 anti-rabies stations (ARS) in the Republic of Serbia, supplying HRIG and rabies vaccines to all ARS, establishing doctrinal and professional medical guidelines in the field of anti-rabies protection, monitoring the occurrence of rabies, preparing reports and informing ARS and government authorities about every registered case of rabies in the country, proposing and implementing measures for its control, diagnosing rabies within the national reference laboratory for rabies, and controlling the achieved immunity following the immunization of people and animals (3).

Post-exposure anti-rabies protection

In the service for the control and prevention of rabies and other infectious diseases of the Pasteur Institute, anti-rabies protection is provided after category III exposure in the urban environment, which according to the World Health Organization (WHO), includes transdermally injured persons with open wounds, persons who only had contact with the mucous membrane of suspected animals, or if the animal which showed aggressive behavior and caused injury cannot be monitored, or dies during 10 days of monitoring (3,4). Rabies is a disease that can be prevented, controlled and eliminated by vaccination (5). Post-exposure prophylaxis (PEP) is of utmost importance to prevent clinical signs of rabies. In Serbia, it involves washing the wound, infiltrating the wound with human anti-rabies immunoglobulin (HRIG), in order to neutralize the virus at the wound site, and implementing vaccines in 4 doses according to the abbreviated Essen protocol, or Zagreb scheme (4). This protocol is based on the recommendation of an expert committee from the Centers for Disease Control (ACIP) in the USA, which reduced the 5-dose regimen of rabies vaccines to 4 doses administered on the following days: 0, 3, 7 and 14, in combination with rabies immunoglobulin administered on day zero (5). This reduction in the number of vaccine doses is based on clinical studies, epidemiological surveillance, and experimental work on animals (6). Since 2018, the WHO has further reduced the vaccination regimen to 3 doses (on days 0, 3, 7 or 0, 3, 21), while the U.S. Advisory Committee on Immunization Practices still recommends 4 doses of vaccine in PEP (4).

According to the reports, which are in the Republic of Serbia sent by ARS to the Pasteur Institute, a total of 7,580 patients were vaccinated from 2015 to 2024, with 17,183 doses of vaccines and 4,744,644 IU of serum used. Forms number 5 – individual reports on the possibility of infection with the rabies virus were used as a source of data, in accordance with the current Law (7).

Pre-exposure anti-rabies protection

On the other hand, preventive (pre-exposure) immunization is implemented in the high-risk populations, such as farmers, people living in regions where rabies is endemic, and people who are exposed to the risk of this disease due to their professions (hunters, veterinarians, employees in public utility services, zoo keepers, biologists who work with bats, employees who work in laboratories that deal with rabies diagnostics), and tourists (7). The need for preventive immunization against rabies is particularly emphasized when one works with bats, which should never be touched by untrained and unvaccinated persons (8). Preventive measures include vaccination of people with intramuscular or intradermal rabies vaccines in three doses on days 0, 7, 21 according to the professional-methodological instructions, which enables the rapid activation of immune response when a person comes into contact with the virus again (9).

Rabies diagnostics

In the Laboratory for Serological Diagnostics of the Pasteur Institute, in previously immunized patients, the titer of rabies antibodies in the serum is determined by the rapid fluorescent focus inhibition test (RFFIT) (3). Its suitability for the prophylaxis of rabies is reflected in the fact that it reliably detects the satisfactory level of antibodies of 0.5 IU/ml (international units per milliliter) and that it shows satisfactory accuracy, 100% specificity, inter-assay variability of 21%, intra-assay variability of 14%, linearity up to about 60 IU/ml (10). Within the Laboratory for Serological Diagnostics, the titer of antibodies to rabies in the serum of pets, vaccinated against rabies, is determined by the fluorescent test for neutralizing antibodies to rabies (FAVN – Fluorescent antibody virus neutralization) (3). This test is performed in cell culture with live rabies virus and therefore, it can only be conducted by the laboratory approved

ljude i životinje NIH testom (NIH – *National Institutes of Health*) (3), dok se u Vivarijumu Zavoda obavlja uzgoj i rad sa laboratorijskim životinjama koje se koriste u pomenutom testu, u biološkim ogledima, kao i za izolaciju i proveru patogenosti pojedinih sojeva virusa besnila (3).

Epidemiološke i kliničke karakteristike besnila

Besnilo je smrtonosna zoonotska bolest koja se može preneti sa životinja na ljude i od koje u svetu svake godine umre oko 50.000 ljudi (4,7). Naziv bolesti potiče od latinske reči „*rabere*”, što znači „biti lud”, ili od reči *Rabbahs*, što na staroin-dijskom jeziku znači „nasilan” (14). Prvi put je prepoznato u Egiptu, oko 2300 godina pre nove ere, i u antičkoj Grčkoj (15). Demokrit je 500 godina pre Hrista opisao simptome besnila životinja, Aristotel je opisao besnilo kod pasa 322. godine pre nove ere, a Celzije je utvrdio povezanost hidrofobije kod čoveka sa besnilom životinja 100 godina pre nove ere. Mogućnost prenošenja besnila preko pljuvačke, sa bolesnog na zdravog psa, dokazivali su Cinke 1804. godine i Gruner i Salm-Rejferšajt 1813. godine. U Brazilu je 1907. godine prvi put opisano da slepi miševi mogu biti rezervoari i vektori virusa besnila (16).

Epidemiološki posmatrano, besnilo se javlja u više od 150 zemalja i predstavlja javnozdravstveni problem za više od tri milijarde ljudi u svetu. (5). U Evropi je besnilo životinja prisutno u Ukrajini, Belorusiji, Poljskoj, Moldaviji, Rusiji i Rumuniji, a pojedinačni slučajevi su zabeleženi i u drugim zemljama. Najveći broj slučajeva besnila ljudi je prisutan u Aziji i Africi (4). Prenosi se najčešće ujedom zaražene životinje, uglavnom ujedom besnih pasa. Virus ne može da proдре kroz netaknutu kožu, ali kontakt zaražene pljuvačke sa sluzokožom ili ranom može dovesti do infekcije. Virus se može preneti transplacentarno ili aerosolom. Prenos sa jednog čoveka na drugog zabeležen je u Etiopiji, a transplacentarni u Turskoj (14). Prosečni period inkubacije traje 20-60 dana, do pojave prvih simptoma. Prosečno vreme, od izlaganja virusu do smrti je 30-90 dana, a može biti i nekoliko dana, do godinu i više dana (17). Prva generacija vakcina protiv besnila je počela sa Luj Pasterom 1885. godine koji je za pravljenje vakcine koristio zaraženu kičmenu moždinu zeca. Vremenom je vakcina unapređena, i danas, u savremenom

svetu, se koriste modifikovana živa vakcina, inaktivirana vakcina protiv besnila i adjuvantna vakcina protiv besnila (7). Više od 15 miliona ljudi širom sveta svake godine primi postekspozicionu zaštitu za koju se procenjuje da sprečava milione smrtnih slučajeva od besnila (18).

Suzbijanje i prevencija besnila

U cilju eliminacije smrtnih slučajeva ljudi uzrokovanih besnilom pasa, 2018. godine je usvojen Globalni strateški plan, napravljen za period do 2030. godine od strane Svetske zdravstvene organizacije (WHO), Organizacije za hranu i poljoprivredu Ujedinjenih nacija (FAO) i Svetske organizacije za zdravlje životinja (WOAH), koji je podrazumevao godišnju vakcinaciju minimum 70% populacije pasa (19). Međutim, u više od 150 zemalja sveta u kojima se besnilo održava endemski ovaj plan još uvek nije ispunjen. Razlozi su višestruki, uključuju pre svega ograničena finansijska sredstva za nabavku vakcine i RIG-a, kao i nedovoljnu obuku zdravstvenih radnika i veterinaru. Suština uspešnog „Jedno zdravlje” pristupa je angažovanje cele zajednice, kao i nadzor nad besnilom (20,21).

Glavni rezervoari besnila u Evropi su crvena lisica i rakunasti pas. Jedini efikasan način za kontrolu besnila u Evropi je oralna vakcinacija ovih životinja putem distribucije vakcinalnih mamaca u njihova staništa. Ovaj program je započet u Švajcarskoj 1978. godine, a od 2001. godine i u drugim evropskim zemljama (22). Regionalni projekat oralne vakcinacije lisica protiv besnila se od 2010. godine sprovodi na teritoriji Republike Srbije. Od 2011. godine započet je monitoring uspešnosti vakcinacije (23). Projekat oralne vakcinacije je doveo do poboljšanja epizootiološke situacije kako u Srbiji, tako i u zemljama u okruženju (7). U Srbiji, urbano besnilo je eliminisano 1980. godine, kao i poslednji slučaj besnila čoveka na teritoriji pokrajine Kosovo i Metohija, dok je poslednji slučaj silvatičnog besnila lisica u Srbiji registrovan 2018. godine (24). U cilju eradikacije besnila neophodna je sinhronizovana aktivnost zdravstvene i veterinarske službe. U prepoznavanju globalnog značaja bolesti neophodna je saradnja na lokalnom, nacionalnom i internacionalnom nivou u cilju prikupljanja i obrade podataka. Pravilno prikupljeni podaci, omogućili bi kvalitetnija epizootiološko-epidemiološka razmatranja (16).

Kretanje besnila u Srbiji je povezano sa situaci-

by the European Union. The certification and validation of the RFFIT and FAVN test is conducted once a year by the reference laboratory for rabies of the European Union (11).

There are no available diagnostic tests that can detect the rabies virus before the development of clinical picture in a patient, and therefore, further research on diagnostic techniques in the field of rabies is of great importance (12). The only possible diagnosis of rabies in animals and humans is post-mortem and it is conducted at the Pasteur Institute within the Laboratory for Rabies Diagnostics by direct immunofluorescence technique (FAT – Fluorescent Antibody Technique), biological experiment on mice (MIT – Mouse Inoculation Test), and application of molecular technique – Polymerase Chain Reaction test (RT-PCR) (3). FAT is considered to be a rapid diagnostic method and gold standard in examining brain tissue for the presence of rabies virus with the use of fluorescent antibodies, and as a confirmatory test, the isolation of rabies virus is conducted by biological assay on mice (MIT) (13). In the laboratory for the diagnostics of rabies, the potency of inactivated rabies vaccines for humans and animals is tested using the NIH test (NIH – National Institutes of Health) (3), while in the Institute's vivarium, laboratory animals are bred and they are used in the above mentioned test, in biological experiments, as well as for the isolation and testing of pathogenicity of certain strains of the rabies virus (3).

Epidemiological and clinical characteristics of rabies

Rabies is a deadly zoonotic disease that can be transmitted from animals to humans and it causes 50,000 deaths in the world every year (4,7). The name of the disease originates from the Latin word 'rabere', which means "to be mad", or from the word 'Rabbahs', which in Old Indian means "violent" (14). It was first recognized in Egypt around 2300 BC, and in ancient Greece (15). Democritus described the symptoms of rabies in animals 500 years BC; Aristotle described rabies in dogs in 322 BC, and Celsius established the connection between hydrophobia in humans with rabies in animals 100 years before Christ. The possibility of transmission of rabies via saliva, from a sick to a healthy dog, was proven by Zinke in 1804 and Gruner and Salm-Reifferscheidt in 1813.

In Brazil, in 1907 it was first described how bats can be reservoirs and vectors of rabies virus (16).

From the epidemiological perspective, rabies occurs in more than 150 countries and it represents a public health problem for more than three billion people in the world (5). In Europe, animal rabies is present in Ukraine, Belarus, Poland, Moldova, Russia and Romania, while individual cases have been recorded in other countries, as well. The largest number of cases of human rabies is present in Asia and Africa (4). It is transmitted most often by the bite of an infected animal, mainly by the bite of rabid dogs. The virus cannot penetrate intact skin, but the contact of infected saliva with a mucous membrane or wound can lead to infection. The virus can be transmitted by the transplacental route or through aerosols. Human-to-human transmission was reported in Ethiopia, and transplacental transmission in Turkey (14). The average incubation period lasts 20-60 days, until the appearance of first symptoms. The average time from the exposure to this virus to death is 30-90 days, and it can be several days to one year or more (17). The first generation of vaccines against rabies began in 1885 with Louis Pasteur who used an infected spinal cord of a rabbit to make the vaccine. The vaccine has been updated over time, and today, in the contemporary world, modified live vaccine, inactivated rabies vaccine and adjuvant for rabies vaccines are used (7). More than 15 million people worldwide receive post-exposure prophylaxis every year, which is estimated to prevent millions of deaths caused by rabies (18).

The control and prevention of rabies

In order to eliminate human deaths caused by dog rabies, a Global Strategic Plan was adopted in 2018, and it was created by the World Health Organization (WHO), the Food and Agriculture Organization of the United Nations (FAO) and the World Organization for Animal Health (WOAH) for the period until 2030, and meant the annual vaccination of at least 70% of dog population (19). However, in more than 150 countries of the world, where rabies is endemic, this plan has not been fulfilled yet. The reasons are multiple, including, first of all, limited financial resources for the procurement of vaccine and RIG, as well as insufficient training of health professionals and veterinaries. The essence of a successful "One-

jom u zemljama sa kojima se naša zemlja graniči: Crna Gora, Bosna i Hercegovina, Hrvatska, Makedonija, Mađarska, Rumunija i Bugarska (23). U zemljama u okruženju, prema izveštaju WHO Rabies Bulletin (25), besnila ima u Mađarskoj, kod 12 domaćih i 24 divlje životinje i u Rumuniji, kod 19 domaćih i 9 divljih životinja. U Crnoj Gori, poslednji slučaj besnila kod životinja zabeležen je 2012. godine, u Bosni i Hercegovini 2020. godine, kod leša lovačkog psa, u Hrvatskoj 2014. godine, a u Makedoniji 2012. godine (25).

U cilju suzbijanja besnila primenjuje se jedan od glavnih principa pod nazivom "Jedno zdravlje", baziran na multidisciplinarnoj saradnji istraživača iz oblasti medicinskih, veterinarskih i bazičnih ekoloških nauka na lokalnom, nacionalnom i globalnom nivou, da bi se obezbedilo optimalno zdravlje za ljude, životinje i životnu sredinu (26). Izazovi podrazumevaju nedovoljno obrazovanje i svest javnosti, kao i ekonomske prepreke za postekspozicionu profilaksu. U cilju uspešne strategije iskorenjivanja besnila, neophodna su isplativa rešenja i kampanje podizanja svesti javnosti (7). Prema istraživanju sprovedenom u Pasterovom zavodu 2023. godine, većina zaposlenih smatra da su njihove funkcije jasno utvrđene, ciljevi konkretni, odgovornosti u organizaciji precizno definisane, te da je radna atmosfera motivišuća, što doprinosi uspešnosti Pasterovog zavoda (27).

Zaključak

Da bi se besnilo iskorenilo neophodna je stalna politička i finansijska angažovanost ugroženih zemalja, politička i finansijska podrška Evropske Unije i bliska saradnja susednih zemalja. Veoma je važno kontinuirano podizati svest stručne javnosti i građana o značaju i opasnosti od ove bolesti zbog mogućnosti širenja bolesti putem trgovine životinjama. Aktivnosti Pasterovog zavoda u Novom Sadu su brojne, a posebno su važne one koje su usmerene na prevenciju i suzbijanje besnila na teritoriji Republike Srbije

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Autori su izjavili da nema konflikta interesa.

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health” approach is the engagement of whole community, as well as the community based rabies surveillance (20,21).

The main reservoirs of rabies in Europe are the red fox and the raccoon dog. The only effective way to control rabies in Europe is oral vaccination of these animals through distribution of vaccine baits in their habitats. This program was started in Switzerland in 1978, and since 2001 in other European countries (22). The regional project of oral vaccination of foxes against rabies has been implemented on the territory of the Republic of Serbia since 2010. Since 2011, monitoring of the success of vaccination has started (23). The project of oral vaccination led to the improvement of the epizootiological situation both in Serbia and in the surrounding countries (7). In Serbia, urban rabies was eliminated in 1980, as well as the last case of human rabies in the territory of the province of Kosovo and Metohija, while the last case of sylvatic fox rabies in Serbia was registered in 2018 (24). In order to eradicate rabies, synchronized activity of health and veterinary services is necessary. The cooperation at the local, national and international level, which is aimed at collecting and analyzing data, is necessary for the recognition of global importance of this disease. Properly collected data would enable better epizootiological-epidemiological considerations (16).

The trends of rabies in Serbia are connected with the situation in neighboring countries: Montenegro, Bosnia and Herzegovina, Croatia, Macedonia, Hungary, Romania and Bulgaria (23). In neighboring countries, according to the report of the WHO Rabies Bulletin (25), rabies is present in Hungary in 12 domestic and 24 wild animals and in Romania, in 19 domestic and 9 wild animals. In Montenegro, the last case of rabies in animals was recorded in 2012, in Bosnia and Herzegovina in 2020, in the carcass of a hunting dog in Croatia in 2014, and in Macedonia in 2012 (25).

In order to control rabies, one of the main principles called “One Health” is applied, based on the multidisciplinary cooperation of researchers from the fields of medical, veterinary and basic environmental sciences at the local, national and global level, in order to ensure the optimal health for people, animals and the environment (26). Challenges include insufficient public education and awareness, as well as economic barriers to post-exposure prophylaxis. In order to achieve

a successful rabies eradication strategy, cost-effective solutions and campaigns that raise public awareness are necessary (7). According to research conducted at the Pasteur Institute in 2023, most employees believe that their functions are clearly defined, goals are specific, duties in the organization are precisely defined, and therefore, the working atmosphere is motivating, which contributes to the success of the Pasteur Institute (27).

Conclusion

In order to eradicate rabies, the constant political and financial involvement of countries at risk, the political and financial support of the European Union and the close cooperation of neighboring countries are necessary. It is of great importance to continuously raise awareness of the professional public and citizens about the importance and danger of this disease due to the possibility of spreading the disease through animal trafficking. The activities of the Pasteur Institute in Novi Sad are numerous, with those aimed at the prevention and control of rabies in the territory of the Republic of Serbia being particularly important.

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Competing interests

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