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Speakers:
Dušan Lalošević, Nenad Vranješ, Marius Raica, Anthony R. Fooks, Charles E. Rupprecht, Anca Maria Cimpean, Srđan Stankov, Claude Sabeta, Marija Romić, Radovan Vodopija, Ivana Knežević, Budimir Plavšić

NINETY FIVE-YEARS OF PASTEUR INSTITUTE IN NOVI SAD

Dušan Lalošević

Abstract

After more than 95 years of Pasteur Institute in Novi Sad works on the prophylaxis of rabies, this scariest infectious disease slowly goes down in history. Today, the number of rabid animals in Serbia is so small, thanks to the European project of vaccination of foxes that looks as it will never be. However, decades earlier, when the number of rabid domestic and wildlife animals was a big („as in medieval epizootics of rabies", A. Hempt 1929), Pasteur Institute in Novi Sad as a central institution for the prophylaxis of rabies in Serbia, worked very successfully that these disease in humans becomes extremely rare in the former Yugoslavia and for over 35 years is gone, although until a few years were a lot of injured patients from proven rabid animals.

On the occasion of the 95th anniversary of the foundation of the Pasteur Institute in Novi Sad, the artistic and historical value of the main buildings and furnishings have been made public. In 1997 the two buildings on the premises of the Pasteur Institute were put under protection as a cultural monument - the main one, built in 1921 and the wooden one, the so called Dr. Hempt's house, built in 1922. The remarkable bust of Louis Pasteur, standing between these two buildings, done by sculptor Jovanović in 1932 is the third element of the cultural heritage named „Complex of the Pasteur Institute in Novi Sad". It was declared as cultural heritage in 1997 by the Official gazette of the Serbian Government. The most important artistic piece within the main building in Pasteur Institute is by all means the oil painting of Louis Pasteur done by Pierre Petit in year 1893, together with old microscopes and other specific pieces of equipment from that time.

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PASTEUR INSTITUTE NOVI SAD TODAY - ONE HEALTH APPROACH IN RABIES PREVENTION

Nenad Vranješ

Abstract

Speaking about rabies in Serbia is almost impossible without mentioning Pasteur Institute in Novi Sad. From its foundation in 1921 up till now all the efforts in Institute have been focused on human rabies prevention as well as on elimination of rabies on its jurisdiction territory i.e. Republic of Serbia.

Nowadays it looks like we are coming to the end after a very long journey of 95 years full of hard working moments. But it seems to be that it has been paid off for all the participants in this battle against rabies, above all for every collaborator of Pasteur institute in Novi Sad in previous time.

Pasteur Institute in Novi Sad today is the national referent institution for rabies in Serbia with main focus on health care in rabies prevention, performing rabies post exposure prophylaxis for all patients endangered of rabies.

Today it is the leading institution in rabies prevention in Serbia, as well as in south east Europe first of all because all the aspects of rabies prevention are put together within one single, very professional institution, which together with remarkable cooperation with the veterinary service represents the key role of success in a fight against rabies nationally as well as internationally. These aspects within Pasteur Institute in Novi Sad are the following ones: 1. Anti rabies treatment of all patients endangered of rabies with human rabies immunoglobulin (HRIG) and modern cell culture rabies vaccines according to the WHO recommendations; 2. Offering round the clock expertise help as well as constant surveillance of rabies post exposure prophylaxis (PEP) in 27 health care organizations - anti rabies treatment centres (ARTC) - which are dispersed thru ought the country (decentralized anti rabies treatment); 3. Adequate supply of all 27 ARTC with HRIG and rabies vaccine; 4. Expertise of up to date medical and doctrinal achievements in PEP according to WHO guidelines and helping incorporating it in legislation procedure; 5. Epidemiological and epizootiological surveillance of rabies cases in the field with making a daily base reports on every diagnosed rabies case in the country, which are then forwarded instantly to the ARTC as well as to the relevant health care and veterinary authorities with a competent suggestions how to cope with the situation; 6. Existence of National reference laboratory for rabies where rabies is precisely and timely adequate diagnosed in humans and animals round the clock, where immunity after rabies vaccination is checked with modern serological tests and where quality control of rabies vaccines and HRIG (potency tests) used for PEP in the field is done; 7. Scientific research of new technologies in rabies prevention; 8. Production of pharmaceuticals (rabies vaccines and HRIG) and other laboratory diagnostics such as conjugate.

This kind of rabies prevention represent an example of good organization in fighting against rabies, where every step in the process of PEP is done in precise and timely adequate manner in order to prevent even the slightest possibility of getting human rabies. The brilliant results of this kind of rabies prevention have shown that we can be very proud on our achievements - no human rabies case in Serbia, not even imported one, since 1989. This represent a great success for Pasteur Institute in Novi Sad and all health care workers dealing with PEP, relevant authorities, but also for veterinary service which did and still does great efforts in fighting against rabies in animals. Especially in the last five years when they have shown a fantastic devotion within the project of oral vaccination of foxes, trying to reach the final goal - Rabies free status for Serbia. With such an approach, "One health" concept found its full acknowledgement in rabies prevention in Serbia through the full cooperation of veterinary and health care service.

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VICTOR BABES-PASTEUR'S DISCIPLE AND FOUNDER OF MICROBIOLOGY IN ROMANIA

Marius Raica

Abstract

Victor Babes (1854–1926) was a Romanian physician, bacteriologist, academician and professor. One of the founders of modern microbiology, Victor Babes is author of one of the first treatises of bacteriology in the world –Bacteria and their role in pathological anatomy and histology of infectious diseases, written in collaboration with French scientist A. V. Cornil in 1885. In 1888, Babes underlies the principle of passive immunity, and a few years later enunciates the principle of antibiosis.

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He made early and significant contributions to the study of rabies, leprosy, diphtheria, tuberculosis and other infectious diseases. He also discovered more than 50 unknown germs and foresaw new methods of staining bacteria and fungi. Victor Babes introduced rabies vaccination and founded serotherapy in Romania.

HISTORY OF EMERGING LYSSAVIRUSES IN EUROPE

Anthony R. Fooks

Abstract

Rabies, a fatal viral zoonotic disease, is one of the most serious viral zoonoses that is presently encountered worldwide and continues to pose a serious public health hazard, despite the availability of biologicals for its control. The Lyssavirus genus includes rabies virus and thirteen other recognised species, differentiated according to their genomic sequence. All are capable of causing clinical rabies in susceptible hosts: Rabies virus (RABV), Lagos bat virus (LBV), Mokola virus (MOKV), Duvenhage virus (DUVV), European bat lyssavirus type-1 (EBLV-1), European bat lyssavirus type-2 (EBLV-2), Australian bat lyssavirus (ABLV), Aravan virus (ARAV), Khujand virus (KHUV), Irkut virus (IRKV), Shimoni bat virus (SHIBV), Bokeloh bat lyssavirus (BBLV), West Caucasian bat virus (WCBV) and Ikoma lyssavirus (IKOV). Two further isolates are awaiting official classification. These two putative members of the Lyssavirus genus detected from the brain of Indian flying-foxes (Pteropusgiganteus) in Sri Lanka and from the brain of an insectivorous bat (Miniopterusschreibersii) in Spain, were named Gannoruwa bat lyssavirus (GBLV) and Lleida bat lyssavirus (LLEBV), respectively. Phylogenetic analysis of complete genome sequences, together with geographic location and host species, provides strong evidence that both viral isolates can be tentatively classified as a new virus species. Bat rabies was first diagnosed in Hamburg, Germany in 1954. Meanwhile, several discoveries in Africa led to establishment of the term 'rabies-related viruses'. One African non-RABV lyssavirus, DUVV, was isolated in 1970 in South Africa from a human bitten by a bat while sleeping, although the ecology of DUVV remains elusive. At the beginning of the 1980s, when monoclonal antibody techniques became readily available for lyssavirus characterisation, it was shown that isolates from European bats were related to DUVV. However, the virus recovered from a human case that occurred after a bat bite in Finland in 1985 had different reactivity patterns, and described as a novel lyssavirus serotype. During the following years, European bat lyssaviruses were characterized as two separate genotypes (referred to now as species), different from the African DUVV and from each other: European bat lyssavirus, type 1 (EBLV-1) associated primarily with serotine bats (Eptesicusserotinus), and type 2 (EBLV-2), associated primarily with Daubenton's and pond bats (Myotisdaubentonii and M. dasycneme, respectively). Whilst the human burden of these non-rabies lyssaviruses remains unclear, human fatalities have been reported. It is remarkable that RABV has never been credibly identified in Old World bats and, conversely, non-RABV lyssaviruses have never been detected in the New World.

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A PERSPECTIVE ON APPLIED RESEARCH PRIORITIZATION IN RABIES PREVENTION & CONTROL

Charles E. Rupprecht

Abstract

A selective glimpse into the recent literature on rabies provides dynamic insights toward a fundamental appreciation of the field as regards this neglected zoonosis. For example, fundamental pathogen detection has continued to identify new lyssaviruses, particularly associated with bats (Gunawardena et al. Emerg Infect Dis. 2016;22:1456). Not only has such discovery enabled a much better appreciation of viral taxonomy, evolution and phylogenetics, but also benefit the public health field as a whole, to incorporate the importance of human exposures beyond domestic animals towards free-ranging wildlife such as the Chiroptera, lest areas mistakenly conclude that they are truly free of disease (Mélade et al. PLoS One. 2016;11:e0160553). While widespread oral vaccination of wild

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carnivores has proven successful in Europe and North America, novel opportunities with non-conventional next generation vaccines are becoming apparent (Murphy et al. Exp Rev Vacc. 2016;15:31). Regarding human prophylaxis, historically, pre-exposure vaccination has been offered to personnel at risk, but needs to expand in much broader operation to better coverage of all first responders, as well as incorporation of childhood vaccine schedules, in certain human populations at large, where health disparities continue to exist and will not be resolved by animal management alone, such as in Amazonia (da Costa et al. PLoSNegl Trop Dis.2016;10:e0004474). Although modern prophylaxis is highly effective, the current schedules are too complicated and need to be simplified with fewer doses and visits (Rupprecht et al. Exp Rev Vacc. 2016;15:731). Over the decades, many monoclonal antibodies (MAbs) have been developed to serve as potential replacements for rabies immune globulin, but very slowly have such products survived the considerable hurdles for economic actualization in developing countries

(www.seruminstitute.com/content/prod_pipe.htm). Moreover, any serious considerations in the use of such MAbs also need a design strategy to address the major antigenic variation represented by the Lyssavirus genus as a whole (De Benedictis et al. EMBOMol Med. 2016;8:407). While dramatic reductions in human mortality have occurred from basic improvements in modern biologics applied before illness, such is not the case after encephalitis presents, where relevant compassionate care is critical at a minimum for reasonable medical management (Warrell. Trop Med Int Health. 201621:456). A greater understanding of the complexities of rabies pathobiology should provide inroads to the design and application of anti-viral therapy, as reflected in the evidence provided by relevant animal models (Gnanadurai et al. Oncotarget 2016;7:10694). Perhaps no other single project requires more prioritization than holistic human rabies prevention via joint One Health activities of enhanced laboratory-based surveillance, targeted educational community outreach and thorough mass vaccination of dogs, to make regional canine rabies elimination a reality in the near future (http://www.missionrabies.com/).

LET'S UNLOCK THE LABYRINTHIC PATHWAY FROM RABIES TO CANCER RESEARCH BY USING BHK 21/C13 „SECRET CODE"!

Anca Maria Cimpean, Dušan Lalošević, Marius Raica

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Abstract

Baby Hamster Kidney Fibroblasts (BHK 21/C13) have the ability to preserve their properties when they are transfected with different viruses and thus, they are used mainly in experimental virology and vaccine production. Few data are available regarding the use of this cell line in experimental cancer research, excepting the observation of their high invasiveness. Their phenotype is not known and this may be the reason for their limited use as an experimental alternative for testing different anticancer therapeutic agents. We aim to characterize this cell line regarding growth factors expression and markers known as therapeutic targets in other malignancies and also to test the behaviorof BHK 21/C13 cell line derived tumors implanted on chick embryo chorioallantoic membrane (CAM) and treated with anti podoplanin antibodies. Immunohistochemiscalassessment showed positive reaction for vimentin, CD117, smooth muscle actin (SMA), vascular endothelial growth factor (VEGF A), epidermal growth factor receptor (EGFR) and PROX 1 and negativity for platelet derived growth factor B (PDGF B), Neuron Specific Enolase (NSE), S 100 protein, CD34, Ewing Sarcoma and podoplanin in tumor cells. Despite of its rapid growth, low to medium proliferative rate has been detected together with a low intratumor blood vessels density. Tumors growing from BHK 21/C13 cells implanted on chick embryo chorioallanotic membrane were sensitive to disodium cromolyn and anti podoplanin antibodies, two therapeutic agents which produced a massive necrosis of implanted tumors. Despite controversial behavior (high invasiveness versus medium proliferation rate and low micro vessel density) observed in the present study, the immunohistochemicalcharacterization mentioned above represents the first step into revealing BHK 21/C13 cell line usefulness as a reliable tool for experimental cancer research.

PROVISION OF RELIABLE HUMAN RABIES IMMUNOGLOBULIN POTENCY TESTING BY THE RAPID FLUORESCENT FOCUS INHIBITION TEST RESULTING FROM LABORATORY STANDARDIZATION, REGULAR PARTICIPATION IN PROFICIENCY TESTING AND INTER-LABORATORY COMPARISON OF RESULTS

Srđan Stankov, Nenad Vranješ, Verica Simin, Dragana Vujin, Dušan Lalošević

Abstract

Rapid fluorescent focus inhibition test (RFFIT) has according to the prescription of the European Pharmacopoeia been used for Human rabies immunoglobulin (HRIG) potency determination. With regard to the need for maximal accuracy and precision for HRIG potency estimation on one hand, and to a relatively high inherent RFFIT variability on the other, repeated testing in at least three consecutive tests for the same sample is useful for attaining a satisfactory precision of the final result. This testing should be done in a laboratory accredited by ISO 17025 or ISO 15189 standard and taking part in proficiency testing for RFFIT at least once a year. In cases of discordant results between different laboratories for the same sample, with potential significant practical consequences, and when the respective reference laboratory is not able to solve the problem, one should be ready to take part in, or even organize an inter-laboratory comparison for finding the final most reliable result. Potency testing by RFFIT of HRIG produced in 2014 by Blood transfusion institute of Serbia in Belgrade was done comparatively in the National reference laboratory for rabies at Pasteur Institute Novi Sad and also in laboratories in Germany, Switzerland and Belgium. Concordance of obtained results was assessed according to 95% confidence limit prescribed by European Pharmacopoeia. Statistical analysis of results showed concordance of results between National reference laboratory for rabies at Pasteur Institute Novi Sad and the Swiss laboratory, while the results of the two other laboratories were significantly different. This example emphasizes the need for an integrative approach for assessment of credibility of laboratory results. Factors that should be taken into account are: accreditation of laboratories by ISO 17025 or ISO 15189 standard, with the respective test included in the scope of accreditation, regular participation in proficiency testingand the frequency of test performance in the laboratory.

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THE RECENT RABIES OUTBREAKS IN GAUTENG PROVINCE (SOUTH AFRICA) RESULTED FROM SEVERAL INTRODUCTIONS

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Keleabetswe Malepe & Claude Sabeta

Abstract

Rabies, a fatal viral disease, and one of the most feared in medical history, is an endemic disease in South Africa. In many parts of the world including Asia and Africa, the disease is a significant public health threat with at least 55 000 human deaths occurring annually mainly in these regions. In South Africa, the rabies situation is complicated by the existence of independent domestic and wildlife rabies cycles underpinned by cross-species transmission of the virus.

From January 2010 to December 2011, 53 animal rabies specimens mostly domestic dogs from southern Johannesburg were laboratory confirmed positive for rabies virus. This was the first report of a rabies outbreak in the greater Johannesburg area (previously considered to be rabies free) with evidence of local transmission in the domestic dog population. Subsequent to the 2010 dog rabies outbreak, there have been incidental dog rabies cases. However, the first half of 2016 recorded a total of 16 laboratory confirmed RABVs (from Gauteng) using the direct fluorescent antibody test and antigenic typing. The viruses were confirmed in the black-backed jackal species (n=10), bovine (n=4), dog (n=3) and a single virus from a honey-badger. The viruses were subsequently characterized using a panel of 16 anti-Nucleoprotein (anti-N) monoclonal antibodies for differentiation of south-

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ern African lyssaviruses. Subsequently, Trizol-extracted viral RNA was subjected to partial gene sequencing of the glycoprotein and G-L intergenic region of the rabies virus. The generated nucleotide sequences together with other previously characterized dog and jackal virus sequences were subjected to phylogenetic analyses using computer algorithms.

The confirmation of the majority of rabies positive cases in the black-backed jackal species probably indicates an expansion of their range. The reactivity patterns for the RABVs involved in the recent outbreak was consistent with that of southern African dog (canid) viruses which are maintained in dogs, jackal species and the bat-eared fox. The 2016 rabies outbreaks were as a result of two separate introductions probably from a wildlife (jackal) cycle and the other from a typical domestic dog rabies cycle. These data further underscore the complexity of rabies epidemiological cycles in South Africa and the challenges posed for the elimination of the disease from both domestic and wildlife reservoirs and vector species. Clearly, parenteral vaccinations of dogs should be upscaled and complimented with oral rabies vaccination of wildlife to effectively reduce RABV positive cases in both domestic and wildlife hosts.

HUMAN RABIES IMMUNOGLOBULIN: TWENTY FIVE YEARS OF PRODUCTION AND USE IN SERBIA

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Abstract

Twenty-five years of partnership between The National Blood Transfusion Institute of Serbia, Belgrade, and the Pasteur Institute, Novi Sad, is based on the mutual goal of producing human rabies immunoglobulin (HRIG).Each party have their specific role in the process whereas: The National Blood Transfusion Institute of Serbia (NBTI) performs: fractionation of human plasma from immunized donors using plasma pheresis and plasma fractionation,necessary laboratory monitoring, registration and preregistration of the final product with the authorities; in this case the Agency for Medicines and Medical Devices of Serbia.The Pasteur Institute is responsible for: vaccines for blood donors,laboratory identification of the content of antibodies in immunized donors and in the final product, distribution of the medicine to end-users via veterinarian clinics.The aim of this paper is to show the summary of results that that have been achieved, underlining the fact that no adverse reactions to human rabies immunoglobulin have been reported.During the twenty-five years of partnership the two institutes have produced 45,000 units of Human rabies immunoglobulin in doses of 1, 2 and 5 ml.

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ORAL VACCINATION OF FOXES IN THE REPUBLIC OF CROATIA – THE CURRENT STATUS.

Radovan Vodopija

Abstract

According to the Expert Committee on Rabies of World Health Organization (WHO), there are only two successful measures for eliminating rabies virus in animals and in humans. They are: 1. vaccination of dogs against rabies; 2. oral vaccination of foxes against rabies, which is the best method for elimination of rabies virus in wildlife. For many countries all over the world who are dealing with urban and sylvatic rabies, these measures represent „a dream“ due to a multitude of problems ranging from economic, financial, religious, all the way to the organization of health and veterinary services and facilities. The only way for these countries is to receive „help from abroad“ which is a multi-level approach including the state and local communities, raising awareness of the need to confront rabies, and properly educating the inhabitants and health and veterinary professionals. These are the main goals of GARC (Global Alliance for Rabies Control), which is promoting the „ONE HEALTH APPROACH“, not only when marking the WORLD RABIES DAY, but continuously. Instances of the success of this approach can be seen in Bali, and some parts of India and Africa. Being a new initiative, GARC aims to

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eliminate rabies all over the world by implementing the following key measures: responsible ownership, vaccination of dogs against rabies, education of the public, raising awareness of importance of fighting and eliminating rabies in dogs and wildlife including local communities, and educating health and veterinary professionals through the competent national authorities. The Republic of Croatia began implementing oral vaccination of foxes in 1991, and the effort lasted until 1996, when it was discontinued due to a lack of funds. During this period, 11 vaccination campaigns were performed in several counties. For the second time, oral rabies vaccination (ORV) started again in 1998, covering only the city of Zagreb and Zagreb County, and it was discontinued again. For the third time, ORV commenced in the Republic of Croatia in 2010, when only autumn campaign was done, and it was continued in 2011 with regular 2 campaigns (spring and autumn) and it is still going on according to this schedule. In several years of continuous performing of ORV in the Republic of Croatia (2010-2015), the results can be described as excellent. In the campaign the used vaccine for ORV was the attenuated rabies virus vaccine with strain SAD Bern, as one out four recommended vaccines for ORV. Result: from 11.3% of positive rabies isolates in domestic and wild animals (16% of foxes!) in 2010; till zero positive rabies isolates in domestic and wild animals (0% of foxes) in 2015. Due to these results, the Office of Veterinary affairs at Ministry of Agriculture is planning to proclaim the Republic of Croatia a rabies free country in 2018.

RABIES IN THE REPUBLIC OF CROATIA – PAST, PRESENT AND FUTURE

Radovan Vodopija

Abstract

The Republic of Croatia – the past

Establishing of the Pasteur Institute in Zagreb in 1918 meant also the beginning of antirabies activity in Croatia, because until then all persons bitten by rabid animals had to go to Vienna or Budapest to receive postexposure prophylaxis (PEP) against rabies. Responsible for the production of domestic vaccine against rabies prepared on infected rabbit brain tissue was Dr. Ljudevit Gutschy. When he produced the first batch of anti-rabies vaccine, Dr. Gutschy posted advertisements on the Zagreb Railway Station informing the public that they do not have to travel to Vienna or Budapest to receive vaccination, but can do it in the Pasteur Institute in Zagreb. On December 26th, 1918 the first domestic vaccine was applied in a bitten woman from Zagreb. This date represents the beginning of an era of anti-rabies activity in Zagreb and the whole of Croatia. From 1918 until 1979 different vaccines were used, all prepared on the animal neural tissue. In this period, three years should be singled out: 1948 when the mandatory vaccination of dogs against rabies was introduced; 1950 when urban rabies was eradicated and 1964 when the last case of human rabies in Croatia was registered.

The Republic of Croatia – the present

The present-day era of anti-rabies activity in the city of Zagreb and Republic of Croatia can be traced back to 1979 when a pregnant woman from Vrbovec received a new anti-rabies vaccine prepared on the culture of human diploid cells. Simultaneously with this accomplishment the cooperation with the National Reference Laboratory for Rabies in Novi Sad which produced and distributed rabies vaccine on animal neural tissue, the so-called Hempt-Nikolić vaccine was severed. Along with the adoption in regular use of the vaccination protocol of HDC vaccine, clinical investigations were carried out with other anti-rabies vaccines on cell cultures and embryonated eggs. In 1985 the book „Improvements in Rabies Post-exposure Treatment" was published in Zagreb, presenting for the first time results with the so-called 2-1-1 vaccination schedule, applying bilateral treatment on the initial day of vaccination. In 1986, the Zagreb Institute of Public Health received a letter from the Pasteur Institute in Paris endorsing the 2-1-1 schedule and stating that it is routinely used there. In 1992 the „Zagreb" or the 2-1-1 schedule was recommended by the WHO Expert Committee for Rabies. This recommendation, a tribute to the work of Professor Ivan JankoVodopija and his co-workers represents the greatest single recognition of Croatian contribution to preventive medicine. In 1989 we registered the first imported case of rabies in the Republic of Croatia, and soon after, in 1995 a second one. Both patients were from Bosnia and Herzegovina.

The Republic of Croatia – the future

Due to its contribution in the prevention and control of rabies, the Anti-rabies Station of the Zagreb Institute of Public Health became the National Reference Centre for Rabies in 2001. In all the years until now, its work was carried out successfully. It briefly lost the

above title in 2013, but it was returned in 2014. In addition to the efforts in the area of human medicine, a great job was done by the Office for Veterinary affairsat the Ministry of Agriculture of Croatia, by introducing oral vaccination against rabies in three turns: from 1991 until 1996, in 1998 on the territory of the City of Zagreb and the Zagreb County, and again in 2010. In 2011 a complete campaign of distributing baits from the airplane was conducted in spring and autumn. The results of this oral vaccination of foxes in the period 2010 – 2015 were incredible: from 11.3% of positive, i.e. proven rabid wild and domestic animals on the area of the Republic of Croatia in 2010, we arrived at 0% of positive, i.e. not a single rabid wild or domestic animal in the country in 2015. The Office for Veterinary affairs at the Ministry of Agriculture of Croatia, based on the above results, plans to declare the Republic of Croatia a rabies-free country in 2018.

WHO STANDARDS FOR EVALUATION OF RABIES VACCINES - CURRENT STATUS AND WAY FORWARD

Ivana Knežević

Abstract

As part of its biological standardization program, the WHO provides international standards that underpin the assessment of vaccines and other biologicals and provide the basis for defining acceptance criteria for licensing these products. In addition, WHO standards also serve as a basis for WHO prequalification of vaccines. In this context, written specifications provide a tool for harmonization of the specifications of biologicals worldwide. The WHO is also responsible for the provision of the International Standards and Reference Preparations that are considered as measurement standards. They are used to standardize biological assays globally. These preparations define the International Unit of biological activity and provide a basis for calibration of assays. They are used as primary standards for the establishment of secondary (working) standards. WHO Collaborating Centers for biological standardization play a pivotal role in the development of international reference preparations.

Both the written and measurement standards are based on scientific evidence and reflect a consensus among experts working in the field in question. They are formally adopted by the WHO Expert Committee on Biological Standardization (ECBS) and are available to the users, free of charge. Detailed information about WHO international standards for biologicals can be found at WHO biologicals web site (http://www.who.int/biologicals/en/).

One of the most important elements in the effective control of human rabies is the use of rabies vaccines of assured quality, safety and efficacy as part of pre-exposure vaccination and post exposure prophylaxis. Evaluation of rabies vaccines requires an excellent expertise in performing in vitro and in vivo assays, conducting analysis and interpreting data that are necessary for licensing and lot release of these vaccines. Since the last revision of WHO Recommendations for inactivated rabies vaccine for human use produced in cell substrates and embryonated eggs in 2005, many efforts were made to improve laboratory testing of these vaccines as well as other aspects of rabies vaccine evaluation.

This presentation will provide overview of the current issues and future directions in characterization of rabies vaccines, cell substrates, genetic sequencing of rabies virus, improvements of potency testing and stability evaluation. In particular, key principles for quality, nonclinical and clinical evaluation of rabies vaccines for human use will be discussed.

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WHO RECOMMENDATIONS FOR POTENCY TESTING OF RABIES VACCINES - 3RS IN THE CONTEXT OF RABIES VACCINE EVALUATION

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Abstract

WHO has played a key role for over 60 years in establishing international biological reference preparations necessary to standardize vaccines and other biological substances as well as developing and updating WHO guidelines and recommendations on the production, control, nonclinical and clinical evaluation of biological products. These norms and standards, based on scientific consensus achieved through international consultations, assist 194 WHO Member States in ensuring the quality, efficacy and safety of biological medicines and related in vitro biological diagnostic tests worldwide. The Organization

accomplishes this work through its biological program, the WHO Collaborating Centres, and the WHO Expert Committee on Biological Standardization (ECBS). This involves close collaboration with the international scientific and professional communities, regional and national regulatory authorities, manufacturers and expert laboratories worldwide.

WHO supports the concept of replacement, reduction and refinement in the use of animals, known as principles of the 3Rs, with respect to developing, producing, testing and characterizing vaccines for human use through its program of biological standardization.

This presentation will provide examples of the application of principles of the 3Rs to potency and stability testing of rabies vaccines for human use. The use of the National Institute of Health (NIH) rabies vaccine potency test, based on a mouse protection assay with multi-dilution doses of vaccine suspension, has long been recognized as a reliable assay for testing potency of rabies vaccine. WHO recommends the use of validated humane end points in recording results of potency testing for rabies vaccines and makes it possible to use a single dilution assay for the NIH potency test. Furthermore, it is clearly stated in WHO Recommendations for rabies vaccines that there is no additional value in performing an accelerated stability test for the purpose of lot release. Since this test is based on the NIH test for potency after exposure to the elevated temperature, this statement led to discontinuation of this test on a lot-to-lot basis in a number of countries, resulting in significant reduction of the number of animals.In addition, recent developments of alternative assays for potency testing of rabies vaccines will be discussed.

REZULTATI ISKORENJIVANJA BESNILA KOD ŽIVOTINJA U SRBIJI U PERIODU 2007-2016.

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Abstract

I pored toga što se radi o najstarijoj poznatoj zoonozi, slučajevi besnila se i dalje neredovno prijavljuju nadležnim službama u pojedinim oblastima širom sveta, iako se zvanično evidentira više desetina slučajeva bolesti kod ljudi svake godine. Svetska organizacija za zdravlje životinja (OIE), zajedno sa Svetskom zdravstvenom organizacijom (WHO) i Organizacijom za hranu i poljoprivredu(FAO), preuzela je liderskу ulogu u smanjenju rizika od pojave besnila kod životinja i ljudi, unapređenjem kapaciteta zemalja članica za kontrolu i eliminaciju bolesti kod životinja, izvora bolesti, praćenjem epizootiološke situacije širom sveta, utvrđivanjem adekvatnih kontrolnih mehanizama i pružanjem podrške u prevazilaženju teškoća sa kojima se suočavaju veterinarske službe u primeni OIE standarda.

Suzbijanje besnila na teritoriji Republike Srbije u cilju potpunog iskorenjivanja kod životinja i zaštite javnog zdravlja, sprovodi se dugi niz godina. U posmatranom periodu, uočavaju se značajni rezultati u sprovođenju definisanih aktivnosti, pri čemu se pozitivni efektiogledaju u povećanju obima vakcinacije pasa, unapređenju monitoringa kod domaćih i divljih životinja, smanjenju broja životinja kod kojih je postavljena sumnja na besnilo i smanjenju broja dijagnostikovanih slučajeva. Sprovođenje programa iskorenjivanja besnila, dovelo je do progresivnog smanjenja broja slučajeva kod životinja: na početku perioda ispitivanja, 2007, 2008. i 2009. godine, dijagnostikovano je 160, odnosno 234 i 183 pozitivnih slučajeva, da bi u narednim godinama došlo do značajnog opadanja, pri čemu je poslednji slučaj kod domaćih životinja zabeležen 2012. godine, dok je kod divljih životinja u poslednje tri godine zabeleženo samo po 3 pozitivna slučaja.

Aktivnosti koje su doprinele signifikantnom poboljšanju epizootiološke situacije u zemlji, bazirane su na unapređenju pravnog okvira, utvrđivanju strategije iskorenjivanja besnila, uvođenju obaveznog obeležavanja pasa i mačaka, primeni modernog veterinarskog i laboratorisjkog informacionog sistema, podizanju dijagnostičkih kapaciteta, obezbeđivanju finansijskih resursa i adekvatnog mehanizma za upravljanjem svim aktivnostima. Od ključnog značaja, kada su domaće životinje u pitanju, bilo je unapređenje vakcinacije pasa i mačaka, kao i evidentiranja vlasnika ovih životinja i njihovog obeležavanja, počev od 2007. godine. Takođe, od jeseni 2010. godine uveden je održiv program vakcinacije divljih mesojeda koji se u kontinuitetu sprovodi do današnjih dana. Istovremeno, značajno je unapređen monitoring i nadzor besnila kod domaćih i divljih životinja, što se ogleda u značanom povećanju broja uzoraka koji se ispituju u ovlašćenim laboratorijama.

U radu su opisani osnovni elementi od kojih zavisi ostvarivanje postavljenog cilja, odnosno eliminacije besnila ne samo u Srbiji već i u širem području Balkana i Evrope, konkretne aktivnosti nadležnih službi, kao i rezultati u sprovođenju strategije iskorenjivanja besnila.