Ann Ist Super Sanità 2016 | Vol. 52, No. 4: 587-597
DOI: 10.4415/ANN_16_04_21

Smallpox as an actual biothreat: lessons learned from its outbreak in ex-Yugoslavia in 1972

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Abstract
Variola (smallpox) virus is classified as class A of potential biological weapons, due to its microbiological, genetic, antigenic and epidemiological characteristics. The potential danger is more real because vaccination against smallpox has stopped since disease eradication in 1979. That is why we want to share our unique, rich experience and acquired knowledge in the fight against this highly contagious and deadly disease during the smallpox outbreak in ex-Yugoslavia in 1972. It was the largest postwar outbreak in Europe when there were officially registered 175 ill patients, 35 of them with lethal outcome. This outbreak was specific by the time of its occurrence, the affected territory, dimensions and some epidemiological characteristics, but also by the well-organized, synchronized and efficient reaction of the competent state services in the fight against it.

Key words
- smallpox-variola
- outbreak
- Yugoslavia
- bioweapons

SMALLPOX AS A HISTORICAL HEALTH THREAT

Variola is considered one of the most deadly diseases in human history that decimated the population and significantly changed the course of civilization development. The origin of smallpox is unknown. It is believed that it first appeared about 10 000 BC in northeast Africa, from where it spread to the Far East, up to India and China. The oldest credible confirmation of the smallpox presence in Africa was found in 1500 BC in Sanskrit writings about the deity-protectors of smallpox, while on the mummy of Egyptian ruler Ramses V (1100 BC) were observed lesions that indicated that he died of smallpox [1, 2].

Hippocrates (460-370 BC) did not mention this disease, while Galen described it in the 2nd century [3]. In the 6th century the epidemic in Mecca was mentioned. It is believed that the virus was introduced into Europe in the period between the 5th and 7th century, during the invasion of the Saracens from North Africa, across the Pyrenees, but variola might have arrived in Europe through natural ways of communication from Asia Minor. It caused frequent outbreaks during the Middle Ages and the New Age, when smallpox was the most deadly disease in Europe causing the death of about 400 000 Europeans annually, including 5 rulers [1]. In the 15th century Spanish conquerors brought a smallpox virus to the territory of Cuba and Mexico, where in the first outbreak wave the entire tribes of native inhabitants perished. At the time when the European colonizers conquered the New World, smallpox was used as a strong biological weapon against powerful empires of the Aztecs and the Incas, and many Indian tribes [4]. In Australia the variola appeared in the 19th century, when the epidemic broke out in Sydney [3].

During the 20th century a smallpox virus caused 300-500 million deaths in the world. In the period between 1950 and 1971, smallpox found its way into Belgium, Canada, Czechoslovakia, Denmark, French, East and West Germany, Spanish, England, Italy, Holland, Poland, Switzerland, Sweden and the USSR, mostly via travelers from endemic foci causing many outbreaks. In each of the mentioned epidemics the number of registered cases was under one hundred [5].

This is why, in 1967, the World Health Organization (WHO) launched a global campaign for the disease eradication, when the vaccination against smallpox included all current and potential foci [6]. The campaign was successfully completed in 1979, and on the 8 May, 1980, WHO proclaimed the eradication of smallpox. It was recommended that only two laboratories in the world (in Russia-the former Soviet Union and the United States) retain the virus, while others were obliged to destroy it. The time of its destruction in these laborato-

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ries was not definitely determined. After eradication, the mass vaccination against smallpox was terminated [7].

BACKGROUND INFORMATION AND TODAY'S CHALLENGE

Variola virus is classified as the genus *Orthopoxvirus*, family *Poxviridae*, together with some animal poxviruses such as vaccinia virus, monkeypox, camelpox, mousepox, rabbitpox, and others [8]. The origin of variola virus is unknown and there is no evidence that the nature of smallpox during the centuries has undergone some changes [9]. In the 20th century, numerous researchers investigated correlation among smallpox and another animal poxviruses with the aim of explaining its origin and thus finding the most biological, immunological and epidemiological similarity between smallpox and monkeypox which can induce illness in humans, and be transmitted from human to human. It was also very hard to confirm differences of smallpox and camelpox-"white poxvirus" [10-17]. During smallpox epidemic in 1975 Lourie *et al*. from trapped rodents-Gerbil in North Africa isolated pox virus that was biologically more similar to variola minor (alastrim) than variola major [18]. According to these findings there is possibility that monkeys or rodents could be natural reservoirs of the smallpox virus in Equatorial Africa, or they could also be infected from some unknown reservoirs in wilderness [19] The infected persons are usually virus reservoirs during the disease outbreaks.

Until the discovery of Marburg and Ebola viruses it has been described as the biggest human virus, whose size is 150-360 nm. It is surrounded with a symmetrical capsid envelope with lipoproteins and hemagglutinins and contains a double-stranded DNA with 200 000 base pairs. Smallpox is spread by direct contact with an infected person, as well as through air-droplets and aerosols. The virus is relatively stable in the environment, so that in the form of an aerosol it preserves the infectivity even for several hours. The disease can be transmitted via contaminated clothes and some other items, when the risk of infection is less [20]. The incubation period usually lasts 7-17 days, after which flu-like symptoms appear: fever, malaise, headache, prostration, back pain, and sometimes abdominal pain and vomiting. The characteristic rash appears after 2-3 days, first on the face, hands, forearms, and later on the body. Lesions occur on the mucous membranes of the nose and mouth quickly transforming into ulcers, then progressing from the macula into the papules, pustules and vesicles finally appearing in the form of the crusts that fall off, leaving typical scars. There are two basic clinical forms of the disease: variola major, which has a more difficult clinical course and mortality up to 30% and variola minor (alastrim), which has a milder clinical course and mortality of less than 1% [21]. The hardest forms of the disease are hemorrhagic and malignant (flat) variola, characterized by severe toxemia with flat confluent lesions and high mortality rate up to 96-100%, after 5-6 days. The infected persons are most contagious during the temperature rise and in the first week of rashes, when the virus is released via the respiratory tract. Contact with the sick in the later stages of the disease rarely leads to infection.

Microbial diagnostics of smallpox includes a direct electron microscopy of all stages of skin lesions samples as well as virus isolation, using *in vivio* (chicken embryo) and *in vitro* (cell culture) systems. Detections of antigens and antibodies in the patient blood are also very useful methods to confirm infection. The methods of molecular genetics such as PCR, which can rapidly and reliably detect the virus particles are certainly of the greatest significance nowadays. Laboratory work with infectious material, containing smallpox virus, should be conducted using the highest level of biological safety containments (BSL4) [20].

The treatment of a smallpox patient is conducted by symptomatic therapy while the vaccine can be used in the post-exposure prophylaxis in 4 days after exposure for obtaining protective immunity, preventing infection and alleviating the symptoms of the disease. Specific monoclonal antibodies can be used for treatment of immunocompromised persons. It is also worth mentioning that the smallpox vaccine was the first vaccine in history made by Edward Jenner in 1796 [22]. The first Law on vaccination against smallpox was adopted in 1874 in Germany. The vaccination in Serbia began in 1881 with the imported vaccines while since 1901 home-made vaccines produced at the Pasteur Institute in Nis, Serbia were used [23]. After first vaccination, the protection level is high in the first five years, after revaccination it is maintained longer, while it lasts about 30 years after the 3rd dose. The vaccine against smallpox causes a large number of adverse effects, especially in infants and people with immunodeficiency and in persons with chronic diseases.

Due to its microbiological, epidemiological and clinical characteristics, then the possibility of the virus spreading with aerosol and among people, the smallpox virus is classified by the CDC in class A of potential biological agents. According to available data, this virus entered the arsenals of biological weapons of the most powerful countries in the world during the Cold War and was the subject of serious research, including its recombination with Ebola virus [24]. The virus is well-studied at the molecular level and it can easily be genetically modified in order to prevent the effects of the vaccine or to increase the virulence. The virus as the biological weapon can be easily cultivated and it is possible to produce large quantities in a relatively short period. It is very resistant to the environmental agents and can survive their impacts for months and years [25]. The use of smallpox as a biological agent is also supported by the fact that a large portion of the world population is vulnerable, susceptible to this virus, since the vaccination was terminated after its eradication, mortality is high, and there is no specific therapy [26]. The real fear of the application of smallpox virus as a potential biological agent is also supported by the fact that in the last years of the 20th century in some countries in the world began the intensive production of vaccine against smallpox. Considering that this is a highly contagious agent where one infected person can transmit the infection to 10 or 20 others, special protection measures are required in the management of patients (room-isolators with negative air pressure and accompanying protective equipment that prevents the infection spreading) as well as during microbiological processing of the samples (BSL 4 laboratories) so that its breakout might lead to big problems in health care activities, as well as in all other public services, especially in undeveloped countries [25, 27].

In today's world of global contradictions, the use of biological weapons, including smallpox, poses a real danger, both in war and in bioterrorist actions when the agent has been acquired by individuals or groups with nefarious intentions over which no one has any control. This danger has particularly come to the fore after 11th September, 2001, and the attack on the World Trade Center in New York-USA and a subsequent anthrax campaign leaving in its wake 11 victims. In this context, the smallpox virus could again become an obvious present-day danger. In view of all the above-mentioned, it is extremely important to strengthen the awareness of this problem, monitor the epidemiological situation and take preventive measures, and, above all, to have adequately prepared human and material resources for the response in case of disease occurrence. In that regard the unique experience and lessons of the previous epidemics and responses of the relevant services in these situations are extremely valuable.

An outbreak of smallpox that engulfed the former Yugoslavia in 1972 was combated quickly and efficiently. The circumstances under which the outbreak started, the number of cases reached before smallpox was identified, the economic damage it caused, as well as the taken measures need to be analyzed carefully.

VARIOLA IN YUGOSLAVIA IN 1972: EPIDEMIOLOGICAL DATA AND ANTI-OUTBREAK MEASURES

The outbreak of smallpox in Yugoslavia broke out just in a period of intense campaign for disease eradication. It was the largest post-war outbreak in Europe. Both then and now, there were doubts and speculations that it might have been a bioterrorist attack on Tito's Yugoslavia as well as many other interpretations [28], although scientific facts do not support these claims. The beginning of outbreak was registered on February 16th, and the last case was reported on April 11th, 1972. The outbreak affected a total of 175 persons, 35 of whom (20%) died. Among the patients there were 99 (56.6%) men and 76 (43.4%) women. The 174 patients were registered in the Republic of Serbia (Central Serbia: 49 cases, 8 of them with lethal outcome; Autonomous Province of Kosovo: 124 ill persons, 26 of them died; the Autonomous Province of Vojvodina: 1 person was infected and died), while one case was recorded in the Republic of Montenegro [29]. Spreading of disease across the country is shown in *Figure 1*.

Epidemiological data and serological tests showed that a pilgrim Ibrahim H. from the village of Danjane (Orahovac near Djakovica) brought the smallpox into Yugoslavia. He visited Mecca and Medina (Saudi Arabia) with another 24 pilgrims from Kosovo and returned by bus across Iraq, visiting dervish shrines around Basra and Baghdad where at that time there were more patients suffering from smallpox [30]. Upon returning to the village, the pilgrim Ibrahim H., according to his own testimony, had some mild symptoms of fatigue and

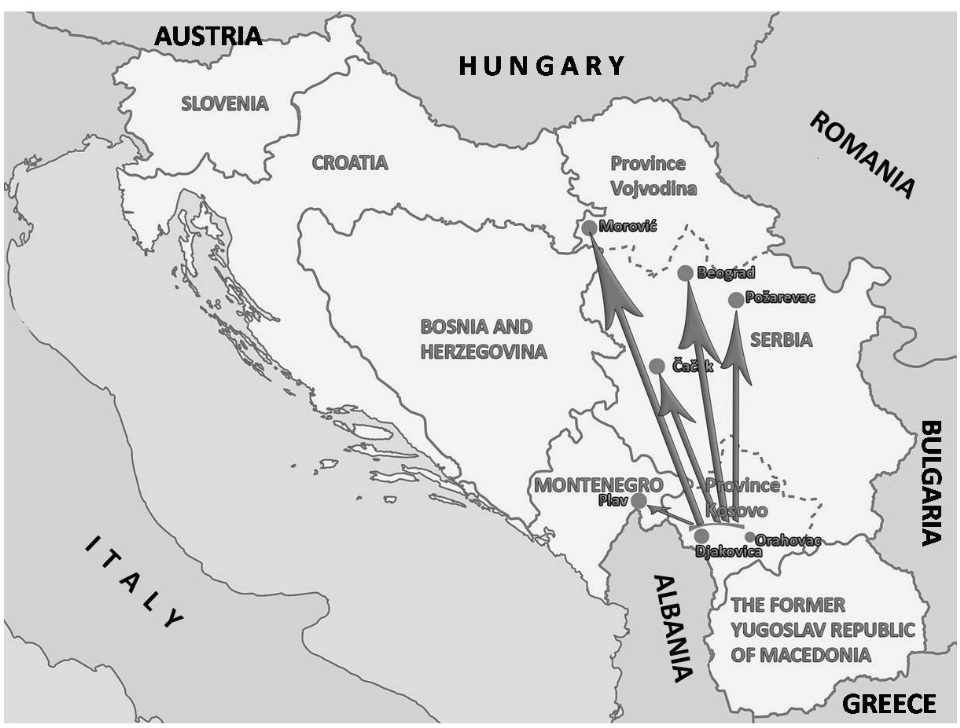

Figure 1
Smallpox in Yugoslavia. Spreading of disease from primary focal point in Kosovo.

chills, and several small pimples on the face that also confirmed the barber who would not do Ibrahim's face treatment. However, a month later, on his face and body were not found any scars, and no traces of vaccination, although it was carried out in December 1971 in the Institute for Health Protection in Skopje (Macedonia), before traveling to Holy places. Following law, all hajj participants were previously vaccinated against smallpox by lyophilized vaccine produced in the Institute of Immunology in Zagreb (Croatia), as well as against cholera. After vaccination, all of them received certificates, under the provisions of the WHO International Health Regulations, but the success of vaccination was not controlled. By testing the sera of passengers who travelled on the pilgrimage by bus in which was the first infected person, it was found that 20 of them had no satisfactory vaccination antibody titer, which opened up a number of issues related to the failures in the implementation of measures of immunization against smallpox [2, 30].

According to the WHO estimates, in Yugoslavia the measures of control of all the passengers coming from infected areas were implemented and pilgrims were treated as a particularly risky group. So it was required that a pilgrimage be organized by plane, with pre-sanitation and checking, health control during the trip, as well as health surveillance after return. All those recommendations were generally enforced, in agreement with the Islamic community, but nevertheless there were some private arrangements, such as the one with the person who travelled on pilgrimage by bus and subsequently brought in the disease [31]. Otherwise, in the WHO's report Iraq first appeared as the smallpox infected area in March of 1972. All pilgrims stated that during the trip they were healthy. They were revaccinated during the outbreak. Serological examination of their samples was performed before revaccination at the Institute of Virology, vaccine and sera in Belgrade, the national reference laboratory for smallpox in Yugoslavia, as well as in the laboratories of the Center for Disease Control and Prevention (CDC) in Atlanta (USA). The results showed significant differences of positive findings in the sera of Ibrahim H. compared with sera of other pilgrims. Therefore, it was considered that Ibrahim H. as an index case was a probable source of infection for next 9 cases [2, 30]. The scheme of infection origin and further spreading is shown in *Figure 2*.

The outbreak in the Province of Kosovo developed into three generations: 9 cases in the first, 100 in the second, and 14 cases in the third, plus the index case. The number of secondary infections from one source was closely connected with the length and intimacy of contact between patients and vulnerable people, and depended on the clinical form and stage of the disease at a time when the contact was established. Patient Ljatif M, one of 9 contacts with index case developed severe atypical changes in the skin and mucous membranes and caused the largest number of secondary infections. He had hemorrhagic and always deadly but unrecognizable form of smallpox. Diagnosis was established post mortem on the basis of virologically confirmed smallpox infection in numerous contacts, the number of platelets and reduced amount of blood coagulation factors. Since he was found to be severely allergic to penicillin, the patient was introduced before his death to the groups of students and also stayed in several medical institutions. Thus, 38 persons were infected in direct contact with him which represents the largest number of infections from one person as reported in the world literature [32].

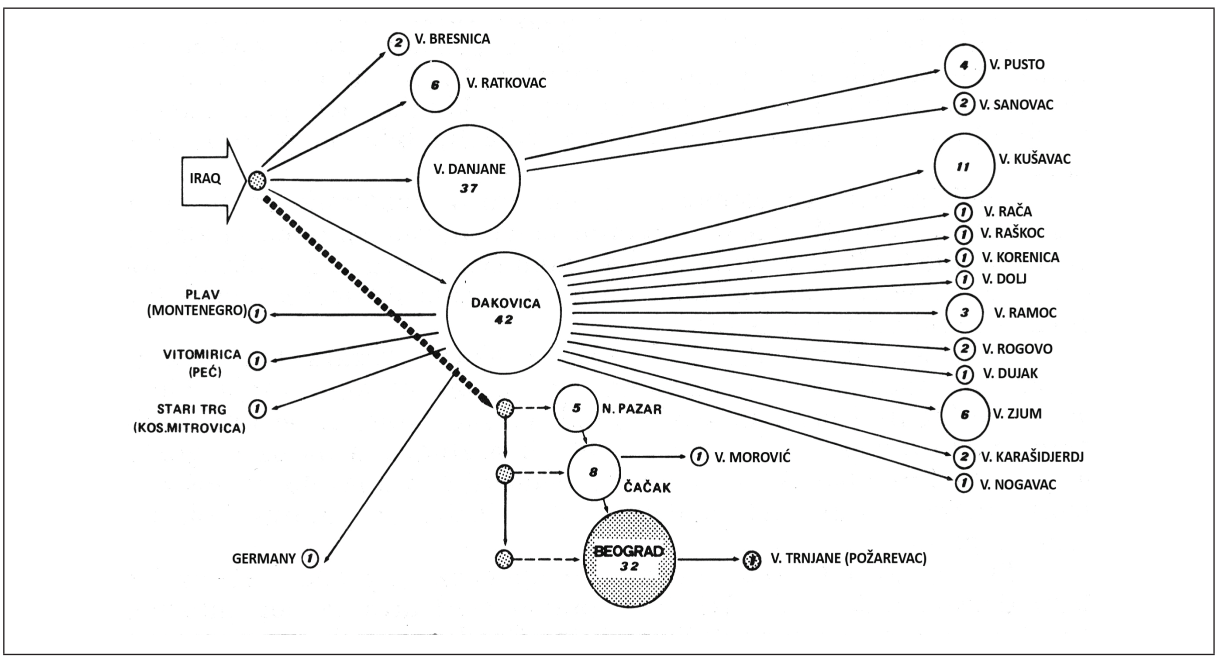

Figure 2
The origin and spread of smallpox epidemic. Source: Dovijanić P, *et al. Social-medical character of combating against smallpox outbreak in Belgrade*. Proceedings of the Symposium Smallpox Outbreak in Belgrade. 1972. p. 15. [In Serbian]

Out of 175 patients, 105 of them (60%) were previously vaccinated, 66 (37.7%) were unvaccinated, while in 4 of them (2.3%) the vaccination status was unknown as it is shown in the *Table 1*. It is necessary to emphasize the big difference in the fatality rate among previously vaccinated (8%) and unvaccinated persons (35%). Otherwise the compulsory vaccination of children in Yugoslavia was carried out at the age of 6 months to 3 years (primary vaccination), with mandatory revaccination at 7 and 14 years. The control of vaccination success in some areas was not adequate, so the significant decline of vaccine immunity after primary vaccination and the lack of revaccination led to disease occurrence in the young population [33].

One of the specificities of this outbreak was a relatively high percentage of hemorrhagic forms of diseases as it is shown in *Table 2*. Early and late hemorrhagic forms appeared in 8.0% of registered smallpox cases with severe pain, bleeding and temperature. All patients died in the first week of illness. This form of disease appeared in both vaccinated and unvaccinated persons. The standard anti-shock therapy did not give positive results, due to continuing increase in viral load and new tissue damage [34]. In the sample of a nurse from Belgrade, with this form of smallpox, just before death, were registered 21 750 viral particles in 1 ml of blood [2]. The other authors previously published similar results but the number of virus particles was never at any time over 10 000 particles in 1 ml of blood [1, 35, 36]. Malignant (flat) form appeared in 19 cases, including 7 under one year of age. Only one person among them, a pregnant woman, had a vaccination scar [37]. Three patients with this smallpox form received a transfusion of fresh blood of vaccinated people and convalescents, which had favorable therapeutic effects, and represented a significant contribution to the practice of treating the disease [38]. Ordinary forms of disease were registered in 72 cases. The prognosis in this form was relatively good. Death outcome occurred in the elderly, immunocompromised, and those with impairments of other organs. In the four of seven deaths, the immunization scarring was not detected. Modified smallpox form was detected in 67 patients, without a single fatality. Most of them, 61, were with the old vaccine scars. This form did not represent a problem in therapy, but it was a diagnostic challenge because the rash drying happened in the stage of papules or vesicles, while pustulisation was rare and did not affect any efflorescence. Due to the scarcity of material the cultivation of the virus became more difficult, while the serological diagnosis was the only available option, although in most patients antibody titers were low. These forms had a good prognosis and required only symptomatic treatment [39]. Variola sine exanthemata was identified in 3 cases on the basis of clinical and serological criteria [40]. It is assumed that there were more patients with subclinical forms of disease, but serological tests were not performed. Eight of 14 affected infants died. The affected children were mostly from Kosovo, they were not vaccinated, but the vaccination status of mothers affected the occurrence of the disease, its manifestation and prognosis [41].

Different clinical manifestations of smallpox in Yugoslavia are shown in *Figure 3*. The previous state, genetic predispositions, immune and vaccination status had a major impact on clinical picture of patients. Three of 6 patients with previous hepatitis infection died, as well as two patients with pertussis, and the patient with tuberculous meningitis. The previous vaccinations had the biggest impact on the clinical manifestations of disease. Ordinary forms occurred more frequently in unvaccinated people, as well as the flat forms, while the modi-

Table 2
Diseased and deceased from various clinical forms of smallpox during Yugoslav outbreak in 1972

Clinical form	Number and percent of diseased	Number and percent of fatal cases
Early hemorhagic	13 (7.4%)	13 (100%)
Late hemorhagic	1 (0.6%)	1 (100%)
Flat (variola maligna)	19 (10.8%)	14 (73.7%)
Ordinary	72 (31.2%)	7 (9.7%)
Modified	67 (38.3%)	0 (0%)
Variola sine exanthemate	3 (1.7%)	0 (0%)

Table 1
Vaccinal status and age distribution of diseased and deceased persons in the smallpox outbreak

		Age groups					
		0	1-6	7-14	15-19	≥ 20	TOTAL
	Vaccinated		1	6	7	91	105
Diseased persons	Not vaccinated	12	14	13	6	21	66
	Unknown					4	4
Total number of diseased persons		**12**	**15**	**19**	**13**	**116**	**175**
	Vaccinated			1	1	6	8
Fatal cases	Not vaccinated	8	3	3	2	7	23
	Unknown					4	4
Total number of fatal cases		**8**	**3**	**4**	**3**	**17**	**35**
Lethality (%)		**66.7**	**20**	**21**	**23**	**15**	**20**

Figure 3
Different clinical manifestations of smallpox in Yugoslavia A: early hemorhagic variola with purpuric skin changes; B: ordinary form: variola pustulosa confluens, 9th day of the illness; C: intrahospital infection; 4-months old baby died on the 14th day of the illness. (Photo: V. Šuvaković, M.Kecmanović; source: *Variola in Yugoslavia in 1972*. Proceedings of the Yugoslav Symposium on Smallpox, Primošten: 1972. [In Serbo-Croatian])

fied forms and variola sine exanthema appeared only in people with vaccine scars. Lethality was also three times higher in people without immunization scars [42].

During Yugoslav smallpox outbreak, microbiological diagnosis was performed in the National reference laboratory for smallpox in the Institute of Virology vaccine and sera in Belgrade using electron microscopy (EM) – method of negative staining, poxvirus antigen detection by immunodiffusion precipitation method in agarose gel (AGID), virus isolation on chorion-allantoic membrane (CAM) of chicken embryos and serologic assays of hemagglutination inhibition (IHA), complement fixation (CF) and neutralization test (NT). The same choice of diagnostic procedures at that time was carried out by the laboratories for smallpox of CDC Atlanta, which had a long experience in combating and eradication of smallpox in West Africa and Brazil [43, 44].

Skin lesions of 93 patients suspected of smallpox were tested. Virus isolation on CAM chicken embryo gave a high percentage of positive results (over 90%) as well as the data about the nature of pox virus isolates (variola or vaccinia). This method was very suitable for the isolation of the virus from the blood in the early days of the disease and especially valuable in fulminant hemorrhagic form, when the patient did not have significant skin lesions or death occurred quickly. The disadvantage of the method was the long duration of the process (48 to 72 hours). The method of EM with negative staining proved to be a fast, highly sensitive and accurate method, but it did not distinguish variola virus from other poxviruses, particularly a vaccinia virus that was used as vaccine in mass. AGID method for detection smallpox infection was also a very fast method, but gave the lowest percentage of positive results (below 60%) and required a greater amount of material. Therefore, the combination of EM and isolation in chicken embryo CAM gave the best result in the virology diagnostics [44]. Serological methods are used for examination of 410 blood samples taken from 124 patients. It was found that the significant antibody titers (1:80 and 1: 160) were registered on the fourth day of the disease, depending on the used methods, while the highest antibody levels were recorded between the third and seventh week of the onset of the disease, which was consistent with results of other authors. The combination of the listed diagnostic methods provided an opportunity for retrograde diagnosis of smallpox, which was particularly important for finding sources of infection and detection of subclinical infections. According to these criteria it was determined that a pilgrim, Ibrahim H., was the index case in the Yugoslav outbreak. In addition to the high positive findings in the IHA, CF and NT, his serum samples taken on March 16, 1972, were positive in agar-gel precipitation with vaccinia and variola antigen. The serum was positive in NT even in the dilution 1: 4.096 that was not registered in any other sera of pilgrims. The obtained results with applied AGID test using variola antigen were different from all published data so far. Precipitins antibodies in our patients were found from the first day of illness up to 4 months. It was also observed that patients with low values of virus neutralizing antibodies, and with the high values of IHA, CF and AGID antibodies died of smallpox. Previous vaccination status had a visual impact on the time of occurrence, as well as the value of antibodies that inhibit haemagglutination, which fix complement and antibodies that neutralize the virus, but had no tangible impact on results in the AGID reaction. Serology tests had important role in discovering of unapparent infections, atypical smallpox cases and discovering source of infection [2].

About 52% or 91 people were infected outside the hospital, while 84 patients or 48% were infected in hospitals. The exception to this percentage represents the focal point in the province of Kosovo, where the outpatient cases were twice as frequent. Otherwise, a common feature of postwar smallpox outbreaks in Europe was that most of the patients were infected in hospitals (index 2.4:1.6), while in the Yugoslav outbreak the situation was reverse (*ratio* 1.1: 2.0) [45]. Another specific feature of the outbreak in the primary focus referred to the fact that the focus of nosocomial infections in this area, in addition to infective was a maternity ward, although the exact way how virus entered the maternity hospitals was not determined. The characteristic of the outbreak was the great number of the affected infants, 14, or 8% of the total number of patients, which was the largest number of the diseased children of this age in all postwar smallpox outbreaks in Europe [41].

Vaccination in the first foci started already on 16th

March, one day after virology confirmation of smallpox diagnosis. By the decision of the competent authority, the Federal Epidemiologic Commission, vaccination was later extended to the entire population of Yugoslavia, so that the measure covered a total of 18 million people. Among vaccinated, were many pregnant women. In 180 of them, the blood samples were taken from mothers and from umbilical cord of their newborns, for detecting of IHA antibodies. In 95 of tested pair sera higher values of vaccinia antibodies (from 2-16 times) were confirmed in new born children than in mothers' sera. The concentrations of IgA and IgM immunoglobulins were higher in sera of mothers, while IgG concentrations were higher in sera of newborns. The isolation of vaccinia virus was tried from fetal tissue of vaccinated mothers after abortion, but it was not successful. Herpes virus was isolated from one tissue sample. Among vaccinated women, we found the data related to about 110 women vaccinated within first 3 months of pregnancy and 300 women vaccinated after 3 months. As most women from the first group had an abortion, the destiny of newborns from 247 vaccinated mothers was monitored. All children were healthy and had normal constitution that is particularly important [46-48].

The treatment by Marboran and vaccinia gamma globulin, hyperimmune anti-variola serum was also conducted during the outbreak [49]. All health institutions in the country undertook adequate measures to combat smallpox and stop bad effects of vaccination on the entire population. Health surveillance of hot spots in the province of Kosovo included the daily tour of the population, temperature taking and checking of the skin and the oral mucosa. In the search for contacts, nearly 3000 surveys were carried out in Belgrade [50]. Contacts were taken care of in special quarantine institutions, but there were also quarantined individual households and whole villages. Restrictions on population movements from infected areas, the control of vaccination success and prohibition of public gatherings were widely applied measures. As the primary immunization after contact was the main protective measure, many people who subsequently came in contact with smallpox patients did not get the disease. Yet primary immunization after contact in the Yugoslav outbreak had no greater impact in terms of reporting milder clinical forms of the disease, which was contrary to the then available literature data on the existence of clinical modifications after the primary vaccination in the first six days after risk contact [51]. But the persons with old scars in most cases had a clearly modified clinical picture, regardless of whether a booster shot after contact was successful or not [52].

ORGANIZATION OF THE YUGOSLAV HEALTH SERVICE AND THE WHOLE SOCIETY IN THE FIGHT AGAINST SMALLPOX

The health service in Yugoslavia was seriously prepared for the case of importing smallpox virus within an organization fighting quarantine diseases. The National Reference Laboratory for smallpox was founded in 1966 at the Institute of Virology, Vaccine and Sera "Torlak" in Belgrade, Serbia. Already in 1967 in the laboratory was isolated and studied the Marburg virus imported with shipment of 300 monkeys from Africa [53]. The adequate equipment including electron microscope was procured. Diagnostic procedures were also being tested. The laboratory team consisted of two experts and one medical technician responsible for virology work and two experts for electron microscopy. Previously, the experts for training visited the laboratories that were involved in the diagnosis of this disease in England and West Germany. The laboratory did not have a separate building. It was located in the same place as a laboratory for arboviruses and hemorrhagic fevers at the building for the entire virology, including the production of viral vaccines. The entire staff of virology sector was vaccinated against smallpox. Once or twice a year the laboratory tested the working methodology, restored positive sera and control antigens and several times intervened in cases of suspicion of smallpox being imported: an ill sailor stranded in Split (Croatia) with suspicious eruptive skin changes, then a suspicious ill passenger from the train from Ljubljana (Slovenia) to Belgrade (Serbia) and a sick female coming from the area where variola was registered. In all three cases the results on smallpox were negative [2].

The first smallpox case in our country in 1972 was atypical; in addition, the majority of doctors had no practical experience in the diagnosis of this disease, since last smallpox case in Yugoslavia was registered in 1930. At the beginning, it was thought that the outbreak would have a local character, although the possibility of its spreading was not neglected, so the taken measures were adequate to the situation. The contaminated areas were identified, and movement of people there was prohibited. The plan of detection and isolation of patients, as well as isolation of persons from contacts was also established, in accordance with the international sanitary regulations and practices. The plan of progressive vaccination of the entire population of the Autonomy Province of Kosovo was also in line with the potential spread of infection. Throughout the Republic of Serbia and other republics of the Former Yugoslavia at the same time began vaccination of all workers in the medical sector, transport, catering industry, internal affairs, and a wider range of the population, according to the epidemiological indications. A plan of taking and sending samples for laboratory testing was made according to the possibilities of a competent laboratory in Belgrade [54].

A state of emergency and the regime of 24 hours duty had been introduced in the laboratory. The staff was vaccinated again and a greater amount of equipment for sample taking was acquired. During laboratory processing of samples, a special regime of personal and collective protection in the laboratory was organized (suits, gowns, masks, goggles, gloves, boots, bathing after work, permanent sterilization of working rooms, strictly controlled transport and sterilization or incineration of all infectious items and materials as well as ceasing the contact of laboratory personnel with the external environment). In this regard it is important to mention that in the course of investigating and isolating smallpox and during prior experience with Marburg virus in the laboratory there were no cases of laboratory infections. This fact indicates the good training and organization of work since then the biosafety standards as we know them today were not in force [55].

Patient samples were taken by a well-trained team that consisted of three experienced microbiologists and epidemiologists who brought the samples to the laboratory in specially prepared sets which contained a list with a pen for a patient's data, a plastic syringe and blood tube, equipment for skin lesions sampling (scalpel, lancet, tweezers, scissors), capillary tube for taking fluid from the vesicles and pustules, small bottles for crust and slides for smear. The taken samples were packed into impervious plastic bags and transported to the laboratory by appropriate transport means (helicopter, plane, car) provided by the republic or federal civil protection staff. During sample collection, the staff wore appropriate suits for personal and collective protection. Such procedure of professional sampling and safe transport was important for the reliability of laboratory tests and presented an adequate biosecurity precaution. In cases of suspected smallpox, on the basis of clinical and epidemiological parameters, a negative answer obtained by one test did not exclude the diagnosis, so it was necessary to wait for the results of virus isolation (3 days), or sub-passaging (3-6 days). The whole working process was documented in details. The efficiency and results of the laboratory were highly rated by the WHO [55].

On the basis of acquired experience during the outbreak, it was clear that a specially equipped laboratory center for working with dangerous pathogens was necessary and that it should be located within a separate building providing adequate conditions for sterilization of the stale air and wastewater as well as the conditions that would provide safety and security of laboratory workers and the environment. The quarantine hospitals or isolation units were required to be preferably placed within these laboratory buildings in terms of major outbreaks. The learned lesson related to the fact that it was necessary to have a larger number of laboratory workers acquainted with working procedures. Providing permanent professional training abroad and adequate funding to maintain the readiness of laboratories and scientific research in this area were supposed to be a priority in the planning allocations [54, 56]. These requirements do not lose its relevance even nowadays, when the conditions for working with dangerous pathogens such as smallpox, are precisely defined.

The isolation of patients during the outbreak was carried out in accordance with the principle of accommodation in special conditions (isolation in hospitals, hotels, motels, spas) in situations where there were no special facilities for the medical treatment of quarantine diseases. Accommodation of persons who were in contact with diseased patients was also performed according to local conditions. Federal headquarters for the fight against smallpox brought a precise decision on the infected areas and the measures which had to be implemented, on the movement of people, traffic etc. Requirements for a sanitary blockade of the whole region of Province Kosovo were without any professional justification, because since the outbreak was confirmed there was no single case of transmission of disease from its territory [57].

Requirements for vaccination of the entire Yugoslav population at that time were not realistic because the infected areas had priority and the amount of vaccines was inadequate. However, the emergence of disease out of affected areas in other cities of Serbia (Novi Sad, Cacak, Belgrade, Sid) and Montenegro, which occurred due to contacts with infected persons in the province before the official start of the outbreak as it is shown in *Figure 1*, gave basis for the decision of the Federal Executive Council of Yugoslavia to start gradual vaccination of the entire population and to take adequate measures for importing of vaccines and hyperimmune gamma-globulin [52].

The public was being informed all the time by the competent professionals about the occurrence and spreading of the disease and the measures that should be taken from the first days of the outbreak. Daily newspapers continuously published the adequate bulletins. The WHO was informed about all facts and its experts were invited in order to coordinate informing of the world public [58].

The work and coordination of all management bodies and state administrative bodies responsible for health affairs were at a high level. The Federal Executive Council followed the work and gave full support to the Federal Headquarters for the fight against smallpox, whose task was to collect and publish data about the disease, coordinate the work of national and provincial headquarters, acquire and distribute vaccines and other means and to define the other measures based on the evaluation of the epidemiological situation. The staffs in the republics and provinces were organs of the Executive Councils or Municipal Assemblies. Medical Service of the Yugoslav National Army (JNA) at full capacity was the integral part of the response of the health service and society in general [59, 60].

CONCLUSIONS: VALUBLE AND ACCURATE LESSONS LEARNED IN YUGOSLAV OUTBREAK

Without neglecting the organizational, technical and other weaknesses, and the lack of practical experience, we can say that the Yugoslav health service quickly and efficiently carried out the task of combating the outbreak, which was large in the number of cases (175) and geographical spread (25 foci) and caused a severe disruption of life and economy in the country. The remarkable commitment of health workers and other social actors, as well as the disciplined behavior of the population certainly significantly contributed to this success. The omissions were related to the undetected first smallpox case (inadequate medical and sanitary control), late detection (only at the beginning of the second wave, when there were already 11 patients in 6 foci) and inadequate implementation of prescribed vaccination of certain categories of the population which facilitated the outbreak spreading (46% of the cases were found among the people which should have been protected in the regular vaccination, and 8% among staff of health institutions). The problem was that the basic anti-outbreak measure - vaccination in focus was not implemented quickly enough, as well as the absence of a unique approach about the quarantine, control and restriction of people's movements to and from infected areas, as well as within them.

The recorded lessons are related to the facts that it is necessary to strengthen the capacities for rapid laboratory diagnosis, provide facilities for isolation and treatment of the patients and develop uniform medical procedures in order to combat the contagious infectious diseases effectively. It is also important to keep enhancing the capacities of the Institute for Health Protection with the training of mobile teams for field work, constant reinforcement of sanitary-epidemiological service and the sanitary inspection, with constant monitoring of the situation in the world and achievements in the field of science. It was emphasized that special point should be given to education and training of personnel, and health education of the population [61]. Key contribution in relatively rapid outbreak suppression had the integrated efforts of specially formed bodies for fighting smallpox at all levels, good organization of health services, support of the Yugoslav National Army (JNA), as well as international solidarity and the WHO support.

Considering all the above-mentioned, it is clear that the variola virus is a dangerous pathogen, which has an important place on the list of potential biological agents due to its characteristics and possible consequences that it might cause. In times of growing threats from bioterrorism and possible misuse of science, all competent bodies must pay special attention to the prevention as well as the preparation of resources for medical treatment in the event of the occurrence of the disease. This include training of the personnel, and improving diagnostic capabilities with respect to prescribed biosafety standards and other capacities required for medical care, as well as knowledge of the necessary tools for crisis management and crisis communications.

Conflict of interest statement

As the authors of the paper with full legal responsibility we state that there does not exist any conflict of interest that could inappropriately bias conduct and findings of this study.

Received on 26 July 2016.
Accepted on 11 October 2016.

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