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Review article

CURRENT SWINE RESPIRATORY DISEASES MORPHOLOGY IN INTENSIVE SWINE PRODUCTION IN SERBIA

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Swine respiratory diseases represent one of the most frequent health issues in pig production worldwide. Despite the great progress that has been made in the field of diagnostics, control and prophylaxis, respiratory diseases still remain the most challenging health problem in modern commercial pig production. The list of infectious agents that cause respiratory diseases in swine is extensive and includes both, bacterial and viral pathogens. In Serbia, more than fifteen years after the introduction of modern vaccines, the list of bacterial pathogens related to swine respiratory infections still include *Mycoplasma hyopneumoniae*, *Actinobacillus pleuropneumoniae*, *Haemophilus parasuis* and *Pasteurella multocida*. On the other hand, most commonly involved viral pathogens are Porcine Reproductive and Respiratory Syndrome Virus, Swine influenza virus, Porcine circovirus type 2 and Pseudorabies virus. The morphological features of pneumonia where several agents are involved, depend on the predominant etiological agent. Expanding knowledge of the main pathogens associated with swine respiratory diseases and the effects of their interactions on the disease outcome is important for further investigations of lung diseases and implementation of control strategies in commercial pig populations in Serbia. This review discusses the latest findings on swine respiratory disease and current trends in Serbian pig production.

Key words: swine, morphology, respiratory diseases, Serbia

INTRODUCTION

Despite the great progress that has been made in the field of diagnostics and control, swine respiratory diseases remain the most challenging health problem in modern pig production worldwide [1-3]. Lung diseases result in economic losses due to poor growth performance, reduced feed efficiency, higher medication costs and eventually has an adverse effect on pig welfare [2,4,5]. It is considered that pleurisy and cranioventral pulmonary consolidation are the most frequent findings in pig lungs at the slaughter

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line [6,7]. Even more, it is believed that only a few pigs reared under commercial conditions can be expected to reach the slaughterhouse without contracting some sort of lung lesion during their productive lives [1,3].

It is well known that the respiratory diseases of swine have multifactorial causes resulting from interactions among different etiological agents, environmental conditions and management practices [4,7,8]. The list of infectious agents that cause respiratory diseases in swine is extensive and includes both, bacterial and viral pathogens [9-11]. Today, more than fifteen years after the introduction of modern vaccines, in the list of frequently detected etiological agents related to swine respiratory infections *Mycoplasma hyopneumoniae* (Mhyo) is still included [12-14]. Other bacterial pathogens frequently involved in swine respiratory diseases are *Actinobacillus pleuropneumoniae* (App), *Haemophilus parasuis* (Hps) and *Pasteurella multocida* (Pm) [15-17]. On the other hand, the list of viral infectious agents includes Porcine Reproductive and Respiratory Syndrome Virus (PRRSV), Swine influenza virus (SIV) and Porcine circovirus type 2 (PCV-2) [18-22].

An important feature of pig production on commercial farms in Serbia is that no vaccination is performed against most of the bacterial and viral agents (App, Hps, Pm, SIV) which are widely recognized as important respiratory pathogens. Some systemic pathogens which do not primarily target the respiratory tract may also cause severe respiratory clinical signs, such as Classical swine fever virus and Pseudorabies virus [3]. It is important to indicate that besides the above mentioned etiological agents, some infectious diseases are endemically present in Serbia for decades, for example, Morbus Aujeszky Disease (AD, Psudorabies) [23,24]. Also, the control of some other important viral infectious diseases in Serbia differs from the Member States of the European Union (EU) [25,26]. At the time of this research, vaccination against Classical swine fever (China strain) was mandatory for all pigs older than 60 days according to the Veterinary Law. Despite the vaccination policy, the last outbreak of Classical swine fever (CSF) in Serbia was reported in 2010 [25]. Results from several experimental and field trials revealed a different level of gross pathological lesions in the lungs of clinically and subclinically (latently) CSF infected pigs caused by secondary bacterial infections [26,27].

In Serbia, commercial pig farrow-to finish farm systems are characterized by the presence of various predisposing factors, which significantly influence the occurrence of respiratory diseases [28-30]. Compared to multi-site production systems, in farrow-to finish swine farms more opportunities for pathogens, environment and management interactions exist [24,25,31]. Today, despite the introduction of modern vaccines against the most important agents causing respiratory diseases of swine (for example *M. hyopneumoniae*, PCV-2, PRRSV) and all efforts implemented from the production aspect in the technology in the swine industry, the situation is even more complicated [29,32-34]. It is a well- known fact that various infectious agents could quite often be introduced into the swine herd after purchasing latently infected animals from another farm with a different health status, causing an outbreak of infectious

disease [23,35,36]. Indeed, results of analysis of the multiple swine respiratory diseases outbreaks in Serbia, indicated that purchasing of breeding animals, with different or unknown health status, represented the most important route of transmission and spreading of the infection to other farms, or different state regions [9,20,23,24,33]. Intensifying of swine production increases the incidence and economic importance of respiratory diseases despite the applied measures for their suppression and eradication [9,23,35]. Considering the complexity of the etiology, respiratory diseases in pigs are often referred to as porcine respiratory disease complex (PRDC) [30,37]. Today it is well known that PRDC is polymicrobial in nature, and results from infection with various combinations of primary and secondary respiratory pathogens [3,6,15]. As a true multifactorial disease, environmental conditions, population size, management strategies and pig-specific factors also play roles in the outcome of PRDC [2,3,9,15].

The expanding knowledge of the main pathogens associated with swine respiratory diseases and the effects of their interactions on the disease outcome is important for further investigations of lung diseases and implementation of control strategies in the commercial pig population in Serbia. Although the knowledge concerning respiratory pathogens and all potentially contributing factors has advanced substantially in the last 15 years, much more needs to be learned about the diagnostic approach and control of swine respiratory disease outbreaks caused by concurrent infections with two or more pathogens. This review discusses the latest findings on swine respiratory diseases and current trends in Serbian pig production.

MATERIAL AND METHODS

In total, eleven commercial pigs farms, all located in Vojvodina Province (Northern part of Serbia) were included in the research study: four fattening and seven farrow-to-finish pig farms (Figure 1). To meet the criteria to be included in the study, the herds had to be of the confined type with a minimum of 200 sows for farrow-to-finish production type or 500 animals for fatteners. A common feature for all included units was a prolonged history of respiratory problems in growing pigs (weaners, fatteners) and/or breeding categories (gilts, sows, boars).

Some basic production characteristics were common to most of the commercial farrow-to-finish farms in the Vojvodina region, with highest density pig population in Serbia. The piglets were commonly weaned at the age of 28-35 days, transferred to weaning and later growing units with pens. Before moving the piglets, sanitation and disinfection of empty pens were performed, but nose-to-nose contact between different age groups of pigs housed in adjacent pens was possible. Finishing pigs were slaughtered at a weight of approximately 110 kg or when reached the age of 25 weeks. At specialized fattening farms, weaned piglets at an average weight of 23 to 25 kg were purchased from commercial farrow-to piglet farms.

At the time of the study, respiratory disease control programs, in general, were similar in all observed herds. Piglets were vaccinated against *M. hyopneumoniae* and PCV-2 in all farrow-to-finish herds, additionally, on two farms vaccination against PRRS was carried on piglets, sows and boars. However, Morbus Aujeszky virus as a major viral causative agent of great importance for the sustainability of pig production, is included in vaccination programs in most farrow-to-finish farms. But, epidemiological surveys showed that the immune status of the swine population in commercial farms considering Aujeszky's disease (AD) is variable: in 80% of examined farrow-to finish farms, the breeding categories (sows, boars) are regularly vaccinated with the commercially available AD vaccine. On the contrary, fattening commercial farms do not vaccinate against AD.

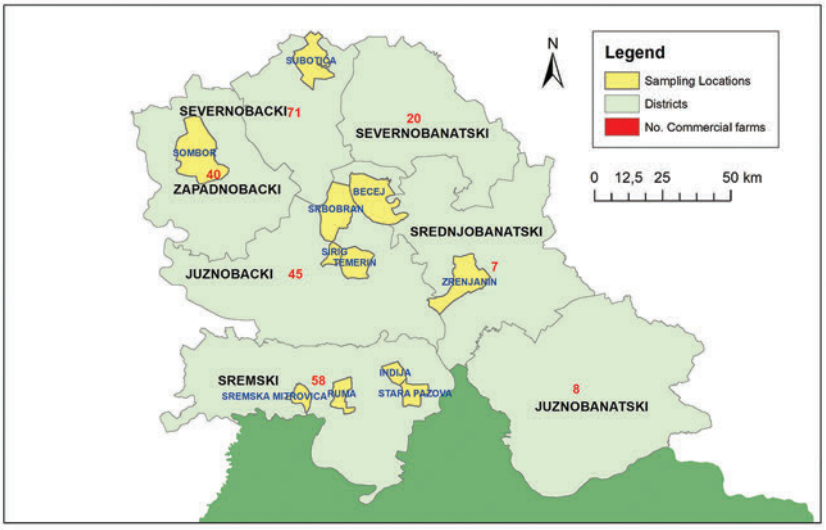

Figure 1: Sampling locations within districts in Vojvodina Province, Northern part of Serbia

An important feature of pig production on commercial farms in Serbia is that no vaccination is performed against most of the bacterial and viral agents (App, Hps, Pm, SIV) which are widely recognized as important respiratory pathogens.

The applied research methods included disease data collection on the disease history, twofold on-farm clinical examinations and gross pathological examinations of dead pigs. If the gross pathological lesions indicative for respiratory disease were observed, the tissue samples (tonsils, lungs, mediastinal lymph nodes) were sampled for further laboratory examination. For each included swine farm, the slaughterhouse check-up was undertaken 3 to 4 weeks after the on-farm visit. Inspections were carried out in slaughterhouses in which the carcasses were not submerged in boiling water, but steamed, which decreased the risk for contamination with respiratory pathogens during the slaughter process allowing microbiological examination of the lungs.

Farm necropsies and slaughterhouse examinations of the swine respiratory system were included in this study. Observed gross pathology changes indicative for respiratory infections were recorded in all fatteners that have reached the slaughter body mass. Complete thoracic organs were removed from the slaughter line for individual macroscopic examination, palpated and visually appraised for pneumonia-like gross lesions and pleurisy. The results of the examination and severity of the changes were recorded according to Christensen et al. (1999). Moreover, tissue samples of 35 altered respiratory organs (lungs, mediastinal lymph nodes, tonsils) were collected from pigs from 11 commercial farms and subjected to further laboratory testing (in total 385 samples).

In the laboratory, the bacteriological examination was performed by standard bacteriological diagnostic methods [38]. Besides this, selected tissue samples, were submitted to molecular diagnostics, by polymerase chain reaction and real time reverse transcriptase - polymerase chain reaction (PCR and real time PCR) for detection of *M. hyopneumoniae* and confirmation of viral pathogens (PRRSV, PCV-2, SIV, MA) [20,33,39,40]. In total, 180 blood samples from fatteners originating from different units, were taken at the slaughter line in order to perform serological investigations on the presence of specific antibodies against viral and bacterial respiratory pathogens using immunoenzyme (ELISA) tests for specific agents: App (IDEXX APP-ApixIV), PRRSV (Ingenasa, Madrid), PCV-2 (Ingenasa, Madrid), *Mycoplasma hyopneumoniae* (IDEXX M. hyo. Antibody test), Influenza virus H1N1 and H3N2 (IDEXX Swine Influenza Virus Antibody test).

Morphologic examination

In addition to the clinical, virological and bacteriological examination of different categories of pigs, the diagnostic process also included the macroscopical examination of carcasses, as well as sampling of biological material for laboratory testing, such as lung tissue and associated lymph nodes. For more detailed information on the cause of pneumonia and the type of changes, histopathology and immunohistochemistry were performed. Tissues for light microscopy were fixed in 10% neutral buffered formalin and processed in the automatic tissue processor LEICA TP1020, embedded in paraffin, and cut at 4 μm. Initial sections for routine histopathological evaluation were stained with hematoxylin and eosin (HE), toluidine blue, and Pas and Grocott's methenamine silver stain. Formalin-fixed paraffin embedded samples of lung tissue and tracheobronchial lymph nodes were cut in 4μm sections and the three-step indirect immunohistochemical (IHC) technique was performed. The sections were treated with methanol containing 0.3% hydrogen peroxide for 15 minutes at room temperature in order to inactivate endogenous peroxidase. Antigen retrieval was achieved by proteinase K for 4 minutes. After antigen retrieval and inactivation of endogenous peroxidase, the sections were incubated with a PCV-2 monoclonal antibody (Rural Technologies, Inc. Brookings, SD) at 1:500 dilution, as well as E2gp55 CSF monoclonal antibody (VMRD, USA) at 1:1000 dilution for 1 h at room temperature. The sections were then

incubated with the secondary antibody. A streptavidin–immunoperoxidase staining procedure (LSAB kit; Dako) was used for immunolabeling. The immunoreaction was visualized with DAB+ (3,3'-diaminobenzidine tetrahydrochloride, DAKO, K3468). Sections were counterstained with Mayer's hematoxylin. Aqueous medium glycergel (DAKO, C563) was used on the stained sections for mounting. Appropriate positive and negative controls were used. Slides for histopathological and immunohistochemical evaluation were analyzed by light microscope (BX51, Olympus Optical, Japan), while digital images were made using an optical microscope Olympus BX51 with digital camera Olympus Color View III.

RESULTS

Bacterial diseases

1. *Actinobacillus pleuropneumoniae* (App)

In the five examined farrow-to-finish commercial farms, outbreaks of respiratory diseases were frequently observed shortly after the growing pigs entered the fattening units, but also in adults and breeding categories (gilts, sows). Clinically, severe symptoms of respiratory disease were detected quite shortly before death. At post mortem examination, severe focal dark hemorrhagic lung lesions associated with fibrinous pleurisy were observed. Considering the results from on slaughter control of healthy animals originating from farms, examination of respiratory organs revealed moderate to severe pathological changes indicative for App infection. In most of the examined pigs, changes in the pleura were established and were manifested as local pleurisy (32.77%) and chronic diffuse pleurisy (21.11%). Also, the pathological signs indicative for App infection (*pleuropneumonia hemorrhagica necroticans*) in 7.77% lung samples were noticed. In a number of fatteners, changes in the heart muscle (*pericarditis villosa* in 8.33 %) and signs of purulent infection of the lungs (*pneumonia apostematosa* in 10.5%) were observed. The percentage of lung lesions associated with App lesions in herds confirms the importance of this pathogen as a causative agent. Chronic pleural lesions are commonly detected at the abattoir, since the resolution of pleural lesions associated with pleurisy can take 3 months or more, very often the process is not completed prior to slaughter [3,6,7].

Despite the severe clinical symptoms in live animals and extensive gross lesions observed post mortem, App was detected bacteriologically only in one farrow-to-finish farm. Similar results were obtained in the samples from pigs in the slaughterhouse. Tissue samples obtained from pigs at slaughter revealed the presence of App in only 2 cases. It is important to stress that in this study the tissue samples were obtained from pigs at the slaughter line which, according to farm veterinary records did not show any clinical respiratory signs 3-5 weeks prior to slaughter. The animals had not been treated with antimicrobial agents in the 3 weeks prior to sample collection. The blood samples collected at the slaughter line from the same farms were analyzed in

the laboratory for the presence of antibodies to App. Serological examination of 180 blood samples revealed the presence of specific antibodies against App in 50% of examined sera. According to the history data, among the five 5 herds with a history of App, only one was vaccinated the pigs. Vaccination against App was not found to be a common practice in commercial pig holdings in Serbia. The gross pathological lesions caused by App are mainly restricted to the respiratory tract. The lesions are bilateral and most commonly focal and located in the cranial and caudal lung lobes. Characteristic lesions include fibrinonecrotic and hemorrhagic pneumonia with little or no fibrinous pleurisy (Figure 2a). The pneumonic lesions are deep red, firm and well-demarcated, while the cut surface is friable [41,42]. If present, pleural adhesions are moist and yellowish. Chronically infected pigs have shrunken encapsulated lesions with areas of chronic fibrosis [43]. Microscopic examination usually shows severe fibrinohemorrhagic pneumonia with foci of necrosis. In addition to fibrin, there are neutrophils, macrophages and karyorrhectic debris in the alveoli, bronchioles and bronchi (Figure 2b). Frequently, vascular thrombosis in the small venules and capillaries of the septa can be observed [44,45]. The pleura often has fibrin strands multifocally adherent to the surface. It is infiltrated with moderate numbers of neutrophils and macrophages [46].

Actinobacillus pleuropneumoniae is considered as one of the most common pathogenic bacteria in the pig industry. The bacterium is the etiological agent of porcine pleuropneumonia, a contagious respiratory disease that affects pigs and causes economic losses in the swine industry worldwide [7,36,47]. The disease is characterized by pneumonia, pleurisy, growth retardation and mortality in the affected population [3,36,44]. Despite the distinctive pathogenic lesions, App is considered to be an obligate bacterium of the porcine respiratory tract. It can be isolated from the nasal cavities, tonsils, middle ear and lungs of infected pigs [48]. Depending on their requirement for nicotinamide adenine dinucleotide (NAD) to grow, App strains can be classified as biovar I (also called typical) and biovar II (atypical). Multiple serovars can be present on a farm and also within one individual pig. So far, 16 serovars of App are known, which differ in their capsular polysaccharide composition [3,47]. Pleuropneumonia can occur in pigs of different ages, but increased disease incidence is frequently associated with stress [48].

Porcine contagious pleuropneumonia can occur in different clinical forms, from peracute to chronic depending on the serotype of infection and, the immune status of the host [3,44,48]. The incubation period can be as short as 12 hrs., especially under the influence of stress factors such as mixing, moving or weaning and the first cases of death can be observed as early as 24 hrs. after infection [2,36]. The peracute form is characterized by a high mortality rate and sudden death. A typical anamnesis is the finding of dead animals without any premonitory signs and with typical bloody and foamy nasal discharge. Pulmonary lesions are characterized by severe edema, inflammation, hemorrhage and necrosis. Most of the pathological consequences of porcine pleuropneumonia can be attributed to the Apx toxins which exert cytotoxic

effects on various cell types [36,47,48]. Pigs that overcome the acute form of the disease remain chronically infected, showing no clinical signs, but harboring chronic lung alternations such as pleurisy and lung tissue sequesters surrounded by fibrotic tissue [3,46,48]. Asymptomatic carriers of the bacterium, either those having survived the acute form of the disease or those that were subclinically infected, are an important source of infection. The severity of disease can be significantly influenced by differences in virulence potential of different isolates and stress factors, different co-infections with other pathogens, and extrinsic factors such as poor husbandry and insufficient biosecurity [28,31,35,49].

Transmission from pig to pig occurs mainly by direct oral or nasal contact or by droplets of aerosol over short distances of 1-2 m. Subclinically infected pigs are of major importance as the source of infection for App spreading. Transmission between herds mostly occurs through the introduction of carrier animals into naïve populations. It is well recognized that, moving and mixing pigs of different origin increase the risks of pleuropneumonia [3,50]. The disease can also take on a chronic form where production losses are affected and pathological lesions at slaughter, such as adherence, pleurisy and lung abscesses are usually seen [6,44,51]. The bacterium is difficult to detect in live pigs due to the labor intensive sampling procedure, and secondly because outbreaks are impossible to predict and develop rapidly, so it is impossible to monitor the course of colonization and infection in animals [3,51]. The disease is endemic in many pig herds. Clinical outbreaks are mainly controlled by giving antibiotics to all pigs. Alternative options to reduce disease impact include vaccination, improvement of housing environment, limiting cross-fostering or movement of pigs across pens. Observational studies have shown that sows transmit the bacterium to their piglets, resulting in about 30% being colonized at weaning, which increases to 50% or more at 10 weeks of age [44,51].

Today, still are lacking the solutions for dealing with the disease under field conditions: how to differentiate subclinically infected pigs and those which do not carry the pathogen, how to prevent App persistence, and how to achieve optimal immunity in endemically infected herds by vaccination [47]. As the presence of pleurisy and pneumonia have a negative influence on farm production parameters, the prevalence and severity of these lesions at the abattoir appear to be good and useful indicators to address control measures at farm level [7,50]. Strategies to prevent porcine pleuropneumonia are mainly based on external biosecurity measures to avoid introduction of new strains by carrier pigs as well as internal biosecurity measures to interrupt the infection chain. The large number of origins of purchased pigs and poor biosecurity measures are significant risk factors for the introduction of the disease [5,35]. Most App commercial vaccines may successfully decrease clinical symptoms, but cannot protect against infection or transmission [47]. Considering the results of our investigation, before deciding to apply the vaccine or to treat the target pig categories, the data from postmortem inspections of target pig categories and slaughter-check results should be thoroughly analyzed. Savic et al. (2015) [30] also indicated the high

prevalence of App in the swine population in Serbia, probably generated from the continuous operation flow and mixing different pig categories that share the same air space. Attention should be payed to the strategic use of antibiotics, but also improved farm biosecurity can reduce the impact of the disease on an infected farm.

2. *Pasteurella multocida*

By clinical examination of diseased pigs, close inspection indicated that some animals were growing slowly and were moving around the pen but were not interested for feeding. Before death, diseased growers and finishers had deep-sounding cough and signs of severe dyspnea, often with mouth breathing. On post-mortem inspection necrotizing and fibrinous lung changes were frequently detected. Bacteriological testing of tissue samples deriving from the section material, revealed *Pasteurella multocida* in 26.83% of examined lung samples. Our results showed that other bacteria that most frequently accompanied Pm in respiratory disease were *Haemophylus parasuis* and *Streptococcus suis*, suggesting that these bacteria should be considered when medication and/or vaccination is used as a mean of controlling respiratory disease outbreaks. Also, *P. multocida* was frequently detected as a secondary bacterium in advanced enzootic pneumonia concurrent to *M. hyopnumoniae*. Respiratory diseases in pigs often involve a mixture of infections, causing a complicated disease complex rather than a single disease. Indeed, *Pasteurella multocida* is a common causative bacterial agent in multifactorial respiratory tract infections in pigs [52]. It is considered that *P. multocida* is not a primary respiratory pathogen, as it frequently follows infections with other agents [3,30]. Pneumonic pasteurellosis is the common final stage of enzootic pneumonia or porcine respiratory disease complex [53-55]. *Pasteurella multocida* is one of the bacterial agents most frequently isolated from pneumonic lungs with a high prevalence in finishing pigs [37]. It is a rarely the primary agent of pneumonia in pigs, but rather is an opportunist that follows infections with other primary predisposing bacterial and viral agents [55].

The pneumonic lesions of *P. multocida* are observed in the cranioventral lobes of the lungs, while in severe cases they may extend to the diaphragmatic lobes [43,56]. Pulmonary consolidation is present together with discoloration that could be red to greyish which depends on the course of the infection [53,57]. There are two types of gross lesions - exudative and necrotizing. The exudative type is characterized by mucopurulent to purulent exudate on the cut surface of the affected lung lobe and frothy exudate in the trachea. Necrotic changes are present in chronic cases as dark-red, dry and firm foci of lung tissue clearly demarcated from the healthy surrounding tissue. Focal, dry pleurisy may be seen in severe cases as well as pleural adhesions [53,54]. A lobular, exudative bronchopneumonia is observed microscopically. Alveoli and bronchioles are filled with a mucopurulent exudate consisting of inflammatory cells, mostly neutrophils [53,54]. In chronic cases, multifocal necrosis can be observed in the lung parenchyma, usually surrounded by inflammatory cells and a fibrous capsule [53].

Another important disease associated with *P. multocida* is atrophic rhinitis [11], which is seldom reported and even neglected in commercial farms in Serbia. In our research, by clinical examination of piglets, fatteners and gilts on three swine farms in Vojvodina region, the clinical symptoms of atrophic rhinitis were detected. In infected pigs nasal discharge, sneezing and reduced growth rate were the most frequently observed. Tear staining that radiates from the medial eye angle and epistaxis was a frequent finding in weaned piglets. Finally, in most of the cases the snout become distorted and different levels of turbinate bones atrophy within the snout were observed. In fatteners, the most common visible manifestation was brachygnatia superior. However, in most of the cases, the infection is present in the subclinical form. It is considered that the etiological agents that cause this disease are *Bordetella bronchiseptica* and *P. multocida*. *B. bronchiseptica* can cause a mild form of rhinitis atrophicans and predispose pigs to infections with toxogenic strains of *P. multocida* and trigger the progressive form of rhinitis atrophicans. The most severe clinical forms of the disease are the consequence of infection with one etiologic agent, toxigenic strains *P. multocida* or in combination with *Bordetella bronchiseptica*. These bacteria have toxins that can specifically attack the bones and cartilage of the nasal turbinate bones. The damage to the nasal bones leads to the highly distinctive twisting and wrinkling of the nose of affected pigs [3,11,55]. However, despite the fact that there are many effective commercial vaccines that provide protection against the two causative bacteria, the disease is common in the subclinical form mainly in the Serbian farms where piglets are derived from various sources of non-vaccinated gilts and are mixed together. Use of commercial vaccines and restocking of the farm with pigs that are free of the disease will lead to the disappearance of the disease.

Pasteurella multocida is a commensal and opportunistic pathogen of the oral, nasopharyngeal and upper respiratory tract. In pigs, *P. multocida* is associated with progressive atrophic rhinitis and together with other respiratory pathogens, plays a significant role in the porcine respiratory disease complex. Coinfection with other respiratory disease agents is the most significant factor contributing to swine pneumonic pasteurellosis [3,55]. Continuous surveillance of antimicrobial resistance in respiratory pathogens, including *P. multocida*, is required due to the increasing use of therapeutic antimicrobials and emergence of new resistant strains. Also farm management changes can significantly reduce the spread of the involved pathogens and decrease the incidence of pneumonia (all-in/all-out production, limiting the introduction of new animals from other farms, minimizing mixing and sorting, reducing animal density etc.) [55].

3. *Haemophilus parasuis*

Haemophilus parasuis is a common health problem and in our research it was frequently detected in weaning-growing categories in Serbian commercial pig production. Clinically, pigs are usually affected in the period soon after weaning, but the disease

lesions can linger and often be visible in older pigs. However, in diseased animals there is usually no clear pattern of coughing or diarrhea. Those are usually runt pigs, which have signs of decreased appetite and weight loss, much smaller in body size comparing to pen mates. At necropsy, distinctive patchy thickening of the serosa overlining the heart, lung and abomen cavity are frequently observed. The results of bacteriological testing revealed *H. parasuis* in 25.39%, of examined samples of changed lung tissue at the slaughter line. The gross pathology changes in the respiratory organs indicative for *H. parasuis* infection were evident at a high rate in clinically healthy fatteners. The different serological and molecular– based laboratory tests are used worldwide for pathogen detection, but in Serbia, the data about serovars distribution in different regions and molecular testing are lacking. The main post-mortem finding in pigs infected with *H. parasuis* is serofibrinous or fibrinopurulent exudate on the serosal surfaces, including the pleura (Figure 2c). Pneumonic lesions are usually not present, but if they are, then they are red and multifocal and are the result of septicemia and hematogenous spread. Histopathological examination reveals the presence of fibrinopurulent exudate on the surface of the pleura (Figure 2d), consisting of fibrin, neutrophils and, to a lower extent, of macrophages [58].

Haemophilus parasuis is an important swine pathogen affecting pigs and causing Glässer's disease, characterized by serofibrinous to fibrinous polyserositis, polyarthritis and meningitis [59, 60]. Acute *H. parasuis* pneumonia, without polyserositis has also been described. The bacterium often produces acute septicemia and its endotoxin induces disseminated intravascular coagulation, resulting in the formation of microthrombi in several organs. Disseminated intravascular coagulation and endotoxic shock exacerbate the clinical signs [60]. The bacterium is a common resident organism of the upper respiratory tract of swine and includes strains with different degrees of virulence. To date, a total of 15 serovars of *H. parasuis* have been identified [61]. All animals are colonized by the bacterium, but only certain types of strains are capable of the causing disease often following other co-infections or induced by stress. The prevalence of *H. parasuis* in weaned pigs is significantly higher than in finisher pigs [61,62]. Correa-Fiz et al. (2016) [63] have recently published a study evaluating the nasal microbiomes of pigs prior to weaning as a predisposing factor in the development of respiratory disease associated with *H. parasuis*. The nasal microbiomes of pigs from farms without respiratory disease had higher diversity of microbial species when compared to farms with Glässer's disease. Today, *H. parasuis* is present in all major swine-rearing countries and remains a significant pathogen in swine production systems [3,59]. Transmission of Glässer's disease occurs through contact of carrier or diseased pigs with susceptible animals. Mixing of pigs of different origin is the most important risk factor [64,65]. Disease control by vaccination resulting in decreased mortality has been achieved by bacterins and autogenous vaccines. However, vaccination failures are frequent due to poor cross protection and the incomplete efficacy of vaccines, so antimicrobials are needed to treat *H. parasuis* infections. Pigs receiving antimicrobials early during infection with *H. parasuis* are usually able to survive. However, it is important to

monitor the susceptibility patterns of *H. parasuis* isolates before administration of therapy [59]. *Haemophilus parasuis* can act as a primary or secondary pathogen. The severity of the disease depends on the virulence of the strain, the immunity of piglets, the concomitant presence of other pathogens in the herd, and the genetic resistance of the host [65]. Co-infection with and interaction between *H. parasuis* and other swine pathogens has been investigated. Pseudorabies infection may destroy respiratory epithelial cells and allow *H. parasuis* to proliferate in the lungs. There is no difference in *H. parasuis* distribution or localization in the tissues in pigs infected or non-infected with PRRSV. These results suggest that there is no influence of the previous infection with PRRSV on the occurrence of *H. parasuis* infection [60]. Bacterial *H. parasuis* pneumonia secondary to SIV infection is often observed in pigs. It is considered that SIV is a significant contributor to respiratory diseases and may predispose to secondary bacterial infection [22]. It is considered that pigs on most farms have a stable flora of strains of *H. parasuis* in their throats but these strains vary from farm to farm. The use of in-feed medication to control the spread of *H. parasuis* in weaner pigs during the post weaning phase is currently an essential part of pig farming [60].

In Serbia, diagnosis of *H. parasuis* infections has been based on clinical signs, presence of characteristic gross lesions at necropsy and bacteriological culture. Serological and molecular laboratory methods are not currently available. In the future, strain classification is certainly of interest in *H. parasuis* diagnosis and disease control programs in commercial pig production. Vaccination is an effective measure to prevent mortality. Therefore, vaccines should include virulent strain(s) isolated and confirmed to be endemic on the selected farm [65].

4. *Mycoplasma hyopneumoniae*

In the investigated commercial swine farms, the main sign was prolonged non-productive coughing, usually worsened by animal movement or exercise. Besides this, individual animals showed signs of severe respiratory distress, with more productive cough and open-mouthed breathing. Outbreaks of respiratory disease were frequently observed shortly after growing pigs entered the fattening units and when some of the feed components where added and/or changed. In the time of examination, vaccination against *M. hyopneumoniae* was not carried out continuously in all examined commercial swine herds. However, today, the vaccination against *M. hyopneumoniae* is a widely used practice in all types of commercial pig farms in Serbia. At post mortem examination severe lung lesions were present in 85% of animals. The pathological process was expressed through purple to gray areas of consolidation of lung tissue and macroscopically, the lung lobes were very similar to the hepatic or pancreatic tissues (Figure 2e). In chronic infections, the lesions were necrotizing, associated with fibrinous pleurisy affecting the caudal parts of the lung lobes. The disease is often complicated by secondary infections and spreading of the process to the distal lung lobes. Most frequently, pleuropneumoniae, pericarditis and fibrin

deposits or the adhesions between the visceral and parietal pleurae were observed. By bacteriological testing of samples derived from dead fatteners, bacteria *H. parasuis*, *P. multocida*, together with *M. hyopneumoniae* were most frequently detected. The pigs' health control in the slaughterhouse revealed the existence of gross pathology changes of respiratory organs indicative of *M. hyopneumoniae* infection. By examination of the respiratory organs of 385 fatteners at the slaughter line, visible changes in the lung tissue were not observed only in 19.44% of examined pigs. In others, the examination of respiratory organs revealed moderate to severe pathological changes indicative for *M. hyopneumoniae* infection (25.55%). Different levels of lung consolidation, usually involving one or two lung lobes (cranial and middle lobe) were detected. Frequently, the lesions were located in the cranial parts of the lung, where consolidation and discoloration were observed. The changes in the pleura were established, manifested as local pleurisy and chronic diffuse pleurisy. Pleurisy was most often located on the caudal lobes, but also the surfaces of the cranial and middle lobes were affected and adhesions between them were observed. In a number of cases, parts of the lungs were missing, most likely because of the firm adhesion to the thoracic wall (chronic pleurisy). Enzootic pneumonia-like lesions are not pathognomonic for *M. hyopneumoniae* infections, as other organisms, such as swine influenza virus or bacterial infection, can produce similar lesions [7,66]. Nevertheless, these lesions were positively associated with herd *M. hyopneumoniae* serological positive results at slaughter.

Serological examination (ELISA test) revealed the presence of antibodies against *M. hyopneumoniae* in 88 % of tested sera samples. In the survey, in total 30 samples indicative for *M. hyopneumoniae* infection were examined by RT-PCR. The positive result was established in 83% tested samples. An etiological diagnosis of *M. hyopneumoniae* by RT-PCR was not performed in all indicative cases in our study, but the gross findings which are characteristic for enzootic pneumonia suggest a significant role of *M. hyopneumoniae* in respiratory problems on the examined swine farms. *M. hyopneumoniae* has emerged as a significant pathogen for the pig industry, especially in high health status farms. The correct diagnosis of infection is essential to establish the appropriate control measures [67,68]. Monitoring the incidence of enzootic pneumonia includes examination of the lungs at slaughter, as well as serum profiling of the herd [69]. Grossly, lung lesions consist of purple to grey consolidated areas affecting the ventral parts of the cranial and middle lung lobes, accessory lobe, and cranioventral portions of the caudal lobes. The cut surface of the affected lung is edematous, rubbery, and firm or catarrhal exudate is usually present in the bronchi [70,71]. Microscopically, *M. hyopneumoniae*-induced pneumonia is characterized by the accumulation of alveolar exudate rich in neutrophils (Figure 2f) [70,72]. As the disease progresses, peribronchial, peribronchiolar, and perivascular accumulations of lymphocytes and monocytes may be present. In severe cases, lymph nodes can be connected to the airways causing narrowing of their lumen [70,73]. There is an increased number in Goblet cells in the airway mucosa, while the bronchial glands are hyperplastic [42].

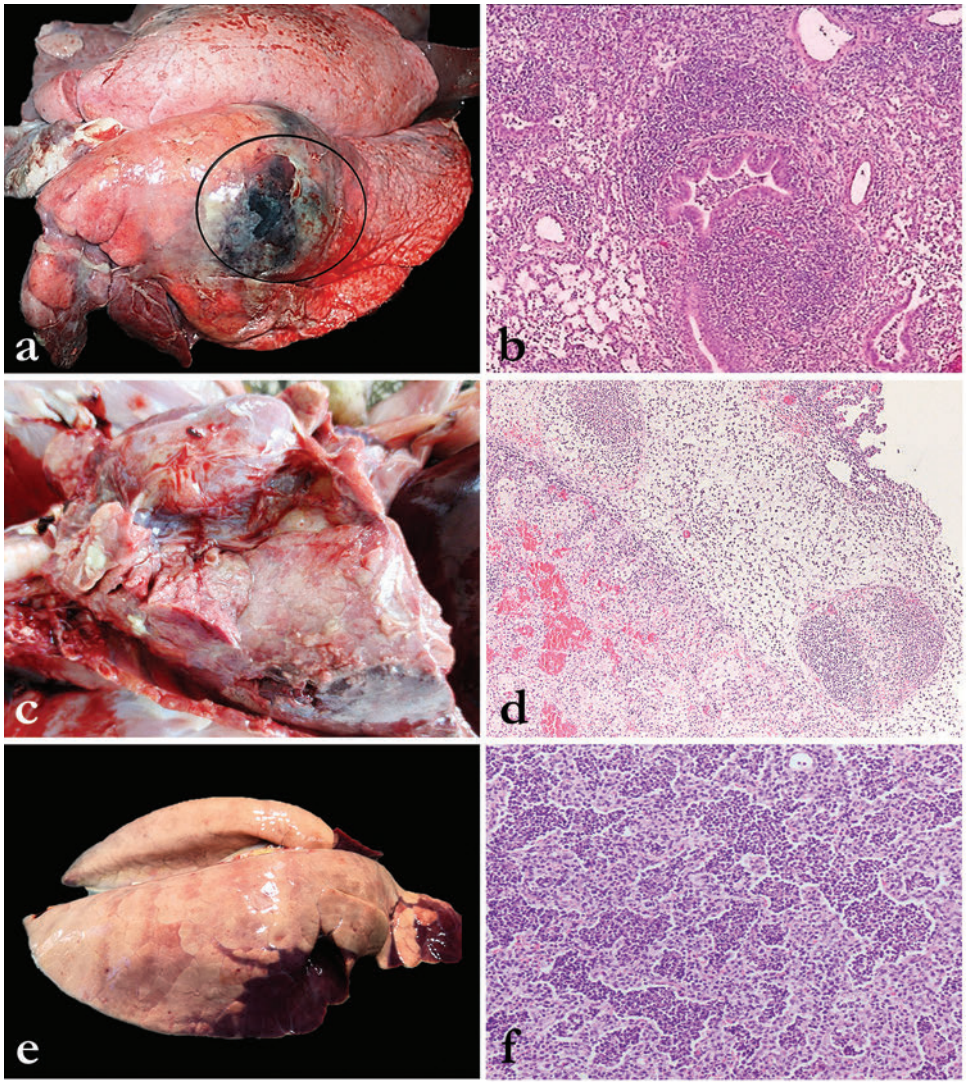

Figure 2. Pig, Lung, Macroscopic and microscopic morphological changes in lungs with confirmed bacterial etiology. **a)** Fibrino-necrotic and hemorrhagic pneumonia associated with fibrinous pleurisy; **b)** Microscopic examination shows severe fibrinohemorrhagic pneumonia with foci of necrosis. Fibrin, neutrophils, macrophages and karyorrhectic debris present in the alveoli, bronchioles and bronchi, HE; **c)** Fibrinopurulent pleurpneumonia; **d)** Fibrinopurulent exudate consisting of fibrin, neutrophils and, to a lower extent, of macrophages HE; **e)** Purple area of consolidation in cranioventral portion of caudal lung lobe; **f)** Accumulation of alveolar exudate rich in neutrophils, HE.

Mycoplasma hyopneumoniae is one of the main pathogens associated within porcine respiratory disease complex (PRDC) and it is the most important pathogen in modern intensive pig farming in Europe [13,16]. Infection mainly affects growing and finishing pigs and it is clinically characterized by a non-productive cough and causes cranio-

ventral pulmonary consolidation [69]. Factors such as management practices, housing conditions, secondary infections and the use of antimicrobials and commercially available vaccines can influence the severity of respiratory diseases in pig herds [13]. The risk of infection with *M. hyopneumoniae* has been shown to be associated with several risk factors, such as the distance between neighboruing herds, herd size, density of pig population in the specific area, lack of vaccination programme and also climatological parameters [74]. Economic losses associated with mycoplasmal infections are related to reduced growth rate, poorer feed conversion, increased medication use and a higher susceptibility to secondary pathogens such as *P. multocida* and App [16]. Diagnosis can be undertaken using a variety of approaches and one of which are the slaughterhouse checks of affected lungs [75,76]. Diagnosis of respiratory diseases in pig herds is based on clinical symptoms, pathological examination of lung tissue and pathogen detection in affected tissue. In fattening pigs, a dry non-productive cough is a typical symptom of enzootic pneumonia and combined with pathogen detection, can be used for diagnostic purposes [77]. The importance of *M. hyopneumoniae* is also linked to its ability to increase the severity of infections caused by viruses as well as bacteria. When these pathogens are in co-infection with *M. hyopneumoniae*, the severity of respiratory lesions is increased [66,77,78].

Airborne transmissions over short distances and purchase of subclinically infected animals are the most relevant ways of introduction into pig herds. The causative agent can be transmitted by air over long distances [79]. Within a herd, transmission by direct contact between pigs is the predominant route of infection [16]. In clinically affected farms, seroconversion, as well as coughing, would appear after, approximately, 1-6 weeks post-infection [13]. Strain genetic diversity has been studied using different genotyping techniques [75]. The strains isolated from different herds may show differences in virulence, but less is known concerning the epidemiology of strains circulating within a herd. Most studies have found only one strain circulating, but these reports were based on a limited number of disease outbreaks [67]. Reports from pig dense areas endemically infected with *M. hyopneumoniae* have revealed that in some herds more than one strain can be present simultaneously [77].

The control measures of the disease are mainly based on prevention and optimization of management conditions. For prevention, there are many live and inactivated vaccines and good results have been achieved through vaccination. However, vaccine protection against clinical pneumonia is incomplete because a commercial vaccine does not prevent colonization. The number of seropositive pigs gradually increased until end of the finishing period, indicating that *M. hyopneumoniae* may continue the circulation in vaccinated animals and cause active infection [8]. Poor management and safety measures are important factors that may cause secondary infections with other pathogens, resulting in further economic losses [12,13].

Mycoplasma hyopneumoniae is the primary pathogen of enzootic pneumonia, a chronic respiratory disease in pigs [69,70]. Infections are highly prevalent worldwide and cause tremendous financial losses to the pig industry, due to costs of treatment and

vaccination, decreased performance and increased mortality as a result of secondary infections [12,13,16]. *M. hyopneumoniae* predisposes animals to concurrent infections with other respiratory pathogens (viruses, bacteria) and also leads to increased use of antimicrobials. Vaccination against *M. hyopneumoniae* is widely practiced but additional control measures include optimizing management and biosecurity and reduction of other disease factors [12,13]. Infection with *M. hyopneumoniae* is often chronic. The host immune response is considered to be the main driver of pulmonary lesions. Different interactions have been described between *M. hyopneumoniae* and other pathogens, but it is well known that *M. hyopneumoniae* predisposes pigs to infections with secondary bacteria. Experimentally, infections with *M. hyopneumoniae* and *P. multocida* or App resulted in more severe lesions comparing to the single infections. Co- or subsequent infections with *P. multocida* and App, *Bordatella Bronchiseptica*, *M. hyopneumoniae*, *Trueperella pyogenes* are commonly found in field outbreaks of enzootic pneumonia [16,69,70]. Studies focusing on the interaction between *M. hyopneumoniae* and PRRSV could not demonstrate a potentiating effect of both pathogens. However, experimentally *M. hyopneumoniae* significantly prolongs and increases the severity of PRRS-induced pneumonia. Also, *M. hyopneumoniae* infection increases the severity of H1N1 SIV but not that of N1H2. Opriessing et al. (2004) [78] indicated that *M. hyopneumoniae* infection potentiates the severity of PCV-2 associated lung lesions. However, Sibila et al. (2012) [16] could not demonstrate an interaction between *M. hyopneumoniae* and PCV-2. The course of the disease implies high morbidity and low mortality.

Avoiding the introduction of *M. hyopneumoniae* into negative farms is crucial to remain free from the infection. The use of general strategies in the biosecurity is recommended [35]. The disease is marked by endemicity, chronicity, decreased average daily gain, poor feed conversion and increased days to market weight [13,80]. The high seroprevalence of *M. hyopneumoniae* (88% at slaughter) is in accordance with previous findings published by other authors in Europe, for which the results indicated greater than 50% seropozitivity [4,6,7]. These findings reinforce the idea that this agent is widely disseminated in the global industry. In Serbia, vaccination against *M. hyopneumoniae* is widespread. Vaccination against *M. hyopneumoniae* is widely used in European swine herds except in some *M. hyopneumoniae*-free countries, such as Switzerland [8]. Therefore, *M. hyopneumoniae* predisposes animals to concurrent infections with other respiratory pathogens including bacteria and viruses [12,69]. Frequently the severity of clinical symptoms increases after infection with secondary bacteria such as *P. multocida*, *H. parasuis*, *S. suis* or App [30, 69]. It is considered that *M. hyopneumoniae* is ubiquitously distributed across most swine producing countries [3,12, 13]. Although pigs of all ages are susceptible, the animals in the growing to finishing phase are most affected. However, in herds without immunity, the disease can affect pigs from all age groups, including suckling piglets and breeding animals [16]. Persistently infected pigs typically have the subclinical form of the disease, and are difficult to detect using currently available diagnostic tools and remain carriers, capable of transmitting the pathogen to susceptible animals [12,16]. The assessment

of respiratory disease within a pig herd by lung 'lesion control' at abattoir inspection is frequently used to estimate the incidence and its impact on carcass market price. Such surveillance may also be useful in detecting subclinical cases which can adversely affect production during the fattening period [1,9,16].

Viral diseases

1. Porcine Reproductive and Respiratory Syndrome (PRRS)

Serological examination of blood samples revealed the presence of specific antibodies against PRRS in all commercial farms that were included in the survey. However, only a limited number of samples from clinical cases have been sent for virus confirmation. The presence of viral genome PRRS-EU was established in 16 samples. Clinical presentation of the disease varied greatly between examined herds, ranging from asymptomatic to devastating. Most frequently, acute PRRS virus infection in weaned, grower-finisher pigs was characterized by transient anorexia, cutaneous hyperemia, dyspnea, rough hair coats and uneven animal groups considering body weight. At the slaughterhouse, different lung lesions were noticed in fatteners. In some cases, there was a diffuse firmness and a mottled, tan color of all the pulmonary lobes. There were also areas of fibrin and pleurisy over areas of the front lobes. Generally, PRRS virus infection was in most cases masked by concurrent secondary bacterial infections (*M. hyopneumoniae*, *P. multocida*, *H. parasuis*).

It is considered that PRRS is an underestimated and uncontrolled respiratory swine disease in Serbia. According to Petrovic et al. (2011) [33] the first suspected cases of PRRS in Serbia occurred in 2001, when serious respiratory disorders associated with high mortality affected pigs on two industrial farms located in the Northern region close to the borders with Croatia and Hungary. The suspected cause of the cases was boar semen illegally imported from neighboring countries. Subsequently in 2001-2002, respiratory syndrome with high morbidity and moderate mortality, which was diagnosed as PRRS, occurred on several commercial farms in the Northern Serbian province of Vojvodina and later on in the central part of Serbia [32,33]. Severe health problems and high economic losses led the Veterinary Directorate to perform PRRS serology screening in 2002, 2004-2005 and 2006-2007. In the majority of the studied herds, PRRSV antibodies were detected in a very high proportion of fatteners. Monitoring in 2006-2007 revealed PRRSV-positive herds in all Serbian regions at prevalence of 1.56-60.86%. No other monitoring or control program against PRRS was proposed at the national level. However, as a consequence of the first virus introduction and resulting outbreak, an emergency PRRS vaccination campaign was carried out on a small number of commercial farms in Northern Serbia in 2002-2003 [32]. The obtained results in the last 15 years suggest that PRRS virus infection is widely distributed in Serbia. Phylogenetic analysis revealed that all genetically typed isolates belong to the EU subtype 1 or Lelystad type viruses that are distributed globally in Europe, as well as in the other parts of the world. This result was expected

regarding the results published from surrounding and other EU countries [32,33,81]. Despite the fact that the disease is widespread in most of the commercial swine farms, there are no legislation procedures regarding PRRSV control in Serbia. To the best of our knowledge, today the vaccination against PRRS virus is used in a number of Serbian commercial pig farms. Also, at the moment PRRS monitoring and surveillance are not undertaken except for the animals imported from another country and in abortion cases that are sent to laboratory testing. However, it needs to be stressed that Serbia as a Western Balkan country annually imports a large number of different categories of live pigs from Western Europe. The preventive measures are only done through serological testing of breeding animals (gilts, sows, boars), farm management and biosecurity protocols.

The underlying PRRS virus has proved to be difficult to control, particularly in areas where there are many pig farms nearby (different family holdings, backyards) and the virus can move around pig farms via aerosols in the wind [82]. Because there are many strains, and new strains are continually evolving, having a recent outbreak of PRRS does not provide any immunity to the next PRRS virus entry and disease outbreak [83]. Various PRRS vaccines are available in Serbia and the modified live PRRS vaccines have been the most frequently used. However, it is often important to establish which strain of PRRS virus is on the farm. Current vaccines do not prevent infections with all PRRS strains and disease can still occur in vaccinated pigs [3].

Gross lung lesions in pigs infected with PRRSV infection may be very different since they are often complicated by lesions resulting from bacterial infection. Independently, PRRSV causes lesions corresponding to interstitial pneumonia accompanied by enlargement of lymph nodes in all ages of swine [3,84]. Lungs are usually mottled, gray, and noncollapsed with prominent intersticial edema (Figure 3a). In severe cases, the lungs become red in color and very moist, especially the cranio-ventral lobes. Tracheobronchial and mediastinal lymph nodes are enlarged and vary from solid to polycystic [84, 85]. Microscopic lesions may include septal thickening by macrophages, lymphocytes and plasma cells, necrotic cell debris with macrophages accumulated in alveolar spaces which all correspond to interstitial pneumonia (Figure 3b). Marked hypertrophy and hyperplasia of type II pneumonocytes are also present. Necrosis and depletion of germinal centers and follicular hyperplasia of lymph nodes are evident [84,86].

PRRS virus was discovered more than 20 years ago and still remains one of the most widespread diseases in the swine industry [81]. The disease has become enzootic in most swine production areas and is responsible for huge economic losses in the swine industry worldwide [87, 88]. The causative agent belongs to the order *Nidovirales*, family *Arteriviridae* and genus *Arterivirus*. Two major PRRS virus genotypes are established: type 1 PRRS virus (European genotype) and type 2 (North American genotype) which share approximately 60% genome nucleotide identity. Viral infection in pigs is associated with reproductive failure in sows and respiratory distress in growing pigs [88]. The infection can be epidemic (after virus introduction in immunologically naive

hosts regardless the age) and endemic (occurrence of the susceptible population with no immunity). However, in one-site farrow-to-finish production, the sows may be exposed to field viruses continuously because the field virus is constantly circulating within the farm. Despite the existence of different commercial vaccines, to date, the virus remains endemic in many countries [89]. Experimental studies have shown that PRRSV sometimes interacts with other pathogens synergistically, depending on the concurrent microorganism and the time sequence of infections [15]. PRRS is generally considered as an immunomodulatory pathogen, being able to compromise the immune functions predisposing to further infections. Interacting with other respiratory viral and bacterial pathogens, the PRRS virus represents an important factor in respiratory disease triggering [90]. PRRS virus is an important cofactor in other disease syndromes, such as porcine respiratory disease complex (PRDC) and PCV-associated disease (PCVAD) [37]. In practice, PRRS is often found to increase the incidence of secondary respiratory infections. It is well known that non-infectious factors related to biosecurity, housing conditions and management practices influence the odds of being infected by pathogens involved in PRDC [90].

Since the beginning of PRRSV outbreaks in Europe and other parts of the world, the development of efficacious vaccines has been a challenge [88,91]. However, it is well known that viral mutation can lead to more pathogenic strains and still, there is a lack of knowledge on how the porcine immune system interacts with all viral proteins. Highly divergent strains make it more difficult to develop a universal vaccine for the virus [83]. Several different vaccines against PRRSV have reached the market, and most of them rely upon the modified live virus (MLV). The results of the study by Fablet et al. (2016) [90] indicate that the vaccine strain may be transmitted to susceptible pigs by direct or indirect contact. Furthermore, the duration of passive immunity in piglets may be an important point to consider when looking at the appropriate window time for vaccination [90,91]. Although it is possible to control some disease outbreaks by use of MLV, there are major safety issues such as a high mutation rate leading to reversion to virulence and recombination among vaccine and wild type strains [3,81]. Cases have been reported in which new viruses have been introduced as a consequence of MLV vaccines. Presently available vaccines have many limitations in terms of heterologous protection, but some efforts have been made by combining new adjuvant formulations with modified live viruses, DNA and peptide vaccines, as well as extracellular vesicles [83,91]. Many factors are important in disease epidemiology, the main are purchase of animals and semen from PRRS positive herds, increasing herd size and proximity to PRRS infected herds [3,87]. It needs to be stressed that the most common commercial herd type in Serbian pig production system is farrow-to-finish production. On the farms where sows and growing pigs are reared on the same premises, observations have revealed close contact between both populations, which is likely to influence virus maintenance within the herd and transmission between herds. Farrow-to-finish farms are continuously occupied by susceptible growing pigs and because the breeding herd may constitute a reservoir of infectious pathogens, the pigs are more likely to be

exposed to enzootic infections compared to breeding farms where young susceptible pigs are removed, or to single-age all-in/all-out rearing systems [30,82,90]. Despite tremendous efforts over the last three decades to understand PRRS pathogenesis, effective vaccines are still lacking. The most common vaccines are modified-live virus or inactivated vaccines. However, so far none of them has been fully effective in preventing the spread of the virus. Attenuated live vaccines shown delayed but effective protection against homologous and some heterologous PRRSV strains. However, their limited immunity and immunogenicity to many circulating strains have raised major concerns regarding vaccine effectiveness [88,89,91]. Certainly that in Serbian swine production system, continuous monitoring of pigs in breeding herds is most important to assess herd stability, and together with implementation of well recognized biosecurity measures for commercial production might improve current disease control measures.

2. Swine Influenza (SI)

Serological examination of blood samples at the slaughter line revealed the presence of antibodies against H1N1 in fatteners from three commercial pig farms. However, the presence of H3N2-specific antibodies has not been established. In just two cases, after evident clinical respiratory disease, the SIV has been confirmed in tissue samples derived from dead animals by PCR. In most of the detected field cases, the lesions induced by SIV were frequently complicated and masked by bacterial infections. Detected co-infection SIV and *H. parasuis* potentiated the severity of lung lesions. The gross lesions found in uncomplicated swine influenza are rarely seen in the field cases. Pathological changes are often limited to the apical and cardiac lung lobes. Gross lesions associated with uncomplicated swine influenza have characteristics of viral bronchointerstitial pneumonia. The lungs are red and consolidated, with prominent interstitial edema (Figure 3c). The firm purplish-red lesions are well demarcated from normal lung tissue and the bronchial and mediastinal lymph nodes may be enlarged [92,93]. However, in naturally occurring cases swine influenza infection is usually complicated by bacterial infections and gross lesions may include mucopurulent inflammation of the airways (Figure 3d), followed by alveolar and interstitial pulmonary edema [85]. In uncomplicated cases, the most prominent lesions are necrosis and desquamation of the bronchial and bronchiolar epithelium. The airway lumens are mainly filled with neutrophils [92,93]. In more severe cases it acquires the characteristics of interstitial pneumonia., characterized by the presence of a large number of alveolar macrophages, infiltration of the alveolar wall with mononuclear cells and hyperplasia of the bronchiolar epithelium [85,92].

In Europe, swine influence virus is one of the most important primary pathogens of swine respiratory disease. Three subtypes of influenza A viruses: H1N1, H3N2 and H1N2 are considered to be endemic in European pig population [94,95]. Swine influenza is an acute, highly contagious respiratory disease of swine, characterized by

low mortality (<1%) and with recovery within 5 -7 days. In addition to the clinical cases, subclinical infections often occur and secondary bacterial infections increase the disease severity and mortality rates [22]. Sign of disease appears suddenly and in a large number of animals and at all animal ages. It is characterized by the acute respiratory disease with a low mortality rate. Secondary bacterial infections can often increase the severity of the disease and may result in complicated pneumonia. Epidemics may be the result of poor husbandry conditions and cold weather, but also concurrent viral and secondary bacterial infections [96].

Influenza viruses infect a wide range of mammalian and avian hosts and cross-species transmission among human, avian, and swine hosts is a reflection of the constant evolution of influenza A viruses. They are single-strained RNA viruses and belong to the family *Orthomyxoviridae*. Type A influenza viruses are further divided into subtypes and only viruses H1N1, H1N2 and H3N2 subtypes have been consistently isolated in swine. In pigs, replication of SIV is restricted to the respiratory tract. The most common clinical signs in pigs affected by SIV include nasal and ocular discharge, sneezing, dyspnea, coughing but also hyperthermia, lethargy and anorexia [96]. Aquatic birds are known to be the source of all influenza viruses for all species [97,98]. Pigs are important host for influenza, because they are susceptible to infection with both avian and human influenza A viruses, often being involved in interspecies transmission [94,95]. Infection of pigs with influenza viruses has direct consequences for pig health and pigs are potential intermediate hosts for the adaptation of avian viruses to human beings. Therefore, the epidemiological consequences are unpredictable [98]. Clinically two forms of disease may occur in swine: endemic and epidemic. In the endemic form, the respiratory disease is more apparent in young pigs. Swine influenza is commonly characterized by fever, respiratory and systemic nonspecific symptoms (i.e. loss of appetite, apathia). Frequently, clinical signs may be less obvious, but the clinical picture is complicated by secondary bacterial infections. Subclinical infection is also quite common [22,95]. On the contrary, epidemic influence is clinically apparent in all herd categories: influenza-induced abortion in sows and respiratory disease in growing pigs [96]. During uncomplicated infection, the morbidity can be as high as 100% but the mortality is relatively low (ranges from less than 1% to 4%). The most common complications of swine influenza are secondary bacterial pneumonia and PRDC [99]. Other respiratory viruses, such as PRRS frequently infect pigs around the same age as SIV. Results from experimental infections trials with SIV in combination with *M. hyopneumoniae* or PRRS virus showed a more severe disease in dual infections as compared to single pathogen infected pigs. Co-infection of pigs with SIV and *M. hyopneumoniae* often leads to the exacerbation of the clinical signs [95]. It is considered that SIV and App are the most important primary pathogens of swine respiratory diseases [15,96]. *Actinobacillus pleuropneumoniae* can potentiate/facilitate SIV replication in the respiratory tissue of dual inoculated pigs, by currently unknown mechanisms [22]. Considering the influence on clinical outcome in dual infections, SIV and App

are frequently isolated from pigs in field conditions and may induce a similar course of infection, which may be sometimes difficult to differentiate clinically [50].

Swine influenza is related to the animal movements and clinical disease usually appears after the introduction of new pigs into a herd. Disease outbreaks are usually more frequently detected in the colder periods of the year [96]. However, studies have also demonstrated that SIV circulate the year round and as swine production has moved to confinement systems, disease seasonality has become less prominent. The primary route of virus transmission is thought to be pig-to-pig contact via nasopharyngeal exposure. In pig farms with low biosecurity standards, on farrow-to-finish farms, the virus seems to be able to persist within the population [95, 99]. Humans can act as a mechanical vector of pathogens if they have been in contact with infected animals and subsequently come into contact with susceptible animals without taking any preventive measures. Therefore, in the frame of farm biosecurity, the first measure to be taken is to limit the number of people with access to the stables to an absolute minimum [35]. In our study, positive serological results point out that the virus infection subtype H1N1 is present in commercial pig populations. Vaccination is the primary means of swine influenza prevention and control. Despite the fact that the swine population in Serbia is in the most of the farrow-to finish unit seasonally affected with SIV, vaccination is not in use.

3. Porcine Circovirus type 2 (PCV-2)

At the time of our survey, in three commercial swine farms the health problem resembling Postweaning Multisystemic Wasting Syndrome (PMWS) in weaned pigs was detected. In most of the diseased animals the clinical picture was characterized by wasting, growth retardation, severe respiratory distress and occasionally icterus. By gross pathology, the enlargement of mesenterial lymph nodes was the most prominent feature in the early clinical phase. Lung gross lesions caused by porcine circovirus 2 depending on the severity of the disease and the presence of other bacterial pathogens were frequently detected. The presence of the PCV-2 viral genome was detected in samples from three commercial farms and 13 samples (lungs and mediastinal lymph nodes) were collected directly at the slaughter line. By serological testing, antibodies against PCV-2 were detected in 80% of examined samples collected at the slaughterhouse. In PCV-2 diseased animals the lungs are commonly firm or rubbery, noncollapsed, enlarged and of a mottled color. Consolidated areas may be often observed in the middle and cranial lobes, while dark red lobes are the result of alveolar hemorrhages in severe cases [100]. The observed changes microscopically correspond to the interstitial pattern of pneumonia. A characteristic microscopic lesion in the lungs of pigs dead due to PMWS is peribronchiolar fibrous hyperplasia. Inclusion bodies were commonly present in some mononuclear infiltrate cells in the interstitium. Changes in the lymph nodes occur in the form of depletion of germinal centers and parafollicular histiocytic inflammatory infiltration [85,100].

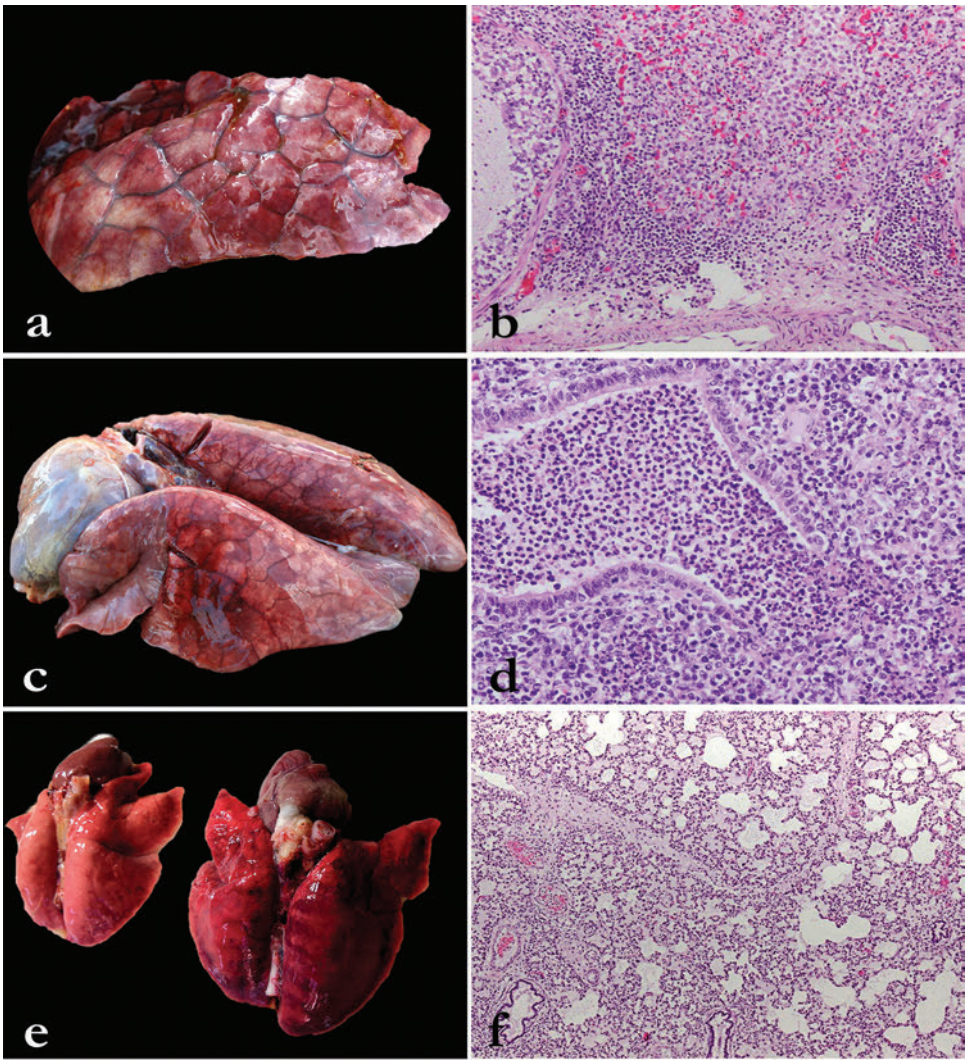

Figure 3. Pig, Lung, Macroscopic and microscopic morphological changes in lungs with confirmed viral etiology. **a)** Mottled, gray-tan and noncollapsing lungs with prominent interstitial oedema; **b)** Interstitial pneumonia - septal thickening by macrophages, lymphocytes and plasma cells and necrotic cell debris with macrophages accumulation in alveolar spaces, HE; **c)** Red and consolidated lungs, with prominent interstitial oedema; **d)** Complicated interstitial pneumonia with mucopurulent exudate in bronchiolar and alveolar spaces, HE; **e)** Pulmonary oedema, scattered foci of hemorrhage; **f)** Alveolar oedema, HE.

In pigs, three circovirus species within the genus Circovirus have been identified so far, including the non-pathogenic Porcine circovirus 1 (PCV-1), the pathogenic Porcine circovirus 2 (PCV-2), and the recently identified Porcine circovirus 3 (PCV-3) [3, 100]. The porcine circovirus associated disease (PCVAD) caused by circovirus type 2 (PCV-2) has been associated with several clinical disease entities such as Postweaning

Multisystemic Wasting Syndrome (PMWS), Porcine Dermatitis and Nephropathy Syndrome (PDNS) and Porcine Respiratory Disease Complex (PRDC). The first PCV2-PMWS cases were detected in Serbia in 2002 and the detection of PCV-2b strains in the majority of herds affected with PMWS confirmed that these strains are capable of inducing the disease [20]. According to Savic et al. (2012) [101] PCV-2b is dominant in the swine population and it is associated with PMWS occurrences in Serbian pig population.

Porcine circovirus type 2 is regarded as a ubiquitous virus and it is present in most, if not all, pig herds [102]. The virus was initially recognized in 1998, but based on retrospective investigations it is now known that virus has been present in the global pig population many decades prior to its discovery. Under field conditions, a number of different pathogens have been found to directly enhance PCV-2 replication, lesions and disease [103]. Nowadays, the worldwide tendency in pig health programs is to massively vaccinate piglets against PCV-2. In such a scenario, the laboratory diagnosis previous to vaccination might not make sense. However, it is important for both field veterinarians and pathologists to be updated regarding PCV-2 infection outcomes, as well as diagnostic possibilities and their correct interpretation [100]. With recent advancements in pathogen detection methods, the importance of polymicrobial diseases has become more evident, and identification of interactions of pathogens and their mechanisms of disease potentiation has become a topic of great interest [103]. Co-infection PCV-2 with other swine pathogens, such as PRRS virus, SIV and *M. hyopneumoniae* is frequently reported. [104]. All of these pathogens are important cofactors that may enhance PCV-2 infection and the severity of the disease. For example, combined infection of pigs with typically low pathogenic organisms like PCV-2 and *M. hyopneumoniae* results in severe respiratory disease [103]. The results of the most researchers have shown that PCV-2 needs one or more co-factors for PMWS to develop into a severe and fatal disease [102]. In Serbia, CSF has been controlled in the recent past by vaccination with China strain [25,27] and differential diagnosis was frequently complicated by the emergence of PDNS on the field [20]. Using immunohistochemistry in these cases we were able in the past to perform specific and sensitive differential diagnosis (Figure 4). It is considered that PCV-2 plays a dominant role during PCV-2 and CSF co-infection. Indeed, PCV-2 may enhance wild-type CSF virus infection by inhibiting the host immune response and also by decreasing the efficacy of the CSF virus vaccine [104]. One important evidence that PCV-2 is playing a substantial role in polymicrobial diseases of pigs is provided by the impact of vaccination. The PCV-2 vaccines become commercially available in 2006 and are among the most commonly used commercial products in growing pigs worldwide [102,103]. Nowadays, the pig population on commercial swine farms in Serbia is routinely vaccinated against PCV-2. However, control and prevention should not be only focused on the efforts to reduce PCV-2 via vaccination but also to reduce the farm-specific pathogen load by applying other non-specific measures [35].

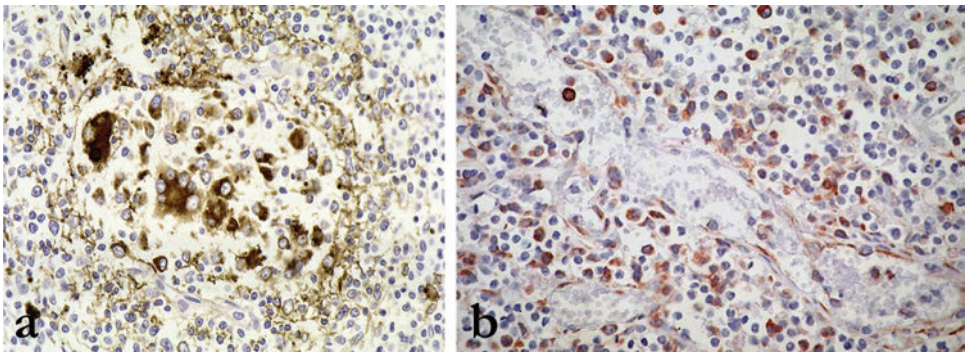

Figure 4. Pig, Tracheobronchial lnn, Imunohistochemistry. **a)** Expression of PCV-2 antigen, LSAB; **b)** Expression of gp55 CSF antigen, LSAB.

4. Aujeszky's disease – Pseudorabies (AD)

In two commercial farms, the health problem in suckling piglets and weaners was suggestive to Aujeszky Disease outbreak. Anamnestically, health disorders in sows and in their litters were observed. By epidemiological investigation, it was discovered that 2 to 3 months before the outbreak new gilts and sows had been introduced. Serologically, in several sows, the presence of specific antibodies against Aujeszky Disease was detected. However, despite the fact that these animals were serologically positive, the origin of immunological status remained unknown: vaccination or infection. In the time of the study two different vaccine types were officially registered and used in Serbian commercial farms: attenuated live vaccine and gene deleted vaccine (Begonia strain) [24]. By clinical examination in sows signs of inappetence, mild apathy and agalactiae were observed. In suckling piglets, the sings of severe disturbance of the central nervous system (wide open eyes, paddling, trembling, ataxia, paresis and paralysis) were clinically detected. In some cases, the whole litter of piglets died within 48 hours. Despite the fact that the sows and piglets were therapeutically treated, there was no evident respond to the applied medication. Clinically, the fatteners also become anorectic, listless and apathic. The gross pathology changes that were detected in dead sucklings indicated lesions characteristic for AD infection (*necroses miliares hepatis, haemorrhagiae corticis renis, tonsillitis diphtheroides necroticans*). By molecular testing from the tissues deriving from dead piglets the presence of virus was confirmed. In the detected disease outbreak cases in Vojvodina Province, gross pathological lesions are often mild or absent, but their existence in pigs depends on the stage of infection and affected age category. In the newborn, suckling pigs lacking passive immunity, multifocal necrosis in the liver and spleen are frequently observed. Typically, depending on days post infection, exudative conjunctivitis, serous to fibrinonecrotic rhinitis, laryngitis and necrotizing tonsillitis may be present. Gross lesions in the lower respiratory tract are more common in weaners and finishers: pulmonary edema, scattered foci of hemorrhage (Figure 3e) or even broncho-interstitial pneumonia [9,23,24]. In

uncomplicated cases, microscopical alveolar edema could be observed (Figure 3f). Macroscopically, small necrotic foci can sometimes occur in the lungs. More obvious lesions are not uncommon in the case of secondary bacterial pneumonia [95, 105]. Microscopically, necrotic bronchitis, bronchiolitis and alveolitis were observed in the lungs. The lumen of alveoli may be filled with fibrin, containing few neutrophils and occasionally erythrocytes. Intranuclear inclusions are frequently present in the respiratory epithelium and pulmonary macrophages [105].

Aujeszky's Disease is an economically important viral disease of pigs and other animal species [106]. The disease is caused by suid herpesvirus 1 or called pseudorabies virus (PRV) or Aujeszky's disease virus (ADV). The virus belongs to the genus *Varicellovirus* in the subfamily *Alphaherpesvirinae* of the family *Herpesviridae* [107,108]. Aujeszky's disease was first described in Hungary more than 100 years ago, as an infectious disease in cattle, cats and dogs. In the epidemiology studies conducted by researchers in the 1980s, it was confirmed that domestic swine is a reservoir host while all other susceptible species (ruminants, carnivores, rodents) were found to be aberrant hosts [106,109,111]. Pigs are the natural host for PRV and the only animals that may become latent carriers [107]. In newborn pigs, AD occurs as an acute fatal clinical disease with dominant central nervous system signs and mortality rates of 90% or higher. On the contrary, in growing and adult animals infections are mild or unapparent but recovered animals remain as virus carriers [106,107]. Mild respiratory disease, listlessness and decreased feed consumption or anorexia for several days is frequently detected in breeding categories [23,24]. During disease outbreaks, in the category of weaned pigs most frequently rhinitis, conjunctivitis, dyspnea and cough can be observed. Finally, in fatteners, depression, anorexia and mild to severe respiratory disease frequently occurs [106]. The recovery of all categories (except baby piglets) significantly depends on the concurrent herd bacterial infections. In swine herds harboring clinically unapparent *A. pleuropneumoniae* or *P. multocida*, infection with this virus could result in an acute outbreak or exacerbated pleuropneumonia or pasteurellosis. Usually infection in growers will appear as a respiratory disease, giving way to secondary pathogens like *A. pleuropneumoniae, M. hyopneumoniae*, PRRS virus, SIV that will most probably increase the disease severity [110]. Also, concurrent bacterial infections, like *S. suis* are commonly found in infected pigs. However, once introduced, pseudorabies virus spreads easily among the susceptible swine population. It needs to be stressed that latently infected pigs can be a permanent source of reinfection in a herd. The latent infection may be reactivated by stress (transport, mixing of pigs) or due to swine feed contamination with different mycotoxins [28,31].

In most parts of Europe, the epidemiology of AD was changed by vaccination. The genetically engineered vaccines provided immunological markers to differentiate vaccinated uninfected from vaccinated infected animals (DIVA) by serological test. The combination of efficacious DIVA vaccines and differential serological test has made eradication of AD in different world areas feasible [107]. Due to control efforts and implementation of national eradication programs the disease has been eradicated

from a number of European countries [109,110,111]. Despite the existence of DIVA vaccine and long term vaccination practice, the infection is still endemically present in the pig population in Serbia. Even more, due to poor biosecurity measures, the virus is now present in all types of production pig systems. The trade and pig movement in the pig production system have provided the environment for disease maintenance and spread of the virus within and among herds, municipalities and districts. Knowing the viral latency in the pig population, the virus is able to persist even in regularly vaccinated herds. Since the vaccination is voluntary at the farmers' expense, there is no financial subsidiary in the case of an outbreak and disease outbreaks are not always reported which further complicates the control program. Consequently, interactions between different pathogens may further exacerbate the disease and animal movement may help in disease spreading [23,24,28].

CONCLUSIONS

Swine breeding is an important part of the Serbian economy, especially in the Northern part of the country (Vojvodina Province). Diseases of the respiratory system in pigs raised on commercial farms are important health issue and have considerable influence on the production results and the efficiency of swine production. Epidemiological data on prevalence of different respiratory pathogens in Serbia are scarce or not available in the scientific literature, as respiratory diseases are not reported and have no legal influence, i.e. do not limit internal commercial trade in the country. The research study results indicate a high level of different respiratory pathogens in fattening and slaughtered pigs under one site production systems and progressive circulation of these agents during the rearing process. Certainly, those animals are important as potential carriers of different infectious agents [112,113]. Pulmonary lesions are associated with significant economic losses, due to a reduction in growth performance and feed efficiency and the requirement for antibiotic treatment. However, changes in the respiratory organs were evident at a high rate in clinically healthy fatteners, resulting in pronounced inconsistency in body mass and carcass quality. Today, most control measures need to be focused on prevention by improving housing conditions, strictly strategic application of antimicrobials and vaccination, but also on important biosecurity issues. In the farrow-to finishing pig production system which is the dominant way of pig production in Serbia, the biosecurity issues and housing conditions are significant factors which affect the infection outcome.

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Authors' contributions

PRJ carried out the epidemiological, clinical trial and slaugher-check control on selected pig farms and participated in the macroscopical examination of pig carcasses and sampling procedures. VI carried out histopathology and drafted the manuscript. PV participated in the sampling process and in the macroscopical examination of pig carcasses. AKS participated in the design of the study and coordination, performed the histopathology and immunohistochemistry and helped to draft the manuscript. All authors read and approved the final manuscript.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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MORFOLOŠKE MANIFESTACIJE AKTUELNIH RESPIRATORNIH BOLESTI SVINJA U INTENZIVNOJ PROIZVODNJI U SRBIJI

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Oboljenja respiratornog sistema svinja predstavljaju jedno od najčešćih zdravstvenih problema u svinjarskoj proizvodnji u svetu. Uprkos činjenici da je načinjen značajan napredak u oblasti dijagnostike, kontrole i profilakse, respiratorna oboljenja i dalje predstavljaju svojevrsni zdravstveni izazov u savremenoj komercijalnoj proizvodnji svinja. Brojni su infektivni agensi koji dovode do respiratornih oboljenja svinja i obuhvataju, kako bakterije tako i virusne uzročnike. Mada je proteklo više od petnaest godina od početka primene savremenih vakcina u Srbiji, u cilju kontrole respiratornih bolesti, na listi bakterijskih patogena još uvek se nalaze *Mycoplasma hyopneumoniae, Actinobacillus pleuropneumoniae, Haemophilus parasuis* i *Pasteurella multocida*. Najčešće virusne infekcije su svinjski reproduktivni i respiratorni virus, influence virus, cirkovirus tip

2, kao i virus Aujeckijeve bolesti. Morfološke karakteristike pneumonija u čijoj je patogenezi često uključeno nekoliko različitih agenasa, svakako zavise od dominantnog etiološkog agensa. Unapređenje saznanja o glavnim etiološkim patogenima respiratornih oboljenja svinja, kao i njihova međusobna interakcija, od velikog su značaja, kako za dalje istraživanja, tako i za primenu odgovarajućih kontrolnih strategija u komercijalnoj proizvodnji svinja u Srbiji. U radu su predstavljena najnovija saznanja o morfologiji respiratornih bolesti svinja kao i aktuelni trend respiratornih infekcija u populaciji svinja u Srbiji.