Etiological structure of pig colibacillosis on the territory of the Russian Federation

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Abstract. In the course of the study, the results were obtained proving that on the territory of pig breeding enterprises in some regions of the Russian Federation, at least 29 E. Coli serogroups are circulating, both intestinal (enterotoxigenic - ETEC, enteropathogenic - EPEC, enterohemorrhagic - EHEC, enteroaggregative - EAEC, diffusely adherent - DAEC), and extraintestinal (uropathogenic - UPEC, neonatal meningitis - NMEC, avian pathogenic - APEC). The O2 serogroup has the largest share in this structure - 10.13%, then comes O4 – 9.13%, O20 – 6.98%, O41 – 6.95%, O35 – 5.74%, O55 – 5.62%, O33 – 5.38%, O26 – 5.02%, O119 – 4.14%, O111 – 3.93%, O18 – 3.23%, O103 – 2.99%, O8 – 2.96%, O1 and O126 - 2.93% each, O127 – 2.54%, O141 – 2.39%, O15 – 2.27%, O78 – 2.21%, O117 – 2.12%, O139 – 1.06%, O101 – 2.00%, O115 – 1.36%, O86 – 1.33%, O138 – 1.12%, O142 and O9 - 0.85%, O149 – 0.67% and O3 – 0.18% each. Most of the E. Coli isolates were not serotyped due to the limited capabilities of the diagnostic kit. Most of the identified Escherichia serogroups (28 out of 29) were isolated from adult sows on a commercial reproducter, which suggests that this physiological group of animals is the main source of E. coli. At the same time, it was recorded that in addition to the vertical path of transmission of the pathogen (from sows to young animals), the horizontal path of transmission (for example, from people, with food, with water, with rodents, etc.) has an important role in the spread of colibacillosis. The results obtained can be useful for practicing veterinary specialists when planning therapeutic measures for pig colibacillosis.

1. Introduction
Colibacillosis (escherichiosis, colienteritis, colidyspepsia) of pigs is an acute infectious disease caused by pathogenic strains of Escherichia coli. The disease manifests itself in the form of diarrhea in newborn piglets, edema disease in weaned piglets, as well as infections of the genitourinary organs, mastitis and septicemia in adult animals. The infection is characterized by significant economic damage due to high morbidity, mortality, reduced weight gain and the cost of treatment, vaccination, etc. [1].

1.1. Pathogen properties
The pathogen of Escherichia coli disease is gram-negative facultative anaerobic polymorphic mobile rods with rounded ends that do not form spores and capsules. The microorganism grows well on conventional nutrient media. Some strains have hemolysis. Of all the existing Escherichia serovars, more than 170 are pathogenic for humans and animals. For serotyping E. coli, it is necessary to define: "O" - lipopolysaccharide-protein complex that determines the serogroup, "K" - capsular antigen, "H" - flagellar antigen [2]. Pathogenic isolates of Escherichia can be identified by serotyping, since a small
number of "O" serogroups are associated with the disease. Moreover, these strains possess many virulence factors - capsules, endotoxins, adhesins responsible for colonization, enterotoxins and other secreted substances [3, 4, 5]. In recent years, with the development of the nomenclature of pathogenic E. coli, the term "pathotype" arose, which characterizes the pathogen by the presence of a certain set of virulence factors and the mechanism of development of the disease. This system divides the types of pathogenic E. coli into two groups: intestinal (causing diarrheogenic diseases of exogenous origin) and extraintestinal (causing extraintestinal diseases and having an endogenous origin).

Intestinal Escherichia are subdivided into 6 pathotypes: Enterotoxigenic E. coli (ETEC) capable of producing one or several enterotoxins that cause secretory diarrhea, precisely, heat-labile (LT) and heat-resistant (ST) ones. Each type of enterotoxin has two subgroups: ST is further subdivided into STA and STB based on methanol solubility and biological activity. Similarly, two subgroups of LT have been described: LTI and LTII. Most strains of enterotoxigenic E. coli isolated from pigs produce LTI, which promotes hypersecretion of fluid in the intestine, thus developing a cholera-like disease. These include O6, O8, O15, O20, O25, O27, O41, O63, O78, O80, O85, O101, O115, O128, O138, O139, O141, O148, O149, O153, O159 and others. [6, 7, 8].

Enteroinvasive E. coli (EIEC) provokes the development of dysentery-like disease. In this type of infection, the pathogen infiltrates and multiplies in the epithelial cells of the lower ileum and colon forming intracellular parasitism. Later the destruction of the mucous membrane develops. In the pathogenesis of infection, adhesion, colonization and invasion play an important role. These include O28, O29, O112, O121, O124, O135, O136, O143, O144, O152, O159, O164, O167 and O173 [9].

Enteropathogenic E. coli (EPEC) pathotype of Escherichia causing post weaning diarrhea (PWD) in pigs. Strains of this pathotype attach to epithelial cells, multiply on their surface and cause the destruction of microvilli, which in turn leads to epithelial erosion. These bacteria do not attach by fimbriae, but have a complex secretion system that introduces more than 20 effector proteins into the host's enterocyte, causing the bacteria to adhere to the host's intestinal epithelium and develop characteristic features. EPEC lacks the virulence factors of ETEC strains which also cause PWD. These include O6, O18, O26, O33, O35, O44, O55, O86, O91, O103, O111, O112, O113, O114, O119, O117, O125, O126, O127, O128, O142 and O158 [10, 11].

Enterohemorrhagic E. coli (EHEC) is a pathotype producing shiga-like toxins or verotoxins. Strains of this pathotype can be called STEC or VTEC. In pigs, this group of Escherichia causes edema disease [12]. Some EHEC serogroups may be present in the intestines and faeces of clinically healthy pigs, although they are zoonotic, as they can cause hemorrhagic diarrhea, hemorrhagic colitis and / or hemolytic uremic syndrome in humans, infected through food or water contaminated with animal faeces. Cattle and other ruminants are the main source of zoonotic EHEC in livestock farming. These include O26, O104, O111, O145 and O157 [13].

Enteroaggregative E. coli (EAEC or EAgEC) do not possess cytotoxins and do not enter epithelial cells. They affect the epithelium of the small intestine and are prone to autoagglutination. Due to fimbrial adhesins AAF (aggregate adherence fimbriae), strains of this pathotype are able to quickly attach to the cell surface, after which the microorganism forms aggregates in the form of brickwork. Then, the production of mucus by cells is stimulated, which leads to the formation of a thick mucous membrane. These include O3, O104, O111, O126 and O139 [11, 14, 15, 16].

Diffusely Adherent E. coli (DAEC) have fimbrial and afimbrial adhesins. The strains attach to epithelial cells in a diffuse distribution. This pathotype of Escherichia is associated with watery diarrhea as well as recurrent urinary tract infections. The pathogen is predominantly common among children [17]. These include O86, O127, O142 and O158 [18].

The second group of extraintestinal Escherichia, ExPEC, are a heterogeneous group of E. coli, so named because their usual habitat is in the intestinal tract, but they are able to invade and cause bacteremia or septicemia, or localized extraintestinal infections such as meningitis or arthritis. ExPEC is not characterized by a constant group of virulence factors. The group consists of the following pathotypes.
Uropathogenic E. coli (UPEC) pathotypes of Escherichia with fimbrial P- and S-adhesins to the epithelium of the urinary tract, specific aphimbrial adhesins, a pronounced capsule, producing a cytotoxic necrotizing factor and having hemolysis due to the presence of an Hly plasmid. The penetration of the pathogen into the urinary tract occurs due to the migration of E. coli from the rectum to the orifice of the urethra, from where it enters the bladder, causing inflammation. The most important role in the development of the inflammatory process belongs to interleukin 8, which is produced by epithelial cells when interacting with uropathogenic strains of such serogroups as: O1, O2, O4, O6, O7, O8, O9, O11, O12, O14, O15, O16, O17, O18, O21, O22, O25, O50, O75, O77, O78, O81, O83, O85, O86 [19, 20, 21].

Neonatal Meningitis E. coli (NMEC) are Escherichia serogroups provoking meningitis in children. Pathogenesis consists in the penetration of the pathogen into the bloodstream, followed by migration into the central nervous system. It is important to note that the considered Escherichia pathotype has a high degree of homology with the pathogen of avian Escherichiosis (Aviaphathogenic E. Coli), since both use similar virulence factors and pathogenesis, and also belong to the same serogroup (for example, O18). The presence of S-fimbriae ensures the adhesion of the microorganism to laminin and fibronectin. Serogroups O1, O8, O18 belong to this pathotype [22, 23].

Sepsis associated pathogenic E. coli (SePEC) have fimbrial and afimbrial adhesins, resistance to phagocytosis. In addition, this pathotype may possess the K2 capsular antigen and P and F17 fimbriae [24]. This pathotype is represented by the serogroup O153 [25].

Avian pathogenic E. coli (APEC) is common in poultry, but can cause severe infectious diseases in humans [26]. Virulence factors typical of APEC include hemolysin, colicin, increased serum survival protein, type I fimbriae, thermosensitive hemagglutinin and siderophores [27, 28]. Strains of this pathotype can cause infections of extraintestinal organs, as well as secondary pathologies in domestic and wild birds, manifested as respiratory tract infections, polyserositis, cellulitis, yolk sac infection, ophthalmitis, swollen head syndrome, sepsis [29]. These include O1, O2, O5, O8, O18 and O78 [30].

1.2. Epizootology
Pig infection caused by E. Coli is widespread in all countries of the world. Most often, sows are bacteria carriers and a source of spread of the pathogen; they seed the environment of the pig complex, bedding, feed and water. Soon after birth, young animals become infected due to the faecal-oral mechanism of infection transmission, by alimentary or contact way [13, 31]. It is important to note that E. coli are also important inhabitants of normal intestinal flora throughout life. Thus, most E. coli strains are commensals and have low virulence or are not virulent at all, but can cause opportunistic infections of various localization, in particular, pathology of the mammary gland or urinary tract [32].

1.3. Pathogenesis
The development of the infectious process caused by E. Coli primarily depends on the pathotype of the pathogen, as well as on the age of the susceptible animal and its physiological state. Pathogenesis of diseases caused by various serogroups E. Coli is similar and has the following pattern: E. coli is staying on the receptors of enterocyte microvilli with the help of pili. Subsequently, they colonize the epithelium, multiply and produce enterotoxins, which cause epithelial cells’ excessive secretion of fluid and electrolytes, which significantly exceed the absorption capacity, leading to the release of tissue fluid into the intestinal lumen. Due to this, a sick piglet can lose up to 40% of its body weight. Enterotoxins, endotoxins and / or adhesins can also damage microvilli and enterocytes, which subsequently leads to a decrease in the absorption of electrolytes, water and endogenous secretions from the intestinal lumen. As a result of diarrhea, the colon loses its ability to absorb fluid. Damage to epithelial cells sometimes leads to septicemia. Diarrhea usually continues until death occurs as a result of dehydration and metabolic acidosis or terminal septicemia [33, 34].
1.4. Clinical signs
Escherichiosis can take several forms, precisely: diarrhea of newborn piglets (neonatal diarrhea), post weaning diarrhea, edema disease, as well as septicemia, urinary tract infections and mastitis.

Newborn piglet diarrhea is most commonly caused by ETEC strains of Escherichia and develops in piglets between the first and fourth days of life. Infection of newborns occurs through contact with skin of the nipples of the sow and surrounding objects contaminated by faeces. Due to the adhesive ETEC antigens, the strains attach to the enterocytes of the jejunum and ileum, where they multiply rapidly, producing enterotoxins. In some cases, the disease may manifest itself in a mild form and end on its own, but in severe cases, vomiting, debilitating diarrhea, leading to rapid dehydration and death may occur. The faeces can vary in colour from clear or gray-white to yellow. Piglets are sluggish, emaciated, they have sunken eyes, the skin becomes dry and takes on a gray tint [2, 35].

Post weaning diarrhea (PWD) is often associated with ETEC, but can also be caused by EPEC, which do not possess any of the virulence factors that are classic for PWD (post weaning diarrhea) or ED (edema disease). Sick piglets experience frequent diarrhea, dehydration, resulting in death. Post weaning diarrhea (PWD) and edema disease (ED) are often combined into one type, since they are often found in the same age group of pigs, the pathogens have some similar factors of virulence, and some E. coli strains cause both diseases. Almost all kinds of Escherichia of this type are α-hemolytic. Both diseases can occur independently of each other, but they can also occur together, as well as affecting one animal. Sick piglets experience frequent diarrhea, dehydration, which ends in death [36].

Edema disease (ED) is characterized by subcutaneous edema of the forehead and eyelids, as well as neurological symptoms such as ataxia, seizures. The disease is caused by E. coli isolates that colonize the small intestine, produce STX, Stx2e, which enters the bloodstream and damages the vascular walls, resulting in soft tissue edema. ED most often is presented by sporadic episodes or small outbreaks limited to a specific age group. Mortality ranges from 50% to more than 90%, and the duration of the course of the disease in a herd is from 4 to 14 days. The disease usually disappears as briskly as it appears [36].

Sepsis due to E. coli can be primary, occurring sporadically or in small outbreaks, predominantly in newborn piglets up to 4 days of age, or secondary when it is associated with diarrhea or other provoking diseases in young pigs. Bacteria pass through the mucous membrane of the digestive tract, probably by endocytic absorption into intestinal epithelial cells or through the intercellular spaces formed by the lateral plasma membranes of adjacent epithelial cells, to localize in the mesenteric lymph nodes before entering the bloodstream. Bacterial invasion can lead to a generalized infection (septicemia, polyserositis), with bacteria spread in various extraintestinal organs such as the lungs, liver, spleen, kidneys, and brain, or in a localized infection (meningitis or arthritis). Clinical signs of septicemia include lameness, ataxia, anorexia, and shortness of breath. These clinical signs may develop within 12 hours after birth, and piglets may die within 48 hours [37].

1.5. Pathological changes
Autopsy of dead or forcibly culled animals reveals that the tissues and organs are dehydrated, the intestinal lumen is dilated and filled with liquid faeces with a large amount of mucus, gas bubbles and casein flakes, the mucous membrane of the small intestine is edematous. There may also be an expansion of the stomach containing undigested milk and venous hemorrhage on the greater curvature of the stomach. Microscopic examination of the mucous membrane of the jejunum and ileum reveals numerous layers of E. coli covering the crypts and the tips of the villi.

2. Materials and methods
The scientific work was carried out in the Federal State Budgetary Scientific Institution "Federal Scientific Centre Russian Research Institute of Experimental Veterinary Medicine named after K.I. Scriabin and Y.R. Kovalenko of the Russian Academy of Sciences" (FGNU FSC VIEW RAS) in the period 2016-2020.
The study of the epizootic situation, clinical examinations of pigs, pathological studies, and selection of material for laboratory studies were carried out at pig breeding enterprises in Belgorod, Pskov and Tambov regions. The following were used as sectional and clinical material from animals: samples of liver, intestines, spleen, lymph nodes, heart, lungs, vaginal washings (9816 samples). The sampling for research was carried out from various types of sites, precisely: a commercial reproducer (CR), a section for growing replacement sows (SGRS), a growers section (GS), a growers and pig reproduction section (GPRS), a fattening section (FS), a fattening section and a commercial reproducer (FSCR), a pig insemination and reproduction section (PIRS). Bacteriological studies, as well as the study of morphological, tinctorial, cultural, pathogenic, serological properties of E. coli isolates were carried out in the laboratory of diagnostics and control of antibiotic resistance of the Federal State Budgetary Scientific Institution FSC VIEW RAS.

For species identification of bacteria, MALDI-ToF time-of-flight mass spectrometry method was applied using Maldi Biotyper equipment (Bruker Daltonics Inc., United States) according to MR 4.2.0089-14 [38].

In the course of the study, the serogroup was determined in 3308 E. coli isolates. For serotyping of E. coli isolates, we used diagnostic sera "O" -coli agglutinating (Federal government enterprise "Arnavir Biofabrika", Russia).

3. Results and discussion

The results of studying the general structure of the pathogens of pig colibacillosis (at all types of production sites for growing animals) are shown on figure 1.

![Figure 1](image-url)

**Figure 1.** Results of studying the serotypic diversity of E. coli at pig breeding enterprises in some regions of the Russian Federation (n = 3308 E. coli isolates, %).
The results obtained indicate that at least 29 different serogroups of E. coli, belonging to various pathotypes, circulate in pig breeding enterprises of the Russian Federation. It was found that with the highest frequency such serotypes were isolated: O2 - 10.13%, O4 - 9.13%, O20 - 6.98%, O41 - 6.95%, O35 - 5.74%, O55 - 5.62%, O33 - 5.38%, O26 - 5.02%, O119 - 4.14%, O111 - 3.93%, O18 - 3.23%, O103 - 2.99%, O8 - 2.96%, O1 and O126 2.93% each, O127 - 2.54%, O141 - 2.39%, O15 - 2.27%, O78 - 2.21%, O117 - 2.12%, O139 - 1.06%, O101 - 2.00%, O115 - 1.36%, O86 - 1.33%, O138 - 1.12%, O142 and O9 each 0.85%, O149 - 0.67%, O3 - 0.18%, respectively. It should be noted, however, that this structure does not reflect a number of untyped serogroups, due to the limited capabilities of diagnostic kits for serotyping.

When analyzing the results of the study, the frequency of isolation of pathogenic serogroups of Escherichia at various production sites was also established. The results are reflected in table 1 and figure 2.

Table 1. Results of studying the serotypic diversity of E. coli at different types of pig breeding sites (% isolation, n = 3308 E. coli isolates).

| Pathotype | Serogroup            | CR      | FS       | SGRS     | GS       | FSCR     | PIRS     | GPRS     |
|-----------|----------------------|---------|----------|----------|----------|----------|----------|----------|
| UPEC, NMEC, APEC | O1 | 2.85 | 0.00 | 0.00 | 0.00 | 0.00 | 18.52 | 22.06 |
| APEC, UPEC  | O2 | 11.00 | 10.25 | 39.29 | 0.00 | 9.32 | 0.00 | 0.00 |
| EAEC       | O3 | 0.28 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| UPEC       | O4 | 11.23 | 8.03 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| ETEC, NMEC, APEC | O8 | 3.68 | 2.49 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| UPEC       | O9 | 1.29 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| ETEC, UPEC  | O15 | 1.79 | 4.99 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| EPEC, UPEC, NMEC, APEC | O18 | 1.33 | 2.49 | 0.00 | 31.87 | 0.00 | 16.67 | 19.12 |
| ETEC       | O20 | 6.07 | 10.39 | 0.00 | 1.10 | 0.00 | 21.30 | 0.00 |
| EPEC, EHEC  | O26 | 5.94 | 4.71 | 7.14 | 1.10 | 0.00 | 0.00 | 0.00 |
| EPEC       | O33 | 5.75 | 7.20 | 3.57 | 0.00 | 0.00 | 0.00 | 0.00 |
| EPEC       | O35 | 5.57 | 7.48 | 10.71 | 0.00 | 10.17 | 0.00 | 0.00 |
| ETEC       | O41 | 5.66 | 13.16 | 14.29 | 0.00 | 6.78 | 0.00 | 0.00 |
| EPEC       | O55 | 5.34 | 4.99 | 0.00 | 0.00 | 28.81 | 0.00 | 0.00 |
| ETEC, APEC, UPEC | O78 | 2.99 | 1.11 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| EPEC, DAEC, UPEC | O86 | 2.02 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| ETEC       | O101 | 0.92 | 2.77 | 0.00 | 0.00 | 22.03 | 0.00 | 0.00 |
| EPEC       | O103 | 4.10 | 0.00 | 0.00 | 0.00 | 8.47 | 0.00 | 0.00 |
| EPEC, EHEC, EAEC | O111 | 3.82 | 2.77 | 0.00 | 0.00 | 6.78 | 0.00 | 27.94 |
| ETEC       | O115 | 1.24 | 0.00 | 0.00 | 0.00 | 0.00 | 16.67 | 0.00 |
| EPEC       | O117 | 2.39 | 2.49 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| EPEC       | O119 | 4.74 | 2.49 | 7.14 | 0.00 | 0.00 | 12.96 | 0.00 |
| EPEC, EAEC  | O126 | 1.06 | 4.99 | 3.57 | 30.77 | 7.63 | 0.00 | 0.00 |
| EPEC, DAEC  | O127 | 3.68 | 0.00 | 10.71 | 1.10 | 0.00 | 0.00 | 0.00 |
| ETEC       | O138 | 0.09 | 2.49 | 3.57 | 1.10 | 0.00 | 13.89 | 0.00 |
| ETEC, EAEC  | O139 | 3.08 | 0.00 | 0.00 | 1.10 | 0.00 | 0.00 | 0.00 |
| ETEC       | O141 | 1.06 | 4.71 | 0.00 | 1.10 | 0.00 | 0.00 | 30.88 |
| EPEC, DAEC  | O142 | 0.00 | 0.00 | 0.00 | 30.77 | 0.00 | 0.00 | 0.00 |
| ETEC       | O149 | 1.01 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
As can be seen from the data in table 2 and figure 2, various pathotypes of Escherichia are common in all age categories of animals, regardless of their physiological state. Thus, pathogenic E. Coli are most widespread on commercial reproducers, on which at least 28 serogroups of various pathotypes were identified. These data indicate that sows are an important carrier and source of the pathogen of colibacillosis. Of course, in this case, it cannot be excluded that the source of the pathogen is not only the animals themselves, but also people, equipment, feed, water, etc. In other words, when carrying out medical and recreational measures to fight outbreaks of colibacillosis, it is necessary to take into account not only the vertical path of the disease transmission, but also the horizontal one. This is confirmed by the fact that individual serogroups (for example O142) were not isolated from sows, but were found in sectional material from growers. The results obtained can be useful for practicing veterinary specialists when planning therapeutic measures for pig colibacillosis.

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