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Review

Bacterial pathogens of pigs with particular reference to *Escherichia coli*: A systematic review and meta-analysis

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Pigs are ungulate animals of the genus *Suis* and family Suidae. They are globally spread but restricted in certain countries due to religious and cultural beliefs. Pork serves as an important source of protein (38% of meat consumed in the world). While pig production remains a profitable enterprise, commercial and particularly the small-scale farmers face huge constraint in this husbandry practice, one of the most important being bacterial infections and its associated with morbidity and mortality. In this work, we reviewed the prevalence of bacterial infections in pigs with particular reference to *Escherichia coli*, a bacterium that is regularly isolated and can lead to multiple infections in pigs. Literatures were searched on selected veterinary and biological data bases in 2016 with focus on natural infections and isolates from natural infections with epidemiological details. Pathotypes, serotypes and serogroups of *E. coli*, the country of origin, source, growth stage, age of pigs infected, disease outbreak, the number of samples and type of samples, numbers and percentage of positive samples and isolates were used as filters. Pathotypes reported include enterotoxigenic *E. coli* (ETEC) 66.7%, enterotoxigenic *E. coli* and shiga toxigenic *E. coli* (ETEC and STEC) 14.3%, STEC only (7.9%), enterotoxigenic *E. coli*/enteropathogenic *E. coli*/enteroaggregative *E. coli* (ETEC/EPEC/EAE) 31.7%. Others were enterohaemorrhagic *E. coli* (EHEC), diffusely adherent *E. coli* (DAEC) (ETEC, EPEC, STEC) and extra-intestinal pathogenic *E. coli* (ExPEC). Twenty-nine countries with documented records of cases of *E. coli* were included with the USA reporting, the highest number followed by China. About 74% of the samples were taken from farms and others were from samples submitted to research laboratories and veterinary faculties for necropsy. Serogroups O141, O149, O139, O138, O8 and O9 were most common. Piglets were most affected (52.3%) followed by weaners (39.6%) and porkers (7.9%) with age ranging from 1 to 392 days old. A total of 24,854 isolates were considered, 10477 (42.2%) were positives and the following genes were carried: STa, STb, LT, stx1, stx2, Stx-2e, F4, F5, F6, F18, F41, AIDA, EAST1, eae, paa and hlyA. The diseases produced by *E. coli* were neonatal diarrhoea, colibacillosis, post-weaning diarrhoea and edema disease. The associated risk factors were poor housing, management and feed changes, extensive use of antibiotics as prophylaxis, overcrowding, and high humidity and temperature changes. India, USA, Japan, Slovakia, Denmark Sweden and Poland were countries with significant reports and high detection of virulence factors (72 to 100%).

Key words: *Escherichia coli,* diarrhea, serogroups, enterotoxigenic, colibacillosis.

INTRODUCTION

Pigs are ungulate animals of the genus *Suis* and family Suidae. Domesticated pigs originated from the European wild boar *Susscrofa* are indigenous to the Eurasian and African continents (Giuffra et al., 2000).The global pig population is estimated to be approximately one billion (Statista, 2016), and although this spread across the world, it may be restricted in certain countries due to religious and cultural beliefs. Pork serves as an important source of protein (38% of meat consumed in the world) and as a means of livelihood especially for women in developing countries (Madzimure et al., 2012). Pigs are also kept for leather, hair, as pets and use in human research (Gosh, 2014).

While pig production remains a profitable enterprise, commercial and particularly the small-scale farmers face huge constraints in this husbandry practice, one of the most important being bacterial infections and its associated with morbidity and mortality. We reviewed the prevalence of bacterial infections in pigs and paid particular attention to *Escherichia coli*, a bacterium that is regularly isolated and can lead to multiple infections in pigs.

The key words used to gather literature for review include; " *Escherichia coli* or *E.coli*", "pig, swine or porcine", "outbreak", "diarrhoea", "Oedema disease", "post weaning diarrhoea", "colibacillosis" and "prevalence". Literature searches were performed on selected veterinary and biological databases including the CAB Abstract, Medline, Pubmed, Science Direct and Google Scholar between January and November, 2016. Particular consideration was given to natural infections and isolates from natural infections with epidemiological details. Pathotypes, serotypes and serogroups of *E. coli*, the country of origin, source, growth stage, age of pigs infected, disease outbreak, the number of samples and type of samples, numbers and percentage of positive samples and isolates were used as filters. All literature considered were in English or where available then the English translations were used.

Extracted and compiled published manuscripts from peer reviewed journals were quality-checked and duplicate documents were removed. All remaining documents (n = 61) were filtered, harmonized and coded in a single Microsoft Excel® spreadsheet. The number of events, sample sizes and outcomes were calculated based on the available data. All data was analysed using the Fixed-effect model (precision-based estimates) in the Meta-analyses software on Excel (Neyellof et al., 2012). Comparison between individual studies was calculated in WinPepi v11.24 (Abramson, 2011) and presented in percentages with 95% confidence intervals. Cumulative events with measures of central tendencies were also produced in forest plots.

Bacterial pathogens of pigs

Based on our evaluation, the bacteria that affect pigs are diverse and vast but are not limited to the following, grouped by areas of primary lesions:

Cutaneous (skin) associated bacteria

Staphylococcus species

Infection in pigs is caused by *Staphylococcus hyicus* resulting in exudative epidermitis (Greasy pig disease) (Andresen, 1998). *Staphylococcus hyicus* is composed of both non-virulent and virulent strains which produces an exfoliative toxin, responsible for skin alteration in exudative epidermitis of pigs (Wegener et al., 1993; Andresen et al., 1997).

It is characterized by sudden onset of excess sebaceous secretion and exudation from the skin without pruritus leading to dehydration, growth depression and possibly death (Taylor, 2013). Other Staphylococcus species that could be isolated are *Staphylococcus chromogenes* and *Staphylococcus Sciuri* (Chen et al., 2007). *Staphylococcus aureus* is another important and common pathogen isolated from swollen ears, umbilical abscesses, subcutaneous abscesses and foot lesions, (Taylor, 2013; De Neeling et al., 2007).

Treponema species

Treponema species are associated with skin or mucous membrane diseases and cause skin ulcers in pigs regularly (Karlsson, 2014). Three major phylotypes are involved in infections which include: Treponema pedis (the most predominant), Treponema parvum and an undesignated phylotype (Karlsson, 2014).

Treponema pedis infection can occur as cutaneous spirochaetosis, ear necrosis and spirochaetal granuloma. They have been indicated as secondary bacterial infection in severe and chronic skin lesions of pigs (Taylor, 2013; Karlsson, 2014), such as ulcerative porcine stomatitis (Jensen et al., 2014) and periodic outbreaks of ear necrosis among weaners and gingival infections (Pringle et al., 2009; Karlsson et al., 2013).

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Reproductive system associated bacteria

Leptospira species

Leptospirosis, caused by *Leptospira* species is a disease that occurs worldwide in pigs and infection which is more common in animals kept outdoors (Ryley and Simmons, 1954). Route of infection is by ingestion, direct contact and through abrasions, trans-placental transmission or the veneral route (Taylor, 2013). *Leptospira* species are fine, spiral, aerobic, motile, gram negative bacteria (spirochete) of about 10 µm in length and 0.2 µm in diameter (Faine, 1994).

Approximately, 13 serovars of *Leptospira* are involved in infections in pigs and associated primarily with reproductive losses in breeding herds. The organisms persist in the kidneys and genital tracts of carrier pigs and are excreted in urine and genital fluids (Taylor, 2013). Routine vaccination may reduce the effect of the bacteria in a herd (Whyte et al., 1982), but elimination may be a difficult target because, pig is a reservoir host for leptospirosis.

Brucella species

Brucella suis infection in pigs, occurs mainly through the venereal or oral route (Xavier et al., 2010). Infection develops as bacteremia may persist for as long as 90 days which may lead to localisation in various tissues with resultant stillbirths, abortions, orchitis, lameness, posterior paralysis, spondylitis, occasional metritis and abscess formation. Infertility may occur in both sexes (Xavier et al., 2010; Deyoe, 1967).

Other pathogenic species in pigs are *B. abortus* and *B. mellitensis* (Godfroid, 2002). Diagnosis is mainly through the brucellosis card (Rose Bengal) test; but serum agglutination tests or complement fixation tests have also been used (Nicoletti, 2010). Brucellosis in pigs has a global distribution however its prevalence in domestic pigs is low in some countries and known to have been eradicated in USA (Godfroid, 2002).

Listeria species

Infection of pigs with *Listeria* species is common and previous study in Japan, Denmark and Yugoslavia suggested that approximately 10% of pigs at slaughter are infected (Taylor, 2013; Lungu et al., 2010). *Listeria monocytogenes* infection rarely causes disease, but sudden death in piglets, septicaemia and nervous signs have been recorded.

Most authors concurred that, porcine listeriosis occurs mainly as a septicaemia in piglets less than ten days old (Ladds et al., 1974; Long and Dukes, 1972; Busch et al., 1971) and multifocal hepatic necrosis is often the most notable necropsy finding in piglets (Lopez and Bildfell, 1989). Abortions, stillbirths and birth of weak piglets may also occur in sows (Taylor, 2013; Vannier, 1999). *Listeria* infection and carriage in domestic pigs or wild boar is a potential source of infection for man (Taylor, 2013; Borch et al., 1996).

Erysipelothrix species

Erysipelothrix rhusiopathiae is a small, facultative anaerobic, Gram positive (G+ve) rod that causes a condition known as swine erysipelas (Opriessnig et al., 2010; Wood and Steele, 1994). The disease outbreak may present as acute, sub-acute or chronic. It is characterized by sudden death or fever associated with characteristic diamond skin lesions (Opriessnig et al., 2010). Arthritis, vegetative endocarditis and abortion in pregnant sows may be observed (Schrauwen et al., 1993).

Necropsy lesions include enlarged and congested lymph nodes, oedematous and congested lungs, splenomegaly, hepatomegaly, petechial haemorrhages on the kidneys and heart. *E. rhusiopathiae* causes considerable economic losses and remains an animal hygiene problem in swine production areas of the world (Takeshi et al., 1999), and up to 50% of pigs in the world are estimated to harbour the organism in their tonsils and lymphoid organs (Opriessnig et al., 2010).

This status results in shedding of the organism in urine, faeces, saliva and nasal secretions (Opriessnig et al., 2004).

Respiratory system associated bacteria

Actinobacillus species

Actinobacillus suis and *Actinobacillus equuli* are two important species that may cause fatal septicaemia, endocarditis and arthritis in pigs of 1 to 6 weeks of age. In older animals, skin lesions and focal necrotising pneumonia, valvular endocarditis, abortion, metritis and polyarthritis may be seen (Radostits et al., 2000; Ramos-Vara et al., 2008). Clinical signs and post-mortem lesions are not specific but suggestive of the disease (Taylor, 2013).

Additionally, *Actinobacillus pleuropneumonia* may cause a respiratory infection of weaned, growing and finishing pigs in which there is fibrinous pleurisy and pneumonia with characteristic infarcts in the lungs. Infection which is highly contagious, often fatal and progressive weight loss in chronically affected pigs may be observed (Taylor, 2013; Frank et al., 1992).

Mycoplasma species

Mycoplasma organisms have been isolated from pigs but

only four species have repeatedly been associated with clinical disease namely (1) *Mycoplasma hyorhinis* which cause polyserositis and arthritis in young pigs of about 3 to 10 weeks; (2) *M. hyosynoviae* causes arthritis in growing pigs weighing between 35kg and 110kg live weight (Taylor, 2013); (3) *Mycoplasma hyopneumoniae* which is a primary pathogen of enzootic pneumonia, a chronic respiratory disease in pigs, highly prevalent in almost all pig producing areas. It is also considered to be one of the primary agents involved in the porcine respiratory disease complex (PRDC) (Thacker, 2006).

The organism is primarily found on the mucosal surface of the trachea, bronchi and bronchioles (Blanchard et al., 1992); and (4) *Mycoplasma suis* (formerly *Eperythrozoon suis*) infection which affects piglets 0 to 5 days of age, but weaners, growers and sowers may also be infected. Route of infection is by parenteral, transplacental or oral transmission and the clinical disease may manifests in 5 to 6 days.

The acute phase involves fever, anaemia, icterus, unthriftiness, jaundice and poor growth in weaned pigs, and is associated with low morbidity at high mortality rates (Messick, 2004). The chronic phase results in low reproductive efficiency, growth retardation, abortions, stillbirths and agalactia in sows (Messick, 2004; Heinritzi, 1989). In addition, a study revealed that *Mycoplasma arthritidis*, a rodent *Mycoplasma* has also been isolated from joints in an outbreak of conjunctivitis, severe polyarthritis and infertility in a boar stud (Binder et al., 1990).

Bordetella species

*Bordetella bronchiseptica*is regarded as the aetiologic agent of atrophic rhinitis, colonises the ciliated epithelium of the upper and lower respiratory tract at about one week of age in piglets. It causes rhinitis characterised by sneezing, shortening or twisting of the snout, hypoplasia, mild nasal turbinate atrophy, persistent purulent bronchitis, haemorrhage, pneumonia and impaired growth (Giles, 1992; Duncan et al., 1966; Mazumder et al., 2012).

Bordetella bronchiseptica predisposes pigs to colonization and disease with other bacteria such as *Pasteurella multocida* and *Haemophilus parasuis* (Brockmeier, 2004; Brockmeier et al., 2001).

Pasteurella species

Pasteurella multocida is associated with pneumonia and atrophic rhinitis in pigs and can result in important economic losses on large pig farms worldwide (Davies et al., 2003; Dziva et al., 2008). Its strains are grouped into five capsular serogroups; A, B, D, E and F , however only serogroup A,B and D have been recovered from pigs (Davies et al., 2003; Townsend et al., 1998; Tang et al., 2009). Toxigenic *P. multocida* serogroups A and D together with *Bordetella bronchiseptica,* coexist to cause atrophic rhinitis (Davies et al., 2003; Backstrom et al., 1988).

Toxigenic *P. multocida* infection results in severe sneezing in non-immune piglets. This is later followed by atrophy of the turbinate bones and a distortion of the nasal septum, shortening and twisting of the upper jaw which may be accompanied by reduction in the rate of weight gain (Taylor, 2013). Similarly, pneumonic pasteurellosis is also a condition that results from the colonisation of existing lung lesions with *P. multocida* which may give rise to fever, respiratory distress and death in some cases and it is typically associated with sub-acute or chronic pleuritis. Common route of transmission is by nose-to-nose contact; however, both vertical and horizontal transfer may occur (Taylor, 2013; Davies et al., 2004).

Mannheimia (Pasteurella) haemolytica has been isolated in piglets from localised areas of fibrinous pleurisy or pleuropneumonia and from outbreaks of diarrhoea in pigs (Taylor, 2013).

Haemophilus species

Haemophilus parasuis is found in the upper respiratory tract of pigs as a commensal bacterium, but invades and cause severe systemic disease under favourable conditions (Oliveira et al., 2003). It causes Glassers disease and acute septicaemia (Peet et al., 1983; Riley et al., 1977). Glassers disease is an infectious, sometimes fatal polyserositis, polyarthritis and meningitis of young pigs (Amano et al., 1994). Bronchitis and other syndromes may occur in older animals in non-immune herds (Taylor, 2013).

Transmission is by direct contact and all age categories of pigs are susceptible to the infection (Oliveira and Pijoan, 2002).Post mortem lesions include serofibrinous or fibrino-purulent exudate on mucosal surfaces, usually in peritoneum, pericardium, pleura or joint surface. In the septicaemic form, petechial and ecchymotic haemorrhages are detected in liver, kidneys and brain (Amano et al., 1994).

Mycobacterium species

Several species of *Mycobacterium* such as *Mycobacterium porcinum, Mycobacterium avium* subsp. *hominisuis*, *Mycobacterium bovis*, *Mycobacterium intracellulare, Mycobacterium fortuitum* and *Mycobacterium tuberculosis* have been associated with tuberculosis in pigs. *Mycobacterium avium* subsp. *hominisuis* is an opportunistic pathogen, infecting mainly pigs and humans (Mijs et al., 2002; Inderlied et al., 1993; Thorel et al.,

2001).

A recent study demonstrated cross-reactions between avian and bovine tuberculin in pigs (Agdestein et al., 2011). *Mycobacteria bovis* is the main agent causing tuberculosis in cattle, while *M. tuberculosis* primarily causes tuberculosis in humans.

However, they both belong to the *M. tuberculosis* complex (MTC) and can lead to infections in pigs (Komijn et al., 1999; Biet et al., 2005). Tuberculosis is mostly observed in pigs at slaughter when gross lesions are detected primarily through the examination of the lymph nodes of the head and the visceral regions and partial or full carcasses condemnation usually follow, because it is a potential risk to human health.

Streptococcus species

Streptococcus suis is an encapsulated gram positive coccus and occurs singly in pairs, or occasionally in short chains. It is a normal flora in the upper respiratory tract of pigs, the genital and digestive tracts (Higgins and Gottschalk, 1999). *S. suis* causes septicaemia, arthritis and meningitis in suckling piglets and post-weaning pigs but less commonly in finishing pigs (Taylor, 2013; Gottschalk et al., 2007). The organism is an emerging zoonotic agent responsible for septicaemia which may sometimes be accompanied by septic shock and meningitis in humans (Goyette-Desjardins et al., 2014).

Streptococcus porcinus infection also occurs in pigs and is sometimes referred to as streptococcal lymphadenitis or streptococcal abcess. It causes abscess particularly in the cervical lymph nodes (Taylor, 2013). The Lancefield group C and β-haemolytic streptococci are other streptococci infections in pigs that are commonly isolated from the upper respiratory tract, pharynx, retropharyngeal lymph nodes and genital tract of carrier pigs. They are associated with vaginitis in sows and neonatal septicaemia in newborn piglets and may be isolated from arthritis and vegetative endocarditis in older animals and froms epticaemic and pneumonic lesions in older finishing pigs (Taylor, 2013). A presumptive diagnosis of infection in pigs is usually based on clinical signs and macroscopic lesions (Staats et al., 1997).

Digestive system associated bacteria

Clostridium species

Clostridial pathogens involved in pig infections include C***lostridium*** *perfringens* (type A, C), *Clostridium defficiletyphocolitis, Clostridium tetani, Clostridium novyi, Clostridium botulinum, Clostridium septicum* and *Clostridium chauvoei* (Taylor, 2013; Baker et al., 2010). *Clostridium perfringens* type C is a large gram positive rod, which occasionally forms spores, bears attachment site and produces very potent toxins. The major toxin produced is protease/trypsin-sensitive β toxin which causes fatal necrotic and haemorrhagic enteritis in piglets less than seven days old and may cause chronic infection in older piglets. Clinical signs include profuse, bloody diarrhoea, loss of weight, palour and death within 12 to 24 h (Taylor, 2013; Songer and Meer, 1996).

C. perfringens Type A causes a similar syndrome but less severe with the major toxin produced being the α-toxin (Taylor, 2013; Songer and Uzal, 2005). *C. difficile* is toxigenic and produce two major toxins, A and B (Taylor, 2013; Diab et al., 2016). It is a recognized cause of antibiotic-associated diarrhoea and pseudomembranous colitis in humans, domestic and laboratory animals (Songer et al., 2000). Infection in pigs (neonatal enteritis) can be asymptomatic or result in diarrhoea and weight loss which may be chronic in suckling pigs (Taylor, 2013). Other clinical signs such as dyspnoea, mild abdominal distension, and scrotal oedema may be observed with characteristic ulcerative lesions present in the colon at post-mortem (Taylor, 2013).

C. tetani causes tetanus which presents as stiffness and abnormal gait leading to spasm and death. The condition occurs sporadically in young pigs and may be associated with umbilical infections, castration, or ovario hysterectomy (Taylor, 2013; Meseko and Oluwayelu, 2012). Additionally, *C. novyi* type B causes sudden death in large fattening pigs and sows. Incidence is worldwide and sporadic particularly in swill-fed pigs and older sows (Duran and Walton, 1997). Food-borne botulism is caused by *C. botulinum* through a preformed toxin of this organism in food resulting in a rare, sometimes fatal flaccid paralysis in pigs. The incidence is worldwide but rarely described (Taylor, 2013; Beiers and Simmons, 1967).

Salmonella species

Salmonellosis in pigs is caused by *Salmonella Enterica* serovar Choleraesuis var kunzendorf (Salmon and Smith, 1886; Stevens and Gray, 2013; Pedersen et al., 2015). It is a host specific, facultative, intracellular pathogen that causes paratyphoid (Gray et al., 1996).

The infection may result in enteric and fatal systemic disease, however, infected pigs may carry the organism in the tonsils, intestines and the gut-associated lymphoid tissue asymptomatically (Fedorka-Cray et al., 2000; Alban et al., 2012). Transmission is primarily through the faeco-oral route (Stevens and Gray, 2013), some studies have shown that the upper and lower respiratory tract may also serve as routes of infection (Fedorka-Cray et al., 1995).The infections may be present in different forms including (1) septicaemic form which is commonest in piglets with up to 100% mortality, (2) the acute enteric form in younger and weaned pigs,(3) the chronic enteric form and (4) the diarrheic form, which is usually due to

the less invasive serotypes such as *Salmonella Typhimurium* (Taylor, 2013).

Brachyspira species

Brachyspira hyodysenteriae is a large anaerobic spirochaete that causes dysentery-infectious mucohaemorrhagic colitis of pigs (Wills, 2000). It affects pigs during the growth and finishing periods, and is characterized clinically by loss of condition with diarrhoea containing varying amounts of mucus, blood and necrotic material (Burrough, 2016).

The bacterium multiplies in the large intestine result in superficial mucosa degeneration, inflammation and multifocal points of bleeding along the mucosa. The organism does not infiltrate beyond the intestinal mucosa and results in decreased reabsorption of endogenous secretions from the unaffected small intestine leading to diarrhea (Kennedy et al., 1988). In instances, a proportion of untreated pigs may die while others may remain stunted (Taylor, 2013). Other *Brachyspira spirochaetes* that may also be involved in diarrhea are *Brachyspira innocens, Brachyspira murdochii, Brachyspira intermedia* and *Brachyspira pilosicoli* (Taylor, 2013).

Campylobacter species

Campylobacter is a gram negative, spiral, non-spore forming rod (Penner, 1988; Epps et al., 2013) and pigs are natural reservoirs with a prevalence rate of approximately 50 to 100% and excretion level of about 102 to 107 CFU/g (Jensen et al., 2006; Alter et al., 2005; Nielsen et al., 1997).*Campylobacter* infection causes a mucoid, creamy diarrhoea, which may contain blood in piglets 3 days-3weeks of age (Taylor, 2013). The species associated with disease in pigs include *Campylobacter coli* (the most common), *Campylobacter jejuni, Campylobacter hyointestinalis* and *Campylobacter sputorum* (Taylor, 2013; Alter et al., 2005*)*.

Other *Campylobacter* species present in the porcine intestine, which may multiply and become associated with enteritis, are *C. hyointestinalis subsp. hyointestinalis, C. hyointestinalis subsp. lawsonii, Campylobacter mucosalis, Campylobacter hyoilei, Campylobacter lari* and *Campylobacter lanienae* (Taylor, 2013).

Helicobacter species

This infection in pigs is caused by *Helicobacter suis*, a gram negative, spiral-shaped bacterium that is commonly found in the gastric mucosa (Hellemans et al., 2007; Grasso et al., 1996; Park et al., 2004). Piglets and porkers have highest colonisation, found in the pyloric region, however, boars and sows, also have high colonization rates in the fundic region of the gastric mucosa (Hellemans et al., 2007).

The clinical infection by this organism is rare, and the main evidence for the pathogenicity of *H. suis* was from experimental studies that showed clear association between *H. suis* infection and the development of gastritis as well as a decrease in daily weight gain (De Bruyne et al., 2012).

Lawsonia species

This organism, *Lawsonia intracellularis* is an obligate, intracellular, gram negative, small, rod-shaped, intestinal, bacterium; it is the cause of proliferative enteropathyin pigs (Guedes and Gebhart, 2003), a frequent diarrhea disease of piglets and weaners characterised by hyperplasia and inflammation of the ileum and colon (Smith and McOrist, 1997).

Study has suggested that it infect mitotically the active epithelial cells of the intestinal crypts, which later multiply and spread in the cells as they divide (Boutrup et al., 2010). The condition is often mild and self-limiting but sometimes may result in necrotic enteritis, regional ileitis and proliferative haemorrhagic enteropathy. Affected pigs appear pale, may be stunted and may die suddenly with clotted blood in the lumen of the small intestine (Taylor, 2013; Guedes and Gebhart, 2003).

Yersinia species

Yersinia species are gram negative bacilli and the species associated with pig infection include (1) *Yersinia enterocolitica,* which easily colonise the gut of neonate piglets and subsequently become healthy carriers (Skjerve et al., 1998), it is capable of causing enteritis and typhilocolitis in weaned pigs and abortion in sows (Bhaduri et al., 2005); (2) *Yersinia pseudotuberculosis* which is also carried normally as gut resident (Taylor, 2013; Laukkanen, 2010).

Acute cases are characterized by enteritis, lymphadenitis and splenomegaly while chronic cases result in granulomatous nodules and localised abscesses affecting various organs, usually the liver and lungs (Brugmann et al., 2001). About 35 to 70% of herds and 4.5 to 100% of individual pigs carry *Yersinia* species asymptomatically (Bhaduri et al., 2005).

Enterococcus species

Enterococcus durans (Lancefield Group D) is a motile gram positive cocci that has been isolated from the intestines and faeces of 3 to 5 day old piglets, usually as commensals but may sometimes be associated with diarrhea (Taylor, 2013; Cheon and Chae, 1996).

Enterotoxins and mucosal damage have been identified with diarrhoea caused by *E. durans* however, decreased activity of digestive enzymes at the mucosal brush borders have suggested that the entire pathogenesis of diarrhoea due to *E. durans* has not been completely understood (Cheon and Chae, 1996; Tzipori et al., 1984).

Bacillus species

Bacillus anthracis causes anthrax but are rare in pigs. Affected animals may die suddenly, pass bloody faeces or die after swelling of the neck. Route of entry is mainly by ingestion of contaminated feed (Taylor, 2013).

Other non-specific bacteria pathogens include

Actinobaculum species

Actinomyces suis reclassified as *Actinobaculum suis* is associated with urinary tract infections in pigs (Lawson et al., 1997; Woldemeskel et al., 2002). It is linked with cystitis-pyelonephritis complex, a syndrome in which a small group of sows or gilts pass bloody purulent urine, often soon after service. They rapidly lose condition and sudden death may supervene (Taylor, 2013).

Chlamydophila species

Chlamydophila pathogens in pigs are *Chlamydia suis, Chlamydophila pecorum, Chlamydophila psittaci* and *Chlamydophila abortus*. The infections from this organism may results in multiple lesions including conjunctivitis, enteritis, pneumonia, pleurisy, pericarditis, polyarthritis, orchitis, infertility, abortion and birth of weak piglets (Taylor, 2013; Szeredi et al., 1996; Jiang et al., 2013).

Miscellaneous bacteria pathogens isolated from pigs

(i) Since 1978, *Arcobacter* species have been associated with reproductive disorders, but excretion by clinically healthy pigs has been frequently reported as well. Information on *Arcobacter* colonization of the porcine gastrointestinal tract is lacking to date (De Smet et al., 2012).
(ii) *Aeromonas hydrophila* has been isolated from enteritis, urine infections and lymphnodes (Igbinosa et al., 2016; Gray and Stickler, 1989).
(iii) *Acinetobacter calcoaceticans, Trueperella (Arcanobacterium) pyogenes, Bacteroides fragilis*are found in the large intestine and have been isolated from diarrhoea in piglets both before and after weaning (Taylor, 2013; Hijazin et al., 2012; Myers and Shoop, 1987).
(iv) *Flavo bacterium*, a ciliated bacillus has been identified in the trachea of pigs. It has been recorded in cases of pneumonia and has been associated with lesions of active tracheitis (Nietfeld et al., 1995).
(v) *Corynebacterium pseudotuberculosis* has been recovered from the vagina and prepuce of healthy swine and from mandibular abscess of black Alentejano pigs (Kudo and Yanagawa, 1987; Oliveira et al., 2014) while *Corynebacterium ulcerance* was recovered from a case of caseous lymphadenitis in Germany (Contzen et al., 2011).
(vi) *Coxiella burneti* antibodies have been demonstrated in pigs (Taylor, 2013).
(vii) *Klebsiella* species sometimes are seen in chronic respiratory tract diseases, enteritis and mastitis (Došen et al., 2007; Ross et al., 1975; Wilcock, 1979).
(viii) *Legionella pneumophila* has been demonstrated in the sera of pneumonic pigs in the UK (Taylor, 2013).
(ix) *Burkholderia pseudomallei is* the cause of meliodosis in pigs in tropical and subtropical regions (Omar et al., 1962; Rampling, 1964).
(x) *Rhodococcus equi* usually present in granulomatous lesions in submandibular lymphnodes (Witkowski et al., 2016; Rzewuska et al., 2014).

Enteric bacteria in pigs

The pig gastrointestinal tract has a complex and dynamic microbial ecosystem, the composition of which differs between individuals, region of the gastrointestinal tract, as well as age of the animal (Konstantinov et al., 2004). This microbial flora has an important role as one of the major defence mechanisms of the animal mainly through competition for nutrients and attachment sites and stimulation of cross-reactive antibodies, which prepares the immune system in defence against pathogenic microbes (Tancrede, 1992).

The large intestine contains most of the microbial flora (over 400 species) (Sørum and Sunde, 2001) and consist of (a) strict Gram postive anaerobes and facultative anaerobes such as *Streptococci*, *Lactobacilli*, *Eubacteria*, *Bacteroides* species, *Fusobacterium* species*, Clostridium s*pecies and *Peptostreptococcus* species; and (b) facultative anaerobes such as *E.coli, Klebsiella* species*, Enterobacter* species and *Enterococcus* species (Sørum and Sunde, 2001; Jensen, 2001). Factors which can cause microbial flora changes in the pig gastrointestinal tract include psychological and behavioural stressors, environment, weaning, age, feeding systems and the pigs genotype (Burrin and Stoll, 2003).

Global pig production is most frequently and economically affected by enteric bacterial infections (Moxley and Duhamel, 1999). Common clinical signs found include diarrhoea, reduced growth rate, weight loss and death (Moxley and Duhamel, 1999). Some changes found in the intestines of pigs with enteric bacterial

infections include: attaching and effacing lesions, in enteropathogenic *E. coli* and *B.pilosicoli* infection, inflammation with *Salmonella enterica* and necrotizing and haemorrhagic lesions with certain *C. perfringens* (Moxley and Duhamel, 1999).

Lactobacilli family dominates the normal bacterial flora in pigs and produces lactic acid as an essential metabolic end-product. The concentration of lactic acid increases several-fold within the first few days post-weaning and results in decreased pH of the gut which eliminates other pathogenic enterobacteria (Janczyk et al., 2007; Pieper et al., 2008). This group of microorganisms is generally considered beneficial as their attachment to the mucosa may protect the animals from gut infection (Houdijk et al., 2002). Furthermore, cultivation-based studies have shown that lactic acid bacteria, *Enterobacteria* and *Streptococci* were the most important first colonisers of the pig intestine (Stewart, 1997). Similarly, 16S rRNA gene clone analysis indicated that ileal samples of two-day old piglets harboured a group of *E. coli, Shigella flexneri, Lactobacillus sobrius, Lactobacillus reuteri* and *Lactobacillus acidophilus* related sequences (Konstantinov et al., 2006).

E. coli

E. coli strains in pigs forms part of the normal faecal flora. However, when they acquire virulent genes they are able to cause disease (Taylor, 2013).These coliform bacteria are commonly used as representatives of the enterobacteria from faecal samples in culture based studies of the intestinal bacterial flora, as they are the major facultative anaerobic bacteria in the intestinal tract of most animal species (Dubreuil, 2012). *E. coli* are gram negative rods, flagellated with variable length and diameter of about 1µm.On culture colonies grow on solid media within 24 h after incubation and may be smooth, rough or mucoid (Fairbrother and Gyles, 2012). Major characteristics associated with pathogenic *E. coli* infections are proteins such as fimbriae and production of enterotoxins usually by the enterotoxigenic *E. coli* (ETEC) and Shiga toxin by Shigatoxigenic *E. coli* (STEC). Other toxins previously described are EAST1, cytotoxins, cytolethal distending toxin, hemolysin; outer membrane proteins (intimin) and adhesin involved in diffuse adherence (Taylor, 2013). In addition, study has shown that F18 was the main colonization factor for STEC and ETEC withF18ab and F18acas subgroups (Cheng et al., 2005).

E. coli strains have been identified as an important cause of several diseases in pigs worldwide including neonatal septicaemia, neonatal diarrhoea, post-weaning diarrhoea, oedema disease (bowel oedema or gut oedema), cystitis, septicaemia, polyserositis, coliform mastitis and urinary tract infections. They can also colonise existing lesions elsewhere in the body (Taylor, 2013; Fairbrother and Gyles, 2012). Post-weaning diarrhoea (post-weaning enteric colibacillosis) and oedema disease have a more significant impact in the porcine industry because they result in high economic losses due to high morbidity and mortality, decrease weight gain, the cost of treatments, vaccination and feed supplementation (Fairbrother and Gyles, 2012).The *E. coli* infections occur at different ages in the pigs. Coli septicaemia occurs in 0 to 4 days old piglets and may be associated with diarrhoea. Enteritis (enteric colibacillosis) which is also associated with diarrhoea, occurs at three main periods in the pigs life; neonatal diarrhoea occurs at 0 to 4 days of age, neonatal-weaning diarrhoea at 4 days to 3 to 4wks and post weaning diarrhoea usually associated with weaning, oedema disease occurs in recently weaned pigs while mastitis and cystitis occur in adult sows (Taylor, 2013).

Outbreaks of *E. coli* diarrhea have increased worldwide with post-weaning diarrhoea being the most common where F4 and F18 are usually associated with adhesion factors (Fairbrother and Gyles, 2006). This could be due to the emergence of more virulent *E. coli* clones, a benign commensal of the gut microflora which multiply rapidly and cause disease through colonisation of the intestinal mucosa or changes in the management of pigs (Fasina et al., 2015).

Furthermore, a potentially beneficial method of feeding behaviour and maintaining gastrointestinal health in pigs is through feeding weaners with liquid feed or fermented liquid feed, in contrast to dry feed, as it is considered a possible feeding strategy to maintain a high and regular feed and water intake of weaners (Canibe and Jensen, 2012). Avoiding a drastic decrease in feed and water intake after weaning is believed to ameliorate the post-weaning lag period in piglets which may predispose them to *E. coli* infections (Canibe and Jensen, 2012).

Classification of *E. coli*

The best approach to classify *E. coli* is by serotyping in association with virulent strains. However, only a small percentage of the organisms are typeable based on O, K, H and F antigens, and only about 175O, 80K, 56H and over 20F antigens have been officially recognized to date, based on proven or suspected pathogenicity of *E. coli* isolates (Fairbrother and Gyles, 2012).

Pathotype is the term used to classify *E. coli* by their virulence mechanisms. The broad classes identified include, Shiga toxin producing *E. coli* (STEC), enterohaemorrhagic *E. coli* (EHEC), enteropathogenic *E. coli* (EPEC) and extraintestinal pathogenic *E. coli* (ExPEC) (Fairbrother and Gyles, 2012) (Table 1).

Enteropathogenic *E. coli* (EPEC)

Enteropathogenic *E. coli* is a pathotype found in post weaning diarrhoea of pigs. This bacterium possesses a

Table 1. Important pathotypes of pathogenic *Escherichia coli* in pigs and associated virulent traits.

Pathotype	Adhesins	Toxins
ETEC	F5(K99), F6 (987P), F41	STa
	F4(K88)	STa, STb, LT, EAST-1, α-hemolysin
	F4(K88), AIDA,	STa, STb, LT, EAST-1, α-hemolysin
	F18, AIDA	STa, STb, LT, Stx (VT), EAST-1, α-hemolysin
EPEC	Eae (intimin)	
STEC (VTEC)	F18, AIDA	Stx2e,(VT2e), EAST-1, α-hemolysin
	Eae (intimin)	Stx1 and/or Stx2
ExPEC	P,S	CNF
	P,S	CNF

complex secretion system that injects over 20 effector proteins into the host enterocyte. This allows intimate adherence of the bacteria into the pigs intestinal epithelium to develop a characteristic “attaching and effacing” (AE) lesion. The EPEC together with other *E. coli* pathotypes that result in AE are collectively known as attaching and effacing *E. coli* (AEEC) (Zhu et al., 1994).

Shiga toxin producing *E. coli* (STEC)

Shiga toxin producing *E. coli,* produce a family of cytotoxins known as Shiga toxin (Stx) or verotoxin (VT). Many STEC are not pathogenic in the intestinal flora but when they possess additional virulence traits, they become highly pathogenic (Fairbrother and Gyles, 2012).

In pigs, the most pathogenic STEC are those that cause oedema disease known as oedema disease *E coli*, with apostrophes before and after as above (EDEC). EDEC produces stx2e and F18ab or F18 ac (DebRoy et al., 2009). Another subgroup of STEC is the enterohaemorrhagic *E. coli* (EHEC) which also possess eae and the same secretion system as EPEC (Fairbrother and Gyles, 2012). However, production of Shiga toxins alone may not be sufficient for *E. coli* O157:H7 pathogenicity (Mead and Griffin, 1998). Other virulence factors such as the intimin protein (involved in the attachment of the *E. coli* O157 to enterocytes), the presence of a plasmid encoded hemolysin, or both, are important in the pathophysiology of haemorrhagic disease (Mead and Griffin, 1998).

Extra intestinal pathogenic *E. coli* (ExPEC)

Extra intestinal pathogenic *E. coli* are a group of heterogeneous *E. coli* in the intestinal tract of pigs that can invade other systems to cause bacteraemia resulting in septicaemia or localised infections such as meningitis and arthritis (Fairbrother and Ngeleka, 1994). The ExPEC possess lipopolysaccharides which protect the bacteria from being killed by serum complement and phagocytes (Fairbrother and Gyles, 2012).

Enterotoxigenic *E. coli* (ETEC)

The ETEC pathotype is the most important among the pathogenic *E. coli* producing one or more enterotoxins that induce secretory diarrhoea in pigs (Fairbrother and Gyles, 2006).This pathotype produces two major enterotoxins; heat stable toxin (ST) and heat labile toxin (LT) which are both further subdivided into STa, STb, LTI and LTII, respectively (Evans et al., 1972; Czirók et al., 1992).The ETEC that causes neonatal diarrhoea produces only STa and possess one or more fimbriae F4 (K88), F5 (K99), F6 (987P) and F41 (Fairbrother and Gyles, 2012). Similarly, ETEC that causes post-weaning diarrhoea produces STa, STb, LT, and enteroaggregative heat stable enterotoxin (EAST-1) (Zhang et al., 2007) while ETEC isolates that produces STb or STb: EAST-1 from weaned pigs may also produce an adhesion involved in diffuse adherence (AIDA-I) (Mainil et al., 2002; Ngeleka et al., 2003; Niewerth et al., 2001).

Enterotoxigenic *E. coli* causes an estimated 840 million gastrointestinal infections and about 380,000 deaths worldwide each year in pigs (Gupta et al., 2008), leading to substantial economic losses for swine producers worldwide (Nagy and Fekete, 2005). The bacteria adhere to and colonize the intestinal mucosa of the small intestine (jejunum, ileum and to a lesser extent, the duodenum) (Arbuckle, 1970; Cox and Houvenaghel, 1993). They also adhere to enterocytes using surface fimbriae (pili) that adhere to specific receptors on enterocytes, without inducing morphological lesions but elaborate enterotoxins that act locally on enterocytes, leading to fluid secretion resulting in the exacerbation of the diarrhoeal illness in pigs (Verbrugghe et al., 2015). A very important illness induced by ETEC toxins is post-weaning diarrhoea in piglets (Verbrugghe et al., 2015).

E. coli post-weaning diarrhoea (PWD)

Post-weaning diarrhoea, also known as post-weaning enteric colibacillosis, is an important cause of death in weaned pigs worldwide. Infection usually occurs during the first weekpost weaning and often results in decreased weight gain (Taylor, 2013). Several factors, such as the stress of weaning, lack of antibodies originating from the sow's milk and dietary changes, contribute to the severity of the disease, manifesting as sudden death or severe diarrhea (Fairbrother, 1999; Amezcua et al., 2002; Maynard et al., 2003).

Most outbreaks have occurred in early-weaned piglets although traditional herds are being increasingly affected (Fairbrother, 1999; Amezcua et al., 2002; Maynard et al., 2003).

Virulence factors of *E. coli* associated with post-weaning diarrhea

Post-weaning diarrhea is caused primarily by ETEC, a pathotype that is characterized by the production of adhesins and alpha-hemolysin, which produce colonies with clear zones of haemolysis on blood agar. Several studies have shown that *E. coli* isolated from weaned pigs with diarrhoea were haemolytic (Frydendahl et al., 2003; Chen et al., 2004).

Alpha-hemolysin, an approximately 110 kDa pore-forming cytolysin, belongs to the RTX family of toxins. The hlyA gene that encodes the hemolysin is part of an operon that is found on plasmids in ETEC. It is a potent cytotoxin that can damage a variety of cells (Frydendahl, 2002). Serological typing has been expanded to include fimbrial antigens, which are virulence factors, as well as O and H antigens which are virulence markers (Chen et al., 2004). Some strains of ETEC that cause PWD possess additional genes that encode Shiga toxin 2e (Stx2e), allowing them to cause edema disease (ED). The ETEC strains that produce Stx (VT) are appropriately called ETEC/STEC or ETEC/VTEC (Nagy and Fekete, 1999).

Enteropathogenic *E. coli* have also been implicated in PWD (Zhu et al., 1994; Zhu et al., 2010; Janke et al., 1989; An et al., 2000). Identification of porcine EPEC (PEPEC) is challenging and veterinary diagnostic laboratories do not routinely seek to identify this pathotype of *E. coli* (Fairbrother, 1999). The eae (*E. coli* AE) gene is a marker for PEPEC, but some eae-positive porcine E. coli isolates may be non-pathogenic. O45 serogroup has been shown to possess genes of the locus of enterocyte effacement (LEE); a locus well established to confer ability for AE lesions (Zhu et al., 1994; An et al., 2000; Helie et al., 1991). Immunity to one strain of pathogenic *E. coli* does not essentially protect from others, while successive strains can pass through herds (Bertschinger, 1999).

Pathogenesis of post-weaning diarrhea

Post-weaning diarrhea is an enteric disease in pigs localised in the small intestine, where digesta flows quickly. The EPEC that causes this condition attaches to the enterocytes lining of the villi or to the mucus covering the villi with the fimbriae or pili, which prevents the bacteria from being flushed to the large intestine. Thereafter, the enterotoxigenic *E. coli* which have colonised the small intestine incites hypersecretory diarrhoea through the release of distinct enterotoxins such as the LT and ST. (Francis, 2002; Zhang et al., 2007).

The LT induces secretion of chloride ions, sodium ions, bicarbonate ions and water into the lumen by binding irreversibly to the mucosal cells and activating the adenylcyclase cyclic AMP system (Thiagarajah and Verkman, 2003; de Haan and Hirst, 2004, Fairbrother et al., 2005) while the ST (STa and STb) inhibits the absorption of sodium and chloride ions from the lumen into the epithelial cell via the guanylcyclase–cyclic GMP system, both resulting in fluid retention. Intestinal colonisation and diarrhoea typically last for about 4 to 14 days, with the organism being spread between animals by the faeco-oral route and aerosols (Bertschinger, 1999).

Pigs displaying PWD harbour massive numbers of haemolytic *E. coli* in the jejunum, whilst there is minimal change in numbers of other bacteria (Smith and Jones, 1963). It is common for EHEC to appear in the faeces of pigs in increased numbers, in the first week after weaning in both healthy and diarrhoeic pigs, although the numbers are higher in diarrhoeic pigs (Kenworthy and Crabb, 1963; Hampson et al., 1985) (Table 2).

The act of weaning is an essential precipitating factor for PWD, regardless of the age at weaning. All of the factors involved with weaning create an environment suitable for the proliferation of *E. coli* in the small intestine. Slower gut transit time and gut stasis immediately after weaning allow bacteria the opportunity to attach and time to multiply (Pluske et al., 2002). An inability of piglets to adequately thermoregulate, combined with sub-standard weaning accommodation, may result in cold stress. This alters intestinal motility and is thought to be a major factor in the pathogenesis of PWD (Wathes et al., 1989). Other factors include social stresses from mixing, fighting and crowding which trigger cortisol release, most likely increasing transit time and depressing the immune response to enhance bacterial infection; moving to a new pen increases the chance of exposure to microbes residing in fresh or dry matter in the environment; the presence of other pathogens such as rotavirus in the environment thereby increasing the likelihood and severity of disease (Lecce *et al.,* 1983). Poor hygiene will also increase the pathogenic *E. coli* load delivered to the small intestine because of faeco-oral cycling (Madec et al., 1998).

Table 2. *Escherichia coli* and its virulence profiles in pigs.

Country	Source	Sample	Pathotype	Serotype	Age(days)	Virulence factor	Summary of result	References
South Africa	Farm	Faeces and intestinal tissues	ETEC	-	35	EAST 1	*E. coli* associated endotoxaemia.	(Fasina et al.,2015)
China	lab samples	Bacterial isolates	ETEC and VTEC	-	-	F18+	F18+ is the main colonization factor for VTEC and ETEC.	(Cheng et al., 2005)
Norway	Abbatior	intestinal content	STEC	O157: H7		stx2, eae, *fli*C-H7	Prevalence of *E. coli* O157:H7 in pigs is low in Norway	(Johnsen et al., 2001)
US	Herd	Isolates	ETEC	-	14	K88, K99, 987P, ST, LT	ETEC produces k88,K99, 987P, LT and ST.	(Moon et al., 1980)
US	Slaughter facility	Colon(faeces)	STEC	O157: H7	-	stx1, stx2, eae, hly	Pigs in the US can habour *E. coli* O157:H7.	(Feder et al., 2003)
Denmark	Lab samples	intestinal content	PEC	O8, O45, O138, O139, O141, O147, O149 and O157	22	F4, F18, STa, STb, LT,ESAT1, VT2e	VTEC and ETEC in PWD and ED belong to limited serogroups and are haemolytic.	(Frydendahl, 2002)
US	Farm	faeces	STEC	-	140	stx1,stx2	The incidence of STEC in swine varies.	(Fratamico et al., 2004)
Canada	Farm	rectal swab	ETEC	O149	35	Sta, STb, LT, Vtx, F18 F4	PWECD is an economically important disease in pigs.	(Amezcua et al., 2002)
US	Farm	Faecal swabs, faeces or intestinal content	ETEC	-	35	K88, K99, STa, STb, LT, F18, F41, stx2e, EAST1, AIDA-1, paa, eae	Broad arrays of virulence genes are associated with PWD in pigs.	(Zhang et al., 2007)
China	Field isolates	Faecal swabs	-	O8, O9, O11, O20, O32, O91, O93, O101, O107, O115, O116 and O131	49	F4, F5, F6, F18, F41 STI, STII, stx2e	Pigs with PWD have *E. coli* enterotoxins and shiga toxin 2 variant.	(Chen et al., 2004)
Mexico	Farm	faeces swabs	-	-	11& 28	LT, STa, STb, Stx1, Stx2 and EAST 1, F4, F5, F6, F17, F18 and F41	There are a there wide variety of virulence genes associated with diarrhoea in piglets.	(Toledo et al., 2012)
Switzerland	Farm	intestinal content	ETEC and VTEC	O139, O141 and O149	56	F107 SLT-IIv, LTI, STIa, STII	F107 are a major colonisation factor in O139: K12 and O141: K85ab *E. coli* serogroups.	(Imberechts et al., 1994)
Japan	Necropsy specimen	intestinal content and rectal swab	ETEC	O149, O157, O141 and O8	26	Sta, LT, K88, K99, 987P, F41, 4F	There are clear differences in strains of ND and PWD in terms of ETEC strain, enterotoxin type and adhesins.	(Nakazawa et al., 1987)
Belgium	Farm	Serum	ETEC	-	392	F4	F4+ ETEC is highly prevalent and widely spread in non-vaccinated pig breeding farms in Belgium.	(Van den Broecket al.,1999)
India		Faeces	STEC and EPEC	O9, O20, O24, O59, O60, O85, O100, O103, O112, O113, O116, O118, O119, O123, O137 and O152	40	stx1, stx2, eaeA, hlyA	STEC and EPEC are associated with diarrhoea in piglets and infants.	(Begum et al., 2014)
Cuba	Farm	Fecal Isolates	EPEC	O141 and O157	30	STb, STa, VT2e, LT, F18, F6	ETEC and VTEC isolates from diarrhoic pigs belong to restricted number of serogroups and serotypes.	(Blanco et al., 2006)
India	Farm	Liver, Lung, Intestine (necropsy)	STEC	-	-	stx2, eae	eae and stx genes are the prime causes of oedema disease in pigs.	(Barman et al., 2008)
Germany	Field strains	Isolates	STEC and ETEC	-	-	F18ac, F18ab	The F18 fimbrial subtypes are significantly associated with pathovars of *E. coli* strains.	(Barth et al., 2011)
Denmark	Institute	Faeces	ETEC	O149 and O138,	21	-	Diarrhoea occurrence is associated with faecal shedding of haemolytic *E. coli*.	(Carstensen et al., 2005)

Table 2. Contd.

Vietnam	Farm	Faeces, intestinal content	ETEC	O149 and O8	16	F4, F5, Sta,STb,LT	A large number of ETEC isolates belong to O8 serogroup, producing Sta, STb and LT but lacked fimbriae genes.	(Do et al., 2006)
Canada	Farm	Lab isolates	EPEC	O8, O116, O147, O138 and O45, O4 and O98	29	-	82% of *E. coli* isolates were enteropathogenic by the ligated intestine test in pigs.	(Gyles et al., 1971)
Uganda	Farm	Faeces	ETEC and VTEC	-	-	F18+, F4, LT, STa, STb and Stx2e	ETEC and VTEC infections are common in central uganda but clinical cases are masked by management practices.	(Okello et al., 2015)
China	Farm	Liver, spleen, kidney, heart, mesenteric lymph node		O107, O101, O9, O60 and O26.		-	O107, O101, O9, O26, and O60 are the dominant serotypes in southern china.	(Chen et al., 2013)
Korea	Farm	ileal contents	EAEC, ETEC	-	14	EAST 1, F4, F5, F6, F41, STa, STb, LT.	EAST1 is prevalent in *E. coli* and it is a virulence determinant in the pathogenesis of enteric colibacillosis of pre-weaned pigs.	(Choi et al., 2001b)
US	Research and diagnostic lab	Lab specimens	ETEC	O8, O9, O20, O101, O141, O149, O157, O138, and O139.		K88, LT, Stx2e; F18, STa, and STb	Loss of virulence genes is not uncommon in ETEC.	(Francis, 2002)
Spain	Farm	Isolates	ETEC	08, 09, 020, 0101, 0141 and 0149	15	F6 (987P), F5 (K99), F4 (K88) and F41	F6 fimbriae were found in higher rates than F5, F4, and F41 in younger and older piglets with ETEC strains.	(Garabal et al., 1997)
US	Farm	Isolates	STEC and ETEC	O138, O139, O141 and O147		f18, sta, stb, and stx2	Serogroup O147 may be a common serotype of oedema disease-causing *E. coli* in the United States.	(Helgerson et al., 2006)
England	Farm	Intestinal content	ETEC	O149	28	LT	Weaning at three weeks of age did not precipitate a profound change in the *E. coli* intestinal flora in the post-weaning period.	(Hinton et al., 1985)
Bulgeria	Farm	faeces and intestinal content	EHEC; VTEC	-	52	F18, F4	In the 2–3 post-weaning weeks, toxin producing *E. coli* that possesses the adhesion factor F4 is responsible for diarrhoea.	(Lyutskanov, 2011)
Zimbabwe	Farm	Faecal swabs	ETEC , VTEC	-	13	STa, STb, LT, Stx-2e F4, F18, F5 and F41, and F6	Vaccination or vaccine development based on F4, F5, F6, F18, and F41 antigens continues to be appropriate for ETEC infections.	(Madoroba et al., 2009)
Canada	Farm	Fecal swabs, faeces or intestinal content	ETEC and EPEC	O7, O157, O149, O26, O69, O139, O141, O103, O108, O109,O119, O20, O21 and O22	29	EAST1, AIDA-I, F4, F5, F6, F18, LT,STb,STa, EAE, Paa	AIDA-I/STb was dominant and EAST-I may not be an important marker for diarrhoea in pigs.	(Ngeleka et al., 2003)
Hungary	Farm	Intestine	-	O8, O138, 0139, 0141, 0147, O149, and 0157	49	K88, STa, STb, LT and VT	73% of K88 isolates had the capability to produce enterotoxins or VT which could contribute to post-weaning diarrhoea in pigs.	(Nagy et al., 1990)
Japan	Farm	Faece, cerebrum, liver, lung, heart blood, kidney, intestinal content, mesenteric lymph node	ETEC	O149: H-, O149: H10, O15:H9, O111:H- and OR: H6	19	STa, LT, K88,	Growth of ETEC was not active in healthy weaning pigs but infection with PRRS virus results in ETEC systemically with per acute death.	(Nakamine et al., 1998)
Germany	Farm			O138, O139, O139, O141, O141, O147 andO149	-	stx2e, fedA, orfA,orfB, AIDA	Porcine *E. coli* strains are a major reservoir for AIDA genes.	(Niewerth et al., 2001)
Canada	Animal health laboratory	Isolates	ETEC	O149		estA (STa), STb, LT, astA (EAST1), K88ac	Recent O149 ETEC associated with PWD in pigs in Ontario are different from the old O149 ETEC, and the new isolates has estAgene.	(Noamani et al., 2003)

Table 2. Contd.

Vietnam	Farm	small intestine, mesenteric lymph node, liver, lung, and spleen	-	O139, O141, O138, and O149	28	VT2e+, fedA(F18), AIDA, Sta, STb	0139:K82+/VT2e+/F18+/AIDA+ seropathotype was predominant and antibiotic resistances is widely distributed in *E. coli* causing ED in northern Vietnam.	(Oanh et al., 2010)
Poland	Farm	Faeces or rectal swabs	-	O139, O141 and O138	35	Stx2e, F18, STI, STII.	Molecular characterization of *E. coli* using the RAPD polymorphism analysis is a quick and convenient method to differentiate *E. coli* bacteria of the same and different serogroups.	(Osek, 2000)
China	Farm	rectal swab	ETEC	O80, O141, O139, O6, O9, O20, O101, O93, O138, O147, O157, O38 and O45.	26	K88, K99, F41, F18, 987P, STa, STb, LT, Stx2e	Novel serogroups O80, O6 and O38 of *E. coli* in pigs were identified in western China.	(Qi et al., 2012)
south Africa	Research council	rectal swab	ETEC, STEC, EAEC	-	73	STa, STb, LT, Stx2e, EAST-1, PAA, AIDA-I, EAE	PAA and AIDA-1 are important in South African pigs.	(Mohlatlole et al., 2013)
Korea	Farm	caecal and ileal contents	ETEC, STEC, DAEC	-	-	AIDA1, F18ab, Stx2e, Sta, STb, EAST1	AIDA gene is not restricted to DAEC strains.	(Ha et al., 2003)
Brazil	Farm	swabs		-	-	F4, F5, F6, F18, F41, STa, STb, LT and STx2e	*E. coli* strains isolated from pigs with diarrhoea possessed the genes for LT or/and ST enterotoxins.	(Vidotto et al., 2009)
Slovakia	Farm	Rectal swab and intestinal content	ETEC	O8, O54, O84, O101, O141, O141, O147, O149, O163, O2, O15, O84 andO157.	14	LT, Sta, STb, Stx1, Stx2, F4, F18, F6, F5, F41, F17, eae, EAST1	There is high prevalence of ETEC that possess LT and STb genes and the F4 colonization factor in piglets with diarrhoea in Slovakia.	(Vu-Khac et al., 2007)
China	Farm	Faeces	ETEC	-	-	EAST1, irp2, paa, STb, AIDA-I, LT-I, ler, hlyA, K88, eae, STa, sepA, F18, afaD, afaE, K99 and Stx2e	Relatively few isolates from the study express K88, K99, LT-I or STa, but EAST1, irp2, AIDA-I, paa and STb were frequent in *E. coli* strains in suckling pigs with diarrhoea in China.	(Liu et al., 2014)
Slovakia	Farm	Intestinal content	ETEC	-	21	F4, F5, F6, F18, F41, STa, STb, LT, STx2e, EAST1	There is a wide distribution of the astA gene among *E. coli* strains isolated from diarrhoeic piglets in Slovakia and a strong association of the astA gene with F4-positive strains.	(Vu-Khac et al., 2004)
Czech Republic	Farm	Rectal swab and intestinal content	ETEC and STEC	O149	-	LT+, STa+, K88, F18, EAST-1, paa.	There is a significantly higher prevalence of astA positive *E. coli* isolates among apparently healthy piglets in comparison with diarrheic piglets.	(Zajacova et al., 2012)
China	Farm	Rectal swab	ETEC and STEC	O141, O9, O32, O2, O116, O107, O147, O139, O91, O45 and O98.	49	AIDA-I, Sta, Stb, Lt, Stx2e, EAST1, F5, F6, F18, F41	AIDA-I represents an occasional virulence factor for PWD and ED in pigs and has the potential to transfer between porcine and human *E. coli*.	(Zhao et al., 2009)
Spain	Farm	Reactal swab	ETEC and VTEC	-	15	STa, LT, VT, CNF1, CNF2, α-hemolysin.	Majority of piglets in this study that produced verotoxin also produced STa enterotoxin but CNF1 was produced from only 1.5% of sick piglets.	(Garabal et al., 1995)
Korea	Pathology department	Ileal and cecal contents	ETEC, STEC	-	-	EAST1, STa, STb, LT, Stx2e, F4, F5, F6, F18, F41.	*E. coli* carries east1 gene in high prevalence in weaned pigs with diarrhoea and/or edema disease.	(Choi et al., 2001a)

Table 2. Contd.

Korea	Farm	Jejunal, ileal and caecal contents	ETEC, STEC	-	-	STa, STb, LT, Stx2e, F4, F5, F6, F18, F41	Genes for F18 and Stx2e are prevalent among *E coli* isolated from post-weaning pigs with diarrhoea or oedema disease.	(Kwon et al., 2002)
Denmark	national vet laboratory	Intestinal content and faeces	-	O149, O139, O138,O101 O8, O64, O147, O141 and O157	4,15,36 and 56	STa, STb, LT, VT, K88, 987P , F107, K99 and F41	Results correlation between genotypic and phenotypic methods was 97.7-100%. VT and F107 genes were more frequent in post-weaning than in neonatal *E.coli* strains.	(Ojeniyi et al., 1994)
Canada	vet medicine faculty	intestinal content	ETEC	O8,O9, O101, O9, O20,O64,O10, O157, O147,O149, O115, O138,O139,O141,O45,O26, O119,O15 and O108	31	F4, F5, F6, F41, STa, STb, LT and VT	The most important pathotypes among enterotoxigenic isolates in this study were F4:LT:STb, F5:STa, STb, F5:F41:STa, F4:STb, F6, STa, and LT.	(Harel et al., 1991)
Brazil	Farm	Faeces	ETEC, STEC	-	11	LT-I, STa, SLT-I, SLT-II, SLTIIv, F18ac.	eaeA gene and intimin production and/or Shiga-like toxins may be an important cause of diarrhoea among piglets.	(Martins et al., 2000)
Poland	Farm	Faeces or rectal swabs	-	-	35	LTI, STI, Stx2e, F4 F5 F6 F17 F18 and F41	Low prevalence of fimbria-positive *E. coli* strains isolated from pigs with PWD was found in this study.	(Osek, 1999)
Poland	Farm	Rectal swabs	ETEC	O1, O8, O9, O66, O138, O141, O147 and O149	35	EAST1-1, F4, LTI STI and STII	EAST1 gene is widely distributed among *E. coli* strains isolated from piglets with post-weaning diarrhoea.	(Osek, 2003)
Poland	Farm	Faecal swabs	ETEC	-	5& 42	Sta, LT, STb, K88, K99, 987P, F1	Enterotoxigenic (LT and STb) *E.coli* from suckling and weaned piglets with diarrhoea were 90.5% and 69.1% respectively and 18.5% of strains from healthy piglets were STa.	(Osek and Truszczyński, 1992)
Poland	Farm	Feaces	-	O157, O149, O66, O138, O139 and O141	-	F4, fedA, eltI, estI, estII, stx1, stx2e	*E. coli* from pigs with post-weaningdiarrhoea (13 out of 21 isolates) or from oedema disease (16 out of 19 strains) are able to produce F18 fimbriae.	(Osek et al., 1999)
Argentina	Farm	Rectal swabs spleen, kidney and liver	ETEC and VTEC	O8, O9, O64, O101, O138, O139, O149 and O162		STIa, STb, LTI, VT2e, VT1, VT2all	ETEC strains predominate in the group of animals with diarrhoea, STIa prevails in ETEC from pigs with diarrhoea, O64 prevails among ETEC and O138 prevails for ETEC/VTEC strains.	(Parma et al., 2000)
Sweden	Farm	faeces and intestinal content	ETEC	O149, O101, O9, O20, and O8,	25	LT, ST, K88, K99, 987P, F41	Frequency of O149 has been reduced, while that of O101 has increased to the same level as that of O149 in sweden.	(Soderlind et al., 1988)
Indonesia	Farm	Rectal swab		O20, O9 and O141	14	987P, ST, K88, K99.	Mixed infections with *E. coli* bearing different fimbrial antigens occur both within a group of piglets and in a single piglet.	(Hirst and Patten, 1991)
Slovakia	Farm	intestinal content and rectal swab	ETEC	-	15	F4, F5, F6 and F41	The frequency of occurrence of individual types of adherence antigens is related to geographical location.	(Vu-Khac et al., 2004)
Brazil	-	-	-	O139, O8, O9, O15, O20, O82, O101, O110 and O153	-	Stx2e, F18ab, STI, STII, LTI	Enterotoxin genes detected in high frequency are responsible for diarrhoea seen in pigs with oedema disease,	(da Silva et al., 2001)

Vaccination against pathogenic bacteria

Vaccination against pathogenic bacteria has become necessary as an alternative control measure due to the development of different serotypes of bacteria and bacterial resistance to a wide range of commonly used antibiotics (Fairbrother et al., 2005). Frequently used vaccines against bacterial diseases in swin

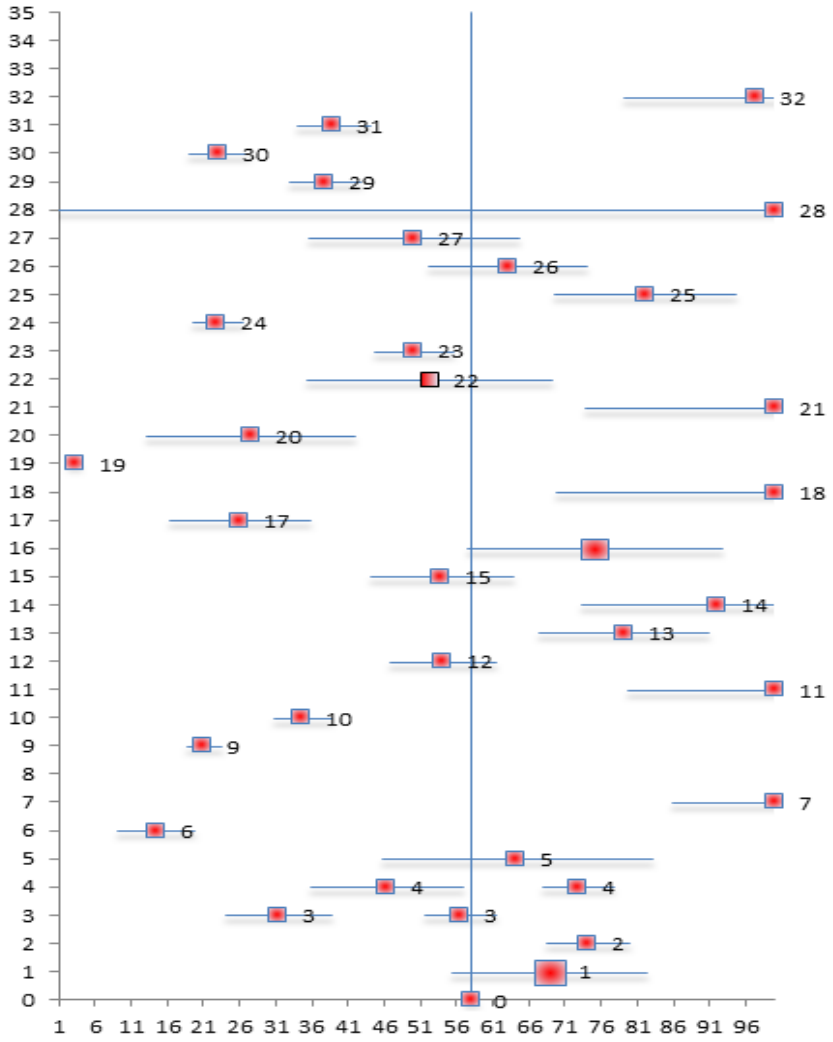

Figure 1. Forest plot of *prevalence of Escherichia coli* virulence factors

contain whole-cell killed micro-organisms, purified microbial components, or recombinant proteins (Haesebrouck et al., 2004). Vaccination against bacteria pathogens in pigs is directed towards either the extracellular bacteria or the exotoxin produced by the bacteria (Haesebrouck et al., 2004).

Exotoxins are produced within the bacterial cytoplasm. Some are excreted through the living cell wall, while others are released only by lysis of bacteria. In diseases caused by exotoxigenic bacteria, antibodies neutralizing that toxin play an important role in protection of the host against disease, provided they are able to prevent binding of the exotoxin to its receptor on the host cell. Vaccines containing the inactivated toxin (toxoid) or a non-toxic but antigenic recombinant protein derived from the exotoxin can be expected to provide protection against disease.

Antibodies generally mediate protection against the surface antigens and certain secreted antigens of extracellular bacteria. Cellular immunity may also play a role (Haesebrouck et al., 2004).

Oral immunization of piglets with live avirulent strains of bacteriais is a new vaccination strategy for bacterial diseases. An example is the administration of avirulent *E. coli* carrying the fimbrial adhesins or oral administration of purified F4 (K88) fimbriae.

Other approaches to control bacterial diseases include supplementation of the feed with egg yolk, antibodies from chickens immunized with F4 or F18 adhesins, breeding of F18 and F4 resistant animals, supplementation with zinc and/or spray-dried plasma, dietary acidification, phage therapy, or the use of probiotics. However, to date, no single strategy has proven to be totally effective (Fairbrother, 2005).

Results of meta-analysis

In the present review, 29 countries with documented records of cases of *E. coli* were included with the USA having the highest number of references followed by

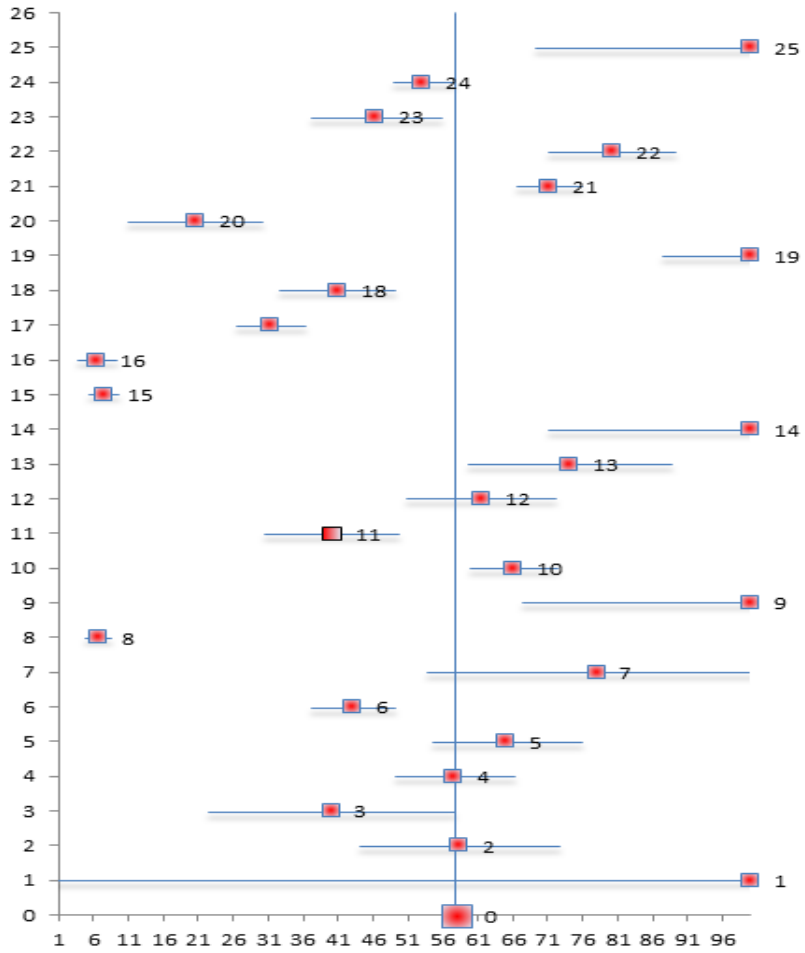

Figure 2. Forest plot for prevalence of *Escherichia coli* virulence factors in weaners.

China. About 74% of the samples were taken from farms and others were from samples submitted to research laboratories and veterinary faculties for necropsy.

In general 7 pathotypes were reported and 66.7% of the pathotypes identified were ETEC, 14.3% were ETEC and STEC, 7.9% were STEC, 31.7% were classified as ETEC/EPEC/EAEC, others were EHEC and DAEC (Table 2). Several serogroups were identified and the commonest were O141, O149, O139, O138, O8 and O9. 33.3% of samples collected were faecal swabs or faeces, 14.2% were intestinal segments, 17.4% were intestinal segments, feaces or rectal swabs and other organs, 6.3% were intestinal segments and other organs, 7.9% were lab isolates (Table 2). Piglets were 52.3%, 7.9% were porkers, 39.6% were weaners and all pigs were between 1 to 392 days old.

A total of 24,854 isolates were considered and 10477 were recorded as positives, the gene looked out for were STa, STb, LT, stx1, stx2, stx-2e F4, F5, F6, F18, F41, AIDA, EAST1, eae, paa, hlyA (Table 2). The diseases examined were diarrhoea in form of neonatal diarrhoea, colibacillosis, PWD and oedema disease. Some of the associated risk factors identified were poor housing, management and feed changes, extensive use of antibiotics as prophylaxis, overcrowding, high humidity and temperature changes (Table 2).

This study showed that India, USA, Japan, Slovakia and Denmark were the countries with the highest detection of virulence factors in piglets (100%; n = 3, 55, 42, 92 and 191 respectively), followed by Sweden (74%; n = 856) and Poland (72%; n =1125) (Table 3). For all the cases of virulence in piglets an overall prevalence of 57.93% (CI_{95}: 57.0 to 58.8) was estimated (n = 12970) (Table 3, Figure 1)

Similarly, South Africa, Cuba, Poland, Denmark, had the highest cases of virulence factor detection in *E. coli* in weaners (100%; n =2, 36, 46, and 240 respectively), followed by Canada (74.1% n = 135), the least detection was in found in China (6.5% n=324) (Table 4). The overall prevalence of virulence factor detection in weaners was 57.9% (CI_{95}: 56.99-58.83; n = 8058) (Table 4, Figure 2). Furthermore, in porkers the overall prevalence of *E. coli* virulence factor detection was36.45% (CI_{95}: 35.73- 37.57). The highest prevalence was found in the USA (70.5%; n = 687) and the lowest was in Norway (0.15% n= 1976) (Table 5, Figure 3).

Table 3. Prevalence of *Escherichia coli* virulence factors in piglets.

S/N	Study	Events	Sample Size	Outcome	SE	CI lower	CI upper	Forest Plot ID	Rate
1	US (herd)	108	111	0.972973	0.093624368	0.789469	1.156477	32	97.2973
2	Denmark (Diagnostic samples)	219	563	0.388988	0.026285344	0.337468	0.440507	31	38.89876
3	Mexico (Farm)	116	503	0.230616	0.021412186	0.188648	0.272584	30	23.06163
4	Japan (Necropsy samples)	214	567	0.377425	0.025800245	0.326857	0.427994	29	37.7425
5	India (Farm)	3	3	1	0.577350269	0.131607	2.131607	28	100
6	Denmark (Research institute)	45	90	0.5	0.074535599	0.35391	0.64609	27	50
7	Vietnam (Farm)	126	200	0.63	0.056124861	0.519995	0.740005	26	63
8	Canada (Farm)	164	200	0.82	0.064031242	0.694499	0.945501	25	82
9	Korea (Farm)	164	720	0.227778	0.017786456	0.192916	0.262639	24	22.77778
10	US (Research institute)	330	660	0.5	0.027524094	0.446053	0.553947	23	50
11	Spain (Farm)	36	69	0.521739	0.086956522	0.351304	0.692174	22	52.17391
12	US (Farm)	55	55	1	0.134839972	0.735714	1.264286	21	100
13	England (Farm)	14	51	0.27451	0.073365831	0.130713	0.418307	20	27.45098
14	Zimbabwe (Farm)	63	1984	0.031754	0.004000632	0.023913	0.039595	19	3.175403
15	Japan (Farm)	42	42	1	0.15430335	0.697565	1.302435	18	100
16	Germany (Farm)	27	104	0.259615	0.049963004	0.161688	0.357543	17	25.96154
17	Vietnam (Farm)	69	92	0.75	0.09028939	0.573033	0.926967	16	75
18	China (Farm)	112	208	0.538462	0.050879833	0.438737	0.638186	15	53.84615
19	Brazil (Farm)	92	100	0.92	0.09591663	0.732003	1.107997	14	92
20	Slovakia (Farm)	174	220	0.790909	0.059958663	0.67339	0.908428	13	79.09091
21	China (Farm)	206	381	0.540682	0.037671129	0.466847	0.614518	12	54.06824
22	Slovakia (Farm)	92	92	1	0.104257207	0.795656	1.204344	11	100
23	Czech Republic (Farm)	277	800	0.34625	0.020804146	0.305474	0.387026	10	34.625
24	Spain (Farm)	280	1334	0.209895	0.012543629	0.18531	0.234481	9	20.98951
25	Denmark (Research Laboratory)	191	191	1	0.072357461	0.858179	1.141821	7	100
26	Denmark (Research Laboratory)	28	194	0.14433	0.027275787	0.090869	0.19779	6	14.43299
27	Brazil (Farm)	45	70	0.642857	0.095831485	0.455027	0.830687	5	64.28571
28	Poland (Farm)	819	1125	0.728	0.025438379	0.678141	0.777859	4	72.8
29	Argentina (Farm)	70	223	0.313901	0.037518387	0.240365	0.387437	3	31.39013
30	Sweden (Farm)	634	856	0.740654	0.029415136	0.683001	0.798308	2	74.06542
31	Indonesia (Farm)	484	858	0.564103	0.025641026	0.513846	0.614359	3	56.41026
32	Slovakia (Farm)	74	160	0.4625	0.053764533	0.357122	0.567878	4	46.25
33	Brazil (Farm)	99	144	0.6875	0.06909635	0.552071	0.822929	1	68.75
-	-	-	-	0.579256	0.0047	0.570044	0.588468	Central Tendency	57.92558

Table 4. Prevalence of *Escherichia coli* virulence factors in weaners.

Serial number	Study	Events	Sample Size	Outcome	SE	CI lower	CI upper	Forest plot ID	Rate
1	south Africa (Farm)	2	2	1	0.707106781	-0.38593	2.385929	1	100
2	China (Lab samples)	63	108	0.583333	0.073493092	0.439287	0.72738	2	58.33333
3	Canada (Farm)	20	50	0.4	0.089442719	0.224692	0.575308	3	40
4	US (Farm)	175	304	0.575658	0.043515647	0.490367	0.660949	4	57.56579
5	China (Field isolates)	140	215	0.651163	0.0550333	0.543298	0.759028	5	65.11628
6	Mexico (Farm)	194	450	0.431111	0.030951974	0.370445	0.491777	6	43.11111
7	Switzerland (Farm)	39	50	0.78	0.12489996	0.535196	1.024804	7	78
8	India	48	720	0.066667	0.009622504	0.047807	0.085527	8	6.666667
9	Cuba (Farm)	36	36	1	0.166666667	0.673333	1.326667	9	100
10	Bulgeria (Farm)	409	619	0.660743	0.032671645	0.596707	0.72478	10	66.07431
11	Canada (Farm)	68	170	0.4	0.048507125	0.304926	0.495074	11	40

Table 4. Contd.

12	Hungary (Farm)	126	205	0.614634	0.054755962	0.507312	0.721956	12	61.46341
13	Canada (Animal health Lab)	100	135	0.740741	0.074074074	0.595556	0.885926	13	74.07407
14	Poland (Farm)	46	46	1	0.147441956	0.711014	1.288986	14	100
15	Korea (Farm)	45	604	0.074503	0.011106298	0.052735	0.096272	15	7.450331
16	China (Farm)	21	324	0.064815	0.014143752	0.037093	0.092537	16	6.481481
17	Korea (Pathology Department)	149	476	0.313025	0.025644024	0.262763	0.363287	17	31.30252
18	Korea (Farm)	94	230	0.408696	0.042153738	0.326074	0.491317	18	40.86957
19	Denmark (National Vet Lab)	240	240	1	0.064549722	0.873483	1.126517	19	100
20	Denmark (National Vet Lab)	17	83	0.204819	0.049675971	0.107454	0.302184	20	20.48193
21	Canada (Vet Medicine Faculty)	872	1226	0.711256	0.024086171	0.664047	0.758465	21	71.12561
22	Poland (Farm)	298	372	0.801075	0.046405044	0.710121	0.892029	22	80.10753
23	Poland (Farm)	96	207	0.463768	0.047333135	0.370995	0.556541	23	46.37681
24	Poland (Farm)	608	1146	0.530541	0.021516279	0.488369	0.572713	24	53.0541
25	Poland (Farm)	40	40	1	0.158113883	0.690097	1.309903	25	100
-	-	-	-	0.579062	0.0047	0.56985	0.588274	Central Tendency	57.90619

Table 5. Prevalence of *Escherichia coli* virulence factors in porkers.

S/No	Study	Events	Sample Size	Outcome	SE	CI lower	CI upper	Forest plot ID	Rate
1	Norway	3	1976	0.001518219	0.000876544	-0.0002	0.003236	1	0.151822
2	US	6	305	0.019672131	0.008031114	0.003931	0.035413	2	1.967213
3	US	484	687	0.704512373	0.03202329	0.641747	0.767278	3	70.45124
4	Belgium	95	135	0.703703704	0.072198477	0.562195	0.845213	4	70.37037
5	south Africa	106	263	0.403041825	0.039146883	0.326314	0.47977	5	40.30418
-	-	-	-	0.36648965	0.0047	0.357278	0.375702	Central Tendency	36.64897

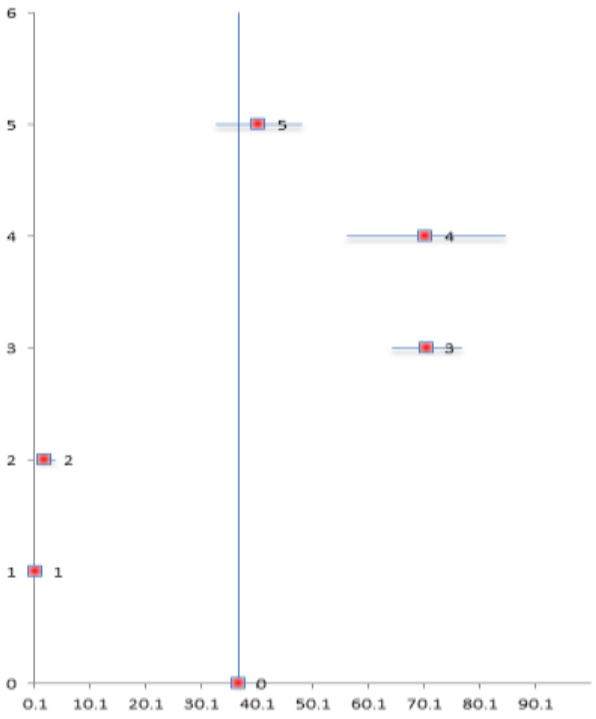

Figure 3. Forest plot for prevalence of *Escherichia coli* virulence factors in porkers.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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Supplementary Table 1. *Escherichia coli* virulence factors in piglets based on published information from different countries.

Location of study	Events	Sample Size	Outcome (es)	SE	Var	w	w*es	w*(es²)	w²	w_v	w_v*es	w_v*(es²)	w_v²
US (herd)	108	111	0.9730	0.0936	0.0088	114.083333	111	108	13015.0069	114.08333	111.00000	108.00000	13015.00694
Denmark (Diagnostic samples)	219	563	0.3890	0.0263	0.0007	1447.34703	563	219	2094813.43	1447.34703	563.00000	219.00000	2094813.431
Mexico (Farm)	116	503	0.2306	0.0214	0.0005	2181.11207	503	116	4757249.86	2181.11207	503.00000	116.00000	4757249.857
Japan (Necropsy samples)	214	567	0.3774	0.0258	0.0007	1502.28505	567	214	2256860.36	1502.28505	567.00000	214.00000	2256860.362
India (Farm)	3	3	1.0000	0.5774	0.3333	3	3	3	9	3.00000	3.00000	3.00000	9
Denmark (Research institute)	45	90	0.5000	0.0745	0.0056	180	90	45	32400	180.00000	90.00000	45.00000	32400
Vietnam (Farm)	126	200	0.6300	0.0561	0.0032	317.460317	200	126	100781.053	317.46032	200.00000	126.00000	100781.0532
Canada (Farm)	164	200	0.8200	0.0640	0.0041	243.902439	200	164	59488.3998	243.90244	200.00000	164.00000	59488.39976
Korea (Farm)	164	720	0.2278	0.0178	0.0003	3160.97561	720	164	9991766.81	3160.97561	720.00000	164.00000	9991766.805
US (Research institute)	330	660	0.5000	0.0275	0.0008	1320	660	330	1742400	1320.00000	660.00000	330.00000	1742400
Spain (Farm)	36	69	0.5217	0.0870	0.0076	132.25	69	36	17490.0625	132.25000	69.00000	36.00000	17490.0625
US (Farm)	55	55	1.0000	0.1348	0.0182	55	55	55	3025	55.00000	55.00000	55.00000	3025
England (Farm)	14	51	0.2745	0.0734	0.0054	185.785714	51	14	34516.3316	185.78571	51.00000	14.00000	34516.33163
Zimbabwe (Farm)	63	1984	0.0318	0.0040	0.0000	62480.254	1984	63	3903782136	62480.25397	1984.0000	63.00000	3903782136
Japan (Farm)	42	42	1.0000	0.1543	0.0238	42	42	42	1764	42.00000	42.00000	42.00000	1764
Germany (Farm)	27	104	0.2596	0.0500	0.0025	400.592593	104	27	160474.425	400.59259	104.00000	27.00000	160474.4252
Vietnam (Farm)	69	92	0.7500	0.0903	0.0082	122.666667	92	69	15047.1111	122.66667	92.00000	69.00000	15047.11111
China (Farm)	112	208	0.5385	0.0509	0.0026	386.285714	208	112	149216.653	386.28571	208.00000	112.00000	149216.6531
Brazil (Farm)	92	100	0.9200	0.0959	0.0092	108.695652	100	92	11814.7448	108.69565	100.00000	92.00000	11814.7448
Slovakia (Farm)	174	220	0.7909	0.0600	0.0036	278.16092	220	174	77373.4972	278.16092	220.00000	174.00000	77373.49716
China (Farm)	206	381	0.5407	0.0377	0.0014	704.665049	381	206	496552.831	704.66505	381.00000	206.00000	496552.8306
Slovakia (Farm)	92	92	1.0000	0.1043	0.0109	92	92	92	8464	92.00000	92.00000	92.00000	8464
Czech Republic (Farm)	277	800	0.3463	0.0208	0.0004	2310.46931	800	277	5338268.45	2310.46931	800.00000	277.00000	5338268.451
Spain (Farm)	280	1334	0.2099	0.0125	0.0002	6355.55714	1334	280	40393106.6	6355.55714	1334.0000	280.00000	40393106.6
Denmark (Research Laboratory)	191	191	1.0000	0.0724	0.0052	191	191	191	36481	191.00000	191.00000	191.00000	36481
Denmark (Research Laboratory)	28	194	0.1443	0.0273	0.0007	1344.14286	194	28	1806720.02	1344.14286	194.00000	28.00000	1806720.02
Brazil (Farm)	45	70	0.6429	0.0958	0.0092	108.888889	70	45	11856.7901	108.88889	70.00000	45.00000	11856.79012
Poland (Farm)	819	1125	0.7280	0.0254	0.0006	1545.32967	1125	819	2388043.79	1545.32967	1125.0000	819.00000	2388043.79
Argentina (Farm)	70	223	0.3139	0.0375	0.0014	710.414286	223	70	504688.457	710.41429	223.00000	70.00000	504688.4573
Sweden (Farm)	634	856	0.7407	0.0294	0.0009	1155.73502	856	634	1335723.43	1155.73502	856.00000	634.00000	1335723.427
Indonesia (Farm)	484	858	0.5641	0.0256	0.0007	1521	858	484	2313441	1521.00000	858.00000	484.00000	2313441
Slovakia (Farm)	74	160	0.4625	0.0538	0.0029	345.945946	160	74	119678.598	345.94595	160.00000	74.00000	119678.5975
Brazil (Farm)	99	144	0.6875	0.0691	0.0048	209.454545	144	99	43871.2066	209.45455	144.00000	99.00000	43871.20661
-	-	-	-	-	-	-	-	-	-	-	-	-	-
-	-	-	-	-	-	-	-	--	-	-	-	-	-
K	16	-	-	-	Sums:	91256.4598	12970	5472	3980098538	91256.45979	12970	5472	3980098538
Df	15	-	-	-	-	-	-	-	-	-	-	-	-

Supplementary Table 1. Contd.

-		-	-	-	-	-	-	-	-	v	0.0758493	-	-
Q	3628.61	-	-	Q_v	3628.6138	-	-	-	-	-	-	-	-
I^2	99.5866	-	-	I^2_v	99.586619	-	-	-	-	-	-	-	-
-		-	-	-	-	-	-	-	-	-	-	-	-
es (fixed)	0.14213	-	-	es (random)	0.1421269	-	-	-	-	-	-	-	-
SEes (fixed)	0.00331	-	-	SEes (random)	0.0033103	-	-	-	-	-	-	-	-
CI (fixed)	0.13564	0.1486151	-	CI (random)	0.1356387	0.14861513	-	-	-	-	-	-	-

Supplementary Table 2. *Escherichia coli* virulence factors in weaners based on published information from different countries.

Location of study	Events	Sample Size	Outcome (es)	SE	Var	w	w*es	w*(es^2)	w^2	w_v	w_v*es	w_v*(es^2)	w_v^2
south Africa (Farm)	2	2	1.0000	0.7071	0.5000	2	2	2	4	2.00000	2.00000	2.00000	4
China (Lab samples)	63	108	0.5833	0.0735	0.0054	185.14286	108	63	34277.878	185.14286	108.00000	63.00000	34277.878
Canada (Farm)	20	50	0.4000	0.0894	0.0080	125	50	20	15625	125.00000	50.00000	20.00000	15625
US (Farm)	175	304	0.5757	0.0435	0.0019	528.09143	304	175	278880.56	528.09143	304.00000	175.00000	278880.56
China (Field isolates)	140	215	0.6512	0.0550	0.0030	330.17857	215	140	109017.89	330.17857	215.00000	140.00000	109017.89
Mexico (Farm)	194	450	0.4311	0.0310	0.0010	1043.8144	450	194	1089548.6	1043.81443	450.00000	194.00000	1089548.6
Switzerland (Farm)	39	50	0.7800	0.1249	0.0156	64.102564	50	39	4109.1387	64.10256	50.00000	39.00000	4109.1387
India	48	720	0.0667	0.0096	0.0001	10800	720	48	116640000	10800.00000	720.00000	48.00000	116640000
Cuba (Farm)	36	36	1.0000	0.1667	0.0278	36	36	36	1296	36.00000	36.00000	36.00000	1296
Bulgeria (Farm)	409	619	0.6607	0.0327	0.0011	936.82396	619	409	877639.13	936.82396	619.00000	409.00000	877639.13
Canada (Farm)	68	170	0.4000	0.0485	0.0024	425	170	68	180625	425.00000	170.00000	68.00000	180625
Hungary (Farm)	126	205	0.6146	0.0548	0.0030	333.53175	205	126	111243.43	333.53175	205.00000	126.00000	111243.43
Canada (Animal health Lab)	100	135	0.7407	0.0741	0.0055	182.25	135	100	33215.063	182.25000	135.00000	100.00000	33215.063
Poland (Farm)	46	46	1.0000	0.1474	0.0217	46	46	46	2116	46.00000	46.00000	46.00000	2116
Korea (Farm)	45	604	0.0745	0.0111	0.0001	8107.0222	604	45	65723809	8107.02222	604.00000	45.00000	65723809
China (Farm)	21	324	0.0648	0.0141	0.0002	4998.8571	324	21	24988573	4998.85714	324.00000	21.00000	24988573
Korea (Pathology Department)	149	476	0.3130	0.0256	0.0007	1520.6443	476	149	2312359.1	1520.64430	476.00000	149.00000	2312359.1
Korea (Farm)	94	230	0.4087	0.0422	0.0018	562.76596	230	94	316705.52	562.76596	230.00000	94.00000	316705.52
Denmark (National Vet Lab)	240	240	1.0000	0.0645	0.0042	240	240	240	57600	240.00000	240.00000	240.00000	57600
Denmark (National Vet Lab)	17	83	0.2048	0.0497	0.0025	405.23529	83	17	164215.64	405.23529	83.00000	17.00000	164215.64
Canada (Vet Medicine Faculty)	872	1226	0.7113	0.0241	0.0006	1723.711	1226	872	2971179.6	1723.71101	1226.00000	872.00000	2971179.6
Poland (Farm)	298	372	0.8011	0.0464	0.0022	464.37584	372	298	215644.92	464.37584	372.00000	298.00000	215644.92
Poland (Farm)	96	207	0.4638	0.0473	0.0022	446.34375	207	96	199222.74	446.34375	207.00000	96.00000	199222.74
Poland (Farm)	608	1146	0.5305	0.0215	0.0005	2160.0592	1146	608	4665855.8	2160.05921	1146.00000	608.00000	4665855.8

Supplementary Table 2. Contd.

Poland (Farm)	40	40	1.0000	0.1581	0.0250	40	40	40	1600	40.00000	40.00000	40.00000	1600
K	16	-	-	-	Sums:	35706.95	8058	3946	220994363	35706.95028	8058	3946	220994363
Df	15	-	-	-	-	-	-	-	-	-	-	-	-
-	-	-	-	-	-	-	-	-	-	v	0.0715685	-	-
Q	2127.5483	-	-	Q_v	2127.548312	-	-	-	-	-	-	-	-
I^2	99.294963	-	-	I^2_v	99.29496313	-	-	-	-	-	-	-	-
es (fixed)	0.2256704	-	-	es (random)	0.225670351	-	-	-	-	-	-	-	-
SEes (fixed)	0.005292	-	-	SEes (random)	0.005292046	-	-	-	-	-	-	-	-
CI (fixed)	0.2152979	0.23604	-	CI (random)	0.215297941	0.2360428	-	-	-	-	-	-	-

Supplementary Table 3. *Escherichia coli* virulence factors in porkers based on published information from different countries.

Location of study	Events	Sample Size	Outcome (es)	SE	Var	w	w*es	w*(es^2)	w^2	w_v	w_v*es	w_v*(es^2)	w_v^2
Norway	3	1976	0.0015	0.0009	0.0000	1301525.3	1976	3	1.694E+12	51.06604	0.07753	0.00012	2607.7405
US	6	305	0.0197	0.0080	0.0001	15504.167	305	6	240379184	50.90039	1.00132	0.01970	2590.8494
US	484	687	0.7045	0.0320	0.0010	975.14256	687	484	950903.02	48.52671	34.18767	24.08563	2354.8415
Belgium	95	135	0.7037	0.0722	0.0052	191.84211	135	95	36803.393	40.33179	28.38163	19.97226	1626.6533
south Africa	106	263	0.4030	0.0391	0.0015	652.53774	263	106	425805.5	47.36150	19.08867	7.69353	2243.1118
-	-	3366	0.3664897	-	-	-	-	-	-	-	-	-	-
K	16	-	-	-	Sums:	1318849	3366	694	1.694E+12	238.18643	82.736812	51.771239	11423.197
Df	15	-	-	-	-	-	-	-	-	-	-	-	-
-	-	-	-	-	-	-	-	-	-	v	0.0195817	-	-
Q	685.40921	-	-	Q_v	23.031651	-	-	-	-	-	-	-	-
I^2	97.811526	-	-	I^2_v	34.872232	-	-	-	-	-	-	-	-
es (fixed)	0.0025522	-	-	es (random)	0.3473616	-	-	-	-	-	-	-	-
SEes (fixed)	0.0008708	-	-	SEes (random)	0.064795	-	-	-	-	-	-	-	-
CI (fixed)	0.0008455	0.0042589	-	CI (random)	0.2203634	0.4743598	-	-	-	-	-	-	-