Andreas Sing *Editor*

Zoonoses - Infections Affecting Humans and Animals

Focus on Public Health Aspects

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Preface

Zoonoses are infectious diseases caused by microorganisms passing from animals to humans and vice versa. In the last few decades most emerging and re-emerging diseases were in fact either of zoonotic origin or zoonotic potential.

The term "zoonosis" was coined by the German physician Rudolf Virchow, mainly known as father of scientific pathology, but also as an important political figure in nineteenth century Germany. Although rooted in a classical faculty-based university system, he and his Canadian disciple William Osler, also a physician by training, very early recognized the need for interdisciplinary collaboration between human and veterinary medicine and also—probably even more importantly—the public health, social and political aspects of zoonotic diseases. While the scientific basis for both of them was pathology, the rise of microbiology as a medical discipline allowed to put the focus on microorganisms as the obvious and easiest walkable bridge between human and animal infectious diseases. This is even more true since the advent of especially DNA-based typing techniques for analyzing microorganisms isolated from different species thus allowing to study their real zoonotic potential.

By incorporating life and social science subdisciplines (e.g. immunology or epidemiology) a systemic paradigm was introduced in medical science thus preparing the ground for inter- and transdisciplinary approaches both in human and veterinary medicine. A striking example for the consequences of this paradigm shift on a population level are the concepts of New Public Health.

Not at last driven by the need for global public health efforts to combat both real or anticipated releases from Pandora's box in an interconnected and globalized world the One Health concept rapidly gained momentum in the last decade after the establishment of the 2004 "Manhattan Principles".

This book is based on the One Health concept with a focus on the public health impacts of zoonoses, both medically and societally. Important aspects in understanding zoonoses are not restricted to more classical issues, e.g. their epidemiology in both humans and animals or disease symptoms in the respective two-legged, four- or more-legged, feathered or unfeathered species, but have to take into account molecularly based epidemiological data and systemic, e.g. ecological approaches.

To give an impression of the wide range of zoonotic research issues, the authors of this book were chosen from a variety of academic and professional backgrounds, from the fields of human and veterinary medicine, from universities and public health institutions, and from all continents. The underlying ideas was not to get an encyclopedic review on all known zoonotic disease entities, but to have a forum for identifying or discussing urgent issues of zoonoses under a public health perspective. Accordingly, the main target groups are the respective scientific communities, medical and veterinary practitioners, their students, public health and veterinary public health practitioners as well as decision makers in the field of public health and veterinary public health.

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Part I
Zoonoses in Food-Chain Animals with Public Health Relevance

Chapter 1
Important Public Health Zoonoses Through Cattle

Mo D. Salman and Katie Steneroden

Abstract Cattle production is a vital component of the global food chain. Animal protein, through meat or milk, is an essential dietary requirement for the majority of people across the world. Increased cattle production will attempt to meet the need for more protein with both positive and negative impacts, including the spread of diseases from livestock to people directly or indirectly through products such as milk, meat, hide or manure. The following zoonotic diseases of cattle are included in this chapter due to their potential severity in humans or cattle population and/or their wide distribution or recent emergence: anthrax, bovine spongiform encephalopathy (BSE), bovine cysticercosis, bovine tuberculosis, brucellosis, cryptosporidium, *Escherichia coli* O157:H7, leptospirosis, methicillin resistant *Staphylococcus aureus* (MRSA), Q fever, Rift Valley Fever, and *Salmonella.*

Cattle production is a vital component of the global food chain. Animal protein, through meat or milk, is an essential dietary requirement for the majority of people across the world. The need for animal protein is increasing. An estimated 50 % increase in demand is expected by the year 2030 (Delgado et al. 1999; Jones and Thornton 2009). Increased cattle production will attempt to meet the need for more protein with both positive and negative impacts, including the spread of diseases from livestock to people directly or indirectly through products such as milk, meat, hide or manure.

Threats from old and new pathogens continue to emerge, with contribution from changes in the environment, agriculture and food production systems, food processing, and the demography and connectivity of our world. At one extreme is low-intensity cattle farming, the type traditionally practiced in developing countries and rural households. The impact of disease outbreaks on the lives and livelihoods of these poor farmers is significant (Jones and Thornton 2009). In contrast, intensive farming systems in developed countries may contribute to the large scale spread of pathogens during disease outbreaks. Zoonotic diseases can have a great impact on national and international trade in addition to contribution to human illness. We are faced with a changing landscape of infectious disease that affects both humans and

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animals. This change poses significant threats to the health and food security of the global citizenry (Atkins and Robinson 2013).

The majority of human pathogens now described are linked to animals. An average of three new infections are reported approximately every 2 years with a new pathogen published every week (Gideon Informatics 2013). Nevertheless, good progress continues to be made in the control of several important livestock pathogens and mechanisms are now in place to bring together the critical scientific expertise and political will to succeed.

The following zoonotic diseases of cattle are included in this chapter due to their potential severity in humans or cattle population and/or their wide distribution or recent emergence: anthrax, bovine spongiform encephalopathy (BSE), bovine cysticercosis, bovine tuberculosis, brucellosis, cryptosporidium, *Escherichia coli* O157:H7, leptospirosis, methicillin resistant *Staphylococcus aureus* (MRSA), Q fever, Rift Valley Fever, and *Salmonella*.

Considerable challenges are presented by zoonotic pathogens to the health and wellbeing of cattle and humans. For some critically important diseases, the first line of defense will be the implementation of scientific approaches to diagnosis and control. What the future will bring with regard to zoonotic diseases is difficult to predict. A future where human and animal health practitioners work together to discover, control and prevent zoonotic diseases will surely bring surprising and meaningful results.

1.1 Anthrax

Bacillus anthracis, the causative agent of anthrax has a worldwide distribution in both animal and human populations. In developing countries anthrax is a significant problem in livestock and wildlife and among occupationally exposed individuals including veterinarians, agricultural workers and butchers (WHO 2013a). In developed countries anthrax is no longer an important disease of livestock due to appropriate control measures including prophylactic vaccination. While anthrax does occur sporadically in developed countries, its main significance lies in its potential use as an agent of bioterrorism.

Bacillus anthracis is a Gram-positive bacterium that forms spores when exposed to oxygen, which are highly resistant and long lasting in the environment. Human cases of anthrax are associated with infection in livestock or exposure to contaminated products such as carcasses, hides or wool. Animal cases of anthrax are associated with spore-contaminated pastures. The incidence of anthrax varies with the soil type, climate, animal husbandry, industrial hygiene, and disease reporting status of the country. Globally, anthrax is underreported in both humans and animal populations due to under-diagnosis and lack of internal and international reporting.

Infection can enter the body by ingestion, inhalation, or direct contact. It is generally considered that animals are infected by ingestion of contaminated food or

water. In humans, infection mainly occurs by direct contact through a break in the skin. Biting flies and other insects have the ability to transmit the disease mechanically.

In cattle, anthrax usually manifests as peracute or acute disease. The peracute form is most common at the beginning of an outbreak and animals are found dead without premonitory signs. After death, discharge of blood from the nostrils, mouth, anus and vulva are common. The acute form runs a course of about 48 h with severe depression, lethargy, abortion and fever. Necropsy findings include absence of rigor mortis and gross enlargement of the spleen with natural orifices exuding dark, tarry unclotted blood. If anthrax is suspected, the carcass should not be opened, as exposure to oxygen will cause spores to form, which may infect individuals and contaminate the environment.

In humans the three main forms of disease are cutaneous, gastrointestinal and inhalation anthrax. Cutaneous anthrax is most common and accounts for the vast majority of cases. The gastrointestinal form occurs from ingesting contaminated meat. Inhalation anthrax occurs through inhalation of the spores and is the most severe form (Decker 2003).

There are different assays for screening and diagnosis of anthrax in cattle. A stained smear of peripheral blood is usually considered as the primary screening test to determine the presence of the bacilli in the blood. Confirmation is by blood culture to identify the bacterial colonies. Fluorescent antibody techniques may also be used to confirm the infection. Animal passage assay may be necessary, if antibiotic therapy is used (Dragon et al. 1999).

Two types of vaccines are currently used in cattle. The most commonly known vaccine is the living attenuated strain of *B. anthracis* that results in long-term immunity (26 months), but there is risk of causing the disease. The second vaccine is the cell-free filtrate of a culture of *B. anthracis*—incapable of causing anthrax, but it has only a short-term immunity (3–6 months) (WHO 2013a).

Treatment in animals and humans is mainly through the application of antibiotics. In animals, penicillin, streptomycin, and oxytetracycline are used. Anti-anthrax serum may be used in animals during the early stages of disease, but severely ill animals are unlikely to recover. Human treatment is by penicillin and other antibiotics (Dragon et al. 1999; CDC 2003).

Control measures are wide range and include the use of vaccination, appropriate carcass disposal methods and decontamination, quarantine, and movement restrictions on milk and meat.

1.2 Bovine Spongiform Encephalopathy (BSE)

Bovine Spongiform Encephalopathy (BSE), also known as “mad cow disease,” is a degenerative neurological disease of cattle. BSE is caused by misfolded proteins (prions) in the host cell that build up in the central nervous system (CNS)

and eventually kill nerve cells. The nature of the transmissible agent is not well understood. The most accepted theory so far is that the agent is a modified form of a normal protein known as prion protein. For reasons that are not yet understood, the normal prion protein changes into a pathogenic (harmful) form that then damages the central nervous system.

BSE is one of several rare neurological diseases called Transmissible Spongiform Encephalopathy (TSE). The other TSE diseases include scrapie, which affects sheep and goats; transmissible mink encephalopathy; feline spongiform encephalopathy; and chronic wasting disease of deer and elk. There are six TSE diseases that affect humans: kuru, classical Creutzfeldt-Jakob disease (CJD), variant Creutzfeldt-Jakob disease (vCJD), Gerstmann-Sträussler-Scheinker syndrome, fatal familial insomnia, and sporadic fatal insomnia.

Variant Creutzfeldt-Jakob disease (vCJD) is a rare human TSE that research from the United Kingdom has associated with consumption of products contaminated with CNS tissue from BSE-infected cattle. There have been about 200 cases of vCJD in the world (most of these in the United Kingdom). Human TSE's also include sporadic Creutzfeldt-Jakob disease (sCJD or CJD), which is not related to BSE. About 85 % of CJD cases are sporadic with an annual incidence of about one case per 1 million people worldwide. The new variant or variant form (vCJD) affects younger people (average age at onset is 26 years), and has different clinical features from CJD.

There is strong epidemiologic and laboratory evidence suggesting that vCJD and BSE are caused by the same infectious agent. All cases of confirmed vCJD have occurred in people who have lived in geographic areas with BSE cases; the majority occurred in the United Kingdom, which has had the largest number of cases of BSE in cattle. The specific foods, if any that may be associated with the transmission of this agent from cattle to humans are unknown. However, milk and milk products are unlikely to pose any risk for human exposure to the BSE agent.

Research indicates that the first probable infections of BSE in cows occurred during the 1970's with the first two cases of BSE being identified in 1986. BSE may have originated from feeding cattle meat-and-bone meal (MBM) that contained BSE-infected products from a spontaneously occurring case of BSE or scrapie-infected sheep products. There is strong evidence and general agreement that the outbreak was then amplified and spread throughout the United Kingdom cattle industry by feeding rendered, prion-infected, bovine meat-and-bone meal to young calves.

There is increasing evidence that there are different strains of BSE: the typical BSE strain responsible for the outbreak in the United Kingdom and two atypical strains (H and L strains). The typical BSE strain is responsible for most of the BSE cases in the world. In cattle naturally infected with BSE, the BSE agent has been found in brain tissue, in the spinal cord, and in the retina of the eye. Additional experimental studies suggest that the BSE agent may also be present in the small intestine, tonsil, bone marrow, and dorsal root ganglia (lying along the vertebral column).

In response to the BSE epidemic, several countries instituted a series of measures to minimize the risk of disease transmission among both animals and humans.

These included a ban on feeding ruminant protein to ruminants and removal of some "high risk" materials (such as brain, spinal cord and intestines) from cattle at slaughter. Following institution of these measures, the number of BSE cases has been decreased significantly (USDA-APHIS 2006, 2007).

To prevent BSE from entering the country, several countries prohibited the importation of live ruminants from countries where BSE is known to exist in native cattle. Some countries eliminated the importation of live ruminants and most ruminant products, including meat, meat-and-bone meal, offal, glands, etc. from all of Europe. The majority of these countries also prohibited the use of most mammalian protein in the manufacture of animal feeds given to ruminants. Testing for BSE under national surveillance program among slaughtered cattle was implemented in several developed countries. Due to these safeguard measures the risk of transmitting BSE agent to humans was becoming negligible (Salman et al. 2012).

1.3 Bovine Cysticercosis—Taeniasis

Although bovine cysticercosis does not in itself represent an exceptionally serious human health risk, it is a signal of much more serious food safety and public health concerns. A finding of bovine cysticercosis is a signal that the animal feed system is contaminated and that cows are consuming human feces. Aside from *Taenia saginata*, other contaminants that pose threats to bovine and human health would also be expected to be present in human feces. These contaminants include, but are not limited to drug resistant bacteria, such as *E. coli* and *Salmonella*, *Taenia solium* (the pork tapeworm), drug residues, pain killers, hormones, other prescription drugs, illicit drugs, heavy metals, solvents and other toxicants.

Taenia saginata (T. saginata) is a cestode tapeworm that causes bovine cysticercosis in cattle and taeniasis in humans. *T. saginata* is found worldwide and human disease is highly endemic in Latin America, Africa, Asia and some Mediterranean countries (Spickler 2003). Bovine cysticercosis occurs in areas where poor sanitation, poor food inspection and close contact between humans and livestock are common (Acha and Szyfres 2003).

T. saginata infection cycles between humans (primary host) and cattle (reservoir host). Humans infected with the tapeworm pass the eggs in their feces. Cattle become infected by ingesting materials contaminated with tapeworm eggs. Larvae form cysticerci in the animal's muscle tissue, humans ingest cysticerci in raw or under-cooked beef, and the cycle continues. Tapeworms cannot be passed from person to person or spread between cattle. Clinical signs of cysticercosis in cattle and humans are mild to non-existent (Acha and Szyfres 2003). The most visible sign of tapeworm infection in humans is the active passing of tapeworm segments through the anus and in the feces.

Diagnosis of bovine cysticercosis is largely done during visual inspection of the carcass at slaughter. Serological tests including ELISA have been used in epidemiological studies for individual and herd diagnosis (WHO 2005). Taeniasis in humans

is diagnosed by finding eggs or cestode segments on the human body or in the feces with peri-anal adhesive tape tests. Feces microscopy, ELISA and molecular tests such as PCR may also be utilized (WHO 2005).

Infection in humans can be prevented by proper meat inspection and handling of meat at slaughter. When disease is found in cattle the meat may be condemned or temperature treated by freezing or heating to kill the parasite. Preventing and treating disease in people will prevent disease in cattle. Tapeworm eggs can survive in the environment for many months depending on humidity and temperature. Infected people can shed hundreds of thousands of eggs each day, so it is important for people to seek treatment to break the cycle.

1.4 Bovine Tuberculosis

Bovine Tuberculosis (BTB) is a zoonotic and economically important disease of livestock. The disease was described over 2000 years ago and is responsible for devastating illness and death in both humans and animals. Bovine tuberculosis has been largely controlled in developing countries through government control programs and milk pasteurization. In developing nations where surveillance and control measures are lacking or inadequate, humans continue to become infected with BTB through animal contact and ingestion of unpasteurized dairy products. Few developing countries have BTB control programs and immune system compromising disease conditions such as HIV allow for co-infection and increased morbidity and mortality (Miller and Sweeney 2013).

Most warm-blooded vertebrates, including humans, are susceptible to the disease causing agents. Although the principle reservoir of *Mycobacterium bovis* (*M. bovis*) is cattle, this organism has a wide host range with the capacity to produce progressive disease. Ungulates differ somewhat in resistance to *M. bovis*, but have similar immune responses and pathological conditions. They all exhibit the classical lesions of tuberculosis.

The infection is caused by the bacterial genus *Mycobacterium*. Mycobacteria are acid-fast, aerobic, non-spore-forming, non-motile, gram-positive rods containing high lipid content. Some of the lipids possess virulent and immunologic properties. The possible pathogenic role and the effect on the immune response of components of the complex mycobacterial cell wall are the subject of much attention and controversy (Behr 2013).

Bovine tuberculosis occurs throughout the world. The prevalence of *M. bovis* in cattle is low in developed countries due to successful eradication programs. Other countries have experienced increases in the rate of infection due to relaxation in surveillance activities.

Risk factors for cattle include overcrowding, introduction of tuberculous animals, soil type, wild life contact in specific geographical regions (UK, Ireland: Badger, New Zealand: Possum), purpose of the cattle: dairy vs. beef; and type of management and husbandry—specifically in the type of disposal of the manure.

The most common mode of transmission of BTB is the aerogenous route. Infection can occur by ingestion and other less likely modes such as milk-borne, congenital, or sexually transmitted. Bacteria are excreted in exhaled air, sputum, feces, urine, milk, and discharges from uterus, vagina, and draining peripheral lymph nodes. Cattle can develop bovine tuberculosis through exposure to other *M. bovis* infected species such as humans, deer, and elk (Bovine TB Advisory Group 2009).

Clinical signs of disease in cattle are variable depending on the location and extent of the lesions. Even with advanced disease, visible signs are frequently absent. If superficial lymph nodes are involved, they may be visibly enlarged and can rupture and drain through the skin. Enlarged internal nodes can cause signs of obstruction. With pulmonary involvement, a chronic cough can develop due to bronchopneumonia. In advanced lung disease, dyspnea occurs with increased respiratory rate and depth. Tuberculosis mastitis causes a marked induration and hypertrophy of the udder. General findings include anorexia, dyspnea, weight loss, weakness, and low-grade fluctuating fever. Often the main sign of tuberculosis is emaciation, despite adequate nutrition and care.

A definitive diagnosis for mycobacterial infection can be made by bacterial isolation and identification, which can be difficult and time consuming. For example, in *M. bovis* cultures visible growth arises following 3–8 weeks of incubation. Conventional mycobacteriological identification procedures on culture media rely on differences in culture growth times, colony morphology, cellular morphology, antimicrobial sensitivity, and various biochemical test reactions. More recent techniques such as radiometric procedures can expedite mycobacterial detection times, whereas gas-liquid chromatography, and DNA robes can accelerate mycobacterial identification from cultures. Research on the use of the DNA probes, specifically polymerase chain reaction (PCR), is currently in progress to be used for molecular epidemiology of the disease in livestock species.

The tuberculin skin test is an in vivo diagnostic test used to evaluate the cell-mediated immune response to mycobacteria exposure. The test is unable to differentiate between disease and immunity. To determine whether or not an animal is infected with *M. bovis*, tuberculin made from either the human or bovine bacilli (the mammalian tuberculins) is injected intradermally into the animal. Reactivity to tuberculin made from either of these bacilli is similar and is normally the greatest in animals sensitized specifically to these bacilli. The inflammatory response to the injection peaks from 24 to 72 h following tuberculin injection and can linger for several weeks before diminishing. Failure of animals with observable evidence of tuberculosis to show a palpable skin response to tuberculin at the time of test reading has been defined as anergy. Anergy is indicative of deficient T lymphocyte function.

Vaccines against *M. bovis* stimulate cell-mediated immunity. BCG (Bacillus of Calmette–Guerin, the modified *M. bovis* vaccine strain named after its two developers) is an attenuated strain of *M. bovis* used in human vaccination. BCG has also been utilized extensively to vaccinate cattle in numerous countries for many years. Protection produced by BCG vaccination of cattle is poor and causes tuberculin

sensitivity in the animals, interfering with control and eradication programs based on tuberculin skin testing. By 1968, none of the national control programs for bovine tuberculosis included vaccination.

Treatment of tuberculosis in animals in general is discouraged due to possible public health hazards in retaining tuberculous animals. However, throughout the years, numerous procedures have been tried without success to treat tuberculous cattle, including injection of live or dead bacilli, specific diets, fresh air, change of climatic conditions, x-ray therapy, serotherapy, pneumothorax, and pneumoperitoneum. Chemotherapeutic drugs, including isoniazid, have been used in cattle and were found to only suppress the bacilli during the duration of drug therapy, with shedding of the organism possible after treatment.

Control measures include test and slaughter, active detection of the lesioned cattle in slaughterhouses followed by trace back systems and control of the disease in wildlife populations.

1.5 Brucellosis

Brucellosis is a zoonotic disease of major social and economic importance in most countries of the world. It is caused by several species of *Brucella* bacteria and effects several livestock species—mainly cattle, sheep, and goats. The economic importance of the disease in cattle is due to a loss of production, primarily decreased milk production, abortion, and infertility. Brucellosis is found worldwide, however in some geographical areas it is limited to a specific *Brucella* species and host species. Several countries have succeeded in the eradication of the disease from specific host species; other countries are engaged in eradication programs. The growing phenomenon of international migration and tourism renew our concern with the prevalence and persistence of human brucellosis.

The *Brucella* spp. have a wide host range, however, they are not readily transmitted from preferential to dissimilar hosts. Non-preferential hosts may harbor the bacteria, but it is considered an incidental infection. This incidental infection is usually localized and/or shows different clinical and pathological manifestations from those observed in the specific host. The host preferences of this bacterial agent are: *Brucella abortus* in cattle, *Brucella melitensis* in sheep and goats, *Brucella suis* in swine and *Brucella ovis* in sheep (Moreno et al. 2002).

The bacteria is an intracellular organism which is an important factor in its survival in the host and may explain both the transitory titers occurring in some hosts following isolated episodes of bacteremia and the disappearance of titers in hosts with latent infection. The bacteria can survive on grass for variable periods depending on environmental conditions. In temperate climates, infectivity may persist for 100 days in winter and 30 days in summer. The organism is susceptible to heat, sunlight, and standard disinfectants, but freezing is conducive to almost indefinite survival (Blasco and Molina-Flores 2011).

Risk factors associated with infection and the diseases in cattle population include: (1) Contact with infected materials—aborted fetus, placenta, semen, secretion, etc.; (2) Direct contact with infected animals—including wildlife species; (3) High population density, particularly in dairy farming systems; (4) Breeding management and husbandry such as contaminated maternity pens, unregulated breeding time; and (5) Poor hygiene/husbandry—particularly during calving seasons.

The infection in humans is nonspecific and manifests as fluctuating fever, pain in joints, sweating, and weakness. Transmission to humans occurs through contact with contaminated materials from infected animals particularly as an occupational hazard; consumption of infected milk and dairy products; non-intentional injection of live animal vaccine; and inhalation of large amounts of bacteria contaminated aerosols. Human infection with brucellosis is most serious when it results from exposure to *B. melitensis*, which is usually linked to exposure to infected goats and sheep (Corbel 2006).

The disease in animals is transmitted through ingestion of contaminated materials; penetration of intact skin and conjunctiva; and contamination of the udder during milking. Intra-herd spread occurs by both vertical and horizontal transmission. Congenital infection due to *in utero* infection does occur, but its importance has not been defined. Horizontal transmission can occur both directly and indirectly. Flies, dogs, rats, ticks, infected boots, fodder, and other inanimate objects are possible ways for indirect transmission. Preventive measures in cattle population are mainly related to early detection of infected cattle with removal of serologically positive animals (test and culling) and the application of vaccine.

No reliable vaccine is available for human use. Humans are usually treated prophylactically with antibiotics if exposure is suspected. Preventive measures for human infection include precaution in handling contaminated materials from infected animals and precautions during the use of the vaccine in animals and avoiding consumption of unpasteurized milk or dairy products.

1.5.1 Cryptosporidium parvum

Cryptosporidium parvum is a coccidian protozoan that is an important cause of diarrhea in cattle and humans worldwide. It has emerged since the 1970's as a major cause calf-hood diarrhea. It is one of the top four agents responsible for moderate to severe gastrointestinal illness in children in developing countries and can be a fatal complication of AIDS (Kotloff et al. 2013) (Mosier and Oberst 2000). Cryptosporidiosis is one of the most common causes of waterborne disease among humans in the United States (CDC 2013a).

C. *parvum* resides in the small intestine of the host where it forms oocysts, which are shed in great numbers in the feces. Transmission occurs through ingestion of food and water contaminated with fecal matter from an infected animals or humans, direct contact with infected feces or ingestion of contaminated water. Large outbreaks have been associated with drinking water, food, swimming pools and lakes.

Community-wide outbreaks of cryptosporidiosis have been linked to drinking municipal water or recreational water contaminated with *Cryptosporidium*. One large-scale outbreak occurred in Wisconsin, USA in 1993 when more than 400,000 people became ill from a malfunctioning municipal water filtration system. The total cost of outbreak-associated illness was US$ 92 million. (Corso et al. 2003) The source of the *Cryptosporidium* oocysts in this outbreak, whether from cattle, slaughterhouse run off or from human sewage, remains speculative (Mac Kenzie et al. 1994).

In healthy humans, infection is usually asymptomatic and self-limiting. In immunodeficient people disease can be severe with profuse watery diarrhea and substantial fluid loss (Acha and Szyfres 2003). Most animals can become infected with *Cryptosporidium* spp., but clinical signs of diarrhea, tenesmus, anorexia and weight loss are most commonly observed in calves less than one month old.

Cryptosporidiosis is diagnosed by examining fecal samples using acid-fast staining, direct fluorescent antibody and/or enzyme immunoassays (CDC 2013a). The oocysts are not shed continuously and repeated sampling may be necessary. Cryptosporidiosis can also be diagnosed in stained biopsy/necropsy specimens or fresh intestinal scrapings. Molecular methods, which can detect *Cryptosporidium* species, are increasingly being used in diagnostic laboratories.

There is no specific treatment available for Cryptosporidiosis; supportive therapy is usually effective. Prevention efforts focus on hand washing, especially after handling or being around animals and before eating or handling food.

1.5.2 E. coli O157:H7

Escherichia coli is in the family *Enterobacteriaceae* and is a normal component of the flora in the large intestine of humans and warm-blooded animals. *E. coli* O157:H7 is a specific pathogenic subset of *E. coli* found worldwide, that produces watery diarrhea, hemorrhagic colitis and rarely, hemolytic-uremia syndrome (HUS) in children.

Cattle are a reservoir hosts, harbor the bacteria asymptomatically and are an important source of infection for humans. Prevalence estimates vary, and it appears that while a large percentage of cattle herds may have infected animals, the actual number of individual infected animals at any one time is relatively low (USDA 2003). The costs associated with attempts to control prevalence in cattle, contaminated food recall, and human healthcare costs make the economic and social burden *E. coli* O157:H7 high (Callaway 2010).

Transmission of *E. coli* O157:H7 occurs through consumption of contaminated food or water, direct contact with infected animals, their feces or contaminated soil. Primary sources of *E. coli* O157:H7 outbreaks are raw or undercooked ground meat products, raw milk and fecal contamination of vegetables. Person-to-person spread can occur during outbreaks (Spickler 2009). Visiting farms and other venues where the general public might come into direct contact with farm animals, particularly

calves, has been identified as an important risk factor for *E. coli* O157:H7 infection (WHO 2011a). A low dose of bacteria is sufficient for infection.

E. coli O157:H7 occurs asymptomatically in cattle and is shed intermittently. In humans, illness can range from mild diarrhea to severe hemorrhagic colitis. In most cases the illness is self-limiting. Hemolytic uremic syndrome, a particularly severe complication, can occur in a small percentage of cases leading to renal failure and death in children and elderly. Selective and differential culture media have been developed to diagnose *E. coli* O157:H7 in human and bovine fecal samples.

Measures to prevent and control *E. coli* O157:H7 in cattle include management changes (biosecurity, housing, transport and stress reduction), water and feed management, including additives and probiotics; bacteriophages and vaccines (Callaway 2010). Pre-harvest strategies are important, but do not eliminate the need for good sanitation in processing plants and households. Good hygienic slaughtering practices reduce contamination of carcasses. Education on hygienic handling of foods is essential for farm workers, abattoir and food production workers to reduce contamination. Household preventive measures are similar to those recommended for other foodborne diseases (WHO 2011a).

1.6 Leptospirosis

Leptospirosis is a zoonotic disease of worldwide importance. Also a neglected tropical disease, leptospirosis largely affects vulnerable rural and semi-urban populations. Global annual incidence of endemic human leptospirosis is grossly underestimated due to lack of awareness, under diagnosis, misdiagnosis and difficulty with diagnostic testing. Efforts to determine the burden of disease are ongoing (WHO 2011b). Leptospirosis is endemic in countries with humid subtropical and tropical climates, epidemics occur often as a result of flooding. Individuals at greatest risk include farmers, ranchers, slaughterhouse workers, trappers, loggers, veterinarians, sewer workers, rice field workers and military personnel.

Leptospirosis is caused by a variety of species of *Leptospira*, a spirochete with more than 250 pathogenic serovars that are adapted to different wild or domestic reservoir hosts. The classification system for *Leptospira* changed in 1989, leading to some confusion, as pathogenic and non-pathogenic serovars are now included in the same species. Serovars vary by geographic region (Spickler 2005). Host adaptation is not a static situation as serovars are adapting to new hosts, vaccine pressures are altering serovars in different species and climate change may be altering hosts and serovars (Hartskeerl et al. 2011). These facts lead to difficulties in prediction, prevention and use of vaccines. Reservoir hosts include wild mammals (rats and rodents are the most common) as well as domestic cattle, pigs, pigs and sheep and dogs. Reservoir hosts experience asymptomatic, mild or chronic disease and can shed for months to years.

Leptospires reside in the kidneys of infected reservoir hosts and are shed in urine into the environment where they can reside for long periods of time depending on

environmental conditions. Freshwater ponds, streams, run-off and groundwater are common water sources of Leptospires. *Leptospira* spp. can also be excreted in vaginal secretions and with aborted fetuses after calving (Spickler 2005). *Leptospira* spp. can be spread directly between individuals, through skin contact with contaminated water or urine, ingested in contaminated food or water or spread via aerosol.

At least 13 serovars of *Leptospira* spp. have been isolated from cattle (Acha and Szyfres 2003). Clinical signs vary with the serovar and in acutely affected calves include fever, anorexia, conjunctivitis and diarrhea. In adult cattle clinical signs may be mild and go undetected. More serious infection may result in abortions, decreased fertility or decreased milk yields (Spickler 2005). Clinical signs are associated with kidney disease, liver disease or reproductive dysfunction; younger animals suffer more severe disease. Differential diagnosis includes brucellosis, neospirosis, bovine viral diarrhea (BVD) and infectious bovine rhinotracheitis (IBR).

In humans, disease ranges from mild to severe depending on the serovar and immune status of the patient. Clinical signs mimic other infectious diseases including influenza, hepatitis, dengue, hantavirus, yellow fever, malaria, brucellosis, borreliosis, typhoid fever, other enteric diseases and pneumonia (Spickler 2005).

Rapid screening tests are available for presumptive diagnosis in humans, but require confirmatory diagnosis by culture, PCR or microagglutination test (MAT). The most commonly used test for diagnosis in animals is the MAT tests; ELISA tests are also used.

Human vaccines against leptospirosis are available in some countries. Animal vaccines are in use and must contain serovars present in the local environment; most of them require yearly boostering. In developed countries cattle, pigs and dogs are routinely immunized. In developing countries vaccines with locally relevant serovars are not as available (Hartskeerl et al. 2011). Prevention programs must be tailor-made and based on predominant serovar and local reservoir hosts. Public health prevention measures include reservoir control through rodent control and vaccination of livestock and dogs, improved sanitation, improvement of water sources that may be contaminated, as well as outreach and education for high-risk individuals and high-risk areas.

1.6.1 Methicillin-Resistant Staphylococcus aureus

Methicillin-resistant *Staphylococcus aureus* (MRSA) are Gram-positive bacteria that are resistant to methicillin and other beta-lactams in this large group of antibiotics that are widely used in veterinary and human medicine. MRSA is found worldwide in humans and animals.

MRSA was first isolated from cattle with mastitis in 1972, which was the first recognition of this emerging disease in animals (Devriese et al. 1972). Since that time MRSA has been found in many species of animals including pigs, horses, dogs, cats, pet birds, zoo animals and marine mammals (Spickler 2011). Most of the strains isolated from animals have been of human origin; this changed, however,

in 2003–2005 with the emergence of a new type of MRSA, CC398, isolated from humans and pigs in The Netherlands. This livestock-associated strain appears to be less host specific than other MRSA strains and has spread to other livestock including cattle (Vanderhaeghen et al. 2010). The livestock-associated MRSA can cause disease in animals and as well as in humans in close contact with them (Vanderhaeghen et al. 2010) and there is evidence of limited human-to-human spread of this strain as well (Voss et al. 2005). The data on this new type of livestock-associated MRSA is limited and the burden of CC398 in cattle is unclear (Vanderhaeghen et al. 2010).

MRSA is transmitted most commonly through direct contact with colonized or infected individuals (animals or humans) (Spickler 2011). Contaminated environments, including air in confinement operations, are other potential routes (Gibbs et al. 2006). Human and livestock-associated strains of MRSA can be found in contaminated food (Jones et al. 2002), meat (van Loo et al. 2007; de Boer et al. 2009), and raw milk products (Normanno et al. 2007).

Cattle colonized or infected with MRSA most commonly present with clinical or subclinical mastitis. MRSA colonization has been associated with veal calves (Graveland et al. 2010) and beef calves (Mooij et al. 2007). MRSA can cause a wide variety of infections in humans including skin and soft tissue infections as well as more invasive infections including pneumonia, endocarditis, septic arthritis and septicemia; MRSA is one of the most prevalent causes of nosocomial infections worldwide (Spickler 2011).

Diagnosis of infection or colonization with *S. aureus* can be accomplished through culture of the organism. Methicillin-resistant strains can be identified through antibiotic susceptibility or genetic testing. Genetic testing can identify the various human and animal associated strains.

In general, prevention and control of MRSA includes good biosecurity and infection control practices including hand washing, barrier precautions and environmental disinfection (Spickler 2011). MRSA is not particularly hardy and can be inactivated by sodium hypochlorite, alcohols and quaternary ammonium compounds (Spickler 2011). The emerging livestock-associated MRSA urgently requires more research to determine the risk factors and transmission routes (Vanderhaeghen et al. 2010).

1.7 Q Fever

Q fever is a highly contagious zoonotic disease caused by *Coxiella burnetii*, an obligate intracellular bacterium. Livestock are the major source of infection in humans worldwide. Q fever can infect a wide range of hosts including pets, wildlife, birds, reptiles and ticks. Because illness can be mild and go undetected, Q fever is under-diagnosed and under-reported globally and the true burden of disease unknown. However, a large outbreak with approximately 4000 human cases occurred in the Netherlands during 2007–2010. Dairy goat farms near densely populated

areas were the source of the outbreak, which was spread via a windborne route (Schimmer et al. 2009).

Animals that carry this organism usually do not show any signs of disease, but abortions and stillbirths can occur with great quantities of bacteria shed. Both symptomatic and asymptomatic animals shed *C. burnetii* in large quantities at parturition. The bacteria can also be shed in feces, urine, and milk. The organisms persist in the environment for long periods, are highly resistant to disinfectants and can be spread long distances by the wind (Spickler 2007).

Human infection usually occurs from inhalation of bacteria from air that is contaminated by feces of infected animals. Q fever is also rarely transmitted to humans by tick bites and through ingestion of unpasteurized milk or milk products (CDC 2013b). Most often, sporadic cases occur in people who are occupationally exposed such as biomedical research facility workers, farmers, ranch-hands, veterinarians, and slaughterhouse workers (CDC 2013b). These cases tend to result from exposure to parturient ruminants; however, cats, dogs, rabbits and other species have also been implicated. Although Q fever is usually asymptomatic or mild, a small percentage of people develop serious disease. Pneumonia or hepatitis may occur in acute cases, and chronic infections can result in endocarditis or a wide variety of other diseases (Spickler 2007).

In humans Q fever is usually diagnosed by serology or PCR. Diagnosis of Q fever in aborting animals involves testing of the fetuses and placentas. Veterinary diagnosticians typically identify the organism by the use of special stains applied to microscopic sections of these tissues, and/or PCR.

Q fever can be prevented in humans by limiting exposure to livestock during birthing, personal hygiene measures and wearing of personal protective equipment and only eating and drinking pasteurized milk and milk products. In animals prevention of Q fever is based on herd management and prevention of contact with wildlife and tick vectors. Isolating infected pregnant animals and disposing of reproductive tissues can decrease transmission (Spickler 2007). Prevention in both humans and animals can be difficult, because Q fever can be transmitted on fomites or in aerosols over great distances. Effective vaccines are available in some countries for both humans and animals.

1.8 Rift Valley Fever

Rift Valley Fever (RVF) is a zoonotic disease that primarily affects ruminants (cattle, sheep, goats and camels) and can also infect humans. Disease can be severe in both humans and animals and may cause severe economic losses as a result of livestock death and abortion. Infection with RVF is caused by a virus in the in the family Bunyaviridae and is primarily transmitted by mosquitoes. Recently, RVF has received more attention as a potential agricultural and zoonotic disease threat in Europe and North America due to the increasing numbers of competent vector species present in those regions (Salman 2013).

RVF is endemic in much of Africa with occasional spread to countries in the Arabian Peninsula. Epidemics occur sporadically when climate conditions supports breeding of mosquitoes. Rift Valley Fever virus (RVFV) was first isolated from lambs in the Rift Valley of Kenya in the 1930s. Major outbreaks have been recorded in many parts of Africa since that time and the virus was first detected outside of the African continent in Saudi Arabia and Yemen in 2000. The first report of RVF outside of Africa was attributed to the importation of cattle and small ruminants from the Horn of Africa (Pepin et al. 2010).

Transmission of infection in cattle is mainly via the bites of infected mosquitoes. As an epidemic progresses, direct contact transmission by infectious animals or contaminated tissues including aborted fetuses may occur. Transmission via infected mosquitoes is important for the dissemination of RVFV between herds over short distances and also over long distances through movement of infected animals or translocation of infected mosquitoes (Abdo et al. 2011).

Disease, especially in young animals, may be severe and includes fever, depression and anorexia. The classic clinical sign of RVF in a herd of cattle is a large number of nearly simultaneous abortions among pregnant animals, regardless of the stage of pregnancy. This abortion storm differentiates RVF from other common infectious causes of abortion in cattle such as Q fever, chlamydiosis, brucellosis, salmonellosis, listeriosis or toxoplasmosis. RVF may also cause sudden death in cattle. Aborted fetal materials and placental membranes contain large numbers of virus particles, which can either contaminate the local environment directly or infect animals or humans in close contact. The RVFV may persist for relatively long periods in the environment.

Direct contact and aerosol exposure to infected tissues or bodily fluids constitutes the main route of infection for humans. Certain groups are at increased risk due to occupation such as herders, farmers, slaughterhouse workers and veterinarians. There is evidence for shedding of the virus into milk so that consumption of unpasteurized milk has major consequences for disease transmission and public health. Most human infections are inapparent or demonstrate mild flu-like symptoms (fever, headache, and myalgia). In some cases, infection progresses with severe complications including hemorrhagic fever, encephalitis, and acute hepatitis.

RVFV can be diagnosed by several different methods including virus isolation from blood and other tissues and by using serological tests such as ELISA.

There is presently no vaccine licensed for human use, though inactivated vaccines have been in development. Both live attenuated virus vaccines and inactivated virus vaccines are available for use in livestock. The live vaccine produces better immunity and requires only one dose, but may induce abortions and birth defects in pregnant animals. Inactivated vaccines require multiple doses in order to provide protection making their use problematic in endemic areas. In endemic areas sustained animal vaccination programs can help to prevent outbreaks.

In order to slow the expansion of RVF movement restrictions of livestock may prevent disease from entering new areas. Outbreaks of RVF in animals precede outbreaks in humans, so sustained surveillance and monitoring systems in animals

can act as an early warning system to public health authorities. Raising human awareness of protective measures for mosquito bites and safe handling practices during slaughter, appropriate barrier precautions and proper pasteurization of milk to prevent spread from animals may prevent human infection. Vector control, RVF forecasting and climatic models to predict when climate conditions are favorable for RVF outbreaks can also help to guide prevention efforts.

1.8.1 Salmonella

Salmonella is a major cause of foodborne disease globally. The global burden of zoonotic disease from *Salmonella* is high. An estimated 93.8 million illnesses and 155,000 deaths result each year from non-typhoidal *Salmonella,* the vast majority of which are foodborne (Majowicz et al. 2010). In the EU alone over 100,000 human cases are reported each year with an estimated overall economic burden as high a 3 billion € a year (EFSA 2013). *Salmonella* strains that are resistant to a range of antimicrobials have emerged since the 1990s and are now a serious public health concern (WHO 2013b). Salmonellosis has a worldwide distribution, but serovars vary geographically. *Salmonella* is most prevalent where livestock are farmed intensively (Spickler 2005).

Salmonella bacteria are classified into over 2500 different serovars based on surface proteins. *Salmonella* are shed in the feces of a wide variety of infected animals including cattle, which are infected by ingestion of contaminated feed, water or grass. The bacteria are hardy and can survive for months to years in the environment (Spickler 2005).

Transmission is generally through the fecal-oral route and humans generally contract salmonellosis through consumption of contaminated food including meat, eggs, poultry and unpasteurized milk products. Less often *Salmonella* is transmitted through green vegetables contaminated by manure. Person-to-person transmission through the fecal-oral route can also occur. Human cases may also occur through contact with infected livestock, which often do not show signs of disease. Most cases of salmonellosis in humans are mild, but can result in severe disease and death depending on host facts and the strain of *Salmonella*. Humans may develop diarrhea, abdominal cramping, and fever, which can be very severe.

Salmonella is often carried asymptomatically in cattle, but young, stressed or pregnant animals are the most susceptible to infection, which may result in enteritis and septicemia (Spickler 2005). *Salmonella* infection is diagnosed by isolating the organism from feces. In cases of disseminated disease bacteria can be isolated from the blood.

To reduce the risk of foodborne transmission basic food hygiene practices and adequate cooking should be used. To prevent transmission from animals to humans, hand hygiene after touching or working with animals is critical. To reduce the risk of *Salmonella* in cattle, herd management strategies and proactive biosecurity, rodent control and *Salmonella*-free feed and water sources should be utilized. Fecal

contamination of water supplies and feed should be prevented. Vaccines are available in some countries for some serovars and can reduce the level of colonization, shedding and clinical disease (Spickler 2005).

1.9 Summary

Zoonotic diseases originating from cattle can cause mild or asymptomatic human infection or severe disease and death. A number of zoonotic diseases were not covered in this chapter, but might be considered to varying degrees depending on geographic location and local circumstances, e.g., listeriosis, rabies, ringworm, and Human African Trypanosomiasis. While some diseases are rare, the potential for serious outcomes makes it critical for veterinarians and public health practitioners to provide outreach to those individuals at greatest risk including farmers—small scale and large.

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Chapter 2
Zoonotic Diseases of Swine: Food-borne and Occupational Aspects of Infection

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Abstract Swine and their products have become a central part of food systems around the world. Global pork production has rapidly increased over the past 30 years, leading to the intensification of the swine industry: though there are fewer farms now, those farms that do persist raise ever-larger numbers of animals. This increases the transmission of pathogens both amongst animal herds, and between animals and their human caretakers. Furthermore, increased stress to animals and the potential for amplification of pathogens in the farming environment can lead to a higher burden of disease-causing organisms in and on meat products, which then make their way to consumers world-wide. As such, swine and their meat products have the potential to introduce new zoonotic diseases into populations via multiple routes of transmission. Here we discuss several examples of zoonotic diseases of swine origin, reviewing diseases with bacterial, viral, or parasitic causes.

2.1 Background and Introduction

Pork is rapidly becoming the world's source of protein. Global pork production increased more than 80% between 1985 and 2010 (Fournie et al. 2012), and this trend has led to the intensification of swine husbandry, with fewer and fewer facilities present, but each raising larger numbers of individual animals. China has been a driver of this market, accounting for approximately 50% of total global pig production (Fournie et al. 2012). As swine production has intensified, so has concern over how these modifications in husbandry may affect the transmission of disease amongst pigs as well as to human caretakers. It has been estimated that more than 60% of emerging diseases are zoonotic (Jones et al. 2008). A recent review (Fournie et al. 2012) identified 77 pathogens that had not been described in swine prior to 1985, including 39 viruses and 32 bacterial species. Not surprisingly, the top 20% of pork-producing countries accounted for 82% of these emerging pathogens. Of these 77 novel species found to infect swine, 30 (39%) are zoonotic, and

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26% of these were identified in the context of an outbreak investigation (Fournie et al. 2012). Densely populated South East Asia is the epicenter of emergence of novel zoonotic diseases due to inter-species transmission. However, outbreaks of host specific lethal zoonoses have occurred in industrialized nations as well (Davies 2012). It is plausible that a dramatic change in swine industry demographics in recent decades without adequate biosecurity may have served as a tonic for the emergence of swine zoonosis (Davies 2012). Zoonotic diseases impose significant economic burden with increased morbidity and mortality globally. A change in ecological niche, climatic change, rapid growth in human population and socio-economic factors are among the major contributing factors for the emergence of zoonoses (Jones et al. 2008).

Outbreaks of human disease related to swine-origin pathogens, including *Streptococcus suis* in China (Lun et al. 2007), Nipah virus in Malaysia (Chua 2012) and the novel H1N1 variant influenza virus have gained significant media attention in the past decade. Here we discuss several examples of zoonotic diseases of swine origin, reviewing diseases with bacterial, viral, or parasitic causes.

2.1.1 Yersinia enterocolitica

Yersinia enterocolitica is a gram negative bacterium in the family *Enterobacteriaceae*. *Y. enterocolitica* is widely distributed throughout nature, having many animal and aquatic reservoirs; however, swine are considered the main reservoir for strains that are pathogenic to humans. It is the main causative agent of yersiniosis, a disease that affects animals and humans worldwide (Holt et al. 2000).

Yersinia enterocolitica can be classified into distinct subgroups based on biochemical characteristics (biotypes) and O-antigen specificity (serotypes). There are six biotypes (1A, 1B, 2, 3, 4, and 5) and 60 serotypes, 11 of which are associated with human illness (Nesbakken et al. 2006; Bottone 1997). Biotype 1B is considered the only highly pathogenic strain, while the others are considered moderately pathogenic, except for biotype 1A, which is considered nonpathogenic although this has recently become a contentious topic due to recent reports of 1A infections (Stephan et al. 2013). Biotype 1B is mainly found in North America and Japan and is different from other biotypes in that it can be found in water and other environmental sources, and can also be carried by swine and rodents. Biotypes 2 and 4 are associated with human infections in Europe; their main reservoirs are pigs and cattle. Biotypes 3 and 5 are uncommon, but are also associated with animal reservoirs (EFSA 2009; Fredriksson-Ahomaa et al. 2006a) .

Yersiniosis is a gastrointestinal disease causing fever and watery, occasionally bloody, diarrhea. Rarely, *Y. enterocolitica* can cause septicemia, and in some cases long-term sequelae can occur. Symptoms generally occur 4–7 days after exposure and may last for up to a month (Bottone 1997; Huovinen et al. 2010). Approximately 16.5 cases per 1,000,000 persons occur each year in Europe (EFSA 2009), while in the United States, approximately 3.5 cases per 1,000,000 are seen each year

(Long et al. 2010). Children are infected more frequently than adults, and infections occur most commonly in temperate locations during colder months (Bottone 1997).

Pigs are commonly asymptomatic carriers of pathogenic strains of *Y. enterocolitica*. The bacteria typically reside in the gastrointestinal tract, especially the tonsils, lymph nodes, intestines and feces (Fredriksson-Ahomaa et al. 2007; Bhaduri et al. 2005). Cattle and goats have also been found to be carriers (Lanada et al. 2005a, 2005b), and milk products from these animals have been the source of numerous outbreaks in human populations (Black et al. 1978; Shayegani et al. 1983; Morse et al. 1984; Tacket et al. 1984; Ackers et al. 2000). Deer, rabbits, rodents (Quan et al. 1974), dogs (Byun et al. 2011), and cats (Fredriksson-Ahomaa et al. 2001) have also been found to carry as well as to be infected with *Y. enterocolitica*. In addition to livestock, water sources including wells, rivers and lakes can serve as reservoirs for the bacteria as a result of contamination by feces of carriers or leakage from latrines.

The major risk factors for developing yersiniosis include eating raw or undercooked pork (Boqvist et al. 2009; Fredriksson-Ahomaa et al. 2006b), drinking contaminated milk (Black et al. 1978; Tacket et al. 1984; Ackers et al. 2000), and consuming contaminated drinking water (Thompson and Gravel 1986; Christensen 1979). Porcine sources are frequently associated with the pathogenic serotypes O:3, O:9, and O:5,27 and sometimes with the highly virulent serotype O:8. Outbreaks in 2006 in Norway were identified as biotype 2 and 4 and indicated a processed pork product to be the likely source (Grahek-Ogden et al. 2007; Stenstad et al. 2007). In the United States, raw pork intestines were found to be the source of an outbreak among infants (Lee et al. 1990; Jones 2003).. The occurrence of pathogenic *Y. enterocolitica* in pigs and pork has been established by PCR in several studies (Korte et al. 2003; Fredriksson-Ahomaa et al. 2003). The *ail* gene located within the genome of pathogenic *Y. enterocolitica* strains is the most frequently used target of amplification for positive identification. In Switzerland, the prevalence of *ail*-positive *Y. enterocolitica* in tonsils of slaughter pigs was shown to be 88 % by PCR and 34 % by culture methods (Fredriksson-Ahomaa et al. 2007). In the USA, *ail*-positive *Y. enterocolitica* were detected in 12 % of pig feces sampled by PCR, and in 4 % of them using culture methods. Similarly, 40 % of the pig lymph nodes were positive by PCR, but none by culturing (Boyapalle et al. 2001). These results indicate that PCR based assays are the most sensitive and accurate means to detect *Y. enterocolitica* colonization.

Clinical presentations of yersiniosis are typical of enteric illness. Infants and children often present with fever, vomiting, and bloody diarrhea that can last from 3–28 days (Metchock et al. 1991; Lee et al. 1991). Adults generally have one to two weeks of fever, diarrhea, and abdominal pain that can mimic appendicitis. In more severe cases of gastroenteritis, necrotizing enterocolitis and ulceration may occur. *Y. enterocolitica* can also cause septicemia, leading to abscesses in the liver and spleen, pneumonia, septic arthritis, meningitis, cellulitis, empyema, osteomyelitis, and may evolve into endocarditis. Post-infection sequelae may also occur, particularly after infections with biotype 4, serotype O:3 (Bottone 1999). Reactive arthritis and erythema nodosum are the most common sequelae, butglomerulonephritis and myocarditis have also been reported (Bottone 1997).

Yersiniosis is diagnosed by positive identification of *Y. enterocolitica* in stool samples, although it is not routinely tested for. It can also be recovered from the throat, lymph nodes, joint fluid, urine, bile, or blood. Most cases resolve on their own, although it may take up to 3 weeks to recover. In severe cases, antibiotics such as aminoglycosides, doxycycline, trimethoprim-sulfamethoxazole, or fluoroquinolones may be prescribed. Prevention is key in avoiding infection. Raw or undercooked pork and unpasteurized milk or milk products should be avoided, as should drinking untreated water. Good hand hygiene when preparing food and after contact with animals should also be practiced to avoid infection.

2.1.2 Staphylococcus aureus

Staphylococcus aureus is a nonmotile, nonspore-forming, Gram positive coccus that occurs singly, in pairs, or in clusters. *S. aureus* produces protein A (*spa*), which is used in molecular testing for strain typing purposes, as well as several other toxins and superantigens (De Vos et al. 2009).

S. aureus is often isolated from the nasal membranes and skin of warm-blooded animals. Approximately 20–30% of the human population is colonized with *S. aureus* in the nose, throat, or both (Smith et al. 2012; Gorwitz et al. 2008; Graham et al. 2006). The most important site for colonization is the anterior nares (Wertheim et al. 2005). Colonization itself is not harmful; however, it is a risk factor for developing subsequent infections (Graham et al. 2006; Fritz et al. 2009). Both asymptomatic carriers and infected individuals may transmit the bacterium to others through close contact. *S. aureus* may also be acquired via contact with fomites contaminated with the organism, as well as with animals that are colonized or infected with *S. aureus*.

Skin infections including furuncles, carbuncles, impetigo, and scalded skin syndrome, as well as more severe infections like pneumonia, osteomyelitis, endocarditis, myocarditis, pericarditis, enterocolitis, mastitis, cystitis, prostatitis, cervicitis, cerebritis, meningitis, bacteremia, toxic shock syndrome, and abscesses of muscles, skin, and organs can occur as a result of *S. aureus* infection.. Other mammals and birds are also susceptible to infections, including mastitis, synovitis, arthritis, endometritis, furuncles, suppurative dermatitis, pyemia and septicemia (De Vos et al. 2009). Pigs are common carriers of *S. aureus*; one study in the U.S. found overall MRSA prevalence was 70% (147/209) from seven farms in the Midwest (Smith et al. 2009). In the Netherlands, surveillance for MRSA on hog farms has shown that isolates obtained from swine and their human caretakers are frequently indistinguishable, suggesting that the organism is transmitted between the two species (Smith et al. 2009; Huijsdens et al. 2006; Khanna et al. 2007).

S. aureus infections are often resistant to many antibiotics. Approximately 1.5% of the U.S. population carries methicillin-resistant S. aureus (MRSA) (Gorwitz et al. 2008). Resistance to methicillin developed within 6 months of the first clinical use and has become a major cause of morbidity and mortality around the world. In the U.S. in 2011, there were 80,461 invasive MRSA infections, an incidence rate of 25.82 cases per 100,000 persons. Many animals, including cows, goats, sheep,

rabbits, and poultry, can be infected by S. aureus, and these infections can have large economic costs (Fitzgerald 2012).

The epidemiology of MRSA has changed rapidly in the past few decades. After developing resistance in the 1960s following methicillin introduction, MRSA became a superbug that primarily affected hospitalized patients. Due to association with the healthcare environment, these infections were called healthcare-associated MRSA (HA-MRSA). More recently, cases of MRSA infection have been detected in people without prior hospitalization and with no underlying illnesses or healthcare related risk factors; these are referred to as community-associated MRSA (CA-MRSA) infections. Cases of HA-MRSA are usually resistant to several classes of antibiotics and tend to carry the methicillin-resistance gene, *mecA*, on the Staphylococcal Chromosome Cassette (SCC) of type II (SCC*mec* type II). They are often associated with *spa* type t002 and multi-locus sequence type (MLST) ST5. Contrastingly, CA-MRSA infections tend to be resistant to fewer classes of antibiotics, carry the Panton-Valentine leukocidin (PVL) encoding gene, and carry SCC*mec* type IV, *spa* type t008, and MLST ST8. A third group of infections, livestock-associated MRSA (LA-MRSA), has recently been identified (Wulf and Voss 2008) and has typically been associated with swine or cattle. LA-MRSA include strains such as ST398 and ST9, often carry SCC*mec* type V, are typically PVL negative, and (like HA-MRSA) tend to be resistant to multiple classes of antibiotics. However, both CA-MRSA and LA-MRSA have caused nosocomial infections in hospitals (Jenkins et al. 2009; Fanoy et al. 2009; van Rijen et al. 2008, van Rijen et al. 2009; Wulf et al. 2008; Kourbatova et al. 2005; Seybold et al. 2006; Tattevin et al. 2009).

Livestock-associated MRSA first came to attention in 2005 after its identification in pigs in France (Armand-Lefevre et al. 2005) and in swine farmers in the Netherlands (Wulf and Voss 2008). Dutch researchers found that swine farmers were colonized with MRSA at a rate of 760 times higher than that of the general population (Voss et al. 2005). Since then, LA-MRSA has been found in a number of countries in Europe, Asia, and the Americas (Smith and Pearson 2011; Graveland et al. 2011; Fluit 2012).

Recent reports from Germany and the Netherlands have found a high proportion of ST398 carriage in areas that have a high density of livestock (Kock et al. 2009; Kock et al. 2011; Wulf et al. 2012). While originally thought not to cause severe infections, there have been increasing reports of invasive disease caused by ST398 (Hartmeyer et al. 2010; Mammina et al. 2010; Potel et al. 2010; Aspiroz et al. 2010). Methicillin-sensitive S. aureus(MSSA) ST398 isolates have also caused invasive disease in the eastern U.S. (Mediavilla et al. 2012), Europe (Witte et al. 2007; Declercq et al. 2008; van Belkum et al. 2008), South America (Jimenez et al. 2011) and Canada (Golding et al. 2010), and at least one death in France (Laurent 2009).

While the majority of individuals colonized or infected with LA-MRSA have had contact with swine, colonization with ST398 has also occurred in individuals lacking any identified contact with a livestock reservoir (Bhat et al. 2009; Aires-de-Sousa et al. 2006). It has been suggested that one mode of transmission into the community is via contaminated food. Numerous studies in the U.S. have found MRSA in 5% of 120 meat samples (Pu et al. 2008), MSSA in 16.4% and MRSA

in 1.2% of 125 meat samples (Hanson et al. 2011), MSSA in 64.8% and MRSA in 6.6% of 256 pork samples (O'Brien et al. 2012), and multi-drug resistant *S. aureus* in 52% of 136 meat and poultry samples (Waters et al. 2011). Additionally, two studies in the Netherlands found rates of 2.5% of 79 pork and beef samples (van Loo et al. 2007) and 11.9% of 2217 meat and poultry samples, respectively (de Boer et al. 2009). However, to date there have not been any confirmed infections with ST398 caused by contaminated food.

Most MRSA skin infections appear as pustules or boils which often are red, swollen, painful, and have pus or other drainage. They often are mistaken for spider or insect bites. These skin infections commonly occur at sites of visible skin trauma, such as cuts and abrasions, and areas of the body covered by hair. Health professionals may provide antibiotics and drainage if necessary to treat such infections. More severe infections may require hospitalization and intravenous antibiotic therapy. Good hygiene is the key to prevention of MRSA infections.

2.1.3 Salmonella

Salmonella is a genus of Gram-negative, rod shaped, non-spore forming enterobacteria with peritrichous flagella. Originally classified utilizing serotyping of the somatic lipopolysaccharide (O) and flagellar protein (H) antigens, each serological variant (serovar) was considered its own species under the *Salmonella* genus (White 1926; Kauffmann 1978) as reviewed in (Beltran et al. 1988). This methodology led to misclassifications due to horizontal transfer of cell surface antigens, leading to classification of genetically distinct strains within the same serovar (Beltran et al. 1988; Selander et al. 1990).

In 2005, the Judicial Commission of the International Committee for Systematics and Prokaryotes (JICSP) decided to change the type species of the *Salmonella* genus to *enterica* with subspecies and serovars (Prokaryotes JCotICoSo 2005). The JICSP indicated *Salmonella enterica* had seven subspecies, *enterica* (type I), *salamae* (type II), *arizonae* (type IIIa), *diarizonae* (type IVb), *bongori* (type V), *houtenae* (type IV), and *indica* (type VI). Subspecies *bongori* was shortly after promoted to species status (Grimont and Weill 2007). A third *Salmonella* species was approved by the JICSP in 2005, named *Salmonella subterranea* (Shelobolina et al. 2004), but this species may not fit within the genus *Salmonella* (Grimont and Weill 2007). *S. bongori* and all subspecies of *S. enterica* besides *S. enterica* subsp. *enterica* are associated mainly with cold-blooded animals (Aleksic et al. 1996; Woodward et al. 1997), (Aleksic et al. 1996; Woodward et al. 1997), but can rarely cause human infection (CDC 2008; CDC 2012). The primary cause of human infection is *S. enterica* subsp. *enterica* (CDC 2008), as referenced in (Desai et al. 2013).

The CDC defines salmonellosis as an infection with a *Salmonella* spp. bacterium. These infections can often manifest with diarrhea (potentially bloody), fever, and abdominal cramps between 12 and 72 h post infection (CDC 2009). The illness often lasts between 4 and 7 days and is usually self-limiting. *Salmonella* infection can necessitate hospitalization in a small number of individuals (Mead et al. 1999).

Each year, *Salmonella* spp. cause roughly 1.3 billion cases of nontyphoidal salmonellosis worldwide (Chimalizeni et al. 2010). Within the United States, there were an estimated 1.4 million cases in 1999, with 95% of these estimated to be caused by foodborne exposure to *Salmonella* (Mead et al. 1999). The burden on the United States economy from these estimated 1.4 million cases was estimated to be between $ 0.5 billion and $ 2.3 billion (Frenzen et al. 2002). These estimates are likely underestimates due to the omission of secondary complications due to *Salmonella* infections. The estimates fail to include complications such as reactive arthritisor costs such as pain and suffering, or travel to obtain medical care.

The most important zoonotic reservoir for *Salmonella* are food animals, with the most important food product being eggs (Ebel and Schlosser 2000). Egg consumption has been shown to be the largest risk factor associated with *Salmonella enterica* infection (Hope et al. 2002). Pork contamination is also a possible source of human infection.. In swine, *Salmonella* infection is mainly subclinical, with rare cases manifesting as enterocolitis or septicemia (Barker and Van Dreumel), as referenced in (Fosse et al. 2009). In the United States, the percentage of farms positive for *Salmonella* are estimated to range between 38.2 and 83% with the number of positive pigs in the US from 6 to 24.6% (Oosterom and Notermans 1983; Davies et al. 1997). Transmission from pig to pig is often due to fecal shedding of the bacteria. Within swine herds, sows were observed to have an increase in *Salmonella* shedding at weaning (Nollet et al. 2005) as well as in their weaned piglets (Kranker et al. 2003). While *Salmonella* is considered primarily fecal borne, swine feed has also been shown to be a potential source of *Salmonella* infection for swine (Harris et al. 1997) with experimental data showing animals may become infected through the consumption of contaminated feed (Smith 1960). Additional risk factors for transmission between herds of swine are: contact with humans, contaminated equipment, or contaminated slurry (Langvad et al. 2006).

Individual outbreaks of *Salmonella* spp. have also been attributed to pork products. In 1989, a small northern England town experienced an outbreak where 206 individuals were infected with serovar Typhimurium (Maguire et al. 1993). Serotyping and antibiotic resistance profiles matched the infective strain to that found in cold cuts of pork purchased from a local butcher shop. In a study by Davies et al., several of the most prevalent serotypes found in swine were also among the most common causes of human infection (Davies et al. 1997).

Attempts to control *Salmonella* spp. prevalence on farms have had mixed outcomes. The use of all-in/all-out systems with multiple sites handling different stages of the rearing process have been shown to have no benefit in reducing *Salmonella* prevalence when compared to farrow-to-finish systems (Davies et al. 1997). These all-in/all-out systems may actually have a greater prevalence of *Salmonella* in finishing pigs than farrow-to-finish systems and fecal shedding of *Salmonella* was higher than observed in farrow-to-finish (Davies et al. 1997). Number of pigs per pen was also observed to be a risk factor for fecal shedding of *Salmonella* (Linton et al. 1970). Acidification or fermentation of feed is postulated to be protective against *Salmonella* contamination as dry feed and trough feeding have been shown to have an increased contamination risk (Lo Fo Wong et al. 2004; van der Wolf

et al. 1999, van der Wolf et al. 2001), but this has not been studied extensively using experimental designs.

In North America, *Salmonella* control programs have been implemented at slaughter to decrease human exposure to *Salmonella* (Funk and Gebreyes 2004). This Pathogen Reduction: Hazard Analysis and Critical Control Point (HACCP) system established slaughter point performance standards for processing plants and has been shown to decrease contamination of pork products with *Salmonella* (Agriculture FSaISUDo 2004). In European Union countries, a farm-to-slaughter program has been implemented to reduce *Salmonella* (Lo Fo Wong et al. 2002). This plan calls for control measures at all production levels and focuses specifically on transportation and handling of the swine to limit the transmission between herds. In addition to prevention methods within the production system, consumer prevention is recommended by the CDC (CDC 2010). In addition to recommendations dealing with protecting infants from *Salmonella* exposure, the CDC suggests cooking meat and poultry thoroughly, washing hands, utensils, and kitchen surfaces following contact with raw meat or poultry.

2.1.4 Campylobacter

Campylobacter is a genus of gram-negative, spiral-spiral shaped bacteria that causes disease in both humans and animals (CDC 2010). *Campylobacter* is the most common cause of gastroenteritis in many developed (Nichols et al. 2012) and developing countries, causing more diarrhea than *Salmonella* globally (WHO 2011). In developing countries, infections of those under the age of two are most frequent (WHO 2011). While there are 17 species in the *Campylobacter* genus, *C. jejuni* and *C. coli* are the most frequent causes of infection (WHO 2011). Most cases are sporadic events and not part of outbreaks (CDC 2010). The main route of transmission from animals to humans is through undercooked meat and meat products, contaminated milk, or contaminated water (WHO 2011).

Disease in humans usually occurs two to five days after infection (WHO 2011) and presents with diarrhea, cramping, abdominal pain, and fever. Most infected individuals recover within five to ten days. In some severe cases, a small amount of people may develop Guillian-Barré syndrome. *Campylobacter* is thought to be responsible for between 20% (Tam et al. 2007) to 40% of cases of Guillian-Barré syndrome (CDC 2010). *Campylobacter* infections tend to be higher in males across all age groups, which suggests a higher susceptibility in males and not participation in at-risk behaviors (Nichols et al. 2012; Louis et al. 2005). In recent years, infections in those over 50 years of age have become more common, especially in men, as has infection in those between 20 and 32 years (Nichols et al. 2012). The increase in infections in those over 50 may be due to use of proton pump inhibitors (PPI's) (Nichols et al. 2012; Leonard et al. 2007). Seasonality of the infection has been noted, with the greatest impact of seasonality being in young children (Nichols et al. 2012). *Campylobacter* infections rates begin to rise in May and peak between

mid-June and mid-July (Nichols et al. 2012; Louis et al. 2005). This seasonality has been observed in many temperate countries (Nylen et al. 2002). Infection rates also tend to be higher in rural compared to urban regions (Strachan et al. 2009; Sibbald and Sharp 1985). This could be reflective of proximity to livestock or differences in access to healthcare (Nichols et al. 2012). Since 1989, there has been a steady increase in the presence of antimicrobial resistant *Campylobacter* isolates. Full and intermediate resistance to ampicillin, ciprofloxacin, nalidixic acid, tetracycline, and erythromycin has been shown (Nichols et al. 2012).

When swine are infected with *Campylobacter*, it is frequently *C. coli*, however, *C. jejuni* has been seen recently as well (Jensen et al. 2006). *Campylobacter* infections can cause diarrhea in pigs, and often colonizes the intestinal tract. Both *C. jejuni* and *C. coli* have been found in the intestinal tract of pigs and are known to be excreted in their feces (Jensen et al. 2006). *Campylobacter* has also been identified in the stomach, tonsils, liver, and carcass surfaces of swine. High colonization rates may represent an occupational health hazard, since a low dose of bacteria can cause infection (Nesbakken et al. 2003). Antimicrobial susceptibility to ciprofloxacin and nalidxic acid has been reported in swine strains. It has also been shown that *C. coli* has higher levels of quinolone resistance than *C. jejuni* in swine (von Altrock et al. 2013). However, it is unlikely that swine are a major source of foodborne *Campylobacteriosis*, as *Campylobacter* is rarely detected in retail pork, but may be a source of occupational exposure (Nesbakken et al. 2003). It has also been shown that while there is contamination of pigs in slaughter houses, *Campylobacter* spp. do not spread throughout the operation (von Altrock et al. 2013).

Campylobacter infections do not generally require treatment and are self-limiting (CDC 2010). When disease is severe, electrolyte and fluid replacement may be necessary. Antimicrobials (erythromycin, tetracycline, and quinolones) can be used to treat severe disease or to eliminate carriage (WHO 2011). Several steps can be taken to prevent *Campylobacter* infection. Proper food handling and hand hygiene can help prevent infection. All meats should be thoroughly cooked and measures should be taken to prevent cross contamination. Hands should be washed thoroughly before handling food and persons with diarrhea should wash their hands frequently to reduce the spread of infection (CDC 2010). Improved biosecurity measures and hygienic slaughtering practices will reduce the fecal contamination of carcasses (WHO 2011). Cooling meat with CO_2 has also been shown to kill the bacteria (Nesbakken et al. 2003). Adequate disposal of feces and decontamination of fecal contaminated articles will also help reduce transmission (WHO 2011).

2.1.5 Streptococcus suis

Streptococcus suis (*S. suis*) is a Gram-positive facultative anaerobe bacterium reported to colonize and cause infections primarily in the swine population worldwide (Fulde and Valentin-Weigand 2013; Wertheim et al. 2009). In conjunction with *Actinobacillus suis* and *Haemophilus parasuis*, *S. suis* completes the triad of the

"Suis-ide" disease agents given its association with a wide range of severe clinical conditions in the swine population (MacInnes and Desrosiers 1999). *S. suis* causes severe infections in pigs resulting in major economic losses to the porcine industry worldwide (Fittipaldi et al. 2012). Zoonotic infections due to *S. suis* have been reported in countries with a high density of pigs and intensive swine production (Lun et al. 2007; Wertheim et al. 2009). The increasing prevalence of infections due to *S. suis* both in swine and humans over the last few years have urged investigators to better understand the epidemiology and zoonotic potential of this primarily "pig pathogen".

S. suis isolates are verified by serotyping using slide agglutination test, capsular reaction, capillary precipitation or a co-agglutination test (Staats et al. 1997). Serotyping is based on polysaccharide capsular antigen detection. Thirty-five serotypes (1–34 and 1/2) have been identified using these tests (Lun et al. 2007; Higgins and Gottschalk 1990; Gottschalk et al. 1989, 1991a, b, 1999; Higgins et al. 1995). Serotypes 32 and 34 are observed to be closely related to *S. orisratti* (Hill et al. 2005). Serotype 2 is the most frequently reported serotype worldwide and is considered the most pathogenic both in pigs and humans. Other serotypes implicated in diseases are types 1–9 and 14 (Gottschalk et al. 2007).

Pigs colonized with *S. suis* typically harbor the organism in their tonsils and may never exhibit clinical signs or symptoms (carriers). Some carrier piglets eventually develop bacteremia, septicemia or meningitis due to dissemination of *S. suis* from tonsils and other mucosal surfaces (Fittipaldi et al. 2012; Staats et al. 1997). Disease syndromes in swine also include arthritis, pneumonia, endocarditis, encephalitis, polyserositis, abscesses and abortion (Wertheim et al. 2009). Death occurs within hours of the onset of clinical signs in pigs with peracute, i.e. very violent or acute forms of infection. Acute disease typically characterized by fever (up to 42 °C), depression, anorexia and lassitude may result in deaths, chronicity, or healthy carriers. In its chronic form, lameness and/or residual central nervous system signs may be apparent (Fulde and Valentin-Weigand 2013). Clinical manifestations of *S. suis* are observed to vary by geographical location (Wangkaew et al. 2006; Yu et al. 2006; Tang et al. 2006). There have been varying reports on the incubation period of *S. suis* ranging from 3 h to 14 days (Yu et al. 2006), and 60 h to 1 week (Mai et al. 2008). Short incubation periods are found to be consistent with direct entry of *S. suis* into the blood stream through skin wounds. There have been no consistent findings in seasonal variation of *S. suis* infection (Wangkaew et al. 2006; Mai et al. 2008; Huang et al. 2005).

S. suis infection is reported in domesticated pigs (Staats et al. 1997). In addition, the organism has been isolated from the intestinal flora of wild boars, dogs, cats, horses, deer and ruminants (Staats et al. 1997; Devriese et al. 1992; Baums et al. 2007; Devriese and Haesebrouck 1992). The rate of asymptomatic carriage in pigs is estimated to be around 80 %, representing a potential source of infection to other animals and humans (Lun et al. 2007; Staats et al. 1997; Arends et al. 1984; Ngo et al. 2011).. Pigs acquire *S. suis* via vertical and horizontal transmission as the sow is capable of harboring *S. suis* in the genital tract (Fulde and Valentin-Weigand 2013; Fittipaldi et al. 2012; Gottschalk 2011). Carrier rates are highest in

pigs between 4 and 10 weeks of age, but infection can occur at any age (Staats et al. 1997; Clifton-Hadley et al. 1984). Environmental contaminants such as feces, dust, water and feed are considered to be secondary sources of infection (Staats et al. 1997). Vectors such as houseflies (Fulde and Valentin-Weigand 2013; Staats et al. 1997; Enright et al. 1987) and mice (Fulde and Valentin-Weigand 2013; Staats et al. 1997; Williams et al. 1988) are also considered to play a role in disease transmission to pigs. Factors such as stress, crowding, poor ventilation, and concurrent disease could potentially predispose herds to an outbreak of *S. suis* infection (Fulde and Valentin-Weigand 2013; Staats et al. 1997). Morbidity rate in pigs ranges from 50%, rarely exceeding 5% (Wertheim et al. 2009). Nevertheless, research has demonstrated that morbidity due to *S. suis* is severely enhanced in the presence of other bacterial and viral infectious agents suggesting the importance of surveillance for *S. suis* (Staats et al. 1997).

Human *S. suis* infection is considered an emerging zoonosis (Lun et al. 2007; Wertheim et al. 2009). Studies observed that longer duration of exposure to pigs and pork affects *S. suis* carriage in the population (Elbers et al. 1999; Smith et al. 2008; Strangmann et al. 2002). Infection rate in individuals with high-risk exposures is estimated to be 1500 times higher than that of the general population (Lun et al. 2007; Arends and Zanen 1988). Pig farmers (Smith et al. 2008; Bartelink and van Kregten 1995; Breton et al. 1986; Sriskandan and Slater 2006; Fowler et al. 2013), abattoir-workers (Arends and Zanen 1988; Bartelink and van Kregten 1995; Breton et al. 1986), veterinarians (Elbers et al. 1999), hunters (Baums et al. 2007; Halaby et al. 2000) and meat-processing workers (Tramontana et al. 2008; Yu et al. 2005) are observed to have a higher risk of *S. suis* infection. Consumption of uncooked or partially cooked pork products is also considered a potential risk factor for *S. suis* infection (Wertheim et al. 2009; Wangsomboonsiri et al. 2008). A mortality rate of 17% was observed in the population and about 2/3 of deaths occurred in the first 24 h after admission (Wangsomboonsiri et al. 2008). Human infections are typically reported as sporadic cases with an exception of two large outbreaks resulting in 25 and 204 cases, and 14 and 38 deaths, respectively (Yu et al. 2006; Tang et al. 2006). Person-to-person transmission is unlikely to occur without very close contact such as with infected blood. Nevertheless, there is strong evidence of *S. suis* transmission from pigs to humans and a great potential for reverse zoonoses, i.e. transmission from humans to animals.

S. suis is sensitive to antibiotics such as penicillin, ampicillin, amoxicillin, ceftriaxone and cephalosporin (Lun et al. 2007). Clinical disease is known to be suppressed by fortifying feed with antibiotics at therapeutic levels (Staats et al. 1997). However, it does not eliminate carriers thus negatively impacting transmission of *S. suis*. One of the major drawbacks is the development of antimicrobial resistant *S. suis* isolated from both pigs and humans (Mai et al. 2008; Gottschalk et al. 1991c; Prieto et al. 1994; Aarestrup et al. 1998; Marie et al. 2002; Shneerson et al. 1980; Wisselink et al. 2006; Vela et al. 2005). Vaccines currently in use prevent outbreak in pig herds, but are observed to have varying efficacy (Lun et al. 2007; Haesebrouck et al. 2004). A human vaccine for *S. suis* is not available (Lun et al. 2007; Wertheim et al. 2009).

Prevention of *S. suis* transmission in both humans and pigs depends on control of contact with sick animals. Improving pig-raising and breeding conditions, and vaccination of pigs could ensure reduction in *S. suis* infection outbreaks and prevent transmission to humans (Lun et al. 2007). In addition, the potential risk of transmission via contact or consumption of contaminated pork products can be diminished by education and increasing awareness on preventative measures to eliminate this mode of transmission (Lun et al. 2007). World Health Organization (WHO) recommends cooking pork to an internal temperature of 70 °C or until juices appear clear rather than pink (Lun et al. 2007). Use of clean gloves and hand hygiene should also be encouraged when handling raw or undercooked pork products. Review of the current literature exposed a knowledge gap on differences in the virulence capacity and geographical variation of *S. suis* strains. Addition of this information to other available epidemiological data on *S. suis* is warranted to prevent further propagation and losses worldwide due to this pathogen.

2.1.6 Shiga-Toxin Producing Escherchia coli (STEC)

Escherchia coli, a short, rod shaped, Gram-negative, non-sporing, facultative anaerobic bacterium belongs to the family *Enterobacteriacae* (Sussman 1985; Mainil 2013). The gastro-intestinal tract of humans and other warm blooded animals are the primary hosts of this organism (Cheleste et al. 2002; Bell 2002). Although most *E. coli* strains are non-pathogenic, and part of normal microflora, some strains have evolved as pathogenic (Mainil 2013; Bell 2002, 2012). Pathogenic strains of *E. coli* acquire mobile virulence gene located on pathogenicity islands, integrated bacteriophages, or on plasmids (Bell 2002, 2011), and are able to cause wide spectrum of diseases in many species including pigs, cattle, rabbits and humans (Mainil 2013; Jay et al. 2007). On the basis of their virulence traits, pathogenic strains of *E.coli* are categorized into at least six groups: entero-pathogenic *E.coli* (EPEC), enterotoxigenic *E. coli* (ETEC), enteroinvasive *E. coli* (EIEC), entero-haemorrhagic *E. coli* (EHEC), entero-aggregative *E. coli* (EaggEC), and diffusely adherent *E. coli* (DAEC) (Bell 2002, 2012; Catalina Lopez-Saucedo et al. 2003) .

Shiga toxin-producing *E. coli* (STEC), also known as verotoxin-producing *E. coli* (VTEC) are a diverse group of pathogens that has become of significant health concern. These strains of *E. coli* are able to cause disease in both humans and animals. Although EHEC 0157:H7 is recognized as the most prominent STEC, over 200 non-O157:H7 STEC serotypes have been identified, and over 100 strains can cause disease in humans (Bell 2002; Josefa et al. 2005; Fratamico et al. 2004; Patricia and Griffin 1991). In the United States, most EHEC strains are serotype O157:H7 that accounts for 30–50 % of EHEC strains (Johnson and Sears 2006). Infection with non-O157:H7 serotype is more common in other nations including Australia, Argentina and many European countries, and may account for the majority of haemolytic uremic syndrome (HUS) infections in these countries (Fratamico et al. 2004). Serotypes 026, 045, 0103, 0111, 0121, and 0145 have been associated

with human disease and may account for approximately 70% of Non-O157:H7 STEC human infections in the United States (Wells et al. 2012). *E. coli* O157:H7 was first identified as pathogenic strain following two outbreaks of hemorrhagic colitis by consuming undercooked ground beef in 1982 in the United States (Josefa et al. 2005; Patricia and Griffin 1991; Pennington 2010; Beilei Ge et al. 2002; phillip Tarr and Chandler 2005). Since the discovery of *E. coli* O157:H7, large food-borne outbreaks and sporadic incidence have been documented in the United States and many parts of the world (Bell 2011; phillip Tarr and Chandler 2005; Tiiomas et al. 1995). Annually, EHEC O157:H7 and other serotypes of STEC accounts approximately 110,000 cases of illness in the United States (Cornick and Helgerson 2004).

STEC is a worldwide public health threat. Over 100 different serotypes can cause human illness (Acheson 1999). The exact global prevalence of STEC infection is unknown since there is no uniform surveillance and reporting system. Annually, an estimated 73,000 cases are caused by *E. coli* O157:H7 in the United States leading to estimated 2168 hospitalizations and 61 deaths (Josefa et al. 2005; Beilei Ge et al. 2002). Non-O157:H7 accounts for 37,740 cases and 30 deaths annually in the United States (Beilei Ge et al. 2002). Studies have indicated that STEC infection is more prevalent in the northern regions of the United States, and is more common in summer season (phillip Tarr and Chandler 2005; Tiiomas et al. 1995). *E. coli* O157:H7 can infect people of any age. However, children and elderly are more prone to develop severe illness and HUS compared to any other age groups (phillip Tarr and Chandler 2005; Bell 2011). Various studies have suggested that animals including cattle, sheep, goats and pigs are reservoirs for different STEC strains (Cheleste et al. 2002; Bell 2002; Fratamico et al. 2004). Although cattle are considered to be the primary reservoir of *E. coli* O157:H7, it is implicated in fecal shedding of other domestic livestock and wildlife (Jay et al. 2007). Evidence from epidemiological studies suggests that domestic pigs are potential reservoirs and biologically competent hosts of *E.coli* O157:H7 (Jay et al. 2007; Fratamico et al. 2004; Cornick and Helgerson 2004). In 2006, spinach associated outbreak of *E. coli* in the United States caused 205 cases of illness and six deaths. A successful isolation of the outbreak strain from feral swine living close to spinach field provides insight on swine-to-swine transmission and transmission between cattle and swine.. A study conducted by Jay et al. was able to recover related *E. coli* O157: H7 subtypes from feral swine, cattle, surface water, soil and sediment that were contaminated with spinach causing the outbreak (Jay et al. 2007). *E. coli* O157:H7-infected swine can shed the bacteria in feces for about two months thus serving as a reservoir host (Cornick and Helgerson 2004). Rios et al. isolated enterohemorrhagic STEC subgroup 026 and 0111 from the intestinal content of pigs. These strains had virulence genes (*stx1*, *stx2*) suggesting they were potential human pathogens (Fratamico et al. 2004; Maritza Rios et al. 1999). Fratamico et al. isolated STEC serogroup O2, O5, O7, O8, O9, O15, O65, O91, O101, O120, O121, O163, and several others from fecal samples of pigs (Fratamico et al. 2004). Other studies have indicated that STEC strains can be isolated from both healthy pigs and pigs with diarrhea and edema disease (Fratamico et al. 2004; Cornick and Helgerson 2004).

Various O, H, and K antigens of *E.coli* are identified (Kauffmann 1947). Virulent strains have gens for fimbriae, adhesions, and wide varieties of exotoxins that help pathogenic *E. coli* to colonize human tissues (Mainil 2013). *E. coli* O157:H7 produces a type III secretion system that injects two types of proteins which disrupt the cells metabolism and provide surface for attachment (Mainil 2013; Pennington 2010). Shiga toxin is the key virulence factor of STEC (Patricia and Griffin 1991; Werner Brunder and Helge 1997), and it causes necrosis of host cells and tissues (Pennington 2010). Although several virulence factors encoded by a 60-MDa plasmid such as a bifuctional catalase-peroxidase, secreted serine protease(EspP), α-hemolysin (EHEC-Hly), and chromosomally encoded enterotoxin EAST1 have been found, their role in pathogenicity still remains unclear (Cheleste et al. 2002; Werner Brunder and Helge 1997; Paul and Mead 1998). All *E. coli* belonging to STEC strains can produce Shiga toxin1 (*Stx1*) and/or Shiga toxin 2 (*Stx2*) or variants of *Stx1 or Stx2*. *Stx2e* variant strain of STEC cause edema disease in swine (Fratamico et al. 2004; Patricia and Griffin 1991).

The incubation period of STEC infection is 2–4 days, but may vary from 1–5 days (Acheson 1999). Many people infected with STEC remain asymptomatic (Pennington 2010); others suffer from mild to severe gastro-intestinal symptoms. STEC infection ranges from mild to life-threatening. Symptoms include watery diarrhea which can be bloody as the disease progresses), severe abdominal pain, low to mild-grade fever and nausea and vomiting. Fecal and peripheral leukocytosis is often present. Most people recover within 5–7 days of the onset of infection (Cheleste et al. 2002; Bell 2002; Patricia and Griffin 1991; Acheson 1999). Hemolytic uremic syndrome (HUS) is developed in 5–10 % of STEC cases (Acheson 1999). HUS is a serious complication characterized by hemolytic anemia, thrombocytopenia, fever, and kidney damage (Cheleste et al. 2002; Josefa et al. 2005; Acheson 1999; Frederick Koster et al. 1978). HUS often develops in children below age 5 as a complication of *E. coli* infection. HUS accounts 15 % of EHEC infection in children below 10 years old. HUS is seen as a complication in 6–9 % of overall infections (Bell 2002; phillip Tarr and Chandler 2005; Tiiomas et al. 1995). 5–10 % of HUS patient may die or develop further complications (stroke) (Cheleste et al. 2002). An estimated 50 % of HUS patients may have permanent kidney damage. Since patients with HUS are in risk of renal failure, they should be hospitalized (Cheleste et al. 2002; Acheson 1999).. The mortality of HUS is approximately 5 % (Acheson 1999), and the case fatality rate of HUS is approximately 10 % (Bell 2002).

The use of antibiotics could aid in Shiga toxin production thus exacerbating the disease; as such, this treatment is not recommended in the United States. Symptomatic treatment along with maintaining hydration is very important to prevent further complications. Prevention is the most important aspect of STEC infection (Acheson 1999; Paul and Mead 1998). Frequent hand-washing is the most effective tools to avoid person-to-person transmission. Proper handling of foods, preventing temperature abuse and cross-contamination of foods as well as maintaining a proper storage temperature is essential. Boiling water before drinking can help to stop waterborne transmission in developing countries where drinking water system is poor. The practice of using animal fecal as manure for crops used for human consumption

should be stopped. Foods should be cooked to the optimum temperature. Undercooked meat and unpasteurized milk should not be consumed (Bell 2002, 2012; Acheson 1999).

2.1.7 Japanese Encephalitis Virus (JEV)

Japanese encephalitis virus (JEV) belongs to the genus *Flavivirus*, family *Flaviviridae* (Weaver and Barrett 2004; Andrew et al. 2009; Solomon 2004). This virus was first isolated from a fatal human encephalitis case in Japan in 1935 (Weaver and Barrett 2004) and from *Culex tritaeniorhynchus* mosquitoes in 1938 (Andrew et al. 2009). This arbovirus (arthropod-transmitted) (Weaver and Barrett 2004; Igarashi 2002) is the leading cause of worldwide epidemics of viral encephalitis (Weaver and Barrett 2004; Tom Solomon et al. 2000). This single stranded positive sense RNA virus with a genome length of 11 kilobases (Weaver and Barrett 2004; Solomon 2004) consists of a spherical virion with a 30 nm core that is surrounded by a lipid envelop. The RNA genome of JEV encodes a single polypeptide that is cleaved into non-structural proteins such as NSI, 2A, 2B, 3, 4A, 4B, and 5, and structural capsid, member (M) and envelope (E) proteins (Tiroumourougane et al. 2002; Spickler 2007). The E protein plays vital antigenic role as it is important for viral attachment and entry into host cells (Solomon 2004; Mouhamadou Diagana and Dumas 2007). This virus has only one serotype and two subtypes, and is closely related to St. Louis encephalitis virus, Murray Valley encephalitis virus, West Nile virus, and dengue fever virus (Solomon 2004; Tiroumourougane et al. 2002; Spickler 2007). On the basis of nucleotide sequencing of the viral pre-membrane (prM), JEV can be categorized into four different genotypes. Moreover, the phylogenic analysis of the viral envelop 'E' gene has classified JEV strains into five genotypes (Health WOfA2009). A wide range of host species might be infected by JEV including cattle, snakes, birds, pigs, horses and other farm animals (Weaver and Barrett 2004; Andrew et al. 2009; Spickler 2007). High heat (56 °C for 30 min), acidic environment (pH 1–3) and various chemicals and disinfectants such as iodine, phenol, and formaldehyde also inactivate the virus. JEV is quite sensitive to ultraviolet light and gamma irradiation (Health WOfA 2009).

JEV is transmitted between wild and domestic birds and pigs by *Culex* species mosquitoes (Tom Solomon et al. 2000; van-den-Hurk et al. 2008). *Culex tritaeniorhynchus* plays a major role, because many animals such as horses, swine, humans, and birds are susceptible hosts. It is also the most important vector for human infections (Weaver and Barrett 2004; Tom Solomon et al. 2000). These mosquitoes particularly breed in pools of stagnant water, especially in flooded rice fields (Tom Solomon et al. 2000; Erlanger et al. 2009). JEV has also been isolated from other species of mosquitoes (Tiroumourougane et al. 2002). Ardeid or wading birds (herons and egrets) are considered as the primary maintenance hosts (Igarshi 2002; van-den-Hurk et al. 2008; Erlanger et al. 2009) and pigs are the main amplifying hosts (Weaver and Barrett 2004; Andrew et al. 2009; Tom Solomon et al. 2000;

Spickler 2007; van-den-Hurk et al. 2008; Erlanger et al. 2009) which are necessary for pre-epizootic amplification of the virus. Pigs can act as maintenance hosts in endemic regions (Andrew et al. 2009). Pigs in close proximity to humans are the most important natural hosts for transmission of JEV to humans (Weaver and Barrett 2004; Solomon 2004; Tom Solomon et al. 2000; Tiroumourougane et al. 2002). Pigs have a prolonged and high viraemia and a high natural infection rate of 98-100 % (Andrew et al. 2009). Domestic pig rearing aids in the transmission to humans (Erlanger et al. 2009). Humans and horses are dead-end or incidental hosts (Andrew et al. 2009; Tiroumourougane et al. 2002). Human-to-human transmission of JVE has not been reported yet (Tiroumourougane et al. 2002).

JEV remains the major cause of viral encephalitis in Southeast Asia (van-den-Hurk et al. 2008), but it is widely spread in eastern and south-eastern Asian countries, the Pacific Rim, and in Northern Australia. However, related neurotropic flaviviruses are found worldwide (Tom Solomon et al. 2000; Erlanger et al. 2009). Japanese encephalitis claims about 50,000 human cases and 15,000 deaths annually (Weaver and Barrett 2004; Tom Solomon et al. 2000). Due to lack of surveillance and inadequate data collection the actual incidence rate might be a lot higher. It is estimated that 175,000 cases of Japanese encephalitis occurs annually worldwide.. 11,000 cases and more than 2000 deaths resulted from JEV outbreaks in Nepal and Northern India between 2005 and 2007 (Andrew et al. 2009). Children under 15 years of age are mainly affected by JEV in endemic areas (Tiroumourougane et al. 2002). Pediatric encephalitis is caused by this virus in many Asian countries including India, Korea and China. More than one third of world populations are at risk of infection of JEV. The epidemiological patterns of JEV involve endemic and epidemic activities in tropical regions and temperate and subtropical areas, respectively. There is no seasonal pattern in endemic areas, but epidemic activity is observed in summer and autumn months in temperate and subtropical areas. Migratory birds help the virus to travel large distances (Weaver and Barrett 2004). Japanese encephalitis is mainly a disease of rural areas. It is endemic in tropical regions and often associated with irrigated rice agriculture (Andrew et al. 2009). The annual incidence of Japanese encephalitis is between 10–100 per 100,000 population in endemic areas (Tiroumourougane et al. 2002).

The incubation period of Japanese encephalitis in man is not exactly known. It varies from 1–6 days, and can be as long as 14 days (Tiroumourougane et al. 2002). Incubation period in horses is 8–10 days (Spickler 2007). Most infections of Japanese encephalitis are asymptomatic. Clinical features are developed only in 1 in 50 to 1 in 1000 infections. The clinical manifestations range from mild flu-like illness to severe and lethal meningoencephalomyelitis (Andrew et al. 2009; Tom Solomon et al. 2000). High grade of fever with or without rigors, headache, general malaise, and vomiting are present in the prodromal stage. It is followed by the encephalitis stage which is characterized by abnormal movements, muscular rigidity, neck stiffness, convulsions, altered neurological functions and other CNS signs (Tiroumourougane et al. 2002). Convulsion often occurs and it is reported in about 85 % of children and 10 % of adults (Tom Solomon et al. 2000). The recovery stage may be accompanied by signs of CNS injury. Thick, slow speech, aphasia and paresis