Australian Government
Department of Agriculture and Water Resources

AUSTRALIAN Pork

Reverse zoonoses affecting pigs, and the risk to Australian pig production
A critical review to direct risk assessment and management recommendations

Final Report
APL Project 2015/030

May 2016

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Acknowledgements

This project is supported by funding from Australian Pork Limited and the Department of Agriculture and Water Resources.

The authors wish to thank those pork producers, consultants, veterinarians and scientists who participated in the online survey to develop ranking metrics. Thanks also to Dr Mitchell Groves for expert input on *Streptococcus suis*, Dr David Jordan for comments and suggestions, Dr Amanda Ash for parasitological input and Dr Kim Nairn for input into recommendations.

Executive Summary

This project was commissioned by Australian Pork Limited (APL), to determine the greatest zooanthroponotic (reverse zoonotic or transmitted from humans to pigs) risks to the Australian pork industry, and to allow for development of recommendations based on the findings.

In order to ensure a balance between industry and academia, a multi-tiered approach was taken to the review and ranking process. Firstly, an extensive literature review was undertaken by the authors of this report, to determine those agents which had some basis in the scientific literature for consideration as zooanthroponotic agents. Secondly, the authors included a small number of organisms which, while not appearing in the literature as confirmed zooanthroponotic agents, none the less were considered as agents which should be assessed for risk. Finally, to determine the ranking of these agents, a semi-quantitative risk prioritization system was developed which relied upon evidence-based expert opinions combined with stakeholder input, in the form of an online survey, from 22 associated members of the Australian pork industry.

The review identified 22 agents with reverse zoonotic potential which could present some risk to the Australian pig production industry. Following development and dissemination of a detailed questionnaire, 22 responses from industry representatives were used to finalise a scoring matrix, and this was then used to rank the pathogens according to their score as outlined in Table 9.

The pathogen rankings and their potential impact on the industry are discussed in detail in the discussion/recommendations section. Briefly, the exotic viral agents Nipah, Reston ebola and SARS rank highly, however this is predominantly due to their high scores in terms of media coverage, public perception and slaughter out requirements – as such they are not considered high risk agents, however we have suggested some quarantine periods for people returning from overseas. Influenza A is the highest ranking virus seen as a true threat, and risk minimisation options including vaccination, education campaigns and surveillance are discussed. The enteric noroviruses and rotaviruses rank further down the list, however some surveillance may be considered to provide background information on current carriage rates and genotypes in Australian pigs.

Taenia solium is the highest ranking parasitic agent, and risk mitigation strategies for introduction of this could include education campaigns, adequate maintenance and positioning of human sewerage systems, and treatment of workers returning from endemic areas.

E. coli, MRSA, *Streptococcus suis* and *Salmonella* sp. rank highly amongst the agents. All have similar potential risks to the industry, and require similar education campaigns as discussed to minimise transmission. Details on potential surveillance programmes are outlined in the discussion.

The major pathways for entry of these pathogens into a herd are via farm workers, water supply and feed supply. A key, early measure which could be easily and rapidly adopted by industry would be an education campaign to be distributed on-farm, using the information in this review to outline to workers the risks of transmission of these organisms. Adequate sanitation of incoming water and high level personal hygiene when mixing feeds or working on feeders, are keys to minimising risk of transmission.

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1 Background to Research

The Australian pig industry is exposed to biosecurity risks associated with transfer of zoonotic diseases from humans to pigs. With increased international movements of people, including overseas workers returning to work in Australian piggeries following visits to their homeland, a review of risks associated with the transfer of diseases including *E. coli*, Salmonella, influenza virus, community acquired MRSA, *Streptococcus suis* and serotypes of *Clostridium difficile* (in addition to ST 078) from humans to pigs is required. This review will provide recommendations to producers, including revised biosecurity procedures and length of quarantine periods, in order to manage such risks.

2 Objectives of the Research Project

The objectives of this research are to:

1. Perform a comprehensive and critical review of the scientific literature addressing zooanthroponoses affecting swine.
2. Perform a qualitative risk analysis/assessment of zooanthroponotic organisms concentrating on likelihood and potential modes of entry into Australian pig production systems.
3. Provide a management document utilising the background information in objective 1 and the risk analysis in objective 2 to provide recommendations on management practices aimed at preventing zooanthroponotic infection in Australian pig herds.
4. Outline knowledge gaps both in Australia and internationally.

3 Introductory Technical Information

3.1 Literature search and filter method

A literature search in the Web of Science™ database was undertaken in November 2015. No language restriction was applied for the literature search, and the publication date was set to include documents from 1990-2015, encompassing literature published in the past 25 years. The following search string was used: ("zoonoses" OR "zoonosis" OR "reverse zoonoses" OR "zooanthroponoses") AND ("pig" OR "swine" OR "porcine"). A total of 227 references were retrieved, however it was apparent that the terms "reverse zoonoses" and "zooanthroponoses" are seldom used. Hence, we used the additional search string; ("human to pig" OR "human to swine" OR "human to porcine"), which retrieved another 55 results which were screened for duplications against references retrieved from the initial search string. Note that pathogens exotic to Australia were not excluded from the searches.

Overall a total of 247 references were initially retrieved and screened for relevance and conclusive evidence of disease transmission from humans to pigs. A batch of 85 references was originally considered relevant, based on the screening of the title and abstract. It was apparent that the majority of references excluded did not provide conclusive evidence of reverse transmission of a pathogen but may have provided some supporting evidence of a potential human-pig link. After reviewing these 85 references, a subset of papers (n=20) were selected in view of extracting information relevant to human to pig transmission. To this corpus some additional relevant references were added (n=7). Diseases/pathogens that were identified as most likely to present a reverse zoonotic risk (Tier 1) for the scope of this review are shown in Table 1. Table 2 outlines pathogens which were retrieved in the initial search and subsequently removed during the filtering process, which the authors considered had significant evidence and potential impact as reverse zoonoses to be included as a separate group for consideration (Tier 2). Table 3 outlines pathogens not returned in any searches but which the authors considered should be included in the risk analysis.

Table 1 Reverse zoonoses in pigs: Tier 1 agents

Pathogen	Base evidence of human to pigs transmission	Mode of transmission from humans to pigs	Mode of transmission from pigs to humans	References
VIRUSES				
Influenza A Viruses	Several outbreaks/pandemic in different countries	Droplets/Aerosol	Droplets/Aerosol	(1-3)
Hepatitis E virus (HEV)	Genetic relatedness and experimental evidence for cross-species infection	Direct/indirect contact; Faecal-oral	Direct/indirect contact Faecal-oral? food-borne?	(Meng et al., 1998; Renou et al., 2007)
Severe acute respiratory syndrome coronavirus (SARS-CoV)	Genetic relatedness	Unknown-Hypothesis; feed (leftover collected from restaurants) or indirect contact	Droplets/Aerosol	(Chen et al., 2005)
Norovirus	Genetic relatedness and experimental evidence for bi-	Faecal-oral	Faecal-oral	(Cheetham et al., 2006; Tian et al., 2007)

	directional transmission			
BACTERIA				
Methicillin-resistant *Staphylococcus aureus* (MRSA)	Genetic relatedness	Direct contact Aerosol	Direct contact Aerosol	(Morgan, 2008; Osadebe et al., 2012; Price et al., 2012)
Clostridium difficile	Experimental infection of conventional neonatal pigs; Genetic relatedness	Direct/indirect contact Faecal-oral	Direct/indirect contact Faecal-oral? food-borne?	(Debast et al., 2009; Lizer et al., 2013)
Brachyspira pilosicoli	Experimental infection of conventional newly weaned pigs	Faecal-oral Feed contamination	Faecal-oral	(Trott et al., 1996)
Mycobacterium ulcerans	Experimental infection model	Direct contact	Direct contact	(Bolz et al., 2014)
PARASITES				
Ascaris suum/lumbricoides	Experimental cross-transmission	Faecal-oral Feed contamination	Faecal-oral	(Peng et al., 2006; Starr and Montgomery, 2011)
Sarcocystis suihominis	Experimental infection	Faecal-oral Feed contamination	Faecal-oral	(Fayer et al., 1979)
Blactocystis hominis	Genetic relatedness	Faecal-oral Feed contamination	Faecal-oral	(Noel et al., 2005)
Cryptosporidia	Experimental infection	Faecal-oral Feed contamination	Faecal-oral	(Moon et al., 1982)

Table 2 Reverse zoonoses in pigs: Tier 2 agents

Pathogen	**Base evidence of human to pigs transmission**	**Mode of transmission from humans to pigs**	**Mode of transmission from pigs to humans**	**References**
VIRUSES				
Porcine calicivirus	Genetic relatedness to human sapovirus	Faecal-oral	Faecal oral	(Martella et al., 2008)
Reston ebolavirus	Detection in both species	Aerosol	Aerosol, sharps punctures during slaughter	(Marsh et al., 2011)
Rotavirus	Genetic relatedness	Faecal-oral	Faecal-oral	(Matthijnssens et al., 2008; Midgley et al., 2012)
Astrovirus	Genetic relatedness	Faecal-oral	Faecal-oral	(Xiao et al., 2012)
Nipah virus	Detection in both species	Unknown	Close contact	(Chua et al., 2000)
PARASITES				
Giardia duodenalis	Detection in both species	Faecal-oral, contaminated water	Faecal-oral	(Farzan et al., 2011)

Table 3 Reverse zoonoses in pigs: Author chosen agents

Pathogen	Base evidence of human to pigs transmission	Mode of transmission from humans to pigs	Mode of transmission from pigs to humans
BACTERIA			
Community acquired MRSA	Detection in both species	Direct contact Nasal and oral discharge Environment	Direct contact Nasal and oral discharge Environment
*Escherichia coli**	Detection in both species	Faecal-oral, Direct contact	Faecal-oral, Direct contact
Salmonella spp.	Detection in both species	Faecal-oral, Direct contact	Faecal-oral, Direct contact
Streptococcus suis	Detection in both species	Direct contact Nasal and oral discharge Environment	Direct contact Nasal and oral discharge Environment
PARASITES			
Taenia solium	Outbreaks in endemic areas	Faecal-oral	Ingestion of meat

*Resistant to critically important antimicrobials

3.2 Review of Tier 1 Agent References

Influenza A Viruses

There is a wealth of literature documenting the transmission of human influenza A viruses to swine and this is reviewed in some detail by Nelson and Vincent (2015). Of note is the detailed phylogenetic analysis of 1545 full length swine influenza A virus genomes, demonstrating twenty discrete introductions between 1965 and 2013, of human seasonal influenza A virus H3 and H1 subtypes into swine populations in North and South America, Europe and Asia (Nelson et al., 2014). This is further validated by a similar study in China, demonstrating at least three transmission events of H3N2 influenza from humans into swine between 1979 and 1992 (Zhu et al., 2015). Following the outbreak of human pandemic H1N1 influenza in 2009, the first documented case of human to swine transmission was reported in Canada (Howden et al., 2009), and since then, transmission events from human to swine with resultant disease outbreaks have been reported worldwide, including in Australia (Holyoake et al., 2011), in what has arguably become the most well documented reverse zoonoses affecting swine.

Hepatitis E Viruses

Hepatitis E virus (HEV) is a zoonotic agent (Renou et al., 2007) which exists as four genotypes (HEV 1-4). Genotypes 1 and 2 are predominantly carried by and transmitted between humans, while genotypes 3 and 4 are carried by swine but can also infect humans and a number of other species. The majority of epidemics are associated with contaminated water and faecal-oral transmission (Fields and Knipe, 2007). Experimental evidence exists that human isolates of HEV can infect swine, with intravenous inoculation of SPF pigs resulting in faecal excretion of the virus and seroconversion (Meng et al., 1998; Feagins et al., 2008). It should be noted however, that in the Meng et al (1998) study the human and swine strains used differed extensively from other strains of HEV and may not reflect the reverse zoonotic potential of other HEV strains. Serological evidence exists for the presence of HEV in Australian pig herds (Chandler et al., 1999), however seropositive results in human patients have predominantly been due to travel to or migration from HEV endemic countries and don't provide evidence for the virus being endemic in the Australian population (Cowie et al., 2005).

Severe Acute Respiratory Syndrome (SARS) coronavirus

There is only a single piece of literature linking SARS coronavirus infection of pigs to a human isolate of the virus. Genetic analysis suggested that the isolate obtained from the infected pig is of human origin, however the evidence for reverse zoonotic transmission is tenuous as the only person in contact with the pigs did not develop anti-SARS antibodies, leading the authors to speculate that virus contaminated feed was the cause of infection (Chen et al., 2005). It has been demonstrated in an experimental model that SARS coronavirus can infect pigs, with detectable genetic material in blood and seroconversion in infected pigs (Weingartl et al., 2004). Sampling in Chinese wet markets, a documented reservoir of SARS coronavirus, only detected viral RNA in the faeces of 1/12 wild boars (Shi and Hu, 2008), indicating, albeit with low confidence given the small sample size, that this virus does not readily infect or spread amongst swine.

Norovirus

Human noroviruses are recognised as the leading cause of gastrointestinal tract (GIT) disease in humans (Glass et al., 2009). Experimental evidence exists which demonstrates the binding of norovirus-like particles to histo-blood group antigens (HBGAs) expressed on the epithelial cells of porcine GIT tissue, proving that porcine GIT tissue expresses similar binding sites to human GIT tissue, and is therefore susceptible to human norovirus infection (Tian et al., 2007). In a more direct model, infection of gnotobiotic pigs with genogroup II human norovirus resulted in clinical GIT disease in 74% of inoculated pigs, with detectable faecal shedding of the virus. It appears that human norovirus infection of pigs is likely to be self-limiting, diarrhoea was of short duration (1-3 days) and only a single pig had mild histological changes in the duodenum (Cheetham et al., 2006). Sampling of swine faecal samples from 10 Canadian farms found 25% of individual samples to be norovirus positive by PCR (n=30) of which four samples belonged to the human GII.4 cluster, indicating natural transmission of human isolates to swine (Mattison et al., 2007).

Methicillin-Resistant *Staphylococcus aureus* (MRSA)

Studies have shown MRSA colonisation of swine farmers to be at a higher rate than the general population (Voss et al., 2005), and as such, swine production systems and livestock systems in general have been implicated in the spread of MRSA, despite strains of MRSA differing in their pathogenic potential between species. MRSA typing studies on swine and farm workers on varying production systems in the United States has revealed evidence of human-to-swine transmission of MRSA and zoonotic transmission. *Staphylococcus aureus* isolates were typed based on pulsed field gel electrophoresis and Staphylococcal Protein A gene typing, and on one farm, a human and pig shared the same hospital-associated strain of MRSA (t007, USA200), indicating a reverse zoonotic event (Osadebe et al., 2012). MRSA lineage clonal complex 398 (CC398) was described in 2005 (Armand-Lefevre, Ruimy and Andremont, 2005), and has become a leading cause of human infection, perceived as being associated and harboured by livestock. Detailed whole genome sequencing suggests that this lineage actually originated from a methicillin sensitive human isolate, which was transferred into pigs via one or more reverse-zoonotic events and subsequently acquired resistance genes before being transferred back into the human population (Price et al., 2012).

Clostridium difficile

An investigation into chronic gastrointestinal disease in neonatal pigs on two Dutch farms isolated a *C. difficile* ribotype 078 from both farms (Debast et al., 2009). This study showed a 39 base pair deletion in the *tcdC* gene of the isolates which had not earlier been reported in swine, along with the presence of toxin producing genes and antimicrobial resistance profiles, all of which had been identified in

isolates from Dutch hospital patients, indicating a possible reverse zoonotic transmission of a human strain to swine. Interestingly, ribotype 078 comprised the majority of swine and cattle isolates in the United States (Keel et al., 2007), but was not isolated in a recent study of 21 Australian pig farms (Knight, Squire and Riley, 2014).

Brachyspira pilosicoli

Weaner pigs can be infected with human isolates of *B. pilosicoli*, with development of clinical signs and gross and histological lesions in the caecum and colon. While this clearly demonstrates pigs are susceptible to human strains of *B. pilosicoli*, it should be noted that only 2/12 challenged pigs developed significant diarrhoea and histological changes, and no significant deleterious effect on weight gain (Trott et al., 1996). Since this organism has been used in pigs just as an experimental agent and this agent is not been associated as a reverse zoonotic agent this bacterium is not discussed further.

Mycobacterium ulcerans

M. ulcerans is the causative agent of Buruli ulcer, an atypical ulcerative disease of humans worldwide, including Australia where it was first discovered (Yotsu et al., 2012). Clinical (nodules plaques and ulcers) and histological signs (necrotic cores and distribution of acid fast bacilli dependant on timecourse) consistent with human Buruli ulcer could be induced by direct inoculation of *M. ulcerans* into the skin of SPF pigs at doses of $2x10^6 – 2x10^7$ colony forming units (Bolz et al., 2014). Since this organism has been used in pigs only as an experimental agent and this agent is not been associated as a reverse zoonotic agent this bacteria is not discussed further.

Ascaris suum/lumbricoides

Despite being referred to as separate species, detailed molecular analysis presents compelling evidence that *A suum* and *A lumbricoides* are the same species (Leles et al., 2012) or variants of the same species (Cavallero et al., 2013). A large scale study on global human and swine ascarid infections demonstrated historic transmission of *Ascaris* from humans to swine in Africa (Betson et al., 2014), however a direct infection study failed to establish infection in swine using a human isolate (Peng et al., 2006). While the prevalence of ascarid infections in the human population is high in developing countries, recent studies in developed nations are rare (Starr and Montgomery, 2011). Given the conflicting evidence on the reverse zoonotic potential, it would be remiss to rule out *A. suum* and *A. lumbricoides* as agents for consideration.

Sarcocystis suihominis

Sarcocystis suihominis is an intracellular protozoan parasite species for which humans are the definitive host and pigs are one of multiple potential intermediate hosts (Fayer, 2004). Sporocysts are shed in the faeces of human hosts, and can be ingested by swine, resulting in development of schizonts in the endothelial cells of blood vessels, and intramuscular cysts (Fayer et al., 1979).

Blastocystis

B. hominis is considered a cause of human gastrointestinal disease. *Blastocystis* isolates from animals are not designated as *B. hominis* but rather *B.* sp, however they are not able to be differentiated on light or electron microscopy and require molecular differentiation. Sequencing of the SSU ribosomal RNA from multiple *Blastocystis* isolates grouped them into seven major groups. It is hypothesised that Group III is a genotype of human origin, and that swine isolates falling within this group may be evidence of human-to-swine transmission events (Moon et al., 1982).

Cryptosporidia

Pigs inoculated via the oral route with a human cryptosporidium isolate (species unidentified), developed diarrhoea, faecal shedding of the organism and characteristic histological signs including atrophied, dysmorphic ileal villi and infection of the ileal, caecal and colonic mucosa (Moon et al., 1982).

3.3 Review of Tier 2 Agent References

Porcine calicivirus (human sapovirus)

Sapoviruses are enteric viruses of the family *Caliciviridae* which cause diarrhoeal disease in host species including humans (genogroups I, II, IV and V) and pigs (genogroup III and VI-X) (Farkas et al., 2004) (Reuter et al., 2009). Examination of the capsid and RNA-dependent RNA polymerase coding regions of porcine enteric caliciviruses has revealed multiple genotypes some of which display higher similarity to human sapovirus isolates than to porcine isolates (Wang et al., 2005). In addition to this, potential recombination sites have been identified between porcine and human strains, indicating that reverse zoonotic transmission could occur, resulting in new genotypes of virus developing in the swine host (Martella et al., 2008; Wang et al., 2005).

Reston ebolavirus

The filovirus *Reston ebolavirus* is genetically related to the highly pathogenic *Zaire ebolavirus* and *Sudan ebolavirus*, but has never been determined to cause clinical disease in humans, despite documented seroconversion events (Miranda et al., 1999; CDC, 1990). While the virus was detected in pigs in the Philippines during investigation into widespread respiratory disease (Barrette et al., 2009), controlled studies at CSIRO AAHL in Geelong have demonstrated that *Reston ebolavirus* can infect pigs subclinically, and it is hypothesised that disease expression may be due to the interaction of multiple infectious agents (Marsh et al., 2011). Given the silent nature of infection in both humans and swine, there is potential for undetected interspecies transmission events to occur.

Rotavirus

Group A rotavirus strains infecting humans and animals are currently classified according to the combination of VP7 (G) and VP4 (P) surface proteins expressed on the viral capsid. As such, various combinations of G and P types are common. Genotyping studies have shown that European swine rotavirus strains cluster closely with human strains (Midgley et al., 2012) and a particular human strain [WA (G1P1A)] has a close genetic relationship with porcine strains (Matthijnssens et al., 2008) which is indicative of a common strain being the origin of both. Neonatal gnotobiotic pigs have been successfully infected with the Wa strain of human rotavirus, resulting in diarrhoea, viral shedding and seroconversion (To et al., 1998). Taken together these results suggest reverse zoonotic transmission of rotaviruses may occur, with recombination events leading to the development of novel viral strains.

Astrovirus

Human astrovirus was originally isolated from the faeces of a child with diarrhoea (Madeley and Cosgrove, 1975) and astroviruses have been isolated from the faeces of piglets with diarrhoeal disease (Indik et al., 2006) (Bridger, 1980), as well as from healthy pigs (Shan et al., 2011). Porcine astrovirus is present as five types, and all five are present in the United States. Phylogenetic analysis groups porcine astrovirus types I and III with human astrovirus isolates (Xiao et al., 2012), indicating the occurrence of cross-species transmission.

Nipah virus

Nipah virus lies within the *Henipavirus* genus of the *Paramyxoviridae* along with *Hendra virus*, and is a cause of severe respiratory disease in pigs and encephalitis in humans (Chua et al., 2000). Despite evidence existing for zoonotic transmission of the virus, there has been no examination of a reverse zoonotic aspect. The majority of viral antigen is present in the central nervous system of infected humans, which fits with a classic encephalitic disease, however a significant proportion of cases show viral antigen within blood vessels of the respiratory system (Wong et al., 2002), providing evidence of a possible route of transmission from humans to swine.

Giardia duodenalis

The presence of *Giardia duodenalis* in swine, the only giardial species known to infect humans, livestock and companion animals (Xiao and Fayer, 2008) , has been reported worldwide including in Australia (Armson et al., 2009) and usually from clinically normal pigs. A Canadian study examining pooled faecal samples from ten farms found more than 50% of samples to be positive by PCR for *G duodenalis*. There are seven assemblages of *G duodenalis* (A-G), and the majority of positive samples in the Canadian study were Assemblage B, a predominantly human assemblage, indicating possible reverse zoonotic transmission of *G duodenalis* to swine (Farzan et al., 2011).

3.4 Pathogen/Disease Summaries

3.4.1 Influenza A Viruses

Agent

Influenza A viruses are enveloped viruses with a single-stranded, negative sense, segmented RNA genome and are part of the *Orthomyxoviridae* family (King AMQ, 2012). The segmented genome allows for recombination to occur when multiple viruses infect the same cell, allowing for the production of novel viruses via gene swapping, while the high mutation rate allows for small changes or drifts in the antigenicity of the virus. The genome codes for eight viral proteins, of which the haemagglutinin (H) and neuraminidase (N) are involved in target cell binding and immune response, and are used to denote the subtype. Currently there are 16 H subtypes and 9 N subtypes identified from avian species, the reservoir hosts of influenza A, although recently novel H and N subtypes have been found in bat species (Mehle, 2014). Influenza viruses generally infect or adapt to one species, however interspecies transmission such as avian to human (Dinh et al., 2006) and human to swine (Nelson and Vincent, 2015) does occur, and can result in the adaptation of the strain to the new host species. While classical, swine-adapted viruses circulate in endemic regions, it is evident that human seasonal influenza viruses often infect swine populations (Nelson et al., 2014).

The development of current classical swine influenza strains is convoluted and involves recombination of influenza viruses from multiple species, although at the simplest level, the subtypes circulating in the US and Europe are H1N1, H1N2, and H3N2. Influenza in swine was first recognised in the United States in 1918 and the classical swine H1N1 evolving from this was stable until the late 1990's. In 1998, investigation of respiratory disease in swine herds in four US states isolated H3N2 subtype viruses, three of which contained genes from human H3N2, swine H1N1 and avian influenza viruses (Zhou et al., 1999) and which became established in the swine population. This genome composition is referred to as the triple reassortant internal gene (TRIG) cassette (Vincent et al., 2008) and the majority of contemporary H1 influenza viruses in the US contain this cassette (Lorusso et al., 2010). A similar evolution of viral strains has occurred in Europe over time, although the progenitor strains were

Eurasian in origin, leading to the presence of an internal gene cassette, and circulating Eurasian avian-like H1N1, human-like H1N2 and H3N2 viruses in swine populations (Kyriakis et al., 2011). The emergence of a new highly transmissible H1N1 strain of virus occurred in humans in 2009, and was found to contain a previously unrecognised assortment of genes with six gene segments descending from the TRIG influenza A viruses of swine US lineage and two genes derived from the Eurasian swine lineage (Emergence of a Novel Swine-Origin Influenza A (H1N1) Virus in Humans, 2009). Due to the origin of the gene segments, the viral strain was given the misnomer 'swine flu', despite never before being recognised in swine, and was subsequently reported worldwide in swine and human populations. This strain is correctly termed pandemic H1N1 influenza 2009 (A(H1N1)pdm09).

Disease in Humans

Seasonal influenza A virus infection of humans is a well-documented disease spread via aerosols or fomites (Tellier, 2006), resulting in varying non-specific clinical signs dependent on severity including high fever, cough, headache, myalgia, arthralgia, severe malaise, runny nose and occasionally diarrhoea. Following infection, the incubation period is between 1 and 7 days (generally 1-4) (Punpanich and Chotpitayasunondh, 2012) (Cao et al., 2009). Viral shedding usually begins 1-2 days before the onset of symptoms, peaks with the onset of clinical signs and rapidly drops over the course of 5-7 days (Lau et al., 2010), although shedding up to 28 days has been reported for A(H1N1)pdm09 infection (Fleury et al., 2009). While some studies suggest approximately one third of infections are asymptomatic (Carrat et al., 2008), high risk groups including the elderly, young children and those with co-morbidities are at risk of developing fatal disease as a result of infection (Schanzer, Langley and Tam, 2008).

Disease in Swine

Swine influenza A infections occur as epizootics, when a strain enters previously unexposed herd, or enzootics, when strains continuously circulate at low levels. Epizootic infections in swine generally present in a similar manner to human infections, with respiratory disease characterized by fever, lethargy, coughing, dyspnoea and sometimes nasal or ocular discharge. The duration of illness is 3 to 7 days and progresses rapidly through a production unit. Enzootic infections in herds often result in circulation with much lower numbers of affected pigs than the epizootic form. Despite the high morbidity, the mortality rate of swine influenza A virus infection is low and the majority of issues relate to decreased weight gain, occasional reduced reproductive performance (likely due to fever and lethargy in sows and gilts) and possible co-infection with other respiratory disease causing agents (Zimmerman, 2012).

Transmission

The transmission of influenza viruses between humans is by either direct contact, inhalation of aerosols or contact with fomites (Tellier, 2006). While large numbers of aerosol particles are generated by sneezing and coughing (Nicas, Nazaroff and Hubbard, 2005), influenza viral RNA has also been demonstrated in the exhaled air of a patient during normal breathing, suggesting standard tidal breathing can result in expulsion of infectious virus (Fabian et al., 2008). Orthomyxoviruses are enveloped, the surface H and N proteins are crucial for cellular attachment and release, and as such their infectivity is reliant on the presence of a functional envelope, making them relatively fragile. Seasonal influenza virus demonstrates a strong seasonal cycle in temperate regions, with the Australian influenza season typically occurring during the winter period. A recent study indicates there are two zones during which influenza epidemics occur, a cold-dry zone, into which the Australian winter fits, and a humid-rainy zone, into which some tropical regions that have a broader influenza season sit

(Tamerius et al., 2013). While this is likely due to a number of interacting factors, lower levels of ambient ultraviolet light and temperature, increased levels of which adversely affect virus survival, are probable causes (Zou et al., 2013; Sagripanti and Lytle, 2007).

Historical outbreaks of swine influenza A virus generally followed a seasonal pattern, as was the case with the introduction and spread of A(H1N1)pdm09 in the Australian influenza season of 2009 (Holyoake et al., 2011), however it has been shown that in Europe, this pattern may not be followed with circulating virus existing year-round (Kyriakis et al., 2011). In addition to this, seasonality may be less common in intensive, confined production systems. While swine influenza is most commonly introduced into herds via infected animals, it may also occur through exposure to an infected human (Holyoake et al., 2011). The virus can be transmitted within the herd by pig-to pig contact, or by aerosol exposure, with high levels of viral RNA detectable in air samples taken from inside and around the buildings of naturally infected swine farms (Corzo et al., 2013).

Prevention and Control

The prevention and control of seasonal influenza viruses in the human population is based primarily on the use of annual vaccines for the northern and southern hemispheres, the composition of which is determined by the World Health Organisation. In addition to this segregation of sick individuals in the home during the period of viral shedding, and simple procedures such as regular hand washing, are also recommended (Grayson et al., 2009).

In countries with endemic swine influenza, vaccination is often used as a method of control. An economical method is to vaccinate sows and gilts pre-farrow, such that protection in the form of maternal antibodies targeting the vaccine strain of virus are transferred in the colostrum to suckling piglets in the first 36 hours of life. In contrast to the process for selecting influenza strains to be included in the annual human influenza vaccine, the production of influenza vaccines for sows is at the discretion of the commercial company. In addition to this, surveillance and typing of swine isolates is undertaken on a much smaller scale, such that information to guide production of the most appropriate vaccine strain may be lacking. While it has been shown that vaccines can provide complete protection against infection with an antigenically matching strain of virus (Bikour et al., 1996), most will reduce clinical signs and rate of virus shedding in infected animals, minimising, but not completely blocking virus transmission (Kyriakis et al., 2010). In some cases, usually when commercially available vaccines fail due to antigenic drift of circulating viruses, autogenous vaccines may be used, whereby the strain of virus circulating on the farm is used as the seed strain for vaccine manufacture. Autogenous vaccines are usually only permitted to be used in the herd of origin, and strict regulatory requirements exist for production and use (Draayer, 2004).

Aside from vaccination, closed herd systems, all-in-all-out systems with disinfection regimes, quarantine of any replacement stock prior to introduction to the herd and on-farm biosecurity protocols are all utilised in control and prevention of influenza (Torremorell et al., 2009).

3.4.2 Hepatitis E Virus

Agent

Hepatitis E viruses (HEV) were initially classified as caliciviruses, but are now within the family *Hepeviridae*, genus *Hepevirus*. They are non-enveloped, positive sense, single-stranded RNA viruses (King AMQ, 2012). The current classification of HEV genotypes is still in a state of flux, however for

the purposes of this review the focus will be on genotypes 1-4, with HEV1 and HEV2 infecting humans only, and HEV3 andHEV4 infecting humans, swine and a number of other animal species (Lu, Li and Hagedorn, 2005).

Disease in Humans

Hepatitis E infection can range from subclinical to acute viral hepatitis, and occasionally chronic viral hepatitis with liver failure. The incubation period is variable, ranging from two to ten weeks, although symptoms of acute viral hepatitis commonly present 5-6 weeks post-infection as anorexia, abdominal pain, nausea and icterus. Biochemistry testing will demonstrate elevated liver enzymes similar to other hepatotropic viral infections (Aggarwal, 2011). While most cases will resolve spontaneously, some progress to fulminant liver failure. Chronic HEV infection tends to be associated with immunosuppression such as following organ transplants (Haagsma et al., 2008) or concurrent viral infections (Dalton et al., 2009) and may lead to liver fibrosis and cirrhosis. Hepatitis E appears to have a higher incidence in pregnant women in endemic countries, with more severe maternal perinatal disease and poorer foetal/neonatal outcomes (Kumar et al., 2004).

Disease in Swine

HEV 3 and HEV 4 infections of swine are asymptomatic, although viral hepatitis may be detectable upon histological examination of livers from infected animals (Meng et al., 1997).

Transmission

Hepatitis E in humans is predominantly transmitted via the faecal-oral route, with outbreaks of HEV1 and HEV2 occurring in endemic regions via contaminated water supply due to poor sanitation (Hyams, 2002), rather than via direct person-to-person transmission. These genotypes occur primarily in developing regions of Asia and Africa, and are loosely geographically associated. In non-endemic regions, sporadic occurrences of HEV in humans are usually related to HEV3 or HEV4, and are thought to be zoonotic in origin, associated with contact with infected animals or the consumption of inadequately cooked pork products (Lewis, Wichmann and Duizer, 2009). It should be noted that transmission can occur in some cases via vertical transmission, or blood transfusions (Hewitt et al., 2014).

Swine hepatitis E virus (HEV3) is present in pig herds worldwide (Pavio, Meng and Doceul, 2015) including Australia (Chandler et al., 1999) and transmission in swine is also via the faecal-oral route. Serological studies indicate that most pigs are infected at around 2-3 months of age, coinciding with the decay of maternal antibodies, and shed virus in the faeces for 3-7 weeks (Meng et al., 1997).

Prevention and Control

Currently, prevention and control measures are not undertaken in swine due to the lack of a vaccine, and the innocuous nature of the agent in swine. In areas where endemic HEV occurs in the human population, prevention is based on improving or maintaining drinking water supplies and sewerage systems, along with personal hygiene. Current recommendations for preventing transmission of HEV, particularly HEV3, from foods containing swine liver are to thoroughly cook liver products, with studies showing that cooking products to an internal temperature of 71°C inactivates the virus, while heating to 56°C for one hour does not (Feagins et al., 2008).

3.4.3 Severe acute respiratory syndrome coronavirus (SARS-CoV)

Agent

SARS-CoV is an enveloped positive sense single stranded RNA virus of approximately 30,000 nucleotides. It is classified as an alphacoronavirus, and sits within this genus along with the porcine pathogens, *Porcine epidemic diarrhoea virus*, *Transmissible gastroenteritis virus* and *Porcine respiratory coronavirus* (King AMQ, 2012; Lin et al., 2015). Despite being enveloped it is relatively stable and can survive for 4 days in diarrheal stool samples with an alkaline pH, and it can remain infectious in respiratory specimens for over 7 days at room temperature (Lai, Cheng and Lim, 2005).

Disease in Humans

The incubation period for SARS-CoV ranges from 2 to 16 days, and symptoms include fever, chills, myalgia, cough, headache and dizziness. Less common symptoms include GIT signs, sputum production and sore throats. A large proportion of cases demonstrate lung changes on radiography ranging from bronchopneumonia in the initial phases to progressive pulmonary infiltration. Admission to intensive care units with the requirement for assisted ventilation has been reported to range from 13.8% (Lee et al., 2003) to 50% (Poutanen et al., 2003), and the overall case fatality rate is 15%.

Disease in Swine

Despite evidence of infection in pigs both naturally and experimentally by demonstration of viral RNA in blood and seroconversion, SARS-CoV does not appear to cause clinical disease (Cheetham et al., 2006; Weingartl et al., 2004).

Transmission

In a similar manner to influenza SARS-CoV is transmitted amongst humans via respiratory droplets, direct contact with infectious secretions or fomites (Chu et al., 2005). Nosocomial infections, involving both patients and hospital staff were common (Lee et al., 2003), and the occurrence of super-spreader events, whereby a single patient infects large numbers of patients have been documented (Wu et al., 2004).

The route of transmission to and between pigs is unclear, although it is feasible to theorise that respiratory infection via droplets may occur. A single study on the susceptibility of pigs to SARS-CoV used multiple routes of infection, making it unclear as to which routes resulted in infection (Weingartl et al., 2004), and a single report of natural transmission to a pig suggested contaminated food as the cause, although it is impossible to deduce whether infection was via ingestion, or inhalation of food particles (Chen et al., 2005).

Prevention and Control

Prevention of transmission relies primarily on early identification and isolation of cases, wearing of appropriate personal protective equipment such as gowns, glasses and P95 respirators by hospital staff, minimisation of aerosol production during treatment procedures and basic hygiene, particularly handwashing and the use of alcohol-based hand gels. There are no antivirals with proven effectiveness against SARS-CoV infection, and a vaccine does not exist. Given the rapid control of the SARS-CoV outbreak, and the last cases occurring in 2003, it is arguable that production of a vaccine is now of low priority.

There are currently no published protocols for prevention or control of SARS-CoV in swine.

3.4.4 Norovirus

Agent

Noroviruses, of the family *Caliciviridae*, genus *Norovirus*, are non-enveloped, linear, positive sense single-stranded RNA viruses of 7.3 to 8.3 kilobases (King AMQ, 2012). Based on the capsid protein, noroviruses are classified into one of five clades or genogroups (GI-GV), and then within these into multiple clusters and then strains. GII clade viruses infect both humans and swine while the other clades are species specific (Zheng et al., 2006). As yet, there is no suitable cell culture system for in vitro growth of noroviruses.

Disease in Humans

As previously stated, human noroviruses are recognised as the leading cause of nonbacterial GIT disease (Glass et al., 2009). The average incubation period for norovirus infection is 1.2 days (Lee et al., 2013) and the majority of clinical disease manifests as self-limiting vomiting and diarrhoea, although in some cases norovirus infection may be asymptomatic. Viral shedding begins approximately eight hours post infection, and has been demonstrated to continue for a range of 13-56 days, although it is unknown if prolonged shedding consists of infectious viral particles or simply remnants of RNA (Atmar et al., 2008). There is evidence of strain variation in pathogenicity (Desai et al., 2012), and the disease can be particularly debilitating and potentially fatal in the those with co-morbidities, the elderly (Harris et al., 2008), and neonates (Turcios-Ruiz et al., 2008).

Disease in Swine

Experimentally, GII human norovirus infection of gnotobiotic swine can cause infection resulting in mild, self-limiting diarrhoea (Cheetham et al., 2006), however in this study only a single pig developed histopathological changes in the small intestine. It is likely that viral infections are often subclinical with one study demonstrating antibody seroprevalence to a swine norovirus strain of 71% in 110 pigs from the US and 36% in 266 pigs from Japan (Farkas et al., 2005).

Transmission

Transmission of noroviruses is through the faecal oral route, either by direct contact with infected persons, through contamination of food or water supplies or fomites. The virus itself is highly infectious, with estimates that ingestion of a single viral particle gives a near 50% chance of infection becoming established (Teunis et al., 2008). Noroviruses are very stable in the environment, remaining infectious on surfaces for up to 2 weeks (Lopman et al., 2012), and in groundwater for at least 61 days (Seitz et al., 2011), providing multiple environmental reservoirs.

There is very little information available on transmission in swine, although it could be assumed that transmission is similar to that in humans, and environmental contamination provides an ongoing source of infection.

Prevention and Control

Personal hygiene is highly important in preventing both initial norovirus infection, and subsequent transmission following episodes of diarrhoea or vomiting. It has been demonstrated that hand washing with soap and water are more efficacious in removing non-enveloped viruses than use of alcohol-based hand gels (Sickbert-Bennett et al., 2005). Segregation of individuals with vomiting or diarrhoea from workplaces and public areas is also recommended. Control also relies on removal of contaminating virus from surfaces. Current CDC guidelines recommend cleaning surfaces with soap and water to

remove organic contaminants, followed by treatment with chlorine bleach at a concentration of 1000-5000 ppm (Duizer et al., 2004).

3.4.5 Porcine calicivirus (human sapovirus)

Agent

The molecular structure of the sapoviruses is very similar to the noroviruses, however they differ morphologically and genetically with enough diversity to be classified as the separate *Sapovirus* genus (King AMQ, 2012). Based on the VP1 gene sequence, sapoviruses can be placed into one of five genogroups (GI-GV) and multiple genotypes (Oka et al., 2011), with the porcine calicivirus strains Cowden and LL14/02/US representing GIII. In addition to the original genogroups I-V, recent discoveries of numerous novel swine isolates which do not group with GIII has led to the proposal of genogroups VI-X (Reuter et al., 2009).

Disease in Humans

Sapovirus infection of humans results in a similar spectrum of clinical signs to norovirus infections including vomiting, diarrhoea and more rarely fever, albeit at a lower severity than with noroviral infection (Sakai et al., 2001). The incubation period ranges from 1-4 days, and the disease is usually self-limiting within two days to one week. Viral particles are shed in the faeces, and viral material is generally undetectable after two weeks, however one study demonstrated that some individuals may shed high amounts of viral RNA in the faeces for 2-4 weeks following resolution of disease (Iwakiri et al., 2009).

Disease in Swine

Sapovirus infection of swine generally occurs early in life. Clinical signs are typical of a gastrointestinal pathogen and include self-limiting vomiting and diarrhoea which can persist for up to 1 week, associated with mild duodenal and jejunal villous atrophy and fusion (Guo et al., 2001; Flynn, Saif, and Moorhead, 1988). There is also evidence of subclinical infection occurring (Zhang et al., 2008).

Transmission

Transmission of sapoviruses is via the faecal-oral route, as is the case for noroviruses, either through direct contact with infected individuals, contaminated food or water, or fomites. Infection has been shown to occur early in life (Nakata, Estes, and Chiba, 1988). As noted above, prolonged faecal shedding in some individuals may act as a short term reservoir of virus.

It has been demonstrated that swine can be infected via the oral route, confirming faecal-oral transmission as a viable route, although interestingly the same study was able to infect pigs via intravenous inoculation. Faecal viral shedding persists for at least 8 days after infection (Guo et al., 2001). It is likely that environmental contamination provides an ongoing source of infection.

Prevention and Control

Given the similarities between noroviruses and sapoviruses, similar prevention and control measures apply.

3.4.6 Reston ebolavirus

Agent

Reston ebolavirus (EBO-R) is a member of the *Filoviridae* family, and lies within the *Ebolavirus* genus, along with Zaire, Sudan, Tai Forest and Bundibugyo ebolaviruses. It is an enveloped, negative-sense, single-stranded RNA virus of 18-19 kilobases (King AMQ, 2012). Filoviruses are stable for extended periods of time (up to three weeks) on surfaces at low temperatures (Piercy et al., 2010), but are inactivated by heating at 60 °C for one hour (Mitchell and McCormick, 1984).

Disease in Humans

Despite evidence of seroconversion to EBO-R in humans, there have been no reports of clinical disease (Miranda et al., 1999; WHO, 1992).

Disease in Swine

Evidence of EBO-R virus infection in swine was first documented following disease outbreaks in 2007 and 2008 in the Philippines, the clinical signs of which were likened to a highly severe Porcine reproductive and respiratory syndrome virus (PRRSV) infection. It was found that co-infection with EBO-R was present only in swine infected with PRRSV, indicating that it may potentiate disease rather than be a cause of disease itself (Barrette et al., 2009). A study in which five week old pigs were inoculated with EBO-R demonstrated viral replication without the occurrence of clinical disease, confirming EBO-R as a subclinical infectious agent in swine (Marsh et al., 2011).

Transmission

There is minimal research on transmission of EBO-R virus, likely given that it appears to be non-pathogenic in humans. However based on documented reports and research into the highly pathogenic filoviruses, it is accepted that contact with bodily fluids such as blood, nasal secretions and urine and faecal material from infected animals (particularly primates) are sources of infection. Routes of entry include inoculation (for example needlestick injuries) and respiratory. There is no evidence of human to human transmission of EBO-R, however this cannot be ruled out based on infection and transmission patterns of other filoviruses (WHO, 2009).

It is likely that transmission patterns between swine are based on the respiratory route, with high levels of viral replications occurring in the lungs (Marsh et al., 2011), however direct investigation of other routes has not been undertaken.

Prevention and Control

There are no documented prevention or control measures for EBO-R virus in swine. Human control measures are based on CDC recommendations for importation of non-human primates are outside the scope of this review.

3.4.7 Rotavirus

Agent

Rotaviruses are members of the *Reoviridae* family, and consist of a segmented (11 segments), linear, double-stranded RNA genome of 18.5 kilobases, within a non-enveloped icosahedral particle (King AMQ, 2012).The segmented genome of rotaviruses is a key feature in recombination and the production of novel strains. Rotaviruses can be grouped into seven main serogroups, A-G, of which

porcine rotaviruses are in groups A, B, C and E. Rotaviruses within group A are further classified on the basis of their surface proteins VP7 (G serotype) and VP4 (P serotype), as these outer capsid proteins elicit immune responses and are important in vaccine development and response (Paul and Lyoo, 1993). Rotavirus virions are relatively resistant in the environment, maintaining infectivity after storage at room temperature for two weeks, and in faeces at 60 °C for 30 minutes and at 10 °C for 32 months (Meng et al., 1987; Ramos et al., 2000).

Disease in Humans

Rotavirus infection is a cause of acute gastroenteritis. Pathogenesis is a result of the virus infecting the mature villi of the upper and middle small intestine, resulting in stunting of the villi and changes to a cuboidal epithelium. This in turn results in a malabsorption syndrome, with a net fluid loss into the intestine, and disturbances in electrolyte homeostasis (Lundgren and Svensson, 2001). In adults clinical signs include self-limiting diarrhoea and vomiting, however in children and infants the disease manifestations are more severe and often result in dehydration and metabolic disturbances requiring hospitalisation (Kovacs et al., 1987).

Disease in Swine

Group A rotaviral infection of swine generally occurs in two to six week old suckling and weaned piglets (Fu and Hampson, 1987), with maternal antibodies obtained from colostral intake providing some protection against early infection (Ward, Rich and Besser, 1996). Disease manifests as mild diarrhoea of two to three days duration, with a yellow-white, watery to creamy consistency. (Bohl, 1979). Mortality is usually low, however co-infection with other intestinal pathogens such as enterotoxigenic *E. coli* and Transmissible gastroenteritis virus may result in more severe disease (Bohl et al., 1978).

Transmission

Transmission of rotavirus is via the faecal oral route, although respiratory shedding of the virus may occur in both humans and swine (Azevedo et al., 2005). Given the environmental stability of the agent, fomites, surface and water contamination also permit transmission.

Prevention and Control

Control of rotaviral disease in humans is centred around basic hygiene procedures aimed at preventing faecal contamination, and vaccination of susceptible age-groups, namely infants and young children. Currently two oral live attenuated rotavirus vaccines are available in Australia, Rotarix®, a human monovalent vaccine and RotaTeq®, a pentavalent human bovine reassortant vaccine. They are not licensed for use in adults.

Control of rotavirus outbreaks in piggeries is difficult, given the stability of the agent and potential long-term contamination of surfaces. There is evidence that monovalent vaccines will produce varying degrees of immunity against multiple or heterotypic serotypes of rotavirus (Jiang, Wang and Glass, 2013), however no vaccines are commercially available in Australia.

3.4.8 Astrovirus

Agent

Mammalian astroviruses, of the family *Astroviridae*, genus *Mamstrovirus*, are non-enveloped, encapsidated viruses with single-stranded, linear RNA genomes of 6.8-7 kilobases (King AMQ, 2012). Based on phylogenetic analysis of the RNA-dependant RNA polymerase gene, there are currently five porcine astrovirus strains (PoAst 1-5) (Laurin, Dastor and L'Homme, 2011). Human astroviruses are classified as types 1-8, with type 1 being the most prevalent (Glass et al., 1996). There is little available data on the resilience of the virus, however it was shown to retain infectivity after heat treatment at 50 °C for 30 minutes (Shimizu et al., 1990), and after holding at 20°C for 7 days (Abad et al., 2001).

Disease in Humans

Astroviruses are a common cause of gastrointestinal disease in humans, particularly children (Glass et al., 1996), resulting in diarrhoea, vomiting and fever generally of a lower severity than rotavirus infection (Dennehy et al., 2001). The incubation period is two to three days, and disease is usually self-limiting within two to three days. Shedding of virus usually occurs for two weeks, however a long-term duration of shedding of 45 days has been documented in a single case (Shastri et al., 1998). There have been rare reports of astrovirus associated encephalitis (Naccache et al., 2015).

Disease in Swine

It is unclear how pathogenic astroviruses are in natural settings, although they likely have a role in enteric disease in association with other pathogens (Bridger, 1980; Shimizu et al., 1990; Shastri et al., 1998). In an experimental setting astrovirus infected CDCD pigs developed mild diarrhoeic disease only (Shimizu et al., 1990).

Transmission

Astroviruses are transmitted via the faecal-oral route, and contaminated water and food have been implicated in outbreak (Oishi et al., 1994). Faecal-oral transmission is also the most likely route for transmission in swine, given that astroviruses can be found in the faeces of swine in multiple countries (Shimizu et al., 1990; Lee, Jang, and Lee, 2015; Zhou et al., 2016).

Prevention and Control

Prevention and control of astrovirus infection is as for other gastrointestinal viruses, namely, personal hygiene. There are no vaccines available. Control of astrovirus infections on swine production facilities is likely to be unfeasible given the wide distribution and environmental stability of the agent.

3.4.9 Nipah virus

Agent

Nipah virus (NiV) is a paramyxovirus, which is grouped along with Hendra virus within the *Henipavirus* genus. It is enveloped and consists of a single-stranded, negative-sense, linear RNA genome, of approximately 18 kilobases in size (King AMQ, 2012). Stability characteristics as noted by the OIE are based on other paramyxoviruses, and include stability between pH 4 and pH 10, inactivation following heating at 60 °C for 60 minutes, and susceptibility to common soaps, detergents and lipid solvents (OIE, 2009).

Disease in Humans

The initial outbreak of Nipah virus in humans in 1998 was associated with severe, febrile encephalitis (CDC, 1999). The full clinical syndrome of Nipah virus is now recognised as having an initial presentation of fever, headache, dizziness, and vomiting followed by neurological signs suggestive of brainstem involvement. The disease has a high case fatality rate approaching 50%. Late or delayed onset neurological dysfunction may also occur (Goh et al., 2000). It is interesting to note that Nipah virus infections in Bangladesh appear to cause more respiratory disease than those in Malaysia (Hossain et al., 2008).

Disease in Swine

Infection of piglets less than four weeks old can result in muscle tremors, limb weakness and high mortality rates (40%). Swine less than six months old develop acute fever and respiratory disease, along with neurological signs including muscle spasms, limb weakness and paresis. In this age group there is high morbidity but low mortality. Older swine develop an acute febrile and neurological syndrome with nystagmus, bruxism, head pressing, spasms and seizures. Morbidity is high but mortality is low. Abortions may occur in the first trimester (Mhod Nor, Gan and Ong, 2000).

Transmission

Transmission of Nipah virus is complex and appears to have a number of potential pathways. Pteropid bats are the natural host of Hendra virus, and studies have demonstrated the widespread presence of antibodies to Nipah virus in Malaysian pteropids and isolation of virus from urine, confirming that they are a reservoir for this agent (Yob et al., 2001; Chua et al., 2002). It is likely that the initial transmission of Nipah virus into swine in 1998 was due to movement of pteropid species into regions where piggeries were situated(Chua, Chua, and Wang, 2002), resulting in contamination of facilities with bat urine, or virus contaminated oral secretions.

Inter-pig transmission can be via oral or parenteral routes, and virus is shed in oropharyngeal and nasal secretions, suggesting the respiratory route or direct contact with infected animals facilitates rapid spread through a herd (Middleton et al., 2002).

Human infection may occur through close contact with infected pigs (Parashar et al., 2000) via respiratory secretions, urine or saliva, human to human transmission (Gurley et al., 2007), or exposure to pteropid urine or saliva, usually as a result of drinking contaminated date palm sap (Salah Uddin Khan et al., 2010).

Prevention and Control

There are no vaccines available for Nipah virus. Prevention of human transmission is currently based on minimising consumption of potentially contaminated raw date palm sap (Nahar et al., 2015). During the initial outbreaks in Malaysia, control methods resulting in eventual cessation of the outbreak involved the culling of over one million swine from affected and surrounding areas (Chua et al., 2000). Biosecurity practices which prevent access of flying foxes into or around swine production facilities are also highly important in prevention of initial outbreaks.

3.4.10 Ascaris suum/lumbricoides

Agent

The intestinal nematodes of the genus Ascaris are common. *A. lumbricoides* is usually deemed to be a human-to-human parasite transmitted by the faecal–oral route. The related nematode *A. suum* is

normally found in pigs, and zoonotic cases have occurred. The infection is more common in areas where sanitation or hygiene routines are inadequate (Leles et al., 2012; Nejsum et al., 2012).

Disease in Humans

The condition may be asymptomatic or initially there may be generalised symptoms of fever and headache. Symptoms derive initially from the immune response to either the organism itself or its metabolic products. Larvae can cause pulmonary symptoms, with asthma, pneumonia, cough and wheeze (Nejsum et al., 2012).

The larvae are usually coughed up or migrate up the bronchi and are then swallowed again. Adults will breed in the gut. The female worm is larger (may reach up to 35 cm) than the male. Symptoms may include gastric cramps, vomiting and diarrhoea. Pancreatitis can occur, as may intestinal obstruction and malnutrition with weight loss. Jaundice may be seen if the common bile duct is obstructed. The whole cycle from egg to adult takes approximately 2 months. Eggs passed in the faeces become infective after 2 weeks (Leles et al., 2012; Nejsum et al., 2012).

A previous infestation does not prevent reinfection, so patients who have been successfully treated can present with the same condition after subsequent exposure.

Disease in Swine

It is usually suckling pigs or weaners that show the worst effects. The condition is rarely fatal, however larvae that migrate to sites other than the gut can produce unusual and severe symptoms. The cycle time from egg to adult is believed to be quicker in pigs infected with *A. suum* than it is in humans (Nejsum et al., 2012).

Transmission

Infection can be by one of two routes, either directly from ingestion of soil contaminated with eggs, or after the ingestion of vegetables or salad containing viable eggs adhering to it. The eggs hatch in the duodenum and migrate through the gut wall and then via the bloodstream to the lungs (Vlaminck et al., 2014).

Prevention and Control

Prevention revolves around good hygiene procedures and the proper use of sanitary facilities and hand washing among farm workers and animal handlers. Pig manure should not be used directly as a fertiliser or slurry on field, where fresh produce is being actively grown (Nejsum et al., 2012; Vlaminck et al., 2014).

3.4.11 Sarcocystis suihominis

Agent

Sarcocystis suihominis, and *S. hominis*, are intracellular protozoan parasites with humans as definitive hosts and are responsible for intestinal sarcocystosis in the human host. Most Sarcocystis species infect specific hosts or closely related host species. For example, humans and some primates are definitive hosts for *Sarcocystis hominis* and *S. suihominis* after eating raw meat from cattle and pigs, respectively. Sarcocysts of *S. hominis* are microscopic in the muscles of cattle, whereas those of S. *suihominis* are macroscopic in muscles of swine (Fayer, 2004). The prevalence of intestinal sarcocystosis in humans is low and is only rarely associated with illness, except in study volunteers who ingest large numbers

of sarcocysts. Most cases have been found in persons living in tropical or subtropical environments (countries in Asia and Southeast Asia) (Thomas and Dissanaike, 1978; Bunyaratvej, Unpunyo, and Pongtippan, 2007).

Disease in Humans

Humans acquire intestinal sarcocystosis from eating Sarcocystis-infected meat. Symptoms appear to be related to the quantity of meat consumed (raw pork), but individual reactions vary considerably. Parasite development and disease manifestations in humans can take two forms (Fayer, 2004);

a) Muscular infection: after infection with oocyst or free sporocysts which develop to form intramuscular sarcocysts within weeks to months, and lasting months to years. This form of disease is clinically manifested by musculoskeletal pain, fever, rash, cardiomyopathy, bronchospasm, subcutaneous swelling.

b) Intestinal infection: after infection with *Sarcocyst* containing bradyzoites which develop to form sexual stages in lamina propria, and the oocysts excreted in faeces, within 3-6 h from ingestion, lasting 36 h. This form of disease is clinically manifested by nausea, loss of appetite, vomiting, stomach ache, bloat, diarrhoea, dyspnoea, and tachycardia.

Disease in Swine

At approximately 4 weeks after ingestion of sporocysts, a subsequent asexual generation matures in vascular endothelial cells with an accompanying acute inflammatory reaction. This reaction is characterized by massive perivascular infiltration of mononuclear cells and multi-organ petechial haemorrhage associated with weakness, fever, abortion, and sometimes death. The severity of infection is dependent on the number of sporocysts ingested. Some animals fail to fully recover from the acute phase, and the infection becomes chronic, characterized by inappetence, weight loss, poor or stunted growth, muscle atrophy, lethargy, and weakness. Histologic examination often reveals widespread myositis, including glossitis and inflammation of cardiac muscle (Reiner et al., 2002).

Transmission

Eating raw or undercooked pork containing mature sarcocysts of *S. suihominis* has resulted in humans acquiring intestinal sarcocystosis (Bunyaratvej, Unpunyo, and Pongtippan, 2007). Volunteers in Germany who ate raw pork containing *S. suihominis* became infected, shed oocysts, and had dramatic symptoms 6 to 48 h later, including bloat, nausea, loss of appetite, stomach ache, vomiting, diarrhoea, dyspnoea, and tachycardia. Volunteers who ate well-cooked meat from the same pigs remained asymptomatic (Fayer, 2004).

Prevention and Control

To prevent infection of food animals, they must be prevented from ingesting the sporocyst stage from human faeces in contaminated water, feed, and bedding.

To prevent humans from becoming infected as intermediate hosts, ingestion of sarcocysts must be prevented. Sarcocysts in pig muscles were rendered non-infectious after cooking meat at 60, 70, and 100°C for 20, 15, and 5 min, respectively. Freezing at −4°C and −20°C for 48 and 24 h, respectively, also rendered bradyzoites in pork non-infectious (Nematollahia et al., 2013).

3.4.12 Blactocystis hominis

Agent

Blastocystis hominis is a common protozoan parasite in the human intestinal tract. *B. hominis*-like organisms have been detected in non-human primates and including pigs (Cirioni et al., 1999). Epidemiological studies showed that animal handlers have a significantly higher rate of infection with *B. hominis* than individuals who do not work with animals, and hence it had been suspected that some Blastocystis isolates from animals have zoonotic potential (Salim et al., 1999).

Disease in Humans

The role of *Blastocystis hominis* in human disease is still intensely debated since most cases are asymptomatic (Sinniah and Rajeswari, 1994). This organism has been recognized as a causative agent of diarrhoea both in immunocompromised and immunocompetent hosts in several studies (Miller and Minshew, 1988). It has been reported from both developed and developing countries, with a high prevalence in tropical areas, ranging between 30 and 50% (Basak, Rajurkar and Mallick, 2013). Zoonotic transmission of *B. hominis* has been speculated; with some molecular-based evidence supporting the zoonotic potential of *Blastocystis* sp. subtype 5 (Alfellani et al., 2013).

Disease in Swine

Blastocystis has been found to be a highly prevalent parasite in pig farms, capable of surviving in pig manure slurry (Snell-Castro et al., 2005). The age of the animals seems to be an important factor that notably affects the specific prevalence of the parasite. This could be due to the fact that weaners still have an immature immune system. Additionally, animals coming from different locations are confined together in a crowded system that differs from the more hygienic and less crowded conditions encountered for sows and piglets (Navarro et al., 2008).

Recent studies in Australia reported a high prevalence of Blastocystis carriage in pigs (up to 76.7%) with all pigs harbouring subtype 5 and a small proportion of pigs harbouring subtypes 1 and/or 3 (Wang et al., 2014). Pigs harbour Blastocystis predominantly in the large intestine, as detected by molecular and histological methods. Histological analysis of PCR-positive porcine intestine revealed no evidence of pathology caused by Blastocystis which is consistent with the majority of human studies (Wang et al., 2014).

Transmission

Several studies have implicated human-to-human, zoonotic and waterborne transmissions by *Blastocystis sp*. Substantial molecular evidence for zoonotic transmission was provided between animal and animal handlers in the Philippines and Australia. In China and Nepal, molecular-based evidence showed that *Blastocystis sp*. subtype 5 in pigs was also detectable in the humans who reared those pigs, suggesting that subtype 5 may be transmitted zoonotically (Sinniah and Rajeswari, 1994; Basak, Rajurkar and Mallick, 2013; Wang et al., 2014).

Prevention and Control

How Blastocystis is transmitted is not known for certain, although the number of people infected seems to increase in areas where sanitation and personal hygiene is not adequate. Common sense and basic hygiene practices serve as the first line of prevention; washing hands with soap and warm water before and after handling animals, using the toilet and before handling food.

3.4.13 Cryptosporidium

Agent

Cryptosporidium spp. are intestinal protozoans that occur in many animal species, including pigs. To date five species/genotypes of Cryptosporidium have been identified in pigs; *Cryptosporidium parvum*, *Cryptosporidium muris*, *Cryptosporidium suis*, pig genotype II, mouse genotype I, and a novel genotype (GenBank Accession No EF489037), with *C. suis* and pig genotype II most commonly found (Kváč et al., 2009; Johnson et al., 2008) .

Disease in Humans

A small number of reports of *C. suis* and *C. muris* infections in both immunocompromised and immunocompetent people. In this critical group, loss of appetite and anorexia can result in severe weight loss. Moreover, in patients with HIV/AIDS the disease may progress chronically, spreading to the bile duct, central nervous system and lungs. Unless treated swiftly, death will follow (Ryan, Fayer and Xiao, 2014).

Disease in Swine

Cryptosporidium can cause diarrhoea at an age of 8 to 21 days. In a study in Western Australia, an overall prevalence of 22.1% (64/289) was identified. In this study *Cryptosporidium* was more prevalent in post-weaned animals. The non-zoonotic *Cryptosporidium* species, pig genotype II was identified in 32 samples and *C. suis* in 6 samples. The zoonotic species *Cryptosporidium parvum* was not detected, suggesting that domestic pigs do not pose a significant public health risk. Pig genotype II was significantly associated with 'normal' stools, indicating an asymptomatic infection in the porcine host (Johnson et al., 2008).

Transmission

Human infection follows either direct contact with animal faeces or consumption of inadequately cleaned or cooked products. There have also been recorded incidents of individuals contracting the disease after swimming or otherwise undertaking water-based recreational activities in contaminated water, often where disinfection routines have become compromised. Person-to-person spread has been recorded, and is a particular risk in care settings (Ryan, Fayer and Xiao, 2014).

Prevention and Control

Currently, there are no effective treatments or disinfectants for porcine cryptosporidiosis and the most effective way to reduce the prevalence of this parasite is to implement strict biosecurity and hygiene measures to minimise the spread of infection. Management factors such as the method and frequency of cleaning, the type of flooring and stocking rates need to be investigated in the porcine host to find new and improved measures for control (Chalmers and Giles, 2010).

The pathogen can be destroyed by freezing, drying, heating materials to greater than 65°C and irradiation. It is resistant to many disinfectants in common use.

3.4.14 Giardia duodenalis

Agent

Giardia duodenalis (syn. intestinalis/lamblia) has the broadest host range and is the species with the greatest public and animal health significance in terms of gastrointestinal disease. *G. duodenalis* is

detected frequently in many mammals and is one of the most common intestinal parasites in pets like dogs and in livestock (Ryan and Cacciò, 2013).

Disease in Humans

The inoculum necessary to produce clinical disease has been estimated at as low as a single viable cyst, making it extremely infective. Infection may be asymptomatic; in other patients, clinical signs appear after a pre-patent period of between 1 and 4 weeks. The disease may present as diarrhoea of either chronic or acute nature, and of either mild or severe character. Unlike other organisms, the stools are associated with considerable gas and are usually fatty, frothy and foul smelling. They are usually free from blood or mucus (Ryan and Cacciò, 2013; Halliez and Buret, 2013).

Disease in Swine

Infected animals may be asymptomatic; alternatively they may have weight loss with chronic diarrhoea and partially formed fatty stools. The parasite matures and reproduces in the host's intestine and is then passed with the stool. Once expelled, the cysts can survive adverse environmental conditions for prolonged periods (Dorny et al., 2009).

An overall *Giardia* prevalence of 31.1% (90/289) was detected in a study in Western Australia. Giardia was detected in 17% (23/123) of pre-weaned piglet faecal samples and 41% (64/156) post-weaned faecal samples analysed. Untreated, the condition normally lasts for 1–2 weeks. Some individuals can develop a chronic form of the disease that may last for months or years (Armson et al., 2009).

Transmission

Faecal contamination of water or food and its subsequent consumption by humans is the most common route of infection. The oral–faecal route of infection is also common, especially in children. The cysts are infectious virtually immediately they are passed in the stool, so person-to-person spread can occur as a result of poor personal hygiene. Fomite spread by faecal contamination of surfaces or objects is well documented (Ryan and Cacciò, 2013; Dorny et al., 2009).

Prevention and Control

The precautions for humans should be based on personal hygiene and the environmental sanitation. In livestock farming focus should be made on drinking water quality; water collection and distribution systems, and the sanitary status of personnel working at the farm. Sanitization of drinking water for livestock is achieved with iodine, while chlorine seems to be less efficacious. Water filtration is justified if there is a very high incidence and heavy losses.

The possibility of zoonotic infection from pigs to human population is questionable. Giardia cysts are degraded in liquid pig manure and it is unlikely that pig manure is a threat for water contamination. On the contrary, reducing the proportion of pig manure by mixing it with human slurry contributes to the survival of cysts (Guan and Holley, 2003).

3.4.15 Limitations of this survey and additional agents

One of the major limitations of this survey is the limited availability of data in the area of reverse zoonosis in pigs. The majority of studies focus on the zoonotic aspects of pathogens rather than the reverse zoonotic potential. A classic example is the host jump of MSSA ST398 from humans to pigs and the evolution of LA-MRSA ST398. This indicates the enormous potential for humans that interact

with pigs to introduce new human pathogens into pigs. Since the human movement across the globe has increased, the risk of zoonotic agents that causes health hazards in overseas countries to be introduced to Australian pigs farms is increasing. The introduction of MRSA ST398 from Europe into Australian pigs is a classic example. In light of this potential we have identified additional organism that are likely to zoonotic agents and these agents are discussed below.

3.4.16 Methicillin resistant Staphylococcus aureus.

Agent

S. aureus are Gram-positive facultatively anaerobic cocci that colonise the skin and the nares of humans and animals and are generally commensals. However, it does cause opportunistic infection when the skin barrier is compromised. Globally, *S. aureus* is responsible for a wide range of community-acquired and hospital-acquired infections ranging from relatively minor skin and soft tissue infections to serious and life-threatening sepsis with associated high mortality. *S. aureus* infections are compounded by the emergence of methicillin-resistant *S. aureus* (MRSA) with limited treatment options in both health care and community settings (Jevons, 1961). Methicillin resistance in *S. aureus* is conferred by methicillin resistant genes (mecA or mecC), located on the staphylococcal cassette chromosome SCCmec. The acquisition of methicillin resistance makes the S. aureus resistance to all classes of beta-lactams except ceftaroline which limits the ability to treat MRSA infection. *Staphylococcus aureus* is a major pathogen in the hospital environment, causing a wide variety of infections that are associated with considerable mortality.

Disease in Humans

Globally, Staphylococcus aureus is responsible for a wide range of community-acquired and hospital-acquired infections ranging from relatively minor skin and soft tissue infections to serious and life-threatening sepsis with associated high mortality. *S. aureus* infections are compounded by the emergence of methicillin-resistant strains with limited treatment options in both health care and community settings. Several studies have indicated that mortality is higher for patients infected with methicillin-resistant S. aureus (MRSA) than methicillin-susceptible *S. aureus* (MSSA) (Whitby, McLaws, and Berry, 2001; Lawes et al., 2012; Hanberger et al., 2011; de Kraker et al., 2011) and that MRSA infections are associated with increased costs due to longer hospital stays and the need for treatment with costly antimicrobials (Cosgrove et al., 2005).

Since the initial identification of MRSA in 1961, only a relatively small number of clonal lineages have been found to cause the majority of MRSA infections in humans throughout the world (Jevons, 1961). These include sequence types (STs) ST22 (EMRSA-15), ST239, and ST8 (USA300) (Harrison et al., 2014; Coombs et al., 2013a; Coombs et al., 2013b). In the remainder of cases of hospital-associated (HA) or community-associated (CA) MRSA infections, clonal lineages that are successful in colonising and causing infections in humans are often unique to different geographical regions (Coombs et al., 2013a; Coombs et al., 2013b; Nimmo and Coombs, 2008; Williamson, Coombs and Nimmo, 2014). For example ST22-IV (UK-15) is the major HA MRSA clone in the U.K, other European countries and most recently, Australia (Harrison et al., 2014; Coombs et al., 2013a; Coombs et al., 2013b). However in North America, ST8 is the most commonly identified HA MRSA strain (Coombs et al., 2013a; Coombs et al., 2013b; Nimmo and Coombs, 2008; Williamson, Coombs and Nimmo, 2014).

In humans, infections with MRSA, which first appeared in the 1960s, have traditionally been seen in hospitals (Jevons, 1961). These 'health care-associated MRSA' (HA-MRSA) strains cause serious and

potentially fatal disease in patients with a wide range of predisposing conditions. Therapy of HA-MRSA is frequently complicated by a propensity for isolates to be resistant to multiple classes of antimicrobials. Although HA-MRSA causes serious infections ranging from skin and soft tissue infection to sepsis, these clones does not cause tissue necrosis by the production of does not Panton-Valentine leukocidin (PVL) toxins (Coombs et al., 2013a; Coombs et al., 2013b). In Australia the most frequently detected HA- MRSA is ST22-IV and ST239-IV (Coombs et al., 2013a; Coombs et al., 2013b).

In the past 15 years new strains of MRSA that transmit between humans outside of healthcare settings have emerged (Udo, Pearman and Grubb, 1993). These 'community-associated MRSA' (CAMRSA) are responsible for a growing burden of disease in otherwise healthy people in Australia and abroad (Udo, Pearman and Grubb, 1993; Otter and French, 2010). These CAMRSA clones are generally less resistant to a range of antimicrobials and associated with skin and soft tissue infection (SSTI) (Nimmo and Coombs, 2008). However, CA-MRSA is regarded as a very serious threat to humans because of their propensity to invoke rapid and extensive necrosis of affected tissues due to the production of Panton-Valentine leukocidin (PVL) toxin (Nimmo and Coombs, 2008). In Australia, the most commonly identified CA-MRSA clone is ST93-IV and nearly all the ST93-IV isolates carry PVL toxin (Coombs et al., 2014). In addition, MRSA ST30-IV, ST-IV and ST45-V are also commonly identified in Australia (Coombs et al., 2014).

In recent years, studies have demonstrated the emergence and clonal spread of methicillin-resistant *S. aureus* (MRSA) in dogs, horses and livestock, and the potential for bi-directional transmission between animals and humans (Harrison et al., 2014; Price et al., 2012).

Disease in Swine

S. aureus is not a major pathogen of pigs. However, it can occasionally cause skin and soft tissue infection including botryomycosis and impetigo of mammary glands. The major problem of *S. aureus* in pigs is the carriage of MRSA predominantly known as livestock associated MRSA (LA-MRSA) in pigs (Price et al., 2012; Cuny et al., 2010). Although LA-MRSA does not cause any disease in pigs, these MRSA can be transmitted to individuals who come in contact with pigs such as pig farmers, workers and veterinarians (Cuny et al., 2010).

Livestock-associated MRSA of the multilocus sequence type (ST) 398 was initially identified as a cause of recurrent infections among a Dutch pig farming family. Subsequent investigation has revealed the detection of this clone the upper respiratory tract among the pig herd owned by the family and the pig workers in the neighbouring herd. This has resulted in the global investigation of MRSA in pigs and has resulted widespread detection of this pig adapted LA-MRSA (ST398) clone in pigs across Europe and Asian countries (Cuny et al., 2010; Lewis et al., 2008). European and North American studies have reported frequency of MRSA ST398 carriage as high as 70% and 49%, respectively (de Neeling et al., 2007; Smith et al., 2009; van Duijkeren et al., 2008).

In Australia, Groves et al reported the first detection of MRSA ST398 at low frequency MRSA (ST398) from 0.9% of 324 pigs across five different commercial pig farms and one feral herd in Australia (Groves et al., 2014). Another study has identified the detection of MRSA ST398 from a veterinarian working in the pig industry (Groves et al., 2016). The low frequency of MRSA ST398 detection in Australian pigs is attributed to Australia's geographical isolation and quarantine restrictions in importing live pigs.

MRSA ST398 rarely causes skin and soft tissue infections in pigs. In humans, MRSA ST398 has been identified as a cause of skin and soft tissue infections, respiratory tract infection, septicaemia, endocarditis, joint empyema and osteomyelitis (van Cleef et al., 2011; Ekkelenkamp et al., 2006; Krziwanek, Metz-Gercek and Mittermayer, 2009; van Rijen, Van Keulen and Kluytmans, 2008). However, there have been no definitive reports of human mortality resulting from MRSA ST398, and most reported infections appear to have involved persons with underlying conditions causing immunological suppression (van Cleef et al., 2011; Ekkelenkamp et al., 2006; Krziwanek, Metz-Gercek and Mittermayer, 2009; van Rijen, Van Keulen and Kluytmans, 2008; Pan et al., 2009).

The evolution of the LA-MRSA ST398 in pigs is a classic example of host jumping of MRSA clones. Methicillin sensitive S. aureus (MSSA) ST398 typically colonises humans and is a well-known community associated MSSA in humans. This clone carries a prophage (ϕSa3) that contains the human invasion gene cluster (IEC) which enables immune evasion in humans (virulence factor). However when this clone jumped from humans to pigs, it lost the ϕSa3prophage and underwent multiple, independent SCCmec (i.e. methicillin resistance) acquisition events. It also acquired tetracycline resistance. Thus a human MSSA became an L.A-MRSA that does carry ϕSa3 prophage.

Transmission

The main mode of MRSA transmission in humans is by direct skin-to-skin contact or with shared items or surfaces such as towels by both colonised and infected people. Several studies have shown human healthcare workers (HCWs) working with MRSA-colonised patients and veterinarians with routine occupational exposure to animals often have a prevalence of MRSA nasal colonisation many times greater than that of the general public (Albrich and Harbarth, 2008; Moodley et al., 2008). For instance, the prevalence of ST398 MRSA colonisation amongst livestock veterinarians in Europe is estimated to be greater than 40% (Verkade et al., 2013; Cuny et al., 2009), and the prevalence of CC8 MRSA colonisation amongst equine veterinary personnel in North America ranges from 9.7% to 18% (Weese et al., 2005a; Weese et al., 2005b; Weese et al., 2006). In a recent Australian study, the prevalence of MRSA nasal colonisation was found to be extremely high among specialist equine veterinarians (21.4%) and well above the average for those veterinarians practicing companion animal medicine only (4.9%) (Jordan et al., 2011). In human medicine in a review of 127 outbreak studies, 4.6% of 33,318 HCWs working with MRSA-positive patients were colonised with MRSA (Albrich and Harbarth, 2008). In a recent nasal MRSA colonisation prevalence study on HCWs working in a Western Australian acute care hospital only 3.4% of 1,542 HCWs screened were MRSA colonised. However, 10.7% of HCWs working in high risk MRSA wards were colonised (Verwer et al., 2011). Studies have shown that people in contact with MRSA ST398 positive pigs or other animals are likely to be colonised with this MRSA clone. Studies in Europe have shown that 22–38% of persons who have contacted MRSA-positive pigs or veal calves were colonised with this MRSA clone (van Rijen, Van Keulen and Kluytmans, 2008; Voss et al., 2005; Denis et al., 2009). European studies have identified that the proportion of MRSA ST398 among humans is correlated with pig and veal calf densities and human population density (van Cleef et al., 2011). However, in the majority of European countries LA-MRSA ST398 is detected in less than 2% of the MRSA cases. In countries or regions with higher MRSA carriage (4-25%) has been identified with areas with high pig/veal calf densities (van Cleef et al., 2011). Individuals are colonised after short term exposure to ST398 MRSA, however in most cases the MRSA colonisation is cleared after 24h (van Cleef et al., 2011). However pig farmers who had long term exposure to pigs positive for MRSA ST398 appeared to retain MRSA (59%) after going on holiday for 7-14 days (Köck et al., 2012). The data from these studies shows that individuals require regular long term exposure with pigs that are

positive for MRSA ST398 to maintain this clone in the upper respiratory tract therefore the exposure to MRSA ST398 is occupational in nature.

Prevention and Control

One of the key measures to prevent MRSA transmission is hand hygiene. Another effective method is active surveillance programs (screening) to identify colonised individuals particularly in hospitals. The active surveillance is important in the situation of an outbreak or case-cluster of MRSA in both healthcare setting and in the community/work place. Since MRSA colonises the nose, swabbing the anterior nares is the appropriate form of testing. MRSA carriers can be decolonised by topical and systemic antimicrobial agents. Even though this method is variably effective, it is likely to reduce the risk of invasive infection and transmission from a colonised individual. As indicated above HCWs has been implicated in the acquisition and spread of MRSA. Decolonising HCWs has been identified as potential control measures for limiting the spread of MRSA in health care settings. Prevention and control of MRSA ST398 in pigs is a major challenge. Breading herds have been implicated as a source for the dissemination of this clone in Europe (Lewis et al., 2008). Although plausible the role of breeding herds is not validated. Since MRSA is a commensal organism in pigs, there is no easy way of eliminating these bacteria from pigs. However, routine monitoring and control of the movement of the positive herds may reduce the transfer of MRSA between pig herds. Previous studies have indicated the introduction of MRSA ST398 from overseas (Groves et al., 2014; Groves et al., 2016). This is likely via farm workers, owners or veterinarians. Regular monitoring and biosecurity measures may play a role in limiting the introduction of these clones into naïve herds.

3.4.17 Clostridium difficile

Agent

Clostridium difficile is a Gram positive, spore forming anaerobic bacterium commonly responsible for causing antibiotic-associated diarrhoea and pseudomembranous colitis in humans. In developed countries, *C. difficile* is also commonly associated with hospital acquired and healthcare-related diarrheal infections (Naggie et al., 2010). Besides humans, *C. difficile* is also recognized as an enteric pathogen in a variety of animals, including companion animals (cats, dogs, horses) and food animals (cattle, sheep, goats, pigs) (Squire and Riley, 2013).

Disease in Humans

In humans, *Clostridium difficile* infections *(CDIs)* generally affect the colon with rare cases involving the small intestine. Infection occurs opportunistically when the normal microflora of the colon is disrupted. Disruption of the gut flora leads to the germination of *C. difficile* spores which results in the production of two major toxins A and B (A, enterotoxin and B, cytotoxin). Once released these disrupt tight junctions between intestinal epithelia and actin cytoskeleton assembly leading to non-haemorrhagic watery diarrhoea. Therefore, the fundamental requirements for CDI includes the disruption of normal microflora of the colon, followed by the presence of the *C. difficile* spores in the immediate environment, and the production of toxins.

Human CDIs typically manifest as non-haemorrhagic watery diarrhoea, accompanied by fever, abdominal pain and leucocytosis (Gebhard et al., 1985). Non-diarrhoeal presentation with gastrointestinal ileus resulting in the collection of faecal fluid in loops of dilated, atonic colon has also been reported (Kelly and LaMont, 1998). In rare cases extra-intestinal infections have also been

reported which includes, soft tissue infection, abscesses of abdominal organs, pleural effusion/empyema and bacteraemia (Jacobs et al., 2001; Elliott et al., 2009). The severity of this disease can vary from mild/self-limiting to severe cases leading to pseudomembranous colitis, toxic megacolon, bowel perforation, and sepsis.

Antimicrobial therapy is considered the most important risk factor for acquiring CDIs in humans, since more than 90% of CDIs occur in conjunction with antimicrobial therapy (Avery et al., 2000). Although most antimicrobials have been implicated in the development of CDIs, broad-spectrum antimicrobial use including clindamycin, cephalosporins, penicillins and fluoroquinolones has frequently been associated with CDI in humans prior to infection (Owens, et al., 2008).

Disease in Swine

In pigs, CDI is strictly an enteric disease that affects neonatal pigs. The clinical manifestation in neonatal pigs includes colonic and cecal enteritis, colonic and mesocolonic edema, diarrhoea, and anorexia. The clinical signs of disease in pigs generally commence soon after parturition with severe weight loss or anorexia with mortality reaching up to 16% of the cases (Songer and Uzal, 2005). The frequency of *C. difficile* in neonatal piglets in North America and Europe ranges from 29 to 73% (Knight, Squire and Riley, 2014). The most commonly detected *C. difficile* clone in North America and Europe, is ribotype (RT) 078 which can be isolated from 75 to 100% of porcine and 90% of bovine sources (Schneeberg et al., 2013; Rodriguez-Palacios et al., 2006; Debast et al., 2009; Keel et al., 2007). Interestingly, RT078 is also the most commonly isolated strain from among the community associated *C. difficile* infections in Europe and North America.

In Australia, a nationwide surveillance study of *C. difficile* demonstrated a 67% carriage in neonatal pigs. The ribotyping of Australian *C. difficile* from neonatal pigs revealed 23 different RTs, several of which are known to cause disease in humans. This includes RT014 (23%; 36/154) and RT033 (13%; 20/154). This study also revealed that certain ribotypes are present in certain states. For example RT033 was found almost exclusively in South Australia and a single sample from Victoria while RT237 was found exclusively in WA (Knight, Squire and Riley, 2014). RT033 has recently been found in calves in both Germany (Schneeberg et al., 2013) and Australia and has been isolated from humans in Australia in the last decade (Knight, Squire and Riley, 2014). In Australia, two RT046 *C. difficile* were found from Victoria pig farms. These clones were previously isolated from neonatal pigs (67%) and from human CDI outbreak cases indicating potential zoonotic transmission (Norén, Johansson and Unemo, 2014). This strain has been recovered in low numbers from the stools of patients presented with CDI in Australia.

Transmission

C. difficile generally spread via the oral-faecal route through the ingestion of metabolically inactive spores. These spores have been isolated from soil, water and the gastrointestinal tract of a number of different animal species. Metabolically inactive *C. difficile* spores are resistant to desiccation, disinfectants and extreme temperature. *C. difficile* can be carried in the gastrointestinal tract without causing infection. The asymptomatic carriage of *C. difficile* is common in health care settings and may play a role in the transmission of CDI in hospitals.

In piggeries, transmission of *C. difficile* is disseminated by contamination of the environment with metabolically inactive spores and increased susceptibility to colonization in neonatal pigs due to the immature colonic microflora and/or exposure to antimicrobials. Once colonised *C. difficile* spores can

be transmitted via faeces in the piggery environment by symptomatic and asymptomatic animals (Hopman et al., 2011). Since *C. difficile* spores are tolerable to relatively harsh conditions and are resistant to almost all the disinfectants used in Australia, the spores remain viable for a longer period of time in the piggery environment posing an increased health risks to the pigs.

Prevention and Control

Reducing environmental spore load in piggeries through the isolation of sick animals is the only way of controlling the spread of this disease. However, it is not practical in a piggery environment. One of the effective ways of controlling *C. difficile* infection is by wearing personal protective equipment such as gloves. This has shown to reduce the spread of *C. difficile* infection in hospitals. Another effective method is using sporicidal disinfectants such as 10% bleach (Gerding, Muto and Owens, Jr., 2008). However using bleach as a routine disinfectant in piggery is a major problem. One of the mechanisms in which the *C. difficile* spores spread in the piggery environment is the re-cycling of effluents. Since these spores are highly resistant to heat and other chemical and environmental factors, it is difficult to destroy the spore. If clean water is used in farrowing units the spread of *C. difficile* can be controlled to an extent.

3.4.18 Critically important antimicrobial resistant Escherichia coli and Salmonella enterica

Agent

Enterobacteriaceae are Gram-negative commensal bacteria of mammalian gastrointestinal tract. Two of the most common species that belong to the *Enterobacteriaceae* family found in pigs are *Escherichia coli* and *Salmonella enterica*.

E. coli are rod shaped, gram negative, non sporulating facultative anaerobes of the lower gastrointestinal tract of humans and other mammals (Hartl and Dykhuizen, 1984; Nataro and Kaper, 1998). *E. coli* is a part of the commensal microflora of mammals and typically colonises the lower GIT within a few hours of birth (Kaper, Nataro and Mobley, 2004; Berg, 1996). Even though *E. coli* usually reside harmlessly confined to the intestinal lumen of mammals, certain groups of *E. coli* can cause a wide spectrum of intestinal and extraintestinal diseases in humans and animals (Kaper, Nataro and Mobley, 2004; Croxen and Finlay, 2012). Human pathogenic *E. coli* may be carried as a commensal in animals. There is a potential for these pathogenic *E. coli* to enter humans via the food chain. For example shiga toxin producing pathogenic *E. coli* is one of the major food borne pathogens from cattle. However the direct transmission of pathogenic *E. coli* from pigs to humans is not common.

Salmonella enterica is a zoonotic pathogen causing a variety of diseases in humans and animals (Lan, Reeves and Octavia, 2009). Over 2500 serovars of *S. enterica* has been identified (Coburn, Grassl and Finlay, 2006). Some of the *S. enterica* serovars are host specific. However there are few broad host adapted serovars that can cause disease in both humans and animals (Hur, Jawale and Lee, 2012). One of the common broad host adapted serovars is *S. enterica* Typhimurium. Despite host specificity all *Salmonella* serovars (except Typhi and Paratyphi) should be considered as zoonotic and pathogenic.

From a reverse zoonotic point of view both *E. coli* and *Salmonella spp.* should be considered as potential reverse zoonotic agent since both the organisms can be carried via healthy or sick individuals. These organisms can readily be transferred from humans to pigs via faecal oral route. The major concern for the transmission of *E. coli* and *Salmonella spp.* is the carriage of multidrug resistance. Numerous studies have demonstrated that both of these organisms can acquire or transfer antimicrobial resistance quite

readily. Therefore these organisms should fall into a special category like the LA-MRSA clones as reverse zoonotic agents as although they may not cause disease in pigs they can transfer antimicrobial resistance genes and plasmids to commensal swine bacteria.

Antimicrobial resistance (AMR)

In the past decade we have seen the emergence and distribution of multi-drug resistant (MDR) bacteria in the humans and animals. The major problem is the reduced treatment options available for management of infections with MDR bacteria. The emergence of multidrug-resistant (MDR) Gram-negative bacteria in hospitals and communities is a global problem. Infections caused by MDR pathogens result in increased hospitalisation costs (by $15,626-$25,573) and higher mortality rates (by 0.04%).

The World Health Organisation has recently highlighted the major public health risks posed by resistance to critically important antimicrobials (CIAs) such as extended-spectrum cephalosporins (ESCs), fluoroquinolones (FQs), and carbapenems among *Enterobacteriaceae* (WHO, 2014). Concerns are heightened when such resistance occurs in livestock, especially when it involves extended-spectrum cephalosporins (ESCs), fluoroquinolones (FQ), and carbapenems. This is due to the risk of transmission of these resistant bacteria to humans through the food chain and/or the environment (Laxminarayan et al., 2013; Woodford et al., 2013). Plasmid-mediated ESC resistance (mediated by bla_{CMY2}) was first detected in *Escherichia coli* from US livestock in 1996 and in *Salmonella* Newport shortly thereafter, with both linked to the use of ESCs in livestock (Bradford et al., 1999; Allen and Poppe, 2002). Similarly, in Asia and Europe, ESC resistance in *E. coli* isolated from livestock has been attributed to emergence and spread of plasmid-mediated ESC-resistance genes (Aarestrup et al., 2006; Yang et al., 2004; Wang et al., 2010; Jiang et al., 2012). In addition, several countries in these regions have extensive use of fluoroquinolones (FQs) in some food-animal species. This has been linked to the emergence of FQ-resistant *E. coli* and *Salmonella* in livestock (Yang et al., 2004; Wang et al., 2010; Jiang et al., 2012; Marshall and Levy, 2011). More recently, resistance to carbapenems have been reported in *Enterobacteriaceae* isolated from livestock systems in both Asia and Europe (Woodford et al., 2013).

Antimicrobial resistance in Australian animals

Recent studies have suggested that the ecology of AMR among *Enterobacteriaceae* isolated from Australian food-producing animals is different to that in other parts of the world (Abraham et al., 2014; Abraham et al., 2014). This is largely attributed to Australia's geographic isolation, restrictions on the importation of livestock and some fresh meat and strong regulation on the use of CIAs such as ESCs, FQs and carbapenem. So far in Australia, resistance to carbapenems has yet to be reported among *Enterobacteriaceae* from Australian livestock. However our recent study has demonstrated the first detection of resistance to critically important antimicrobials among clinical *E. coli* isolates from Australian food-producing animals, attributable largely to globally disseminated FQ and ESC-resistant zooanthroponotic *E. coli* lineages (Abraham et al., 2015). Only three FQ and/or ESC-resistant *E. coli* were detected from 114 isolates from pigs. However only one pig pathogen (Porcine enterotoxigenic *E. coli* [ETEC]) was detected (ST100) and two out of three strains from this study has been previously reported in humans overseas (ST744 and ST1). One isolate was the ESC and FQ-resistant strain (ST744) and it has been identified previously as an ESBL-producing lineage associated with wild birds in Bangladesh and with human extraintestinal infection in Laos (Hasan et al., 2012). To our knowledge, these ESC-resistant, potentially zooanthroponotic *E. coli* strains have not been identified previously in Australia either from food-producing animals or from clinical human infections. Their low frequency among clinical isolates from Australian animals suggests that they have likely been introduced plausibly

via human carriers or migratory wild birds (Hasan et al., 2012; Manges and Johnson, 2012; Poirel et al., 2012). Since FQ use in Australian livestock is illegal, it is unlikely that the ST744-A strain evolved from an animal-associated susceptible progenitor strain under local fluoroquinolone selection pressure.

In Australia, until recently, carbapenemase producing Enterobacteriaceae have been reported only in hospital settings, from both clinical and environmental sources. The *bla*$_{IMP-4}$ gene is considered endemic to Australia and is often carried on a *bla*$_{IMP-4}$*-qacG-aacA4-catB3* cassette array (Espedido, Partridge and Iredell, 2008; Partridge et al., 2012; Sidjabat et al., 2014; Sidjabat et al., 2015; Sidjabat, Robson and Paterson, 2015). This *bla*$_{IMP-4}$ cassette array is generally found on IncA/C or IncL/M plasmids in New South Wales and Victoria, (Espedido, Partridge and Iredell, 2008; Partridge et al., 2012) and IncHI2 or IncL/M plasmids in Queensland (Sidjabat et al., 2015; Sidjabat, Robson and Paterson, 2015).

In a recent study we have identified the first report of carbapenemase-producing *Salmonella enterica* Typhimurium carrying a *bla*$_{IMP-4}$ gene in an Australian cat. Molecular characterization revealed the acquisition of multi-drug resistant IncHI2 plasmid that carried *bla*$_{IMP-4}$*-qacG-aacA4-catB3-sul1* cassette array by a broad host range *S. enterica* Typhimurium sequence type (ST19) (Authors SA/MO). In addition, another recent study has identified the presence of *bla*$_{IMP-4}$ in a range of bacterial species, primarily *E. coli,* from a single seagull colony in Wollongong, NSW, Australia (Dolejska et al., 2016). This study also identified the *bla*$_{IMP-4}$*-qacG-aacA4-catB3* cassette array among these isolates.

Transfer and maintenance of critically important antimicrobial resistance
Transfer of critically important antimicrobial resistance can occur via two possible methods: 1) Direct transmission of *E. coli* or *Salmonella sp.* from humans to pigs or 2) Transfer of mobile genetic elements from humans to pigs from commensal human flora into pig *E. coli* or *Salmonella sp.* Once entered in to a pig production system these organisms can be circulated and maintained in the production system for an indefinite period.

Since most of the CIA resistance is encoded on mobile genetic elements such as plasmids, the transfer of these genes can readily occur between bacterial species and between humans and animals. In addition, critically important antimicrobial resistance is linked to other low and high importance antimicrobial resistance. For example a carbapenem resistance plasmid may also have resistance genes to β-lactams, sulfonamides, tetracyclines, marcaloides, trimethoprim and ESCs. As a result these drug resistance promiscuous plasmids can be selected, transferred and maintained in a production system through the use of first line drugs such as ampicillin, tetracylines or CIAs such as ceftiofur. Therefore antimicrobial resistance transfer and maintenance is complicated and special consideration is required to limit or prevent the entry of the CIA resistant bacteria in pig production system.

Disease in Humans
E. coli: Even though *E. coli* usually reside harmlessly confined to the intestinal lumen of mammals, certain groups of *E. coli* can cause a wide spectrum of intestinal and extraintestinal diseases in humans and animals (Kaper, Nataro and Mobley, 2004; Croxen and Finlay, 2012).

Salmonella enterica: The non-typhoidal *S. enterica* serovars cause enterocolitis/diarrhoea and bacteraemia.

Disease in Swine

E. coli: In pigs ETEC causes neonatal diarrhoea, post-weaning diarrhoea and oedema disease. Porcine ETEC is not acquired from humans and since it does not cause human infection. However, CIA resistance from human CIA-resistant can be acquired into ETEC since mobile genetic elements can be transferred readily between Gram-negative organisms. Most of the Australian ETEC are MDR (Abraham et al., 2014; Smith et al., 2016).

S. enterica: S. enterica Choleraesuis is one of the common pathogens in pigs and causes enteritis, pneumonia and septicaemia. Numerous other *Salmonella* serovars have been detected in pigs and, some of them have been associated with human foodborne illness. The commonly detected serovars in pigs includes *S. enterica* Typhimurium, Derby, Heidelberg, Worthington and Infantis. These serovars may cause mild to moderate diarrhea in pigs and are likely to be multi-drug resistant. Our recent study has identified that *S. enterica* Typhimurium are more likely to be MDR than other serovars form clinical infection in Australian pigs (Abraham et al., 2014).

Transmission

E. coli and S. enterica are transmitted generally via faecal oral route. However contaminated feed and water can also transmit these organisms.

Prevention and Control

Prevention of CIA-resistant *E. coli and S. enterica* is very difficult. As with MRSA, one of the key measures to prevent MRSA transmission is hand hygiene. Another effective method is active surveillance programs (screening) to identify colonised herds and monitoring of the heads. Active surveillance is important in the situation of an outbreak or case-cluster of CIA-resistant *E. coli and S. enterica* in pig herds.

Prevention and control of MRSA ST398 in pigs is a major challenge. Breeding herds may play a role in the dissemination of of CIA-resistant *E. coli and S. enterica* however no documented evidence is available to support this notion. Since *E. coli* and *S. enterica* can survive in pig production systems as commensal organisms, there is no easy way of eliminating these bacteria from pigs. However, routine monitoring and control of the movement of the positive herds may reduce the transfer of these bacteria. Our previous study has detected ESC and FQ resistant *E. coli* in Australia pigs that has previously detected overseas in humans and birds (Abraham et al., 2015). This has possibly been introduced via farm workers, owners or veterinarians or wild birds. Regular monitoring and biosecurity measures may play a role in limiting the introduction of these clones into naïve herds.

3.4.19 Streptococcus suis

Note: So far this agent is identified as a zoonotic agent. Reverse zoonotic potential is not documented. However reverse zoonotic potential should not be discounted.

Agent

Streptococcus suis is an important pig pathogen and is also recognised as an zoonotic agent in pigs around the world (Zimmerman et al., 2012). It is a Gram positive, facultative anaerobic bacteria that naturally colonises porcine respiratory, genital and gastrointestinal tracts (Zimmerman et al., 2012). There are 35 different serotypes of *S. suis* characterised on the basis of immunologically distinct capsular antigens (Okura et al., 2013). There are highly virulent, moderately virulent, and completely

avirulent (commensal strains) of *S. suis* (Gottschalk, Higgins, and Quessy, 1999; Fittipaldi et al., 2011). So far, only five serotypes have ever been reported to cause clinical disease in humans (Kopic, Paradzik, Pandak, 2003; Arends and Zanen, 1988; Haleis et al., 2009; Nghia et al., 2008). Although a number of serotypes have been reported to cause infection in pigs, serotypes 1 to 9 and serotype 14 are the most frequently detected pathogenic serotypes (Gottschalk, Segura and Xu, 2007; Wisselink et al., 2000). Despite the variation in serotypes detected, serotype 2 causes the majority of *S. suis infection in* both pigs and humans (Wisselink et al., 1999; Ma et al., 2008; Jiang, Fan and Lu, 2009).

Disease in Humans

S. suis can cause severe, invasive and occasionally fatal disease that is often associated with endocarditis, meningitis, or toxic shock syndrome in humans (Kerdsin et al., 2009; Gottschalk et al., 2010). Nearly all the human infections are attributed to *S. suis* Serotype 2 (Gottschalk, Segura and Xu, 2007). The primary route of exposure of humans is via direct contact with infected pigs or contaminated pig products (van de Beek, Spanjaard and de Gans, 2008). *S. suis* infection is common among east and Southeast Asian countries (Thi Hoang Mai et al., 2008; Yu et al., 2006). However, in developed countries *S. suis* infection among humans is rare due to the stronger emphasis on hygiene in the pig production and processing systems. In recent years, the frequency of reported zoonotic *S. suis* infection has increased in humans. This is primarily attributed to two large outbreaks in China, and the recognition of *S. suis* serotype 2 is a zoonotic meningitis causing agent in Southeast Asia (Thi Hoang Mai et al., 2008; Hui et al., 2005; Takamatsu et al., 2008).

S. suis infection in developed countries is often sporadic, isolated infections manifesting in a variety of clinical diseases with low mortality rates (Gottschalk, Segura and Xu, 2007; van de Beek, Spanjaard and de Gans, 2008; Tramontana et al., 2008). Risk factors for infection in developed countries include routine or occupational exposure to pigs, pig carcases or pork products (Arends and Zanen, 1988; van de Beek, Spanjaard and de Gans, 2008; Barlow et al., 2003; Strangmann, Fröleke and Kohse, 2002). This pattern is typically observed in developed countries such as North America, Europe, Japan and possibly in Australia (Tramontana et al., 2008; Barlow et al., 2003; Fowler et al., 2013; Schultsz et al., 2012). In countries such as the Netherlands, the annual risk of *S. suis* meningitis can be 1500 times greater for pig farmers and abattoir workers than those individuals that does not work with pigs or pig products (Arends and Zanen, 1988).

In China, large-scale S. *suis* outbreaks have been reported (Yu et al., 2006; Wang et al., 2007). This large scale outbreak was observed between 1998 and 2005 across multiple provinces in China. It was characterised by a large number of temporally and spatially related *S. suis* cases associated with toxic shock syndrome and high mortality rate (up to 17%) (Yu et al., 2006; Ye et al., 2006). The major risk factors for this epidemic pattern of *S. suis* outbreak include backyard butchering of dead or diseased pigs and the presence of skin abrasion on the hands and feet of individuals that perform backyard butchering (Yu et al., 2006).

There are few studies that investigated the carriage of *S. suis* in healthy individuals. Three studies have demonstrated low level carriage of *S. suis* in the human respiratory tract without clinical disease using culture based method (Goyette-Desjardins et al., 2014). In Italy, 2/10 volunteer slaughterhouse workers were positive for *S. suis* serotype 2 (Sala, Colombo, and Gerola, 1989). A study performed in Mexico has shown that, 4/69 slaughterhouse workers were positive (Rojas, Gottschalk, and Velazquez, 2001). In Germany, 7/132 meat workers were positive for *S. suis* carriage (Strangmann, Fröleke and Kohse, 2002). Serological studies have identified the presence of *S. suis* antigens in 6-20% of pig farmers

(Goyette-Desjardins et al., 2014). Taken together, these studies do demonstrate that pig workers can carry *S. suis.*

Disease in Swine

Virulent *S. suis* causes a range of invasive infection associated with mortality in pigs around the globe (Wertheim et al., 2009; Staats et al., 1997). This includes septicaemia, endocarditis, arthritis and meningitis, and pneumonia (Zimmerman et al., 2012; Staats et al., 1997). Often, pigs are found dead without any clinical signs. Typically, for *S. suis* meningitis in pigs, loss of appetite, reddening of skin, fever, depression, loss of balance, lameness, paralysis, paddling, shaking and convulsing are also observed. Although, all age groups of pigs are affected, young pigs especially weaners are most severely affected (Zimmerman et al., 2012).

Carriage rate of *S. suis* have been reported as high as 100% (Wisselink et al., 1999; Greger, 2007; Clifton-Hadley et al., 1984). However, *S. suis* infection rarely exceeds 5% in individual herds (Gottschalk, Segura and Xu, 2007). There is greater variation in the prevalence and carriage of pathogenic strains among pig herds (Gottschalk, Segura and Xu, 2007).

Transmission

S. suis is generally transmitted nasally and/or orally. *S. suis* colonizes the palatine tonsils of both healthy and clinically ill pigs. The neonatal pigs become colonised after contact with colonized sows. Transmission of *S. suis* between pigs to humans occurs through 1) occupational exposure via direct contact of infected/ colonised live pigs or from abattoirs 2) Consumption of raw or minimally cooked pig products such as offal.

There is limited literature regarding the transmission of *S. suis* from humans to pigs. However the likelihood of humans infecting pigs should not be discounted since studies have demonstrated the carriage of pathogenic *S. suis* by pig farmers and abattoir workers (Goyette-Desjardins et al., 2014) . Studies have demonstrated that *S. suis* can colonise tonsils of healthy individuals for up to three weeks. However it is unclear whether this is due to repeated exposure to infected/carrier pigs (Goyette-Desjardins et al., 2014).

Prevention and Control

Currently, *S. suis* is recognised as a zoonotic agent and not as reverse zoonotic agent. As a result there are no documented prevention measures identified to limit the transmission of *S. suis* from humans to pigs.

Infected or carrier farm workers could potentially infect pigs with pathogenic strains of *S. suis* particularly after overseas travel. As a result increased hand hygiene may help in preventing the transmission of *S. suis* from humans to pigs. Some of the measures identified to control *S. suis* infection in pigs include autogenous vaccines, strategic antibiotic in-feed medication and alteration of management to minimise stress from overcrowding.

3.4.20 Taenia solium

Despite this agent not being retrieved using the search strings specifying reverse zoonoses as outlined above, there is a broad range of literature outlining the transmission cycle of *Taenia solium* from the

definitive human host, to the intermediate porcine host and associating this predominantly with faecal contamination of porcine feed/water, or giving swine direct access to human faecal material (Sarti et al., 1992; Pouedet et al., 2002).

Agent

Taenia solium is a cestode parasite commonly referred to as the pork tapeworm.

Disease in Humans

Despite being referred to as the pork tapeworm, humans are the definitive host for *T. solium*, however can also act as an intermediate host. As definitive hosts, humans are infected by eating undercooked pork containing the cysticercal stage of the parasite. The larvae then mature in the small intestine and after approximately 8 weeks begin producing gravid proglottids which are excreted in the faeces. The symptoms are mild or non-existent, and proglottids may not be noticed in the stool (Flisser, 1994).
The more serious condition is cysticercosis, where humans ingest *T. solium* eggs directly from other humans through faecal oral transfer (Garcia and Del Brutto, 2000). The oncospheres are freed from the eggs in the intestines, cross the gut wall and are carried to various tissue where they form cysts. This is most damaging when they enter the central nervous system. After a variable, prolonged period, cysyts grow large enough to block passage of CSF or break down resulting in inflammatory lesions, leading to varied neurological signs including seizures (Nash and Neva, 1984).

Disease in Swine

Disease in swine is generally clinically inapparent. Aside from the public health issues, carcass condemnation through detection of cysticerci cysts in muscle and tongue is factor for pork producers.

Transmission

The life cycle of *T. solium* is relatively complex. As mentioned above, when humans act as the definitive host, they excrete gravid proglottids (with eggs) in the faeces, which are ingested by pigs. Cysticerci then encyst in pig muscle and can be ingested by humans, to develop into adults and complete the cycle. As a dead-end route of transmission, humans can ingest eggs directly from other humans (through faecal contamination), resulting in cysticerci encysting in various tissues (García et al., 2003).

Prevention and Control

Prevention of cysticercosis in both humans and swine is directly linked to sanitation and adequate cooking of pork products. As the faecal-oral route is required for transmission from humans to pigs and from humans to humans, ensuring swine are not exposed to human sewerage, and minimising human exposure to sewerage in endemic areas are key prevention measures. Efficacy of anthelmintics in pigs has been investigated for use in endemic areas, however no standard dosing levels have been set (Lightowlers, 2013).

4 Research Methodology

4.1 Prioritization of Human-Swine Reverse Zoonoses Relevant to the Pig Industry in Australia: A Weighted Multi-Criteria Approach

Zoonotic diseases have a significant impact on public health, accounting for more than 60% of all infectious diseases causing illness in humans. Furthermore, some zoonotic pathogens negatively impact animal production, hinder international trade of animals and their products.

Recently there have been an increasing number of reports indicating that humans are transmitting pathogens to animals, including swine. Hence, the terms "reverse zoonoses" or "zooanthroponosis" have re-emerged as scientific terms that refer to any pathogen normally reservoired in humans that can be transmitted to other vertebrates.

The literature review (part 1) of this project identified a list (Table 4) of 22 pathogens with documented scientific evidence (or expert determination of their inclusion for consideration) indicating their reverse zoonotic potential for transmission between humans and pigs. As resources for research, surveillance, prevention and control of animal diseases in Australia are becoming increasingly limited, the need for prioritization of the list of potential human-swine reverse zoonoses must be considered. This prioritization process should take into consideration the local situation and the opinion of the Australian stakeholders. Literature based evidence from other countries can be generally informative, but cannot be directly transferred to the Australian pig industry setting.

Table 4 List of pathogens[#] compiled from literature review (part 1) as human-swine reverse zoonotic diseases*

Ascaris suum/lumbricoides
Astrovirus
Blactocystis hominis
Campylobacter coli[#]
Clostridium difficile
Community acquired MRSA[#]
Cryptosporidia
Eschericia coli[#]
Giardia duodenalis
Hepatitis E virus
Influenza A Viruses
Methicillin-resistant *Staphylococcus aureus* (MRSA)
Nipah virus
Norovirus
Porcine calicivirus
Reston ebolavirus
Rotavirus
Salmonella spp.[#]
Sarcocystis suihominis
Severe acute respiratory syndrome coronavirus
Streptococcus suis[#]
Taenia solium[#]

*Listed in alphabetical order, [#]expert chosen pathogens

4.2 Aims

(1) Identify domains and criteria relevant for prioritization of human-swine reverse zoonoses.
(2) Determine the weights of importance of these criteria based on stakeholders/expert opinions.
(3) Illustrate the use of these weights for ranking the list of pathogens compiled from the literature review (part 1).

4.2.1 Selection of the domains and criteria

Methods for prioritization have been adapted to identify infectious disease, of both public and animal health importance, for national surveillance, risk ranking and rank assessment. The domains and criteria adopted in this exercise were extracted based on a critical review of 10 recently published studies (Table 5) on prioritization of zoonoses, emerging and infectious diseases. Various methods used for criteria selection and weighting, and the scoring of pathogens or diseases are often described as qualitative, quantitative, or semi-quantitative in nature based on the scoring system used and the type of data required.

The majority of the reviewed publications have recommended using more quantitative methods for prioritization. Also, these publications recognized that a range of five to nine domains of criteria groups is recommended as an optimum for design targeting elicitation of stakeholder/expert opinions. None of the reviewed studies were examining the emerging problem of reverse zoonoses.

Table 5 References for extracting selection criteria relevant for prioritization of human swine reverse zoonoses

Reference	Purpose	Country/ organization	No. of Domains	Approach
(Stebler et al., 2015)	Prioritization of zoonotic diseases	Switzerland	5	Delphi panel/Quantitative
(McFadden et al., 2015)	Prioritization of zoonoses in developing countries	Magnolia	5	Multi-criteria risk ranking/Semi-Quantitative
(Brookes et al., 2014)	Prioritization of exotic diseases for the pig industry	Australia	9	Multi-criteria decision analysis/Quantitative
(Rist, Arriola and Rubin, 2014)	One Health tool for prioritization of zoonoses	CDC	5	Collaborative decision-making/Semi-Quantitative
(Ng and Sargeant, 2013)	Prioritization of zoonosis in United State and Canada	North America	21	Online adaptive conjoint analysis/Semi-Quantitative
(Ng and Sargeant, 2012)	Prioritization of zoonosis in United State and Canada	North America	21	Online adaptive conjoint analysis/Semi-Quantitative
(Humblet et al., 2012)	Prioritization of diseases of food producing animals	Europe	8	Questionnaire/ Semi-Quantitative
(Havelaar et al., 2010)	Prioritization of emerging zoonoses	The Netherlands	9	Panel/ Questionnaire/Quantitative

(Cardoen et al., 2009)	Prioritization of food and water-borne zoonoses	Belgium	5	Workshop/Semi-Quantitative
(McKenzie, Simpson and Langstaff, 2007)	Prioritization for wildlife disease strategy	New Zealand	4	Rapid risk analysis/ Semi-Quantitative

The goal of the critical analysis of these 10 recent studies was to select and group the minimum number of objective prioritization criteria that sufficiently covered the most important aspects concerning human-swine reverse zoonoses. Following consultation within the research team and taking into account relevance to the pig industry in Australia, a list of 29 criteria was developed, and these criteria were grouped into 6 domains: Impact on public health, impact on animal health, impact on industry economy, impact on wider society, pathogen epidemiology and prevention and control measures (Table 6).

Table 6 The 29 criteria classified under 6 domains for prioritisation of human swine reverse zoonoses

Domains	**Criteria**
1 Impact on public health	1. Reported incidence of the disease in the Australian human population in the last 5 years; 2. Threat potential to people associated with swine; 3. Severity of human disease; 4. Availability and efficacy of diagnostic tools in humans; 5. Cost and efficacy of available treatment.
2 Impact on animal health	1. Reported incidence of the disease in Australian swine in the last 5 years; 2. Threat potential to other associated livestock; 3. Severity of disease in swine; 4. Availability and efficacy of diagnostic tools in swine; 5. Cost and efficacy of available treatment for swine.
3 Impact on pig products: industry and economy	1. Effect from productivity loss; 2. Effect from mortality risk; 3. Impact on international food trade; 4. Impact on domestic food supply; 5. Added cost – mandatory slaughter; 6. Added cost – treatment and disinfection; 7. Added cost – vaccination.
4 Impact on wider society	1. Public awareness/perception; 2. Potential impact on media; 3. Impact on related industries (eg trucking, animal feed).
5 Pathogen epidemiology	1. Mode of transmission; 2. Environmental persistence; 3. Presence of vector and/or reservoir in Australia; 4. Epizootic potential
6 Prevention and control measures	1. Prevention in humans; 2. Prevention in pigs; 3. Effectiveness of control/prevention measures in pigs that are not relying on available treatment/vaccination; 4. Surveillance (diagnostic test availability, ease of field diagnosis).

4.2.2 Component and score of prioritisation criteria

Prior to an expert panel assessing each of the 18 pathogens according to the criteria outlined in Table 7, domains and criteria were weighted according to industry stakeholder and expert opinion. In order to determine the final weightings, a survey was produced asking respondents to rank the domains 1-6. Respondents were then asked to rank the criteria within each domain in descending importance. All responses were compiled and an adjusted rank weighting was given to each, and within that domain, a rank weighting to each of the criteria.

A five-tiered measurement scale was set for each of the human-swine reverse zoonoses prioritization criterion, which are outlined in Table 7. The scale was developed based on consensus agreement between the research team members. The scales were established based on the review of existing prioritization models and tailored to the level of qualitative and quantitative information available about the 22 short listed reverse zoonoses (Table 4). The expert panel then assessed each pathogen according to the criteria in Table 7. A consensus score was given for each criterion on the tiered measurement scale, and this was fed into the weighted criteria to give a final scoring system

Ranking Score = ∑[pathogen criteria score x (weighted domain score x weighted criteria score)]

Table 7 Criteria ranking measurement

	0	1	2	3	4	5
Domain- 1: Impact on Public Health						
1. Reported incidence of the disease in the Australian human population in the last 5 years;	Never reported	1 to 2999 cases/year	3000 to 5999 cases/year	6000 to 8999/year	9,000 to 11,999/year	≥ 12,000/year
2. Threat potential to people associated with pigs;		Low		Medium		High
3. Severity of human disease;		Short duration/patient completely recovers	Short duration/with sporadic severe complications	Severe acute illness	Severe chronic illness	High mortality rate
4. Availability and efficacy of diagnostic tools in humans;		Very High: clinical signs are pathognomonic and clinical diagnosis is very certain	High: field and commercial tests are widely available	Medium: laboratory diagnosis is possible	Low: only in very specialized laboratories	None: no reliable test available
5. Cost and efficacy of available treatment.	Not generally treated	Rarely required to be treated (<1%) + High success (>80%)	Medium cost (1 or more doctors' visits and/or use of drug) + High success (>80%)	High cost (hospitalization or long term treatment) + High success (>80%)	Medium cost (1 or more doctors' visits and/or use of drug) + Low to medium success (50-80%)	High cost (hospitalization or long term treatment) + Low to medium success (50-80%)
Domain- 2: Impact on Animal Health						
6. Reported incidence of the disease in the Australian Pigs in the last 5 years;	Never reported as etiologic agent of clinical disease in pigs	Accidental: few clinical cases reported	Rare: clinical disease reported in few cases	Occasional: clinical disease occasionally reported	Frequent: clinical disease frequently reported in	>1 National outbreaks were reported in Australian pigs in the last 5 years

7. Threat potential to other associated livestock;		1 host species	2 host species	3 host species	4 host species	>4 host species
8. Severity of disease;		short duration/animal completely recovers	short duration/with sporadic severe complications	Severe acute illness	Severe chronic illness	High mortality rate
9. Availability and efficacy of diagnostic tools in Pigs;		Very High: clinical signs are pathognomonic and clinical diagnosis is very certain	High: field and commercial tests are widely available	Medium: laboratory diagnostic is possible	Low: only in very specialized laboratories	None: no reliable test available
10. Cost and efficacy of available treatment.	Not generally treated	Rarely required to be treated (<1%) + High success (>80%)	Medium cost + High success (>80%)	High cost + High success (>80%)	Medium cost + Low to medium success (50-80%)	High cost + Low to medium success (50-80%)
Domain- 3: Impact on Industry Economy						
11. Effect from productivity loss;	Null: no impact on animal productivity	Low: losses of productivity <20%		Moderate: losses of productivity of 20%–50%		Severe: losses of productivity >50%
12. Effect from mortality risk;	Null: negligible	Low (less than 1%)		Medium (1-5%)		High (>5%)
13. Impact on international food trade;	Absent: no impact	Local: restrictions of animal and/or by-products movements limited to surveillance areas implemented when cases are confirmed		National: animal and/or by-products movements limited in an area greater than the surveillance zone but only in 1 state		International: limitation of importations of animal and by-products from Australia to other countries.
14. Impact on domestic food supply;	Absent: no impact	Low: temporary disturbance of supply and demand in a limited area and low impact on prices		Moderate: temporary disturbance of supply and demand and decrease in prices		High: major disturbance of supply and demand and decrease in prices

15. Added cost – mandatory slaughter;	Not required			Outbreaks only		Outbreaks and zone restriction areas
16. Added cost – treatment and disinfection;	Not required			Moderate: only the animals with serious clinical signs require treatment, application of basic sanitary measures		High: systematic treatment of animals with clinical signs; application of stricter sanitary measures
17. Added cost – vaccination.	Not required/ Not available			Moderate: vaccination not mandatory but possible in particular cases		High: mandatory vaccination
Domain- 4: Impact on Wider Society						
18. Public awareness/perception;		Low public awareness/ Low political priority	Low public awareness/ informal political expectations	Medium public awareness/ informal political expectations	High public awareness/ explicit political agendas	High public awareness/ international duties/ explicit political agenda
19. Potential impact on media;	Null: no impact of media on consumption habits	Low: short-term and minor impact on consumption habits		Moderate: long-term but minor impact on consumption habits		High: major and long-lasting impact on consumption habits (rejection of a particular by-product)
20. Impact of related industries (trucking, animal feed).	Absent: no impact	Low: turnover reduction <20% in >1 related sectors		Moderate: turnover reduction 20%–50% in >1 related sectors		High: turnover reduction >50% in >1 related sectors
Domain- 5: Specific Epidemiology						
21. Mode of transmission;	No vector-borne transmission (not contagious)	Contamination by direct contact	Contamination by indirect contact	Vector-borne transmission	Airborne contamination	
22. Environmental persistence;	None: no persistence in	Rare:	No data available on presence/survival of	Wildlife reservoir(s)/vector(s):	Environment:	

	the environment, no vector(s) or wildlife reservoir(s) identified in Australia	anecdotal isolation in a potential vector(s) or the environment	pathogenic agent in reservoir(s), vector(s) or the environment	pathogen agent persistent in wildlife reservoir(s) and/or vector(s)	agent naturally surviving in the environment (soil, water)	
23. Presence of vector and/or reservoir in Australia.	Not vector-borne disease and/or no known reservoir	Absence of vector(s)/reservoir(s) in all Australia		Localized presence: reservoir(s) and/or vector(s) in a limited area of >1 states		Generalized repartition: repartition of vector(s) and/or reservoir(s) throughout entire Australia
24. Epizootic potential		Never: only sporadic cases, epizootics never reported	Rare: most cases are sporadic; possibility of localized epizootic if conditions are ideal: e.g., abnormal multiplication of reservoir(s) and/or vector(s)	Localized: pathogen characterized by localized epizootic potential essentially related to the transmission mode.	(Inter)national: epizootic characteristics well known after introduction, possibility of wide spatiotemporal expansion	
Domain- 6: Prevention and Control Measures						
25. Prevention in humans;		High: effective prevention tools or there is no need for prevention		Medium: prevention tools are not very effective or difficult to implement or not established		Low: no prevention tools available or prevention tools are not effective, strong need for further research on preventive measures
26. Prevention in pigs;		High: diva vaccine, simple control of animal movement,	Medium: effective vaccine, effective	Low: vaccine preventing carriage and excretion, bans	Very low: vaccine is only limiting clinical expression, no	None: no vaccine, bans not effective,

	effective bans, measures efficient	bans, special movement measures	difficult to implement (wildlife) but specific movement measures effective	completely immune protection, bans difficult to implement, movement control difficult	movement control difficult or ineffective
27. Effectiveness of control/prevention measures in pigs those are not relying on available treatment/vaccination;	High: effectiveness of implemented control measures (quarantine, slaughter, and restriction area); effective epidemiologic investigation (origin of the infection rapidly identified and quick implementation of control measures)	Moderate: effectiveness of implemented control measures (quarantine, slaughter, and restriction area); epidemiologic investigation poorly conclusive (incomplete traceability of animals and by-products)	Low: limitation of control measures implemented (quarantine, slaughter, and restriction area), limiting dissemination of pathogen; epidemiologic investigation inconclusive	Null: ineffectiveness of implemented control measures (quarantine, slaughter, and restriction area) and/or control measures not indicated because of characteristics of pathogen; epidemiologic investigation inconclusive	
28. Surveillance.	High: clinical or pathological surveillance easy, sensitive and specific tests, DIVA vaccine, zoning <1 km	Moderate: clinical surveillance difficult, pathological surveillance possible, sensitive and specific tests, no DIVA vaccine, zoning 1–10 km	Low: clinical and pathological surveillance difficult, tests not sensitive, zoning >10km	Very low: clinical surveillance impossible, pathological surveillance difficult, tests not sensitive or specific, zoning >>10 km	None: clinical and pathological surveillance impossible, no reliable test, zoning not effective

Criteria ranking measurements as presented in Table 7 were then used to develop an online survey using the Survey Monkey software. The survey was made available online on the 23/2/16, and email alerts sent to members of the Australian Pig Veterinary group via APL. The survey was closed on the 6/5/16, and a total of 22 responses were returned and compiled for analysis. Results and scores for each criteria are presented below (Table 8).

Table 8.1 Response rankings – domain ranking

	1	2	3	4	5	6	Total	Score
The impact on animal health (pigs and other livestock)	33.33% 7	28.57% 6	0.00% 0	23.81% 5	9.52% 2	4.76% 1	21	4.38
The impact on the pork industry (productivity, trade, treatment and control costs)	14.29% 3	42.86% 9	14.29% 3	9.52% 2	19.05% 4	0.00% 0	21	4.24
The impact on public Health	38.10% 8	9.52% 2	9.52% 2	4.76% 1	9.52% 2	28.57% 6	21	3.76
Prevention and control measures (ie the importance of effective prevention/control)	0.00% 0	9.52% 2	38.10% 8	23.81% 5	14.29% 3	14.29% 3	21	3.14
The pathogen epidemiology and spread (does it spread easily, is it carried by insects, does it remain on surfaces)	0.00% 0	10.00% 2	30.00% 6	20.00% 4	25.00% 5	15.00% 3	20	2.95
The impact on wider society (public perception, media perception, effect on related industries)	14.29% 3	0.00% 0	9.52% 2	19.05% 4	23.81% 5	33.33% 7	21	2.62

Table 8.2 Response rankings – public health

	1	2	3	4	5	Total	Score
Severity of human disease	78.95% 15	21.05% 4	0.00% 0	0.00% 0	0.00% 0	19	4.79
Potential threat to people associated/working with pigs	15.79% 3	52.63% 10	21.05% 4	10.53% 2	0.00% 0	19	3.74
Reported incidence of the disease in the Australian population in the last 5 years	0.00% 0	21.05% 4	42.11% 8	5.26% 1	31.58% 6	19	2.53
Availability and usefulness of diagnostic tests in humans	5.56% 1	0.00% 0	27.78% 5	33.33% 6	33.33% 6	18	2.11
Cost and effectiveness of available treatment	0.00% 0	5.26% 1	10.53% 2	47.37% 9	36.84% 7	19	1.84
Severity of human disease	78.95% 15	21.05% 4	0.00% 0	0.00% 0	0.00% 0	19	4.79

Table 8.3 Response rankings – animal health

	1	2	3	4	5	Total	Score
Reported incidence of the disease in Australian pigs in the last 5 years	10.53% 2	15.79% 3	21.05% 4	10.53% 2	42.11% 8	19	2.42
Potential threat to other livestock species	0.00% 0	31.58% 6	31.58% 6	26.32% 5	10.53% 2	19	2.84
Severity of the disease in pigs	73.68% 14	21.05% 4	5.26% 1	0.00% 0	0.00% 0	19	4.68
Availability and usefulness of diagnostic tools in pigs	10.53% 2	10.53% 2	26.32% 5	26.32% 5	26.32% 5	19	2.53
Cost and effectiveness of treatment	5.26% 1	21.05% 4	15.79% 3	36.84% 7	21.05% 4	19	2.53

Table 8.4 Response ranking – impact on industry

	1	2	3	4	5	6	7	Total	Score
Productivity loss	31.58% 6	26.32% 5	26.32% 5	10.53% 2	5.26% 1	0.00% 0	0.00% 0	19	5.68
Mortality risk	21.05% 4	21.05% 4	21.05% 4	0.00% 0	10.53% 2	15.79% 3	10.53% 2	19	4.53
Effect on international trade	26.32% 5	26.32% 5	10.53% 2	5.26% 1	0.00% 0	10.53% 2	21.05% 4	19	4.58
Effect on domestic food supply	15.79% 3	21.05% 4	10.53% 2	15.79% 3	5.26% 1	10.53% 2	21.05% 4	19	4.11
Cost of mandatory slaughter	5.26% 1	0.00% 0	21.05% 4	15.79% 3	21.05% 4	15.79% 3	21.05% 4	19	3.21
Cost of treatment and disinfection	0.00% 0	5.26% 1	5.26% 1	31.58% 6	36.84% 7	15.79% 3	5.26% 1	19	3.32
Cost of vaccination	0.00% 0	0.00% 0	5.26% 1	21.05% 4	21.05% 4	31.58% 6	21.05% 4	19	2.58

Table 8.5 Response ranking – impact on wider society

	1	2	3	Total	Score
Public awareness and perception	73.68% 14	15.79% 3	10.53% 2	19	2.63
Impact of media/reporting	5.26% 1	52.63% 10	42.11% 8	19	1.63
Impact on related industries (eg animal feed, livestock transport)	21.05% 4	31.58% 6	47.37% 9	19	1.74

Table 8.6 Response ranking – pathogen epidemiology and spread

	1	2	3	4	Total	Score
Mode of transmission	10.53% 2	36.84% 7	26.32% 5	26.32% 5	19	2.32
Persistence in the environment	0.00% 0	21.05% 4	47.37% 9	31.58% 6	19	1.89
Presence of a vector or reservoir in Australia	10.53% 2	26.32% 5	26.32% 5	36.84% 7	19	2.11
Epizootic/epidemic potential (potential for widespread disease in pigs)	77.78% 14	16.67% 3	0.00% 0	5.56% 1	18	3.67

Table 8.7 Prevention and control measures

	1	2	3	4	Total	Score
Importance of prevention in humans	63.16% 12	5.26% 1	0.00% 0	31.58% 6	19	3.00
Importance of prevention in pigs	11.11% 2	44.44% 8	44.44% 8	0.00% 0	18	2.67
Effectiveness of control/prevention measures in non-vaccinated or non-treated pigs	10.53% 2	21.05% 4	36.84% 7	31.58% 6	19	2.11
Effectiveness and ease of disease surveillance	15.79% 3	26.32% 5	21.05% 4	36.84% 7	19	2.21

4.2.3 Pathogen Ranking

Pathogens listed in Table 4 were assessed using the criteria in Table 7 and the response ranking weightings from the online survey to give each pathogen a quantitative ranking. Table 9 lists the pathogens in decreasing order along with their ranking score. Complete scoring metrics are presented in Appendix 1.

Table 9 Pathogen ranking scores

Pathogen	**Score**
Nipah virus	834.7286
Eschericia coli	815.5974
MRSA	757.5497
Streptococcus suis	703.7736
Salmonella	684.44
Reston ebolavirus	613.8236
SARS coronavirus	606.1502
Influenza A	561.0199
Taenia solium	521.7342
Norovirus	474.8947
Giardia	452.3434
Cryptosporidia	448.1804
Clostridium difficile	424.1734
Campylobacter coli	412.346
Rotavirus	407.2421
Ascaris suum/lumbricoides	348.0923
Blactocystis	342.4579
Astrovirus	337.3365
Hepatitis E virus	326.0568
Sarcocystis suihominis	324.4703
Porcine Calicivirus	306.0334

Note also that respondents were given the opportunity to make any comments at the completion of the survey. Five of 22 respondents commented and these are listed below:

'Review down time biosecurity of pig workers going back to work from holiday overseas. Certain restrictions has to be put into place like - not allowing exposure to overseas pig farms/abattoi(sic)r. It is fairly common practice to revisit previous friends working in the farm. If the person fell ill prior going back to farm work, he/she must have a clearance from GP prior he/she resumes to work, especially if the disease is zoonotic.'

'Most being exotic to Australia require Australia to have a strong national level of biosecurity to prevent entry but also important is ensuring piggeries have adequate on-farm biosecurity measures. Education plays a key role in this.'

'Effective surveillance and serious disease prevention are costly and their (sic) might not be enough funds available. But also a head in the sand approach is cheaper UNTIL.....'

'Baseline data for a number of diseases is required.'

'Influenza I see as a major thread.'

5 Discussion

This study has used a robust, criteria weighted methodology, inclusive of inputs from experts in academia and industry, to determine and rank the 20 most likely reverse zoonotic agents of risk to the Australian pig industry, as determined by literature review and expert analysis.

It can be seen from Table 9, that the 20 agents can be grouped into three tiers; those scoring below 400, those scoring between 400 and 500, and those scoring above 500. Those scoring below 400 are considered to be of negligible risk to the industry and will not be considered further.

5.1 Nipah virus, Reston ebolavirus, SARS coronavirus

The top ranking agents include four viral pathogens; *Nipah virus* which scored highest of all agents, *Reston ebolavirus*, SARS coronavirus and the Influenza A viruses. There are a number of reasons for the ranking positions of these viruses, particularly the three which are currently exotic to Australia. If the scoring matrix (Appendix 1) for Nipah, Reston and SARS is examined closely, it can be seen that a large proportion of the scores are attributable to the likely impact on the industry's economy, through slaughter out policies, movement standstills and related industry downturn, potential for human fatalities, and in part due to the fact that they are exotic, such that an expensive stamping out campaign may be undertaken. In addition to this the public and media perceptions of these highly emotive viral agents (even for Reston ebola a widespread public awareness campaign would have to be undertaken to differentiate it from the highly pathogenic Zaire ebola) would also have the potential to be devastating to the industry. Nipah also rates highly due to the potential reservoir of endemic flying fox species. However despite this, examination of these agents in detail reveals that the likely risk of them becoming established in Australian pig herds through a reverse zoonotic event is very low, although the outcome may be catastrophic.

Nipah virus has caused outbreaks of disease in Malaysia, Singapore and India. However, as outlined in section 1, it causes characteristic clinical signs of encephalitis in humans. The most likely potential route for introduction of this virus into the Australian herd is through itinerant piggery workers entering the system from, or returning from family holidays in, South-east Asia. Given the incubation period for *Nipah virus* infection is between 6 and 11 days (Hossain et al., 2008), consideration of a simple biosecurity measure of a 14 day quarantine period for workers who have had contact with pigs outside of Australia before entering a piggery may be sufficient to prevent transmission. A similar situation exists for SARS coronavirus, which has an incubation period of 5 – 7 days (Donnelly et al., 2003) along with the added caveat that the last confirmed human case of SARS was in 2004 (http://www.who.int/csr/don/2004_05_18a/en/). It is therefore highly unlikely that a worker will bring SARS coronavirus into an Australian piggery, however a quarantine period of 14 days as for Nipah is still recommended. There are few human cases of *Reston ebolavirus* seroconversion, with the silent nature of infection meaning that the incubation period is unknown, therefore it is difficult to know if, or when, a human will excrete the virus following infection. However WHO guidelines state the incubation period for pathogenic ebolaviruses to be 21 days, and one study has recommended a 25 day incubation period be considered (Eichner, Dowell and Firese, 2011). Geographically, the Philippines is the highest risk area for *Reston ebolavirus* (Miranda and Miranda, 2011), and theoretically, the large number of Filipino workers may be a risk factor for introduction of the virus.

The quarantine scenarios stated are currently unlikely to be feasible for industry to adopt. Workers have four weeks of leave per year, therefore if they visited their family for one week they would need

three weeks of leave to be used as quarantine when they return to Australia. Nipah is potentially the most damaging of these three viruses to the industry, and a compromise between feasibility for industry and incubation period of the disease could be the implementation of a seven day quarantine period upon workers returning from Asian regions.

5.2 Eschericia coli, MRSA, Streptococcus suis, Salmonella sp.

These are the top ranking reverse zoonotic bacterial agents arising from this review. Critically important antimicrobial resistant *E. coli, S. enterica* and MRSA are not pig pathogens. However they pose public health risks due to the resistance to critically important antimicrobials and limited antimicrobial therapy if they cause infection in humans. In addition, these agents can circulate among the pigs and environment and act as large reservoirs for these organisms. Since these organisms are treated with extreme care in health care setting these is also a public relations issues arising from these organisms being present in pigs.

Currently *S. suis* is recognised as a zoonotic agent and not as reverse zoonotic agent. However, *S. suis* can colonise humans, and as a result there is a possibility that *S. suis* from overseas could potentially be introduced into the Australian herd. This has been seen with the detection of European LA-MRSA clones in Australian pigs. However, the likelyhood of these organisms entering the Australian pig industry is low. It is important to note that in Australia, we do not have the hyper-virulent epidemic strains ST7 responsible for large-scale S. *suis* outbreaks in China (Lachance et al., 2013). It is therefore important to prevent or limit the introduction and spread of such strains in Australia. Resistance to agents such as tetracylines, macrolides, β-lactams, amino-glycosides, trimethoprim–sulfamethoxazole, chloramphenicol, and fluoroquinolones are common among *S. suis* from other countries (Soares et al., 2014; Palmieri, Varaldo and Facinelli, 2011). In Australia, antimicrobial resistance among *S. suis* is unknown. However, generally in Australia, *S. suis* is not associated with multi-drug resistance and *S. suis* infections are controlled by first line β-lactams.

The only probable route for the introduction of overseas strains of *S. suis* in Australian pigs is via human transmission. As a result, strict biosecurity is key in keeping these strains away from Australian pig industry. Since it is unclear how long these strains colonises humans, it is very difficult to recommend quarantine restriction for overseas workers returning from overseas particularly Asia. Industry may wish to explore whether testing returning workers for these agents, followed by treatment before return to work if positive results are returned, is an option.

It is important to perform routine surveillance of virulent pathogenic *S. suis* from an animal health point of view. However, cost associated with large scale surveillance is likely to be a major hurdle. Routine monitoring and molecular typing of pathogenic *S. suis* submitted to veterinary diagnostic laboratories will provide passive data collection for the Australia pig industry.

Questions which could be considered regarding this group of bacterial pathogens include the following;

1) What is the likelihood of these pathogens being carried by people who have direct contact with pigs?

2) What are current frequencies of occurrence of these organisms in Australian pig industry?

3) What is the real public and animal health impact of mobile genetic elements such as plasmids that encode critically important antimicrobial resistance?

4) What proportion of the faecal flora consists of the critically important antimicrobial resistant *E. coli* and *S. enterica* in pigs. Is it low or high? If it is low what are the chances of that organism disseminating in the pigs and piggery environment with the use of routine antimicrobials used in the pig industry?

5) How long do these agents survive in human gastrointestinal and respiratory tract microflora?

Addressing these issues will enable the industry to perform appropriate risk assessment and identify effective control measures and policies to limit the transmission of these organisms in to Australian pigs.

Options for addressing these questions may include:

1) Identify the baseline carriage of CIA-resistant *E.coli* and *Salmonell* sp., MRSA and *S. suis* in Australian pig workers and Australian pigs

2) Identify the molecular characteristics to these agents to assess the potential transmission of these agents between humans and pigs.

3) Perform routine herd monitoring via pooled sampled surveillance.

4) Develop an education campaign for on-farm/worker dissemination regarding potential routes of transmission of CIA resistant organisms. This could be tied in with the abovementioned education campaign suggestions.

If monitoring in pigs was to be undertaken, it would be cost effective and informative to investigate all organisms at the same time. Once the baseline is established routine monitoring can be performed cost effectively by using pooled herd samples. This has been used in past for other pathogens such as Bovine Johne's Disease surveillance and detection.

5.3 Influenza A viruses

Influenza does not have the same public stigma as Nipah, SARS and Ebola (although as seen from the pandemic H1N1 outbreak, media labelling can be to the industry's detriment). It is not a trade barrier, and human strains are not exotic, all of which combine to lower the ranking compared to these other agents. Influenza A viruses are endemic in Australia, both in the human population, where seasonal strains circulate in a generally well characterised temporal pattern, and in avian reservoir host populations (Grillo et al., 2015). In addition to this, the well characterised spillover event from humans to pigs of pH1N1 (2009) influenza occurred in 2009 (Holyoake et al., 2011), with investigations undertaken at the time demonstrating evidence of other H1 and H3 influenza subtypes within some herds (Wong et al., 2018). Due to these demonstrated events, the previously discussed reasons explaining the ranking and risk of the exotic viruses and the position of influenza A in the top grouping

of the table, we consider influenza A to be the viral agent most likely to be involved in reverse zoonotic events in the Australian swine industry.

Given the evidence of variant influenza A viruses present in Australian swine (Wong et al., 2018), the paucity of data in relation to the current situation in Australian swine, and the potential for influenza viruses to remain endemic in populations and cause production losses (Vincent et al., 2008), the options for dealing with the potential risk associated with this agent are twofold. Firstly, transmission of seasonal influenza A from humans to swine is likely to be markedly reduced by vaccination of all piggery workers annually with the seasonal vaccine, and this is the key recommendation to be adopted. It should also be emphasised to workers, perhaps through on-farm educational campaigns, that staying away from piggeries when suffering from influenza-like illness is highly important in preventing potential transmission of disease to pigs. Secondly, APL may wish to oversee a structured surveillance programme, using de-identified sampling, to determine which subtypes are circulating (or indeed if any are circulating) in Australian piggeries. Presently, any response to respiratory disease precipitated by reverse zoonotic transmission of Influenza A would be markedly complicated by the lack of information regarding other circulating strains. Varying levels of cross-reactivity in serological assays between strains and subtypes will make interpretation of laboratory results difficult unless some data on which subtypes have previously circulated through a herd is available. In addition to this, very little research has been performed on the impact of seasonal human influenza strains on swine production. Current vaccines available in the United States are based on circulating H1 and H3 subtypes, however due to extensive antigenic drift and shift (Anderson et al., 2015), more producers are relying on autogenous vaccines targeted towards particular strains on-farm. It may be feasible that any surveillance programme undertaken, be combined with a clinical disease and/or production analysis research programme to determine a) if Influenza A viruses are affecting production in Australian piggeries through destabilisation of respiratory (and general) health status and b) if there is a requirement for development of a vaccination programme.

5.4 Norovirus and Rotavirus

The key features of norovirus and rotavirus reverse zoonotic transmission relate to their faecal-oral transmission cycles, persistence in the environment and high levels of infectivity. There is little evidence linking noroviruses to disease in swine, however there is molecular evidence linking human isolates to those found in swine, and the presence of separate swine isolates and human isolates may lead to recombination events if swine are infected concurrently with both (Chao et al., 2012). In contrast, rotaviral disease in swine can be a significant issue, particularly in suckling piglets (Theuns et al., 2016) and in a similar situation to noroviruses there is evidence of recombination between human and swine isolates of rotaviruses (Santos et al., 1999). There is little available on the presence or genotypes in Australian swine, with the last published study appearing to be in the late 1980's (Huang et al., 1989). It is difficult to accurately assess the levels of these viruses in the general population, as despite notification systems, these only capture laboratory confirmed cases, although it has been documented that the national rates of rotaviral gastroenteritis have decreased following implementation of vaccination programmes in children (Dey et al., 2012).

Our recommendations for the prevention of transmission of rotaviruses and noroviruses from humans to swine are biosecurity and hygiene related. Workers suffering from gastroenteritis should not be allowed to enter the piggery. An education campaign outlining the importance of this could be undertaken across piggeries. The campaign should address the basic principles of transmission of these

viruses, and emphasise the importance of personal hygiene, and hand washing techniques, in particular the use of prolonged, thorough, soap and water washing, as alcohol based gels are not particularly effective against non-enveloped viruses. A separate wash station and clothing change area may be provided for feed preparation operations, as dissemination of viral particles through feed is a possibility. This would not be required for fully automatic operations where workers do not touch feed materials, and automating feed supply as much as possible would aid in mitigating the risk of transmission. On piggeries where this is not feasible, risk will be minimised by workers wearing disposable latex gloves when measuring out feed, and wearing disposable gloves under standard work gloves when working on feed machinery or cleaning blocked feeders.

Providing the piggery with a well maintained, potable water supply is essential to preventing the transmission of a number of pathogens from humans to swine. Of the top 15 listed agents, 9 can be transmitted via the faecal-oral route, and as a result by contaminated water. Breaking this pathway by routine water sanitation/disinfection is a key component of minimising risk. Complete separation of human effluent pathways (septics/sewerage) from any incoming potable water system is essential, as contamination of water supplies with human waste is a key transmission pathway for these viruses. It would be advisable for piggeries to undertake a basic mapping survey marking positions of effluent flow (both from within the piggery and associated buildings), incoming water flow and gradients of the land ie to determine if pipe leakage of an uphill sewer system could result in leaching into piggery water. The risk of this could then be assessed and practical measures taken to minimise leakage and leaching.

Aside from prevention aspects, a small scale surveillance project to characterise (if present) currently circulating genotypes may be useful to the industry. In a similar manner to influenza investigations, the lack of data on enteric viruses would make establishing causation between an introduced human strain and any disease aspects very difficult to achieve. In addition, should human-swine recombinant viruses be detected through public-health channels in the future, it would benefit the industry to be able to demonstrate the genetics of viruses circulating in pigs. This could be easily performed through lairage faecal sampling and genotyping PCRs, or potentially on a pilot scale by utilising samples taken for the APL antimicrobial resistance survey.

5.5 Taenia solium

Control of *T. solium* infection of pigs from humans is primarily dependent on breaking the faecal-oral transmission cycle. In endemic areas, pigs have easy access to human sewerage which potentiates the transmission cycle, an issue which is not seen in Australia's highly biosecure commercial piggeries. However, in order to minimise risk, a review of human sewerage systems adjacent to piggeries is advisable to ensure cross-contamination of piggery water or feed supplies is not possible. As Australia is free of *T solium*, entry of this parasite into piggeries is most likely to occur via the return of foreign piggery workers who have eaten insufficiently cooked pork while overseas. In order to minimise this risk, education on transmission of this parasite and hygiene measures to prevent faecal-oral contamination can be disseminated to staff. Additionally, in consultation with health authorities, risk could be minimised by treating all workers returning from *T. solium* endemic regions with an appropriate dose of anthelmintic prior to starting or resuming work.

5.6 Giardia and Cryptosporidia

The infection of pigs with zoonotic species and genotypes, including *C. parvum* and *G. duodenalis* assemblage A, indicates that they may play a potential role as sources of infection for humans. However studies from Western Australia concluded the absence of the zoonotic species *Cryptosporidium parvum*, suggesting that domestic pigs do not pose a significant public health risk. Although sporadic cases of *C. suis* in humans have been reported, its contribution to the epidemiology of cryptosporidiosis in humans, is very limited.

The application of swine manure in the cultivation of food and forage crops, as well as the spreading of swine slurry onto pasture and tillage land for the sole purpose of disposal, are common practices. Swine manure can be highly prevalent for *Cryptosporidium* spp. Proper composting of manure at ≥55°C for 3–15 days can yield safe fertilizer by destroying a number of different pathogens, however, and while *Giardia* cysts are degraded in swine manure holding tanks, *Cryptosporidium* could be still detected in some of the treated swine slurry (Xiao et al., 2006). The presence of *Cryptosporidium* oocysts or Giardia cysts in swine manure can manifest as direct contamination of produce and indirect contamination of water supplies through agricultural run-off.

The faecal-oral transmission is the key source for initiating the reverse zoonoses cycle of Giardia and Cryptosporidia between a human carrier and pigs. This could be logically avoided by maintaining sanitary facilities on farm (water and feed as discussed above) and educating piggery workers on the importance of good farming practices and the need to maintain basic hygiene and healthy behaviours in the farm environment.

5.7 Clostridium difficile

Studies have shown that based on ribotyping, certain strains of *C. difficile* such as RT033 and RT046 have been identified from both pigs and humans in Australia (Knight, Squire and Riley, 2014; Norén, Johansson and Unemo, 2014). However, based on the limited studies in this area, we cannot conclusively identify this *C. difficile* as a major zoonotic or reverse zoonotic agent in Australia. In addition, full molecular characterization and whole genome sequencing analysis would be required to conclusively establish the zoonotic or reverse zoonotic potential. Despite of the inconclusive nature of the evidence, it is advisable to be cautious and proactive in dealing with this pathogen since *C. difficile* is a major human pathogen and can also cause disease in pigs. In addition, *C. difficile* can persist in the piggery environment for a long period of time. Furthermore, we recommend the industry to educate pig farmers and persons linked to pig production regarding the risks of *C. difficile*. Periodic survey of *C. difficile* in Australian pigs, while not essential to minimising ongoing risk, may be considered to evaluate the emergence of human associated clones in Australian pig industry.

5.8 Campylobacter coli

Campylobacter is the most common cause of bacterial gastroenteritis in Australia. Poultry has been recognized as the primary reservoir of *C. jejuni*, while pigs are mostly implicated as reservoirs of *C. coli*. European studies highlighted *C. coli* as an important human pathogen due to its ability to show increased resistance to greater number of antimicrobials.

Transmission of *Campylobacter* spp from pigs appears to be non-evident for *C. jejuni* and of very low risk for *C. coli* and this is confirmed by Kramer et al (2001) and also by Smerdon et al (2001), where only two out of 4604 incidents of infectious intestinal disease, investigated and reported to the Public Health Laboratory Service in the UK, over an eight year period, were linked to pig meat and one of these was due to cross contamination (Kramer et al., 2000; Smerdon et al., 2001). As for *Giardia* and *Cryptosporidia*, reducing the risk of transmission from workers to swine is based on hygienic practices. We recommend an education campaign on hygiene as related to faecal-oral transmission of these pathogens be prepared for farm workers as the best method to minimise risk of transmission.

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7 Publications Arising

List publications and where possible append copies of published articles. Note that all publications arising from the project, either during or after completion, must be approved by APL on the standard APL Request for Disclosure form before release.