

The vertical transmission of *Salmonella* Enteritidis in a One-Health context

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ABSTRACT

Salmonella enterica serovar Enteritidis (S. Enteritidis, SE) is a foodborne zoonotic pathogen, causing economic losses in animal husbandry and large numbers of human deaths and critically threatening economic development and public health. Human infection with SE has complex transmission routes, involving the environment, animal reservoirs, and water in a One-Health context. Food-producing animals, particularly poultry and livestock, are regarded as the most common sources of SE infection in humans. However, there is little known about the vertical transmission of SE in a One-Health context. In this review, we analyze the ecological significance of SE in a One-Health context. Importantly, we focus on the difference in vertical transmission of SE in poultry, livestock, and humans. We introduce the transmission pathway, describe the immune mechanisms, and discuss the models that could be used for studying the vertical transmission of SE and the strategy that prevention and control for vertical transmission of SE into the future from a One-Health perspective. Together, considering the vertical transmission of SE, it is helpful to provide important insights into the control and decontamination pathways of SE in animal husbandry and enhance knowledge about the prevention of fetal infection in human pregnancy.

1. Introduction

Salmonella is a major zoonotic food-borne pathogen of worldwide importance [1]. It is estimated that *Salmonella* causes 93 million enteric infections and 155,000 deaths each year globally [2]. According to the human isolates of *Salmonella* collected from the laboratories of 37 countries between 2001 and 2007, *Salmonella enterica* serovar Enteritidis (SE) ranked as the first serotype of all *Salmonella* isolates [3]. SE can cause human gastrointestinal tract infection, leading to diarrhea and death [4]. Between 2016 and 2020, SE affected 18 countries in Europe causing a child and an elderly person to die due to the infection [5]. Human infection with SE has complex transmission routes, involving the environment, animal reservoirs, and water in a One-Health context. Food-producing animals, particularly poultry and livestock, are regarded as the most common sources of SE infection in humans [6,7]. However, there is little known about the vertical transmission of SE in a One-Health context. In this review, we focus on the difference in vertical transmission of SE in poultry, livestock, and humans. Together,

considering the vertical transmission of SE in a One-Health context, it is helpful to provide important insights into the control and decontamination pathways of SE in animal husbandry and enhance knowledge about the prevention of fetal infection in human pregnancy.

2. Ecological significance of SE transmission from a One-Health context

The transmission of SE in a One-Health context involves many ecological routes, including foodborne, waterborne, cross-species, and vertical transmission (Fig. 1). The foodborne transmission of SE may occur through the fecal-oral route, which is related to the environment polluted by SE excreted by animals or humans through their feces [8,9]. SE is transmitted to humans through contaminated eggs or meat products [10–12]. Rodents and insects are the main carriers of SE contamination and foodborne transmission [13,14]. Another transmission route of SE is caused by polluted waterborne, mainly due to human activities, such as poor management of farm manure and waste, which leads to

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polluted runoff entering many aquatic environments such as oceans, rivers, streams, and lakes [15,16]. The cross-species transmission is frequently raised as an important driver of SE transmission in animal husbandry. SE can be transmitted between chickens and pigs through contaminated feed or the environment in a free-range environment [17]. At the same time, studies have shown that SE in contaminated pastures can be transmitted between buffalo and pigs [18]. Importantly, the vertical transmission of SE cannot be ignored in poultry, livestock, and human beings. Inside the poultry, SE colonizes the ovarian tissue of hens and contaminates eggs through vertical transmission, which causes massive economic losses to the poultry industry and infects humans [19,20]. In livestock, studies suggested that SE was isolated from pregnant sow and gilt, and recovered from various tissues of viable newborn calves immediately after parturition, demonstrating that vertical transmission can occur in livestock [9]. In humans, early studies reported that SE infections in pregnant women caused preterm birth with the baby died 4 h after birth from septic shock and were cultured from blood cultures and swabs of the premature infant and from the placenta and uterus [21]. The complexity of transmission routes in animal husbandry and human from a One-Health perspective increases the risk of SE infection and vertical transmission.

3. The pathways for vertical transmission of SE

SE can colonize mammalian uterus and poultry ovary. More concretely, SE colonizes the intestinal tract and then invades the dendritic cells in the intestinal epithelial cells after entering the host [22]. It invaded the macrophages to survive through the phagocytosis of macrophages reaching the submucosa [23,24]. The bacteria type III secretion system (T3SS), adhesion, and pili play important roles in this process [25]. SE can form vacuoles containing SE after entering macrophages [26,27]. After entering the microfold cells, SE is transported to the intestinal lymphatic follicles and mesenteric lymph nodes, and part of it is transported to the reticuloendothelial cells of the liver and spleen [28,29]. Some of SE go into the mother's uterus and colonize mammals. The reproductive and excretory tracts are shared, and SE has the potential to occupy the reproductive tract and ascend to the ovary in poultry.

3.1. Vertical mechanism of SE contamination of eggs

Eggs and egg products are not only the main way for humans to obtain protein but also the most common food vehicles for human infection with SE [30]. SE can colonize chicken ovaries for a long time to form persistent asymptomatic infection, which will not only lead to a decline in egg production and egg quality but also lead to egg pollution

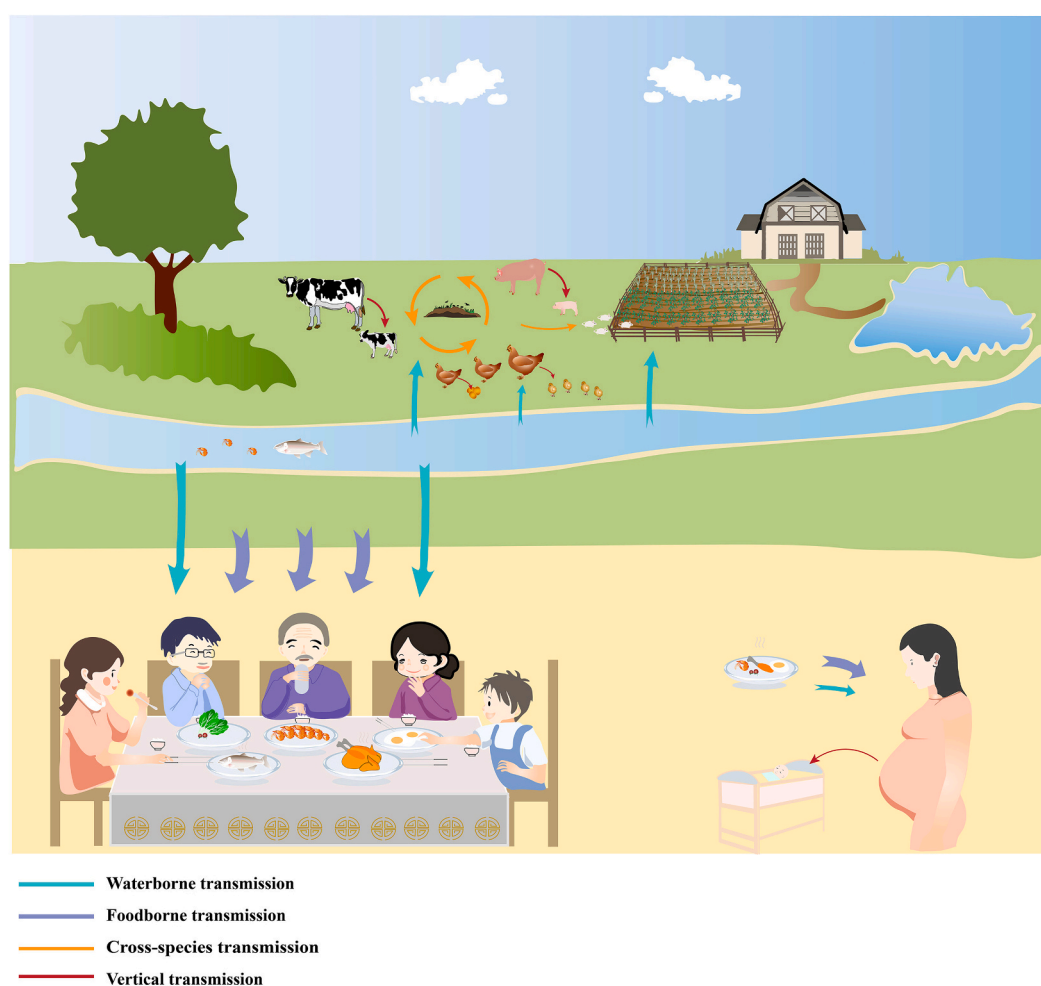


Fig. 1. Ecological significance of SE transmission from a One-Health context. Rodents and insects are the main vectors of SE contamination and cross-species transmission and can transmit the bacteria through feces. In a free-range environment, SE can be transmitted between chickens, cattle, and pigs through contaminated feed or the environment. At the same time, SE in contaminated pastures can be transmitted between cattle and pigs. SE is transmitted to humans through contaminated eggs or meat products.

[31,32]. There are two possible ways for SE to contaminate eggs. Eggs can be contaminated by penetrating the eggshell from colonized intestines or contaminated feces during or after spawning (horizontal transmission) [33]. The second possible way is to directly contaminate the albumen, yolk, shell membranes, or eggshell before spawning, resulting from genital infection with SE (vertical transmission) [34,35]. The albumen is most often contaminated, indicating that the fallopian tube is the site of colonization [36]. However, protein restricts the growth of SE because it contains a variety of antibacterial components that can induce cell wall and DNA damage [37]. Others pointed out that the yolk was the most common site of contamination [38,39].

Egg yolk contamination may occur due to the colonization of SE in the ovaries [40,41]. During ovarian colonization, SE can lead to contamination of mature developing eggs throughout the reproductive cycle by attaching to developing and mature follicular granulosa cells [42,43], which leads to the decline of developing egg production and developing egg quality pollution [31]. SE is more likely to deposit on the outside of the yolk membrane during ovarian colonization. The number of bacteria in the theca was higher than that in the yolk itself before ovulation, indicating that SE was still attached to the yolk membrane during transmission through the ovary [40]. When the yolk membrane was inoculated, SE was detected in the yolk, indicating that it migrated from the egg white to the yolk [44,45]. The yolk membrane in fresh eggs inhibits the invasion of SE into the egg yolk. As the yolk membrane loses its integrity during storage and gradually deteriorates, causing nutrients to leak into the protein, it is possible to attract bacteria that can penetrate the yolk membrane and multiply in the nutrient-rich yolk [46]. Therefore, SE infects the ovaries, attaching to the vitelline membrane, migrating and colonizing the yolk after laying eggs, which is the pathway of vertical transmission in poultry (Fig. 2(a)).

3.2. The entry of vertical transmission of SE in mammals

Livestock and their products are the primary sources of human meat and the primary route by which SE contaminates and infects humans through foodborne sources. Foodborne illnesses with average annual increases for SE are increasing the risk in pregnancy [47].

In humans, SE infection can cause complications such as sepsis, chorioamnionitis, fetal infection, neonatal sepsis, and miscarriage [48,49]. Recently a case reported that the vertical transmission of SE leads to septic abortion and acute respiratory distress syndrome (ARDS) during pregnancy [50]. The placental culture was positive for SE. In the human placenta, syncytiotrophoblast (SYN) cells provide effective protection against pathogens [51,52]. Human SYN is resistant to a variety of pathogens, but its precise molecular mechanism is not fully understood. However, there is evidence that SYN exploits a variety of pathogen-dependent mechanisms. The SYN acts as a biophysical barrier to the bacteria. Pathogens that ascend through the genitals to the decidua of the uterus infect invasive extravillous trophoblast (EVT) cells. The main way of transmission of pathogens through the placenta is through the initial infection of decidua and then to EVT. Human SYN can be used as a barrier against *Salmonella Typhimurium* infection. Overall, it has been speculated that the most likely mechanism of vertical transmission of SE may be through infection of fetal invasive SYN cells in mammals (Fig. 2(b)).

In livestock (pig, sheep, cattle), *Salmonella* causes abortion [53–55]. However, only a few cases of SE with vertical transmission are found in the literature. SE was identified in maternal blood cultures and placenta, consistent with SE being a pathogen that crosses maternal blood through the placenta.

SE infections are common and usually not serious. However, they can lead to life-threatening infections and fetal loss during pregnancy [56]. While salmonellosis can be controlled with antibiotic treatment, our study highlights the risk to pregnant women given the increased

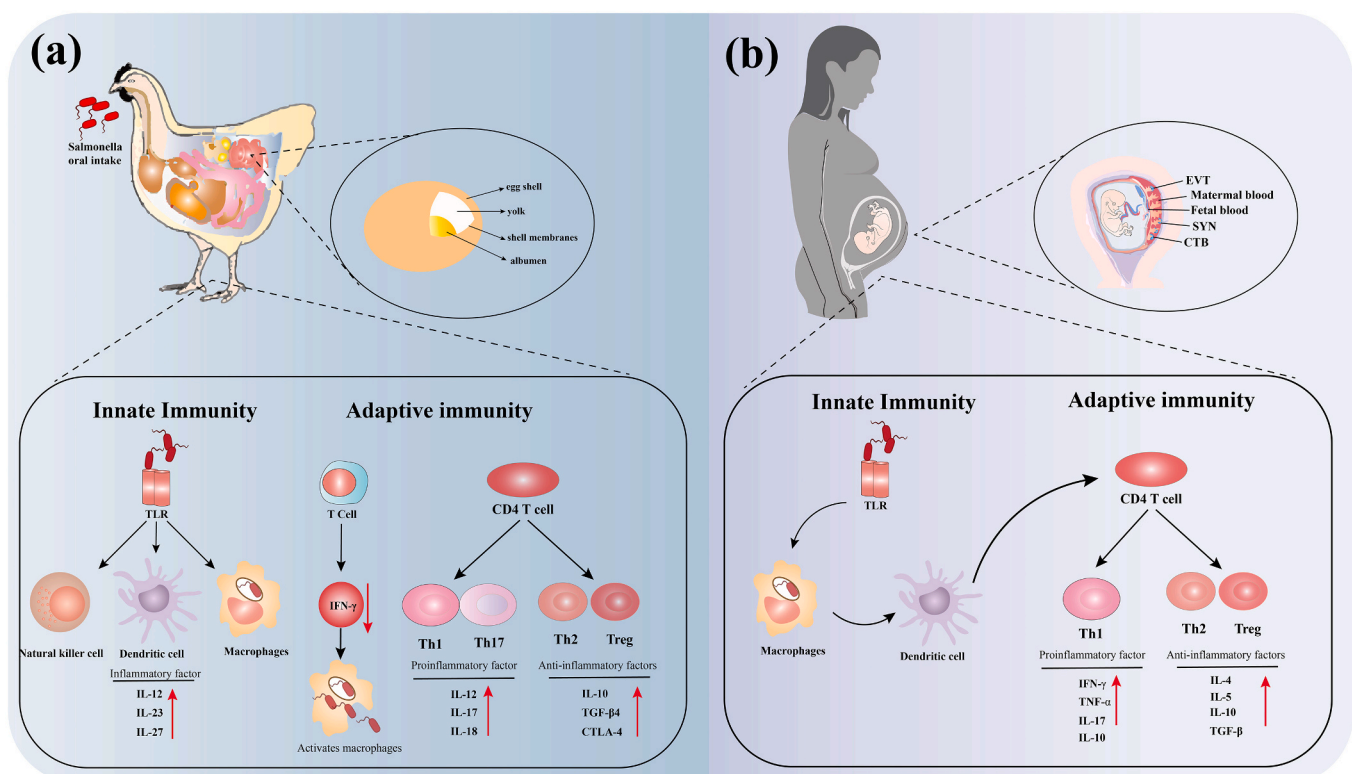


Fig. 2. Vertical transmission mechanism and immune response of SE. (a): Vertical transmission mechanism and immune response of SE in poultry. (b): Vertical transmission mechanism and immune response of SE in mammals.

incidence of this foodborne infection. Therefore, pregnant women are advised to be more vigilant against foodborne infections.

4. The immune responses for vertical transmission of SE

The immune response to SE infection during egg production and early pregnancy may facilitate its vertical transmission. In poultry, SE infection-induced innate and adaptive immune responses may support its vertical transmission (Fig. 2(a)). In the maternal, the immune responses and tolerance to SE during pregnancy may adversely affect the fetus in mammals and increase facilitate vertical transmission (Fig. 2(b)).

4.1. SE infection-induced immune responses may support its vertical transmission in poultry

Innate immunity could affect the probability of pathogen transmission to their offspring in birds [57]. SE-induced innate immunity may be associated with vertical transmission. Innate immunity cells including natural killer (NK), macrophages, and dendritic cells (DCs) were activated within one week of SE infection, which promotes host inflammatory responses. NK cells are activated directly via Toll-like receptors (TLRs) after SE infection [58]. The NK cell-mediated *IFN-γ* genes were upregulated within the one-week response to SE infection, which may lead to more systemic infection and colonization of the reproductive tract [59]. Macrophages, as the carrier of systemic transmission, are not only the major effector cells eliciting innate immunity, but also play an important role in SE-contaminated eggs in chicken [60]. Recently, infection with SE has been shown to inhibit NO production in macrophage HD11 cells [61], which contributes to survival within HD11 cells, and increases systemic transmission and reproductive organ colonization resulting in internal egg contamination [62]. Besides macrophages, DCs came into focus as important cells mediating immune responses against SE in recent years [63]. DCs produce IL-12, IL-23, and IL-27 after LPS/TLR4-dependent induction by SE, which are used to coordinate cell-mediated immune responses [63]. Overall, SE-induced innate immunity may contribute to increased reproductive tract colonization and internal egg contamination.

In addition to innate immunity, T cell-mediated adaptive immunity also has implications for SE infection and transmission to eggs. From one side, the T cell activation of the host after SE infection results in the production of *IFN-γ*, which in turn activates macrophages, leading to a reduction in the initial acute systemic infection and the formation of a carrier state macrophages [64]. The carrier state is maintained by the production of *IFN-γ* through T cells. The onset of egg laying results in marked immunosuppression, loss of T cell activity, and disruption of carrier state leading to reproductive tract infection and egg transmission. On the other side, activated CD4 T lymphocytes after SE infection secrete various cytokines to mediate immune responses. Th1 and/or Th17 involvement in IL-12, IL-18 *IFN-γ*, and IL-17-related cytokine expression in CD4 T cells enhances host clearance of SE [65,66]. Th2 and Treg cytokines including IL-10, TGF-β4, and CTLA-4 in CD4 T cells limit the inflammatory response, which may promote immune-evasive clearance of SE leading to persistent infection and increase the likelihood of vertical infection [67]. When chickens start laying eggs, SE proliferates intracellularly and spreads into the reproductive tract, and the ovary uses a similar strategy to directly inhibit T cell proliferation to promote vertical transmission.

4.2. Maternal immune responses to SE during pregnancy may adversely affect the fetus in mammals

Mammals with *Salmonella* infection lead to spontaneous abortions, and fatal outcomes for fetuses, which is related to the immune response during pregnancy [68]. The immune response to SE infection during early mammal pregnancy relies on an innate phagocytic system

including fetal macrophage-like phagocytes (FM), neutrophils, and DCs [69]. Innate FM can sequester endocytic antigens, differentiate into DCs, and present antigens to T cells later in life to trigger adaptive immunity [70]. The adaptive immune response following SE infection in mice and humans is a Th1-biased phenotype, which is achieved by macrophage activation of cytokines such as *IFN-γ* and TNF-α [70,71]. The expression of *IFN-γ*, TNF-α, IL-17, and IL-10 is upregulated in response to SE in the placenta, amniotic fluid, and maternal serum [72]. Increased *IFN-γ* in the placenta was associated with placental damage and increased levels of markers of infiltration and hypoxia (Cyclooxygenase-1 and Cyclooxygenase-2 expression, respectively) that may contribute to pre-term birth [73,74]. Elevated IL-17 may be detrimental to pregnancy maintenance and may promote inflammation at the fetal-maternal interface.

Immunological adaptations in mammals during pregnancy allow maternal tolerance of the semi-allogeneic fetus, which may increase and facilitate the vertical transmission of SE. Fetal immune tolerance is essential to the maintenance of pregnancy, achieved in large part by the ability of Th2 and T_{reg} cells [75]. Fetal exposure to SE flagellin induces Th2-skewed immune responses with enhanced IL-4 and IL-5 but not heightened *IFN-γ* production, which is a simplistic explanation for promoting tolerance during pregnancy [76]. However, the T_{reg} cell's responses that express the forkhead box p3 (Foxp3) transcription factor, and secrete anti-inflammatory cytokines such as IL-10 and transforming growth factor-beta (TGF-β) during pregnancy may contribute to the exacerbation of *Salmonella* infection in pregnant mice [77]. Overall, maternal Th2 and T_{reg} cells suppress the maternal immune system to maintain pregnancy, which makes it easier for SE to pass through the host-placental barrier to the fetus.

5. The current models in studying the vertical transmission of SE

Vertical transmission of SE causes severe harm to poultry and livestock, increasing the risk in humans during pregnancy. However, there is currently a lack of appropriate model systems for research. We discuss and compare models that can be used to study the vertical transmission of SE to explore SE methods that can help improve the understanding of fetal infection prevention during pregnancy in humans (Table 1).

5.1. Mouse model

The mouse is the most powerful mammal model used to explore the virulence and immune response of pathogenic microbes infection [78,79]. Immunization with SE through the intranasal or intraperitoneal route in the mouse model can induce significant humoral and mucosal immune responses [80]. Mouse models were used to analyze the virulence and immune responses of pathogens to placental infection and to perform genetic manipulation [81]. Like the human placenta, the mouse placenta is a blood chorionic membrane, the trophoblast invades the maternal decidua, and they have a similar composition of decidual immune cells [82,83]. However, mouse placentas are maze-like and less invasive, and their morphology may have led to the evolution of features different from human trophoblasts [84]. The mouse had a labyrinth of placenta with two layers of SYN and a complete monocyte trophoblast [85,86]. By contrast, humans have a villous placenta, maternal blood in direct contact with the placenta, and only a layer of SYN bathed in maternal blood [87,88]. The maternal blood of mice was in direct contact with a layer of mononuclear trophoblast (MNT), which covered two layers of SYN. Nutrients, gases, and waste must pass through the double layers of MNT and SYN to reach the fetal blood [89,90]. The pregnant mouse models can be used to understand how the host immune system balances fetal tolerance and maternal and fetal defense against pathogens [72]. Such models can be used to investigate how SE colonization and transmission occur during pregnancy [73]. The mouse model can also test the role of specific cell types and cytokines on the maternal-fetal interface.

Table 1

Comparison of advantages and disadvantages of various models for studying placental pathogens in SE.

Models	Features	Function	Advantages	Disadvantages
Mouse	Invasion of hemochorial and trophoblasts into maternal decidua; Similar to decidual immune cell composition	Testing the roles of specific cell types and cytokines at the maternal-fetal interface; Determining how colonization and dissemination occur	Investigating the immune responses to SE; Carrying out a large set of genetic knockouts and a short gestation with a large litter	Labyrinthine and less invasive; The interface with the maternal blood is thicker
Non-human primates	The placental structure and immune response most similar to those of humans	Investigating immune regulation in placentas	The villous hemochorial placentades into the decidua	A single fetus has two discoid placentas with a long gestation period
Human placental organ explants	Simulating the process of human placental infection with SE and eliminating the differences caused by other animal models	Understanding how the human placenta resists SE infection and exploring how the maternal uterine layer defends against pathogens	Removing the concern of a species artifact	A first-trimester sample differs considerably from a sample obtained after delivery; Genetic differences between donors
Embryo model	The avian embryo consists of a flat; Two-layered blastoderm that lies on the surface of the yolk and therefore is readily accessible	Focusing on the molecular basis of cell development or cell-cell interactions, immunology, and the relatively new field of epigenetics	The chicken embryos develop very fast; The incubation of chicken eggs can be terminated at any time; Both in-ovo and ex-ovo chicken embryos are easy to visualize	The abiotic factors have been found to influence embryonic development and adult phenotype; The maternal effect is restricted to egg composition

5.2. Non-human primates

Non-human primates (NHP) have the most similar placental structure and immune response to humans [91]. Like humans, NHP have blood villous placenta that invades the decidua [92]. SE can be colonized clinically in NHP [93], but it is rarely used to study vertical transmission. NHP has a long gestation period and a small number of fetuses per pregnancy. Ethical and legal need considerations regarding the use of these animal standards. In addition, it is common for these models to have two placentas in a fetus, whereas in humans each fetus has one.

5.3. Human placenta organ explant

Human placenta organ explant is the preferred path for research vertical transmission to human pathogens, it can simulate the process of human placental infection with pathogens and eliminate the differences caused by other animal models, but the samples obtained in the early stage of pregnancy are very different from those obtained after delivery [94]. The placenta and decidua change throughout pregnancy. Because the law may restrict or completely prohibit donation, the genetic differences between donors may vary greatly in the results. Finally, human tissues *in situ* cannot be genetically manipulated by standard cell culture techniques. Human placental culture has led to key discoveries of how the placenta can resist infection, and the ability to image and infect human placental tissue using differentiated and spatial tissue cell types can be a useful tool for understanding the placental defense. Decidual organ culture can also be used to explore how the maternal uterine layer can resist pathogens.

5.4. Embryo model

As an important animal model for basic research on poultry, chicken has a very special evolutionary status between mammals and vertebrates, such as an important model used in classical experimental embryology, immunology, behavior, reproduction, and vertical transmission of pathogens [67,95,96]. The chicken embryo develops very quickly compared with the model of mammals. Poultry embryos consist of two flat layers of blastocysts located on the surface of the yolk when spawning, so it is easily accessible. In addition, the egg hatch can be terminated at any time, thus providing certain experiments in the development stage of the embryo. Because chicken embryos are similar to human embryos at molecular, cellular, and anatomical levels, chicken embryos play a vital role in biomedical research. Another important advantage of a chicken embryo over a mammalian model is that it can be easily incubated and manipulated inside and outside the egg at a very low cost. Importantly, both intra- and extra-egg chicken embryos are

easy to visualize, and a variety of cell labeling techniques can be used to track cell movement and fate in real-time in chicken embryos.

6. Prevention and control strategy for vertical transmission of SE into the future from a One-Health perspective

The vertical transmission of SE brings economic losses to the breeding industry, in poultry, and which products poses a grave threat to human life and health [97,98]. The prevention and control strategy for vertical transmission of SE into the future from a One-Health perspective need consideration of a multiple factors involving the inter-relationship between human, animal, economic, and environmental health, and establishment of a multidisciplinary, cross-sectoral approach to control SE infection and mitigation of complex public health problems. In Canada, the National Integrated Enteric Pathogen Surveillance Program (C-EnterNet), collected data along the farm-to-fork continuum and provide information about exposure routes and sources of enteric organisms, suggesting that SE is frequently recovered from a variety of animal species along the farm-to-fork continuum and is particularly common among chicken samples [99]. However, even when corrective measures were taken, some of the farms were still found to be contaminated with the same outbreak strain or even multiple outbreak strains in Europe [100]. Recently, several international consortia (e.g., One Health European Joint Programme [<https://onehealthjp.eu/>], Public Health Alliance for Genomic Epidemiology [<https://github.com/pha4ge/pha4ge.github.io>], and Genomic Epidemiology Ontology [<https://genepio.org/>]) will provide data support for the traceability of SE. Therefore, in the future, the vertical transmission of SE in the One-Health environment needs to use the “One Health” a multidisciplinary and cross-sectoral cooperation approach involving partners in public health, food safety, veterinary and environmental sectors (Fig. 3).

7. Conclusion

In poultry and livestock, SE causes huge economic losses. Poultry and livestock and their products with contaminated SE adversely affect human pregnancy. In poultry, SE is transmitted to the next generation of poultry by infecting the ovaries, attaching to the vitelline membrane, and colonizing the yolk after spawning. In addition, SE is unique in that it can enter and multiply in eggs without causing noticeable changes. However, it remains to be seen whether male sperm is transmitted vertically. Unlike mammals, eggs do not develop in the safe environment of the uterus but are constantly protected by the hen's immune system. The inflammatory response induced by SE infection may support its vertical transmission in poultry.

In humans and poultry, the placenta can be considered the most critical barrier limiting vertical transmission of SE. At the same time, it

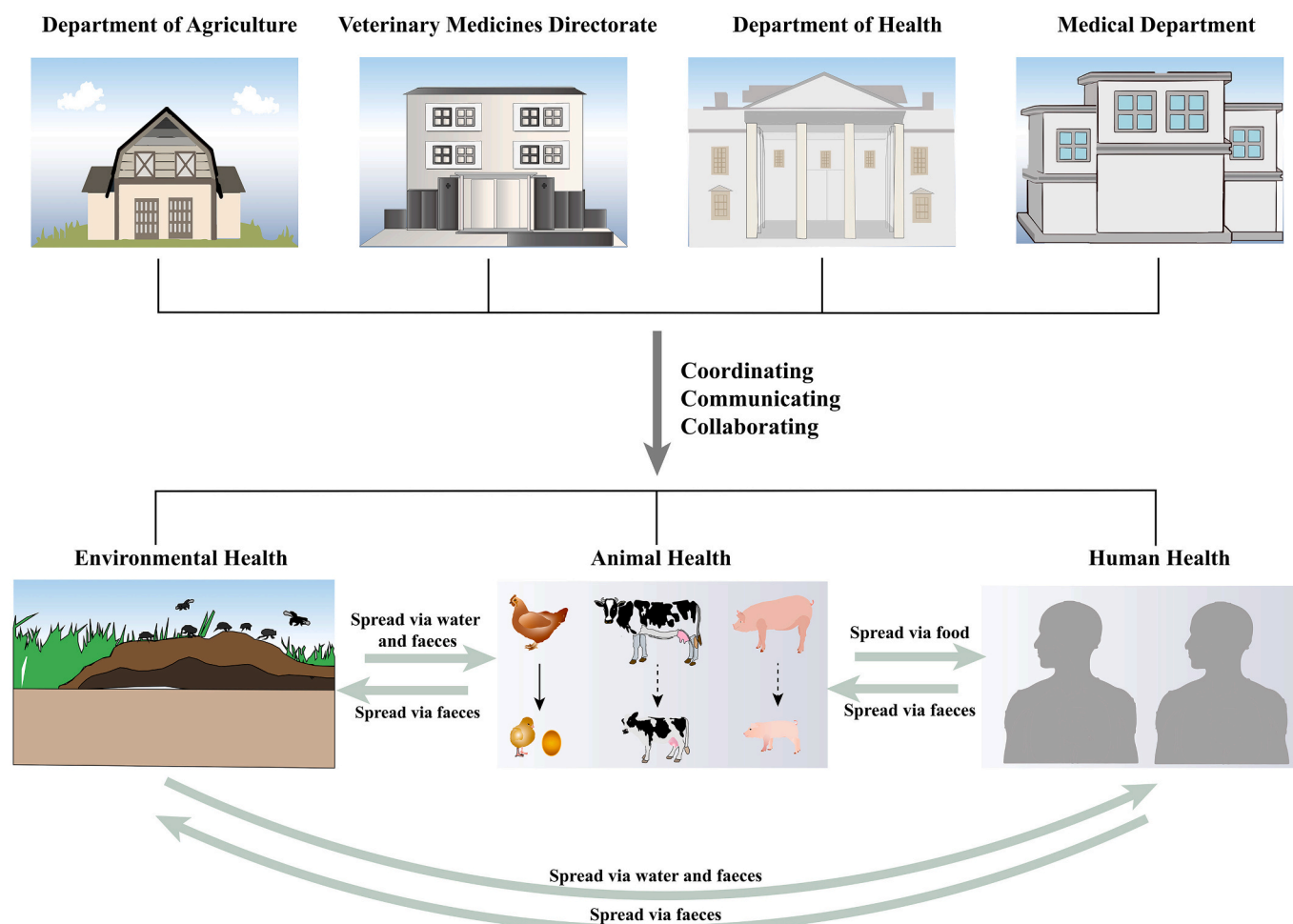


Fig. 3. Prevention and control strategy for vertical transmission of SE into the future from a One-Health perspective.

enters and colonizes the uterus of livestock, and enters the placenta through the SYN. Are the risks posed by infected pregnant women and pregnancy after infection the same? The pro- and anti-inflammatory responses may affect vertical transmission in humans and livestock. The placentas of many small animals show significant anatomical differences. It is difficult to develop a laboratory model that summarizes the complexities of vertical transmission of SE in humans and the stages of pregnancy. This is a major obstacle to understanding the mechanism of vertical transmission. Considering the vertical transmission of SE helps to provide important insights into the control and decontamination pathways of SE in animal husbandry, increasing the understanding of how these pathways can be therapeutic targets in humans and helping to improve the prevention of fetal infection during human pregnancy.

Author contributions

BBL designed the concept of the review article. BBL, XJZ, PB, and XYD contributed to writing the manuscript. GQZ critically read and corrected the manuscript. All authors read and approved the final manuscript.

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Declaration of Competing Interest

The authors declare that the review was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data availability

No data was used for the research described in the article.

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