The Journal of Animal & Plant Sciences, 30(2): 2020, Page: 259-279
ISSN: 1018-7081

REVIEW PAPER

MECHANISMS FOR *SALMONELLA* INFECTION AND POTENTIAL MANAGEMENT OPTIONS IN CHICKEN

M. Mkangara[1, 2,*], R. Mwakapuja[4], J. Chilongola[3], P. Ndakidemi[1], E. Mbega[1] and M. Chacha[1]

[1]School of Life Sciences and Bioengineering, Nelson Mandela African Institution of Science and Technology, P. O. Box 447, Arusha, Tanzania.
[2]Department of Science and Laboratory Technology, Dar es Salaam Institute of Technology, P.O. Box 2958, Dar es Salaam, Tanzania.
[3]Department of Biochemistry and Molecular Biology, Kilimanjaro Christian Medical University College, P.O Box 2240, Moshi, Kilimanjaro, Tanzania
[4]Tanzania Veterinary Laboratory Agency, P.O. Box 9254, Dar es Salaam, Tanzania
[*]Corresponding author's email: mkangaram@yahoo.com

ABSTRACT

Salmonella enterica is the largest species in genus *Salmonella* with its serovars responsible for infection in chickens and other warm-blooded hosts. After oral ingestion, *Salmonella* penetrates the mucosal layer of the gastrointestinal tract (GIT). It then provokes gastroenteritis and systemic infection to chickens of all ages depending on the serovar involved. The paper explains about *Salmonella* infection via Type Three Secretion System (TTSS) encoded Pathogenicity Islands (PIs) and how the bacterium survives the acidic environment of GIT. It also explains the roles of TTSS-1 and TTSS-2 in translocation of effectors that interfere with host proteins and later internalisation of *Salmonella* in *Salmonella*-containing vacuole (SCV). Other virulence factors such as plasmid, biofilm and lipopolysaccharides are highlighted, and their importance in inducing pathogenicity to host was also included in the paper. Therefore, several factors are geared toward survival, infection, and replication of *Salmonella* in the host cells. Hence, this article explains the mechanisms of *Salmonella* infection in chicken, its persistence in different environments and the approaches in controlling chicken salmonellosis.

Keywords: *Salmonella*, Type three Secretion System, Pathogenicity Islands, Chicken, Infection.

https://doi.org/10.36899/JAPS.2020.2.0050 *Published online March 02, 2020*

INTRODUCTION

Genus *Salmonella* is a Gram-negative, rod-shaped; facultative anaerobes bacilli that belongs to family *Enterobacteriaceae* (García *et al.,* 2011; Popoff and Le Minor, 2015). The genus is divided into two species *Salmonella enterica* and *Salmonella bongori* (Ryan *et al.,* 2017). In the classified *Salmonella* species, there are over 2600 serovars with the majority from *S. enterica* (Ranieri *et al.,* 2013; Shi *et al.,* 2015). The *S. enterica* is classified into six different subspecies *enterica* (I), *salamae* (II), *arizonae* (IIIa), *diarizonae* (IIIb), *houtenae* (IV) and *indica* (VI) (Lamas *et al.,* 2018). The subspecies *enterica* with more than 1500 serovars is of economic importance to chickens and other warm-blooded hosts (Roer *et al.,* 2016). The *S. enterica* serovar Gallinarum is restricted to all gallinaceous birds and contains two biovars, which are Gallinarum and pullorum (Parvej *et al.,* 2016). The biovars are invasive, highly host adaptive and induce systemic infection to chickens (Xiong *et al.,* 2018). Other serovars in subspecies *enterica* with broad hosts, invasive but non-adaptive to chickens are *S. typhimurium*, *S. enteritidis, S. heidelberg*, *S. kentucky*, *S. montevideo* and *S. hadar* (Andino *et al.,* 2014; Dhanani *et al.,* 2015). They elicit gastroenteritis but rarely induce systemic infection.

Non-*enterica* subspecies of *S. enterica* are related to cold-blooded animals, and their pathogenicity is very limited (Lamas *et al.,* 2018). The subspecies *arizonae*, *diarizonae* and *salamae* were reported to be found in chickens like resident microbiota with the importance of inhibiting other pathogenic bacteria (Maciel *et al.,* 2017). Similarly, the phages of *diarizonae* and *salamae* display activity against pathogenic serovars of subspecies *enterica*, namely *S. typhimurium*, *S. enteritidis* and *S. infantis* (Lamas *et al.,* 2018). The phages work against pathogenic *Salmonella* and are essential bactericidal for treatment of salmonellosis in chickens. Other approaches of minimising chicken salmonellosis discussed in this review include probiotics, antibiotics, vaccination, biosecurity measures and natural or purified herbs.

Colonisation and virulence of *S. gallinarum, S. pullorum, S. enteritidis* in chickens are mediated by virulence plasmids and the cluster of genes located in chromosomes called *Salmonella* pathogenicity islands (SPIs) (IIyas *et al.,* 2017). During the early stage of infection, SPI-1 encoded type three secretion systems

(TTSS-1) translocate effectors across the host cell membrane (Hurley *et al.,* 2014). The effectors are essential for bacterial invasion of host intestinal epithelial cell and stimulation of intestinal inflammation (Lorkowiski *et al.,* 2014). Following the introduction of effectors into the epithelial cell of the host, *Salmonella* alters host cell functions to enable survival, replication and finally, transmission (Fuentes *et al.,* 2008).

Internalisation of *Salmonella* occurs in membrane-bound vesicles termed as *Salmonella*-containing vacuole (SCV). *Salmonella* expresses the TTSS encoded *Salmonella* Pathogenicity Island-2 (SPI-2) within the SCV and plays a role of systemic infection (Foley *et al.,* 2013). During systemic infection, the bacteria spread all-over the body fluids and organs of a host including liver, spleen, bone marrow, and other organs rich in phagocytic cells (Barrow *et al.,* 2012). The genetic basis of this ability is not clear. However, breeders and researchers have endeavoured to understand the *Salmonella* adaptation to its host by studying specific genes with potential roles in disease resistance (Calenge *et al.,* 2010). The functions and contributions of TTSS and SPIs to infection in the host cells of a chicken are explained in the sections of this article.

***Salmonella* infection:** *Salmonella* in chickens occurs through horizontal transmission by the faecal-oral route or vertically through the ovarian transmission. In horizontal transmission, the infection arises after the bacterium survives the stomach acidic pH through Peyer's patches and caecal tonsils to invade non-phagocytic cells, the microfold (M) cells colonisation of the GIT (Smith, 2003; Ribet and Cossart, 2015). The M cells are specialised epithelial cells for the identification of the antigenic substance in the GIT (Ohno, 2015). The microfold invasion leads to inflammation, which is followed by phagocytosis of bacteria by heterophils and macrophages on the lumenal surface of the intestine (Jepson and Clark, 2001; Sekelova *et al.,* 2017). The inflammation triggers the drainage of water/fluids into the GIT and causes diarrhoea (Figure 1).

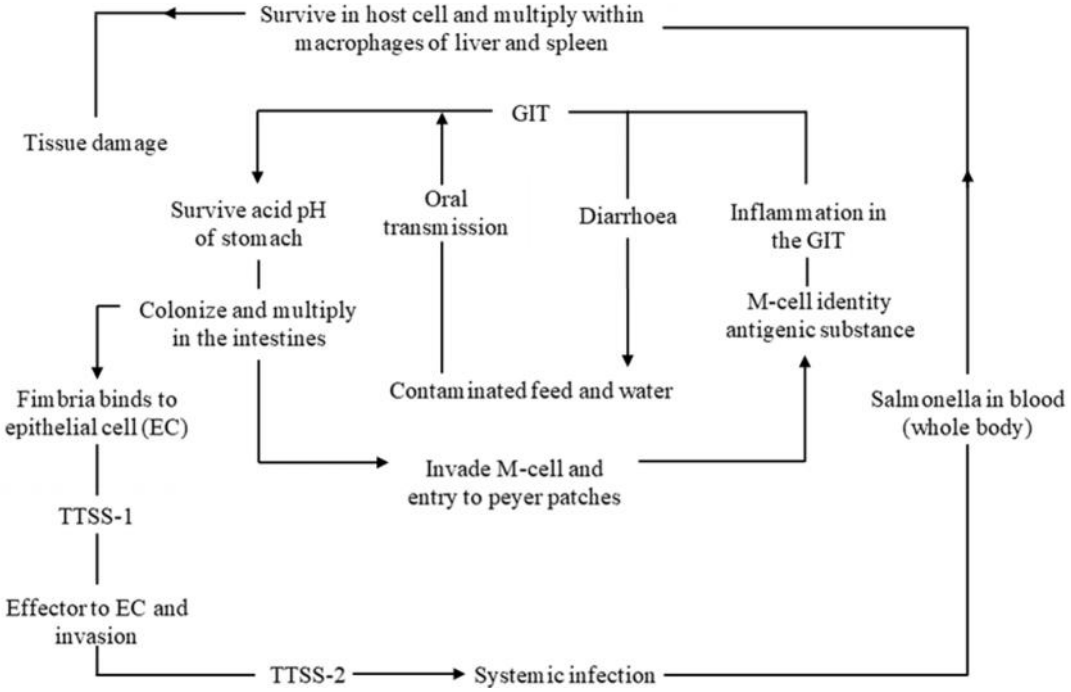

Figure 1: Schematic representation for *Salmonella* infection. Oral transmission of contaminated water and feed elicit gastrointestinal inflammation. The inflammation causes diarrhoea and elimination of *Salmonella* to the environment. The colonisation and multiplication of *Salmonella* in the epithelial cells of the gut will result in an expression of TTSS-1. The TTSS-1 injects effectors and brings *Salmonell*a internalisation to deeper tissues. After internalisation *Salmonella* express TTSS-2 to induce systemic infection and favour multiplication in macrophages of the reticuloendothelial system

Salmonella penetrates the lymphatic tissues and blood vessels, targets specific types of cells such as dendritic cells, macrophages, mesenteric lymphatic nodes and later to deeper tissues (Kabir, 2010). Upon penetration to deeper tissues *Salmonella* spreads and multiplies in several reticuloendothelial organs, bone marrow, gall bladder, and reproductive tract (Stevens *et al.,* 2009). The invasion of *Salmonella* in the reproductive tract is crucial for transovarian transmission and hatchery contamination (Pande *et al.,* 2016). The transmission is

facilitated by the combined activity of effectors, which resulting in *Salmonella* penetration and internalisation by host tissues (Knodler, 2015). On the other hand, the infected gall bladder continues to secrete bile for digestion (Revolledo and Ferreira, 2012), which makes *Salmonella* available for reattachment in the gut epithelial cells or released out to contaminate the environment (Lawley *et al.,* 2008). Therefore, persistence and colonisation of *Salmonella* are also maintained by reattachment in the GIT. Chicken host adaptive serovars, such as *S. gallinarum* and *S. pullorum* persist in the liver and spleen and result in a carrier state by shedding live *Salmonella* for more than a year post-infection (Eng *et al.,* 2015). However, in non-adaptive serovars such as *S. typhimurium* and *S. enteritidis*, the bacterium persists in faecal material which later enters the food chains (Revolledo and Ferreira, 2012).

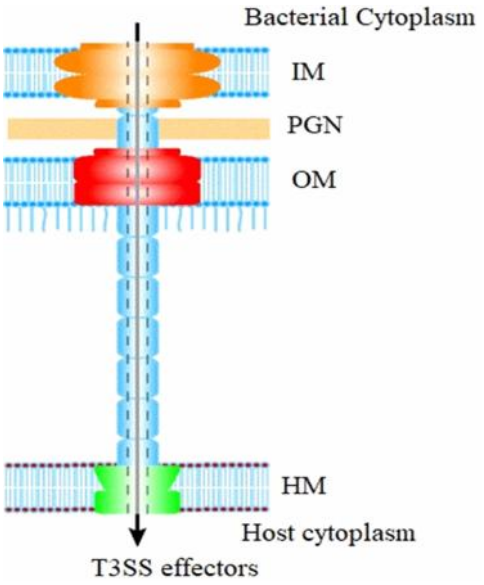

Figure 2: The T3SS apparatus consists of rings that serve as a continuous pathway across the inner (IM) and outer (OM) bacterial membranes, forming a hollow tube-like the structure of a needle through which effector proteins are transported to host cytosol. (Coburn *et al.,* 2007).

Host adaptive strains such as *S. gallinarum* elicit systemic infection to a broader range of domestic poultry including chickens, turkeys, ducks, and other gallinaceous birds (Clayton *et al.,* 2008). The disease upon *Salmonella* spp. in chickens is attained when the three phases of invasion, systemic infection and resolution of infection have taken place.

Colonisation and adhesion of *Salmonella:* Crop is the first chicken's environment encountered by pathogen after ingestion. The morphology and chemistry of crop are essential in influencing the survival and virulence of *Salmonella* even in the remainder of the intestinal tract (Crhanova *et al.,* 2011; Durant *et al.,* 1999). The acidic environment in the crop with less amount of lactic acid is not a threat to *Salmonella,* unlike other pathogens. However, at higher acidic concentration, the population of *Salmonella* is highly reduced (Dunkley *et al.,* 2009). Therefore, factors that influence *Salmonella* colonisation to a particular host species, such as chickens, are complex and occur through many factors involving the host genetic background, the pathogen, and extrinsic pressures (pH and competition of the GIT microflora) (Foley*et al.,* 2008).

Generally, adhesins and invasins hold much in the colonisation of *Salmonella* to host cells (Chousalkar and Gole, 2016; Wagner and Hensel, 2011). *Salmonella* uses pili or fimbriae to adhere to different body surfaces. The fimbrial adhesion (Fim fimbriae), autotransporter adhesins (e.g. MisL or SadA) and T1SS substrates (e.g. BapA or SiiE) are known adhesins among several large numbers of adhesive proteins in *S. enterica* (Wagner and Hensel, 2011). *Salmonella* invades and polarises epithelial cells; thus invasiveness correlates with the concentration of surface-anchored with adhesins (Griessl *et al.,* 2013). The adhesin proteins present at the tip of fimbriae allow *Salmonella* to colonise the tissues and bind tightly to specific sugars on the target tissue (Pizarro-Cerdá and Cossart, 2006). Furthermore, *Salmonella* uses fimbriae to bind to M cells of the epithelial lining during infection and stimulate the cell membrane to engulf the bacteria (Jepson and Clark, 2001). After the bacteria is surrounded by the host epithelial cells, trigger a type III secretion device to introduce pore-forming factors and effector molecules into the host cells (Schlumberger and Hardt, 2006; Coburn *et al.,* 2007) (Figure 2).

Salmonella utilises a device to promote its uptake into the vacuolar environment and live intracellularly within the *Salmonella*-containing vacuole (SCV) (Steele-Mortimer, 2008). Through the TTSS-2, effector proteins are secreted to SCV and interact with cytoskeletons, which later form the *Salmonella*-induced filaments (SIF) (Chadfield *et al.,* 2003). The SIFs radiate outward from SCV upon onset of bacterial replication (Knuff and Finlay, 2017). On the other side, the SIFs ease fusion of SCV with endosomes in the host cell and play a role for *Salmonella* survival and replication (Foley *et al.,* 2013). Thus, the presence of SCV also facilitates *Salmonella* replication in epithelial cells and macrophages (Figure 3). Furthermore, the SCV in macrophages makes *Salmonella* uneasy about being cleared by the immune response of the host. Therefore, inside SCV the *Salmonella* migrates from intestines to liver, spleen and ovaries and colonise other cells, which later induce them to take up the bacteria (Ricke, 2003) (Figure 3).

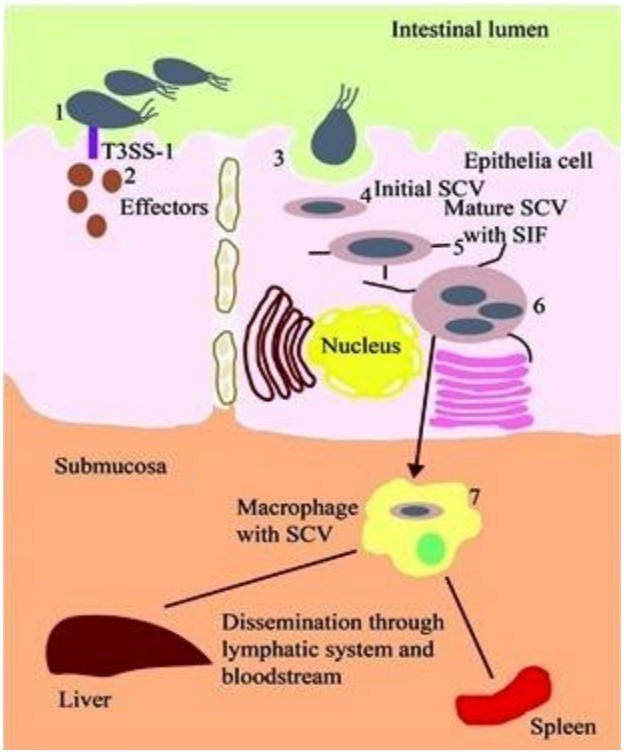

Figure 3: *Salmonella* overcomes the low pH environment of the intestinal lumen and adheres to the intestinal epithelium by adhesins (1). After attached to the epithelial layer, *Salmonella* expresses TTSS-1 to inject bacterial effector proteins (2). Effectors of TTSS-1 mediate cytoskeleton rearrangement through a trigger mechanism to internalise *Salmonella* (3). Inside the epithelial cell, *Salmonella* is enclosed in a membrane-bound vesicle known as Salmonella-containing vacuole (SCV) (4). TTSS-2 effector proteins are secreted to SCV for intracellular survival of *Salmonella* and interaction with the cytoskeleton to form *Salmonella*-induced filament (SIF) (5). Mature SCV with SIF migrate to the Golgi apparatus and replicate intracellularly (6). *Salmonella* crossed the epithelium to sub-mucosa layer is engulfed by macrophages (7). Migration of macrophages results in systemic dissemination of *Salmonella* in the bloodstream and reticuloendothelial system.

Salmonella gallinarum causes systemic disease in chickens after intestinal colonisation in the distal ileum, caecum and bursa of Fabricius (Setta *et al.,* 2012). *S. typhimurium* and *S. enteritidis* persist in the digestive tract of a chicken for months without triggering clinical signs. However, these species are severely affecting young chicks, with higher mortality rates (De Buck *et al.,* 2004). The study conducted by Dieye *et al.* (2009) on *S. typhimurium*, discovered that the SPI-1 was very useful in colonising both the caecum and spleen in chickens, unlike SPI-2 which was found to colonise the spleen, but not the caecum. Thus, suggesting that *S. typhimurium* much depends on SPI-1 than on SPI-2 for colonisation of the younger intestinal tract (Rychlik *et al.,* 2009).

Eswarappa *et al.* (2010) reported that the *Salmonella* establishes in the host cell by decreasing the number of acidic lysosomes inside the host cell. This condition is vital for *Salmonella* survival because the infected cell is left with insufficient acidic lysosomes to target the increasing number of SCVs. Thus, the fold increases of SCVs favour the survival and proliferation of *Salmonella* inside the host cell. Wiedemann *et al.* (2015) observed that the majority of *Salmonella* serotypes are internalised into the host cell through trigger mechanism mediated by TTSS-1 and enclosed in SCV. The *Salmonella* inside the SCV can quickly multiply and form SIF which delivers nutrients to SCV (Figure 3). However, in some cases *Salmonella* damage the SCV membrane, triggering vacuole destruction, release *Salmonella* to the cytosol and enhance *Salmonella* multiplication in epithelial cells, or allow *Salmonella* destruction by activated macrophages (Bakowski *et al.,* 2008).

In line with microbiomes in the intestines, the infection of *Salmonella* in the GIT is influenced by the potential of its effectors and toxins produced to outcompete other beneficial bacteria in the GIT. Therefore, *Salmonella* combined effects of effectors are of advantageous during the invasion, penetration to deeper tissues, survival and replication in different host cells.

***Salmonella* survival in the expense of host cell death:** *Salmonella* induces host cell death using TTSS dependent and independent mechanisms. In the course of the enteric phase of infection, *Salmonella* adheres to the intestinal epithelial cell, inject effector proteins which interfere with cellular functioning to enhance their replication and survival (Zhang *et al.,* 2018). The apoptosis and pyroptosis are forms of programmed cell death that demonstrate how epithelial cell infected with the pathogen is programmed to die (Behar and Briken, 2019). Both TTSS-1 and TTSS-2 are responsible for triggering apoptosis in epithelial cells infected with *Salmonella* while caspase-1 is involved in pyroptosis.

TTSS independent mechanism of cell death involves intracellular and extracellular signals of caspases. The *in vivo* and *in vitro* studies categorise caspases in three subgroups which are initiators, execution/effector and inflammatory (Connolly and Fearnhead, 2017). The initiator caspases (caspases-2, -8,-9 and -10) activate one or more executioner or effector caspases (caspase-3, -6 and -7) by cleavage of their pro-enzymes (McIlwain *et al.,* 2013). Inflammatory caspases

(-1,-4 -5, -11, -12, -13, -14) do not function in apoptosis but are instead involved in inflammatory cytokine signalling and other types of cell death such as pyroptosis (Shi *et al.,* 2015). The activation of caspases for eliciting apoptosis employs two pathways. The intracellular pathway (mitochondrial pathway), starts by signal factors from mitochondria and releases cytochrome C in the presence of Apaf-1 activates Apaf-1/ caspase -9 complexes (Shalini *et al.,* 2015). On the other side, the extracellular pathway activates caspase -8 after it has received apoptotic stimuli through death receptors (Tummers and Green, 2017).

Both caspase -9 and -8 are pro-enzymes which afterwards activate caspase -3 as a final executor of apoptosis (Julien and Wells, 2017). The caspase 3 plays a central role in cleave cellular substrates and express some features associated with apoptosis. The features of apoptosis expressed in the infected epithelial cell include cell shrinkage, chromatin condensation, DNA fragmentation, reduced mitochondrial membrane, cytoskeleton cleavage, cell surface exposure of phosphatidylserine and membrane blebbing (Ramos-Morales, 2012). Upon apoptosis characteristics, the *Salmonella* are retained within apoptotic bodies and engulfed by phagocytic cells without accompanying inflammatory responses *in vivo*. (Jorgensen *et al.,* 2017) (Figure 3 green - left). The mechanism assists the survival, dissemination and persistence of *Salmonella*.

Small leucine- rich proteoglcan (SlrP) promotes cell death by facilitating the ubiquitylation of thioredoxin under ubiquitin ligase (Narayanan and Edelmann, 2014; Lin and Machner, 2017). This process depletes the thioredoxin level in the host cell and makes a cell vulnerable to oxidative damage and lead to apoptosis. The SlrP also bind to chaperon ERdj3; a protein that binds to unfolded proteins in the endoplasmic reticulum (E.R) for proteasomal degradation (Jeong and Joe, 2016). Cordero-Alba *et al.* (2016) suggested that by preventing the binding of unfolded proteins, SlrP can lead to the accumulation of unfolded proteins in the E.R which induce apoptosis *in vitro*. The AvrA (strongly inhibits c-Jun N-terminal kinase (JNK) signal pathway) and SopB are responsible for the delay of apoptosis. To uphold the delay, SopB sustains activation of Akt because failure to activate Akt resulted in increased levels of apoptosis while AvrA via JNK stabilises intestinal tight junctions (Zhang *et al.,* 2015). The delay is beneficial for the *Salmonella* to have a stable intracellular niche in order to avoid adaptive immunity (Behnsen *et al.,* 2015). (Figure 3 green - right). The mechanism where *Salmonella* effectors AvrA and SopB postponed host cell death remains unclear (Zhang *et al.,* 2015).

Pyroptosis is a type of inflammatory programmed cell death that is coordinated by inflammasome-mediated caspase-1 activation (Walle and Lamkanfi, 2016). Caspase-1 is a central mediator of innate immunity that is not activated in apoptosis. In the course of pyroptosis, there is a competition between the host cell and pathogen control, which struggles to continue to survive and replicate (Jorgensen *et al.,* 2017). The pyroptosis occurs when a pathogen such as *Salmonella* in the macrophage cell express TTSS-1 effectors (SipB) into the cytoplasm to activate caspase-1. The typical inflammasomes that identify *Salmonella* in the cytoplasm are NOD-like receptor (NLR) family of proteins, namely NLRP3 and NLRC4 (Xia *et al.,* 2019). This is because all classic inflammasomes contain NLRs (Behnsen *et al.,* 2015). However, NLRC4 inflammasome can sense flagellin and T3SS-1 rod effectors PrgJ and PrgI, and activate caspase-1 to mediate pyroptosis (Qu *et al.,* 2016). It was revealed that the TTSS-1 translocate SipB which is involved in pyroptosis through direct interaction with caspase-1. The caspase-1 requires inflammasome activated by flagellin and TTSS rod protein PrgJ to produce active interleukin 1β (IL-1β) and interleukin 18 (IL-18), prompt cell lysis and release of proinflammatory intracellular substances (Lamkanfi and Dixit, 2014; Sahoo *et al.,* 2011). The pyroptosis mediated by caspase-1 dependent programmed cell death is unlike apoptosis because of strong inflammatory response. (Figure 3 blue).

Persistence of *Salmonella* in a host: Host-adapted strains act as a reservoir, and their importance is seen in the persistence of bacteria for microbial survival and transmission of pathogens (Murugadas *et al.,* 2015; Monack, 2013). The persistence of *Salmonella* inside the chicken epithelial cells is associated with secreted effector proteins that depend on TTSS determined by SPI-1 and SPI-2 (Tierrez and García-del Portillo, 2005). The SPI-1 encoded TTSS is functional in SCV long after bacteria entry and contribute to bacteria growth in epithelial cells (Tierrez and García-del Portillo, 2005). The SPI-2 also plays the role of distancing the SCV from the producer of reactive oxygen species and reactive nitrogen species (Chakravortty *et al.,* 2002). Several *Salmonella* strains contain factors that cope with ROS (NADPH oxidase) and RNS (INOS), giving them the influence to persist within the host (Behnsen *et al.,* 2015; Gallois *et al.,* 2001). The SPI-2 contributes to persistent infection in *S. pullorum* in young chickens; however, the specific association with the long-term persistence of *S. pullorum* is obscure (Wigley *et al.,* 2001).

Invasion and translocation of effector protein such as SipB, SipC, and SipD are also required for persistence of *Salmonella* infections to a host from SPI-1 genes as revealed by Lawley *et al.* (2008) and Ruby *et al.* (2012). In order to maintain survival within the SCV, there is translocation of a group of bacterial effectors into the host cell cytosol (Drecktrah *et al.,* 2005). This ability gives rise to chronic infections or persistence within macrophages for the lifetime of the host.

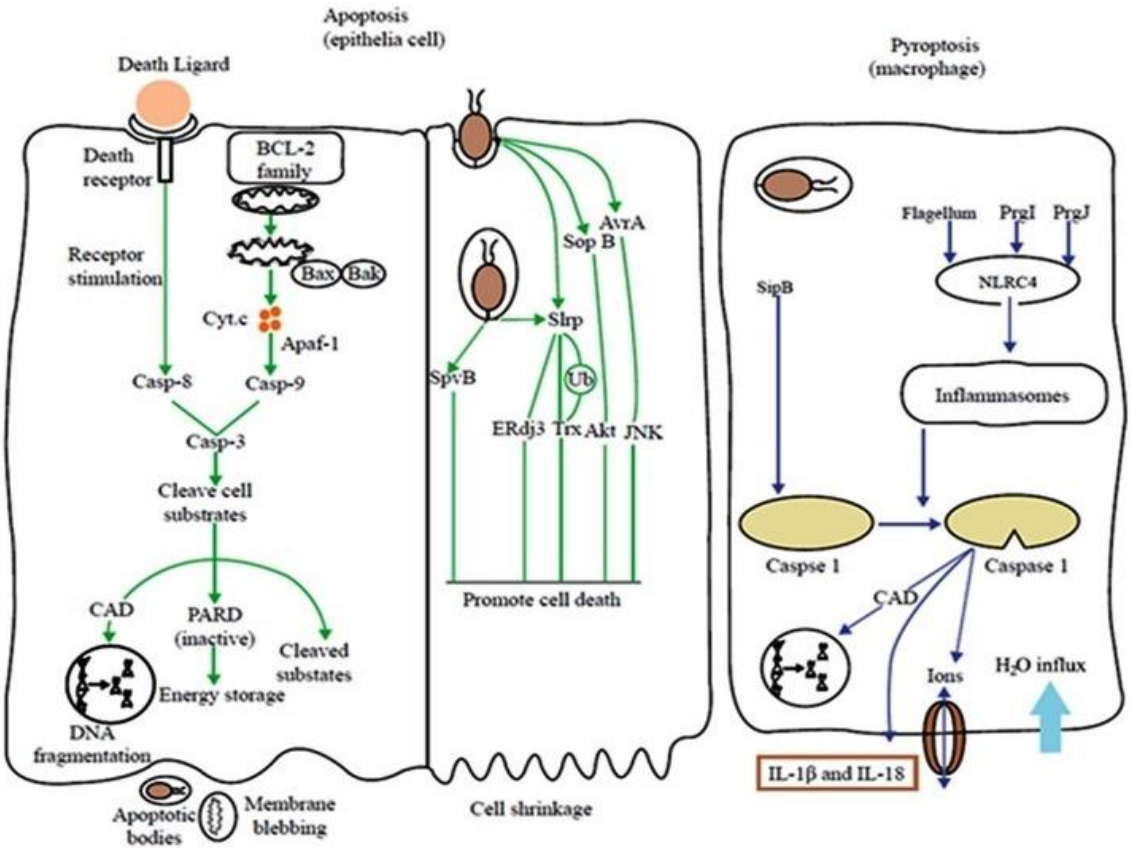

Figure 4: *Salmonella* induces epithelial cell death by apoptosis and pyroptosis. Apoptosis is mediated by ligation of cell surface death receptor and release of cytochrome c which activate caspase -8 and -9, respectively. The two caspases activate executioner caspase -3 which cleave cellular substrates in different forms to provide features for apoptosis. The caspase-3 in the presence of DNase (CAD) results in DNA fragmentation. Inactivation of poly (ADP-ribose) polymerase (PARP) prevents DNA repair and serves for the preservation of ATP for apoptosis (Left panel, green). TTSS effectors SlrP, SopB and AvrA are responsible for apoptosis through different mechanisms (Left panel, red). In macrophage, *Salmonella* expresses TTSS-1 to induce rapid pyroptosis. SipB activates the caspase-1. In the presence of inflammasomes flagellin and TTSS-1 rod protein, PrgJ activated caspase-1 to produce active IL-1β and IL-18. The activated IL-1β and IL-18 lead to loss of ionic equilibrium and water influx which finally end into osmotic lysis of epithelial membrane (Right panel, blue). (Fink and Cookson, 2007; Ashida *et al.*, 2011)

Pathogenicity Islands (PIs) and *Salmonella* virulence: Virulence of *Salmonella* strains is determined by virulence factors which are controlled by virulence genes clustered in regions of the bacteria chromosome known as the pathogenicity islands (Kaur and Jain, 2012). The most studied SPIs include SPI-1, SPI-2, SPI-3, SPI-4, and SPI-5 (McClelland *et al.,* 2001; Foley *et al.,* 2013). Among five pathogenicity islands, the invasive phenotypical genes required for intestinal penetration and invasion of host cells are clustered in a defined region in a chromosome of *S. enterica* termed as SPI-1 with 40 kb region at centisomes 63 (Winnen *et al.,* 2008). The translocation of virulence proteins into host target cell occurred when SPI-1 and SPI-2 encoded TTSS; however, the roles of SPI-1 and SPI-2 in virulence are entirely different (Schmidt and Hensel, 2004; Que *et al.,* 2013).

The SPI-1: Function of SPI-1 is identified as 40kb DNA region required for the invasion of host cells and intracellular pathogenesis (Marcus *et al.,* 2000). SPI-1 is an important virulence trait of *S. enterica.* A recent study by Rosselin *et al.* (2011) revealed that *Salmonella* infection might occur independently of the TTSS-1. Generally, TTSS mediate the delivery of proteins by extracellular *Salmonella* species into the host cells (Kubori *et al.,* 2000). Among a set of effector proteins encoded by SPI-1 and secreted through TTSS are InvJ, SipA/B/C/D, SptP, AvrA, SopA/B/D/E/E2. These proteins interfere with the function of host cell proteins (Lostroh and Lee, 2001). Different scholars have well

studied the functions of effector proteins in TTSS-1, and the summary is listed in Table 1. However, more researches are investigating the genetic aspects of all effectors of TTSS-1 and their association with effectors of TTSS-2 in the process of pathogenesis of *Salmonella.*

Table 1. Secreted effector proteins of TTSS-1 from *Salmonella* and their significance in disease.

Salmonella effectors	Significance in disease	Reference
AvrA	Necessary for the invasion of the epithelial cell. Induces inflammation and inhibition of the NF-kB pathway,	Lu *et al.,* 2010; Ramos-Morales, 2012;
SipA	Effector. For cytoskeleton rearrangement. Is for actin-binding protein and plays a crucial role in bacterial entry	Zhou and Galan, 2001; Agbor *et al.,* 2011
SipB	Translocon	McGhie *et al.,* 2002; Myeni *et al.,* 2013
SipC	Translocon, Recruits exocytic vesicle at the entry site in epithelial cell-for membrane ruffling, Induces actin bundling, For cytoskeleton rearrangement	Zhou and Galan, 2001; Myeni *et al.,* 2013
SipD	Translocon, TTSS effector protein translocation through eukaryotic cell membranes	Lunelli *et al.,* 2011; Rathinavelan *et al.,* 2014
SptP	Effector protein, interferes with functions of host cell proteins of a family GTPases	Jimenez *et al.,* 2016; Johnson *et al.,* 2017
SopE	Effector protein, interferes with functions of host cell proteins of a family GTPases, Stimulates actin cytoskeleton rearrangement	Vonaesch *et al.,* 2014
SopE2	Effector protein, interferes with functions of host cell proteins of a family GTPases, stimulates actin cytoskeleton rearrangement, 70% sequence similar to SopE	Vonaesch *et al.,* 2014
SopB	Leads to major cytoskeletal rearrangements, activation of secretory pathways, promotes intestinal inflammation	Hapfelmeier *et al.,* 2004; Agbor and McCormick, 2011
InvJ	Exportation apparatus, Controls the size of the needle in TTSS	Deng *et al.,* 2017

The SPI-2, SPI-3, SPI-4 and SPI-5: *Salmonella* pathogenicity islands (SPI) have a significant role in inducing pathogenicity to host cytosol. In addition to that, there are virulence factors that facilitate *Salmonella* infection to hosts. The virulence factors explained in this article include plasmid, biofilm and lipopolysaccharide layer

SPI-2 has 39 kb locus, which encodes a second type III secretion referred to as TTSS-2 (Velge *et al.,* 2012). SPI-2 is required for bacteria systemic infection, growth, survival and replication in both epithelial cells and within macrophages of the host (Guiney and Fierer, 2011). Moreover, the SPI-2 components affect the phagosome arrangement and the recruitment of NADPH oxidase to the phagosome membrane (Gallois *et al.,* 2001). Thus, SPI-2 is involved in modifying the intracellular environment encountered by *Salmonella* (Silva-Herzog and Detweiler, 2010). Among the TTSS-2 effector proteins, SseB/C/D are responsible for promoting pore formation through which proteins reach the host-cell cytoplasm (Jennings *et al.,* 2017). In general, TTSS-1 brings about host cell invasion, inactivation of phagocytic cells, apoptosis and interference with intracellular transport processes (Ohl and Miller, 2001).

Virulence phenotype due to SPI-2 is linked to the ability of *S. enterica* with different serovars to survive in phagocytic cells and replicate within SCV in a variety of membrane-bound cells (Knodler *et al.,* 2010). The SPI-2 encoded TTSS is required for the protection of the pathogen within SCV against effectors of the innate to avoid fusion with the lysosomes (Ruby *et al.,* 2012). The SCVs play critical roles in the survival and proliferation of *Salmonella* in intestinal cells and macrophages (Vonaesch *et al.,* 2014). The best of the *Salmonella* within SCV is when more of these bacteria are multiplying and get access to new vesicles using SIFs get in touch with vesicles by projecting out of SCV (Foley *et al.,* 2013). The TTSS encoded SPI-2 enables *S. enterica* to modify functions of the host cells, and thus, essential for survival and replication of *S. enterica* inside host macrophages (Monack *et al.,* 2004).

SPI-3, which is 17 kb large, is accommodated at 10 open reading frames, with the *mgtC* gene enables *Salmonella* to grow in a low-magnesium environment (Lee and Lee, 2015). Moreover, it also allows *Salmonella* to survive in the macrophages (IIyas *et al.,* 2017). The SPI-4 is a 25 kb large island needed for intra-macrophage survival and is likely to carry a type I secretion system involved in toxin secretion and apoptosis (Kiss *et al.,* 2007). It is speculated that SPI-4 is associated with secretion of cytotoxin responsible for infecting macrophages and coding for non-fimbrial adhesins seen

in several *Salmonella* species during intestinal phase of the disease (dos Santos *et al.,* 2019). The sequence analysis of the ±11 kb (25cs) large SPI-5 revealed the presence of six genes, including the *SopB*, a gene encoding multiple TTSS effector proteins (Rychlik *et al.,* 2009). The role of SPI-5 is mainly associated with enteropathogenesis and in *S. typhimurium* is vital for systemic infection in chicks (Cao *et al.,* 2014).

***Salmonella* Plasmid:** *Salmonella* has highly conserved plasmid with 7.8 kb for all serovars with operon of five genes of *Salmonella* plasmid virulence (*spv*) locus (Hur *et al.,* 2011). The locus harbours virulent genes in serovars of *S. enterica* designated as *spvRABCD* (Osman *et al.,* 2014). The *spvR* is named first and encodes positive activator for the other four genes, namely *spvA*, *spvB*, *spvC* and *spvD* (Addwebi *et al.,* 2014). The serovars with spv locus are of veterinary significance, differ from one to another, but all have 7.8kb (Pal *et al.,* 2017). They are involved in intra-macrophage survival of *Salmonella* serovars (Riychlic *et al.,* 2006). The serovars include *S. abortusequi*, *S. abortusovis*, *S. choleraesuis, S. dublin* and *S. gallinarum*/*pullorum* (Barth and Bauerfeind, 2005). However, the broad host serovars such as *S. enteritidis* and *S. typhimurium* are also in this group. They have been observed in human and food products from animals including chicken meat and eggs (Barth and Bauerfeind 2005). It has been found that the presence of *spv* in a chicken leads to the death of the host frequently and rapidly. The signal in *spv* locus is expressed in term of growth limitation, minimised nutrient supply or lowered pH (Rychlik *et al.,* 2006). The central effector genes of this operon are *spvB* and *spvC*, and the existence of *spvBC* couples a missing virulence plasmid in *S. typhimurium*. The product of *spvR* is a proper regulatory protein which is vital for the expression of other *spv* genes (Wu *et al.,* 2016). They promote survival and rapid growth of *Salmonella* in the host and affect the interaction of *Salmonella* with the host immune system (Singh, 2015).

Salmonella gallinarum like serovars *S. abortusovis*, *S. heidelberg*, *S. dublin*, *S. typhimurium*, *S. choleraesuis*, *S. pullorum*, *S. enteritidis* and many more others are reported to contain the *Salmonella* plasmid virulence (*spv)* locus. The locus has a vital function of multiplication in the reticuloendothelial tissues in the liver, spleen, reproductive parts (Asten and Dijk, 2005). However, not all serovars may carry virulence gene. This makes virulence plasmid of *S. gallinarum*/*pullorum* capable of restoring mouse virulence to *S. typhimurium* because of horizontal transfer of virulence genes (Marcus *et al.,* 2000).

Biofilm: Biofilm is layers formed by bacteria when sticking to surfaces and start to excrete slimy, a matrix of extracellular polymeric substance (Rossi *et al.,* 2017). The layer anchor and run through different surfaces such as medical implant materials, metals, plastics, soil particles, animal tissue (Lu *et al.,* 2015). The layer contributes to *Salmonella* resistance to antibiotics and interferences in the host immune response, which with time, causes chronic infection (Parsek and Singh, 2003). The biofilm is difficult to remove even in cleaning procedures and chemical disinfection. *Salmonella* biofilm was found to increase the ability to resist acidification, desiccation, chlorination, heating, ionisation, radiation and antimicrobial agents (Chylkova *et al.,* 2017). The number of antibiotics that became ineffective to adhesions on exopolysaccharides secreted into host cells like chickens' intestinal epithelium, or HEp-2 cells was observed during culture conditions (Peng, 2016). It was revealed that *S. typhimurium* form biofilm on Hep-2 cells in type 1 Fimbria-dependent manner (Ledeboer and Jones, 2005). The extracellular *Salmonella* biofilms are serovar specific linking with contact surfaces (Koo *et al.,* 2017).

Biofilm is generally characterized by a mixture of secretions of macromolecules (polysaccharides, glycoproteins, and glycolipids) and extracellular DNA collectively known as extracellular polymeric substances (Koopman *et al.,* 2015). The functions of extracellular polymeric substance are related to concentrating nutrients, inhibiting biocidal agents and increasing hydration to surfaces (Rossi *et al.,* 2017).

Descriptions of biofilm macromolecules include 1. Curli (amyloid fimbriae) mediates cell adhesion and invasion with properties of inflammatory responses to a host. 2. Cellulose which is the exopolysaccharide secreted by *Salmonella* biofilm composed of β (1 → 4)-linked D-glucose units. The two form a hydrophobic network, which is a matrix of the tightly packed cell (Gerstel and Romling, 2003). 3. Biofilm-associated protein (BapA) is a large secreted protein required for biofilm formation (Latasa *et al.,* 2005) 4. O-antigen capsule is unimportant for multicellular behaviour; however play an important role in attachment and persistence of *Salmonella* (Barak *et al.,* 2007) and 5. Extracellular DNA inhibits and stabilises biofilm development of *Salmonella* on abiotic surfaces such as metal, plastic and glass (Cappitelli *et al.,* 2014). All these features are geared with several regulated genes positioned on operons encode adhesins which identify biofilm formation. Biofilm ruins food safety and is the reservoir of *Salmonella* in the different abiotic and biotic environment and enhancing the likelihood of colonising new host and persistence (Koopman *et al.,* 2015).

Lipopolysaccharides (LPS): *Salmonella* LPS consists of three components: an outer O- polysaccharide coat, a middle portion (R core) and inner lipid A coat. **(**Garmiri *et al.,* 2008**).** The outer O- polysaccharide coat differentiates strains due to the difference in structure and composition. *Salmonella* missing the complete sequence

of O-sugar repeating units are rough while those with it are called smooth (Murray *et al.,* 2003). Lipopolysaccharide (LPS) in *Salmonella* is a potent activator of the acute phase and inflammatory reactions which release endotoxin during infection **(**Liu *et al.,* 2016**)**.

Lipopolysacharides protect bacteria against host defence mechanisms such as gastric acidity, bile salts and the bactericidal activity of complement and phagocytes (Morgan *et al.,* 2004). Like other bacteria, *S. gallinarum*, *S. pullorum* and *S. enteritidis* have LPS layer which is the complex of lipid and polysaccharide with an influence of attachment to the epithelial cells of the alimentary canal of a chicken (Ramasamy *et al.,* 2014). The study by Guard-Bouldin *et al.* (2004) on chemotyping of LPS mutant revealed that high molecular mass LPS influence the biology of the avian reproductive tract with loss of production. The LPS in *Salmonella* is a virulence determinant essential for swarming motility in *Salmonella* grown in agar to depict behaviour when propagated in solid media (Toguchi *et al.,* 2000). Others are the colonisation of intestinal epithelial cells after penetrating the mucosa layer, serum resistance which is reduced by an increase in chain length in LPS and resistance to killing by macrophages, all of which are vital for successful infection of *Salmonella* to chicken epithelial cells (Kong *et al.,* 2011).

Acid pH stress and adaptation of *Salmonella:* *Salmonella typhimurium* was observed to adapt to different stressed conditions inside gut and host cells due to the presence of a set of genes termed as stimulons (Lianou *et al.,* 2017). The stimulons are expressed under control of positive regulatory elements. A study by Foster and Spector (1995), observed that low pH stress in the gut with *S. typhimurium* is regulated by RpoS, AtbR, MviA and Fur under the influence of *str* gene. The regulons OxyR, SoxRS, RpoS and oxidative stress stimulons sodA, katG, katE, and their products prevent *S. typhimurium* from oxidative damages of DNA, proteins and membranes (Foster and Spector, 1995). Therefore, adaptation to acid, salt, heat, hydrogen peroxide (H_2O_2) and oxygen radicals promotes the survival of *Salmonella* in the adverse environment including acidic stomach, macrophages and phagolysosomes (Álvarez-Ordóñez *et al.,* 2011).

Phases in acid adaptation occur either by pre-shock or acid shock responses that require protection of *Salmonella* against severe acid stress (Álvarez-Ordóñez*et al.,* 2010; Baik *et al.,* 1996). *Salmonella* has been found to respond to the acidic environment through a complex adaptive system called the pre-shock acidification tolerance response proteins (PsATRP). The preshock response is termed when the exponentially growing cells at the pH 7.6 grow to one to two-fold when shifted to up to pH 4.5 and below (Álvarez-Ordóñez*et al.,* 2012). The acid shock response in *Salmonella* makes cells to cease reproduction and requires alteration of synthesis of over 52 acid shock proteins (Foster, 1991). From the synthesis of over 52 proteins, four are distinctive PsATRP namely, the RpoS $^{\delta}$-factor, Ada, Fur and PhoPQ. The first three RpoS $^{\delta}$-factor, Ada, Fur have enormous tolerance to organic acid stress with lesser effects in inorganic acid stress (Bearson *et al.,* 1998).

In contrast to the PhoPQ system (PhoP and PhoQ), the two-component regulatory systems PhoP (identified as Acid Shock Protein-ASP29) and PhoQ proved to be essential for the tolerance to organic acid stress with little effect to it (Foley *et al.,* 2013). Bearson *et al*. (1998) reported that *S. typhimurium* RpoS and PhoPQ provided protection against inorganic acids and PhoP- PhoQ represses genes essential for induction of micropinocytosis in macrophages and epithelial cells. Thus, RpoS and FurR offered protection against organic acids induce acid resistance and regulate iron homeostasis (Ramos-Morales, 2012; Foley *et al.,* 2013). Therefore, the ability of *Salmonella* to tolerate different pH of organic and inorganic acids allows it survives in the crop and the small intestine. These adaptations are essential for colonisation and persistence of *Salmonella* in the GIT.

Approaches and challenges for *Salmonella* control

Probiotics: Roles of probiotics in health and disease of animals are increasingly being recognised. However, they are well implemented in developed countries with facilities and technologies for quality assurance criteria for probiotics compared to developing countries (Park *et al.,* 2016). The essential criteria for probiotics include phenotype and genotype stability, as well as plasmid stability; tolerance to bile and stomach acid and survival and growth in GIT; intestinal epithelial adhesion properties; production of antimicrobial substances; ability to inhibit gut pathogens and immunogenicity (Tuomola *et al.,* 2001).

Probiotics are non-pathogenic live microorganisms, which in sufficient amount antagonising pathogens by improving host intestinal microbial balance (Servin and Coconnier, 2003; Tellez *et al.,* 2012). Studies have found that probiotics enhance intestinal barrier against deleterious agents and reduce chances of antibiotic use for prevention of infection (Nava *et al.,* 2005; Griggs and Jacob, 2005; Lim *et al.,* 2015). Probiotics have control over the immune response of a host by enhancing innate immunity and regulate intestinal epithelial haemostasis (Vanderpool *et al.,* 2008).

Mechanisms probiotics use to maintain healthy balances of microorganism within the intestines are competitive exclusion, pathogen antagonism, and stimulation of the immune system (Ritzi *et al.,* 2014). The observation of Kabir (2009) in competitive exclusion reported that the newly hatched chickens were conferred

protection against colonisation of *S. enteritidis* by giving them the suspension of gut content from healthy adult chickens. However, the small amount of acidic pH of probiotics is insignificant to most of *Salmonella* species which have the mechanism of overcoming acidic pH of the crop, stomach and intestine through acid tolerance response (Álvarez-Ordóñez *et al.,* 2012).

Generally, the probiotics possess anti-infective properties after adhering to intestinal surfaces and compete for mannose and glycoproteins receptors used by pathogens (McFarland, 2000; Lebeer *et al.,* 2010).

Pathogens fail to outcompete beneficial bacteria like *Lactobacillus* and *Bifidobacterium* strains of intestinal origin (Kailasapathy and Chin, 2000). It has been observed that the use of lactic acid bacteria (LAB) such as *Lactobacillus, Streptococcus, Pediococcus, Enterococcus* and *Weissella* in animal feed minimise survival of pathogenic *Salmonella* spp. in chickens. The LAB inhibit pathogenic bacteria by (i) preventing pathogen adhesion, (ii) producing inhibitory compounds, (iii) competing for nutrients, (iv) modulating the host immune system, (v) improving nutrients digestibility, feeding conversion and (vi) reducing toxins bioavailability (Vieco-Saiz *et al.,* 2019). The bifidobacteria was found to be effective in inhibiting both Gram-positive and Gram-negative bacteria by producing a bacteriocin-like compound, which is toxic to pathogenic bacteria (Vanderpool *et al.,* 2008). A study by Brisbin *et al.* (2011) reported that lactic acid strains inhibit diarrhoeagenic bacteria by producing metabolites such as acetic and lactic acids which lower the pH and thus useful in inhibiting the growth of pathogenic bacteria in the gastrointestinal tract. Also, Harimurti and Hadisaputro (2015) supported the observations which documented that several probiotics agents through their ability to increase the production of intestinal mucins inhibit adherence of pathogenic bacteria to intestinal epithelial cells.

Probiotics improve the immune system of chickens (Kechagia *et al.,* 2013). For example, the increased systemic antibody reaction against pathogenic bacterial and viral was observed to chicken received probiotics containing *Lactobacillus acidophilus*, *Bifidobacterium bifidum* and *Streptococcus faecalis* (Otutumi *et al.,* 2012). Additionally, intestinal IgG and serum IgG and IgM were also increased in chicken supplemented with probiotics (Alkhalf *et al.,* 2010). This suggests that the use of probiotics supports the induction of natural antibodies for maintaining chicken health. However, the exact mechanism(s) by which probiotics bacteria bring about the aforementioned immune modulation is not clear and require further research (Choi *et al.,* 2014).

Antibiotics: Since 1960, the chemotherapeutical antibiotics were used to reduce mortality in chickens caused by varieties of pathogens, including *Salmonella* (Barrow *et al.,* 2012). However, the extensive use is ill-advised and created concern over the selection pressure for resistant strains of bacteria (De Gelder *et al.,* 2008). Therefore, much use of antimicrobial agents for treatment or promoting growth should be prevented to reduce multidrug resistance strains in different ecosystems (Chattopadhyay, 2014). For example, the burned of antibiotic use in growth promotion of chickens which started in 1997 and completed in 2006 in Europe and America has significantly reduced antibiotic resistance bacteria in poultry population (Barrow *et al.,* 2012).

Moreover, resistant bacteria against antibiotics are still dangerous to chicken survival. The evidence is that some newly discovered antibiotics have failed to treat diseases of bacteria, for example, resistance experienced in colistin, which is an antibiotic of last resort (Poirel *et al.,* 2016). Thus, success use of vaccines will be a weapon against antibiotics resistant strains in the chicken industry (Jansen *et al.,* 2018).

Vaccination: Elimination of hosts identified to be at carrier state of *Salmonella* by test and cull seemed to be of less impact in comparison to vaccination of chickens to prevent infection (Bäumler *et al.,* 2000). However, the use of vaccines is well implemented in developed countries, unlike developing countries where most of the rural farmers live under poor infrastructure and unable to meet the cold chain treatment for vaccines.

Vaccinations stimulate cell-mediated immune response and reduce clinical signs and shedding of live *Salmonella* from chickens infected with *S. gallinarum*, *S. pullorum*, *S. enteritidis* and *S. typhimurium* (Revolledo and Ferreira, 2012). The 9R live vaccine developed in 1956 was used to control *Salmonella* in poultry and helped to eradicate *S. gallinarum* and S. *pullorum* in Europe and America (Smith, 1956; Baumler *et al.,* 2000). However, there was an outbreak of *S. enteritidis* in 1960 following the fall of *S. gallinarum* and *S. pullorum* (Bäumler *et al.,* 2000). The observation was that *S. enteritidis* was found to carry a common antigen O9 which enable it to fill the niche of *S. gallinarum*/*pullorum* (Cogan and Humphrey, 2003). The theory suggests that *S. gallinarum* was able to competitively exclude *S. enteritidis* from poultry flocks and the elimination of *S. gallinarum* and *S. pullorum* in poultry led to an epidemic increase of *S. enteritidis* infections in chickens in the 1980s (Yang *et al.,* 2018).

Despite the above challenges, the developed countries have managed to control chicken salmonellosis with huge success (Desin *et al.,* 2013; Andino and Hanning, 2015). Nevertheless, the control of *S. gallinarum, S. pullorum*, *S. typhimurium* and *S. enteritidis* in developing countries has remained a burden in the poultry industry with enormous loss (Rajagopal and Mini, 2013).

Phages therapy: Therapeutical use of bacteriophages was found to be promising in clearing pathogens when introduced to an infected organism (Thiel, 2004). Bacteriophages are defined as viruses that can infect, multiply and kill susceptible bacteria (Connerton *et al.,* 2011). In recent years the use of bacteriophage or their products has been proposed as a possible tool for treatment or prevention of salmonellosis in poultry farms (Sillankorva *et al.,* 2010). However, the obstacles include phage resistant bacteria which emerge rapidly in the course of therapy, narrow host range of many phages and the activeness of phages occur shortly after bacterial infection (Capparelli *et al.,* 2010). Despite these problems, the pros of using phages outweigh cons because phages are bactericidal that can kill and clear pathogens, and their multiplication on the duration of treatment is higher enough to inhibit pathogenic bacteria.

Phages minimally disrupt normal flora and are equally effective against antibiotic-sensitive and antibiotic-resistant bacteria and can have low inherent toxicities (Loc-Carrillo and Abedon., 2011). The ΦSH19 and Vi01 are lytic bacteriophages adapted to infect several *Salmonella* serovars. The ΦSH19 was isolated from pig intestine and revealed a bio-control against strains of *S. typhimurium* (Hooton *et al.,* 2011). Huang *et al.* (2018) observed the high capacity of phage LPSE1 in controlling different *Salmonella* serovars in ready to eat foods after reducing *Salmonella* count for a range of 0.49 $\log_{10}$ at 4°C to 0.52 $\log_{10}$ at 28°C. In connection to these results, Atterbury *et al*. (2007) also observed the reduction of *S. enteritidis* by ≥4.2 $\log_{10}$ CFU and *S. typhimurium* by ≥2.19 $\log_{10}$ CFU in caecal samples of broiler within 24 h after treatment with phages φ151 and φ10, respectively. These phages were isolated from broiler farm, poultry abattoirs and wastewater plant. From the above observations, the bacteriophages are the potential antibacterial agent that can clear pathogens in infected chickens and ready to eat chicken products (Westwater *et al.,* 2003).

Biosecurity measures: Despite vaccines and antibiotics seen efficient in preventing and treating salmonellosis in chicken; still, biosecurity measures are essential in reducing infection between and within chickens and surrounding environments (Agunos *et al.,* 2014). Biosecurity practices are implemented to prevent infection and spread of disease in a farm through isolation, traffic control and sanitation measures (Jeffrey *et al.,* 2001). During isolation, chickens are confined within a controlled environment. The management keeps inside the chickens which have been separated by age group while other animals are kept out.

Animals like rodents, reptiles carry vectors such as bugs, ticks and contribute to the spread of salmonellosis in the farm (Jeffrey *et al.,* 2001). Therefore, periodic cleaning of the floor, metal parts inside the farm should be done to break the cycles of diseases (Fasina *et al.,* 2012). Sanitation measures should be taken into account by use of disinfectant to workers getting into a farm, equipment used and vehicles entering the farm. These will minimise infection and reduce antibiotics used for prevention and treatment of salmonellosis.

Natural or purified herbs: Attention of using botanicals as an alternative to antibiotics for the treatment of various diseases in chicken production has increased in the last few decades (Dhama *et al.,* 2015). The herbs, spices and different plant extracts are mostly used in organic chicken production due to growth-promoting effects, antimicrobial properties, and other health-related benefits (Diaz-Sanchez *et al.,* 2015). The positive effects of natural medicines are linked to the activity of bioactive constituents, including alkaloids, terpenoids, phenolics, glycosides, glucosinolate (Wenk, 2006). For this reason, many herbs, spices and plant extracts have activity against pathogens and can be used against diseases and in health promotion of chickens.

Aloe vera (family *Asphodelaceae*) comprises of over 75 biologically active compounds with a broad range of pharmacological activities including the anti-inflammatory, antibacterial, antioxidative and antitumor effect (Surjushe *et al.,* 2008). The *Aloe* species have been observed to be efficacious in preventing bacterial infection in chickens, in different communities around rural settings of Africa (Masimba *et al.,* 2011). A study by Waihenya *et al.* (2002) observed the antibacterial activity of *Aloe secundiflora* leaf against *S. gallinarum* in village chicken after increasing the survival rate of the infected flock with fowl typhoid. In supporting this study, Mlimbe *et al.* (2016) tested *Aloe vera* leaf against *S. gallinarum* and observed no death of infected flock with salmonellosis compared with the control group. The antibacterial activity of *Aloe* species is attributed to active phytocompounds flavonoid catechins, anthrones, chromones and anthraquinone (Lopez *et al.,* 2013).

Bioactive compounds work against pathogens in multiple ways. They can disrupt the cellular membrane of pathogens, stimulate the immune system of a host, protect intestinal mucosa from pathogen colonisation and promote the growth of beneficial bacteria (Windisch and Kroismayr, 2007). The bark of cinnamon (*Cinnamomum zeylanicum*) significantly reduced *S. enteritidis* in cecal contents of infected chicken without affecting the total cecal endogenous population (Upadhyaya *et al.,* 2014). These findings are supported by other scholars who revealed the higher antibacterial activity of essential oils of cinnamon (*C. zeylanicum*) against strains of *Salmonella enterica* after disrupting bacterial cell membrane (Vazirian *et al.,* 2015; Solarte *et al.,* 2018). Other species with essential oils effective in inhibiting *Salmonella* spp. in chickens are clove (*Eugenia caryophyllata*), oregano (*Origanum vulgare*), common

thyme (*Thymus vulgaris*), and red thyme (*Thymus zygis*). (Solarte *et al.,* 2018).

Punica granatum peel, garlic (*Allium sativum), pawpaw (Carica papaya),* neem (*Azadirachta indica)* and *Citrus* species are also among natural antimicrobials reported to be effective in promoting chicken health (Dhama *et al.,* 2015). They stimulate the flow of gastric juices, modify digestive secretion, stabilise microbiome which reduces microbial toxins and improve digestion (Mlimbe *et al.,* 2016; El-Azzouny *et al.,* 2018). The extracts of *P. granatum* peel are used as antibacterial, antispasmodic, anti-inflammatory and hemostatic agents in folk medicines (Arun and Singh, 2012). Moreover, the peels are also used as a food supplement to maintain intestinal microbiota and contribute in the modulation of the immune response against pathogenic microbes in chickens. Khan *et al.* (2018) observed that shiitake mushroom (*Lentinula edodes*) has higher inhibition against *S. enteritidis* in broiler chicken because of major active component heteroglycan protein. The heteroglycan proteins are essential in modifying intestinal microbiota and provide them with chances of outcompeting pathogenic bacterial like *S. enteritidis.* The primary active compounds of *Ginkgo biloba,* namely Flavonoids (glycosides) and terpenoids (ginkgolide, bilobalide) were reported to prevent biofilm formation in the intestines of chickens (Wu *et al.,* 2016). The biofilms enhance colonisation and persistence of *Salmonella* spp. in the epithelial layer of intestines (Srivastava *et al.,* 2017)

Dietary plant-derived phytochemicals are also essential in translational regulation of genes associated with immune regulation (Hoensch and Weigmann, 2018). Many of the genes responsible for metabolism, immunity, antigen presentation and inflammatory response have been reported to be modulated by phytochemicals such as capsaicin from genus *Capsicum*, oleoresin and cinnamaldehyde (Kim *et al.,* 2010). Du *et al.* (2016) tested the effects of thymol from *Thymus vulgaris* and carvacrol from *Origanum vulgare* on intestinal integrity and immune response of broiler chickens challenged with Gram-positive bacteria. Results revealed increases of interleukin-1β and TLR-2 mRNA which are critical in inflammatory responses, cell proliferation, differentiation and apoptosis.

Observed pharmacological activities of natural antimicrobials are attributed to phytocompounds present, thus justify their uses in fighting against infectious diseases. Therefore, the vast of medicinal plants in the globe with several secondary metabolites are the solution towards infectious diseases, including salmonellosis in the chicken industry.

Conclusion: There are more than 2600 *Salmonella* serovars in the world, and this number keeps on increasing from discoveries. Salmonellosis is a global problem due to the presence of these serovars to a broader population of hosts in different environments from aquatic to terrestrial. The problem is enormous because of the complexity in the mode of infection and the behaviours of *Salmonella* in escaping the host immune system. Chickens infected with *Salmonella* may continue to live and shed live *Salmonella* for an extended period. At this point, a chicken becomes a chronic carrier of *Salmonella.* The chronic carrier chickens are critical in spreading the disease to the new batches of hatcheries through vertical contamination of the egg yolk. Similar to the vertical transmission of bacteria, the horizontal contamination also magnifies the infection in the cage after chickens eat contaminated feeds. Moreover, the formation of biofilm layers by *Salmonella* in metal, floor and instrument in abattoirs maintain survival and persistence of *Salmonella* which in turn contaminate chicken meat along the value chain. The hazards due to *Salmonella* infection in chickens make human at higher risk of acquiring the diseases than any other organism. Therefore, mode of *Salmonella* infection to chickens, newly discovered serovars and multidrug-resistant strain of bacteria from different ecosystems necessitate for more scientific information to stakeholders.

Still little is known about the mechanism of *Salmonella* infection in chickens. Most of the researches on the mechanism of *Salmonella* infection were done using mice model and have dominated in developed countries of the world. Some aspects such as survival of *Salmonella* in phagocytic cells, functions of some effector proteins of SPI-1, SPI-2 and pathogenicity of *Salmonella* in the chicken are not clear. The knowledge out of the mice model may be applied to reduce infections in chickens. However, this creates a concern for more investigation on chickens because some serovars which induce systemic infections are highly host adaptive.

The combined approaches discussed in this review will help reduce *Salmonella* infection in chickens, and the production of safer products across the world will reduce the zoonosis of the disease and the multidrug-resistant strains of *Salmonella* spp.

REFERENCE

Addwebi, T.M., D.R. Call, and D.H. Shah (2014). Contribution of *Salmonella* Enteritidis virulence factors to intestinal colonization and systemic dissemination in 1-day-old chickens. Poult. Sci. 93(4): 871-881.

Álvarez-Ordóñez, A., M. Prieto, A. Bernardo, C. Hill, and M. López (2012). The acid tolerance response of *Salmonella* spp. an adaptive strategy to survive in stressful environments prevailing in foods and the host. Food Res. Inter. 45(2): 482-492.

Álvarez-Ordóñez, A., A. Fernández, A. Bernardo, and M. López (2010). Arginine and lysine decarboxylases and the acid tolerance response of *Salmonella* Typhimurium. Inter. J. of food Microbiol. 136(3): 278-282.

Álvarez-Ordóñez, A., M. Begley, M. Prieto, W. Messens, M. López, A. Bernardo, and C. Hill (2011). *Salmonella* spp. survival strategies within the host gastrointestinal tract. Microbiol. 157(12): 3268-3281.

Alkhalf, A., M. Alhaj, and I. Al-Homidan (2010). Influence of probiotic supplementation on the immune response of broiler chicks. Egypt. Poult. Sci. 30(1): 271-80.

Andino, A., S. Pendleton, N. Zhang, W. Chen, F. Critzer, and I. Hanning (2014). Survival of *Salmonella enterica* in poultry feed is strain-dependent. Poult. Sci. 93(2): 441-447.

Andino, A. and I. Hanning (2015). *Salmonella enterica*: survival, colonisation, and virulence differences among serovars. The Sci. World J. 2015.

Agbor, T.A., Z.C. Demma, K.L. Mumy, J.D. Bien, and B.A. McCormick (2011). The ERM protein, ezrin, regulates neutrophil transmigration by modulating the apical localisation of MRP2 in response to the SipA effector protein during *Salmonella* Typhimurium infection. Cell Microbiol. 13(12): 2007-2021.

Agbor, T.A. and B.A. McCormick (2011). *Salmonella* effectors: important players modulating host cell function during infection. Cell Microbiol. 13(12): 1858-1869.

Agunos, A., L.Waddell, D. léger, and E. Taboada (2014). A systematic review characterising on-farm sources of *Campylobacter* spp. for broiler chickens. PLoS One. 9(8): 104905.

Arun, N., and D.P. Singh (2012). *Punica granatum*: a review on pharmacological and therapeutic properties. Inter. J. of Pharm. Sci. and Res. 3(5): 1240.

Asten, A. J. and J. E Dijk (2005). Distribution of "classic" virulence factors among *Salmonella* spp. Pathog. Dis. 44: 251-259.

Ashida, H., H. Mimuro, M. Ogawa, T. Kobayashi, T. Sanada, M. Kim, and C. Sasakawa (2011). Cell death and infection: a double-edged sword for host and pathogen survival. The J. of Cell Biol. 195(6): 931-942.

Atterbury, R.J., M. A.P. Van Bergen, F. Ortiz, M. A. Lovell, J.A. Harris, A. De Boer, J.A. Wagenaar, V.M. Allen, and P.A. Barrow (2007). Bacteriophage therapy to reduce *Salmonella* colonisation of broiler chickens. Appl. Environ. Microbiol. 73(14): 4543-4549.

Baik, H.S., S. Bearson, S. Dunbar, and J.W. Foster (1996). The acid tolerance response of *Salmonella* Typhimurium provides protection against organic acids. Microbiol. 142(11): 3195-3200.

Bakowski, M. A., V. Braun, and J.H. Brumell (2008). *Salmonella*-containing vacuoles: directing traffic and nesting to grow. Traf. 9(12): 2022-2031.

Barak, J.D., C.E. Jahn, D.L. Gibson, and A.O. Charkowski (2007). The role of cellulose and O-antigen capsule in the colonisation of plants by *Salmonella enterica*. Mol. Plant Micr. Inter. 20(9): 1083-1091.

Barrow, P.A., M.A. Jones, A.L. Smith, and P. Wigley (2012). The long view: *Salmonella*–the last forty years. Avian Pathol. 41(5): .413-420.

Barth, S. and R. Bauerfeind (2005). Virulence plasmids of *Salmonella enterica*--incidence and properties. Berl. Munch.Tierarztl.Wochenschr. 118(1-2): 8-23.

Baumler, A. J., B.M. Hargis, and R.M. Tsolis (2000). Tracing the origins of *Salmonella* outbreaks. Sci. 287:50–52.

Behnsen, J., A. Perez-Lopez, S.P. Nuccio, and M. Raffatellu (2015). Exploiting host immunity: the *Salmonella* paradigm. Trends in Immunol. 36(2): 112-120.

Bearson, B. L., L. Wilson, and J.W. Foster (1998). A low pH-inducible, PhoPQ-dependent acid tolerance response protects *Salmonella* Typhimurium against inorganic acid stress. J. Bacteriol. 180: 2409-2417.

Behar, S.M. and V. Briken (2019). Apoptosis inhibition by intracellular bacteria and its consequence on host immunity. Curr. Opin. in Immunol. 60: 103-110.

Brisbin, J. T., J. Gong, S. Orouji, J. Esufali, A.I.Mallick, P. Parvizi, and S.Sharif (2011). Oral treatment of chickens with *Lactobacilli* influences the elicitation of immune responses. Clin. and Vacc. Immunol. 5(3): 45-56.

Calenge, F., P. Kaiser, A.Vignal, and C. Beaumont (2010). Genetic control of resistance to salmonellosis and to *Salmonella* carrier-state in fowl: a review. Genet. Select. Evol. 42: 11-19.

Cao, G., M. Allard, E. Strain, R. Stones, S. Zhao, E. Brown, and J. Meng (2014). Genetic diversity of *Salmonella* pathogenicity islands SPI-5 and SPI-6 in *Salmonella* Newport. Foodborne Path. and Dis. 11(10): 798-807.

Capparelli, R., N. Nocerino, M. Iannaccone, D. Ercolini, M. Parlato, M. Chiara, and D. Iannelli (2010). Bacteriophage therapy of *Salmonella enterica*: a fresh appraisal of bacteriophage therapy. The J. of infect. Dis. 201(1): 52-61.

Chadfield, M.S., D.J. Brown, S. Aabo, J.P. Christensen, and J.E. Olsen (2003). Comparison of intestinal invasion and macrophage response of

Salmonella Gallinarum and other host-adapted *Salmonella enterica* serovars in the avian host.Vet. Microbiol. 92(1-2): 49-64.

Chattopadhyay, M.K. (2014). Use of antibiotics as feed additives: a burning question. Front. in Microbiol. 5: 334.

Cappitelli, F., A. Polo, and F. Villa (2014). Biofilm formation in food processing environments is still poorly understood and controlled. Food Eng. Rev. 6:29-42.

Chakravortty, D., I. Hansen-Wester, M. Hensel (2002). *Salmonella* pathogenicity island 2 mediates protection of intracellular *Salmonella* from reactive nitrogen intermediates. J. Exp. Med. 195: 1155–1166.

Choi, Y.J., S.R. Lee, and J.W. Oh (2014). Effects of dietary fermented seaweed and seaweed fusiforme on growth performance, carcass parameters and immunoglobulin concentration in broiler chicks. Asian-Australasian J. of Anim. Sci. 27(6): 862.

Chousalkar, K. and V.C. Gole (2016). Salmonellosis acquired from poultry. Current Opin. in Infect. Dis. 29(5): 514-519.

Chylkova, T., M. Cadena, A. Ferreiro, and M. Pitesky (2017). Susceptibility of *Salmonella* Biofilm and Planktonic Bacteria to Common Disinfectant Agents Used in Poultry Processing. J. Food Prot. 80(7):1072-1079.

Clayton, D.J., A.J. Bowen, S.D. Hulme, A.M Buckley, V.L. Deacon, N.R. Thomson, P.A. Barrow, E. Morgan, M.A. Jones, M. Watson, and M.P. Stevens (2008). Analysis of the role of 13 major fimbrial subunits in the colonisation of the chicken intestines by *Salmonella enterica* serovar Enteritidis reveals a role for a novel locus. BMC Microbiol. 8(1): 228.

Coburn, B., I. Sekirov, and B.B. Finlay (2007). Type III secretion systems and disease. Clin. Microbiol. Rev. 20(4): 535-549.

Cogan, T., and T. Humphrey (2003). The rise and fall of *Salmonella* Enteritidis in the UK. J. Appl. Microbiol. 94: 114-119.

Connolly, P.F., and H.O. Fearnhead (2017). Viral hijacking of host caspases: an emerging category of pathogen-host interactions. Cell death and diff. 24(8): 1401.

Connerton, P. L., A.R. Timms, and I.F.Connerton (2011). *Campylobacter* bacteriophages and bacteriophage therapy. J. of Appl. Microbiol. 111(2): 255-265.

Cordero-Alba, M., J.J. García-Gómez, J. Aguilera-Herce, and F. Ramos-Morales (2016). Proteomic insight into the effects of the *Salmonella* ubiquitin ligase SlrP on host cells. Bioch. and Biophys. Res. Comm. 472(3): 539-544.

Crhanova, M., H. Hradecka, M. Faldynova, M. Matulova, H. Havlickova, F Sisak, and I. Rychlik (2011). Immune response of chicken gut to natural colonisation by the gut microflora and to *Salmonella enterica* serovar Enteritidis infection. Infect. and Immun. 79(7): 2755-2763.

De Buck, J., F. Van Immerseel, F. Haesebrouck and R. Ducatelle (2004). Colonisation of the chicken reproductive tract and egg contamination by *Salmonella*. J. Appl. Microbiol. 97: 233-245.

De Gelder L., J.J. Williams, J.M. Ponciano, M. Sota, and E.M. Top (2008). Adaptive plasmid evolution results in host-range expansion of a broad-host-range plasmid. Genet. 178: 2179–2190.

Deng, W., N.C. Marshall, J.L. Rowland, J.M. McCoy, L.J. Worrall, A.S. Santos, N.C. Strynadka, and B.B. Finlay (2017). Assembly, structure, function and regulation of type III secretion systems. Nat. Rev. Microbiol. 15(6): 323.

Desin, T.S., W. Köster, and A.A. Potter (2013). *Salmonella* vaccines in poultry: past, present and future. Expert Rev. of Vacc. 12(1): 87-96.

Dhama, K., S.K. Latheef, S. Mani, H.A Samad, K. Karthik, R. Tiwari, R.U. Khan, M. Alagawany, M.R. Farag, G.M. Alam, and V. Laudadio (2015). Multiple beneficial applications and modes of action of herbs in poultry health and production-A review. Int. J. Pharmacol. 11(3): 152-176.

Dhanani, A.S., G. Block, K. Dewar, V. Forgetta, E. Topp, R.G. Beiko, and M.S. Diarra (2015). Genomic comparison of non-typhoidal *Salmonella enterica* serovars Typhimurium, Enteritidis, Heidelberg, Hadar and Kentucky isolates from broiler chickens. PLoS One. 10(6): 0128773.

Dieye, Y., K. Ameiss, M. Mellata, and R. Curtiss (2009). The *Salmonella* Pathogenicity Island (SPI) 1 contributes more than SPI2 to the colonisation of the chicken by *Salmonella enterica* serovar Typhimurium. BMC Microbiol. 9(1): 3.

Diaz-Sanchez, S., D. D'Souza, D. Biswas, and I. Hanning (2015). Botanical alternatives to antibiotics for use in organic poultry production. Poult. Sci. 94(6): 1419-1430.

dos Santos, A.M., R.G. Ferrari, and C.A. Conte-Junior (2019). Virulence factors in *Salmonella* Typhimurium: the sagacity of a bacterium. Curr. Microbiol. 76(6): 762-773.

Drecktrah, D., L.A. Knodler, K. Galbraith, and O. Steele-Mortimer (2005). The *Salmonella* SPI1 effector SopB stimulates nitric oxide production long after invasion. Cell Microbiol. 7(1): 105-113.

Du, E., W. Wang, L. Gan, Z. Li, S. Guo, and Y. Guo (2016). Effects of thymol and carvacrol

supplementation on intestinal integrity and immune responses of broiler chickens challenged with Clostridium perfringens. J. of Anim.Sci. and Biot. 7(1): 19.

Dunkley, K. D., T.R. Callaway, V.I. Chalova, J.L. McReynolds, M.E. Hume, C.S. Dunkley, and S.C. Ricke (2009). Foodborne *Salmonella* ecology in the avian gastrointestinal tract. Anaerobe. 15(1-2): 26-35.

Durant, J.A., D.E. Corrier, J.A. Byrd, L.H. Stanker, and S.C. Ricke (1999). Feed deprivation affects crop environment and modulates *Salmonella* Enteritidis colonisation and invasion of leghorn hens. Appl. Env. Microbiol. 65(5): 1919-1923.

El-Azzouny, M.M., A.S. El-Demerdash, H.G. Seadawy, and S.H. Abou-Khadra (2018). Antimicrobial effect of Garlic (Allium sativum) and Thyme (Zataria multiflora Boiss) extracts on some foodborne pathogens and their effect on virulence gene expression. Cell Mol. Biol. 64(10).

Eng, S.K., P. Pusparajah, A.B Mutalib, H.L. Ser, K.G. Chan, and L.H. Lee (2015). *Salmonella*: a review on pathogenesis, epidemiology and antibiotic resistance. Front. Life Sci. 8(3): 284-293.

Eswarappa, S. M., V.D. Negi, S. Chakraborty, B.C. Sagar, and D. Chakravortty (2010). Division of the *Salmonella*-containing vacuole and depletion of acidic lysosomes in Salmonella-infected host cells are novel strategies of *Salmonella enterica* to avoid lysosomes. Infect. and Immun. 78(1): 68-79.

Fasina, F.O., A.M. Ali, J.M. Yilma, O. Thieme, and P. Ankers (2012). The cost-benefit of biosecurity measures on infectious diseases in the Egyptian household poultry. Prev. Vet. Med. 103(2-3): 178-191.

Fink, S.L. and B.T. Cookson (2007). Pyroptosis and host cell death responses during *Salmonella* infection. Cellul. Microb. 9(11): 2562-2570.

Foley, S.L., A.M. Lynne, and R. Nayak (2008). *Salmonella* challenges: Prevalence in swine and poultry and potential pathogenicity of such isolates. J. Animal Sci. 86(14): 149-162.

Foley, S. L., T.J. Johnson, S.C. Ricke, R. Nayak, and J. Danzeisen (2013). *Salmonella* pathogenicity and host adaptation in chicken-associated serovars. Microbiol. Mol. Biol. Rev. 77: 582-607.

Foster, J. W., and M.P. Spector (1995). How *Salmonella* survives against the odds. Annu. Rev. Microbiol. 49: 145-174.

Foster, J.W (1991). Salmonella acid shock proteins are required for the adaptive acid tolerance response. J. of Bacteriol. 173(21): 6896-6902.

Fuentes, J.A., N. Villagra, M. Castillo-Ruiz, and G.C. Mora (2008). The *Salmonella* Typhi hlyE gene plays a role in invasion of cultured epithelial cells and its functional transfer to *S.* Typhimurium promotes deep organ infection in mice. Res. Microbiol. 159(4): 279-287.

Gallois, A., J.R. Klein, L.A. H. Allen, B.D. Jones, and W.M. Nauseef (2001). *Salmonella* pathogenicity island 2-encoded type III secretion system mediates exclusion of NADPH oxidase assembly from the phagosomal membrane. J. Immunol. 166: 5741-5748.

García, C., J.M. Soriano, V. Benítez, and P. Catalá-Gregori (2011). Assessment of *Salmonella* spp. in faeces, cloacal swabs, and eggs (eggshell and content separately) from a laying hen farm. Poult. Sci. 90(7): 1581-1585.

Garmiri, P., K.E. Coles, T.J. Humphrey, and T.A. Cogan (2008). Role of outer membrane lipopolysaccharides in the protection of *Salmonella enterica* serovar Typhimurium from desiccation damage. FEMS Microbial. Lett. 281(2): 155-159.

Gerstel, U., and U. Romling (2003). The csgD promoter, a control unit for biofilm formation in *Salmonella* Typhimurium. Res. Microbial. 154: 659-667

Griessl, M.H., B. Schmid, K. Kassler, C. Braunsmann, R. Ritter, B. Barlag, Y.D Stierhof, K.U. Sturm, C. Danzer, C. Wagner, and Schäffer, T.E. (2013). Structural insight into the giant Ca2+-binding adhesin SiiE: implications for the adhesion of *Salmonella enterica* to polarised epithelial. Cell. Struct. 21(5): 741-752.

Griggs, J. P., andJ.P. Jacob (2005). Alternatives to antibiotics for organic poultry production. J. of App. Poult. Res. 14(4): 750-756

Guard-Bouldin, J., R.K. Gast, T.J. Humphrey, D.J. Henzler, C. Morales and K. Coles (2004). Subpopulation characteristics of egg-contaminating *Salmonella enterica* serovar Enteritidis as defined by the lipopolysaccharide O chain. App. Env. Microbial. 70(5): 2756-2763.

Guiney, D.G., and J. Fierer (2011). The role of the spv genes in *Salmonella* pathogenesis. Front. in Microbiol. 2: 129.

Hapfelmeier, S., K. Ehrbar, B. Stecher, M. Barthel, M. Kremer, and W.D. Hardt (2004). Role of the *Salmonella* pathogenicity island 1 effector proteins SipA, SopB, SopE, and SopE2 in *Salmonella enterica* subspecies 1 serovar Typhimurium colitis in streptomycin-pretreated mice. Infect. Immun. 72(2): 795-809.

Harimurti, S., and W. Hadisaputro (2015). Probiotics in Poultry. In Beneficial Microorganisms in Agriculture. Aquac. and other Areas. 1: 1-19.

Hoensch, H.P., and B. Weigmann (2018). Regulation of the intestinal immune system by flavonoids and its utility in chronic inflammatory bowel disease. World J. of Gastroenterol. 24(8): 877.

Hooton, S.P., A.R. Timms, J. Rowsell, R. Wilson, and I.F Connerton (2011). *Salmonella* Typhimurium-specific bacteriophage ΦSH19 and the origins of species specificity in the Vi01-like phage family. Virol. J. 8(1):498.

Huang, C., S.M. Virk, J. Shi, Y. Zhou, S.P. Willias, M.K Morsy, H.E. Abdelnabby, J. Liu, X. Wang, and J. Li (2018). Isolation, characterisation, and application of bacteriophage LPSE1 against *Salmonella enterica* in ready to eat (RTE) foods. Front. in Microbiol.9.

Hurley, D., M.P. McCusker, S. Fanning, and M. Martins (2014). Salmonella–host interactions–modulation of the host innate immune system. Front. in Immunol. 5: 481.

Hur, J., J.H. Kim, J.H Park, Y.J Lee, and J.H. Lee (2011). Molecular and virulence characteristics of multi-drug resistant *Salmonella* Enteritidis strains isolated from poultry. The Veter. J. 189(3): 306-311.

Ilyas, B., C.N. Tsai, and B.K Coombes (2017). Evolution of *Salmonella*-host cell interactions through a dynamic bacterial genome. Front. in Cellul. and Infect. Microbiol. 7: 428.

Jansen, K.U., C. KnirschandA.S. Anderson (2018). The role of vaccines in preventing bacterial antimicrobial resistance. Nat. Med. 24(1): 10.

Jeffrey, J.S., E.R. Atwill, and A. Hunter (2001). Farm and management variables linked to fecal shedding of Campylobacter and Salmonella in commercial squab production. Poult. Sci. 80(1): 66-70.

Jennings, E., T.L. Thurston, and D.W. Holden (2017). *Salmonella* SPI-2 type III secretion system effectors: molecular mechanisms and physiological consequences. Cell Host. and Micr. 22(2): 217-231.

Jepson, M. A., and M.A. Clark (2001). The role of M cells in *Salmonella* infection. Microb. Infect. 3: 1183-1190.

Jeong, C.H., and S.H. Joo (2016). Downregulation of reactive oxygen species in apoptosis. J. of Cancer Prevent. 21(1): 13.

Jimenez, A., D. Chen, and N.M. Alto (2016). How bacteria subvert animal cell structure and function. Annual Rev. of Cell and Develop. Biol. 32: 373-397.

Johnson, R., A. Byrne, C.N. Berger, E. Klemm, V.F. Crepin, G. Dougan, and G. Frankel (2017). The type III secretion system effector SptP of *Salmonella enterica* serovar Typhi. J. Bacteriol. 199(4): 00647-16.

Jorgensen, I., M. Rayamajhi, and E.A. Miao (2017). Programmed cell death as a defence against infection. Nature Rev. Immunol. 17(3): 151.

Julien, O., and J.A. Wells (2017). Caspases and their substrates. Cell Death and Diff. 24(8): 1380.

Kabir, S. M. (2009). The role of probiotics in the poultry industry. Int. J. of Mol. Sci. 10(8): 3531-3546.

Kabir, S. M. (2010). Avian colibacillosis and salmonellosis: a closer look at epidemiology, pathogenesis, diagnosis, control and public health concerns. Int. J. Environ. Res. Pub. Health. 7:89-114.

Kailasapathy, K., and J. Chin (2000). Survival and therapeutic potential of probiotic organisms with reference to *Lactobacillus acidophilus* and *Bifidobacterium* spp. Immun and Cell Biol. 78(1): 80-88.

Kaur, J., and S. Jain (2012). Role of antigens and virulence factors of *Salmonella enterica* serovar Typhi in its pathogenesis. Microbiol. Res. 167: 199-210.

Kechagia, M., D. Basoulis, S. Konstantopoulou, D. Dimitriadi, K. Gyftopoulou, N. Skarmoutsou, and E. M. Fakiri (2013). Health benefits of probiotics: A review. ISRN Nutrit. 2013.

Khan, S.H., N. Mukhtar, and J. Iqbal (2018). Role of Mushroom as Dietary Supplementt on Performance of Poultry. J. of Diet. Suppl. :1-14.

Kim, D.K., H. S. Lillehoj, S. H. Lee, S. I. Jang, and D. Bravo (2010). High-throughput gene expression analysis of intestinal intraepithelial lymphocytes after oral feeding of carvacrol, cinnamaldehyde, or *Capsicum oleoresin*. Poult. Sci.89(1): 68-81.

Kiss, T., E. Morgan, and G. Nagy (2007). Contribution of SPI-4 genes to the virulence of *Salmonella enterica.* FEMS Microb. Letter. 275(1): 153-159.

Knodler, L. A., B.A. Vallance, J. Celli, S. Winfree, B. Hansen, M. Montero, and O. Steele-Mortimer (2010). Dissemination of invasive *Salmonella* via bacterial-induced extrusion of mucosal epithelia. Proc. Natl. Acad. Sci. 107: 17733-17738.

Knodler, L. A. (2015). *Salmonella enterica*: living a double life in epithelial cells. Curr. Opin. in Microbiol. 23: 23-31.

Knuff, K., and B.B. Finlay (2017). What the SIF Is Happening—The Role of Intracellular *Salmonella*-Induced Filaments. Front. in Cell. and Infect. Microbiol. 7: 335.

Kong, Q., J. Yang, Q. Liu,P. Alamuri, K.L. Roland and R. Curtiss (2011). Effect of deletion of genes involved in lipopolysaccharide core and O-

antigen synthesis on virulence and immunogenicity of *Salmonella enterica* serovar Typhimurium. Infect. Immun. 79: 4227-4239.

Koo, H., R.N. Allan, R.P. Howlin, P.Stoodley, and L. Hall-Stoodley (2017). Targeting microbial biofilms: current and prospective therapeutic strategies. Nat. Rev. Microbiol. 15(12): 740.

Koopman, J.A., J.M. Marshall, A. Bhatiya, T. Eguale, J.J. Kwiek, and J.S. Gunn (2015). Inhibition of *Salmonella enterica* biofilm formation using small-molecule adenosine mimetics.Antimicrob. Agents Chemother. 59(1): 76-84.

Kubori, T., A. Sukhan, S.I. Aizawa and J.E. Galán (2000). Molecular characterisation and assembly of the needle complex of the *Salmonella* Typhimurium type III protein secretion system. Proc. Natl. Acad. Sci. 97: 10225-10230.

Lamas, A., J.M. Miranda, P. Regal, B. Vazquez, C.M. Franco, and A. Cepeda (2018). A comprehensive review of non-enterica subspecies of *Salmonella enterica*. Microbiol. Res. 206: 60-73.

Lamkanfi, M., and V.M. Dixit (2014). Mechanisms and functions of inflammasomes. Cell. 157(5): 1013-1022.

Lawley, T. D., D. M. Bouley, Y.E. Hoy, C. Gerke, D.A. Relman,and D.M. Monack (2008). Host transmission of *Salmonella enterica* serovar Typhimurium is controlled by virulence factors and indigenous intestinal microbiota. Infec Immun. 76: 403-416.

Latasa, C., A. Roux,A. Toledo-Arana, J.M. Ghigo, C. Gamazo, J.R. Penadés, and I. Lasa (2005). BapA, a large secreted protein required for biofilm formation and host colonization of *Salmonella enterica* serovar Enteritidis. Mol. Microbiol. 58(5): 1322-1339.

Lebeer, S., J. Vanderleyden, and S.C. De Keersmaecker (2010). Host interactions of probiotic bacterial surface molecules: comparison with commensals and pathogens. Nature Rev. Microbiol. 8(3): 171.

Ledeboer, N.A., and B.D. Jones (2005). Exopolysaccharide sugars contribute to biofilm formation by *Salmonella enterica* serovar Typhimurium on HEp-2 cells and chicken intestinal epithelium. J. Bacterial. 187(9): 3214-3226.

Lee, J.W., and E.J. Lee (2015). Regulation and function of the *Salmonella* MgtC virulence protein. J. of Microbiol. 53(10): 667-672.

Lim, S., S. Cho, K. Caetano-Anolles, S.G. Jeong, M.H. Oh, B.Y. Park, and J.H. Lee (2015). Developmental dynamic analysis of the excreted microbiome of chickens using next-generation sequencing. J. of Mol. Microbial. and Biotech. 25(4): 262-268.

Lianou, A., G. J. E. Nychas, and K.P. Koutsoumanis (2017). Variability in the adaptive acid tolerance response phenotype of *Salmonella enterica* strains. Food Microbiol. 62: 99-105.

Lin, Y.H., and M.P. Machner (2017). Exploitation of the host cell ubiquitin machinery by microbial effector proteins. J. Cell Sci. 130(12): 1985-1996.

Liu, Q., Q. Liu, X. Zhao, T. Liu, J. Yi, K. Liang, and Q. Kong (2016). Immunogenicity and cross-protective efficacy induced by outer membrane proteins from *Salmonella* Typhimurium mutants with truncated LPS in mice. Inter. J. of Molec. Sci. 17(3): 416.

Loc-Carrillo, C., andS.T. Abedon (2011). Pros and cons of phage therapy. Bacterioph. 1(2): 111-114.

López, A., M. de Tangil, O. Vega-Orellana, A. Ramírez, and M. Rico, (2013). Phenolic constituents, antioxidant and preliminary antimycoplasmic activities of leaf skin and flowers of Aloe vera (L.) Burm. f. (syn. A. barbadensis Mill.) from the Canary Islands (Spain). Molec. 18(5): 4942-4954.

Lorkowski, M., A. Felipe-López, C.A. Danzer, N. Hansmeier, and M. Hensel, (2014). *Salmonella enterica* invasion of polarized epithelial cells is a highly cooperative effort. Infec. and Imm. 82(6): 2657-2667.

Lostroh, C. P., and C.A. Lee (2001). The *Salmonella* pathogenicity island-1 type III secretion system. Microb. Infect. 3:1281-1291.

Lu, R., S. Wu, X. Liu, Y. Xia, Y.G. Zhang, and J. Sun (2010). Chronic effects of a *Salmonella* type III secretion effector protein AvrA in vivo. PloS one. 5(5): 10505.

Lu, Y., Z. Yue, W. Wang, and Z. Cao (2015). Strategies on designing multifunctional surfaces to prevent biofilm formation. Front. of Chemical Sci. and Engin. 9(3): 324-335.

Lunelli, M., R. Hurwitz, J. Lambers, and M. Kolbe (2011). Crystal structure of PrgI-SipD: insight into a secretion competent state of the type three secretion system needle tip and its interaction with host ligands. PLoS Pathog. 7(8): 1002163.

McFarland, L. V. (2000). Normal flora: diversity and functions. Microb. Ecol. in Health and Dis. 12(4): 193-207

McGhie, E.J., P.J. Hume, R.D Hayward, J. Torres, and V. Koronakis (2002). Topology of the *Salmonella* invasion protein SipB in a model bilayer. Mol. Microbiol. 44(5): 1309-1321.

Maciel, B.M., R.P. Rezende, and N.K. Sriranganathan (2017). Salmonella enterica, Topics in

Salmonella and Salmonellosis. Mares M. Ed. InTech Open; Rijeka, Croatia :41-58 p

Masimba, E.S., D.T. Mbiriri, M.T. Kashangura, and T. Mutibvu (2011). Indigenous practices for the control and treatment of ailments in Zimbabwe's village poultry. Livest. Res. Rural Dev. 23: 257.

Marcus, S. L., J.H. Brumell, C.G. Pfeifer, and B.B. Finlay (2000). *Salmonella* pathogenicity islands: big virulence in small packages. Micr. Infect. 2: 145-156.

McClelland, M., K.E. Sanderson, J. Spieth, and S.W. Clifton (2001). Complete genome sequence of *Salmonella enterica* serovar Typhimurium LT2. Nat. 413: 852.

McIlwain DR, T. Berger, T.W. Mak (2013). Caspase functions in cell death and disease. Cold Spring Harb Perspect. Biol. 5: 008656

Mlimbe, M.E., E.E. Ndemanisho, and A. Mzula (2016). In vitro activity of Allium sativum and Aloe vera extract against *Salmonella* enterica subspecies enterica serovar Gallinarum. J. of the Open Univ. of Tanzania, 22(1): 93-99.

Monack, D. M., D.M. Bouley, and S. Falkow (2004). *Salmonella* Typhimurium persists within macrophages in the mesenteric lymph nodes of chronically infected Nramp1+/+ mice and can be reactivated by IFNγ neutralisation. J. Exp. Med. 199:231-241.

Monack, D.M. (2013). Helicobacter and *Salmonella* persistent infection strategies. Cold Spring Harb. Perspect. Med. 3(12): 010348.

Morgan, E., J.D. Campbell, S.C. Rowe, J. Bispham, M.P. Stevens, A.J. Bowen, P.A. Barrow, D.J. Maskell, and T.S.Wallis (2004). Identification of host-specific colonisation factors of *Salmonella enterica* serovar Typhimurium. Mol. Microbiol., 54:994-1010.

Murugadas, V., S. Visnuvinayagam, V. Purushothaman, T.G. Prabhakar, P. Prabhahar, and K. Ventakaraman (2015). Prevalence of chicken host and non-host adapted *Salmonella* in retail outlet of Chennai, India. Asian J. of Anim. and Veter. Adv.10: 885-893.

Murray, G.L., S.R. Attridge, and R. Morona (2003). Regulation of *Salmonella* Typhimurium lipopolysaccharide O antigen chain length is required for virulence; identification of FepE as a second Wzz. Mol. Microbiol. 47(5): 1395-1406.

Myeni, S.K., L. Wang, and D. Zhou, (2013). SipB-SipC complex is essential for translocon formation. PLoS One. 8(3): 60499.

Narayanan, L.A., and M.J. Edelmann (2014). Ubiquitination as an efficient molecular strategy employed in *Salmonella* infection. Front. in Immunol. 5: 558.

Nava, G. M., L.R. Bielke, T.R. Callaway, and M.P. Castaneda (2005). Probiotic alternatives to reduce gastrointestinal infections: the poultry experience. Animal Health Res. Rev. 6(1): 105-118.

Ohl, M. E., and S.I. Miller (2001). *Salmonella*: a model for bacterial pathogenesis. Annu. Rev. Med. 52: 259-274.

Ohno,H., (2015). Intestinal M cells. J. of Biochem. 159(2): 151-160.

Osman, K.M., S.H. Marouf, A.M. Erfan, and N. Alatfeehy (2014). *Salmonella enterica* in imported and domestic day-old turkey poults in Egypt: repertoire of virulence genes and their antimicrobial resistance profiles. Inter. Office of Epizoot. 33(3): 1017-1026.

Otutumi, L.K., M.B. Góis, E.R. de Moraes Garcia, and M.M. Loddi (2012). Variations on the efficacy of probiotics in poultry, probiotic in animals. Intech Open; England. 160-264 p

Pal, S., S. Dey, K. Batabyal, A. Banerjee, S.N. Joardar, I. Samanta, and D. P. Isore (2017). Characterisation of *Salmonella* Gallinarum isolates from backyard poultry by polymerase chain reaction detection of invasion (invA) and *Salmonella* plasmid virulence (spvC) genes. Veter. World. 10(7): 814.

Pande, V.V., R.L. Devon, P. Sharma, A.R. Mcwhorter, and K.K. Chousalkar (2016). Study of *Salmonella* Typhimurium infection in laying hens. Front. Microbiol. 7: 203-228.

Park, Y.H., F. Hamidon, C. Rajangan, K.P. Soh, C.Y. Gan, T.S. Lim, W.N.W. Abdullah, and M.T. Liong (2016). Application of probiotics for the production of safe and high-quality poultry meat. Korean J. for Food Sci.of Anim. Resour. 36(5): 567.

Parsek, M.R. and P.K. Singh (2003). Bacterial biofilms: an emerging link to disease pathogenesis. Annu. Rev. Microbiol. 57(1): 677-701.

Parvej, M.S., K.N.H. Nazir, M.B. Rahman, M. Jahan, M. F. R. Khan, and M. Rahman (2016). Prevalence and characterisation of multi-drug resistant *Salmonella Enterica* serovar Gallinarum biovar Pullorum and Gallinarum from chicken. Veter. World. 9(1): 65.

Peng, D. (2016). Biofilm Formation of *Salmonella*.In Microbial Biofilms-Importance and applications. Intech Open; England. 231-248 p

Pizarro-Cerdá, J., and P. Cossart (2006). Bacterial adhesion and entry into host cells. Cell. 124(4): 715-727.

Poirel L., N. Kieffer, N. Liassine, D. Thanh and P. Nordmann (2016). Plasmid-mediated carbapenem and colistin resistance in a clinical

isolate of *Escherichia coli*. Lancet Infect. Dis. 16: 281-300.

Popoff, M.Y., and L.E. Le Minor(2015). *Salmonella*. Bergey's Manual of Systematics of Archaea and Bacteria. 1: 1

Qu, Y., S. Misaghi, K. Newton, A. Maltzman, A. Izrael-Tomasevic, D. Arnott, and V.M Dixit (2016). NLRP3 recruitment by NLRC4 during *Salmonella* infection. J. of Exper. Med. 213(6): 877-885.

Que, F., S. Wu, and R. Huang (2013). *Salmonella* pathogenicity island 1 (SPI-1) at work. Current Microbiol. 66(6): 582-587.

Rajagopal, R., and M. Mini (2013). Outbreaks of salmonellosis in three different poultry farms of Kerala, India.Asian Pac. J. of Trop. Biomed., 3(6): 496-500.

Ramasamy, K.T., P. Verma, and M.R. Reddy (2014). Toll-like receptors gene expression in the gastrointestinal tract of *Salmonella* serovar Pullorum-infected broiler chicken.Appl. Biochem. and Biotechnol. 173(2): 356-364.

Ramos-Morales, F. (2012). Impact of *Salmonella enterica* type III secretion system effectors on the eukaryotic host cell. Cell Biol. 1: 2012

Ramos-Morales, F., (2012). Acidic pH: enemy or ally for enteric bacteria?. Virul. 103-106

Ranieri, M.L., C. Shi, A.I.M. Switt, H.C. DenBakker andM. Wiedmann (2013). Comparison of typing methods with a new procedure based on sequence characterisation for *Salmonella* serovar prediction. J. Clin. Microbiol. 51(6): 1786-1797.

Rathinavelan, T., M. Lara-Tejero, M. Lefebre, S. Chatterjee, A.C. McShan, D.C. Guo, C. Tang, J.E Galan, and R.N. De Guzman (2014). NMR Model of PrgI–SipD Interaction and Its Implications in the Needle-Tip Assembly of the *Salmonella* Type III Secretion System.J. of Molec. Biol., 426(16): 2958-2969.

Revolledo, L., and A.J.P. Ferreira (2012) Current perspectives in avian salmonellosis: Vaccines and immune mechanisms of protection. J. Appl. Poult. Res. 21: 418-431.

Ribet, D. and P. Cossart (2015). How bacterial pathogens colonise their hosts and invade deeper tissues. Micr. and Infect.17(3): 173-183.

Ricke, S.C. (2003). The gastrointestinal tract ecology of *Salmonella* Enteritidis colonisation in molting hens. Poult. Sci. 82(6): 1003-1007.

Ritzi, M. M., W. Abdelrahman, M. Mohnl,andR.A. Dalloul (2014). Effects of probiotics and application methods on performance and response of broiler chickens to an Eimeria challenge. Poultry Sci. 93(11): 2772-2778.

Ryan, M. P., J. O'Dwyer, and C.C. Adley (2017). Evaluation of the complex nomenclature of the clinically and veterinary significant pathogen *Salmonella*. Bio.Med. Research Inter. 2017.

Rychlik, I., D. Gregorova, and H. Hradecka (2006). Distribution and function of plasmids in *Salmonella enterica*.Vet. Microbiol. 112(1): 1-10.

Rychlik, I., D. Karasova, A.Sebkova, J. Volf, F. Sisak, H. Havlickova, V. Kummer, A. Imre, A.Szmolka, and B. Nagy (2009). Virulence potential of five major pathogenicity islands (SPI-1 to SPI-5) of *Salmonella enterica* serovar Enteritidis for chickens. BMC Microbiol. 9(1): 268.

Roer, L., R.S. Hendriksen, P. Leekitcharoenphon, O. Lukjancenko, R.S. Kaas, H. Hasman, and F.M. Aarestrup (2016). Is the evolution of *Salmonella enterica* subsp. enterica linked to restriction-modification systems?. Msyst. 1(3): 9-16.

Rosselin, M., N. Abed, I.Virlogeux-Payant, E. Bottreau P.Y. Sizaret, P. Velge, and A. Wiedemann (2011). Heterogeneity of type III secretion system (T3SS)-1-independent entry mechanisms used by *Salmonella* Enteritidis to invade different cell types. Microbiol. 157(3): 839-847.

Rossi, D.A., R.T. Melo, E.P. Mendonça, and Monteiro, G.P. (2017). Biofilms of *Salmonella* and *Campylobacter* in the poultry industry. Poult. Sci. InTech.

Ruby, T., L. Mclaughlin, S. Gopinath, and D. Monack (2012). *Salmonella*'s long-term relationship with its host. FEMS Microbiol Rev. 36: 600-615.

Sahoo, M., I. Ceballos-Olvera, L. del Barrio, and F. Re (2011). Role of the inflammasome, IL-1β, and IL-18 in bacterial infections. The Scient. World J. 11: 2037-2050.

Sekelova, Z., H. Stepanova, O. Polansky, K. Varmuzova, M. Faldynova, R. Fedr, I. Rychlik, and L. Vlasatikova (2017). Differential protein expression in chicken macrophages and heterophils in vivo following infection with *Salmonella* Enteritidis. Veter. Res. 48(1): 35.

Shalini, S., L. Dorstyn, S. Dawar, and S. Kumar (2015). Old, new and emerging functions of caspases. Cell Death and Diff. 22(4): 526.

Singh, V., (2015). Host factors and compartments accessed by *Salmonella* Typhimurium for intracellular growth and survival. M.Sc. Dissertation. Faculty of Life Sciences., Humboldt Univ. of Berlin., Germany.

Sillankorva, S., E. Pleteneva, O.Shaburova, S. Santos, C. Carvalho, J. Azeredo and V. Krylov (2010). *Salmonella* Enteritidis bacteriophage candidates for phage therapy of poultry. J. of Applied Microbiol. 108(4): 1175-1186.

Schmidt, H., and M. Hensel (2004). Pathogenicity islands in bacterial pathogenesis. Clin. Microbiol. Rev. 17: 14-56.

Setta, A.M., P.A. Barrow, P. Kaiserand, M.A. Jones (2012). Early immune dynamics following infection with *Salmonella enterica* serovars Enteritidis, Infantis, Pullorum and Gallinarum: cytokine and chemokine gene expression profile and cellular changes of chicken cecal tonsils. Comp. Immunol.Microbiol. Infect. Dis. 35(5): 397-410.

Servin, A. L., and M.H. Coconnier (2003). Adhesion of probiotic strains to the intestinal mucosa and interaction with pathogens. Best Pract. and Res. Clin. Gastroenterol. 17(5): 741-754.

Schlumberger, M.C., and W.D. Hardt (2006). *Salmonella* type III secretion effectors: pulling the host cell's strings. Curr.Opin. Microbiol. 9: 46–54.

Shi, J., Y. Zhao, K. Wang, X. Shi, Y. Wang, H. Huang, Y. Zhuang, T. Cai, F. Wang, and F. Shao, (2015). Cleavage of GSDMD by inflammatory caspases determines pyroptotic cell death. Nat. 526 (75): 660.

Smith, J. L. (2003). The role of gastric acid in preventing foodborne disease and how bacteria overcome acid conditions. J. of Food Protect. 66(7): 1292-1303.

Silva-Herzog, E., and C.S. Detweiler (2010). *Salmonella enterica* replication in hemophagocytic macrophages requires two type three secretion systems. Infect Immun.78: 3369-3377.

Solarte, A.L., R.J. Astorga, F.C. de Aguiar, C. De Frutos, B. Barrero-Dominguez, and B. Huerta (2018). Susceptibility distribution to essential oils of *Salmonella enterica* strains involved in animal and public health and comparison of the Typhimurium and Enteritidis Serotypes. J. of Medic. Food. 21(9): 946-950.

Srivastava, A., J. Gupta, S. Kumar, and A. Kumar (2017). Gut biofilm-forming bacteria in inflammatory bowel disease. Microb. Pathog. 112:.5-14.

Surjushe, A., R. Vasani, and D.G. Saple (2008). *Aloe vera*: a short review. Indian J. of Dermat. 53(4): 163.

Smith, H.W. (1956). The use of live vaccines in experimental *Salmonella* Gallinarum infection in chickens with observations on their interference-effect. Epidemiol. Infect. 54(3): 419-432.

Steele-Mortimer, O. (2008). The *Salmonella*-containing vacuole moving with the times. Curr.Opinion in Microbiol. 11(1): 38-45.

Stevens, M. P., T.J. Humphrey, and D.J. Maskell (2009). Molecular insights into farm animal and zoonotic *Salmonella* infections. Biol. Sci. 364: 2709-2723.

Tellez, G., C. Pixley, R.E. Wolfenden, S. L. Layton, and B.M. Hargis (2012). Probiotics/direct-fed microbials for *Salmonella* control in poultry. Food Res. Inter. 45(2): 628-633.

Thiel, K., (2004). Old dogma, new tricks 21st-century phage therapy. Nat. Biotechnol. 22(1): 31.

Tierrez, A., and F. García-Del Portillo (2005). New concepts in *Salmonella* virulence: the importance of reducing the intracellular growth rate in the host. Cell Microbiol. 7: 901-909.

Toguchi, A., M. Siano, M. Burkart, and R.M. Harshey (2000). Genetics of swarming motility in *Salmonella enterica* serovar Typhimurium: critical role for lipopolysaccharide. J. Bacteriol. 182: 6308-6321.

Tummers, B. and D. R. Green (2017). Caspase-8: regulating life and death. Immunol. Rev. 277(1): 76-89.

Tuomola, E., R. Crittenden, M. Playne, E. Isolauri, and S. Salminen (2001). Quality assurance criteria for probiotic bacteria. The American J. of Clin. Nutr. 73(2): 393-398.

Upadhyaya, I., A. Kollanoor-Johny, M.J. Darre, and K. Venkitanarayanan (2014). Efficacy of plant-derived antimicrobials for reducing egg-borne transmission of *Salmonella* Enteritidis. J. of Appl. Poult. Res. 23(2): 330-339.

Vanderpool, C., F. Yan and B.D. Polk (2008). Mechanisms of probiotic action: implications for therapeutic applications in inflammatory bowel diseases. Inflamm Bowel Dis. 14(11): 1585-1596.

Vazirian, M., S. Alehabib, H. Jamalifar, M.R. Fazeli, A. Najarian Toosi, and M. Khanavi (2015). Antimicrobial effect of cinnamon (Cinnamomum verum J. Presl) bark essential oil in cream-filled cakes and pastries. Res. J. of Pharmac. 2(4): 11-16.

Velge, P., A. Wiedemann, M. Rosselin, N. Abed, Z. Boumart, A. Chausse, O. Grepinet, F. Namdari, S. Roche, and A. Rossignol (2012). Multiplicity of *Salmonella* entry mechanisms, a new paradigm for *Salmonella* pathogenesis. Microbiol. Open. 1: 243-258.

Vieco-Saiz, N., Y. Belguesmia, R. Raspoet, E. Auclair, F. Gancel, I. Kempf, and D. Drider, (2019). Benefits and inputs from lactic acid bacteria and their bacteriocins as alternatives to antibiotic growth promoters during food-animal production. Front. in Microb. 10: 57.

Vonaesch, P., M.E. Sellin, S. Cardini, V. Singh, M. Barthel, and W.D Hardt (2014). The *Salmonella* Typhimurium effector protein SopE transiently localises to the early SCV and contributes to intracellular replication. Cellular Microbiol. 16(12): 1723-1735.

Wagner, C., and M. Hensel (2011). Adhesive mechanisms of *Salmonella enterica*. Adv. Exp. Med. Biol. 715: 17–34.

Waihenya, R.K., M.M.A. Mtambo, G. Nkwengulila, and U.M. Minga (2002). Efficacy of crude extract of Aloe secundiflora against *Salmonella* gallinarum in experimentally infected free-range chickens in Tanzania. J. of Ethnopharm.79(3): 317-323.

Walle, L.V., and M. Lamkanfi (2016). Pyroptosis. Curr. Biol. 26(13): 568-572.

Westwater, C., L.M. Kasman, D.A. Schofield, P.A. Werner, J.W. Dolan, M.G. Schmidt and J.S. Norris (2003). Use of genetically engineered phage to deliver antimicrobial agents to bacteria: an alternative therapy for treatment of bacterial infections. Antim. Agents and Chemother. 47(4): 1301-1307.

Wenk, C., (2006). Are herbs, botanicals and other related substances adequate replacements for antimicrobial growth promoters. Antimicr. Growth Prom. 329:340.

Wiedemann, A., I. Virlogeux-Payant, A.M. Chaussé, A. Schikora, and P. Velge (2015). Interactions of *Salmonella* with animals and plants. Front. in Microbiol. 5: 791-803

Windisch, W. and A. Kroismayr (2007). Natural phytobiotics for health of young piglets and poultry: mechanisms and application. J. of dairy Sci. 90: 643-643.

Wigley, P., A. Berchieri, K. Page, A. Smith, and P. Barrow (2001). *Salmonella enterica* serovar Pullorum persists in splenic macrophages and in the reproductive tract during persistent, disease-free carriage in chickens. Infect. Immun. 69: 7873-7879.

Winnen, B., M.C. Schlumberger, A. Sturm, K. Schüpbach, S. Siebenmann, P. Jennyand W.D. Hardt (2008). Hierarchical effector protein transport by the *Salmonella* Typhimurium SPI-1 type III secretion system. PloS one. 3(5): 2178.

Wu, S.Y., L.D. Wang, J.L.Li, G.M. Xu, M. L. He, Y.Y. Li, and R. Huang (2016). *Salmonella* spv locus suppresses host innate immune responses to bacterial infection. Fish and Shellfish Immunol. 58: 387-396.

Xia, X., X. Wang, Y. Zheng, J. Jiang, and J. Hu (2019). What role does pyroptosis play in microbial infection?. J. of Cellul. Physiol. 234(6): 7885-7892.

Xiong, D., L. Song, Z. Pan, and X. Jiao (2018). Identification and discrimination of *Salmonella enterica* serovar Gallinarum biovars Pullorum and Gallinarum based on a one-step multiplex PCR assay. Front in Microbiol. 9.

Yang, Y., G. Tellez, J.D. Latorre, P.M. Ray, X. Hernandez, B.M. Hargis, S.C. Ricke, and Y.M. Kwon (2018). *Salmonella* excludes *Salmonella* in poultry: confirming an old paradigm using conventional and barcode-tagging approaches. Front. in Vet. Sci. 5.

Zhang, K., A. Riba, M. Nietschke, N.Torow, U.Repnik, A.Pütz, M. Fulde, A. Dupont, M. Hensel, and M. Hornef (2018). Minimal SPI1-T3SS effector requirement for *Salmonella* enterocyte invasion and intracellular proliferation in vivo. PLoS Pathog. 14(3): 1006925.

Zhang, Y., S. Wu, J. Ma, Y. Xia, X. Ai, and J. Sun, (2015). Bacterial protein AvrA stabilizes intestinal epithelial tight junctions via blockage of the C-Jun N-terminal kinase pathway. Tiss. Barriers. 3(1-2): 972849.

Zhou, D., and J. Galán (2001). *Salmonella* entry into host cells: the work in concert of type III secreted effector proteins. Microb. Infect. 3(14-15): 1293-1298.