One Too Many Hamburgers

Question 4: The Immune Response Questions
PATH 417
Case 4, Week 1

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The Case

10-year-old Ronnie McDonald has developed abdominal cramps, bloody diarrhea and a low-grade fever. His parents take him to see the family doctor. The doctor asks about what Ronnie may have eaten in the past week and his parents recall that last weekend at a neighbor's barbecue they were concerned that the hamburgers may not have been cooked thoroughly and Ronnie had eaten two burgers. The doctor performs a physical examination noting no rebound tenderness just some mild periumbilical tenderness. He asks the parents to collect a stool sample for the Microbiology Laboratory and to take Ronnie to the local lab for some routine blood work.

What's wrong with Ronnie?

Before beginning to answer the host immune response questions, it is important to know what is causing Ronnie to feel ill.

Based on his symptoms (abdominal cramps, bloody diarrhea, low-grade fever), and the fact that Ronnie ate two hamburgers last weekend which may have been undercooked, it is likely that Ronnie has acquired a foodborne illness which is affecting his gastrointestinal tract (GIT).[1] The most common bacterial causes of foodborne illness are:[1]

(1) *Salmonella,* a bacterium found in raw and undercooked meat, poultry, dairy products, eggs, seafood
(2) *Campylobacter jejuni,* a bacterium found in raw or undercooked chicken and unpasteurized milk
(3) *Shigella,* a bacterium present in the stools of people who are infected; if they infected person does not wash their hands thoroughly after using the bathroom, they can contaminate the food that they handle or prepare
(4) *Escherichia coli,* bacterium found in raw or undercooked hamburger, unpasteurized fruit juices and milk, and fresh produce; strain O15: H7 produces the most severe illness in humans
(5) *Listeria monocytogenes,* found in raw and undercooked meats, unpasteurized milk, soft cheeses, and ready-to-eat deli meats and hot dogs
(6) *Vibrio,* a bacterium that contaminates fish or shellfish
(7) *Clostridium botulinum,* a bacterium found in improperly canned foods and smoked and salted fish

The case provides us with a lead that the cause of Ronnie's illness may be the undercooked hamburgers he had last weekend. Following this lead, we can eliminate *Vibrio* and *Clostridium botulinum* as possible causative agents of Ronnie's illness since these bacteria are not found in undercooked meat.

To further fine-tune my discussion of the host immune response, I will focus on *Salmonella* (specifically *Salmonella enterica* serovar Typhimurium and *Salmonella enterica* serovar Enteritidis) as a candidate infectious agent in Ronnie's case. I believe *Salmonella* may be a candidate infectious agent in Ronnie's case because infections with *Salmonella* present with the signs and symptoms that Ronnie is experiencing, and *Salmonella* is found in undercooked meat.[2]

[1] Viruses, parasites, and chemicals may also cause foodborne illness. For the purposes of this course, only bacterial causes of foodborne illnesses are listed.

Question 1

Host response: What elements are of the innate and adaptive (humoral and cellular) immune response are involved in this infection?

Overview of the Immune System

The immune system can be classified into: (1) innate immune system and (2) adaptive immune system.[3] The innate immune system is comprised of cellular and humoral elements, as well as anatomical (chemical, physical and biological) barriers which together serve to protect against, detect and destroy microorganisms (Table 1). An example of an anatomical barrier is the gastrointestinal tract (GIT), which provides additional defense mechanisms through peristalsis, secretion of gastric acid, bile acids, digestive enzymes, thiocyanate and defensins. The gut flora of the GIT also provide an additional defense mechanism as these commensal bacteria prevent colonization by pathogenic bacteria by competing for nutrients required for growth.[4]

The innate immune system is non-specific, and relies on a limited number of receptors and secreted proteins which recognize features common to many pathogens. The innate immune system, although generic, is able to discriminate effectively between host cells and pathogens and is thus able to provide initial defenses and also contribute to the activation of the adaptive immune system.[5]

Table 1: The various elements of the innate and adaptive immune systems involved in *Salmonella* infection

	Innate	**Adaptive**
Cellular elements (and secreted cytokines)	Natural killer cells Phagocytes • Macrophages • Neutrophils • Dendritic cells	B cells Plasma cells T cells • T helper cells (CD4) • Cytotoxic T cells (CD8)
Humoral elements	Complement proteins Antimicrobial peptides	Antibodies
Other	Anatomical barriers • Chemical • Physical • Biological	

In contrast, the adaptive immune system is capable of making fine distinctions between closely related molecules, and is thus more specific than the innate immune system. Similar to the innate immune system, the adaptive immune system also comprises both cellular and humoral elements (Table 1).[6]

The major differences between the innate and adaptive immune systems are summarized in Table 2.[7]

Table 2: Comparison of the characteristics of the innate and adaptive immune systems.

	Innate	**Adaptive**
Self/non-self discrimination	Present, reaction is against foreign particles/organisms	Present, reaction is against foreign particles/organisms
Lag phase	Absent, response is immediate	Present, response takes at least a few days
Specificity	Limited, the same response is mounted to a wide variety of agents	High, the response is directed only to the agents that initiated it
Diversity	Limited, hence limited specificity	Extensive, and resulting in a wide range of antigen receptors
Memory	Absent, subsequent exposures to agent generate the same response	Present, subsequent exposures to the same agent induce amplified response

As noted above, both the innate and adaptive immune systems are comprised of cellular and humoral elements. Cellular elements comprise cell-mediated immunity, which is an immune response that involves the activation of immune cells, such as phagocytes and antigen-specific cytotoxic T-lymphocytes, as well as the release of various cytokines in response to an antigen.[8] On the other hand, humoral elements give rise to humoral immunity for which the protective function of immunization is found in the humor (cell-free bodily fluid of serum).[9]

Cell-mediated immunity is directed primarily at intracellular microbes (although in some cases it may be directed at extracellular microbes – see below), whereas humoral immunity is directed at extracellular or dead microbes (Figure 1).[10]

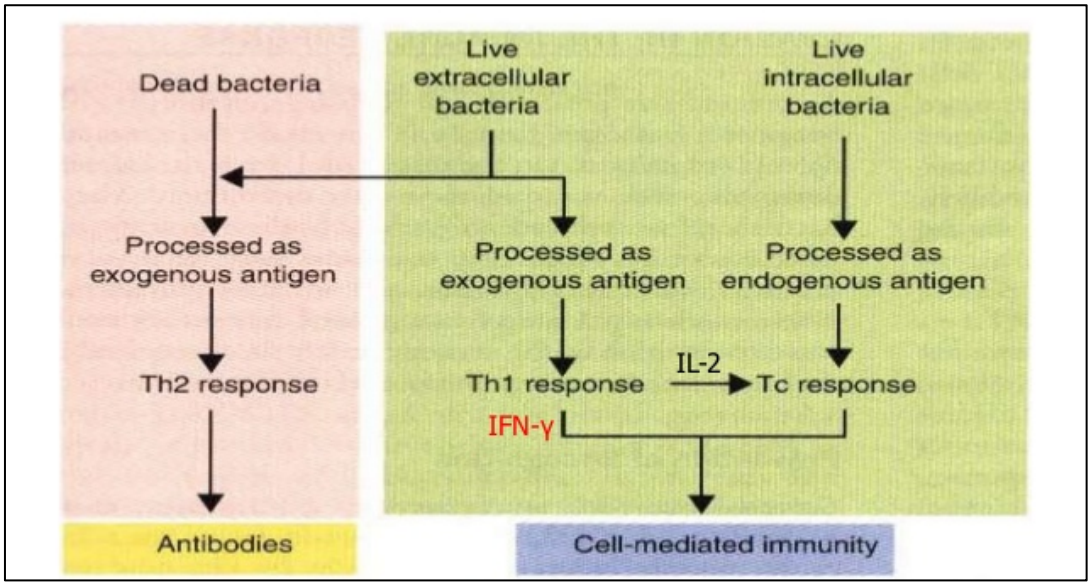

Figure 1: Humoral versus cell-mediated immunity. The type of immune response stimulated by the bacteria depends on whether the bacteria are live or dead and whether they are extra- or intracellular.

The response to an encounter with pathogens occurs in 3 phases, and is summarized in Figure 2.[11] When a pathogen succeeds in breaching one of the host's anatomical barriers, some innate immune mechanisms start to act immediately. These include: (1) antimicrobial enzymes such as lysozyme which digest bacterial cells walls; (2) antimicrobial peptides such as defensins which lyse bacterial cell membranes directly and (3) complement system

which is a system of plasma proteins that functions to target pathogens for lysis and for phagocytosis by immune cells.

In the second phase of the response, innate immune cells sense the presence of a pathogen by recognizing pathogen-associated molecular patterns (PAMPs) via pattern-recognition receptors (PRRs) (see below for more detail).

If an infectious agent is able to breach these first two lines of defense, then the third phase of the response to a pathogen will be activated, namely the adaptive immune response which leads to the expansion of antigen-specific lymphocytes that target the pathogen specifically and lead to the formation of memory cells that provide long-lasting specific immunity (see question 4).

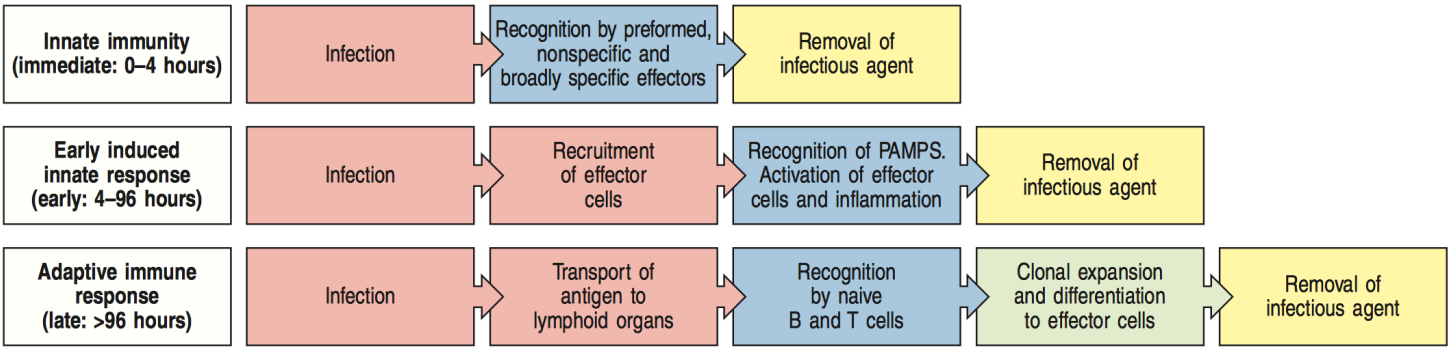

Figure 2: The stages of the immune response. Innate immune responses are initiated first following a breach of the anatomical barriers. If these responses are unsuccessful in the removal of the infectious agent, the adaptive immune responses are initiated.

The Gastrointestinal Immune System and *Salmonella* Infection

Specific to our case, the immune system of the gastrointestinal tract is particularly important since this is where the pathogen(s) causing Ronnie's illness entered his body. The gastrointestinal tract is particularly vulnerable to infection because of its large surface area and thin epithelium, which are characteristics required by the gastrointestinal tract to perform its physiological function - to absorb nutrients.[12]

Innate Immune Response

After being ingested with contaminated food, such as undercooked meat, *Salmonella* reach the gut lumen where they must compete with gut flora for nutrients. As such, gut flora act as a mechanism to prevent infection by enteric pathogens.[13]

The primary cellular barrier of the gut is a single layer of intestinal epithelial cells called enterocytes.[14] Enterocytes are critical for both nutrient uptake and to provide a physical and chemical barrier. Each enterocyte is joined to its neighbouring cell through tight junctions, which ensure that the surface of the gut is sealed so that foreign particles or microbes cannot invade the tissue. *Salmonella* may gain entry into intestinal tissue via enterocytes using a type 3 secretion system encoded by *Salmonella* Pathogenicity Island – 1 (SPI-1).[15]

In addition to enterocytes, non-hematopoeitic cells maintain the physical barrier of the gut.[16] Such cells include goblet cells and Paneth cells (Figure 2). The thick layer of mucus secreted by goblet cells is one of the first obstacles faced by *Salmonella*. In addition to mucus, antimicrobial peptides, such as defensins, RegIIIβ/γ, and lysozymes, are secreted by Paneth cells which function to disrupt the integrity of the bacterial cell membrane.

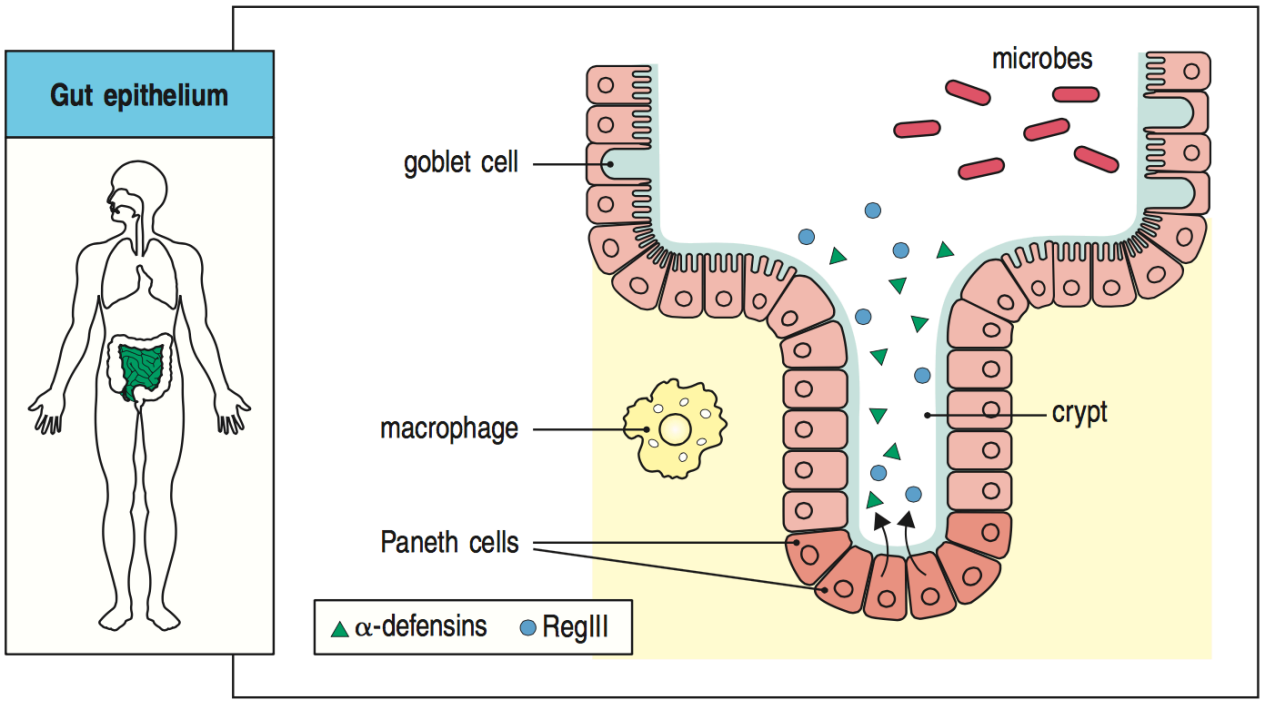

Figure 3: In the intestine, specialized cells deep in the epithelial crypts called Paneth cells produce several kinds of antimicrobial proteins, including defensins and RegIII. Goblet cells produce mucus, which functions to trap and get rid of pathogens.

Underlying the epithelial cell layer of the gut is the lamina propria.[17] The lamina propria contains gut-associated lymphoid tissue (GALT), which is described as a "highly organized lymphoid tissue." The GALT is comprised of: (1) aggregated lymphoid follicles called Peyer's patches and (2) diffuse population of immune cells.

Peyer's patches are surrounded by a specialized epithelium, known as follicle-associated epithelium (FAE).[18] The FAE contains specialized cells known as micro-fold cells, or M cells. M cells function to transport luminal antigens and bacteria to the basolateral cell surface through a process known as transcytosis (Figure 4). At the basal cell membrane, the M cell is extensively folded around lymphocytes and antigen-presenting cells, which take up the transported material from M cells and process it for antigen presentation. M cells are more accessible than enterocytes, and are thus targeted by enteric pathogens, including *Salmonella,* which exploit M cells to gain access to the subepithelial space.

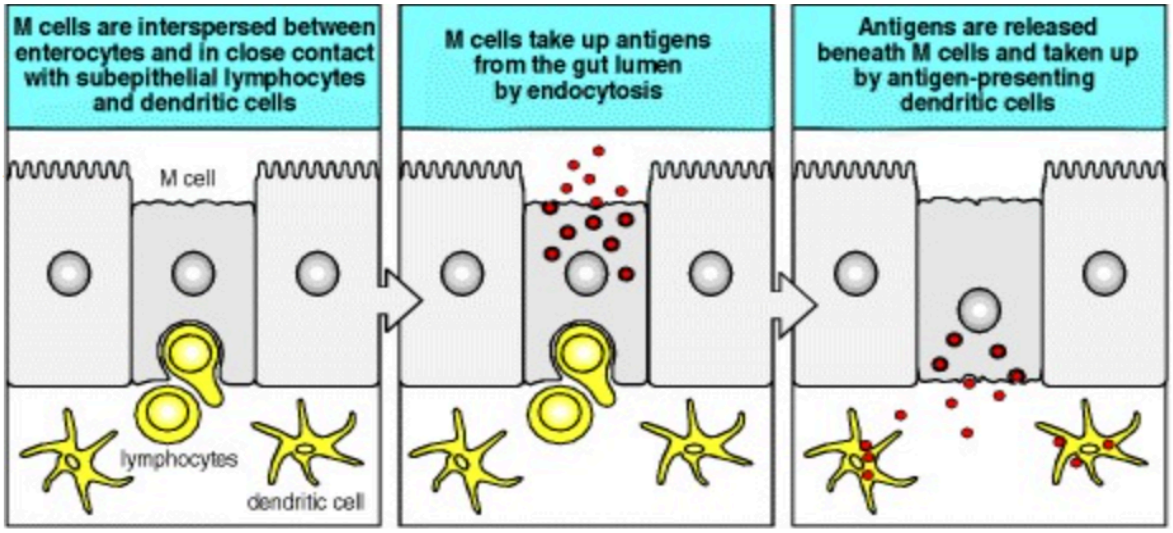

Figure 4: M cells take up antigens from the gut lumen by transcytosis and present them to antigen-presenting cells and lymphocytes of the mucosal immune system.

After crossing the intestinal barrier through M cells or enterocytes, bacteria are taken up by phagocytic immune cells of the GALT, such as macrophages and dendritic cells.[19] These cells function to regulate inflammatory responses to bacteria and antigens which breach the epithelial layer of the gastrointestinal tract. Furthermore, these cells protect the mucosa against harmful pathogens and scavenge dead cells and foreign debris. Antigen-presenting dendritic cells, in particular, send processes between intestinal epithelial cells and sample antigens from both commensal and pathogenic gut bacteria.[20] Dendritic cells are professional antigen-presenting cells and respond to recognition of bacterial LPS or flagellin by increasing the expression of major histocompatibility complex class II (MHC II) and the co-stimulatory molecules CD80, CD86 and CD40. This maturation process allows dendritic cells to efficiently present antigen to naïve CD4 T cells located in the GALT. Thus, antigen-presenting cells represent a crucial link between the innate immune system and the activation of the adaptive immune system (see below).

Following phagocytosis, *Salmonella* replicate in an intracellular compartment named the *Salmonella* - containing vacuole (SCV).[21] Infected macrophages can be activated to kill or limit the replication of *Salmonella* by producing lysosomal enzymes, reactive oxygen intermediates, reactive nitrogen intermediates and other antimicrobial peptides.

Although *Salmonella* can replicate to high numbers before exiting the cell and infecting new host cells, it cannot escape host cell sensing within the intracellular niche of the SCV. All monocytic cells express pattern-recognition receptors (PRRs) which are capable of detecting microbial antigens known as pathogen-associated molecular patterns (PAMPs) (Figure 5A).[22] Toll-like receptors (TLRs) are a family of PRRs which function to detect a variety of extracellular and endosomal PAMPs such as LPS, bacterial lipoproteins, peptidoglycan, flagellin, DNA, RNA and others. Upon ligand binding, TLRs engage MyD88 and TRIF (signalling adaptors) which initiate signalling cascades leading to the activation of transcriptional factors NFκB and IRF3. NFκB induces the production of inflammatory cytokines (IL-8, IL-10, IL-1β and others), whereas IRF3 induces the production of a type I IFN response.[23]

In addition to TLRs, the NOD-like receptor (NLR) family of PRRs is able to detect cytosolic PAMPs, leading to the initiation of different signalling cascades as well as to the assembly of a large multi-protein signalling complex known as the inflammasome.[24] The inflammasome functions to promote the maturation of the inflammatory cytokines IL-1β and IL-18. In addition, the inflammasome induces a process known as pyroptosis which, similar to apoptosis, is a form of programmed cell death. However, in contrast to apoptosis, pyroptosis leads to formation of pores in the cell membrane and subsequent release of cellular contents and pro-inflammatory cytokines. In this way, pyroptosis serves to amplify the inflammatory response and eliminates the intracellular niche of *Salmonella* by re-exposing it to extracellular immune defenses.

In addition to the cytokines described above, recognition of PAMPs by PRRs also leads to the expression and secretion of key cytokines such as IL-18 and IL-23, which serve to amplify the immune response (Figure 5B).[25] These cytokines induce massive secretion of IFNγ, IL-22 and IL-17 by mucosa-resident T cells (see adaptive immune response below). Together, these cytokines result in mucosal inflammation in the gut. Inflammation is characterized by: (1) swelling (2) pain (3) redness (4) heat.[26] Inflammation functions to both prevent the spread of the infection and to promote pathogen clearance and tissue repair. Redness and heat are due to increased blood flow to the inflamed site; swelling is caused by accumulation of fluid and pain is due to the release of chemicals such as bradykinin and histamine that stimulate nerve endings. It is important for the body to control inflammation, as excessive inflammation leads to host damage (see question 2).

During inflammation, additional immune cells such as neutrophils, dendritic cells, inflammatory monocytes and macrophages are recruited to the site of infection.[27] Neutrophils are recruited to the infected mucosa through a process known as chemotaxis (Figure 5C). The production of IL-17 stimulates the production of chemokines by intestinal epithelial cells and granulopoiesis in the bone marrow by inducing the production of granulocyte colony-stimulating factor. Neutrophils function to prevent the dissemination of *Salmonella* from the gut through ingestion

and killing of *Salmonella* when they exit epithelial cells in order to spread to new host cells.[28] However, the recruitment of neutrophils also results in host damage (see question 2).

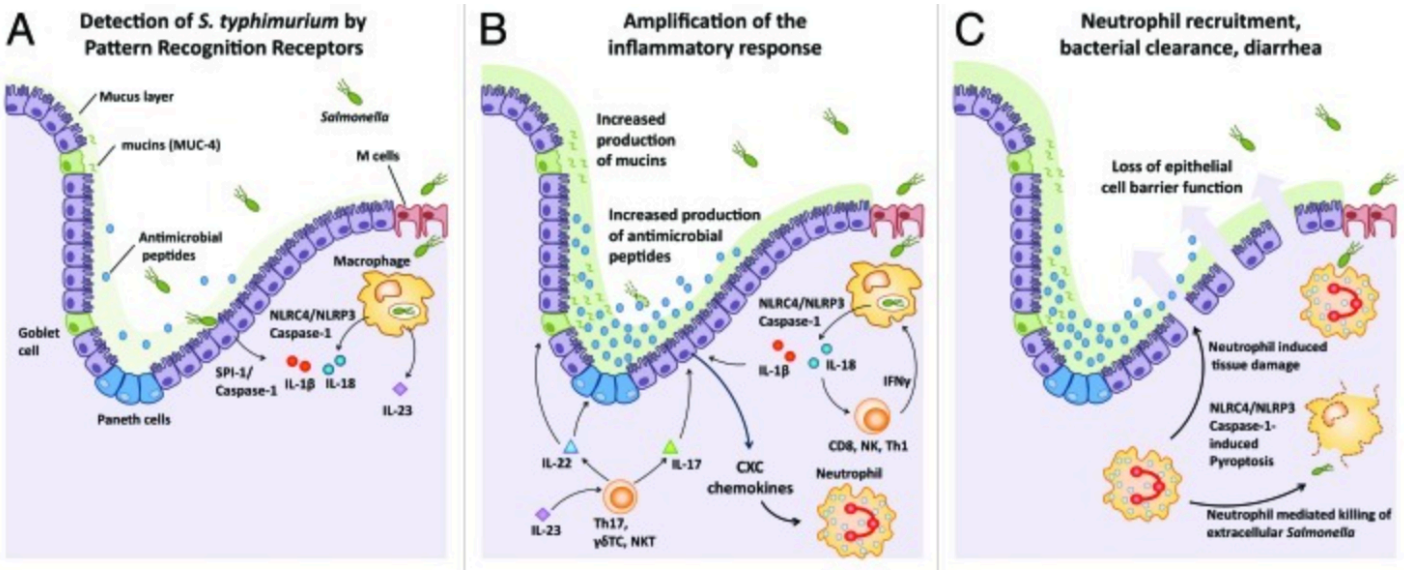

Figure 5: (A) Following invasion of the mucosa, pattern-recognition receptors (PRRs) on phagocytes detect the presence of *Salmonella* through pathogen-associated molecular patterns (PAMPs). Extracellular *Salmonella* are detected by Toll-like receptors, whereas intracellular *Salmonella* are detected by NOD-like receptors. (B) Release of various cytokines leads to the amplification of the immune response. (C) Infiltrating neutrophils function to kill extracellular *Salmonella*, and also lead to damage to intestinal tissue.

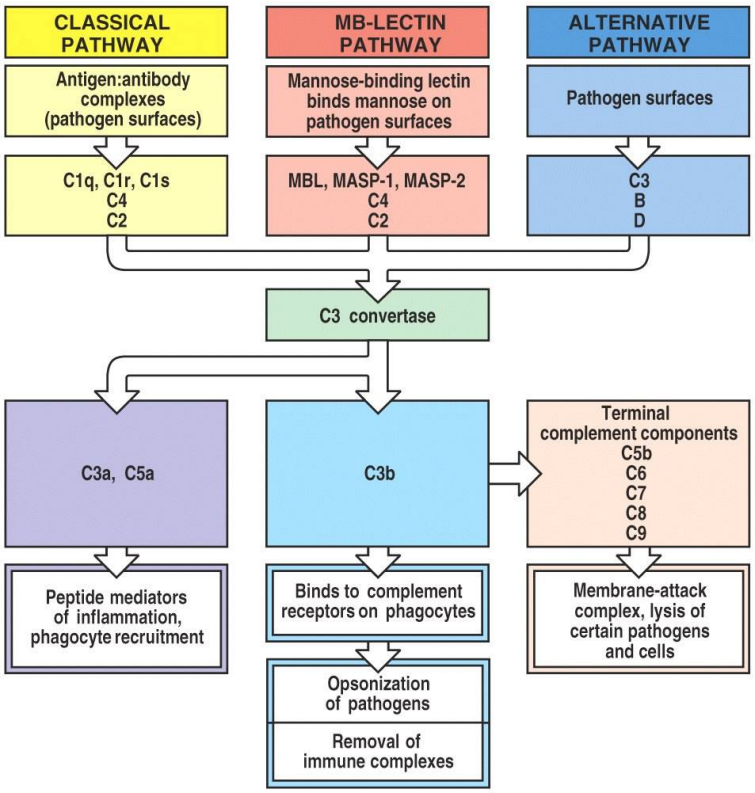

Figure 6: An overview of the complement system activation and functions.

During an acute phase response to inflammation, complements proteins are rapidly produced by hepatocytes.[1] There are over 30 proteins in the complement system, including both soluble proteins activated through a cascade of proteolytic activity, and receptors for detection of activated complement proteins. The 3 pathways of complement activation, and their functions, are summarized in Figure 6.

As a powerful defence mechanism, tight controls on the complement system are necessary to prevent excessive activation and collateral damage to the host (see question 2).

In the case of *Salmonella* infections, both cell-free complement-mediated killing and opsonisation of bacteria by complement fragments have shown to be important.[29] Following rapid opsonisation of *Salmonella* by C3 and specific antibodies, both phagocytosis by macrophages and complement-mediated lysis occur. However, phagocytosis occurs immediately, whereas lysis is delayed. This finding can be attributed to the observation of the slow formation of the membrane-attack complex resulting in significant numbers of bacteria avoiding complement-mediated lysis and instead being taken up by phagocytes and transported to an intracellular environment more favourable for bacterial survival.

In terms of the role of complement in the gastrointestinal mucosa, it has been suggested (although further work is required) that passive leakage of serum proteins, including those of the complement cascade, into surrounding tissue and the gut lumen is likely during infection and inflammation due to increased vascular permeability and impairment of the normal barrier function of the gastrointestinal epithelium.[30] Further, infiltrating leukocytes produce complement proteins. For example properdin is stored in neutrophil granules for release on cytokine or anaphylotoxin stimulation.[31] As such, complement may play an important role in providing immunity in the gastrointestinal tract against *Salmonella* infections.

Adaptive immune response

T cells

Studies have shown that the earliest *Salmonella*-specific CD4 T helper cell activation occurs within the Peyer's patches and is initiated 3 – 6 hours after initial encounter with the pathogen.[32] Early activation of CD4 T cells requires the presence of dendritic cells in the Payer's patches as well as the recognition of *Salmonella* antigens by the T cell receptor. CD4 T helper cells are the most important cells of the adaptive immune response against *Salmonella* infections. CD8 cytotoxic T cell and humoral responses are activated as well, but to a lesser extent (see below).

Once activated, *Salmonella*-specific CD4 T cells rapidly acquire Th1 effector functions, which include the ability to secrete IFNγ, TNF-α and IL-2. These cytokines, especially IFNγ, serve to activate macrophages within infected tissues (Figure 7).[33] Activated macrophages are more efficient at killing intracellular pathogens, however they also lead to destruction of normal, healthy host cells.

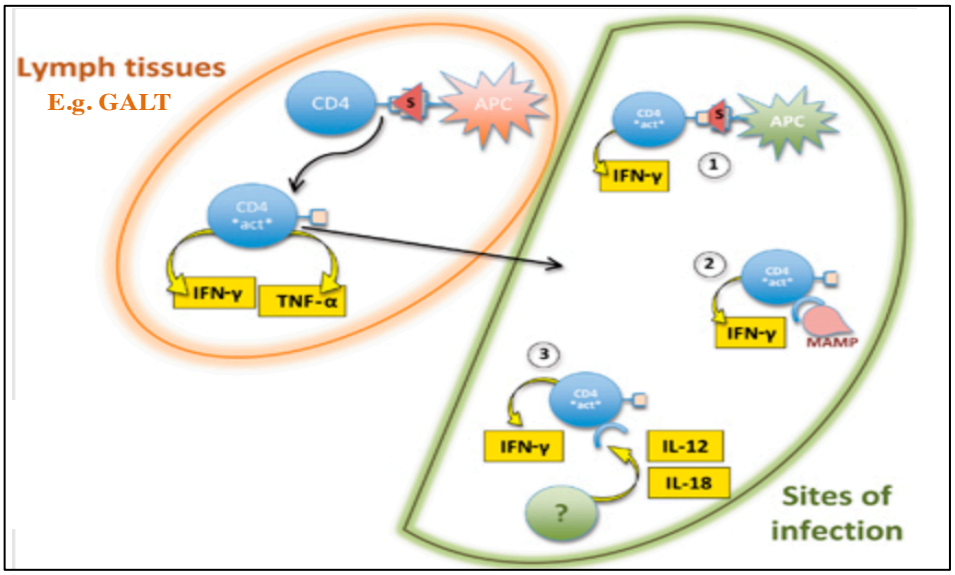

Figure 7: The activation of CD4 T cells requires the presence of dendritic cells and recognition of bacterial antigen by the T cell receptor. Once activated, the CD4 T cells acquire Th1 abilities and begin to secrete a variety of cytokines, of which IFNγ is the most important as it serves to activate macrophages in the infected tissues.

In addition to the subset of CD4 Th1 cells, regulatory T cells (Tregs) and Th17 cells also play an important role in protective immunity against *Salmonella*.[34] Tregs serve to both enhance and suppress effector T-cell responses. Th17 cells are important in mediating immunity to extracellular bacterial infections by initiating or enhancing neutrophil infiltration to intestinal tissues (see above). Furthermore, Th17 cells produce cytokines which induce production of antimicrobial peptides by epithelial cells.

Salmonella-specific antigens that are displayed on atypical MHC I molecules (MIC-A and MIC-B) will serve to activate CD8 cytotoxic T cells expressing the NK receptor NKG2D.[35] MHC I molecules are expressed on all nucleated cells in the body. As such, infected cells will be able to signal that there is an infection to cytotoxic T cells, which will then function to induce apoptosis in infected cells (Figure 8). The dying enterocyte is then removed from the epithelium and the local tissue injury is repaired.

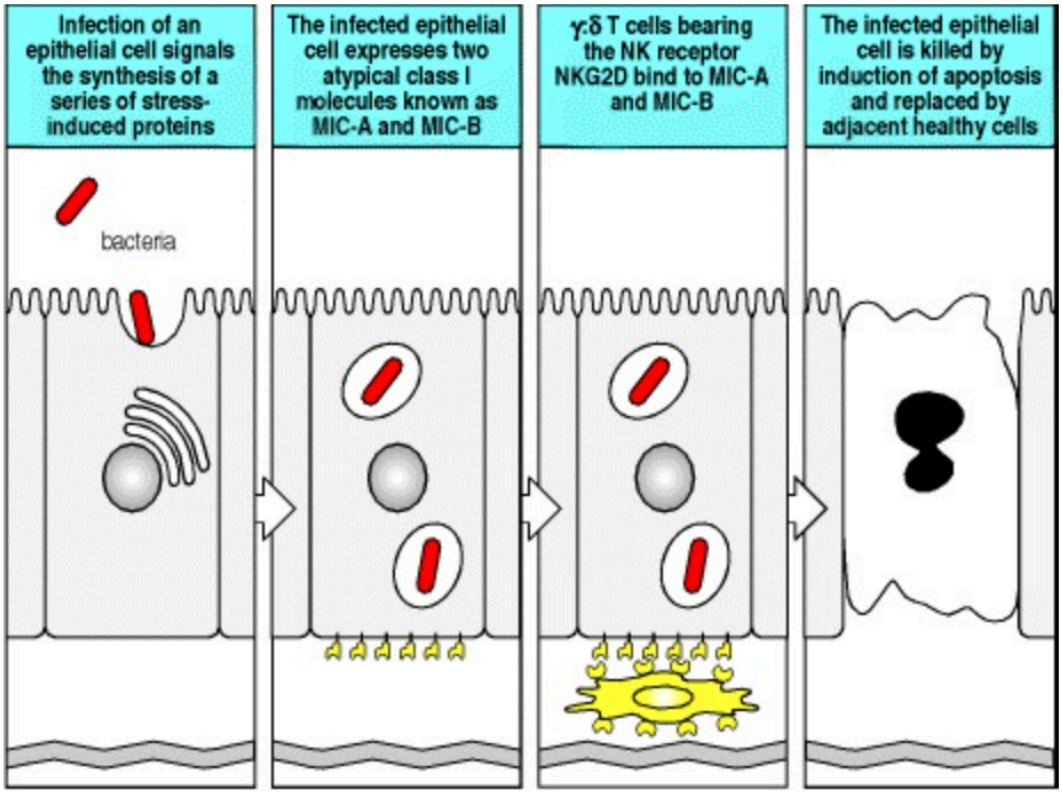

Figure 8: Cytotoxic T cells function to induce apoptosis in infected enterocytes.

B cells, Plasma cells and Antibodies

Although *Salmonella* are generally found within SCVs in phagocytic cells, there is a short period during the infection cycle when bacteria are extracellular, namely when the bacteria induce infected cells to undergo apoptosis. After apoptosis, the bacteria are presumably found in the extracellular compartment before infecting a neighbouring phagocyte.[36]

During this time, when *Salmonella* bacteria are extracellular, it is possible for the activation of B cells.[37] Using the B cell receptor (BCR), B cells will engage with bacterial antigens and start the process of activation. The bacterial antigens are internalized by B cells and displayed on MHC II molecules. This complex is then recognized by CD4 T cells, which secrete cytokines to fully activate B cells. Once fully activated, the B cell begins clonal expansion and some B cells will become antibody-producing plasma cells.

The *Salmonella*-specific antibodies secreted in the intestinal mucosa are mainly of the IgA class, although IgG and IgM are involved as well.[38] The IgA antibody is found in humans in two isotypic forms, IgA1 and IgA2. The expression of IgA differs between the two main compartments in which it is found, namely the blood and mucosal

secretions. In the blood, IgA is mainly found as a monomer and the ratio of IgA1 to IgA2 is approximately 4:1, whereas in mucosal secretions, IgA is almost exclusively produced as a dimer and the ratio of IgA1 to IgA2 is approximately 3:2. A number of common intestinal pathogens possess proteolytic enzymes that can digest IgA1, whereas IgA2 is much more resistant to digestion.

Once synthesized by plasma cells, immature epithelial cells located at the base of the intestinal crypts transport IgA and IgM into the gut lumen.[39] Immature epithelial cells express Ig receptors on their basolateral surfaces, and are thus able to bind to IgA or IgM and transport these antibodies by transcytosis to the luminal surface of the gut.

Once at the luminal surface of the enterocyte, the antibodies are released into secretions and bind to the mucus layer overlying the gut epithelium. Here, these antibodies bind to neutralize enteric pathogens as well as their toxic products (Figure 9).

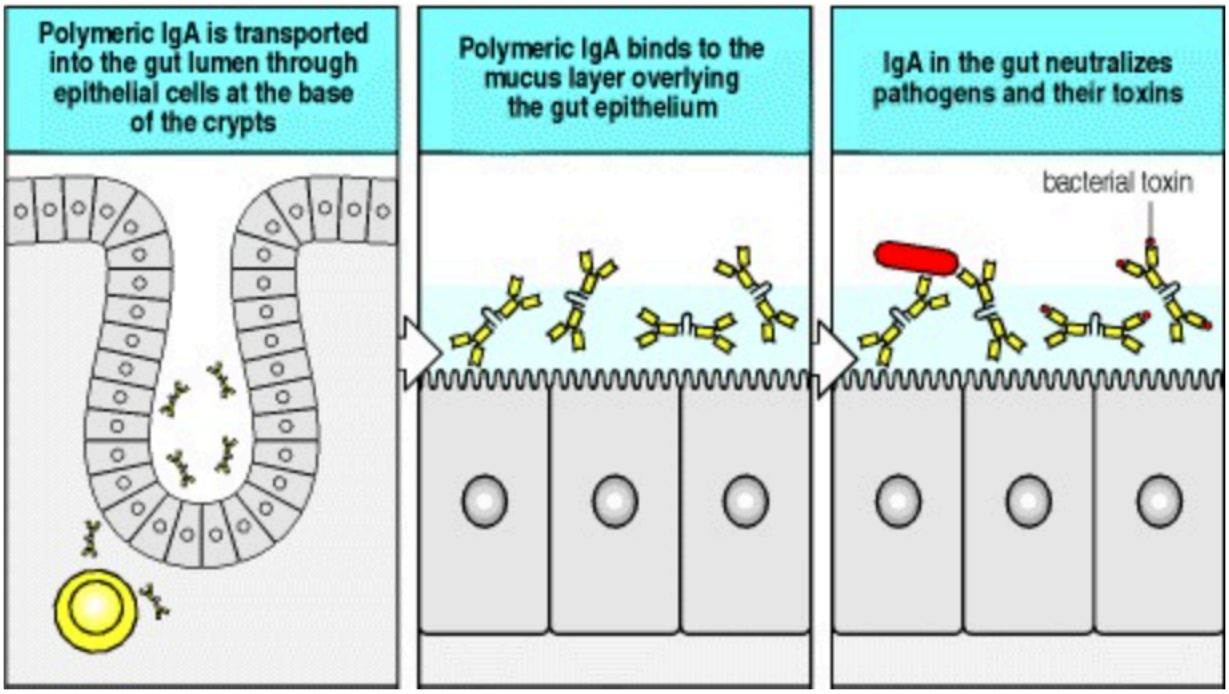

Figure 9: The major antibody class present in the gut lumen is secretory polymeric IgA. IgA is synthesized by plasma cells in the lamina propria and transported into the gut lumen through epithelial cells via transcytosis. In the gut lumen, IgA binds to the mucus layer overlying the gut epithelium and provides defense against pathogens and their toxins.

Question 2

Host damage: what damage ensues to the host from the immune response?

As mentioned above, neutrophils are important for host defence against *Salmonella*, however infiltrating neutrophils are also a major cause of tissue damage in the mucosa.[40] This tissue damage leads to a loss of epithelial barrier function, resulting in an increase in inflammation (gastroenteritis) and diarrhea – which is one of Ronnie's symptoms. Neutrophils may also contribute to diarrhea by stimulating chloride secretion from epithelial cells.[41] Chloride secretion results in an accumulation of negative charge in the lumen, which attracts sodium into the lumen as well. The resultant salt secretion (NaCl) into the lumen creates an osmotic gradient which draws water into the gut lumen, resulting in diarrhea.

More so, M cells that contain bacteria die and disintegrate, thereby comprising the integrity of the gastrointestinal epithelium. This allows for the bacteria to gain entry into deeper tissues, and an increased risk for systemic infection.[42]

Blood in the stools, as in Ronnie's case, can be attributed to bacterial invasion and replication within the intestinal mucosa accompanied by an inflammatory response resulting in blood-containing diarrhea.[43] Since the integrity of the gut epithelium is compromised, blood can leave the tissues and enter the gut lumen and subsequently into stools.

Abdominal cramps may be attributed to the chemicals released during inflammation, namely bradykinin and histamine. As mentioned above, these chemicals are responsible for the pain associated with inflammation. As such, they may be implicated in the cause of abdominal cramps that Ronnie is experiencing.[44]

Mild periumbilical tenderness, which the doctor notes as one of Ronnie's signs, may be due to intestinal obstruction, mesenteric occlusion or enteritis.[45]

Assuming that Ronnie does not have an autoimmune disorder, the antibodies secreted by activated B cells will generally do little damage to the host due to the specificity of the adaptive immune response and its ability to discriminate between self and non-self.[46]

In contrast, inflammation is part of the innate immune response and is thus non-specific. After phagocytosis by macrophages, the phagolysosome (containing anti-microbial toxic substances) may leak its content causing harm to normal, uninfected cells. Furthermore, the characteristics associated with inflammation (pain, heat, redness, swelling) may be uncomfortable for the host. Thus, it is important that inflammation in the body be tightly regulated and not occur for prolonged periods of time[47].

Just as inflammation must be tightly regulated, complement activation must be as well. Uncontrolled complement activation may lead to host damage, such as destruction of healthy host cells.[48]

Question 3

Bacterial evasion: how do the bacteria attempt to evade these host response elements?

Several studies have demonstrated that *Salmonella* uses its virulence factors to induce intestinal inflammation during the intestinal phase to gain a growth advantage over normal gut flora. For example, reactive oxygen species generated during inflammation react with endogenous, luminal sulphur compounds to form tetrathionate.[49] Tetrathionate functions as a respiratory electron acceptor for *Salmonella,* but not for normal gut flora. As such, *Salmonella* can outcompete normal gut flora, which must grow by fermentation instead.

Additional resistance mechanisms to innate defenses in the gut include the expression of enzymes encoded by the *iroBCDE iroN* locus.[50] These enzymes function to alter the structure of the *Salmonella* Fe^{+} binding protein (Ent), thereby preventing it from being bound and sequestered by host lipocalin-2. Normally, lipocalin-2 is produced by host cells and functions to sequester iron which is needed for *Salmonella* growth. However, with the help of enzymes encoded by the *iroBCDE iroN* locus, *Salmonella* is able to acquire iron from the host using Ent and continue to grow.

The ability of *Salmonella* to survive within the phagosome is mediated by *Salmonella* Pathogenicity Island 2 (SPI-2), which encodes a type-III secretion system.[51] This system prevents movement of reactive nitrogen intermediates and reactive oxygen intermediates into the phagosome where *Salmonella* reside. In addition, the *Salmonella* PhoP-PhoQ two-component signal transduction system inhibits fusion of the SCV with toxic lysosomes and endosomes.[52] Thus, *Salmonella* are able to effectively "hide" within SCVs and evade the host immune response.

Salmonella Pathogenicity Island 1 (SPI-1) encodes virulence factors which alter dendritic cell function.[53] *Salmonella* are able to differentially modulate the entrance to dendritic cells, avoid lysosomal degradation and prevent antigen presentation by MHC molecules. As such, T cell priming by dendritic cells is impaired – contributing to bacterial survival and dissemination inside the host. SPI-1 also encodes virulence factors which inhibit apoptosis of phagocytes, thereby allowing bacterial survival within the phagocyte.

Further still, *Salmonella* can down regulate the expression of flagellin in vivo, thereby evading detection by TLRs during the innate immune response.

Other evasion strategies of *Salmonella* include inhibition of secretion of antimicrobial peptides and inflammation induced by the macrophage.

A summary of the evasion strategies of *Salmonella,* and the virulence factors which allow for these evasion strategies, are summarized in Figure 10.

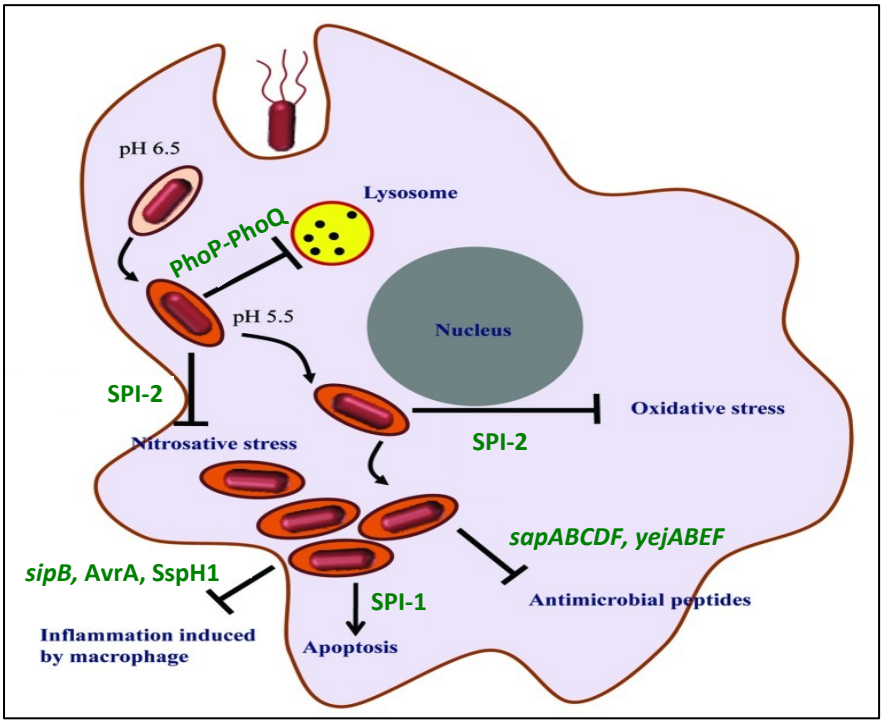

Figure 10: The evasion strategies used by *Salmonella* to counteract the host immune responses.

Question 4

Outcome: is the bacteria completely removed, does the patient recover fully and is there immunity to future infections with these candidate infectious agents?

Salmonella is not part of the normal flora in humans.[54] As such, during a *Salmonella* infection, the immune system will work to completely remove the bacteria from the body.

Most children and adults with *Salmonella* do not need any specific treatment, unless the patient is very young (under 6 months old), elderly, pregnant or immunocompromised.[55] Antibiotics may be given if symptoms are severe, or if complications develop, and will serve to shorten the duration of infection. Complications include:[56]

- Dehydration
- Reactive complications such as arthritis, conjunctivitis, or uveitis
- Bacteremia
- Irritable bowel syndrome

Over time (usually a few days), the immune system works on its own to clear the infection and it is very likely that an immunocompetent patient will fully recover from an infection with *Salmonella*.[57]

In order to develop immunity to future infections with *Salmonella*, the proliferation of naïve B cells into plasma cells and memory cells is required.[58] Plasma cells function to produce antibodies, whereas memory cells are stored in the event of a secondary infection by the same pathogen. Memory cells are able to quickly divide and differentiate into effector cells, thereby allowing the immune response in cases of re-infection to be faster and more robust.

In the case of *Salmonella,* antibodies specific for *Salmonella* are produced during the short period of time during the infection cycle that *Salmonella* is extracellular (see above). These antibodies are believed to play an important protective role in re-infections with *Salmonella*.[59] However, as there are many serovars of *Salmonella,* it is unlikely that an infection with one serovar will provide protection against infection with another serovar.

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