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MINI-REVIEW

Association of quorum sensing and biofilm formation with Salmonella virulence: story beyond gathering and cross-talk

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Abstract

Enteric fever (typhoid and paratyphoid fever) is a public health concern which contributes to mortality and morbidity all around the globe. It is caused mainly due to ingestion of contaminated food and water with a gram negative, rod-shaped, flagellated bacterium known as *Salmonella enterica* serotype *typhi* (typhoid fever) or *paratyphi* (paratyphoid fever). Clinical problems associated with Salmonellosis are mainly bacteraemia, gastroenteritis and enteric fever. The bacteria undergo various mechanisms to escape itself from immune reaction of the host, modulating immune response at the site of infection leading to virulence factor production and anti-microbial resistance. Biofilm is one of the adaptation mechanisms through which *Salmonella* survives in unfavourable conditions and thus is considered as a major threat to public health. Another property of the bacteria is "Quorum Sensing", which is a cell–cell communication and most of the pathogenic bacteria use it to coordinate the production of several virulence factors and other behaviours such as swarming and biofilm formation. Earlier, quorum sensing was believed to be just a medium for communication but, later on, its role in virulence has been studied. However, there are negligible information relating to interaction between quorum sensing and biofilm formation and how these events play crucial role in *Salmonella* pathogenesis. The review is a summary of updated information regarding how *Salmonella* uses these properties to spread more and survive better, making a challenge for clinicians and public health experts. Therefore, this review would help bring an insight regarding how biofilm formation and quorum sensing are interrelated and their role in pathogenesis and virulence of *Salmonella.*

Keywords Enteric fever · Salmonella · Biofilm · Quorum sensing

Introduction

Salmonella infection, which is a major public health concern, causes morbidity and mortality throughout the world. It is a gram negative, rod-shaped, flagellated bacterium having two species, *Salmonella enterica* and *Salmonella bongori*, which are again divided into different sub-species. *Salmonella enterica* has six subspecies: *arizonae, diarizonae, houtenae, salamae, indica, enterica* and each subspecies has different serovars which differ by their antigenic specificity. Interestingly most of the human pathogenic *Salmonella* serovars belong to *enterica* subspecies that includes *S. enterica* serovar *typhi, paratyphi, typhimurium, enteritidis and choleraesuis*. Throughout our article, all these serovars will be mentioned with genus and serovar names such as *S. typhi*, S. *typhimurium,* etc., *S. typhimurium* is a common inhabitant of gastrointestinal track of ruminants and its infection causes gastroenteritis and fever in human and mice, respectively (Chaudhuri et al. 2018). Similarly, *S. enteritidis* causes gastrointestinal disorders and food poisoning in human. The major source of this infection in human is contaminated chicken eggs. It causes systemic infection in chicks and laying hens with a prolonged shedding in faeces, which also makes chicken an asymptomatic carrier (Mon et al. 2015). However, *S. choleraesuis* poses highest threat of food borne infections in human. It causes septicaemic

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disease in human and paratyphoid fever in swine. Its resistance to many antibiotics and association with development of mycotic aneurysm make it a difficult pathogen to treat (Chiu et al. 2004). Another disease caused by *Salmonella* in human is typhoid fever, for which the responsible pathogen is *Salmonella typhi.* According to the most updated WHO evaluation, approximately 11–21 million people suffer from typhoid fever and it claims 128,000–161,000 deaths annually across the globe. Poor response to treatment and delayed diagnosis may lead to serious health complications such as gut wall damage, cerebral dysfunction, gastrointestinal haemorrhage and shock (Mukhopadhyay et al. 2019). Chronic infection with *S. typhi* and longer persistence in gall bladder combined with continuous excretion to environment have made this pathogen a high risk to public health (Xu et al. 2010). Its persistence and colonization on gallstone have been found to be promoted by biofilm production (Di Domenico et al. 2017). Biofilm formation is an important defence attribute of multidrug-resistant bacteria to survive in unfavourable condition. Since decades, it has attracted many researchers due to its associated high risks including virulence factor production and anti-microbial resistance (Young et al. 2002). Biofilm formation is important for *Salmonella* spreading as it saves the pathogen from physical, chemical and mechanical stress whereas biofilm formation in gall stone is considered as the hall mark of *S. typhi* carrier (Marin et al. 2009; Scher et al. 2005; Joseph et al. 2001). *Salmonella* strains other than *S. typhi* and *S. paratyphi* are named as non-typhoidal *Salmonella* which are mainly found in animal reservoirs. Another property of bacteria called "quorum sensing" is also known to affect the virulence of both typhoidal and non-typhoidal strains of *Salmonella*. Quorum sensing is a method that bacteria adopt to transmit cell–cell signals and coordinate gene expression. Though it was initially thought to simply play role in signalling and cross-talk among bacteria, it is involved in biofilm formation and production of virulent factors in pathogenic microorganisms (Aswathanarayan and Vittal 2018). *luxS* protein, a central molecule of quorum sensing is essential for expression of virulent genes in *S. typhimurium* (Choi et al. 2007). Besides, *LsrR*, a transcription regulator of quorum sensing regulates the invasion of *Salmonella* into epithelial cells (Choi et al. 2012). However, detailed knowledge on the interaction between quorum sensing and biofilm formation and their solo/combinatorial effect on *Salmonella* pathogenesis is still scanty. This review is an updated version of most of the important and necessary information regarding how quorum sensing regulates biofilm formation and role of these two events in *Salmonella* pathogenesis, virulence and how the whole process makes the pathogen more difficult to treat clinically.

Quorum sensing and Biofilm: platforms for bacteria to gather and talk

For their growth, survival and reproduction in changing environments, microbes create different platforms to communicate within cells. This type of communication that happens between cells is called quorum sensing which is directly dependent upon the microbial cell density and induces multiple factors such as production of virulent factors and biofilm formation in microbes (Choi et al. 2012). Though this special kind of microbial communication was first discovered in bacteria, it was subsequently observed in fungi as well (Mehmood et al. 2019).

Another way of communication among microbes is through biofilm formation. Microbes make an association by attaching themselves with each other and also to a surface bound inside a self-made extracellular matrix. Bacteria form biofilms to adapt to unfavourable environmental conditions and interact with their host. When *E. coli* are in the process of biofilm formation, they convert their single planktonic growth mode to biofilm mode where they switch off their flagella production and in turn production of curli fimbriae and extracellular polymeric substances (EPS) is switched on. *CsgD* is known as the master regulator of biofilm formation which activates production of curli fimbriae and EPS. It not only regulates the expression of csg operon, but also a number of genes including adrA, required for modulating the cell physiology according to biofilm lifestyle (Simm et al. 2004). Cell motility for planktonic growth is supressed by CsgD which promotes the switch to biofilm formation and preventing CsgD expression abolishes synthesis of curli and cellulose which ultimately affects biofilm formation (Ogasawara et al. 2011; Khambhati et al. 2021). EPS are known to have key role in biofilm formation and development by modulating surface attachment, mechanical stability, hydrophobicity, porosity, water content, etc. (Flemming and Wingender 2002). At the time of surface colonization, bacteria produce EPS which in turn makes the biofilm matrix. The matrix not only provides protection, it also acts as an adsorbent sieve for nutrition and signalling molecules. There exist some genes such as sdiA and adrA that are involved in EPS production, which are also known to be controlled by quorum sensing (Pellock et al. 2002). sdiA plays a role in biofilm formation and adhesion to epithelial cells whereas adrA activates cellulose synthesis which is a major constituent of biofilm matrix especially in *Salmonella* (Culler et al. 2018; Da Re and Ghigo 2006). In a recent report, both sdiA and adrA genes were found to be present in all *S. enteritidis* strains isolated from poultry farm environment and human faeces (except one strain) in Poland (Cwiek et al. 2020). The presence of these genes might provide advantage to *Salmonella* biofilm formation by producing EPS components and

establishing quorum sensing communication. *S. typhi* is one such bacteria that heavily depends upon biofilm formation to continue long persistence inside an existing host and further transmission to a new host (Moshiri et al. 2018). Though, quorum sensing and biofilm formation are two types of communication platforms for bacteria, approximately 80% of infections occur due to quorum sensing-induced biofilm formation (Arciola et al. 2012). It has been reported that, in pathogens including *Salmonella, Escherichia coli (E. coli), Campylobacter, Staphylococcus aureus, Listeria monocytogenes and Bacillus cereus*, quorum sensing has a key role in the process of biofilm formation (Machado et al. 2019). According to Cui et al. 2020, deletion of Cas3 in a type I-E CRISPR-Cas system of *S. enteritidis*, upregulated quorum sensing-related genes and downregulated genes related to biofilm formation and virulence (Cui et al. 2020). Interestingly, the CRISPR-Cas system seems to regulate quorum sensing signalling and biofilm formation in many bacteria (Cui et al. 2020). Besides directly regulating genes involved in biofilm formation, quorum sensing induces production of extracellular DNA which interacts with extracellular matrix to form biofilm (Jennings et al. 2015). There are many quorum sensing regulated factors which influence biofilm formation. The ability to form siderophores (for iron availability) by bacteria is thought to be essential for biofilm formation. Pyoverdin is a quorum sensing-controlled siderophore and mutants incapable of producing this iron chelator were found to be unable to produce biofilm aggregates (Da Silva et al. 2017). Another important finding shows that, acyl homoserine lactone-based quorum sensing enhances biofilm formation by *S. enteritidis* in anaerobic condition, a situation that is relevant to its pathogenesis (De Almeida et al. 2017). Because of the major involvement of quorum sensing in biofilm formation, strategies used to inhibit quorum sensing have also been found to be useful against reducing bacterial biofilm and pathogenicity (Remy et al. 2018). Berberine, an isoquinoline has been found to be an anti-biofilm agent in *S. typhimurium* based on its quorum sensing inhibiting property (Aswathanarayan and Vittal 2018). However, a lot of further research need to be done to screen more effective anti-quorum sensing compounds to control biofilm formation in pathogenic bacteria.

Quorum sensing and *Salmonella* pathogenesis

A variety of bacteria phenotypes are regulated by quorum sensing leading to increased pathogenesis and virulence. *S. typhimurium* is one of the main serovars isolated from human sources and its pathogenicity is contributed by many factors including its flagella (Conceiçao et al. 2015). In *S. typhimurium*, quorum sensing has been found to increase motility by inducing expression of genes involved in assembly of flagella (Conceiçao et al. 2015). The QseC quorum sensing sensor kinase also has been found to have role in motility and swine colonization of this pathogen. In the same study, deletion of *luxS* gene also resulted in down regulation of motility related genes, genes present in *salmonella* pathogenicity island and chemotaxis (Jesudhasan et al. 2010). Isolation of bacteria strains from different environmental conditions and their culture in different settings sometimes become responsible for contrasting results. The quorum sensing mechanism in *Salmonella* species functions through three types of autoinducers (AI), auto inducer I, II and III (Perrett et al. 2009). Both AI-II and III play important role in regulating pathogenic molecules in *Salmonella* (Widmer et al. 2007; Moreira et al. 2010). The first and crucial step during infection is adhesion of the pathogen to host cell surface. Effect of quorum sensing on adhesion and biofilm formation has been studied in *S. typhi* (Prouty et al. 2002), *S. enteritidis* (Chorianopoulos et al. 2010) and nine other serovars but resulted in ambiguous conclusion (Wang et al. 2013). In addition to its effect on virulence and pathogenesis, quorum sensing in *S. typhimurium* critically modulates its behaviour during pre-stationary growth phase (Surette and Bassler 1998). The *luxS* gene is vital for growth of this bacteria and its mutation results in poor growth (Widmer et al. 2012). When it becomes tough for the bacteria to survive under harsh conditions, quorum sensing comes into rescue. Chronic persistence of *S. typhi* in gall bladder has to deal with bile production as well as generation of reactive oxygen species by producing anti-oxidative enzymes. There is proof that, quorum sensing system of this pathogen keeps its hold on managing the level of these enzymes when the bacteria are under oxidative stress (Walawalkar et al. 2016). Though, *Salmonella* infection is a risk to human health, Swofford et al. 2015 engineered non-pathogenic *Salmonella* with integration of a quorum sensing switch that only induces drug expression carried by the bacteria in closely packed colonies present inside the tumor. They have shown that, this quorum sensing engineered *Salmonella* expressed anti-tumor proteins only inside the tumor and can be used for tumor-specific drug delivery (Swofford et al. 2015). Some of the key roles of quorum sensing in *Salmonella* virulence are presented in Fig. 1C.

Association of biofilm with *Salmonella* virulence

In natural condition, most of the bacteria are believed to exist in biofilm forming conditions and research findings showing "approximately 80% bacterial infections are associated with biofilm", emphasize the importance of this event in bacteria associated diseases (Davies 2003). Some important

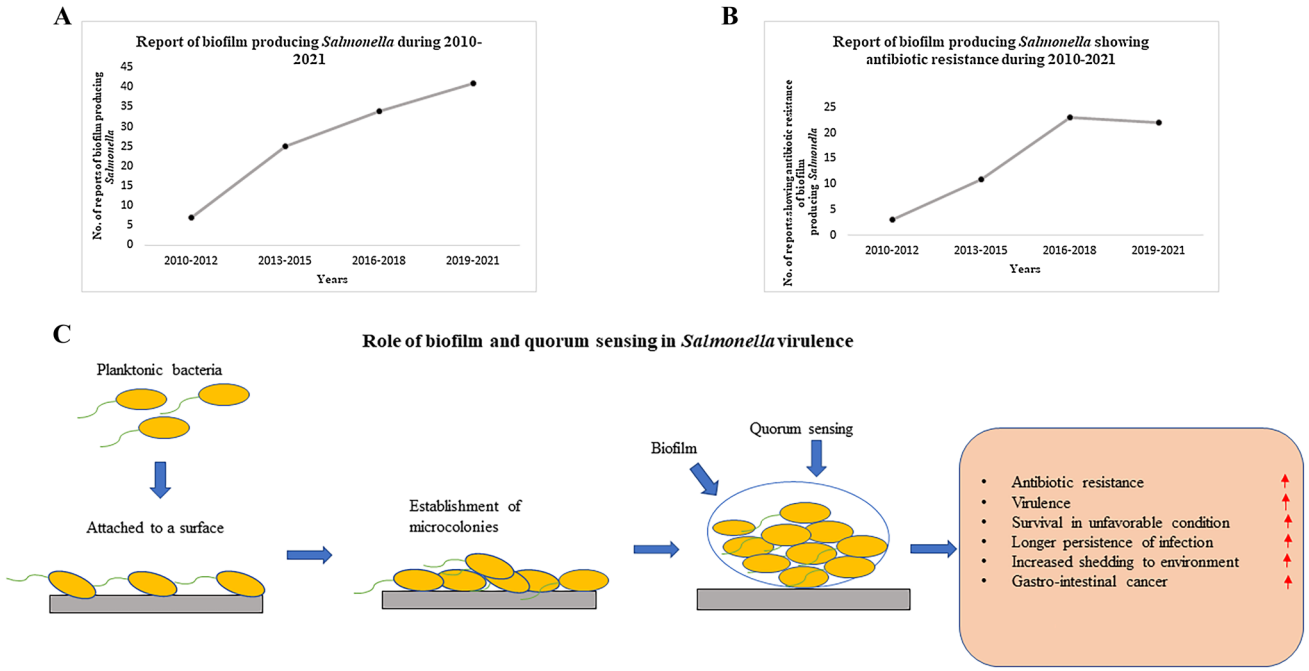

Fig. 1 **A** The graph represents total no. of articles published which reported biofilm producing *Salmonella* during a period of 2010–2021, **B** the graph represents total no. of articles published which reported antibiotic resistance property of biofilm producing *Salmonella* during a period of 2010–2021, **C** schematic presentation of role of biofilm and quorum sensing in *Salmonella* virulence

contributing factors of biofilm to *Salmonella* virulence are presented in Fig. 1C. The increasing number of reports on biofilm forming *Salmonella* and their antibiotic resistance during past one decade (Fig. 1A and B, the references of articles presented in these figures are provided in supplementary file, Table 1) provides an alarming picture of its severity if not taken care of appropriately in time. Below is a thorough description of how biofilm formation provides advantages to *Salmonella* to survive in harsh conditions and promote its virulence, making it a more difficult pathogen clinically.

Antibiotic resistance

Around 60% of nosocomial infections found in humans are thought to be biofilm associated and biofilms increase resistance of bacteria towards host innate defence and antibiotics (Chen and Wen 2011). Of note, acute bacterial infections can be cured with a certain profile of antibiotic treatment whereas the treatment does not show efficacy against an infection caused by biofilm producing bacteria which has a risk of recurrent infection. Sometimes, replacing the initial antibiotic therapy as a treatment regimen helps in resolving these kinds of infections (Song et al. 2013). Biofilm producing bacteria show heterogeneity in replication and metabolism which modulates the biofilm structure and the action of antibiotic, hence making the anti-microbial agent less effective (Dykes et al. 2003). In case of *S. typhi*, emergence of MDR strains has become a major risk as many easily available antibiotics are no more effective (Wang et al. 2013). The problem becomes more severe in case of gall stone patients, as in most cases, antibiotic treatment does not work effectively because of *S. typhi* colonization, ultimately leaving gall bladder removal as the only possible therapy (Gunn et al. 2014). Another study, which seconds this finding, proves that, biofilm formation provides protection to *S. typhi* and *S. typhimurium* from ciprofloxacin in vitro as well as in a mouse model of chronic carriage (González et al. 2018). Not only biofilm formation induces antibiotic resistance, but also multidrug efflux pump in *S. typhimurium* plays important role in biofilm formation (Baugh et al. 2012). A study showed that, *S. typhimurium* biofilms, formed on microplates, exhibited 2000-fold more resistance to ciprofloxacin in comparison to their planktonic cells (Tabak et al. 2019). A significant increase in biofilm and extra polysaccharide production by sub-inhibitory concentration of cefotaxime in clinical *Salmonella* isolates indicates the threat of uncontrolled use of antibiotics (Majtan et al. 2008). This is a major concern as ciprofloxacin combined with ceftriaxone or cefotaxime are usually administered for treatment of non-typhoidal Salmonellosis (Parry and Threlfall 2008). In another study, 194 *S. enterica* strains isolated from infected children were tested for their biofilm forming

Table 1 Role of various genes in biofilm formation, virulence or quorum sensing in different pathogenic bacteria

Sl. No	Bacteria name	Gene name	Functions of Gene	References
1	*Salmonella typhimurium*	*InvA, spvC*	Biofilm formation, virulence, antibiotic resistance	Krishna and Dhanashree (2020)
		STM4263 & yjcC	Biofilm formation	Kim and Wei (2009)
2	*Salmonella paratyphi*	*InvA, spvC*	Biofilm formation, virulence, antibiotic resistance	Krishna and Dhanashree (2020)
2	*Staphylococcus aureus*	*LytN, atlA*	Biofilm formation	Shi et al. (2019)
3	*Klebsilla pneumoniae*	*mrkA, luxS, pga, wbbM, wzm,*	Quorum sensing	Vuotto et al. (2017)
		Ompk35, ompk36, acrB	Biofilm formation, antibiotic resistance	
4	*Pseudomonas aeruginosa*	*Ps1A*	Biofilm formation	Heydari and Eftekhar (2015)
5	*Acinetobacter baumannii*	*rhiiR, lasiR*	Quorum sensing, biofilm formation, antibiotic resistance	Al Marjania et al. (2021)
6	*Salmonella enteritidis*	*InvA, avrA, csgD*	Biofilm formation	Romeu et al. (2020)
		Bap A	Biofilm formation & host colonization	Latasa et al. (2005)
7	*Escherichia coli*	*YcfR*	Biofilm formation	Zhang et al. (2007)
8	*Salmonella typhi*	*Mig14*	Antibiotic resistance & biofilm formation	Sheng et al. (2019)
		QseB, QseC	Biofilm formation, virulence & quorum sensing	Ji et al. (2017)
		AsfD	Biofilm formation	Chen et al. (2020)
		RibS	Biofilm formation	Zhao et al. (2018)
		Bap A	Biofilm formation & host colonization	Latasa et al. (2005)
9	*Salmonella enteritidis*	*Bap A*	Biofilm formation & host colonization	Latasa et al. (2005)

capacity. Surprisingly, 56% of them formed biofilms and simultaneously showed resistance to nine antibiotics with highest resistance against gentamicin and ampicillin (Papavasileiou et al. 2010). Several reports from 2013–2021 have shown an induced antibiotic resistance of different biofilm forming *Salmonella* species isolated from food sources or clinical samples from different parts of globe (Gong et al. 2013; Tezela et al. 2016; Trampari et al. 2021; Farahani et al. 2018).

Stimulation of Virulence factors and survivability in harsh conditions

Evidences showing that bacterial biofilm may affect the virulence of the pathogen, have led to increased attention of researchers to study diseases from the aspect of their biofilm forming ability. Biofilm formation in *Salmonella* is considered as one of the virulence weapons which provides survival advantage to the bacteria (Fàbrega and Vila 2013). The extracellular matrix of biofilm contains polysaccharide layers that protects the bacteria from its harsh environment (Jason Chin et al. 2017). Transcriptomic study of *S. typhi* biofilms revealed that, there is significant increase in expression of genes associated with extracellular matrix and antibiotic resistance which are crucial virulence factors of the pathogen (Jason Chin et al. 2017). Another two important virulence markers involved in *S. typhimurium* pathogenicity are *Salmonella* enterotoxin (*stn* gene, causes mainly gastroenteritis) (Nakano et al. 2012) and invasion gene (*invA* gene, that helps the pathogen to invade into intestinal epithelium) (Bruno et al. 2009). Expression of these two genes has also been found to be upregulated in biofilm forming *S. typhimurium* (Xu et al. 2010). Similarly, biofilm formation is also reported to induce expression of type 1 fimbria operon genes in *S. typhimurium* and these genes are associated with biofilm attachment to abiotic surfaces and colonization on mucosal surface of gut (Escobedo and Gunn 2013). There are some examples of different genes playing key role either in biofilm formation, quorum sensing, antibiotic resistance or virulence of different pathogenic bacteria, presented in Table 1. During their life cycle and pathogenesis, *Salmonella* has to travel through different types of hosts and different kind of unfavourable environmental conditions including interaction with preservatives, anti-microbial peptides, reactive nitrogen/oxygen species, changing temperature and pH and limited availability of nutrients, etc. The adaptation to changing environment leads to change in its growth pattern, survival and virulence. The polysaccharide matrix of biofilm that covers the biofilm forming *Salmonella*, protects the bacteria from the outer harsh environmental condition (Jason Chin et al. 2017). A transcriptional analysis of stress response genes of biofilm forming *S. typhimurium* showed an important role of biofilm in inducing enterotoxin and invasion gene of the pathogen when cultured in varied pH such as pH 5, 6 and 7 (Xu et al. 2010). As acid tolerance

response (ATR) is believed to play key role in invasion and colonization making the pathogen more virulent (Abdelwaheb and Ahmed 2009), the increased production of enterotoxin and invasion by *S. typhimurium* under acidic stress conditions is certainly a matter of worry. Furthermore, stimulating effect of biofilm on the whole stress-response process suggests its involvement in providing survival advantage to this pathogen under unsuitable condition. In a parallel situation, in vitro experiments have shown that both *S. typhi* and *S. typhimurium* can produce biofilm on gall stone surface and biofilm provides them protection against high concentration of bile as well as antibiotics (Prouty et al. 2002). In physiological condition, bile acts as a lipid emulsifier, detergent and a potent anti-microbial agent by disrupting cellular homeostasis. As bile containing gall bladder is the main colonizing site of *Salmonella*, to identify the bile response mechanism, some studies have identified biofilm formation as the major strategy of these pathogens to survive in bile enriched site (Prouty et al. 2002; Crawford et al. 2008). In vivo imaging has shown that biofilm helps the pathogen survive longer outside the host by well-equipped counter mechanisms to tolerate outside extreme conditions (White et al. 2008). However, further research is needed to understand whether *S. typhimurium* forms biofilm in human gall bladder or not.

Longer persistence inside host and prolonged shedding into environment

From the microbiological point of view, the capability of a pathogen to establish a persistent infection inside host is crucial for its survival as well as transmission which makes the microbe an active reservoir. *Salmonella* is a common source of zoonotic disease and infectious to both humans and animals. Systemic persistence of *S. enterica* for a long time inside human body makes the patient asymptomatic carrier in most cases and poses high risk to public health (Dutta et al. 2000). These chronically infected asymptomatic carriers shed bacteria through faecal route and thereby transmit the disease to naive hosts. Faecal-oral route is the common route of spread for *Salmonella* and humans get infected mostly after getting contact with food contaminated with faeces of infected animal (Mukhopadhyay et al. 2019). There are multiple reports showing a significant number of typhoid patients are asymptomatic, chronic carriers of *S. typhi* and shed pathogen in their urine and stool for long period of time, sometimes even for life time (Ruby et al. 2012; House et al. 2001). Besides human body, non-typhoidal *Salmonella* have been found to persist on the surface of raw fruits and vegetable and cause disease outbreaks in the past decade (Beuchat 2002). Interestingly, there are evidences of bacterial biofilm formation on food products and food contact surfaces which may become a potential transmission route of food-borne pathogens (Lee et al. 2020). The profound role of biofilm in attachment and persistence of bacteria on both biotic and abiotic surfaces has led to studies trying to elucidate the mechanism by which biofilm makes the bacteria adhere to the surface for long period. *S. typhimurium* can form biofilms on glass, polysterene, stainless steel, human epithelial cells, fruits, vegetables and its ability to form biofilm and remain attached on these surfaces is an important strategy of survival (Prouty et al. 2002; Arnold and Bailey 2000; Boddicker et al. 2002; Zogaj et al. 2001; Avila-Novoa et al. 2021). Spread of *S. saintpaul, S. rubislaw* and *S. javiana* by paprika, isolation of *S. typhimurium, S. ofda, S. tennessee,* and *S. poona* from sesame paste and seed are some examples that have contributed to food born outbreaks (Lehmacher et al. 1995; Brockmann et al. 2004). There was a correlation found between biofilm formation of *Salmonella* and its persistence in fish meal and feed factories (Vestby et al. 2009). *Salmonella* is known to produce biofilm on surfaces of plant and plant products and biofilm promotes its persistence by protecting from washing and sanitization (Andino and Hanning 2015). In a study carried out by Hamilton et al. 2009, biofilm of *S. typhimurium* has been proven as an inducer of bacterial attachment to abiotic surfaces, potential infection reservoir and stimulator of genes involved in tryptophan biosynthesis (*trp*) and transport. Deletion of *trp*E gene resulted in decreased attachment of the bacteria showing the importance of its biofilm-mediated induction (Hamilton et al. 2009). A 2–5% of *Salmonella*-infected patients fail to completely get rid of the bacteria from their body thus becoming chronic carriers. In the situation of chronic infection, *Salmonella* chooses gall bladder as its niche and invades gall bladder either from liver, small intestine or via biliary tract. Once it is settled on the organ, it starts forming biofilm on the surface leading to many complications including reinfection of intestine, gall stone and transmission to naive host through faecal route (Crawford et al. 2010). A recent finding has very elegantly shown that, *Salmonella* exists in the form of biofilm in persistently infected host and in absence of biofilm, it kills the host in short span of time by inhibiting innate immune response of the host. In a *Caenorhabditis elegans* infection model, biofilm formation by *Salmonella* was found to activate host defence and thereby obtained some growth advantages in vivo. During biofilm formation, downregulation of *Salmonella* SP-1 virulence genes stimulated the activation of host innate immune pathway and thereby created a state of dormancy for its prolonged survival inside host (Desaia et al. 2019). Another major risk biofilm forming *Salmonella* in gall bladder causes is gastrointestinal cancer which is still an enigmatic area for the researchers (Koshiol et al. 2016).

Biofilm and gastrointestinal cancer

Though the association of bacteria induced inflammation and cancer progression has been the focus of researchers since many years, the mechanism by which bacteria induce tumorigenesis is poorly understood. Reports have shown that, carriers of *S. typhi* and *S. paratyphi* are more susceptible to pancreas, colon, lung and gall bladder cancer (Caygill et al. 1994). According to several epidemiological studies carried out at different places including Ecuador, Bolivia, Chile, Pakistan, Japan, Korea and some parts of India, about 90% of chronically infected *S. typhi* carriers also have gall stones and this relationship is a major factor for gall bladder cancer development (Gunn et al. 2014; Caygill et al. 1994; Dutta et al. 2000; Nath et al. 2008; Escobedo et al. 2011). Though genetics and life style are two important factors for any kind of malignancy, infection with *S. typhi* and gall stone remain the most significant cause for gall bladder cancer (Nagaraja and Eslick 2014). In a study carried out in Mexico City, which is a typhoid endemic site, *S. typhi* carriers were found to have gall stones and biofilm was clearly visible on gall stones. Furthermore, using a *S. typhimurium* infected mice model, the group has shown presence of biofilm on mice gall stone in addition to human patients and its role in facilitating gall bladder colonization and shedding of the pathogen (Caygill et al. 1994). Despite plenty of evidences showing positive corelation between *S. typhi*, gall stone and gall bladder cancer, their actual role in the cancer initiation is still a matter of debate. Production of biofilm by *S. typhi* might be the key player in development of gall bladder cancer, as its stimulatory effect on colonization and chronic persistence of the pathogen in gall bladder, leading to formation of gall stone. *Salmonella* biofilm embeds the gall stone which becomes a favourable site for bacteria persistence, causes reinfection of intestine, induces transmission through faecal shedding and most importantly chronically making the gall bladder epithelium more vulnerable towards bacteria produced carcinogenic factors (Di Domenico et al. 2017). *S. typhi* produces many factors of carcinogenic potential such as glucuronidase, nitroso compounds and cytolethal destending toxins (CDT), etc., which might be the contributing factors for gall bladder cancer (Di Domenico et al. 2017). Moreover, biofilm on gall stone provides all kind of advantages to *S. typhi* (protection from antibiotics, bile and other harsh conditions etc.) to grow and survive better as well as produce carcinogenic factors making a conducive environment to development of gall bladder cancer. Though there is a strong association between *S. typhi* chronic carriers' status and presence of gall stone, the putative link between these events and gall bladder cancer has not been explored till date. Molecular characterization of events regulating biofilm formation on gall stone, *S. typhi*-mediated inflammation and damage of gall bladder and role of CDT toxins that induce damage in DNA and activation of MAPK-AKT is needed to understand the mechanistic ground. However, early detection of *S. typhi* can be considered as a critical clinical practice to develop preventive measures for gall bladder cancer.

Conclusion

The recent past decade has extensively focussed on generating a wealth of knowledge about how microbes utilize quorum sensing and biofilm as their media of communication and coordination of their diverse functions. This knowledge has further been exploited as a foundation pillar to investigate the role of these events beyond just cross-talk among microbial population. This emerging field of research and its findings are relevant to the interest of this review which aims at understanding how both quorum sensing and biofilm help *Salmonella* to achieve success in infection establishment in diversified environmental conditions. The current review gathers most important information related to involvement of these two phenomena in *Salmonella* pathogenesis. Comparatively lesser number of studies on the association of quorum sensing with *Salmonella* virulence was a major challenge to point out its probable role in the process of disease incidence and progression. Another experimental issue with *S. typhi* is that, this pathogen is human host restricted. Though *S. typhimurium* infection in animal models mimics *S. typhi* infection closely, investigating the exact role of *S. typhi* biofilm formation in gall stone and gall bladder cancer would have been the ultimate system. Figures presented in this review show the associated risk of biofilm forming *Salmonella* as their increasing antibiotic resistance could become a public health threat. So, screening for biofilm forming *Salmonella* during initial period of infection is strongly recommended for better treatment strategy and administration of suitable antibiotics. However, future studies with thorough investigation are required to shed light on biofilm-mediated modulation of host immune system as well as biofilm-induced molecular markers aggravating the pathogenesis. Understanding, whether both quorum sensing and biofilm are directly making the pathogen more virulent or the pathogen is just taking the advantage of the favourable environment made by these events indirectly will also enlighten us regarding developing effective regimens to inhibit their association.

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Declarations

Conflict of interest Authors have no conflict of interest.

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