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The Importance of Mobile Genetic Elements in the Evolution of *Salmonella*: Pathogenesis, Antibiotic Resistance and Host Adaptation

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1. Introduction

Since the divergence from *Escherichia coli*, more than 100 million years ago, *Salmonella* has acquired by lateral gene transfer a repertoire of genes that confers a set of physiological features that define its particular ecological niche (Ochman and Groisman 1994; Ochman et al., 2000). Some of these chromosomally-encoded genes can be considered as part of the “core genome” of *Salmonella* (i. e. genes present in all the strains), whereas some other chromosomally-encoded genes are part of the “accessory genome” (i. e. genes present in some of the strains) along with mobile genetic elements such as plasmids, bacteriophages, transposons and integrons. In this chapter we review the role that mobile genetic elements have played in *Salmonella* evolution, particularly in pathogenicity attributes, antibiotic resistance and host adaptation.

2. Pathogenicity islands

Pathogenicity islands are large genomic regions that are present in pathogenic variants but less frequently present in closely related non-pathogenic bacteria. They often carry virulence-associated genes, have a G+C content that differs from that of the rest of the chromosome, are frequently associated with tRNA genes and are flanked by repeated sequences (Dobrindt et al., 2004). *Salmonella* pathogenicity islands (SPIs) are large gene cassettes within the *Salmonella* chromosome that encode determinants responsible for establishing specific interactions with the host, and are required for bacterial virulence in a given animal. Like other pathogenicity islands, SPIs generally have a G+C content lower (between 37 and 47%) than the rest of the bacterial chromosome (about 52%), and are often inserted into tRNA genes. Therefore, SPIs have likely been acquired by horizontal transfer from bacteriophage or plasmids of unknown origin, and they are highly conserved between the different *Salmonella* serovars. It is sometimes unclear how certain DNA regions are designated as pathogenicity islands. Small DNA regions (often single genes), which are acquired horizontally, are numerous and their distinction from pathogenicity islands is in some cases arbitrary (Marcus et al., 2000). More than twenty SPIs have been described (Sabbagh et al., 2010). Most SPIs have become part of the core set of genes of *S. enterica* and

encode species-specific traits. A smaller subset of SPIs is limited to certain subspecies or serovars. These SPIs harbor genes associated with DNA mobility and are likely to represent more recent acquisitions (Hensel 2004). SPI1 and SPI2 both encode type III secretion systems (TTSS), which mediate the respective virulence phenotype by translocating bacterially-encoded proteins into the host cell cytoplasm (Hansen-Wester and Hensel 2001). TTSS are used by many bacterial pathogens to deliver virulence factors to the host cell and interfere with or subvert normal host cell signaling pathways. They consist of many components, including more than twenty proteins, some of which are homologous to those involved in flagellar assembly. Effector proteins generally require specific chaperones which prevent incorrect folding, degradation and premature association, and may even aid delivery of the effector into host cells. These systems are highly regulated, and proteins are only secreted when the bacteria sense specific environmental cues (Marcus et al., 2000; Cornelis 2006). A remarkable observation is the functional interaction of SPI1 and SPI2 with further loci encoding effector proteins, including SPI5 and some mobile DNA elements (Hensel 2004).

3. *Salmonella* genomic island

A chromosomal island called *Salmonella* genomic island 1 (SGI1) was initially described in the epidemic multiple-drug-resistant (MDR) *Salmonella enterica* serovar Typhimurium phage-type DT104 (Boyd et al., 2001). In this respect, phage-typing is carried out by infecting a *Salmonella* isolate with a number of phages listed in the phage-typing scheme for a specific serovar (Kropinski et al., 2007). The present phage-typing scheme for Typhimurium consists of 34 phages and identifies 207 phage types, referred to as definitive types (DT) (Anderson et al., 1977). Since the original identification of SGI1 in Typhimurium DT104, variants of SGI1 have been described in a wide variety of *Salmonella* serovars (Levings et al., 2005). The 43 kb SGI1 contains 44 open reading frames (ORFs), many of them without homology to known gene sequences. In all the serovars, SGI1 showed the same chromosomal location. In the first part of the island, a number of ORFs showing homology to plasmid-related genes are present. The 13 kb-antibiotic resistance gene cluster is located near the 3' end of SGI1 (Levings et al., 2005). The MDR cluster confers resistance to streptomycin and spectinomycin, sulfonamides, chloramphenicol and florfenicol, tetracyclines, and beta-lactam antibiotics. The G+C content for the MDR cluster is 59%, while for the rest of the SGI1 it is 49%, as compared with 52% for the Typhimurium chromosome, suggesting a mosaic structure (Boyd et al., 2001). SGI1 is an integrative mobilizable element which contains a complex class 1 integron (see below) named In104, located within the antibiotic resistance cluster located at the 3' end of the island (Boyd et al., 2001; Doublet et al., 2005; Mulvey et al., 2006). In 2005, Doublet et al. reported that SGI1 could be conjugally transferred from an *S. enterica* donor to *E. coli* recipient strains where it integrated into the recipient chromosome in a site-specific manner (Doublet et al., 2005). First, an extra-chromosomal circle of SGI1 was formed, and this circular intermediate was transferred in the presence of an IncC helper plasmid, which provided the mating apparatus. This study demonstrated that the mobilization of SGI1 probably contributes to the spread of antibiotic resistance genes between *S. enterica* serovars and possibly to other bacterial pathogens (Doublet et al., 2005). As predicted by Doublet et al. (2005), a variant of SGI1 has been reported in *Proteus mirabilis* (Boyd et al., 2008). Moreover, a recent report showing the ability of IncA/C plasmids to mobilize SGI1 has implications for the worldwide spread of these MDR elements (Douard et al., 2010).

4. Antimicrobial resistance and virulence plasmids

A substantial amount of the variation in bacteria is due to the presence of plasmids (Levin and Bergstrom 2000). Plasmids are part of the flexible genome, which is defined by the high plasticity and modularity of its genetic elements and high rates of gene acquisition and loss (Heuer et al., 2008). They are typically composed of conserved backbone modules coding for replication, maintenance and transfer functions as well as variable accessory modules. The capture of genetic modules by plasmid backbones can increase phenotypic diversity and thereby increment the chances of responding to uncertain environmental changes or exploit an opportunity for niche expansion (Souza and Eguiarte 1997; Frost et al., 2005; Heuer et al., 2008; Norman et al., 2009). Often, antimicrobial or heavy metal resistance, or virulence factors that allow their bacterial host to adapt to changing environments are encoded by plasmids. Plasmids are classified according to incompatibility (Inc) groups, that are based on the inability of plasmids with the same replication or segregation mechanisms to co-exist in the same cell (Couturier et al., 1988). Plasmids of *Salmonella enterica* vary in size from 2 to more than 200 kb. The best described plasmids are the so-called virulence plasmids present in some serovars. Another group of high molecular weight plasmids are responsible for antibiotic resistance, which are in most of the cases conjugative, contributing to the spread of genes in bacterial populations (Rychlik et al., 2006). The low molecular weight multi-copy plasmids are widespread in *Salmonella*, but are less studied and are referred as cryptic, although some of them have been shown to increase resistance to bacteriophage infection due to the presence of modification systems (Rychlik et al., 2006).

Eight *Salmonella enterica* serovars harbour a large (50-285 kb) plasmid named the *Salmonella* virulence plasmid, containing the *spv* operon, which is a major determinant of virulence in their specific hosts (Gulig et al., 1993; Chiu et al., 2000; Fierer and Guiney 2001). In addition to the *spv* operon, other plasmid genes are involved in virulence. The *rsk* and *rck* genes are required for serum resistance, and *traT*, a surface exclusion protein for plasmid transfer, is also responsible for serum resistance (Chu and Chiu 2006). Within a single serovar some strains can carry the virulence plasmid while others not (Olsen et al., 2004). Despite many common properties shared by these plasmids, each virulence plasmid seems to be specific to its serovar, but the outcome of the infection in different animal hosts may be variable. For example, Typhimurium strains that harbour the virulence plasmid are highly virulent to mouse, but there is lack of evidence of an association between the carriage of virulence plasmid and the bacteremia caused in humans (Chiu et al., 2000). Whether the virulence plasmid is necessary to produce systemic infections in humans has been subject of intense debate. Some authors claim that there is lack of evidence of an association between the carriage of the virulence plasmid and human bacteremia (Chiu et al., 2000). Other authors suggest that *spv* genes promote the dissemination of Typhimurium from the intestine (Fierer 2001). In recent reports contrasting results have been found. We studied more than 100 Typhimurium strains isolated from human and food-animal sources in Mexico, and found that only 30% of the strains harboured the plasmid (Wiesner et al., 2009). The presence of the virulence plasmid was significantly associated with human isolates, but only one of the six isolates recovered from patients with systemic infection had the virulence plasmid. Our data support the notion that the virulence plasmid has a role in host adaptation (Baumler et al., 1998); however, it was not consistent with the view that it is associated with systemic infection in humans (Wiesner et al., 2009). In a recent study, Littrup et al. (2010) analyzed 21 Typhimurium strains isolated from patients with mild and sever infections with the aim of

correlate genomic content with the outcome of disease. They used a DNA microarray targeting 281 known virulence factors, and found that the presence or absence of the virulence plasmid did not correspond to disease symptoms (Litrup et al., 2010). On the other hand, Heithoff et al. (2008) found that all the Typhimurium strains isolated from animals or humans with bacteremia possessed the virulence plasmid, while 34% of the strains isolated from human gastroenteritis lacked the plasmid (Heithoff et al., 2008). These contrasting results highlight the complex nature of specific host-pathogen interactions, and call to avoid making generalizations since the diversity of environmental (biotic and abiotic), host, and bacterial genetic conditions may produce different outcomes.

Large antimicrobial resistance plasmids are of public health concern. The global scene is that the therapeutic options for MDR microbes are reduced, periods of hospital care are more extended and costly and, in some cases, the strains have also acquired increased virulence and enhanced transmissibility. Realistically, antibiotic resistance can be considered a virulence factor (Davies and Davies 2010). Resistance mechanisms are pandemic and create an enormous clinical and financial burden on health care systems worldwide (Davies and Davies 2010). The resistance genes found in *Salmonella* are closely related to, or are indistinguishable from, those found in other bacteria, including not only members of the *Enterobacteriaceae* but also distantly related bacteria. It is most likely that *Salmonella* acquired these genes from other bacteria, and probably *Salmonella* strains also play a role in the further dissemination of these resistance genes to other bacteria (Michael et al., 2006). Frequencies of conjugative transmission in nature are probably several orders of magnitude higher than those observed under laboratory conditions, and occur readily in networks of multi-host interactions (Dionisio et al., 2002; Sorensen et al., 2005; Davies and Davies 2010).

The IncA/C plasmids exemplify the problematic of resistance plasmids in *Salmonella*. They have attracted the attention of the research community due to their ability to acquire antimicrobial resistance traits and to mobilize across geographical and taxonomical borders (Fricke et al., 2009). Recent comparative studies have addressed the evolutionary relationships among the IncA/C plasmids from *Salmonella enterica*, *Escherichia coli*, *Yersinia pestis*, *Yersinia ruckeri*, *Vibrio cholera*, *Photobacterium damsela* and *Aeromonas salmonicida* (Welch et al., 2007; Kim et al., 2008; McIntosh et al., 2008; Pan et al., 2008; Fricke et al., 2009; Call et al., 2010). The genomic comparison of seven IncA/C plasmids showed that these plasmids share a common backbone, including the origin of replication and a conjugative plasmid transfer system (Welch et al., 2007; Fricke et al., 2009). Several loci containing antimicrobial resistance determinants are distributed along the plasmids, and are integrated at few sites within the conserved plasmid backbone; they are generally located as resistance gene arrays, composed of resistance genes and mobile genetic elements such as insertion sequences, transposons or integrons (Fricke et al., 2009). For example, in the IncA/C plasmids of *Yersinia pestis* and *Salmonella* Newport, a Tn21 transposon is inserted in a similar location but some nucleotide divergence is evident and its orientation is reversed (Welch et al., 2007; Fricke et al., 2009). These studies suggest an evolutionary model in which each IncA/C plasmid diverged from a common ancestor, through processes of stepwise integration events of horizontally-acquired resistance genes arrays (Welch et al., 2007; Fricke et al., 2009).

Over the last decade, increasing attention has been focused on plasmids that harbour the antimicrobial resistance gene *bla*_{CMY-2}, which encodes an AmpC-type beta-lactamase that hydrolyzes third-generation cephalosporins (Bauernfeind et al., 1996; Zhao et al., 2001;

Carattoli et al., 2002; Wiesner et al., 2009; Wiesner et al., 2011). In *Salmonella enterica*, *bla*_{CMY-2} is frequently carried by IncA/C or IncI1 plasmids (Bauernfeind et al., 1996; Carattoli et al., 2002; Hopkins et al., 2006; Lindsey et al., 2009). In a recent study, Call et al. (2010) analyzed five *E. coli* and *Salmonella* Newport IncA/C plasmids carrying *bla*_{CMY-2}, and showed that although they share a common ancestor with the *Yersinia* and *Photobacterium* plasmids, they are genetically distinct (Call et al., 2010). In a population study we found that IncA/C plasmids were associated to the Mexican Typhimurium ST213 genotype. We determined that the *bla*_{CMY-2} gene was carried in IncA/C plasmids, and genetic variability was observed using a plasmid typing scheme, targeting ten conserved regions in IncA/C plasmids (Wiesner et al., 2009; Wiesner et al., 2011). The Typhimurium *bla*_{CMY-2}-bearing IncA/C plasmids possessed most of the accessory elements found in other *Salmonella* and *E. coli* plasmids (Call et al., 2010), but also more than half contained a class 1 integron (*dfrA12-orfF-aadA2*). The screening of the total Mexican Typhimurium population showed the presence of another IncA/C plasmid harboured by ST213 strains, yet lacking *bla*_{CMY-2}. These plasmids also carried antibiotic resistance determinants, but they shared only three of the ten genetic markers used to study the IncA/C plasmids, and were smaller than the *bla*_{CMY-2}-bearing IncA/C plasmids (100 vs. 150-160 kb). Nevertheless, the nucleotide sequences of the regions shared with the *bla*_{CMY-2}-bearing IncA/C plasmids were identical, suggesting that the *bla*_{CMY-2}-bearing plasmids could be the result of the insertion of DNA modules into this smaller precursor plasmid (Wiesner et al., 2009; Wiesner et al., 2011). The general agreement from the analysis of the genetic structure of the IncA/C group is that plasmid evolution progresses faster through the insertion/deletion of DNA stretches rather than by point mutations (Welch et al., 2007; Kim et al., 2008; Fricke et al., 2009; Call et al., 2010; Wiesner et al., 2011).

Large resistance plasmids circulate among microbial populations in distinct environmental niches, even in the absence of antibiotic selective pressure. In other environments the target of the selective pressure could be, for example, mercury resistance carried by many transposons, such as Tn21 (Liebert et al., 1999; McIntosh et al., 2008). Regardless of the primary selective agent, the complete battery of resistance determinants will be maintained, imposing a global health risk (Liebert et al., 1999; Frost et al., 2005; Welch et al., 2007; McIntosh et al., 2008; Pan et al., 2008; Davies and Davies 2010). Another worrisome situation is the emergence of *Salmonella* virulence-(antibiotic) resistance plasmids. Several studies had reported large hybrid virulence-resistance plasmids in serovars Typhimurium, Choleraesuis and Enteritidis, isolated from Spain, Italy, Czech Republic, Taiwan and the United Kingdom (Chu et al., 2001; Guerra et al., 2001; Guerra et al., 2002; Guerra et al., 2004; Villa and Carattoli 2005; Chu and Chiu 2006; Herrero et al., 2008a; Herrero et al., 2008b; Hradecka et al., 2008; Herrero et al., 2009; Rodriguez et al., 2011). In some of the studies it was demonstrated that the hybrid plasmids were conjugative, which may lead to their spread to new recipients and allow the co-selection of the antibiotic and virulence genes, representing a hazard to human and animal health (Fluit 2005).

5. Integrons

Integrons are assembly platforms that incorporate genes by site-specific recombination and convert them to functional genes by ensuring their correct expression. They are composed of three key elements: a gene encoding an integrase, a primary recombination site, and a promoter that directs the transcription of the captured genes. The integrase can recombine discrete units of circularized DNA known as "gene cassettes"; they are transcribed only

when captured into an integron, since most of them lack a promoter. Integration occurs downstream of the resident promoter, at the primary recombination site, allowing the expression of the genes in the cassette (Figure 1). The integron inserted gene cassettes share specific structural characteristics and contain an imperfect inverted repeat at the 3' end, called the "59-base element". This site functions as a secondary recognition site for the site-specific integrase, and can further integrate gene cassettes. The ability to capture disparate individual genes and to physically link them in arrays suitable for co-expression is a trait unique to integrons, and theoretically facilitates the rapid evolution of new phenotypes (Stokes and Hall 1989; Recchia and Hall 1995; Fluit and Schmitz 1999; Holmes et al., 2003; Fluit and Schmitz 2004; Mazel 2006; Boucher et al., 2007; Joss et al., 2009).

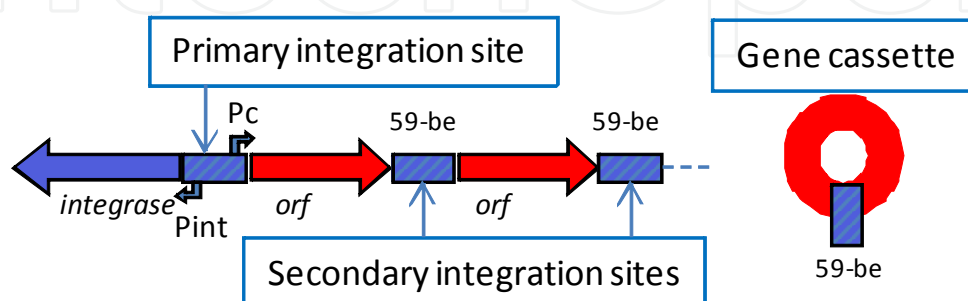


Fig. 1. Diagrammatic representation of the basic features of an integron. Integrons consist of the gene for the integrase, the promoters for the expression of the integrase (Pint) and the gene cassettes (Pc), and the primary recombination site, where the cassettes are integrated. Gene cassettes consist of a single promoter-less gene and a recombination site known as a 59-base element (59-be), which functions as a secondary recognition site for the site-specific integrase, and can further integrate gene cassettes (Stokes and Hall 1989; Hall and Collis 1995; Levesque et al., 1995). An integron carrying an array of two inserted cassettes, and a free circularized gene cassette is shown.

Analyses on the diversity of gene cassettes in environmental samples have shown a great diversity of predicted genes, suggesting that essentially any DNA-encoded function may be contained within a gene cassette (Stokes et al., 2001; Holmes et al., 2003). However, the main part of the gene cassettes found in mobile integrons from cultured bacteria contain antibiotic-resistance determinants (Levesque et al., 1995; Fluit and Schmitz 1999, 2004). Class 1 integrons are found extensively in clinical isolates, and most of the known antibiotic resistance gene cassettes belong to this class (Fluit and Schmitz 2004). Although gene cassettes conferring resistance to nearly every major class of antibiotics have been identified, there are some antibiotic resistance determinants that are preferentially associated to integrons, such as streptomycin, trimethoprim, sulfafurazole, and the early aminoglycosides (White et al., 2001; Fluit and Schmitz 2004). Moreover, it has been reported that MDR is associated significantly with the presence of integrons (Leverstein-van Hall et al., 2003; Fluit 2005; Wiesner et al., 2009). Integrons themselves are not mobile although they can be part of transposons, which are capable of moving from one carrier replicon to another (Fluit and Schmitz 1999; Liebert et al., 1999). A well-known example are the integrons found in Tn21 and related transposons. These transposons generally are located on plasmids, which further enhances the spread of gene cassettes (Fluit and Schmitz 1999; Liebert et al., 1999). The association of integrons with mobile elements and resistance genes has led to their rapid dispersal among various bacteria found in environments exposed to antibiotics (Martinez-Freijo et al., 1999; White et al., 2001; Boucher et al., 2007).

Since the discovery of the importance of integrons in the dissemination of antibiotic resistance, many studies have addressed the presence of integrons in *Salmonella*. At the moment of writing there were more than 300 research papers regarding integrons in *Salmonella* (<http://www.ncbi.nlm.nih.gov/pubmed>). An overview of these studies shows that integrons have been detected in many different *Salmonella* serovars (i. e. Agona, Albany, Anatum, Braenderup, Branderburg, Bredeney, Brikama, Derby, Dublin, Emek, Enteritidis, Eppendorf, Goldcoast, Grumpensis, Hadar, Haifa, Heildelberg, Infantis, Javiana, Kedougou, Kentucky, Kingston, Krefekd, Mbandaka, Muenster, Newport, Panama, Paratyphi B, Rissen, Rough, Saintpaul, Schwarzengrund, Stanley, Senftenberg, Tees, Tshiongwe, Typhimurium, Virchow, Weltevreden, Wien and Worthington), that were isolated from diverse sources (i. e. animal feed, beef, chicken, camel, environment, feline, foodstuff, goat, horse, human, milk, pork and turkey), and from countries all around the world (i. e. Albania, Algeria, Brazil, China, Chile, England, Ethiopia, Germany, Great Britain, Iran, Ireland, Italy, Japan, Lithuania, Mexico, Portugal, Slovak Republic, Spain, Thailand, The Netherlands, United States and Vietnam). Among the most studied cases are the chromosomally-located integrons present in the SGI1. There is a great diversity of integron cassettes detected in *Salmonella*, most of them encoding antibiotic resistance genes, carried in a wide variety of cassette arrays. It is noteworthy that similar cassette arrays are found in different *Salmonella* serovars isolated from different sources and distant countries, and even in other bacterial species. For example, in the study of the integrons present in a Mexican Typhimurium population (Wiesner et al., 2009), we found that the two most abundant integrons (*dfrA12-orfF-aadA2* and *dfrA17-aadA5*) were reported for other *Salmonella* serovars (Anatum, Branderup, Brikama, Enteritidis, Mbandaka, Rissen and Saintpaul) and in other *Enterobacteriaceae* (Lindstedt et al., 2003; Antunes et al., 2006; Su et al., 2006; Molla et al., 2007; Zhao et al., 2007). More surprising was that these integrons were also found in different species of the Gram-positive genera *Staphylococcus* isolated in China (Xu et al., 2008), providing evidence of the successful spread of these integrons around the world and across bacterial phyla (Wiesner et al., 2009).

6. Bacteriophages

Although bacteriophages carrying antibiotic resistance genes have rarely been identified (Davies and Davies 2010), their role in the dissemination of virulence factors has been widely documented (Boyd and Brussow 2002). Bacteriophage-encoded virulence factors can convert their bacterial host, in a process known as phage conversion, from a non-pathogenic strain to a virulent strain or a strain with increased virulence. The phage-encoded proteins involved in lysogenic conversion provide mechanisms to invade host tissues, avoid host immune defenses, and damage host cells (Boyd and Brussow 2002). The extra genes present in prophage genomes which do not have a phage function, but may act as fitness factors for the bacteria, are termed "morons". The moron-encoded genes are not required for the phage life cycle. Their expression is controlled by an autonomous promoter and, thus, can be expressed while the rest of the prophage genes remain silent (Hendrix et al., 2000). Morons enhance phage replication indirectly since moron-encoded functions enhance fitness of the lysogen. This hypothesis provides the theoretical framework for phage-mediated horizontal transfer of fitness factors between bacteria (Hendrix et al., 2000). The ecological success of a lysogenic bacterium contributes to the dissemination of phage genes, providing a case of co-evolution of viruses and bacteria. It has been hypothesized that the driving force behind the emergence of new epidemic clones is the phage-mediated re-assortment of virulence and

fitness factors, optimizing the *Salmonella*-host interaction (Miroid et al., 1999; Figueroa-Bossi et al., 2001; Brussow et al., 2004). The contribution of phages to *Salmonella* evolution is one of the best documented cases, and many phage-encoded virulence factors have been documented (Table 1). In particular, the functional biology of many phage-encoded genes has been studied in detail for Typhimurium strains.

Phage	Gene	Protein	Function in virulence
Fels-1	<i>sodC-III</i>	Superoxide dismutase	Intracellular survival
Fels-1	<i>nanH</i>	Neuraminidase	Intracellular survival
Gifsy-1	<i>gogB</i>	Type III effector	Involved in invasion
	<i>gipA</i>	IS-like	Critical for survival in Peyer's patches
Gifsy-2	<i>ssel (gtgB)</i>	Type III effector	Involved in invasion
	<i>sodC-I</i>	Superoxide dismutase	Intracellular survival
	<i>gtgE</i>	Type III effector	Required for full virulence
Gifsy-3	<i>sspH1</i>	Type III effector	Involved in invasion
	<i>pagJ</i>	<i>phoPQ</i> -activated gene	Bacterial envelope for invasion
Fels-1 and Gifsy-2	<i>groA</i>	Antivirulence gene	Decreases the pathogenicity in the host
P22	<i>gtrB</i>	Glucosyl transferase	O-antigen conversion
	<i>gtrA</i>	Flippase	O-antigen conversion
SopEΦ	<i>sopE</i>	Type III effector	Involved in invasion
ε34	<i>rfb</i>	Glucosyl transferase	Altering antigenicity

Table 1. Bacteriophage-encoded virulence factors of *Salmonella enterica* (Figueroa-Bossi et al., 2001; Boyd and Brussow 2002; Porwollik and McClelland 2003; Ehrbar and Hardt 2005; Kropinski et al., 2007).

Prophages contribute significantly to the diversity among *Salmonella* strains (Boyd and Brussow 2002), and different Typhimurium strains harbor distinct sets of prophages (Figueroa-Bossi et al., 2001; Miroid et al., 2001; Mmolawa et al., 2002). Most of them belong to the P2 family (SopEΦ, Fels-1, and Fels-2) or the lambda family (GIFSY-1, GIFSY-2, GIFSY-3 and P22). Several of the Typhimurium prophages encode the so-called type three effector proteins, which are injected by the bacterium into animal cells via a type three secretion system (TTSS) (Ehrbar and Hardt 2005). These effector proteins manipulate signal transduction pathways of the cells, which provoke a strong intestinal inflammation and diarrhea. The SopE effector, encoded by SopEΦ, is one of the better studied cases. It is injected into the intestinal cells by the TTSS encoded by SPI-1, and its expression is co-regulated with other genes. The proper timing of SopE expression and delivery into the host cell depends on the regulatory circuits of SPI-1 (Miroid et al., 1999; Brussow et al., 2004; Ehrbar and Hardt 2005). Since the earlier studies, Miroid et al. (1999) demonstrated that SopEΦ is capable of infecting a range of Typhimurium strains (Miroid et al., 1999). In an experimental study, it was demonstrated that the lysogenic conversion of the laboratory Typhimurium strain ATCC14028 with SopEΦ provided increased enteropathogenicity compared with the wild-type strain (Zhang et al., 2002). Thus, it was shown that the horizontal transfer of phage-mediated genes may contribute to the emergence of more pathogenic epidemic clones. Moreover, Miroid et al. (2001) provided evidence for the

transfer of the SopE cassette between lambda and P2-like phages families (Miold et al., 2001). They proposed that the transfer of virulence factors between phages increases the flexibility of the re-assortment of effector protein repertoires, by circumventing restrictions imposed by immunity functions or the occupancy of the attachment sites by resident prophages (Miold et al., 2001). By this mean, phages would contribute a great deal to the evolution of bacterial pathogens, and might explain the rapid emergence of new epidemic clones and the ability of *Salmonella* to adapt to a broad range of hosts.

The development of genome-based methods such as microarrays, and the tools to compare complete genome sequences, has opened a new era in the study of *Salmonella* evolution. Several studies have addressed the importance of bacteriophages in the evolution of *Salmonella*, and the role of prophage-encoded virulence factors in pathogenicity. Comparison of complete genomes have pointed out that the prophage content is one of the most important differences between genomes of *Salmonella* serovars, and specially among strains within a single serovar (McClelland et al., 2001; Parkhill et al., 2001; Porwollik et al., 2002; Porwollik et al., 2004; Thomson et al., 2004; Hermans et al., 2005; Cooke et al., 2007; Vernikos et al., 2007; Litrup et al., 2010). The detection of prophage sequences has been recently developed and proposed as a tool for the subtyping of strains (Hermans et al., 2006; Cooke et al., 2007). Recent population studies are supporting the notion that the prophage content is one the most dynamic part of the genome, indicating that phage integration/excision are frequent events shaping *Salmonella* genome evolution (Hermans et al., 2006; Cooke et al., 2007; Drahovska et al., 2007; Matiasovicova et al., 2007; Cooke et al., 2008; Litrup et al., 2010). These observations are in agreement with the phage remnants found in the genomes of *Salmonella* (McClelland et al., 2001; Parkhill et al., 2001; Porwollik et al., 2002; Chan et al., 2003; Porwollik and McClelland 2003; Matiasovicova et al., 2007).

7. Host adaptation

More than a decade ago, Baumler (1998) postulated that the genus *Salmonella* evolved in three phases (Baumler 1997; Baumler et al., 1998). The first phase involved acquisition of SPI1 by an ancestral lineage to all *Salmonella*, since it is present in all phylogenetic lineages of the genus *Salmonella* but absent from *E. coli* and other enterobacteria. In the second phase, the split of *S. enterica* from *S. bongori* involved the acquisition of SPI2, which is not present in *S. bongori* serovars (Ochman and Groisman 1996). Finally, the lineage of *S. enterica* branched into several phylogenetic groups. The formation of *S. enterica* subspecies *enterica* (I) involved a dramatic expansion in host range: while *S. bongori* and *S. enterica* subspecies II, IIIa, IIIb, IV, VI and VII are mainly associated with cold-blooded vertebrates, members of *S. enterica* subspecies I are most frequently isolated from avian and mammalian hosts. The host adaptation of *S. enterica* subspecies I to warm-blooded vertebrates, characterized the third phase in the evolution of virulence in the genus *Salmonella*. The immune system of higher vertebrates is more developed and organized than that of cold-blooded vertebrates. The common ancestor of subspecies I, II, IIIb and VI acquired mechanisms of flagellar antigen shifting (diphasic condition), which is thought to play a role in adaptation to warm-blooded hosts (Li et al., 1995; Baumler et al., 1998; Porwollik and McClelland 2003). The mechanism of phase shifting is amazing and involved the acquisition of the *fljBA* operon, which contains *hin*, encoding for a recombinase that catalyzes the reversible inversion of a segment of the chromosome containing the promoter for the *fljBA* operon. In one orientation, the promoter directs the transcription of the *fljA* (repressor of *fliC*) and *fljB* (phase 2 flagellin)

genes, inducing the repression of *fliC* (phase 1 flagellin). In the other orientation, *hin*, *fljB* and *fljA* are not expressed and *fliC* is expressed (Zieg et al., 1977). A schematic representation of *Salmonella* evolution is presented in Figure 2 (Silva and Wiesner 2009).

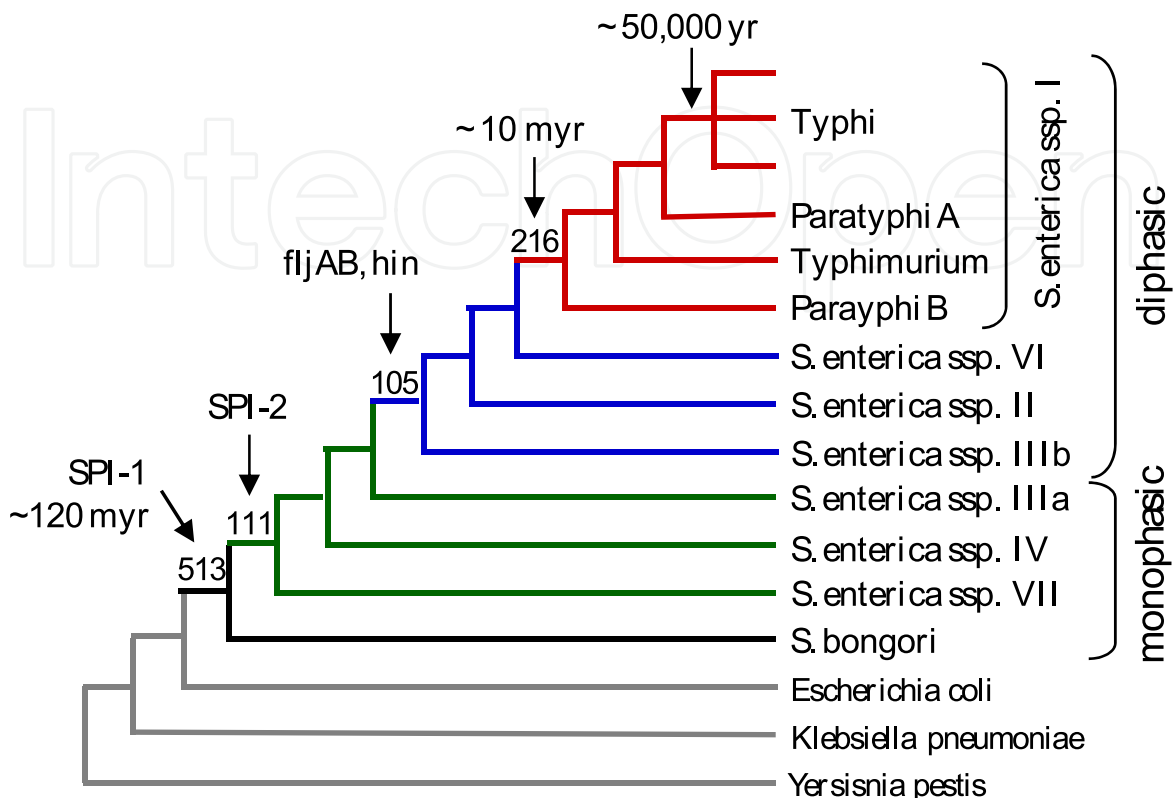


Fig. 2. Schematic representation of *Salmonella* evolution. The cladogram shown is a modified version of that proposed by Porwollik & McClelland (2003), and published by Silva & Wiesner (2009). The number of genes acquired at crucial steps in *Salmonella* evolution is indicated on the nodes along with prominent examples (Porwollik et al., 2002). During the divergence of *E. coli* and *Salmonella*, about 120 million years (myr) ago (Ochman and Wilson 1987), more than 500 genes were acquired, including *Salmonella* pathogenicity island 1 (SPI-1). In the divergence between *S. bongori* and *S. enterica* more than 100 genes were acquired in the *S. enterica* lineage, including those of the SPI-2 (Ochman and Groisman 1996). Along the diversification of the *S. enterica* lineage, about 100 genes were acquired by the common ancestor of subspecies IIIb, II, IV and I, among them were the phase shifting genes (*fljBA* and *hin*), required to confer the diphasic condition to *Salmonella*. During the evolution of subspecies I, which is the most diverse of the subspecies and adapted to warm-blooded vertebrates, more than 200 genes were acquired. Kidgell et al. (2002) estimated that the time of divergence among serovars was around 10 myr, and that the last common ancestor of serovar Typhi existed about 50,000 yr (Kidgell et al., 2002).

However, not everything is said about *Salmonella* evolution. The report of serovar Senftenberg human clinical isolates lacking SPI-1 (Hu et al., 2008) is an example of subsequent loss of genetic determinants during the diversification of *Salmonella*. Another example is the loss of the diphasic trait in some of the serovars of subspecies I (e. g. Typhi) and II. They have reverted to the monophasic condition, usually by loss of expression of phase 2 flagella. In Enteritidis and serovar 4,5,12:i:- the phase 2 flagellin gene (*fljB*) has been

deleted rather than merely silenced (Selander et al., 1996; Echeita et al., 2001). Likewise, in a study analyzing *E. coli* and *Salmonella* genomes, Retchless and Lawrence (2007) found that their chromosomes diverged over a 70 million year period, and that the regions flanking SPI1 and SPI2 diverged more recently, suggesting that they did not promote the separation of *E. coli* and *Salmonella* (Retchless and Lawrence 2007).

The distribution of pathogenicity islands, fimbrial operons, and capsular biosynthesis genes among *S. enterica* suggests that during evolution, new combinations of virulence determinants arose through multiple horizontal transfer events, a process which may have driven the development of host adaptation. In addition, deletion events and sequence divergence by point mutations were likely among the events which contributed to changes in the host range of *S. enterica* serovars (Baumler et al., 1998; Porwollik and McClelland 2003). The *S. enterica* subspecies I serovars form a group of pathogens that differ widely in their spectrum of host range within mammals and birds. For classification purposes, they can be categorized into three different groups: broad-host range, host-adapted, and host-restricted serovars. For example, serovars Typhi, Gallinarum, and Abortusovis are host-restricted serovars that are associated with systemic disease in humans, fowl and ovine hosts, respectively. Serovars Dublin and Cholerasuis are host-adapted serovars that are often associated with systemic disease in cattle and pigs, respectively, but can cause disease in other animals. Typhimurium and Enteritidis are broad-host range serovars capable of causing systemic disease in a wide range of animals, but are usually associated with gastroenteritis in a broad range of phylogenetically unrelated host species (Baumler et al., 1998; Kingsley and Baumler 2000; Rabsch et al., 2002). However, even within a single serovar there are differences in host range. For example, Rabsch *et al.* (2002) showed that two Typhimurium variants (DT2 and DT99) were almost exclusively associated with pigeons during decades, over a wide geographic range, indicative of a narrow host range; while other Typhimurium variants, such as DT104, are truly broad-host-range, thus circulating in cattle, swine, poultry and humans. Therefore, it may be more accurate to describe serovar Typhimurium as a collection of variants that vary significantly in their host range and degree of host adaptation. One possible mechanism by which such variants arise is through phage-mediated transfer, of a small number of host-specific virulence factors (Rabsch et al., 2002; Porwollik and McClelland 2003; Brussow et al., 2004; Porwollik et al., 2004; Ehrbar and Hardt 2005; Vernikos et al., 2007). There is currently no genetic explanation for the phenotype of host adaptation; it is unlikely that a single locus will be found to be responsible for this complex biological trait. Instead, a combination of multiple genes is likely to contribute to the overall virulence phenotype (Fierer and Guiney 2001).

8. How much lateral transfer occurs in natural populations?

In this chapter, we have provided extensive evidence on the importance of lateral transfer of genetic information in the evolution of *Salmonella*. Compiling evidence on the role of gene loss and acquisition in the origin of the genus *Salmonella* has been presented in several evolutionary studies (Groisman and Ochman 1997; Lawrence 1999; Porwollik et al., 2002; Lerat et al., 2005; Retchless and Lawrence 2007; Vernikos et al., 2007), exemplified by the acquisition of pathogenicity islands (Ochman and Groisman 1996; Porwollik and McClelland 2003; Hensel 2004). Likewise, the evolutionary processes shaping the genetic structure within serovars and host-adapted ecotypes involve in many cases lateral transfer events, such as prophage insertions (Porwollik and McClelland 2003; Thomson et al., 2004;

Hermans et al., 2006; Cooke et al., 2007; Vernikos et al., 2007). The selective pressure that antimicrobial drugs have imposed on the survival of *Salmonella* probably has increased the acquisition of resistance determinants, often carried by mobile genetic elements that are acquired by lateral transfer. These processes are the result of a long evolutionary history of adaptation to changing environments and hosts. However, we do not want to leave the misconception that the amount of lateral transfer is so rampant that there are no limits to genetic exchange in *Salmonella* populations.

Since more than two decades ago, the clonal nature of *Salmonella* species was documented by several studies based on multilocus enzyme electrophoresis analysis (Beltran et al., 1988; Reeves et al., 1989; Selander et al., 1990; Boyd et al., 1996; Spratt and Maiden 1999). Evidences for the clonal structure of *Salmonella* include the global distribution of certain genotypes, the congruent relationships between isolates derived from several housekeeping genes, and the robust subspecies structure (Reeves et al., 1989; Boyd et al., 1996; Selander et al., 1996; Falush et al., 2006). In the past decade, multi-locus sequence typing (MLST) studies, analyzing *Salmonella* populations for epidemiological purposes, showed concordant results with the studies based on enzyme electrophoresis, which support the view that *Salmonella* has a clonal population structure. Among these results are the almost strict association between multilocus genotype and serovar, the low genetic diversity within serovars, and the maintenance of old globally-distributed clones (Sukhnanand et al., 2005; Harbottle et al., 2006; Tankouo-Sandjong et al., 2007; Wiesner et al., 2009). The clonal nature of *Salmonella* populations was observed in our study based on a survey of more than 100 Mexican Typhimurium strains. MLST and macrorestriction fingerprints by pulsed-field gel electrophoresis were used to address the core genetic variation, and genes involved in pathogenesis and antibiotic resistance were selected to evaluate the accessory genome. SGI1 was found in a defined subset (16%) of the strains. They were in a compact cluster conformed by strains belonging to the second most abundant genotype (ST19), and in most of the cases they also carried the *Salmonella* virulence plasmid (Figure 3). On the other hand, the strains with the most abundant genotype (ST213) lacked *Salmonella* virulence plasmid or SGI1, but in most of the cases carried a multiple-drug resistant (MDR) IncA/C plasmid. The ST19 isolates carrying the virulence plasmid were significantly associated with the human host, whereas ST213 isolates were more frequently isolated from animal sources, indicating that the distinct accessory genes carried by these genotypes are probably involved in the interaction with the host (Wiesner et al., 2009). No strain carrying both the *Salmonella* virulence plasmid and the MDR IncA/C plasmid, nor hybrid virulence-resistance plasmids, was detected. We concluded that, in the Mexican Typhimurium population, the association between distinct core and accessory genes creates a structure of genetic subgroups within the population, which could be due to the existence of barriers to genetic exchange among subgroups (Wiesner et al., 2009).

It is intriguing why if *Salmonella* evolution is marked by lateral transfer events and genome rearrangements, the genetic structure of populations seems to be extremely clonal. It is possible that in an evolutionary time scale (millions of years) there were several occasions where the mismatch repair system was impaired and large scale recombination events occurred and marked the genomes of diverse *Salmonella* lineages (Taddei et al., 1997; Matic et al., 2000; Didelot et al., 2007). However, in the ecological time scales (thousands of years to decades) the recombination events are rare.

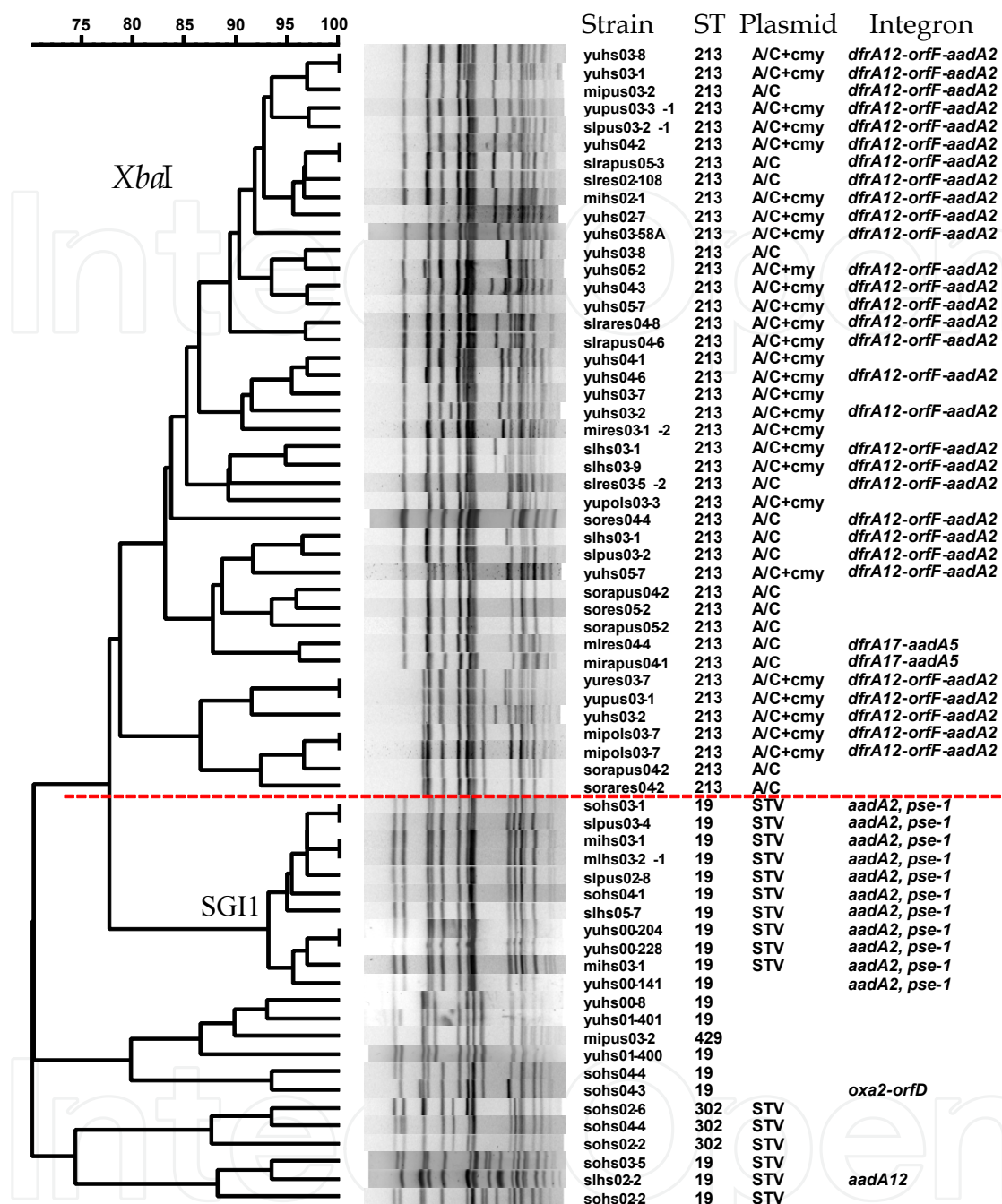


Fig. 3. Dedrogram depicting the genetic relationships between 65 representative Mexican Typhimurium strains, and the associations among core and accessory genes. The data were obtained from Wiesner et al. (2009) and Wiesner et al. (2011). The *Xba*I restriction fingerprints were clustered by the UPGMA algorithm using Dice coefficients. The first column contains the strain designation. The second column displays the multi-locus sequence type (ST) for each strain. The plasmid column indicates if the strains harbored the *Salmonella* virulence plasmid (STV), the *bla*_{CMY-2}-bearing IncA/C plasmid (A/C+cmy) or the smaller *bla*_{CMY-2}-lacking IncA/C plasmid (A/C). The last column shows the integrons carried by the strains. The horizontal dashed line separates the ST213 strains from the remaining STs. SGI1 indicates the cluster containing the strains with the *Salmonella* genomic island.

9. Concluding remarks

Mobile genetic elements are key to understanding *Salmonella* evolution and ecology. Actually there is a wealth of information regarding the record of horizontal gene transfer in *Salmonella*; for a revision we recommend the review of Porwollik & McClelland (2003) and the paper of Vernikos *et al.* (2007). In *Salmonella* many of the virulence factors are present as part of pathogenicity islands on the chromosome, yet some virulence factors are encoded on plasmids or bacteriophages. Their composition, presence or absence determines at large differences in pathogenicity and host range between serovars and strains (Fluit 2005). We certainly need to expand our vision, in order to integrate the knowledge about the great variety of genetic virulence determinants in *Salmonella* and the antibiotic-resistance “tool kit”. A vision is emerging regarding different molecular routes that determine the plasticity of the accessory genome, which are subject to intricate interactions that we still do not completely understand. Complex interactions among pathogenicity islands, bacteriophages, plasmids and other mobile elements, such as transposons and integrons, are increasingly being evidenced. For example, the transfer of the resistance phenotypes associated with Typhimurium DT104 SGI1, by phage-transduction experiments, suggest the involvement of phages in the mobilization of SGI1 (Lawson *et al.*, 2002b; Fluit 2005). In another example, derivatives of the original Typhimurium DT104 clone have emerged over the more than 20 years after the first report. Different phage-types, such as DT12 or DT120, are indistinguishable from the DT104 clone by genotyping, suggesting that they arose from DT104 through changes that led to different phage susceptibility patterns (Fluit 2005). These shifts in phage-type are probably due to the gain or loss of prophages. More than three decades ago, Threlfall *et al.* (1978) showed that changes in phage-types can be the result of the loss or acquisition of plasmids (Threlfall *et al.*, 1978). Likewise, in another study related to Typhimurium DT104 and SGI1, some strains showed to be phage-untypeable or DT104B, and it was found that these strains carried a larger plasmid (140 kb) resulting from the recombination between a resistance and virulence plasmid (Guerra *et al.*, 2002). In these latter cases, the changes in the plasmid content could be associated with the loss of determinants required by phages (Fluit 2005), such as surface lipopolysaccharides (Lawson *et al.*, 2002a). Of particular concern is the increasing number of reports of co-integrates of resistance and virulence plasmids, envisioning that new *Salmonella* strains will arise posing a threat to public health (Fluit 2005).

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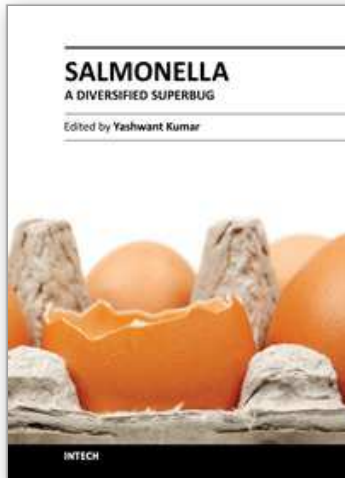
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Salmonella is an extremely diversified genus, infecting a range of hosts, and comprised of two species: enterica and bongori. This group is made up of 2579 serovars, making it versatile and fascinating for researchers drawing their attention towards different properties of this microorganism. Salmonella related diseases are a major problem in developed and developing countries resulting in economic losses, as well as problems of zoonoses and food borne illness. Moreover, the emergence of an ever increasing problem of antimicrobial resistance in salmonella makes it prudent to unveil different mechanisms involved. This book is the outcome of a collaboration between various researchers from all over the world. The recent advancements in the field of salmonella research are compiled and presented.

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