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SALMONELLA TYPHIMURIUM UNVEILED: IN SILICO INSIGHTS WITH QSAR, DOCKING, AND SIMULATION-REVIEW ARTICLE

S. Reethu, Dr.J. Gopala Krishna

Dr. KV Subba Reddy Institute of Pharmacy, Kurnool

Abstract:

Salmonella enterica serovar Typhimurium is a primary enteric pathogen infecting both humans and ani8mals. Infection begins with the ingestion of contaminated food or water so that salmonellae reach the intestinal epithelium and trigger gastrointestinal disease. In some patients the infection spreads upon invasion of the intestinal epithelium, internalization within phagocytes, and subsequent dissemination. In that case, antimicrobial therapy, based on fluoroquinolones and expanded-spectrum cephalosporins as the current drugs of choice, is indicated. To accomplish the pathogenic process, the Salmonella chromosome comprises several virulence mechanisms. The most important virulence genes are those located within the so-called Salmonella pathogenicity islands (SPIs). Thus far, five SPIs have been reported to have a major contribution to pathogenesis. Nonetheless, further virulence traits, such as the split virulence plasmid, adhesins, flagella, and biofilm-related proteins, also contribute to success within the host. Several regulatory mechanisms which synchronize all these elements in order to guarantee bacterial survival have been described.

Keywords: *Salmonella; Mutagenicity, TA98+S9 Modelling, TA98-S9 Modelling, QSAR, Molecular Docking.*

Corresponding author:

Dr. J.Gopala Krishna., M.S Pharm, Ph.D

Department of Pharmaceutical Chemistry.

Dr. K.V. Subbareddy Institute of Pharmacy, Kurnool-518218

Mobile: 6302184843

E-mail: reethuravindrareddy@gmail.com

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INTRODUCTION:

Salmonella enterica serovar Typhi, also known as Salmonella Typhi, is a gram-negative bacterium belonging to the family Enterobacteriaceae. It is classified among the first class of Salmonella serovars within the subspecies enterica [1]. This human-specific pathogen is responsible for causing typhoid fever, a serious illness often contracted by ingesting water or food contaminated with human faeces [2]. In regions with poor sanitation, particularly in developing nations, typhoid fever remains a significant health concern, leading to numerous fatalities. Infection occurs when Salmonella Typhi from contaminated sources enters the host's gastrointestinal tract. The bacterium then targets the distal ileum, subsequently reaching the specialized intestinal epithelial M-cells in the Peyer's patches [3]. After invading the intestines, the pathogen travels to the mesenteric lymph nodes and persists within macrophages. Its further spreads through the bloodstream and lymphatic systems to reach vital organs like the liver, spleen, and bone marrow, where it multiplies, leading to systemic infection [4].

Salmonella infection remains a major public health concern worldwide, contributing to the economic burden of both industrialized and underdeveloped countries through the costs associated with surveillance, prevention and treatment of diseases [5]. Gastroenteritis is the most common manifestation of Salmonella infection worldwide, followed by bacteraemia and enteric fever. Salmonella is a rod shaped, Gram-negative facultative anaerobe that belongs to the family Enterobacteriaceae. Within the genus Salmonella, around 2600 serotypes have been identified with the use of the standard Kauffman–White scheme and most of these serotypes have the ability to adapt within a variety of animal hosts, including humans [6]. Salmonella and Campylobacter are the most frequently isolated foodborne pathogens, and are predominantly found in poultry, eggs and dairy products. Other food sources that are involved in the transmission of Salmonella include fresh fruits and vegetables [7]. In general, food animals such as swine, poultry and cattle are the prime sources of Salmonella infections. The major dissemination routes of the pathogens involve trade in animals an uncooked animal food product, The slaughtering process of food animals at abattoirs is considered one of the important sources of organ and carcass contamination with Salmonella. The emergence of antibiotic-resistant foodborne pathogens has raised the concern of the public as these pathogens are more virulent, causing an increase in the mortality rate of infected patients [8].

Typhimurium Species Background:

- Salmonella enterica serotype Typhimurium is a gram-negative bacterium.
- It is a species of the genus Salmonella, belonging to the Enterobacteriaceae family.
- Typhimurium causes a common type of salmonellosis in humans and animals [9].

Epidemiology:

- Typhimurium is one of the most prevalent serotypes of Salmonella worldwide.
- It is responsible for a significant number of foodborne outbreaks.
- Human infections are often associated with the consumption of contaminated food, especially raw or undercooked poultry, eggs, and dairy products [10].

Clinical Presentation:

- In humans, Typhimurium infections usually manifest as gastroenteritis.
- Symptoms include diarrhea, abdominal cramps, fever, and occasionally vomiting.
- In severe cases, the infection can spread beyond the gastrointestinal tract, leading to bacteremia and systemic illness [11].

Pathogenesis:

- Typhimurium can invade and replicate within the epithelial cells lining the intestines.
- It produces virulence factors, such as adhesins and effector proteins, which aid in colonization and evasion of the host immune response.
- The bacteria can also produce toxins that contribute to the pathogenesis of the infection [12].

Antibiotic Resistance:

- Typhimurium has developed resistance to multiple antibiotics over time.
- This resistance is primarily acquired through the acquisition of resistance genes via - plasmids or transposons.
- The emergence of multidrug-resistant strains poses a significant challenge for the treatment of infections caused by this bacterium [13].

Diagnosis:

- Laboratory diagnosis of Typhimurium infection involves the isolation and

identification of the bacterium from clinical specimens, such as stool samples.
- Techniques like culture, serotyping, and molecular methods, such as PCR, are used for accurate identification.

- Antimicrobial susceptibility testing is crucial for guiding appropriate treatment [14].

Prevention and Control:

- Prevention of Typhimurium infections involves good hygiene practices, such as proper handwashing and safe food handling.
- Public health measures, including surveillance, outbreak investigations, and monitoring of food production, are essential for control [15].

Summary:

- Vaccines for Typhimurium are available for use in animals, but no human vaccines are currently approved.
- Typhimurium is a prevalent serotype of Salmonella causing gastroenteritis in humans.
- It possesses virulence factors that aid in colonization and evasion of the host immune response.
- Antibiotic resistance and contamination of food sources pose challenges for prevention and control [16].

Mutagenicity on Salmonella Typhi:

- Mutagenicity refers to the ability of a chemical substance to cause mutations in DNA.
- Nitro and amino aromatic compounds are important classes of chemicals that have been associated with mutagenic effects.
- QSAR (Quantitative Structure-Activity Relationship) modelling is a computational method used to predict the mutagenic potential of chemicals based on their structural properties

Some of the reported mechanisms leading to mutagenicity:

Modes of mutagenicity:

1. Alkylation:

Mechanism: Most of the Alkylating agents damage the DNA with the formation of N2-alkylG (where G stands for guanine) and other lesions; for example, formaldehyde reacts with the exocyclic amino group of deoxyguanosine to produce N2-methylG (Yasui et al., 2001). Some other examples of alkylating agents include ethanol which enzymatically get oxidized to acetaldehyde and thus forms N2-ethylG found in liver DNA and urine of alcoholic patients (Cheng et al., 2008). Other alkylating agents having sufficient mutagenic potential include polycyclic aromatic hydrocarbons (PAH-DNA adducts), nitrosamines (formation of the O6-methylG (O6-MeG)) and bis-electrophilic agents like 1, 3-Butadiene (BD can be oxidized to 1, 2, 3, 4-diepoxybutane (DEB), a prominent bis-electrophilic carcinogenic metabolite).

2.Oxidation:

Mechanism: Oxidizing agents can produce 7, 8-dihydro-8-oxo-2′-oxodeoxyguanosine (8-oxodG) lesions. 8-oxodG is a ubiquitous lesion arising from the oxidation of the C8 atom of G to form a hydroxyl group by free radical intermediates of oxygen that are produced by chemical oxidation, ionizing radiation, or UV irradiation (Degan et al., 1991; Fraga et al., 1990). The enol (a lactam) at the C8-N7 position of G is converted to the more stable 8-oxodG lactam form.

3. Amination:

Mechanism: Several aminating agents like aryl amines and N-acetyl aryl amines possess higher propensity to act like potential mutagenic substances. This group is extensively studied for their mutagenic activity and also implemented in several in silico studies due to their presence in various occupational settings like tobacco smoke, chemical dyes etc. These chemicals go on to form adducts like 2-aminofluorene (AF-dG) and N-acetyl2-aminofluorene (AAF-DG) through amination of the C8 atom of guanine (via an initial N7 reaction, linking the amine group of the aryl amine) (Vrtis et al., 20130).

4. Co-ordination:

Mechanism: Heavy metal ions also produce mutagenicity with the formation of DNA- DNA intra-strand and inter-strand cross-links via coordination bonds. For example, chromium (VI) complex permeates the cell membranes and gets reduced to form chromium (III) complex, following which it then coordinates with oxygen atoms of phosphate backbone of two adjacent nucleotides within one DNA strand or between two DNA strands, yielding chromium (III)-DNA intra-strand thus yielding an inter-strand cross-link.

5. Photo-addition:

Mechanism: The ultra violet (UV) radiation leads to the formation of photoproducts (e.g., CPD) by cycloaddition of the C5-C6 double bonds with adjacent pyrimidine bases; thus, it behaves like a non-chemical mutagenic agent. Six diastereomers are generated, depending on the position of pyrimidine moieties with respect to the cyclobutene ring (cis/trans stereochemistry) and on the relative orientation of the

two C5-C6 bonds (syn/anti radiochemistry) (Cadet et al., 1985). The cis-syn form is formed preferentially to the trans-syn diastereomers within double-stranded DNA. The trans-anti and trans-syn photoproducts are only present within single-strand or denatured DNA.

6. Hydrolysis:

Mechanism: The final proposed mechanism for mutagenesis is by hydrolysis, where AP (apurinic/apyrimidinic) sites are generated by spontaneous reactions, chemical induction or by enzyme-catalysed hydrolysis of the N-glycosyl bond resulting in the loss of genetic information. In mammalian cells, it has been estimated that approximately 12,000 purines are lost spontaneously per genome per cell generation (20h) in the absence of any protective effects of chromatin packaging. It was subsequently shown that depyrimidination occurs at a rate about 100 times more slowly than depurination (Wilson Iii and Barsky, 2001). Damaging chemicals, e.g., free radicals and alkylating agents, promote base release, mostly by generating base structures that destabilize the N-glycosyl linkage due to positively-charged leaving groups [17].

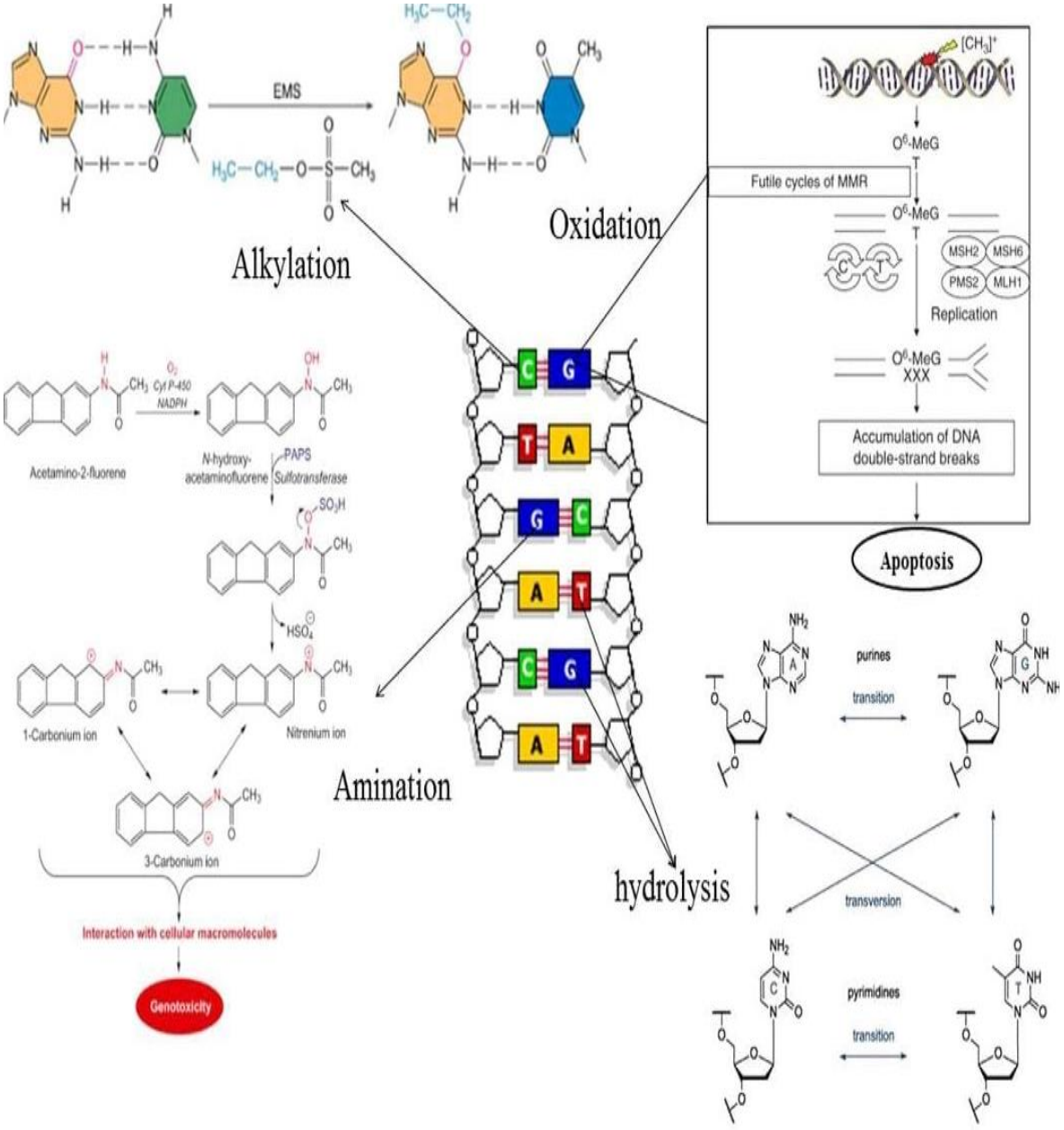


Fig: Mechanisms of Mutagenicity

TA98+S9 Modelling in Salmonella Typhi:

- TA98+S9 is a specific strain of Salmonella Typhi commonly used in genetic toxicology studies.
- Modelling TA 98+S9 in Salmonella Typhi allows for the evaluation of mutagenic potential of various compounds [18].

Principles of TA 98+S9 Modelling

- TA98+ S9 modelling is based on the observation that certain substances require metabolic activation to become genotoxic.
- The process involves exposing Salmonella Typhi strains to the test compound in the presence of liver enzymes (S9 fraction).
- The S9 fraction mimics the metabolic activation that occurs in mammalian systems, enhancing the sensitivity of detection [19].

Advantages of TA 98+S 9 Modelling

- TA 98+S9 modelling provides a cost-effective and time-efficient way to screen large numbers of compounds for genotoxicity.
- It allows for the identification of potential mutagens and carcinogens, aiding in the development of safer chemicals and pharmaceuticals [20].

Experimental Procedure of TA 98+S9

- The use of Salmonella Typhi as a model organism provides a simpler and more standardized system compared to mammalian models.
- The test compound is typically dissolved in an appropriate solvent and added to a growth medium containing Salmonella Typhi.
- The S9 fraction, prepared from liver homogenates of rats or other mammalian species, is then added to the medium.
- Following incubation, the plates are evaluated for the presence of relevant colonies, indicating mutagenic activity [21].

Data Interpretation in TA98+S9

- The number of revertant colonies is compared to a negative control (solvent-treated) and positive control (known mutagen) to determine genotoxic potential.
- Statistical analysis is often performed to determine if the observed effects are statistically significant [22].

Limitations of TA 98+S 9 Modelling

- TA 98+S9 modelling primarily detects point mutations, and may not capture other types of DNA damage
- The metabolic activation in the S 9 fraction may not fully represent the complexity of in vivo metabolism.
- Different strains of Salmonella Typhi may vary in their sensitivity to specific mutagens, requiring the use of multiple strains for comprehensive analysis [23].

Applications of TA 98+ S9 modelling

- TA 98+ S9 modelling is extensively used in the pharmaceutical industry for drug development and safety assessment.
- It is also employed in the screening of chemicals, food additives, and environmental pollutants for genotoxic potential.
- The data generated from TA 98+S9 modelling contributes to regulatory decision-making and risk assessment processes [24].

Current Advances in TA 98+S 9 Modelling

- Advances in genomics and bioinformatics have facilitated the integration of TA 98+S9 modelling with other omics technologies
- Development of engineered Salmonella Typhi strains with specific genetic modifications allows for targeted analysis of mutagenic pathway [25].

Future Perspectives of TA 98+S9 Modelling:

Continued advancements in genotoxicity testing methodologies will enhance the accuracy and reliability of TA 98+S9 modelling.

- Integration of computational modelling and predictive toxicology approaches will streamline the identification of genotoxic compounds.
- The expansion of TA 98+ S9 modelling to include other endpoints and molecular mechanisms will provide a more comprehensive understanding of genotoxicity.
- TA 98+S9 modelling in Salmonella Typhi is a valuable tool for the assessment of genotoxic potential in various compounds.
- It offers advantages in terms of cost, time, and standardization compared to mammalian models [26].

TA98-S9 Modelling in Salmonella Typhi:

- It is commonly used in research to study the pathogenicity and virulence of Salmonella Typhi.
- TA 98-S9 is known for its ability to cause severe systemic illness in humans

Genetic Features of TA 98-S9

- TA 98-S9 possesses specific genetic markers that distinguish it from other strains of Salmonella Typhi.
- These genetic markers are essential for the identification and characterization of TA 98-S9 in laboratory settings.
- Understanding the genetic features of TA 98-S9 is crucial for conducting accurate research and diagnostics [27].

Clinical Significance of TA 98-S9 Infection

- Infections caused by TA 98-S9 are typically associated with typhoid fever.
- Typhoid fever is characterized by high fever, abdominal pain, and gastrointestinal disturbances.
- Without proper treatment, TA 98-S9 infections can lead to serious complications, such as intestinal perforation or septicemia.

Laboratory Diagnosis of TA 98-S9 Infections

- Laboratory diagnosis of TA 98-S9 infections relies on various methods, including culture and identification techniques.
- Isolation of TA 98-S9 from clinical specimens, such as blood or stool samples, is crucial for accurate diagnosis.
- Molecular techniques, such as PCR, can also be employed to detect specific genetic markers of TA 98-S9[28].

Overview of QSAR Modelling

- QSAR modelling is a technique that uses mathematical models to establish quantitative relationships between chemical structures and their biological activities.
- It involves the development of predictive models based on a training set of known mutagenic compounds.
- QSAR models can then be used to predict the mutagenic potential of new chemicals based on their structural features.

Case Study: QSAR Modelling of Nitro and Amino Aromatic Compounds.

- A dataset of known nitro and amino aromatic compounds with mutagenic and non-mutagenic activity in Salmonella Typhi was collected.
- Descriptors representing various structural and physicochemical properties of the compounds were calculated.
- A QSAR model was developed using a machine learning algorithm and validated using cross-validation and external validation [29].

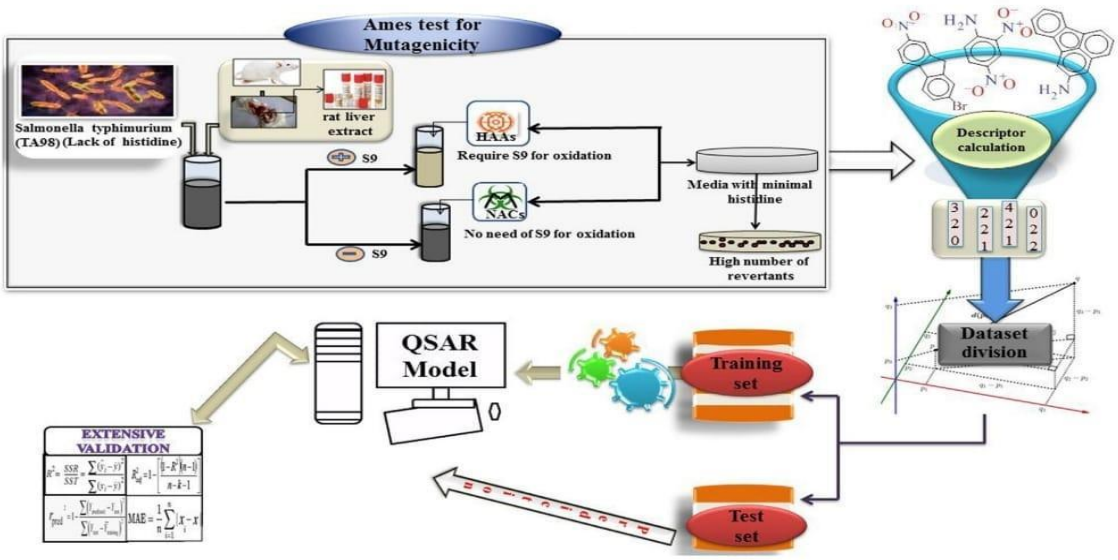


Figure: flowchart for Chemometric modelling of salmonella typhimurium.

Nitro and Amino aromatic compounds against Salmonella Typhimurium

- Nitro and amino aromatic compounds have shown promising potential in combating Salmonella Typhi.
- Salmonella Typhi is a bacterium responsible for causing typhoid fever, a serious and potentially fatal disease.
- The development of new drugs using nitro and amino aromatic compounds can help in the fight against Salmonella Typhi.

Mechanism of Action:

- Nitro aromatic compounds exert their antimicrobial activity by inhibiting bacterial enzymes involved in essential metabolic pathways.
- They disrupt the electron transport chain, leading to the production of toxic reactive oxygen species that damage bacterial cells.
- Amino aromatic compounds act by inhibiting specific enzymes that are crucial for the survival and growth of Salmonella Typhi.

Nitro Aromatic Compounds

- Nitrofurans, such as nitrofurantoin, have been used for the treatment of urinary tract infections caused by Salmonella Typhi.
- Nitrofurans inhibit bacterial DNA synthesis and disrupt bacterial cell membrane integrity.
- Nitroimidazoles, like metronidazole, have shown activity inhibiting protein synthesis.

Amino Aromatic Compounds

- Aminoquinolines, such as chloroquine, have demonstrated activity against Salmonella Typhi by interfering with the parasite's ability to break down and utilize hemoglobin.
- Aminoglycosides, like gentamicin, inhibit bacterial protein synthesis by binding to the bacterial ribosome and preventing translation.
- Aminobenzene sulphonamides, such as sulfamethoxazole, block the synthesis of folic acid, an essential component for bacterial growth.

Resistance Mechanisms

- Salmonella Typhi has developed various resistance mechanisms against nitro and amino aromatic compounds.
- Resistance can arise due to the acquisition of resistance genes or mutations in target enzymes.
- Efflux pumps, which actively remove the drugs from bacterial cells, can also contribute to resistance.

Research Advances

- Ongoing research aims to identify novel nitro and amino aromatic compounds with improved efficacy against Salmonella Typhi.
- Combination therapies involving multiple drugs are being explored to combat resistance and enhance treatment outcomes.
- Efforts are being made to understand the molecular mechanisms of resistance to guide the development of new drugs.

Clinical Applications

- Nitro and amino aromatic compounds are used in the treatment of typhoid fever and other Salmonella Typhi infections.
- These compounds may be administered orally or intravenously, depending on the severity of the infection.
- Proper dosage, duration of treatment, and monitoring for adverse effects are essential for successful therapy [30].

Salmonella Typhi from Blood Cultures

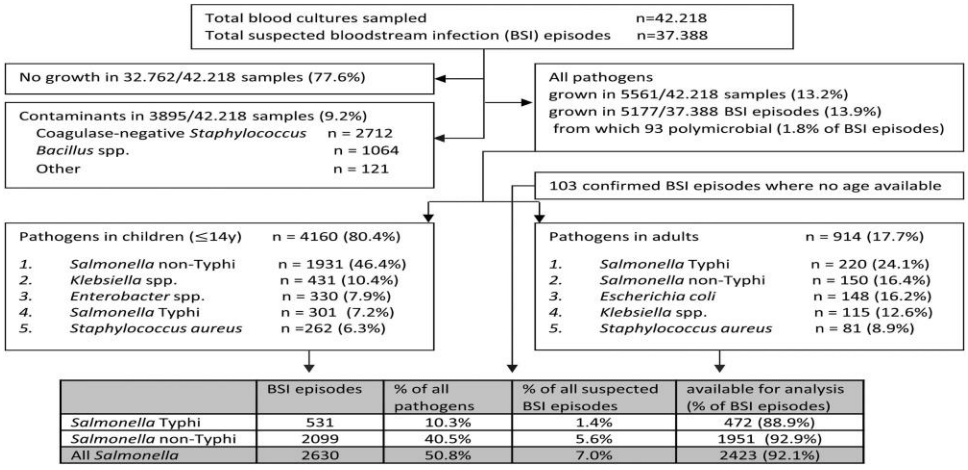
This study gives an overview of a decade (2007–2017) of hospital-based *Salmonella* Typhi bloodstream infection (BSI) surveillance in the Democratic Republic of the Congo (DRC), at 4 main sampling sites.

Blood cultures were sampled in hospital-admitted patients with suspected BSI, according to standardized clinical indications. The results of the surveillance period 2015–2017 were compiled with those of previous surveillance periods (2007–2010 and 2011–2014). Whole genome sequencing of isolates with decreased ciprofloxacin susceptibility (DCS) was performed.

Salmonella Typhi was isolated in 1.4% (531/37 388) and 10.3% (531/5177) of suspected and culture-confirmed BSI episodes, respectively. *Salmonella* Typhi ranked first among the BSI pathogens in adults (n = 220), but was mostly (n = 301 [56.7%]) isolated from children, of which 72.1% (217/301) and 31.6% (95/301) were <10 years and <5 years old, respectively. Multidrug resistance (MDR), DCS, and combined MDR/DCS were found in 38.3% (n = 180), 24.5% (n = 115), and 11.9% (n = 56) of 470 first isolates, respectively. MDR and DCS rates had increased since 2007, but remained stable during 2015–2017 with no geographical clustering at the province level. Most (91/93 [97.8%]) DCS isolates sequenced belonged to Geno typhi genotype 2.5.1, and gyr S83 was the most frequent DCS mutation (76/93 [81.7%]). Infections occurred perennially, but increased during the rainy season.

Proportions of Salmonella Typhi Among Grown Blood Cultures

Overall, Salmonella Typhi accounted for 1.4% (531/37 388) and 10.3% (531/5177) of suspected and confirmed BSI, respectively. Among adults, *Salmonella* Typhi consistently ranked first among the pathogens recovered, representing 24.6% (110/447), 22.9% (67/293), and 24.3% (42/173) for the successive surveillance periods [31].



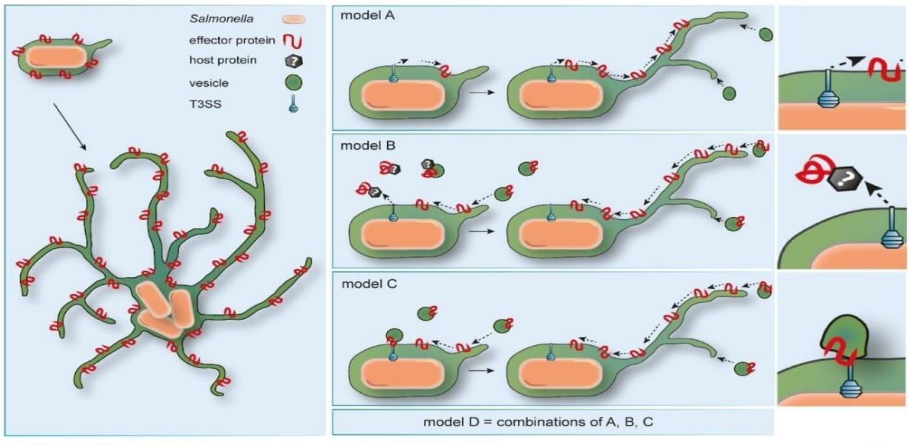
	BSI episodes	% of all pathogens	% of all suspected BSI episodes	available for analysis (% of BSI episodes)
Salmonella Typhi	531	10.3%	1.4%	472 (88.9%)
Salmonella non-Typhi	2099	40.5%	5.6%	1951 (92.9%)
All *Salmonella*	2630	50.8%	7.0%	2423 (92.1%)

Molecular dynamic studies on Salmonella Species:

So far, many studies are referred the salmonella species for dynamic simulations one of them is "Single molecule analyses reveal dynamics of Salmonella translocated effector proteins in host cell endomembrane" in this study The facultative intracellular pathogen *Salmonella enterica* remodels the host endosomal system for survival and proliferation inside host cells. *Salmonella* resides within the *Salmonella*-containing vacuole (SCV) and by *Salmonella*-induced fusions of host endomembrane, the SCV is connected with extensive tubular structures termed Salmonella-induced filaments (SIF). The intracellular lifestyle of *Salmonella* critically depends on effector proteins translocated into host cells. A subset of effectors is associated with, or integral in SCV and SIF membranes. How effectors reach their subcellular destination, and how they interact with endomembrane remodelled by Salmonella remains to be determined. We deployed self-labelling enzyme tags to label translocated effectors in living host cells, and analysed their single molecule dynamics. Translocated effectors diffuse in membranes of SIF with mobility comparable to membrane-integral host proteins in endomembrane. Dynamics differ between various effectors investigated and is dependent on membrane architecture of SIF. In the early infection, host endosomal vesicles are associated with *Salmonella* effectors. Effector-positive vesicles continuously fuse with SCV and SIF membranes, providing a route of effector delivery by translocation, interaction with endosomal vesicles, and ultimately fusion with the continuum of SCV/SIF membranes. This mechanism controls membrane deformation and vesicular fusion to generate the specific intracellular niche for bacterial survival and proliferation.

Models for SPI2-T3SS effector targeting too endomembrane

It is not known how hydrophobic effector proteins insert into host cell endomembrane. We built several hypotheses for the route of SPI2-T3SS effector proteins from translocation to their final destination. In model **a**, effector proteins are directly integrated into SCV membranes after translocation. In model **b**, effector proteins are translocated into the host cell cytosol, and a fast interaction with unknown bacterial or host cell proteins enables insertion into host endomembrane. In model C, direct delivery of effector proteins into host vesicular membranes is mediated by the SPI2-T3SS itself, and no cytosolic effector intermediates are present. In model **a**, peripheral distribution of effector proteins is mediated by tubulation of SCV membranes containing effector proteins. In models **b** and **c**, effector proteins are first inserted into endosomal membranes that subsequently fuse with developing SIF. We would also consider combinations of the models, and distinct modes of delivery for different effector proteins. We set out to test these models by applying a recently developed LCI approach for translocated effector proteins on single molecule level [32].



SPI2-T3SS effector proteins are highly dynamic on SIF membranes

To follow the dynamics of SPI2-T3SS effector proteins on or in SIF membranes, we deployed single-molecule localization and tracking microscopy. As host cells, HeLa cells were used that constitutively express LAMP1-monomeric enhanced green fluorescent protein (LAMP1-GFP) to allow visualization of SCV and SIF. Host cells were infected with STM mutant strains deficient in genes for specific effectors. The strains harboured plasmids encoding effector proteins fused to Halo Tag, a SLE tag, and infected cells were labelled with Halo Tag ligand coupled to the fluorescent dye tetra methyl rhodamine (HTL-TMR). As previously shown the effector proteins SseF, SifA, and PipB2 fused to Halo Tag can be localized in infected host cells 8 and a complete colocalization with LAMP1-GFP-positive SCV and SIF membranes.

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