



## Review Article

# Mechanisms of Antibiotic resistance in *Salmonella typhi*

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## A B S T R A C T

### Keywords

Antibiotic resistance, *Salmonella typhi*, chloramphenicol, ampicillin

*Salmonella typhi*, the causative agent of typhoid fever, is a gram-negative, motile, rod shaped, facultative anaerobe. It is solely a human pathogen and there is no animal reservoir. Antibiotic therapy is the mainstay for the treatment of typhoid fever and the complications associated with it. The drugs of choice are chloramphenicol, ampicillin, trimethoprim-sulphamethoxazole, quinolones and cephalosporins. Resistance of *S. typhi* against chloramphenicol was first reported in England in 1950. Several workers have reported occurrence of multidrug resistant *S. typhi* strains in recent years around the world and in different parts of Nigeria. Mechanisms of antibiotic resistance in *S. typhi* include inactivation of drug, alteration of the target site, and active efflux. These mechanisms could either be chromosomal or plasmid mediated. Plasmids of incompatibility group HI1 and C are important vectors of antibiotic resistance in some strains of *S. typhi*. The chromosomal-mediated drug resistance phenomenon against fluoroquinolones has been reported recently and attributed to a single point mutation in the quinolone resistance determining region (QRDR) of the topoisomerase gene *gyrA*, which encodes DNA gyrase. It has been opined that the initial development of resistance by *S. typhi* and most other bacterial pathogens occurred as a result of human practices such as over prescription and indiscriminate use of antibiotics as well as inappropriate use in animals. Mass immunization in endemic areas with either the oral live attenuated Typhi 21a or the injectable unconjugated Vi typhoid vaccine, rational use of antibiotics, improvement in public sanitation facilities, availability of safe drinking water, promotion of safe food handling practices and public health education are vital in the prevention of antimicrobial resistance.

## Introduction

*Salmonella typhi* is a particular *Salmonella* serovar that causes typhoid fever, a major public health problem in developing countries (Qamar *et al.*, 2014). Typhoid fever is a systemic disease, without therapy, the illness may last for three to four weeks and

death rate ranges between 12% and 30%. Although the global burden of typhoid fever has reduced, emergence of multidrug-resistant *S. typhi* (MDRST) is still a threat to public health.

*S.typhi* is a motile, facultative anaerobe that is susceptible to various antibiotics. Currently, 107 strains of this organism have been isolated; many containing varying metabolic characteristics, levels of virulence, and multi-drug resistance genes that complicate treatment in areas that resistance are prevalent (Parkhill *et al.*, 2001; Deng *et al.*, 2003). Diagnostic identification can be attained by growth on MacConkey and Eosine Methylene Blue agars, and the bacteria is strictly non-lactose fermenting. It also produces no gas when grown in Triple Sugar Iron agar, which is used to differentiate it from other Enterobacteriaceae.

Despite the emergence of newer antibacterial drugs, enteric fever has continued to be a major health problem (Zaki and Karande, 2011). *S.typhi* gained resistance to antibiotics like ampicillin, ceftriaxone, and co-trimoxazole, besides developing resistance to efficacious drugs like ciprofloxacin. The emergence of multidrug resistance to the commonly used antibiotics has further complicated the treatment and management of enteric fever and this is recognized as one of the greatest challenges in the management of this disease (Sehra *et al.*, 2013).

### **Taxonomy of *S.typhi***

Domain: Bacteria  
Phylum: Proteobacteria  
Class: Gammaproteobacteria  
Order: Enterobacteriales  
Family: Enterobacteriaceae  
Genus: *Salmonella*  
Specie: *Salmonella enterica*  
Subspecies: *Salmonella enterica enterica*  
Serovar: *Salmonella enterica serovar Typhi*

This gram-negative enteric bacillus belongs to the family Enterobacteriaceae. All

Enterobacteriaceae ferment glucose, reduce nitrate, and are oxidatively negative (Ong *et al.*, 2013).

### **Structure and Antigenic Types of *S.typhi***

*S.typhi* is a Gram-negative, flagellated, facultatively anaerobic bacillus possessing three major antigens: H or flagellar antigen; O or somatic antigen; and Vi antigen. H antigen may occur in either or both of two forms, called phase 1 and phase 2. The organism tends to change from one phase to the other. O antigens occur on the surface of the outer membrane and are determined by specific sugar sequences on the cell surface. Vi antigen is a superficial antigen overlying the O antigen. The Vi antigen distinguish *S.typhi* from other *Salmonellae* (Midala *et al.*, 2005).

Antigenic analysis of *salmonellae* by using specific antisera offers clinical and epidemiological advantages. Determination of antigenic structure permits one to identify the organisms clinically and assign them to one of nine serogroups (A-I), each containing many serovars. H antigen also provides a useful epidemiologic tool with which to determine the source of infection and its mode of spread (Ochai and Kolhatkar, 2008).

### **Pathogenicity of *S.typhi***

*S.typhi* has a combination of characteristics that make it an effective pathogen. This species contains an endotoxin typical of Gram negative organisms, as well as the Vi antigen which is thought to increase virulence. Many of the *S.typhi* virulence factors, such as adhesion, invasion, and toxin genes are clustered in certain areas of the chromosome known as “Salmonella pathogenicity islands” (SPI) (Kaur and Jain, 2012). The SPI can be located on the

chromosome or on a plasmid, are flanked by repeat sequences, and tend to have a varied G/C composition as compared to surrounding region. SPI are characterized by a base composition different from the core genome and are often associated with tRNA genes and mobile genetic elements, like IS elements, transposons or phage genes. By now, 15 SPIs have been identified in *S.typhi* (Vernikos and Parkhill, 2006). It also produces and excretes a protein known as "invasin" that allows non-phagocytic cells to take up the bacterium, where it is able to live intracellularly. It is also able to inhibit the oxidative burst of leukocytes, making innate immune response ineffective.

### **Pathogenesis of *S.typhi***

The organisms attach themselves to the epithelial cells of the small intestines, penetrate the sub-mucosa, and pass from there into the blood stream via the lymphatics. A transient bacteremia follows and the bacteria seed the reticulo-endothelial system (liver, spleen, bone marrow) and the gall bladder and kidneys. The organisms re-enter the intestine from the gall-bladder where it involves the Peyer's patches, inflammation and ulceration. The incubation period is about 5 to 21 days (Kaur and Jain, 2012).

### **Epidemiology**

Typhoid fever cases and deaths occur among populations without access to drinkable water, adequate sanitation, and hygienic facilities primarily in south Asia and sub-Saharan Africa (Crump and Mintz, 2010). Report shows an estimate of 21.5 million infections and 200,000 deaths from typhoid fever globally each year. In Africa, about 4.36 million cases occur out of an estimated population of 427 million and it is often encountered in tropical countries including

Nigeria (Zige *et al.*, 2013). In the tropics enteric fever tends to be more common during the hot dry seasons when the concentration of bacteria in rivers and streams increases, or in the rainy season if flooding distributes sewage to drinking water sources. In some areas the incidence of typhoid may be as high as 1,000 cases per 100,000 populations per year. In such areas typhoid is predominantly a disease of children, and stool excretion of *S.typhi* during and after infection is the main source of the infection. In such areas *S.typhi* infections are commonly mild and self-limiting. Severe disease represents the "tip of the iceberg". In temperate countries persistent carriers are a more important reservoir of infection (Kaur and Jain, 2012). For travelers the highest attack rates are associated with visits to Peru [17 per 105 visits], India [11/105 visits], and Pakistan [10/105 visits]. Although Indonesia has a reported annual incidence up to 1%, the attack rate for travellers is low. In general the mortality of enteric fever is low (< 1%) where antibiotics are available, but in poorer areas, or in the context of natural disasters, war, migrations, large concentrated refugee populations, and other privations, the mortality may rise to 10-30%, despite antibiotic therapy. Typhoid tends to cluster in families (Connor and Schwartz 2005), presumably reflecting a common source of the infection and is associated with poverty and poor housing.

### **Clinical Manifestations of Typhoid Fever**

The symptoms begin after an incubation period of 10 to 14 days. Enteric fever caused by *S.typhi* may be preceded by gastroenteritis, which usually resolves before the onset of systemic disease. The disease is characterized by prolonged fever, abdominal distension, constipation, headache, apathy, rash, malaise, loss of

appetite, nausea, vomiting, hepatosplenomegaly and leukopenia (Akinyemi *et al.*, 2005). Enteric fevers are severe infections and may be fatal if antibiotics are not promptly administered.

### **Mode of Transmission**

Typhoid is transmitted mainly by the fecal-oral route. In most cases an asymptomatic carrier of *S.typhi*, or an individual who has recently recovered from the infection, continues to excrete large number of organisms in the stool and contaminates food or water, either through direct food handling, through transfer of bacteria by flies and other insects, or by contamination of potable water (Butler, 2011). Approximately 10% of patients recovering from typhoid fever excrete *S.typhi* in the stool for three months, and in the past 2-3% became permanent carriers (Zige *et al.*, 2013).

### **Laboratory Diagnosis**

The clinical diagnosis of typhoid is confirmed by culture of the organism from blood, bone marrow or urine. Isolation of the organism from the duodenal secretions or the stool in a febrile patient is also suggestive of enteric fever (although of course fever from a different infection may occur in someone who has recently recovered from typhoid or in a chronic carrier). Stool cultures are positive in approximately 60% of children and 25% of adults. Excretion of *S.typhi* in the stool is more likely with higher blood bacterial counts, and children tend to have higher bacteremia than adults (Ramyil *et al.*, 2014). Blood cultures are positive in 60% - 80% of patients with yields maximized by taking a large volume of blood. Lysis centrifugation and lysis plating methods accelerate identification of *S.typhi* from blood (Parry *et*

*al.*, 2011). Approximately two thirds of these organisms are within phagocytic cells, and thus located in the buffy coat. Blood bacterial counts decline as the disease progresses. Bone marrow counts are approximately ten times higher than blood culture, this, according to Parry *et al* (2011), is principally due to approximately ten times the concentration of viable organisms in bone marrow than in the blood. Bone marrow culture increases the diagnostic yield from blood cultures by approximately 30%. Biopsies of the rose-spots are also usually culture positive (Parry *et. al.*, 2011). *S.typhi* is usually present in the duodenum and can be recovered using the string test. This is also useful for identifying chronic gallbladder carriers. *S.typhi* is sometimes excreted in the urine, urine antigen tests have been described recently but these have not been evaluated sufficiently. Several PCR methods have been described, but these are not used widely, although molecular typing is important in distinguishing recrudescence from newly acquired infections in endemic areas (Levy *et al.*, 2008). Serological diagnosis is widely relied upon. Widal test which measures the antibody titres to the somatic O and flagella H antigens is relied upon widely, although there are very divergent views on its utility. There have been several well documented epidemics in which the Widal was usually negative, but other epidemiological settings where it has proved useful. Overall sensitivity is approximately 70-80% with specificity ranging from 80-95%. New IgM and IgG based rapid serological tests have proved useful in some areas (Baker *et al.*, 2010) but are not validated sufficiently for widespread adoption.

### **Antimicrobial therapy of typhoid fever**

Antimicrobial therapy is the mainstay for the treatment of enteric fever and the

complications associated with it. Penicillins such as amoxicillin and ampicillin, cephalosporins such as ceftriaxone and cefuroxime, aminoglycosides such as streptomycin and gentamycin, macrolide such as erythromycin, fluoroquinolones such as ciprofloxacin, ofloxacin, and perfloracin, and tetracyclines are used for treatment of *S.typhi* infection (Richard *et al.*, 2007).

Chloramphenicol has been the treatment of choice for typhoid fever since its discovery in 1947. Because of the alarming spread of plasmid mediated chloramphenicol resistant *S.typhi* throughout the world, newer antibiotics with good in vivo activity against *S.typhi* are needed. Typhoid fever responds slowly to ampicillin, amoxicillin, cotrimoxazole or trimethoprim alone. Among fluoroquinolones, ciprofloxacin, ofloxacin and perfloracin are most widely used antimicrobial agents. They act by inhibiting bacterial enzymes DNA gyrase which is responsible for division, coiling and supercoiling of bacterial DNA during multiplication. Of the third generation cephalosporins; ceftriaxone, cefotaxime and cefoperazone are effective therapeutic alternative in multidrug resistant *S.typhi* infected cases (Arora and Arora, 2011).

When a strain of microorganism acquires resistance to a drug, another drug must be found to treat the resistant infections effectively. If resistant to second drug develops, a third drug is needed and so on (Black, 2005).

The fluoroquinolones (ciprofloxacin and ofloxacin), third generation cephalosporins (ceftriaxone and cefixime), and azithromycin came up as the second line of treatment for multidrug resistant strains. Aztreonam and imipenem are also potential third line drugs that have been used recently in serious infections. The azalide antimicrobial, azithromycin is also an option

in the treatment of multidrug resistant enteric fever (Raveendran *et al.*, 2010).

### **History of antimicrobial resistance in *S.typhi***

In 1948, when chloramphenicol was discovered, it was the most effective and commonly used drug for typhoid fever. Within two years, due to its rampant and indiscriminate use, chloramphenicol-resistant *S.typhi* isolates were reported from England (Calquhoun and Weetch, 1950). However, it was not until 1972 that chloramphenicol-resistant *S.typhi* strains became a major problem, with outbreaks being reported in Mexico (1972), India (1972), Vietnam (1973) and Korea (1977). These strains were also resistant to ampicillin. Co-trimoxazole remained an effective alternative drug in treating these resistant strains until 1975, when resistance to it was reported in France. By the late 1980s, strains of *S.typhi* resistant to all three first-line drugs were in existence (Bhutta, 2006). The epidemic of drug resistance in the late 1980s compelled pediatricians throughout the world to use ciprofloxacin, despite a lack of data regarding its safety for use in children. Fortunately, follow-up studies done in children found it to be safe, effective, and less expensive with a very high sensitivity pattern. Thus, fluoroquinolones became the drug of choice for the treatment of MDRTF worldwide. However, this was soon followed by reports of isolates of *S.typhi* showing resistance to fluoroquinolones, with the first case being reported in 1992 in the United Kingdom. Subsequently, similar cases were reported from several other countries including India. With the development of quinolone (nalidixic acid) resistance, third-generation cephalosporins were used for treatment, but sporadic reports of resistance to them also followed (Saha *et al.*, and Kumar *et al.*, 2007).

African countries that have reported MDRTF include South Africa (1992), Kenya (2000), Nigeria (2005) and Egypt (2006). Even developed countries such as the United Kingdom (1990), America (1997) and Italy (2000) have reported MDRTF; most of the cases were found among travellers who had returned from regions where MDR strains of *S.typhi* had caused outbreaks or had become endemic (Akinyemi *et al.*, 2005, Zaki and Karande, 2011). Multidrug-resistant typhoid fever (MDRTF) is defined as typhoid fever caused by *S.typhi* strains which are resistant to all the three first-line recommended drugs for treatment, i.e., chloramphenicol, ampicillin, and co-trimoxazole (Zaki and Karande, 2011).

### Origin of antimicrobial resistance

Antibiotic resistance has been around for as long as antibiotics have been used to treat infection. The origin of antibiotic resistance extends much further back in evolutionary terms and reflects the attack and counter-attack of complex microbial flora in order to establish ecological niches and survive (Denyer *et al.*, 2011). Early treatment failures with antibiotics did not represent a significant clinical problem because other classes of agents, with different cellular targets were available. The major problem in the clinic today is the emergence of multiple-drug resistance, i.e. resistance to several types of antimicrobial agent (Amenu, 2014).

The origin of antibiotic resistance genes are unclear; however, studies using clinical isolates collected before the introduction of antibiotics demonstrated susceptibility, although, conjugative plasmids were present (Denyer *et al.*, 2011).

Mechanisms of antibiotic resistance in *S.typhi* is mediated by two factors

- Acquisition of foreign genes via plasmids
- Mutation on chromosome (Holt *et al.*, 2008).

Resistance can be achieved by horizontal acquisition of resistance genes, mobilized via insertion sequences, transposons and conjugative plasmids, by recombination of foreign DNA into the chromosome, or by mutations in different chromosomal loci.

Plasmid encoded chloramphenicol resistance emerged first in the early 1970s followed by large epidemics in Central America. Although slightly less effective than chloramphenicol, ampicillin was used both for therapy and for elimination of carrier state, again plasmid-encoded resistance soon developed. Also, co-trimoxazole was introduced in 1980 and plasmid – encoded resistance to trimethoprim and sulfonamides was observed shortly afterward. The first cases of typhoid due to *Salmonella enterica serovar typhi* carrying plasmid-encoded resistance to chloramphenicol, ampicillin and co-trimoxazole were reported from south East Asia (Mirza *et al.*, 2000). Among isolates resistance to ampicillin, chloramphenicol, co-trimoxazole, and tetracycline are plasmid mediated; the plasmids are unstable in *S.typhi*, and other enteric bacteria like *Escherichia coli*, *Klebsiella pneumoniae* and *Proteus vulgaris* and are found to be the potential source of dissemination of such plasmid to *S.typhi* (Shyamapada *et al.*, 2012).

### Mechanisms of antimicrobial resistance in *S.typhi*

*S.typhi* resists the action of antimicrobials by the following ways:

- Inactivation of the antimicrobial agent

- Efflux or transport of the antimicrobial
- Modification of the antimicrobial target site
- Reduced permeability of the antimicrobial agent

Most drug resistance is due to a genetic change in the organism, either a chromosomal mutation or the acquisition of a plasmid or transposon (Denyer *et al.*, 2011)

### **Plasmid mediated resistance**

Antibiotic resistance in *S.typhi* is often plasmid mediated. Plasmids of incompatibility group (Inc) HII are important vectors of antibiotic resistance in *S.typhi* (Wain, 2008). The first reported *S.typhi* harboring an IncHII plasmid was isolated during a large outbreak of resistant typhoid fever in Mexico City in 1972 and was found to be resistant to chloramphenicol, tetracycline, streptomycin, and sulphonamides. Subsequently, MDR *S.typhi* spread globally and, by 1998, IncHII plasmids could be isolated from MDR *S.typhi* worldwide. Since 1989, however, multidrug-resistant *S.typhi* strains that are no longer susceptible to chloramphenicol, ampicillin and trimethoprim have emerged. Indeed, these multidrug-resistant *S.typhi* strains have become a serious problem globally and have been reported not only in Latin America, Egypt, Nigeria, China, Korea, Vietnam, and the Philippines (Shanahan *et al.*, 1998).

Plasmid resistance often code for enzymes that destroy or modify drugs; for examples, the hydrolysis of penicillin or the acetylation of chloramphenicol and aminoglycoside drugs. Plasmid associated genes have been implicated in resistance to aminoglycosides, chloramphenicol, penicillin's, cephalosporin's, erythromycin, tetracycline,

sulphonamides and others (Willey *et al.*, 2013).

The mechanism of drug resistance usually mediated by acquisition of R plasmids involves:

#### **(1) Inactivation of the drug.**

This is a common cause of resistance that destroys or inactivates antimicrobial agents. The bacterial pathogens resist attack by inactivating drugs through chemical modification. One enzyme of this type is  $\beta$ -lactamase. Several  $\beta$ -lactamase exist in various bacteria. The best known example is the hydrolysis of the  $\beta$ -lactam ring of Penicillin by the enzyme penicillinase. They are capable of breaking the  $\beta$ -lactam ring of penicillin and some cephalosporin. The initial strains of antibiotic-resistant *S.typhi* carried chloramphenicol acetyltransferase type I, which encodes an enzyme that inactivates chloramphenicol via acetylation (Zaki and Karande, 2011). Chloramphenicol contains two hydroxyl groups that can be acetylated in a reaction catalyzed by the enzyme chloramphenicol acetyltransferase with acetyl CoA as the donor. Aminoglycosides can be modified and inactivated in several ways. Acetyltransferase catalyzes the acetylation of amino groups. Some aminoglycoside-modifying enzymes catalyze the addition to hydroxyl groups of either phosphates (phosphotransferases) or adenylyl groups (adenyltransferases) (Black, 2005 and Willey *et al.*, 2013).

#### **(2) Reduced membrane permeability**

Pathogens often become resistant simply by preventing entrance of the drug. The alteration in membrane permeability occurs when new genetic information changes the nature of proteins in the membrane. Such

alterations change a membrane transport system pores in the membrane, so an antimicrobial agent can no longer cross the membrane. In *S.typhi*, resistance to tetracycline, quinolones, and some aminoglycosides have occurred by this mechanism. A decrease in permeability can also lead to sulfonamide resistance (Black, 2005, and Willey *et al.*, 2013).

### (3) Modification of target site

Resistance arises when the target enzyme or cellular structure of the pathogen is modified so that it is no longer susceptible to the drug. This mechanism is found in *S.typhi* and other sulfonamide-resistant bacteria. These organisms have developed an enzyme that has a very high affinity for p-aminobenzoic acid (PABA) and a very low affinity for sulfonamide. Consequently, even in the presence of sulfonamides, the enzymes work well enough to allow the bacterium to function (Black, 2005).

### (4) Rapid extrusion or efflux of the antibiotic

This resistance mechanism works by pumping the drug out of the cell after it has entered. Some pathogens have plasma membrane translocases, often called efflux pumps, that expels drugs. Because they are relatively nonspecific and can pump many different drugs including quinolones, these transport proteins often are called multidrug-resistance (MDR) pumps. Many are drug/proton antiporters i.e, proton enter the cell as the drug leaves (Willey *et al.*, 2013).

Resistance to sulfonamides is mediated by a plasmid encoded transport system that actively exports the drug out of the cell (Denyer *et al.*, 2011).

Many genes, such as plasmid mediated  $\beta$ -

lactamases, tetracycline-resistance genes, and aminoglycoside-modifying enzymes, are organized on transposons (Richard *et al.*, 2007).

### Chromosome mediated-resistance

Chromosomal resistance has been attributed to a mutation in the gene that codes for either the target of the drug or the transport system in the membrane that controls the uptake of the drug (Denyer *et al.*, 2011). The frequency of spontaneous mutations usually ranges from  $10^{-7}$  to  $10^{-9}$  which is much lower than the frequency of acquisition of resistance plasmids. Therefore, chromosomal resistance is less of clinical problem than is plasmid-mediated resistance.

The chromosomal-mediated drug resistance phenomenon against fluoroquinolones has been reported recently as a result of selective pressure on the bacterial population due to their uncontrolled use. This has been attributed to a single point mutation in the quinolone resistance determining region (QRDR) of the topoisomerase gene *gyrA*, which encodes DNA gyrase (Zaki and Karande, 2011).

Resistance to trimethoprim is due primarily to mutations in the chromosomal gene that encodes dihydrofolate reductase, the enzyme that reduces dihydrofolate to tetrahydrofolate. Also, resistance to sulfonamides has been found to be mediated by a chromosomal mutation in the gene coding for the target enzyme dihydropteroate synthetase, which reduces the binding affinity of the drug (Denyer *et al.*, 2011).

### Prevention and control strategies

Contaminated water and food are important vehicles for transmission of typhoid fever.

Historical surveillance data suggest that enteric fever was endemic in Western Europe and North America and that rate decreased in parallel with the introduction of treatment of municipal water, pasteurization of dairy products, and the exclusion of human feces from food production (Crump and Mintz, 2010). At present, enteric fever prevention focuses on improving sanitation, ensuring the safety of food and water supplies, identification and treatment of chronic carriers of *S.typhi*, and use of typhoid vaccines to reduce the susceptibility of hosts to infection.

### **Vaccines**

Currently, there are two vaccines available for the prevention of typhoid fever. The Ty21a vaccine is a live, attenuated, oral vaccine containing the *S.typhi* strain Ty21a, and the parenteral Vi vaccine is based on the *S.typhi* Vi antigen. Ty21a is available as enteric capsules and is licensed in the United States for use in children 6 years of age and elsewhere including Nigeria, for children as young as 2 years of age. The Vi-based vaccine is licensed in the United States for children aged 2 years.

The effectiveness of parenteral Vi vaccine has recently been confirmed in young children, and the protection of unvaccinated neighbors of Vi vaccines has been demonstrated (Sur *et al.*, 2009). A new conjugate vaccine under development, Vi-rEPA, includes Vi antigen bound to a nontoxic recombinant protein that is antigenically identical to *Pseudomonas aeruginosa* exotoxin. In addition, efforts are underway to develop and evaluate improved live, attenuated, oral vaccines with the goals of maintaining safety while improving efficacy and reducing the number of doses required (Marathe *et al.*, 2014).

### **Non-Vaccine Measures**

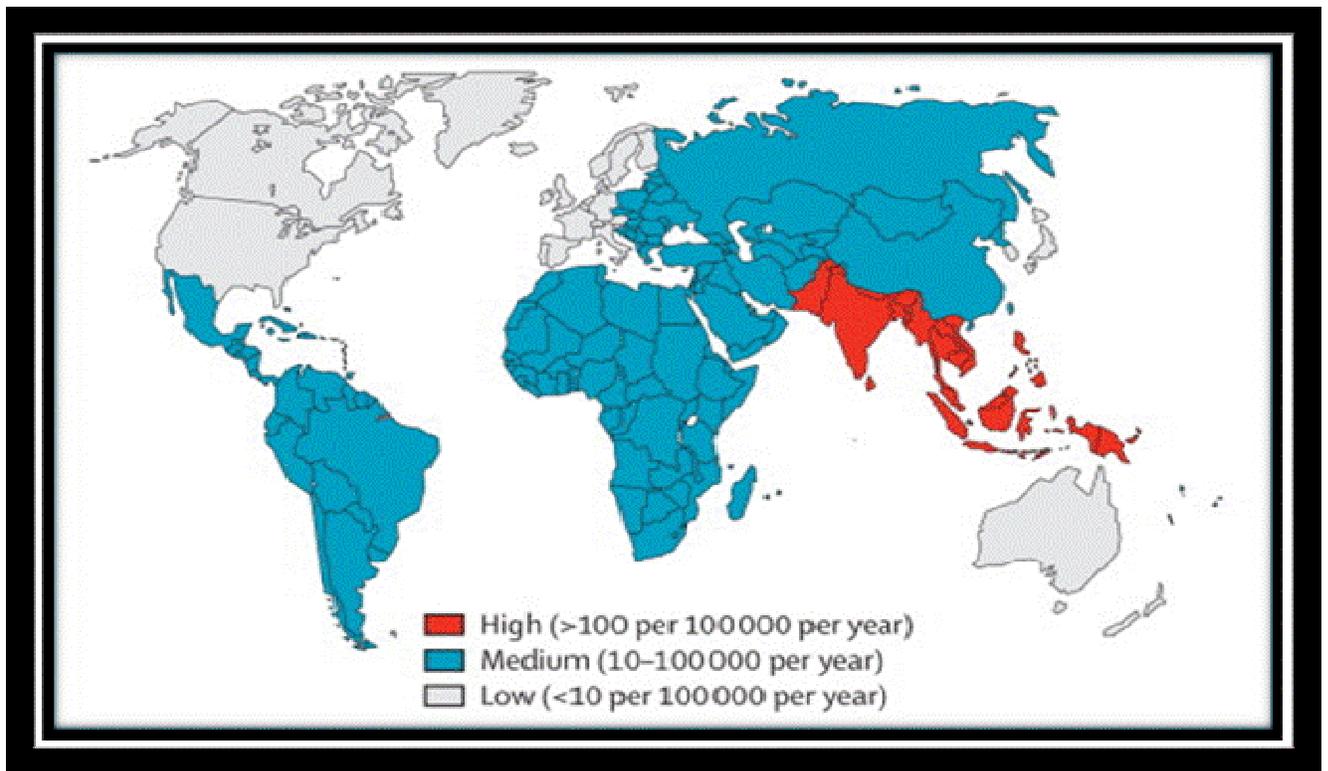
Extending the benefits of improved sanitation and the availability of safe water and food that was achieved in industrialized countries a century ago to low- and middle-income countries has proved to be a challenge. United Nations Millennium Development Goal 7 sets a target to halve, by 2015, the proportion of the population without sustainable access to safe drinking water and basic sanitation. Recent evidence suggests that interventions to improve the quality of drinking water may be relatively more important for the prevention of enteric infection relative to sanitation measures than was previously thought (Clasen *et al.*, 2007). Although centrally treated reticulated water for all is an important goal, a growing body of research suggests that improving water quality at the house hold level, as well as at the source, can significantly reduce diarrhea (Clasen *et al.*, 2007). Although not formally evaluated with enteric fever as an outcome, it is likely that interventions that reduce the rate of diarrheal diseases transmitted through contaminated water, food, and poor hygiene would have similar effects on rates of enteric fever.

The identification and treatment of *S.typhi* carriers, particularly those involved with food production, has proven to be an important strategy for the control of typhoid fever in low-incidence settings. Although carriers can be identified by serial culture of stool specimens, this approach is labor intensive. Anti-Vi antibody assays have proven to be a useful alternative to stool culture for identifying carriers in outbreak settings (Zige *et al.*, 2013). However, when used at the community level in an area where typhoid is endemic, the high background levels of anti-Vi antibody appear to render the method impractical (Gupta *et al.*, 2006).

**Table.1** A list of antimicrobial agents and their modes of action

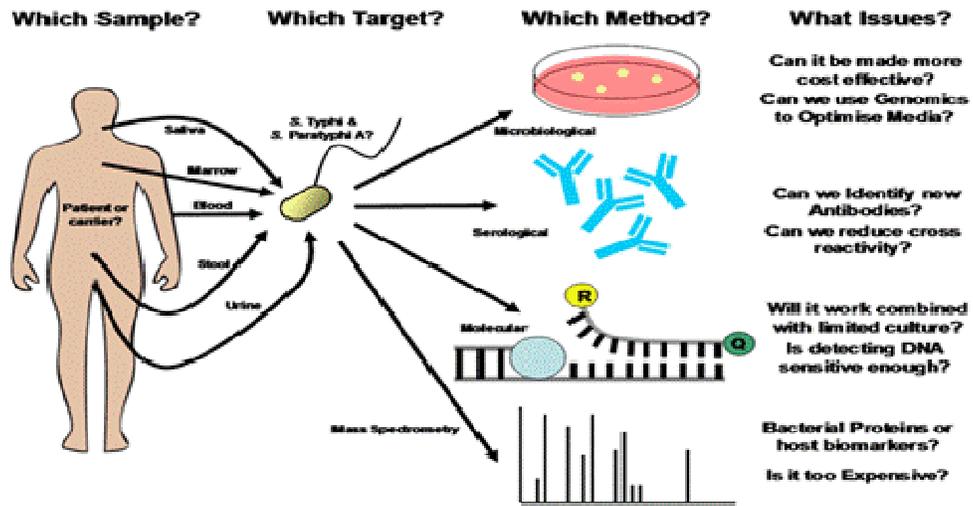
Antimicrobial agent	Group	Mode of action
Chloramphenicol	Chloramphenicol	Inhibitor of protein synthesis
Erythromycin	Macrolides	„
Azithromycin	„	„
Ampicillin	Penicillins	Inhibitor of cell wall synthesis
Amoxicillin	„	„
Augmentin	„	„
Ceftriaxone	Cephalosporins	„
Cefotaxime	„	„
Ciprofloxacin	Quinolones	Inhibitor of Nucleic acid synthesis
Perfloxacin	„	„
Nalidixic acid	„	„
Cotrimoxazole	Sulfonamides	Antimetabolites

**Figure.1** Map showing the distribution of typhoid fever around the globe



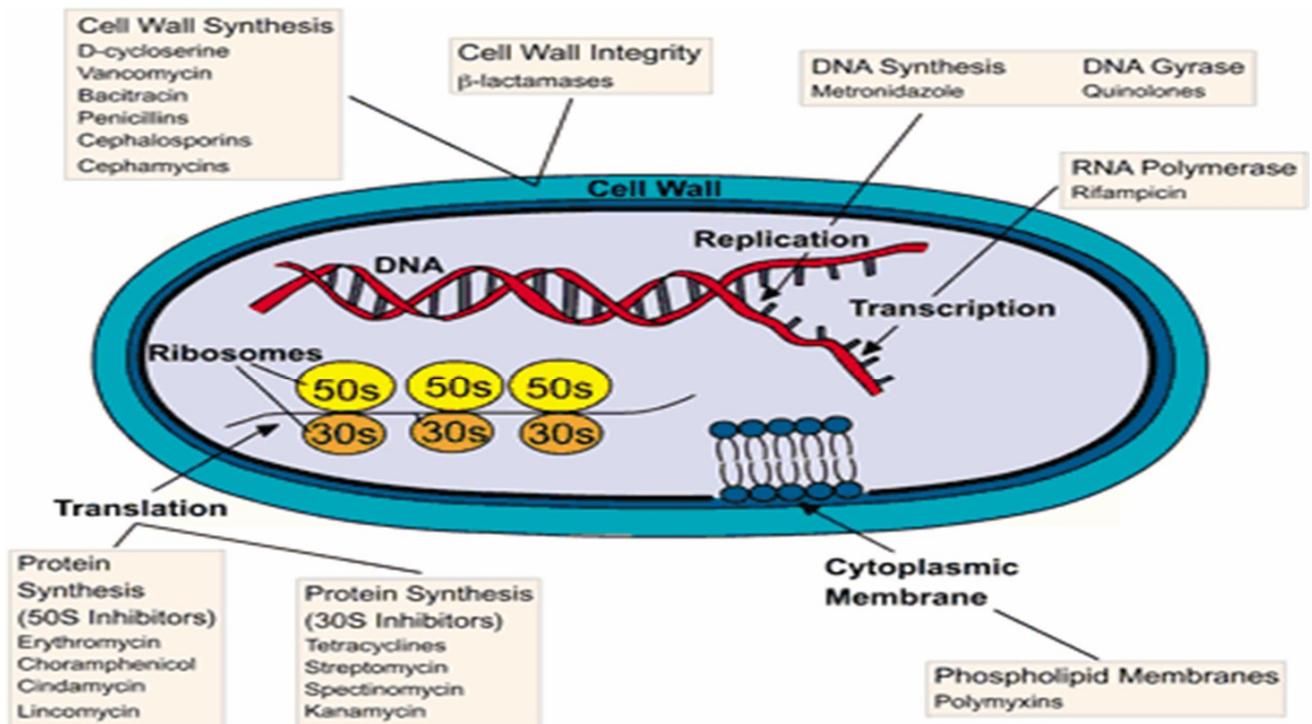
**Source:** Crump and Mintz, 2010

Figure.2 Methods of Diagnosing *S.typhi* in the laboratory



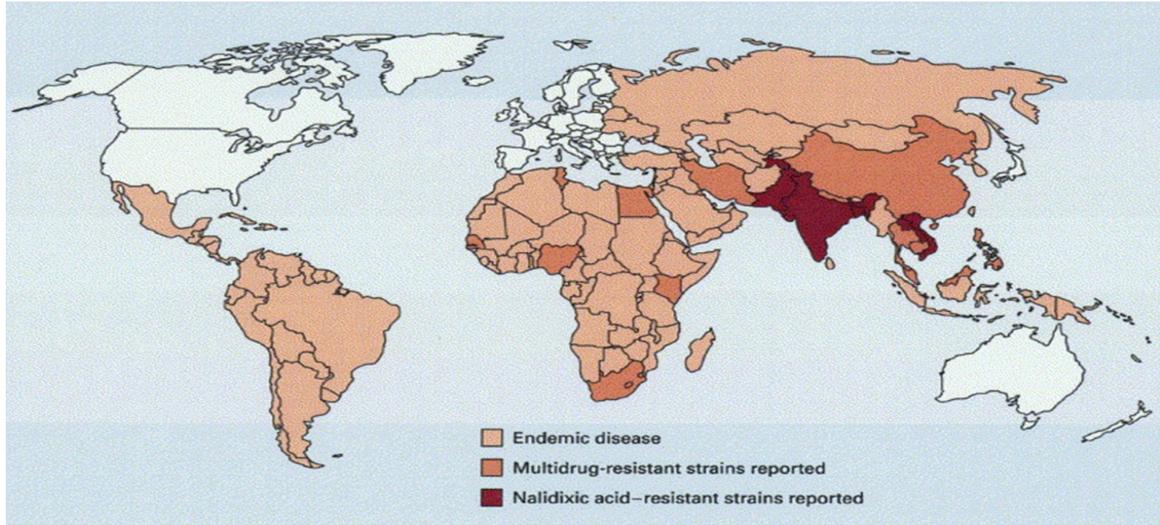
Source: Baker *et al*, 2010

Figure.3 Diagram showing target sites of antimicrobial agents



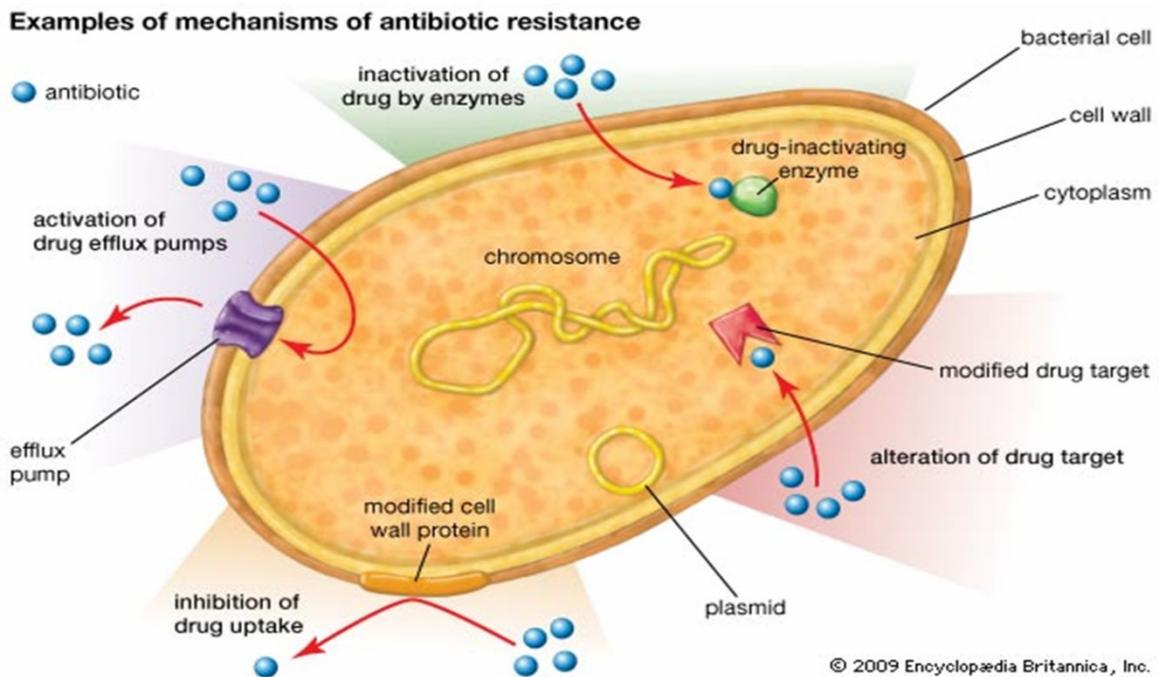
Source: <http://textbookofbacteriology.net> (accessed October 1, 2014)

**Figure.4** Global distributions of Multi-drug resistant strains of *S.typhi*



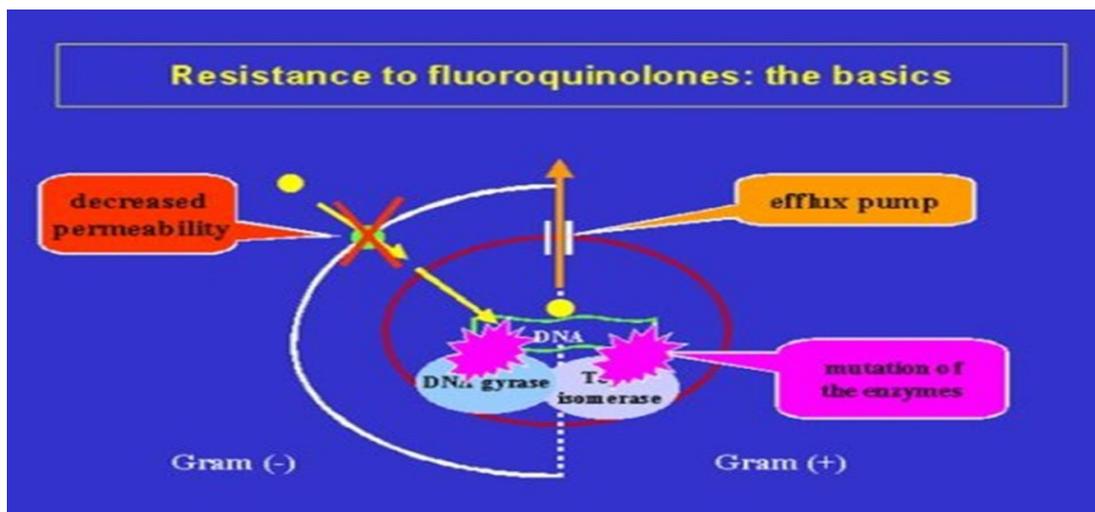
Source: Crump and Mintz, 2010

**Figure.5** Diagram showing the different mechanisms of resistance by *S.typhi*



Source: <http://textbookofbacteriology.net>

**Figure.6** Chromosome-mediated resistance of *S.typhi* to fluoroquinolones



Furthermore, the method would also have limitations in settings where Vi-based vaccine use is widespread

In conclusion, enteric fever remains a major public health challenge. Antimicrobial resistance continues to emerge in *S.typhi* resulting in loss over time of the value of traditional first-line drugs and fluoroquinolones. Added to the increasing complexity of managing enteric fever because of antimicrobial resistance, there is a strong case for much greater effort in disease control through improvements in sanitation, greater access to safe water and food, identification and treatment of *S.typhi* carriers, and the more widespread use of currently available vaccines in populations at high risk of infection.

So,

- There is need for a strong collaboration between the physicians and the laboratory in the choice of antibiotics for the treatment of typhoid fever.
- The identification and treatment of *S.typhi* carriers, particularly those involved with food production should be encouraged.

- In vitro studies show that some plant extracts are active against antibiotic resistant *S.typhi* clinical isolates. Therefore, more work should be done on medicinal plants in order to reduce MDRTF (Doughar *et al.*, 2007).
- The use of vaccine should be based on an understanding of the local epidemiology of typhoid fever to target vaccine to groups at high risk of disease, such as pre- school or school-age children.
- Ultimately, the adoption of typhoid vaccine in settings of endemicity would be greatly aided by the availability of vaccines that are efficacious in infants to facilitate integration with Expanded Programs of Immunization, that can be administered as a single dose, and that are produced locally to reduce cost.

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