Plant Environment Development 4(1):01-05, 2015 (February)
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e-mail: plant.environ.dev@ru.ac.bd

Print ISSN 1994-1501
Online ISSN 2311-3529

An Updated Review on Multi-drug Resistant Patterns of *Salmonella* in Bangladesh along with its Neighbouring Countries

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Abstract

Salmonella infections are the very challenging food borne enteric infections in humans from the past to the present era in medical science all over the world. Multiple antibiotics are usually and randomly used to treat this infection in both the developed and developing countries. Thus multiple drug resistant *Salmonella* strains are increasing more rapidly in the developing than the developed countries due to lacking of proper prescription, application, sanitation and unconsidered use of antibiotics in treatment. The drug resistant genes can also be inherited and disseminated from generations to generations to make super resistant microbial flora. As a result, drug therapies are getting hurriedly inactivated. The aims of this study are to focus the comparisons of the resistant pattern of *Salmonella* strains in vulnerable countries like Bangladesh, India, Bhutan, Nepal and Pakistan to aware the people about using drugs and finally to encourage the scientists to establish phage therapy through extensive researches. Therefore, it has been obligatory to isolate and well characterize *Salmonella* phages for various strains of multi drug resistant *Salmonella* considering the different issues such as stability, host range, infections of the phages etc, which ensures the destruction of resistant bacteria avoiding horrible biohazard..

Keywords: *Salmonella*, antibiotics, multi drug resistant, phage therapy.

INTRODUCTION

Salmonella infection is very familiar food-borne infection worldwide. *Salmonella enterica* serotype (*S. typhi*) is the causing agent of human typhoid fever which leads to increase the higher mortality rate. Food-borne diseases and poisoning are very common and public health threat for both the developed and the third world countries. Typhoid fever is an epidemic problem for Bangladesh, Indian subcontinent, South and Central America and Africa. Typhoid and paratyphoid fevers caused by multidrug-resistant bacterial strains are one of the major health problems in Bangladesh even though newly developed antibacterial drugs are used (Islam *et al.*, 2008). So, this is a rigorous and life-threatening public health illness over 21.6 million cases and annually at least 250,000 deaths are happened (Kothari *et al*., 2006, Srikantiah *et al*., 2006). About 80% of the cases and deaths are in Asia but the rest occur mainly in Africa and Latin America (Nagshetty *et al.,* 2010). Owing to poor sanitary conditions and water supply management, it has been most frequent in developing and less industrialized countries (Mirza *et al.*, 2000). The developed countries constantly have low frequency and usually related with travelling to endemic regions (Lewis *et al.,* 2006, Muehlen *et al*., 2007). To tackle the vigorous challenges, the health care managements and medical centres are adopted to use the antibiotics along with the super

generations. As a result, the bacterial populations are ameliorating day by day in the extent of multi drug resistance through their reproduction. Though emergence of plasmid-mediated chloramphenicol resistance was reported in Mexico and India in early 1970s, outbreaks occurred in Vietnam, Indonesia, Korea, Chile and Bangladesh in the next five years (Harish and Menezes,, 2011). *Salmonella typhi* (*S. typhi*) is now rapidly turning into resistant to cipropfloxacin and fluoroquinolone along with other conventional antibiotics as reported in different parts of the world to impose newly emerged challenges to treat typhoid fever (Rushdy *et al*., 2013, Choudhary *et al.*, 2013). Azithromycin can be prescribed as an alternative to ciprofloxacin in cases of resistance but due to the emergence of resistance it has recently lost the credibility (Islam *et al.*, 2008, Rahman *et al.*, 2008). Especially in developing countries like Bangladesh and its neighboring countries (Nepal, Bhutan, Pakistan, and India), people do not have the minimal awareness of resistance, antibiotics and infections. So, the controlling approach of *Salmonella* infections should be the isolation, characterization and selection of suitable *Salmonella* phages for phage therapy to avoid drug therapy.

Sources of *Salmonella* Infection

Animals and humans are the reservoir of *Salmonella*. Food, water, raw meats, milk and shell eggs may be contaminated with *Salmonella*. The most common vehicle for the spreading of *Salmonella* is food and eggs. (Patrick *et al*., 2004). It has been reported that the internal contents of eggs can be contaminated with *Salmonella* and this contamination is considered as a high risk factor in the emergence of human illness (Patrick *et al*., 2004). A study in 2009 reported that 14% of broiler chickens were found with *Salmonella* at grocery stores (Consumers Union, 2010). Moreover, the outbreaks of *Salmonella* infection commonly occur in summer (Fjaerli *et al*., 1993) to affect mainly the children. The infected carriers cause its distribution through 'five Fs' i.e. food, fingers, flies, fomites and faeces (Old and Threlfal, 1998). *Salmonella* strains can infect a wide range of reptiles, birds, mammals, livestock, poultry, dogs, and cats so that the chance of pathogenic effect of acute fatal diseases is greatly increasing.

Prevalence of Multi-drug Resistant *Salmonella*

Many drugs are always prescribed for patients that cause inappropriate and indiscriminate use of antibiotics in Bangladesh (Parry *et al.*, 2008, Rahman *et al.*, 2007). Such indiscriminate use of antibiotics in human and veterinary medicine leads to the widespread drug-resistant *Salmonella* (Bouchrif *et al.*, 2009, Ochiai *et al.*, 2008). Besides, resistance gene(s) can be transferred from resistant to susceptible bacterial cell through horizontal (Tenover, 2006) and vertical gene transfer. Gene transfer also occurs among the bacterial populations through conjugation, transformation and transduction (McManus, 1997). The transmission of drug resistant gene is more effective in the developing country than the developed one. As Bangladesh is a developing country, increasing population and urbanization may lead to the multiplying of resistant bacteria and gene (Ioannidis *et al.*, 2013). A very recent study on antibiotic resistance pattern of *Salmonella typhi* in Bangladesh found 64.28% multidrug resistant and the drugs were nalidixic acid (29%), cefixime (12%), levofloxacin (9%) and ciprofloxacin (8%) (Mannan *et al.*, 2014). *Salmonella typhi* also gained the emerged multidrug resistance capacity to ampicillin, chloramphenicol, and cotrimoxazole and thus the treatment and management of enteric fever is turning into complicated (Butt *et al.*, 2003). Another recent multi-centric study conducted across five Asian countries including China, India, Indonesia, Pakistan and Vietnam that are endemic for typhoid and the prevalence of multidrug-resistant *S. typhi* strains ranging from 7% to 65% (Ochiai *et al.*, 2008). Multi-drug resistant strains were also considerably more prevalent in Iraq (83%) and Pakistan (52%) (Rahman *et al.*, 2014). Therefore, the highly prevalence of multi-drug resistant *Salmonella* (Table 1) has become a burning and challenging public health issue in our country along with our neighbouring countries.

Phage Therapy

Indiscriminate use of antibiotics and due to different methods of gene transfer among the bacterial population, the antibiotic resistant bacteria are increasing sharply. An updated comparison of antibiotic resistant rates in Bangladesh and its neighbouring countries has also showed very higher rates. So, the drug-based health care and management system of the developing countries is getting out of order. The rising problems of multi-drug resistant bacteria drew attentions of researchers to reconsider the application of phages to treat against experimental *E. coli* infections in mice, calves, lambs and piglets (Smith *et al.*, 1987). Therefore, we should adopt phage therapy as an effective and alternative approach for the killing system of multi-drug resistant bacteria like *Salmonella* spp. using lytic capacity of bacteriophages. *Salmonella* phages play the pivotal roles in *Salmonella* evolution and to transfer virulence genes among *Salmonella* strains (Porwollik and McClelland, 2003).

Table 1: Comparison of resistant incidents of *Salmonella* spp. of Bangladesh and its neighbouring countries

Drug name	Bangladesh		Bhutan		Nepal		India		Pakistan	
	Resistance (%)	Reference	Resistance (%)	Reference	Resistance (%)	Reference	Resistance (%)	Reference	Resistance (%)	Reference
Nalidixic Acid	100	Akter *et al.* 2012	96.15	Dahal *et al.* 2008	91.1	Chand *et al.* 2014	100	Monica *et al.* 2014	75	Kazi *et al.* 2015
Ciprofloxacin	82	Afroz *et al.* 2013	1.92	Dahal *et al.* 2008	100	Baral *et al.* 2012	100	Monica *et al.* 2014	19.2	Mushtaq 2006
Chloramphenicol	15.04	Akter *et al.* 2012	-	-	57	Pokharel *et al.* 2006	28.42	Nagshetty *et al.* 2010	66.8	Qamar *et al.* 2014
Trimethoprim-Sulpamethoxazole	68	Afroz *et al.* 2013	1.92	Dahal *et al.* 2008	71	Pokharel *et al.* 2006	97.2	Pratap *et al.* 2012	66.5	Qamar *et al.* 2014
Ampicillin	100	Akter *et al.* 2012	-	-	57	Pokharel *et al.* 2006	100	Das *et al.* 2012	66.1	Qamar *et al.* 2014
Erythromycin	17.82	Akter *et al.* 2012	-	-	-	-	100	Rather *et al.* 2013	100	Akhtar *et al.* 2010
Cotrimoxazole	17.27	Akter *et al.* 2012	-	-	6.5	Prajapati *et al.* 2008	17.89	Nagshetty *et al.* 2010	29.91	Abdullah *et al.* 2012
Azithromycin	5.57	Akter *et al.* 2012	-	-	2.14	Chaudhary *et al.* 2011	31.25	Monica *et al.* 2014	-	-
Tetracycline	100	Hassan *et al.* 2014	-	-	50	Malla *et al.* 2005	4.8	Sivasankaran *et al.* 2013	28.57	Akhtar *et al.* 2010
Amoxycillin	100	Hassan *et al.* 2014	11.54	Dahal *et al.* 2008	100	Baral *et al.* 2012	33.33	Senthilkumar and Prabakaran 2005	96.48	Abdullah *et al.* 2012
Cephalexin	68.75	Nawas *et al.* 2012	5.77	Dahal *et al.* 2008	-	-	15.6	Kumar *et al.* 2008	-	-
Norfloxacin	20	Akond *et al.* 2012	-	-	100	Baral *et al.* 2012	57.9	Sivakumar *et al.* 2012	-	-
Cefuroxime	-	-	-	-		-	81.25	Das *et al.* 2012	53.1	Mushtaq 2006
Penicillin-G	100	Akond *et al.* 2012	-	-	-	-	68.75	Das *et al.* 2012	85.71	Akhtar *et al.* 2010
Cephalothin	-	-	-	-	-	-	68.75	Das *et al.* 2012	-	-
Cephotaxime	-	-	-	-	10	Acharya *et al.* 2012	94.73	Sivakumar *et al.* 2012	21.1	Mushtaq 2006
Streptomycin	20	Mamun *et al.* 2004	-	-	51	Malla *et al.* 2005	78.94	Sivakumar *et al.* 2012	92.85	Akhtar *et al.* 2010
Kanamycin	50	Hassan *et al.* 2014	-	-	-	-	78.94	Sivakumar *et al.* 2012	42.85	Akhtar *et al.* 2010
Riphampicin	60	Akond *et al.* 2012	-	-	-	-	83.33	Senthilkumar and Prabakaran 2005	-	-
Cefixine	50	Akond *et al.* 2012	-	-	-	-	6.25	Monica *et al.* 2014	-	-
Colistin	50	Hassan *et al.* 2014	-	-	-	-	48.1	Singh *et al.* 2006	-	-
Doxycycline	50	Hassan *et al.* 2014	-	-	-	-	37	Singh *et al.* 2006	-	-
Ceftriaxone	-	-	-	-	5.9	Acharya *et al.* 2012	6.31	Nagshetty *et al.* 2010	17.9	Mushtaq 2006
Amikacin	16.67	Hossain *et al.* 2013	-	-	7.7	Acharya *et al.* 2012	68.4	Sivakumar *et al.* 2012	12.3	Mushtaq 2006
Gentamicin	33.33	Hossain *et al.* 2013	-	-	11.1	Acharya *et al.* 2012	63.2	Sivakumar *et al.* 2012	78.57	Akhtar *et al.* 2010
Ofloxacin	-	-	-	-	29	Pokharel *et al.* 2006	63.2	Sivakumar *et al.* 2012	4.26	Abdullah *et al.* 2012

Thus, multi-drug resistant *Salmonella* spp. is becoming ubiquitous so that phage therapy would be an emergency treatment option. As the genetic constitutions of all the phages are not similar, so all the naturally occurring bateriophages are not suitable for phage therapy. It needs isolation and characterization of the desired *Salmonella* phages taking into account the O-antigen attachment site (Salgado *et al.*, 2004; Zayas and Villafane, 2007) and others necessary pros and cons of therapy. Though Burnet (1930) designated four phage groups as A, B, C and D, later Boyd (1950) mentioned two main groups of bacteriophages designated as subgroup A and subgroup B. The resistance can also be overcome by utilizing a diverse phage isolates or a modified isolate in terms of its host range (Goodridge, 2010). Phage therapy should be used as the primary tool for successful treatment of multi-resistant infections and prevent enteric diseases. JSC Biochimpharm, a new company of Georgia manufactured a specialized form of phages against a range of *Salmonella* and prepared the phage tablets against *Salmonella typhi* specially causing typhoid (Kutter, 2010). On the other hand, it is demonstrated that only phages were active when administered shortly after bacterial infection, and phage-resistant bacteria emerged rapidly in the course of the therapy (Capparelli *et al*., 2010). As the effectiveness of phage therapy has not yet been properly assessed, it is high time to analyze and characterize the whole genome of *Salmonella* along with its special phages to make efficacious therapy.

CONCLUSION

The potential unique advantage of phage treatment over antibiotic is the narrow host range of phages without killing the normal intestinal microflora. Isolated and characterized *Salmonella* phages do not cross their generic boundaries. On the other hand, excess prevalence of multi-drug resistant *Salmonella*, drug therapy is on the way to be inactivated in Bangladesh, India, Bhutan, Nepal and Pakistan. So, it has opened a new window to isolate and well characterize phages to meet the upcoming drug crisis, especially in Bangladesh and India. Besides, stability, internationally recognized phage in human, multiple infections of phages, antibodies production against phages, transfer of toxin genes between bacteria, shelf life of phages and responses of human immune system toward phages should be considered to characterize the different desired phages for different strains of *Salmonella*.

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